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I, **Abdullah Bdaiwi**, hereby submit this original work as part of the requirements for the degree of Master of Science in Physics.

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Categorizing Cortical Dysplasia Lesions for Surgical Outcome Using Network Functional Connectivity

by

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A thesis submitted in conformity with the requirements

for the degree of Master of Science

Department of Physics

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Under the Supervision of Professor

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Categorizing Cortical Dysplasia lesions for surgical outcome using network functional connectivity

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Abstract

Lesion-symptom mapping is a powerful and broadly applicable approach that is used for linking neurological symptoms to specific brain regions. Traditionally, it involves identifying overlap in lesion location across patients with similar symptoms. This approach has limitations when symptoms do not localize to a single region or when lesions do not tend to overlap. In this thesis, we show that we can expand the traditional approach of lesion mapping to incorporate network effects into symptom localization without the need for specialized neuroimaging of patients. Our approach involves assessing the functional connectivity of each lesion volume with the rest of the typical healthy brain using a database of healthy pediatric brain imaging data (C-MIND), available at CCHMC. Our study included 24 subjects that had cortical dysplasia lesions and underwent surgery for seizures that did not respond to drug therapy. We tested our approach using healthy brain imaging data across all ages (2-18 years old) and using age & gender specific groupings of data. The analysis sought categorization of lesion connectivity based on five subject characteristics: gender, cortical dysplasia pathology, epilepsy syndrome, scalp EEG pattern and surgical outcome. Our primary analysis focused on surgical outcome. The results showed that there are some substantial connectivity differences in the outcome analysis. Lesions with stronger connectivity to default mode and attention/motor networks tended to result in poorer surgical outcomes. This result could be expanded with a larger set of data with the ultimate goal of allowing examination of lesions of cortical dysplasia patients and predicting their seizure outcomes.

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Author

Abdullah Bdaiwi

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List of Abbreviations and symbols

CD	Cortical dysplasia
MCD	Malformations of cortical development
TSC	Tuberous sclerosis complex
FCD	Focal cortical dysplasia
IA, IB, IIA, IIB	Cortical dysplasia types
BOLD	Blood-oxygen-level dependent
VBM	Voxel-based morphometry
MRI	Magnetic Resonance Imaging
SOZ	Seizure-onset zone
SPECT	Single positron emission computed tomography
EEG	Electroencephalogram
NMR	Nuclear magnetic resonance
fMRI	Functional magnetic resonance imaging
ROI	Regions of interest
MEG	Magnetoencephalography
VLSM	Voxel-based lesion–symptom mapping
PET	Positron emission tomography
RS-fMRI	Resting-state functional Magnetic Resonance Imaging
SD	Standard deviation
ILAE	International League Against Epilepsy
C-MIND	Cincinnati MR Imaging of Neuro Development
CSF	Cerebrospinal fluid
SPMs	Statistical Parametric Mapping
T1	Longitudinal relaxation time
T2	Transverse relaxation time

1. Background and Motivation

1.1 Cortical Dysplasia in children

1.1.1 Definition of Cortical Dysplasia

Neurodevelopment in humans is a complex, dynamic process that involves the creation of neurons, their growth and differentiation, moving to their final destination. Therefore, some developmental errors can occur during this complex process (Kostovic and Rakic., 1990). The fate of neuronal development is dictated and influenced by both genetic and environmental factors cumulatively (Isaac et al., 2009). Cortical dysplasia (CD) occurs as a result of aberrant cell migration and differentiation, the most common histopathological substrate in surgical cases of pediatric epilepsy (Lerner et al., 2009; Hauptman et al., 2012).

Taylor and colleagues were the first to report focal cortical dysplasia in 1971 (Taylor et al., 1971). They discussed in detail 10 cases of patients (adults and children) with refractory epilepsy undergoing surgical resection. They claimed that the pathological changes of the focal CD were probably the cause of their seizures. The characterization of other focal malformations of cortical development (MCD) subtypes that have the same pathological changes with FCD—such as hemimegalencephaly (Sims J. 1835) and tuberous sclerosis complex (TSC) (Bourneville, D. M. 1880).—goes back to the 1800s. New FCD syndromes have been described recently, including autosomal dominant temporal lobe epilepsy and cortical dysplasia, and Pretzel syndrome (Peter B. Crino, 2015).

1.1.2 Classifications of CD

Focal cortical dysplasia (FCD) designation was restructured and subdivided into type IA, IB, IIA, IIB, IIC and type III by the Palmini classification system (Santos et al., 2014). Focal cortical dysplasia type I is described by abnormal /cortical layering with radial microcolumns, and it is divided into three subtypes; FCD type IA, IB and IC. (Blümcke et al., 2011). Focal cortical dysplasia type II is very common among epilepsy surgical cases and is a main cause of drug resistant epilepsy. It is mostly found in areas outside the temporal lobe, particularly in the frontal lobe, and is of two subtypes; FCD type IIA and IIB (See figure 1.1 FCD type IIA and

IIB compared with normal cortex). FCD type III associates with substantive brain lesions, and it is four different subtypes include IIIA, associated with hippocampal sclerosis; IIIB, associated with tumors; IIIC, associated with vascular malformations; and IIID, associated with any other lesion acquired during early life life (Peter B. Crino, 2015).

Figure (1.1), Simplified diagram of architectural and cellular abnormalities in cortical dysplasia compared with normal cortex. This chart was inspired by a figure in reference (Peter B. Crino, 2015).

1.2 The Role of Imaging to Improve Surgical Outcome

Progress in brain imaging and image processing is clinically valuable, especially for FCD. It helps to reduce the occurrence of postoperative deficits and in improving the rate of postoperative seizure freedom. Images generated by MRI are constantly improving besides advances in post processing. High-resolution and high-sensitivity techniques such as blood oxygen level dependent (BOLD) functional imaging and diffusion tensor imaging have been improved by steadily increasing magnetic field and gradient strengths (Duyn, J. H., 2012). By using these high-resolution images with advanced computer-aided methods, distinct quantitative information can be assessed without the need of exposure to ionizing radiation (Guerrini et al., 2015).

These automated image-processing methods for instance, can identify the differences in tissue density at the voxel level. Voxel-based morphometry (VBM) can detect structural abnormalities associated to MRI-visible FCDs in single patients. VBM detects increases in gray matter concentration, colocalizing with the CD lesion in 63–86% of cases (Bernasconi et al., 2001).

Furthermore, it is possible to detect automatically about 80% of dysplastic anomalies by blending models like cortical thickness, tissue intensity, and some other models with the quantification of high-order image texture features that cannot be recognized by the human eye (see figure 1.2). In addition, cortical thickness studies have shown that there is an increase in the width of the cortex in up to 91% of histologically proven FCD, providing a high diagnostic yield even in a single patient. The pathologic features of FCD lesions do not appear to depend on the lesion size (Bernasconi et al., 2011). To validate hypotheses about the seizure-onset zone (SOZ), it can be advantageous to combine advanced imaging modalities. These combinations require spatial transformations to align all imaging modalities which may have different voxel sizes, and orientation (See figure 1.3). Powerful techniques are available such as maximization of mutual information, but they need to be reproducible and applicable with little manual input (Guerrini et al., 2015).

Figure (1.2) Surface-based computational models of focal cortical dysplasia. This patient has frontal lobe epilepsy and was reported as normal, likely because of the subtle nature of the dysplasia, as demonstrated by the axial T1-weighted MRI section (right lower corner; red arrow shows the lesion (Bernasconi et al., 2011)).

Figure (1.3). Different imaging modalities led to problems of dissimilar voxel sizes. In this figure, brain (A) has higher resolution (smaller voxel sizes) and is rotated relative to brain (B) (Guerrini et al., 2015).

We can integrate multimodal, multisubject data by spatially transforming all images to a common space, allowing comparison of measurements between different patients and the identification of well-defined normative and aberrant regional values. In complex cases, we can also identify the seizure-onset zone and minimize the resection size, and reduce the need of invasive EEG monitoring by using multimodal neuroimaging (Kim et al., 2011; Cross et al., 2006). However, to date, multimodal techniques have not demonstrated the ability to affect treatment decisions or improve functional outcomes. The main challenges and limitations of current efforts are small sample size, lack of randomization, lack of control populations, and nonblinded assessment (Gaillard WD et al., 2011). There is a high priority for healthcare researchers to address these shortcomings (Guerrini et al., 2015).

1.3 Voxel-based lesion–symptom mapping (VLSM)

1.3.1 Historical background

Lesion-symptom mapping studies investigate relationships between damage to different brain regions and the associated behavioral deficits in order to make inferences about the functional neuroanatomy of linguistic or cognitive processes. Broca and Wernicke (1861-1874) and some even earlier observations in 1860 were the first to use this general approach for language.

Although some early authors studied a series of patients, the early literature was dominated by case reports of single patients. It was unclear how generalizable many of the findings were and because of that there was a significant limitation of using this method (Wilson, S. M. 2016).

1.3.2 VLSM

Though lesion–symptom mapping studies have yielded valuable insights into the relationships between brain regions and behavior deficits for more than a century, new imaging techniques have allowed improvements. One of the new methods is called “voxel-based lesion symptom mapping” (VLSM) to analyze the relationship between tissue damage and behavior on a voxel-by-voxel basis, as in functional neuroimaging.

New information about brain–behavior relationships in patient populations continues to arise from the localization of cognitive processes through lesion analysis (Adolphs et al., 2000; Chao et al., 1998; Dronkers, N. F. 1996). Patients are typically recruited for such studies according to either behavior category or by lesion type/localization.

In the category of the ‘lesion-defined’ method, the behavioral performance of a group of patients with a common area of brain damage is compared to that of a control group (Friedrich et al., 1998), (Chao et al., 1998). This approach is valuable for estimating the functional roles of specific regions of interest (ROIs), but sometimes ROI contains multiple subregions that each contribute to behavior leading to some lost information regarding that region. Furthermore, regions may be overlooked if they are part of a distributed functional network and outside the ROI. (Bates et al., 2003).

In the category of the ‘behavior-defined’ method, patients are grouped according to whether they show a particular behavioral deficit or not, and their lesions are reconstructed in a common stereotactic space (Adolphs et al., 2000; Chao et al., 1998; Dronkers, N. F. 1996). This approach simply takes the lesion reconstructions from patients with the deficit and overlay them to find common area(s), and then compare to lesion overlays from patients without the deficit. These contrasting overlays are efficient in identifying brain regions that could contribute to a cognitive skill, but a cut-off must be applied if the behavioral measures are continuous rather than binary, and information reflecting varying degrees of performance can be lost (Bates et al., 2003).

New results that have reproduced previous lesion-based models of neural organization have been obtained using functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) (Petersen et al., 2000; Price, C. J. 2000). The same voxel-based steps that are used to analyze functional neuroimaging data have been used in the VLSM method while avoiding some of the restrictions of traditional lesion analysis. Here we should mention that the VLSM method makes use of continuous lesion and behavioral information because this method does not require patients to be classified by lesion site or behavioral cutoff. VLSM is also related to recent VBM studies that associate gray and white matter tissue density with continuous behavioral data by analyzing

continuous behavioral data on a voxel-by-voxel basis (Maguire et al., 2000) work correlating continuous metabolic data for a number of ROIs with continuous behavioral measures is another important precursor as well (Metter et al., 1990). An example of VLSM method is shown in the figure (1.4) below.

Figure (1.4) Representative slices from VLSM maps computed for fluency and auditory comprehension performance of 101 aphasic stroke patients. VLSM maps computed for fluency and auditory comprehension performance of 101 aphasic stroke patients that has been used to show an example of VLSM method. These VLSM maps are colorized representation of t -test results evaluating the performance of patient on voxel basis (Bates et al., 2003).

VLSM applies all available information, eliminating reliance on cutoff scores, clinical diagnoses or specified ROIs, and that is an improvement on previous lesion symptom mapping techniques. Thus, this improvement will allow additional areas to emerge in the exploration of networks that support a given behavior. It also can act as a bridge between modern functional imaging and the classic procedures that are used in lesion symptom mapping (Bates et al., 2003).

1.4 Magnetic Resonance Imaging (MRI)

1.4.1 Definition

MRI is a type of medical imaging that is used in radiology to identify anatomical and physiological irregularities in the body, such as those arising from injury or disease. MRI does not expose the patient to harmful radiation like X-rays. MRI is very helpful of providing doctors with invaluable information about the details of a patient's injury or disease (Hanson, L. G. 2009).

MRI is based on the science of nuclear magnetic resonance (NMR). When the body is placed in an external magnetic field, some atomic nuclei in the body can absorb and emit radio frequency energy. Hydrogen atoms exist naturally in biological tissue because the human body is made of 70% water. The radio-frequency signals that were generated by hydrogen nuclei, are detectable and they can be received by antennas in close proximity to the anatomy being examined. Therefore, MRI scan essentially maps the location of water and fat in the body. The pulses of radio waves will excite the nuclear spin energy transition, and magnetic field gradients localize the signal in space. We can do different contrasts between tissues based on the relaxation properties of the hydrogen atoms therein by varying the parameters of the pulse sequence. MRI has proven to be a highly versatile imaging technique since its early development in the 1970s and 1980s (Edelman et al., 1993).

The MRI scanner is a tube surrounded by a circular magnet. The patient is placed on a bed that is inserted into the magnet. The magnet creates a strong magnetic field (B_0) that aligns hydrogen atoms, on average, in the patient's body. These protons are then exposed to radio waves with frequency equal to the Larmor frequency. There will be a resonance between the protons and the radio waves. This resonance will allow the energy to transfer from the radio waves to the protons (excitation). After receiving the energy, there will be 90 degree rotation of the protons spinning axis. Then the radio waves is no longer applied, the protons will go back to the original alignment with (B_0) over a period of time (relaxation time). During the relaxation time, the protons will loss energy and produce a faint signal (in time domain) that is detected by the receiver portion of the MRI scanner. The receiver information is processed by a computer using Fourier transform to produce an image.

The Fourier transform is a decomposition of a signal into sine and cosine components. It allows the signal in the time domain to be expressed as a series of component strengths according to frequency (see figure 1.5).

Figure (1.5) Fourier transform (www.reddit.com)

2D Fourier transformation performed in post processing generates a digital image. The digital image is a matrix of numbers that correspond to spatial location. These numbers representing each voxel may be color or intensity coded in the image (see figure 1.6). 3D images are generated by extending the Fourier transform to 3 dimensions or by stacking 2D images, depending on imaging protocol.

Figure (1.6) An image as a graphical representation of a matrix. The grey scale values in the image at left correspond to numbers, which is shown for a set of particular voxels in the close-up section.

3D coordinates are traditionally labeled X, Y, Z in the directions shown in Figure (1.7).

Figure (1.7) A depiction of the three main axes used in the standard coordinate space for MRI.

1.4.2 Functional magnetic resonance imaging (fMRI)

Functional magnetic resonance imaging (fMRI) is a procedure that measures brain activity by detecting associated changes in blood flow. Brain activity is measured through changes in BOLD signal from neuronal tissue (DeYoe et al., 1994)

fMRI takes advantage of the difference in magnetization between oxygen-rich and oxygen-poor blood as its basic measure. Frequently, noise from various sources can corrupt this measure, therefore extracting the underlying signal must be done by some statistical procedures (Bandettini, P. A. 2009).

The BOLD signal reflects the amount of deoxyhemoglobin (dHb) in the blood, which attenuates signal due to its paramagnetic nature. It arises from the interplay of blood flow, blood volume, and blood oxygenation in response to changes in neuronal activity. When we have a change to an active neuronal state, there is a hemodynamic response that momentarily increases blood flow to the region. Consequently, the concentration of diamagnetic oxygenated hemoglobin increases leading to the homogenization of local magnetic susceptibility. Consequently, $T2^*$, relaxation arising from local gradients in magnetic susceptibility, will lengthen, increasing the BOLD signal (see figure 1.8). The BOLD signal change is blurred in time because the hemodynamic response is relatively slow, peaking at approximately 5 seconds (Poldrack et al., 2011). See Figure 2.7 for an illustration of BOLD response to a boxcar pattern of brain stimulation.

Figure (1.8) Illustration of BOLD fMRI time series in active voxel and illustration of an unconvolved signal used to model the signal. The BOLD signal for an active voxel (blue) and stimulus time series (red) is shown.

Experiments with fMRI typically stimulate the brain with a task intended to exercise a cognitive domain of interest. In a voxel-wise manner, BOLD response is statistically fitted to a deliberate pattern of task stimulation. Neuronal activation of interest is determined by the goodness of fit. Color-coding can be used to present graphically the resulting brain activation and determine the strength of activation across the brain or the specific region studied (see Figure 1.9) (Bandettini, P. A. 2009).

Figure (1.9), these fMRI images are from a study showing parts of the brain lighting up on seeing houses and other parts on seeing faces. The 'r' values are correlations, with higher positive or negative values indicating a better match. From US Department of Health and Human Services: National Institute of Mental Health (Haxby 2001).

1.4.3 Resting-state fMRI

Our current understanding of brain function has been obtained by fMRI using task-based or stimulus driven paradigms. Resting-state fMRI (rsfMRI) is a functional brain imaging method that is used to evaluate low-frequency (<0.1 Hz) spontaneous fluctuations in BOLD signal that occur when a subject is not performing a task. In recent years, the interest in the application of rsfMRI has been increasing because it has been observed that spatially distinct brain regions can have synchronous resting activations with spatial distributions that coincide with recognized functional networks from task experiments (Lee et al., 2013).

By using this resting-state approach one can explore the brain's functional organization and examine if it is altered in neurological or psychiatric diseases. A number of networks are consistently found in healthy subjects, at different stages of consciousness, and across species by resting-state functional connectivity research (Biswal, B. B. 2011; Rosazza, C., & Minati, L. 2011; Cole et al., 2010).

1.5 Brain connectivity

1.5.1 Introduction

One of the oldest debates of neuroscience centers on the localization of brain function. Specific mental functions might be localized to specific brain regions or they might rely more upon integration across the entire brain (Finger. 1994). Franz Gall was the first one who attempted to localize mental functions to specific brain regions building his assumptions based on the shape of the skull (Zola-Morgan. 1993), but he was wrong about his assumptions. Karl Lashley one of the researchers in the twentieth century who argued against localization of function in the brain, showed that cortical lesions in rats had relatively global effects on behavior. Nowadays, most neuroscientists agree that there is some degree of localization of mental function, but to realize coherent mental function and behavior, the function of each of the brain regions must also be integrated. These concepts are known as functional specialization and functional integration, respectively (Friston. 1994).

1.5.2 Brain Functional connectivity

The synchronization of brain regions to form networks in rsfMRI led to the notion that functional connectivity can be defined by the correlations in BOLD activity between spatially remote brain regions.

Figure (1.10) A depiction of the various ways in which correlated activity between two regions A and B. They can arise either through direct influence or indirect influence through another region.

It should be noted that there are a variety of ways that two regions can appear to be synchronized. First, there can be a direct influence of one region on another in a directional fashion, known as effective connectivity (see Figure 1.10). For example, the connections between two regions could result in correlated activity in these two regions by the signals along those connections if one region sends efferent connections to another. Second, functional connectivity between two regions could result from mediation by a third region. Third, a common input to two regions could also lead to their synchronization. For example, if the visual cortex sends outputs to two different regions, and both of these regions receive the same inputs from the visual cortex, then it will be activity that is correlated between those two different regions caused by the presentation of visual stimuli, even if there is no direct influence between these two regions. This is known to be the problem of stimulus-driven transients. As we can see there are different reasons for brain functional connectivity, and only the first reason, effective connectivity, represents direct causal influence between regions. For this reason, we need to be

very careful in interpreting the results from functional connectivity analyses (Poldrack et al., 2011).

1.5.3 Correlation

Correlation in imaging is measuring the strength of association between the signals in two voxels. A positive correlation indicates the extent to which those voxels increase or decrease in parallel and a negative correlation indicates the extent to which one voxel increases as the other decreases.

Sometimes, we must choose a lower limit threshold for the correlation such that any voxels that have a correlation value higher than the threshold are concluded to be significant (Stroman, P. W. 2016).

1.5.4 Brain connectivity networks

A brain connectivity network is a collection of nodes and edges. The nodes indicate basic elements within the system, such as regions of interest in the brain and edges indicate the associations between those elements (connectivity strength). Vital for network construction is an accurate method, for brain networks specifically, for defining the most essential elements of a network. They can be characterized at different spatial levels (Sporns et al., 2005).

Nodes can be defined, for instance, as the regions from an anatomical atlas in MRI.

Magnetoencephalography (MEG) channels and EEG electrodes can also serve as nodes. The functional or structural associations among different neuronal brain elements define the edges among nodes. Functional associations can be measured by two ways, one is the temporal correlation between spatially remote nodes, which is called functional connectivity. In some circumstances, the influence that one neural system or node exerts over another in a directional fashion can be discerned and is known as effective connectivity (Friston et al., 1993). A network example is the default mode in the brain. The default mode network is most commonly shown to be active when a person is not focused on the outside world and the brain is at wakeful rest, such as during daydreaming and mind-wandering (as it is shown in figure (1.11) below) (Buckner et al., 2008).

Figure (1.11). The default mode network (DMN) includes regions in the medial pre-frontal cortex, precuneus, and bilateral parietal cortex (Graner et al., 2013)

1.5.5 Seed to voxel correlation

Sometimes, when comparing connectivity between subjects, a particular region or “seed” can be identified as central to a network of interest. So, this approach begins by extracting a timecourse from the voxels of a seed region, which can be determined by some a priori hypothesis. Next step is computing its correlation with all of the other voxels across the whole brain. We can represent the seed timecourse as the mean of the voxel timecourses in the seed or as the first eigenvariate of the signal from the seed region. The first eigenvariate, reflects the component of variance which is orthogonal to all other components and accounts for the most variance in the signal. Using this method is useful to get the strongest signal in case if there are multiple signal sources within the region. The mean method will reflect a combination of multiple sources while the first eigenvariate will reflect the strongest single source of variability.

2. Methods used for the CD lesion mapping study

2.1 Imaging Method

We focused on a group of patients (children) with cortical dysplasia who underwent surgery for seizures that did not respond to drug treatment. Our aim in this work was to find how each of their lesions are connected to the rest of a typical healthy brain by using the seed-to-voxel analysis approach. Our method is lesion network mapping, using normative human connectivity data to identify the distribution of regions likely to be functionally affected by a given brain lesion. For each lesion, a lesion-derived network is identified using resting-state functional connectivity MRI from a database of healthy children, which examines correlations in spontaneous, low frequency fluctuations of the BOLD signal (Fox and Raichle, 2007). In contrast to previous studies that collected resting state functional connectivity MRI in patients with brain lesions we use a large normative resting state functional connectivity MRI database (C-MIND; 222 resting-state datasets from healthy children) to identify regions likely to be affected by each brain lesion, without the need for specialized imaging of the patients (Boes et al., 2015).

2.2 Subject selection and ethical approval

We studied 24 children, (10 boys, 14 girls), aged from 35 to 6460.5 days (0.09-17.7 years), (mean = 7.28 years, SD = 5.20). Participant data were obtained in clinical Radiology at Cincinnati Children's Hospital Medical Center. The study was approved by the Institutional Review Board (IRB) of Cincinnati Children's. IRB approval is found in Appendix A1 at the end of the thesis.

One subject, who turned out to be seizure free and did not require surgery, was removed from the study. All of the remaining 23 subjects had surgery for FCD seizure and most of them were seizure free after surgery (18/23). We could categorize our subjects according to five characteristics: gender, pathology (FCD type IIA or IIB), International League Against Epilepsy (ILAE) syndrome (Frontal/none Frontal), scalp EEG seizure locus (Frontal/Parietal) and (Left/Right), and surgical outcome (still with seizures/seizure free), as they are shown in table (2.1)

and the syndromic classification is illustrated in table (2.2). Also, each lesions's location is shown in Figure (2.1).

Participant NO.	Age	Gender	Pathology	ILAE syndrome	scalp EEG F/P	scalp EEG L/R	ILAE outcome
1	5.8	F	IIB	OF	RF	RF	1
2	15.5	F	IIA	FP	RF	RF	1
3	6.3	F	IIA	SMA	RP	RF	1
4	6.6	F	IIB	PAR	RP	RF	1
5	17.1	M	IIA	PAR	RP	RF	3
6	10	M	IIA	PAR	RP	RF	1
7	4.9	F	IIB	CING	LP	LP	1
8	8.5	M	IIB	FP	RF	RF	1
9	4.7	F	IIB	OF	RF	LF	1
10	4.7	F	IIB	CING	RP	RP	3
11	2.5	F	IIA	AMYG	LT	LT	1
12	17.7	F	IIA	AMYG	LT	LT	1
13	16.3	F	IIA	SMA	BIF	BIF	3
14	1.2	F	IIA	SMA	RP	RP	1
15	7.3	M	IIA	FP	RF	RF	1
16	7.7	F	IIA	PAR	RF	RF	5
17	There was no epilepsy in this subject						
18	8.5	M	IIB	SMA	RF	RF	1
19	10.9	F	IIB	CING	RF	RF	1
20	4.1	M	IIB	MOT	LF	LF	1
21	0.09	M	IIB	OPERC	LP	LP	1
22	3.3	M	IIB	SMA	LF	LF	3
23	No data was provided for this subjects						
24	1.4	M	IIA	MOT	LF	LF	1
25	2.4	F	IIB	SMA	LO	LO	1
		M/F=10/14	IIA/IIB=11/12	F/nonF=17/6	F/P=11/8	L/R=9/13	Sfree/S=18/5
		Female	FCD-IIA	Frontal	Frontal	Left	SeizureFree
		Male	FCD-IIB	noneFrontal	Parietal	Right	Seizure

Table (2.1) Analysis categories

The syndromic classification was based on the guidelines in “Proposal for Revised Classification of Epilepsies and Epileptic Syndromes”, Commission on Classification and Terminology of the International League Against Epilepsy. 1989

ILAE syndrome		Scalp EEG	ILAE Outcome
Temporal lobe	AMYG=amygdalo- hippocampal LAT=lateral temporal	L=Left R=Right BI=Bilateral F=Frontal T=Temporal P=Parietal O= Occipital	Ordinal Scale 1-6 1=seizure free
Frontal lobe	SMA=supplementary motor CING=cingulate FP=anterior frontopolar OF=orbitofrontal DL=dorsolateral OPERC=opercular MOT=motor cortex		
Parietal lobe	PAR=parietal		
Occipital lobe	OCC=occipital		

Table (2.2) Analysis categories classification

Methods: Seizure types reviewed in office notes. Reviewed up to 3 seizures per seizure type, when present, in Stellate and Natus recordings, reviewed video and EEG tracings in at least two montages in standard settings.

Figure (2.1). Lesion locations

2.3 Scanning

MRI was acquired prior to surgery as part of routine clinical protocol for patients with seizures. The protocol included T1-weighted, T2-weighted, and susceptibility-weighted images together with diffusion tensor imaging and blood flow via arterial spin labeling (ASL) techniques. FCD were identified using a combination of these image contrast weightings by a neuroradiologist. Each lesion was traced manually in 3 dimensions by the neuroradiologist, creating a lesion mask.

EEG data before surgery were acquired using standard international 10-20 placement. Results were reviewed by a neurologist after applying a 1 Hz high pass and 70 Hz low pass filter, with notch filter to remove 60 Hz artifact; standard timescale was used. Digital signals were reviewed using a minimum of two montages (anterior-posterior bipolar and either average reference or transverse montages).

Each seizure type, as determined by detailed history in office notes, was reviewed independently for video EEG localization. Up to 3 seizures were reviewed per seizure type. Seizure onset was carefully reviewed prior to time of first clinical change. Localization by EEG was determined based on a consistent early ictal change. Semiology was determined by review of office notes for aura, if any, and video of reviewed seizures, fitting the patient's semiology to ILAE syndrome.

2.4 C-MIND Project

Data used for connectivity analysis in this work were obtained from the database known as Cincinnati MR Imaging of Neuro Development (C-MIND), provided by the Pediatric Functional Neuroimaging Research Network. This Network and the resulting C-MIND database was supported by contract from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (HHSN275200900018C).

Background Information:

The primary objectives of the C-MIND project were to develop standardized BOLD fMRI and ASL protocols for use with typically developing children, and to recruit and assess children between the ages of infancy and 18-years-old for brain perfusion using ASL and passive fMRI

including rsfMRI. In addition, typically developing children in the age range 0-3 years (n=40) and 7-9 years (n=30) were assessed longitudinally using imaging and behavioral measures including concurrent ASL/BOLD fMRI during language stimulation. None of the children were sedated or given medication to reduce movement while being scanned. Members of the Network have begun to mine the C-MIND data set to look at developmental changes in white matter structure, gray matter structure, structural and functional connectivity, perfusion, neurovascular coupling and correlations between behavioral measures and brain development. The C-MIND database includes imaging and behavioral data from over 200 typically developing children for a cross-sectional look at the differences in brain function throughout the age range (Vannest et al., 2014).

2.5 Data analysis

2.5.1 Preprocessing

The subject anatomical images and the lesions were preprocessed by using Statistical Parametric Mapping software (SPM12, Wellcome Trust Center for Neuroimaging:

<http://www.fil.ion.ucl.ac.uk/spm/>)

In order to compare lesions across subjects and in order to use each lesion mask as a seed region for seed-to-voxel connectivity analysis with C-MIND datasets, each traced lesion had to first be transformed into a common standard space.

This was accomplished in SPM12 by a combined process on the T1-weighted anatomical clinical image of each subject that both segments the image into gray matter, white matter, and cerebrospinal fluid (CSF) tissue classes and normalizes the image to a standard template. The normalization process involves both rigid-body translation/rotation and any necessary local warping to maximize the match to the template. Once the transformation is established for the anatomical image, it can be applied to the lesion mask image to localize the lesion in the standard space.

Each rsfMRI dataset from the C-MIND database had also been preprocessed in SPM12. After rigid-body realignment of all the functional images in each rsfMRI dataset, the normalization process described above was carried out. Normalized C-MIND data were then fed into software for performing functional connectivity analysis (CONN, v17a, a Matlab-based cross-platform

software for the computation, display, and analysis of functional connectivity in fMRI, <https://www.nitrc.org/projects/conn>). CONN calculates the correlation of BOLD signal from the rsfMRI series after accounting for potential confounds from motion and other physiological sources. In part, this is achieved by regressing out variability of signal arising from white matter and CSF (assumed to be unrelated to neuronal fluctuations). CONN also allows for the definition of regions of interest to use as seeds for generating connectivity maps.

2.5.2 Adding the lesions into C-MIND as masks (ROIs)

After generating the normalized lesions, we added them as masks into CONN after processing a collection of C-MIND rsfMRI datasets for connectivity. We used 222 subjects from C-MIND in the age range of 2.1 to 18.8 years. Here, we should mention that in our analysis we avoided subjects that were asleep when the MRI scan was done especially in the early age subjects (less than 3 years old). In CONN, we performed seed-to-voxel analyses using each of the lesions as seeds. This created a correlation map for each lesion across all of the 222 subjects in C-MIND.

2.5.3 Statistical analyses

FCD is a challenging situation for an epilepsy surgery team. Researchers have been trying to improve the surgical outcomes of FCD patients by newer anatomic and functional imaging and neurophysiological (EEG and MEG) methods. Therefore, the main focus of our statistical analysis was to examine how the surgical outcome characteristics (seizure free vs. seizure) might be related to specific functional connectivity patterns (network connectivity).

In exploratory analysis, we also determined whether any of the other distinctions among the FCD subjects, i.e. gender, ILAE syndrome, scalp EEG locus, FCD pathology, might also result in distinct connectivity characteristics.

In addition, our primary analysis used C-MIND connectivity maps from children across the whole age span (2-18 years) available. We also explored the idea that each subject with a lesion should only be referred to data from C-MIND that matched that subject in both age and gender. This is because there is evidence that connectivity maps might depend on age and gender, with age dependence being the strongest for younger ages.

2.5.3.1 Analysis using all ages in C-MIND

We generated connectivity maps corresponding to the lesion for each FCD subject using data across all ages in C-MIND. Then, using SPM12, we did a one sample t-test for each FCD subject across all 222 corresponding C-MIND connectivity maps. This produced a mean connectivity map corresponding to each lesion (each FCD subject). Following this, we compared the connectivity maps between FCD subject groups according to surgical outcome or one of the other characteristics. Group differences were assessed via two sample t-test. The contrast was determined for each category in table (2.1). After thresholding the T-maps, we were able to discern distinct connectivity patterns according to FCD subject group and categorization.

2.5.3.2 Age and gender specification analysis

When dealing with human subjects during the childhood years, we have to consider a very important factor which is the age. In humans, brain development continues for an extended period postnatally. The size of the brain increases by four-fold during the preschool period, and by age 6 it will reach approximately 90% of adult volume (see Figure 2.2). Through childhood and adolescence, the structural changes in both the major gray and white matter compartments will continue and these changes in structure parallel changes in functional organization. The level of connectivity throughout the developing brain far exceeds that of adults, especially during the early postnatal period. (Stiles, J., & Jernigan, T. L. 2010).

Many imaging studies also find that there are gender differences in structural and functional measures.

Due to these changes in the developing brain, we examined application of our analysis with an attempt to match the C-MIND datasets used for each lesion according to the age and gender of the corresponding FCD subject.

Figure (2.2) “Human brains grow rapidly before birth through the first year and into childhood. Image courtesy of Karen Carr Studios” (Smithsonian Institution, <http://humanorigins.si.edu>)

We generated mean connectivity maps for each FCD subject using the closest 15 C-MIND subjects with an age and gender match. In the age ranges 0-3 years and 15-18 years, some of the 15 subjects from C-MIND were more than 3 years older or younger than the subject, and in the age range of 3-15 years, the 15 subjects from C-MIND were within a year of the subject’s age. Here, we should mention that we ignored asleep cases and we only used awake cases among C-MIND subjects. Then we processed with same steps as in section 2.5.3.1 above.

3 Results

One subject (Number 17) was excluded from the analysis due to not having epilepsy, yielding a total group size of $N = 23$. For each category analysis, we show both signs of the contrast between subject groups.

When it came to interpreting the results, we had to consider the signs of the connectivity (correlation) being compared in the 2-sample T-test. We considered, for each voxel, the signs of the coefficients being contrasted (+ +), (+ -), (- +), & (- -), to determine whether the functional connectivity difference was between two positive values or two negative values. Negative values correspond to anticorrelation between brain regions. We used MRIcron and XjView for visualization and interpretation of the results.

3.1 Results of analysis using all ages from C-MIND

The surgical outcome was the characteristic of the FCD subjects that we focused on because the analysis has the potential to find how the surgical outcome depends of how the lesions functionally connect to the rest of the brain. Finding the impact of different lesions based on their functional connectivity could be a powerful tool for predicting surgical outcomes for FCD patients.

We also did the analysis for other subject categories (in table 2.1) as further work for more understanding of the functional connectivity of the lesions.

3.1.1 ILAE Surgical Outcome Analysis Result

The surgical outcome analysis result showed that lesions resulting in persistent seizures after surgery have more positive correlation to the attention areas and more negative correlation to the default mode network in the brain compared to lesions with seizure-free surgical outcomes. It should be noted that in addition, seizure free lesions tended to have positive correlation to the default mode network. In figure (3.1) we viewed brain slices of the positive and negative correlations for both seizure and seizure-free lesions post surgery, where (+ , +) means that we

are comparing only positive correlation between seizure and seizure free contrast and (- , -) means we are comparing only negative correlation between seizure and seizure free contrast, and (+ , -) or (- , +) we are comparing a mixture of positive and negative correlations.

Figure (3.1) Slice images of all ages surgical outcome result in four cases.

In these figures, we demonstrate both positive and negative correlations for both seizure and seizure free surgical outcome analysis result. (A) showed both positive and negative correlations, (B) showed where is the positive correlation for seizure leaions, and (C) showed where is the neagtive correlation for seizure leasions.

(A)-Slice images of all ages outcome result seizure free vs seizure

(B)-Seizure has more positive correlation than seizure free to these areas

Left&Right Cerebrum-Parietal Lobe-Inferior Parietal Lobule
Left&Right Cerebrum-Frontal Lobe-Inferior Frontal Gyrus
Left&Right Cerebrum-Frontal Lobe-Superior Frontal Gyrus
Left & Right Cerebrum-Limbic Lobe-Anterior Cingulate

(C)-Seizure has more negative correlation to the default mode than seizure free includes regions in the medial pre-frontal cortex, precuneus, and bilateral parietal cortex

Figure (3.2) outcome positive correlation for seizure and seizure free

Here in figure (3.3), we show overlay of all lesion to demonstrate the lesions's locations,

3.1.2 Gender Analysis Result

Here we are showing both contrast (1 -1) is in the black color (Red color on the brain visualization image) and (-1 1) is in the gray color (Blue color on the brain visualization image).

In the first contrast, there was no cluster showing up on the map with threshold ($T=2.8$) and a small number (64 voxels) with ($T=2$) leading that there was very small functional connectivity in the contrast of ($F > M$) females are greater than males. However, there was a strong functional connectivity with cluster value of (2691 voxels) in the ($M > F$) contrast.

Figure (3.4) Gender glass brain of both contrasts

We used the first contrast (1 -1) map ($F > M$) to determine this shared functional connectivity was based on positive correlations or negative correlations. The result showed that males have more positive correlation than females in this Left Cerebrum- Frontal Lobe- Middle Frontal Gyrus as shown in the figure below

Figure (3.5) Gender analysis result as it shows that males have more positive correlation than females in this Left Cerebrum- Frontal Lobe- Middle Frontal.

3.1.3 Pathology Analysis Result

Here we can see that the largest two cluster in both contrasts are (1042 voxels) in the first one (IIA > IIB) and (1554 voxels) in the second one (IIB > IIA).

Figure (3.6) Pathology glass brain of both contrasts

And by examining the map to find the source of these functional connectivity clusters, the result yielded that IIA has more positive correlation in the Right Cerebrum-Limbic Lobe and has more negative correlation in the Left Cerebrum-Sub-lobar as shown below in figure (3.7).

3.1.4 ILAE syndrome Analysis Result

Here, we are comparing frontal with nonfrontal syndrome. In figure (3.8), there is no large cluster in the first contrast where (Frontal > nonFrontal). However there was some functional connectivity like an upside down pyramid corners that Frontal has more positive correlation in those areas than nonFrontal as shown in figure (3.9) below

Figure (3.8) Syndrome glass brain of both contrasts

Figure (3.9) Syndrome analysis result

3.1.4 Scalp EEG Analysis Result

Here, we are comparing scalp EEG frontal and those with parietal EEG loci. There is a small cluster in the first contrast and large one in the second and both showed positive correlation. The contrast was (Frontal EEG > Parietal EEG) as shown in figure (3.10), and the result in figure (3.11)

Figure (3.10) Scalp EEG glass brain of both contrasts (Frontal/ Parietal)

Figure (3.11) Scalp EEG (F/P) analysis result

Figure (3.12) Scalp EEG glass brain of both contrasts (Left/ Right)

In (Left > Right) contrast, the result showed that there are more functional connectivity in multiple regions in the left cerebrum than the right, in positive and negative correlations.

Figure (3.13) Scalp EEG (L/R) analysis result

3.2 Age and Gender specification analysis results

There was some similarity between the results of analysis using all ages and the age & gender matched analysis result. In the age/gender specification result, there are more connectivity voxels showing up on T maps. This was because we used only the nearest 15 subjects from C-MIND subjects to the main subject's age. In other words we were only using 6.7% of the main data set from C-MIND subjects which is 222 subjects.

These figures in table (3.1) are glass brains which are a unity-3D brain visualization that displays source activity and connectivity, inferred in real-time for both contrasts, (1 -1) is in the black color and (-1 1) is in the gray color.

Analysis Category	Across all subjects T map	Age and Gender specification T map
Gender
Pathology

Syndrome
Scale EEG F/P
Scale EEG L/R
Outcome

Table (3.1) Comparison between the across all ages analysis and age & gender analysis result.

4 Discussion

4.1 Discussion about the Findings

Here we demonstrated the brain functional connectivity in children with cortical dysplasia lesions. Our analysis was based on gender, pathology, syndrome, scalp EEG (Frontal/none Frontal, Left/Right), and surgical outcome.

Before we start with the interpreting of our result, it is a good idea to take a look at the brain structure and their functions in the body.

Figure (4. 1) the brain structure and their functions in the body (<http://humanbrainfacts.org>).

First, the first key finding of the surgical outcome analysis indicated that lesions associated with persistent seizures after surgery have more positive correlation in the attention areas in the brain which are “Left & Right Cerebrum - Parietal Lobe - Inferior Parietal Lobule” and Left & Right Cerebrum - Frontal Lobe - Superior Frontal Gyrus. Conversely, the result also showed another substantive finding which is that those lesions also had stronger negative correlation to the brain’s default mode network.

One can gain insights that if a lesion is strongly decorrelated to the default mode and more strongly correlated to other, task-related areas shown in the figure below, then excision of this lesion may not result in freedom from seizures. This is a significant result that one can have an idea about the epilepsy cases and what to expect for surgical outcomes.

Unfortunately, we had just a small number of subjects (only 24) and this size of data is not good enough to get significant results after correcting for multiple comparisons among all voxels in the brain. Furthermore, the imbalanced dataset in our data, especially in the surgical outcome data (18/5) and syndrome analysis (17/6), also limited our ability to get good results. Also, we threshold at ($T > 2$), but this was not significant statistically after correction for multiple comparisons.

Second, the human brain is a highly complex organ. There are apparent gender differences that have been found by studies of perception, cognition, memory and neural functions. These differences may be attributed to various genetic, hormonal, and environmental factors and do not reflect any overall superiority advantage to either sex. These differences between men and women brains include processing, chemistry, structural differences, and blood flow and brain activity. For example, they use different parts of the brain to encode memories, sense emotions,

recognize faces, solve certain problems and make decisions (Zaidi, Z. F. 2010). Our result for gender analysis showed that there was not many functional connectivity voxels showing up on the T map for the (F > M) contrast. However, the result also showed that males who have lesions tend to have more positive correlation than females in the Left Cerebrum-Frontal Lobe-Middle Frontal which associates with movements and behavior. If we go back to the lesion's location, we see that subject 22 and 24 are both male and they have large size lesions on the left side of the brain. Also, based on our subjects, we have 4 male subjects who had their lesions in the left cerebrum and have almost exactly same pathology and syndrome, suggesting that it may be those lesions have a strong functional connectivity to themselves. Unlike the females who have smaller lesions and different locations and symptoms.

Third, in the pathology analysis we are comparing to types of cortical dysplasia IIA and IIB (Section 1.1.2) Focal cortical dysplasia type IIA is characterized by dysmorphic and cytomegalic neurons, but lacking balloon cells. FCD type IIB is characterized by dysmorphic/ cytomegalic neurons and balloon cells. Balloon cells have an enlarged cell body and opalescent, glassy appearing eosinophilic cytoplasm (Peter B. Crino, 2015). Our analysis result showed that IIA has more positive correlation than IIB in the Right Cerebrum-Limbic Lobe-Parahippocampal Gyrus which associates with emotional lives (Isaacson, R. 2013). Although, IIA has more negative correlation than IIB in the Left Cerebrum-Sub-lobar-Caudate which associates with motor processes (Malenka RC et al., 2009) . We cannot say much about why the two types are connected to those regions because we need to consider the location of the lesions and what each part of the brain made of. Also, we need to know what is the structure of the balloon cell and how they exist in the brain so we can have a sense about why each type connects to a particular region in the brain.

Fourth, our syndrome analysis result showed that the frontal syndromes have more positive correlation in “Right Cerebrum-Frontal Lobe-Middle Frontal Gyrus”, “Right Cerebrum- Parietal Lobe- Inferior Parietal”, “Left Cerebrum- Frontal Lobe- Middle Frontal” and “Left Cerebrum- Parietal Lobe- Inferior Parietal Lobule, which they are responsible for executive processes and the attention areas in the brain (Culham et al., 2001). The result also showed that Frontal has more negative correlation than nonFrontal in the Right Cerebrum-Limbic Lobe – Uncus-

Temporal_Pole_Mid_R. In humans, atrophy of the right Temporal Pole and surrounding regions, found in right temporal variant of frontal temporal dementia, is distinguished by profound changes to personality, emotional regulation and social behavior (Olson et al., 2007).

Fifth, An EEG (electroencephalogram) is a test that gives information about the health and functioning of the brain. The electrodes will pick up activity in the brain (Thoresen et al., 1997). . In our analysis, the EEG was used to help localize the generator of the seizures. Here we used scalp EEG to compare the lesions that are in the frontal/parietal parts, and left/right parts. Our result for the frontal/parietal comparison yielded that Frontal has more positive correlation than Parietal in the “Left and Right Cerebrum -Frontal Lobe - Medial Frontal Gyrus”. No surprises here because most of our lesions are in the frontal lobe and they tend to connect to where they are or near by areas. As we also see the parietal lobe has more positive correlation than frontal lobe at the junction between those two lobes.

In the left/right comparison, the result showed that there are more functional connectivity in multiple regions in the left cerebrum than the right, in positive and negative correlations. This is because most of our lesions were on the left specially the larger ones (see page 28).

4.2 Comparing our approach to functional neuroimaging of patients

The technique of functional brain imaging in patients has been used to relate symptoms to the network effects of brain lesions. The first difference between the two approaches is that our work does not require collecting functional neuroimaging data from patients as is the case for the functional brain imaging approach.

Second, when it comes to the functional connectivity, post-lesion functional neuroimaging is not able to investigate the physiology or connectivity of the lesion location itself, because this tissue has been damaged by the lesion. This contrasts with our current technique, which investigates properties of the lesion location based on a cohort of intact subjects, not only by the location and the size of the lesion but also the way they connect.

Finally, the abnormalities of functional neuroimaging in patients represent a combination of functional changes that are induced by direct lesion and secondary compensatory responses

(Grefkes and Fink, 2014). Our technique is based on connectivity alone and it might isolate or emphasize the functional changes that are induced by direct lesion. In fact, combining the two techniques may prove a powerful approach for differentiating direct versus compensatory processes (Boes et al., 2015).

5 Limitations & Future directions

There are several limitations to the present work, some of which provide important avenues for further research. First, the goal of the present study was to provide validation of a technique for identifying the distribution of regions likely to be functionally affected by a given Cortical Dysplasia lesion.

Second, lesion network mapping appears capable of identifying which regions are likely to be functionally affected by a lesion, but further work is needed to determine whether we can predict how these regions will be affected. There are dynamic compensatory mechanisms that unfold after a lesion occurs and predicting these effects is likely to require further work combining the present technique with longitudinal post-lesion imaging of patients.

Third, the present analysis focused on shared network overlap across a group of lesions. It remains unknown whether individual differences in lesion-based networks relate to individual differences in symptoms.

Fourth, there are limitations in lesion size such that localizing results to specific area in brain is difficult. Our approach is more effective with small size lesions.

Fifth, the sample size is a major factor in any analysis, unfortunately we had just a small number of 24 and this number of subjects is not good enough to get significant results. In addition, there was imbalanced dataset in our surgical outcome data (18/5) and syndrome analysis (17/6), the more balanced data we use the better result we get. Also, we threshold at ($T > 2$), but this was not significant statistically after correction for multiple comparisons.

Sixth, there was another limitation in C-MIND dataset that we used in our age & gender specification analysis. In younger and older age ranges, we had to include datasets up to 3 years different than the FCD subject's age. This could make a big difference in term on functional connectivity especially in early ages (1-3 years) due to the brain developments.

Another direction for extending these results is the investigation of functional connectivity across other networks of the brain. The current method may also be used to identify a priori regions of interest in which to investigate the network effects of lesion patients undergoing functional

imaging (Boes et al., 2015). An ROI-to-ROI approach could be a very powerful technique that can provide more information about how each lesion connects to a specific part of the brain leading to improvement of the surgical outcome predictions.

6 Conclusion

In conclusion, cortical dysplasia (CD) occurs as a result of aberrant cell migration and differentiation, the most common histopathological substrate in surgical cases of pediatric epilepsy (Lerner et al., 2009; Hauptman et al., 2012). Epilepsy is a disorder in which nerve cell activity in the brain is disturbed, causing seizures (Epilepsy Society, 2015). In a lot of cases the epilepsy patients and their families need to know how much time they need to recover and what kind of therapies they will need to speed up the recovery process. In this work, we report how healthy brain regions are likely to be functionally affected by a lesion based on five analysis categories. We examined our approach in age and gender specification, and showed a slight difference due not using as many subjects. There was a substantial result in the surgical outcome analysis that could lead to a new understanding of epilepsy cases that go to surgery. Finally, our work introduces an important technique that might lead to the building of a prediction system in which one can examine the lesion of epilepsy patients headed for surgery and predict what are the likely outcomes. Knowing the functional connectivity of lesions will help doctors to determine what is the best way to treat patients with seizures.

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Appendix A1: Research ethics approval

The study was approved by the Institutional Review Board (IRB) of Cincinnati. The confirmation of ethics approval is included on the following page.

**Institutional Review Board - Federalwide Assurance #00002988
Cincinnati Childrens Hospital Medical Center**

Date: 11/30/2016
From: CCHMC IRB
To: Principal Investigator: Hansel Greiner
Neurology
Study ID: 2015-2905
Re: Study Title: Epilepsy Prevalence and Clinical Predictors in Pediatric
Patients with an MRI Identified Focal Cortical Dysplasia

This study expires on: 6/26/2017.

An amendment to the above referenced protocol was reviewed and **APPROVED** using an **EXPEDITED** review procedure as set forth in 45 CFR 46.110(b) on **11/30/2016**.

The following was reviewed:

Revised Study Documents

IRB Protocol Version 4_uploaded 10_20_2016 clean

Amendment Documents:

Bdaiwi CR
Bdaiwi HSR
Bdaiwi ARHC

Study staff removed:

Lauren Maynard

Study staff added:

Abdullah Bdaiwi
Mark DiFrancesco

Please note the following requirements:

OTHER APPROVALS: Principal investigators are responsible for maintaining approval from other applicable review committees and performance sites. This

includes, but is not limited to, Divisional Scientific Review committee, General Clinical Research Center (GCRC), Radiation Safety, Institutional Biosafety Committee (IBC), Conflict of Interest (COI) Committee, and any sites (i.e. schools, hospitals) where the research may be conducted. Principal investigators are also responsible for maintaining approval from the FDA and a valid contract between the sponsor and this institution, as applicable. If any of these entities require changes to the IRB-approved protocol and/or informed consent/assent document(s), the changes must be submitted to and approved by the IRB prior to implementation.

AMENDMENTS: The principal investigator is responsible for notifying the IRB of any changes in the protocol, participating investigators, procedures, recruitment, consent forms, FDA status, or conflicts of interest. Approval is based on the information as submitted. New procedures cannot be initiated until IRB approval has been given. If you wish to change any aspect of this study, please submit an Amendment via ePAS to the IRB, providing a justification for each requested change.

CONTINUING REVIEW: The investigator is responsible for submitting a Continuing Review via ePAS to the IRB at least 30 days prior to the expiration date listed above. Please note that study procedures may only continue into the next cycle if the IRB has reviewed and granted re-approval prior to the expiration date.

UNANTICIPATED PROBLEMS: The investigator is responsible for reporting unanticipated problems promptly to the IRB via ePAS according to current CCHMC reporting policy found on CenterLink.

STUDY COMPLETION: The investigator is responsible for notifying the IRB by submitting a Request to Close via ePAS when the research, including data analysis, has completed.

Statement regarding the International Conference on Harmonization and Good Clinical Practices: The Institutional Review Board is duly constituted (fulfilling FDA requirements for diversity), has written procedures for initial and continuing review of clinical trials prepares written minutes of convened meetings, and retains records pertaining to the review and approval process; all in compliance with requirements defined in 21 CFR Parts 50, 56 and 312 Code of Federal Regulations. This institution is in compliance with the ICH GCP as adopted by FDA/DHHS.

Thank you for your cooperation during the review process.

§46.110. Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research.

§46.108(b) An IRB may use the expedited review procedure to review either or both of the following:

1. some or all of the research appearing on the list and found by the reviewer (s) to involve no more than minimal risk,
2. minor changes in previously approved research during the period (of one year or less) for which approval is authorized.

Under an expedited review procedure, the review may be carried out by the IRB chairperson or by one or more experienced reviewers designated by the chairperson from among members of the IRB. In reviewing the research, the reviewers may exercise all of the authorities of the IRB except that the reviewers may not disapprove the research. A research activity may be disapproved only after review in accordance with the non-expedited procedure set forth in §46.108 (b).