Summer 2012

Table of Contents

*Using Automated Methods to Accurately Distinguish Patients with Epilepsy from Patients with Psychogenic Seizures* ................................................................. 2-8
Aaron Trefler, Faculty Mentor: Mark Cohen, Ph.D

*The Role of Functional Networks in the Resting Brain* ............................................. 9-15
Kaori Ito, Faculty Mentor: Jesse Rissman, Ph.D
Using Automated Methods to Accurately Distinguish Patients with 
Epilepsy from Patients with Psychogenic Seizures

Aaron Trefler

PNES: psychogenic non-epileptic seizures
MR: magnetic resonance
VEEG: video electroencephalogram
EEG: electroencephalogram
LHS: left hippocampal sclerosis
RHS: right hippocampal sclerosis

Introduction

A major clinical challenge for physicians today is accurately deciding whether seizing patients are suffering from epilepsy or are experiencing seizures due to psychogenic (non-epileptic) activity. In some cases physicians must rely on eyewitness descriptions of a patient’s seizures alone to make a decision. It has been shown that many eyewitness accounts of seizures are inaccurate and tend to error with regard to specific seizing characteristics that correlate with either epilepsy or PNES (1). Consequently, physicians can easily be misled into making an inaccurate diagnosis. A more accurate means of collecting data of a patient’s seizures relies on VEEG recordings. Typically VEEG recordings involve the patient remaining in a medical institution while future seizures are recorded using both video and EEG. The gold standard for diagnosing a patient with epilepsy or PNES is done by a medically trained expert on epilepsy that has access to accurate eyewitness descriptions and VEEG recordings of a patient’s seizures. However, setting up VEEG recordings can be inefficient and costly (2). Furthermore, not all medical institutions have staff with the necessary expertise to analyze the results of the VEEG
recordings. Due to current practices it is not uncommon for patients with PNES to be diagnosed with and treated for epilepsy for years (3).

The accuracy of correctly determining whether a seizing patient is suffering from either epilepsy or PNES is important because this determination will dictate how the patient is medically treated. When diagnosed with epilepsy, patients will likely be put on anti-epileptic drugs. Anti-epileptic drugs can have major benefits for patients with epilepsy, sometimes being able to suppress the seizures almost entirely (4). However, anti-epileptic drugs have significant side effects that include: dizziness, mental slowing, drowsiness, weight gain, metabolic acidosis, nephrolithiasis, angle closure glaucoma, skin rash, hepatotoxicity, colitis, and movement and behavioral disorders (5). Alternatively, treatments of psychogenic seizures do not include anti-epileptic drugs and instead incorporate such mechanisms as: meeting with a psychotherapist to manage the stressors that lead to seizures and using relaxation exercises and mental imagery before seizure onset to decrease seizing intensity (6). For patients with PNES, anti-epileptic drugs will not help to reduce seizures in quantity or intensity and can actually undermine the patient's recovery by presenting psychologically adverse side effects (6). The quicker an accurate diagnosis of the cause of seizure onset can be made the quicker an appropriate treatment plan can be put into place and executed. Automated mechanisms for aiding physicians in determining whether a patient is suffering from epilepsy or PNES can make the diagnosing process more efficient and help to minimize type I and II errors.

*Automated Diagnosing*
Within the last year there have been several scientific papers published that provide support for the possibility of using automated computer programs to assist in accurately determining whether seizing patients are suffering from epilepsy or PNES. In these papers the ability to use automated classification methods to distinguish between subjects with and without epilepsy based on quantitative data derived from MR images is successfully shown. In a paper published by Gerarad et al automated classification methods were performed on quantitative volumetric MR imaging data to distinguish patients with temporal lobe epilepsy from healthy control subjects with high sensitivity (86.7%–89.5%) and specificity (92.2%–94.1%) (7). In a paper published by Keihaninejad et al automated classification methods were performed on structural volumetric values taken from MR imaging data to distinguish patients with temporal lobe epilepsy (including hippocampal atrophy) from controls with an accuracy of 96.62% and temporal lobe epilepsy (not including hippocampal atrophy) from controls with an accuracy of 86.62% (8). Most recently, Fock and colleagues published a paper that employed a completely automated process on MR images that segmented brain regions and analyzed grey matter volumes in order to discriminate epileptic patients with LHS from healthy controls and epileptic patients with RHS from controls, attaining accuracy rates of 90.4% and 97.5% respectively (9). Although patients suffering from PNES tend to show more brain abnormalities than healthy control subjects, patients suffering from PNES still show less brain abnormality than patients with epilepsy (10). Therefore, it may be possible to distinguish patients with epilepsy from patients with PNES using similar methods as the aforementioned papers. Showing that automated methods are capable of differentiating with statistical significance
between patients with epilepsy and patients with PNES could potentially lead to beneficial advances for the clinical practice of diagnosing epilepsy.

**Current Project Status**

The goal of our current project is to establish evidence that supports the idea of using automated methods on MR imaging data to differentiate between patients suffering from epilepsy or PNES. We will be utilizing MR images provided by the UCLA Medical Center of both patients with epilepsy and PNES. Quantitative data from these MR images will be first derived and then stored on computer servers in the form of text files. So far 37 patients’ quantitative MR imaging data is available for testing with more data scheduled to be uploaded in the near future. The quantitative values which we will be extracting from all brain regions for each one of the patients are: curve index, fold index, Gaussian curvature, grey volume mass, mean curvature, number of vertices, surface area, thickness average, and thickness standard deviation. During summer session C, I have written Matlab code that has given our lab the ability to take quantitative data stored in the text files and convert it into Matlab arrays that can be easily converted into file formats suitable for automated machine learning classification. I have also have performed preliminary classification using a machine-learning program called Weka. Although no results so far have shown statistical significance, the classification results are promising and show potential to produce significant results as the subject pool grows in size. Interestingly, out of all the quantitative measurements derived from the MR images, thickness average has so far shown the best ability to differentiate patients with epilepsy from those with PNES. To our best knowledge, as of August 2012, there has not been a paper published showing that
automated methods based on quantitative data derived from MR images can be used to
differentiate patients with epilepsy from those with PNES.
References


The Role of Functional Networks in the Resting Brain

Kaori Ito

An increase in resting state connectivity network (RSN) studies has developed within the cognitive neuroscience community within the last few years. According to the 2010 article by Cole, Smith, and Beckmann, RSNs are defined as “patterns of connectivity between multiple ROIs (regions of interest) within spatially distributed, large-scale networks.” Resting state networks, or ‘intrinsic connectivity networks’, are a reflection of synaptic plasticity—the idea that “neurons that fire together, wire together”. Cognitive activity occurring during task periods in studies demonstrated that functional connectivity between brain areas involved in the task are strong during task performance, but connectivity of non-involved regions in the task decreased during task performance (Hampson et al., 2011). As core networks in the brain, RSNs are heritable, have been found across subjects, different developmental stages, degrees of consciousness and across species, and is correlated to behavioral performance, disease, and pharmacological manipulation (Cole et al., 2010). Locating RSNs through the use of functional magnetic resonance imaging (fMRI) will help find functional response properties, and will therefore be a useful tool in further brain imaging studies. In the Reasoning, Perception, and Memory (RPM) study in which I am currently participating, one of the goals is to identify spontaneous blood-oxygenation-level-dependent (BOLD) signal fluctuations in the resting state. By examining interactions between brain regions that are simultaneously activated across the time-series, we aim to locate the resting state connectivity networks in order to
analyze task-based connectivity. In the present paper, I will discuss the RPM study set-up, briefly examine notable resting state networks, and relate the RSNs back to the RPM study.

The Reasoning, Perception, and Memory study has three main tasks. The study is set up so that the reasoning, perception, and memory tasks are mixed up within a single block, with a rest “task” in between each task. Prior to each task, “R”, “P”, or “M” will appear on the screen to indicate which task the subject will be performing for the next few trials. Very briefly, in the reasoning, or “R” task, the subject will be given two word-pairs, and must decide whether the relationship between the word-pairs is analogous, semantic, or unrelated. In the perception task, “P”, the subject is shown four words, and is to decide which of the four pairs has the most number of straight lines. In the memory task, “M”, the subject is again given four words, one of which may be a word that was given to the subject on the previous day during a memory encoding session. The subject’s task is to recognize if a word they had been previously shown is present among the words, and remember the cue associated with the word. During the rest “task”, the subject must keep his or her eyes focused on a fixation cross in the middle of a blank screen. This rest “task” is a crucial component of locating the resting state networks.

Resting state functional connectivity examines correlations in slow spontaneous fluctuations in the BOLD signal (Fox et al., 2005). The brain has several low-frequency RSNs, including visual, auditory, and language processing networks within the somatomotor system (Biswal et al., 1995). However, I will primarily be focusing on the dorsal attention system, the default mode network and the frontoparietal network in the present paper as the RPM study is built around these networks.
The dorsal attention system (DAS) consists of the intraparietal sulcus (IPS), frontal eye field (FEF) of the precentral sulcus, and the middle temporal region (MT+) (Fox et al., 2005; Vincent et al., 2008). The DAS is correlated to externally-focused attention, including shifts of attention, eye movements, and hand-eye coordination (Vincent et al., 2008). Search and detection tasks are thought to be moderated by the default attention network. Specifically, the 2008 Vincent article says that DAS activity is “increased at the onset of search displays, maintains activity while awaiting a target and further increases activity when targets are detected”. The DAS follows top-down influences to perform tasks that are externally oriented.

In a study by Fox et al. published in 2005, the dorsal attention system was found to be anticorrelated with another resting state connectivity network now called the default mode network (DMN). Both networks are based on spontaneous correlations, however, when regions associated with the dorsal attention system were activated during the task, regions associated with the default network exhibited activity decreases. The study had three conditions in which the subject was put under the fMRI scanner: visual fixation on a crosshair, eyes closed, and eyes open (without fixation). Throughout all three tasks, the same findings were reproduced—the dorsal attention system regions were task-positive while the default network regions were task-negative. This study is significant, as it suggests that the DMN and DAS have segregated competing processes. The anticorrelation between the two networks is thought to be attributed to the dissonant roles of processing information from the external world versus analyzing information internally (Vincent et al., 2008).
The default mode network was originally thought to only be suppressed during tasks of external attention, as was demonstrated in the Fox 2005 study. However, later studies showed that the DMN is correlated with mind-wandering, spontaneous recollection of one's past or imagining of one's own future (Spreng et al., 2010). The default mode network, also known as the hippocampal-cortical memory system (HCMS), is associated with spontaneous and non-goal directed thought processes. The DMN consists of the medial prefrontal cortex (MPFC), posterior cingulate cortex (PCC), lateral and medial temporal lobes, and posterior and inferior parietal lobule (pIPL). As a network that is active during memory recollection, the default network overlaps with regions that have been implicated in episodic memory retrieval (Vincent et al., 2006, 2008). The DMN is labeled thus because the system is active when the mind is not occupied by external events.

The frontoparietal control network (FPCS) mediates planning across different domains (Spreng et al., 2010). It is composed of the rostrolateral prefrontal cortex (RLPFC), middle frontal gyrus (MFG), anterior insula/frontal operculum (aIPO), the dorsal anterior cingulate cortex (dACC), precuneus (PCu), and the anterior inferior parietal lobule (aIPL) (Vincent et al., 2008; Spreng et al., 2010). The FPCS is associated with supporting cognitive control and decision-making processes. The Vincent et al. study published in 2008 found that the FPCS is positioned anatomically to integrate information from the default mode network and the dorsal attention system.

In a study by Spreng and colleagues (2010), the FPCS was found to be able to couple with the DAS and the DMN according to the task domain. The study had the subjects implement both autobiographical and visuo-spatial planning. The autobiographical planning engaged the default mode network and visuo-spatial planning was a reflection of
the use of the dorsal attention network. Participants were given tasks of planning for personal futures (e.g., steps to do well on a test) for autobiographical planning, and given tasks of solving the Towers of London puzzle for visuo-spatial planning. In both cases, a goal state was provided, aimed to activate regions related to the frontoparietal control system. The study found that the default-mode network was able to perform goal-directed cognition when it is coupled with the FPCS, and that the FPCS was the mediator between switching from the DAS to the DMN. The FPCS combines information gathered from the external world with internally stored information.

In the ongoing RPM study, the main goal is to explicate the role of the rostral prefrontal cortex (RPFC). The RPFC has been found to be the executive center of the FPCS. To further explore the role of the RPFC, the RPM study was created so that the reasoning, perception, and memory tasks were constructed to reflect the frontoparietal control network, the default mode network, and the dorsal attention system. As the FPCS is the resting state connectivity network thought to be in charge of processing and combining information from multiple sources, the reasoning task has the subjects verify analogies. The default mode network is engaged in the episodic memory task, as subjects must search through their memory to remember whether they had seen specific words before, during the memory encoding trial. Lastly, the DAS is designed to be task-positive during the perception task, in which attention is focused solely on the number of lines in words rather than internally-focused. The rest “task” does not require the subject to focus on anything; the passive state allows mind-wandering, the activity associated with the DMN, or taking in and analyzing information about the environment, which is associated with the DAS. During the resting state, it will become possible to examine large fluctuations in the brain
in simultaneous activity when subjects are not performing tasks. The rest “task” will allow us to find how the brain prepares itself to perform and switch between tasks—a reflection of goal-oriented cognitive function, associated with the FPCS. By setting up the RPM study to reflect the three major resting brain state networks, we will be able to better understand the cognitive function of the RPFC.

Resting state connectivity networks play a large role in normal human brain function. Understanding the functional connectivity of the brain is vital to a better understanding of not only atypical developmental processes, but also neurologically-related disorders or dysfunctions, such as Alzheimer’s, schizophrenia, and other mood and/or anxiety disorders (Hampson, Shen, and Constable, 2011). Due to its critical value in mapping out the functional architecture of the human brain, further studies exploring RSNs and its role in organizing the brain’s processes should be expected.
References


