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Altered Brain Networks In Patients with Psychogenic Non-Epileptic Seizures (PNES) Using Ultra High Field MRI

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

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Abstract

Background: Psychogenic Non-epileptic Seizures (PNES) are attacks that appear similar to epileptic attacks. However, they lack abnormal electrical discharges in the brain and have psychological underpinnings and causes. The gold standard of diagnosis is video-EEG which is not widely accessible, creating a poor prognosis for patients. Resting state functional magnetic resonance imaging can aid in the diagnosis and treatment of PNES by helping better understand brain networks in patients with PNES. This study examines brain networks in patients with PNES with a focus on the default mode network and salience network.

Methods: Twelve patients with PNES between the ages of 18-56 and twelve age- and sex-matched healthy participants between the ages of 18-59 were recruited. Participants underwent 7T resting-state fMRI scanning. Independent Components Analysis (ICA) and whole brain functional connectivity making use of region of interest analysis (ROI) was used to study the default mode network and the salience network.

Results: No Significant differences in functional connectivity between regions in the default mode network (DMN) as well as the salience network (SN) were found when comparing patients with PNES to healthy control participants.

Conclusions: In the current study patients with PNES do not show altered connectivity between brain regions in the default mode network as well as the salience network. Limitations and future directions of the current study will be discussed.

Keywords: PNES, resting-state fMRI, ICA, ROI, brain networks, functional connectivity, default mode network, salience network

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Chapter 1

1.0 Introduction

1.1 Seizures and Psychogenic Non-Epileptic Seizures (PNES)

Seizures can be separated into two major categories: epileptic seizures and psychogenic non-epileptic seizures (PNES) (LaFrance et al., 2013). An epileptic seizure is considered to produce excessive and hyper synchronous electrical discharges in the brain as evident by electroencephalography (EEG). Epilepsy is one of the most common neurological disorders and is considered a disease of the brain that predisposes one to develop and generate epileptic seizures (Fisher et al., 2005). People are considered to have epilepsy if they are diagnosed as having an epilepsy syndrome or if they have two seizures occurring more than 24 hours apart (Fisher et al., 2014). PNES are often mistaken as epileptic seizures. Although PNES appear similar to epileptic seizures in appearance they lack the abnormal electrical discharges in the brain that accompany epilepsy and are thought to have psychological underpinnings and causes such as, abuse, death of a loved one and other traumatic experiences (LaFrance, Reuber & Goldstein, 2013). The prevalence of PNES is between 2 and 33 per 100,000, with about 35% of patients diagnosed with epilepsy also experiencing PNES. Patients have gone through some sort of traumatic experience, with most having a comorbid diagnosis of other psychological disorders such as anxiety, depression, somatization disorders and many more making the treatment and diagnosis of PNES quite challenging (Alsaadi & Marquez,

2005). In a study by Fiszman et al., (2004) looking at 17 related research articles they found that patients diagnosed with PNES had experienced some sort of traumatic event in their lifetime (44-100%) as well as having experienced some form of abuse (23-77%). This suggests that traumatic experiences play a role in the development and progression of PNES. Alongside the challenges that come with PNES as a result of the disorder being so complex, patients are often misdiagnosed as having epilepsy as appearance and manifestation of spells are similar. Early referral to a physician for proper diagnosis of PNES is critical in alleviating the symptoms and worsening of spells but diagnosis is often delayed with a mean of about seven years between manifestation of spells and accurate diagnosis. Unfortunately, because PNES are not a single entity or disorder, the course and duration are often variable and depend on the underlying cause.

1.1.1 Diagnosis of PNES

The diagnosis of PNES is made predominately using video-EEG through epilepsy monitoring units (Reuber & Elger, 2003). The diagnosis and treatment of PNES is challenging and presents many complications. Patients are often diagnosed late as video-EEG is not widely accessible and waiting periods for admission into the epilepsy-monitoring unit is upward of 1 year (Bodde et al., 2009). Patients are forced to wait for proper diagnosis and care leading to an overall decrease in quality of life as they are not able to participate in everyday activities such as driving a car or working (Ettinger et al., 1999). Problems that arise from late diagnosis include the utilization of many health care

resources like frequent visits to neurologists and emergency departments. Delayed diagnosis is costly for our health care system and frustrating and time consuming for patients awaiting proper diagnosis and care. Early diagnosis is critical from a financial perspective, as it has been shown that there is an 84% reduction in total medical expenses 6 months following proper diagnosis of PNES (Alsaadi & Marquez, 2005). Family physicians play a significant role in the initial referral process and need to be more informed and aware of PNES so they can re-direct patients to an epilepsy center.

Preceding the initial referral, patients are frequently misdiagnosed as having epilepsy and prescribed unnecessary antiepileptic drugs (AEDs) which can cause additional health concerns. Additionally, 12 patients from the current study came into the epilepsy-monitoring unit on one to three different AEDs and were discharged on none (Table 1).

Although referral and admittance into an epilepsy monitoring unit with proper resources helps some patients with PNES, there are still some issues with this approach. For example, patients may not experience any spells while in the unit forcing neurologists to delay diagnosis, as causes cannot be determined. Although video-EEG is currently the gold standard of diagnosis many patients remain confused about their condition.

Alongside video-EEG the Minnesota Multiphasic Personality Inventory 2 (MMPI-2) is used in epilepsy monitoring units as an adjunct to confirm the diagnosis of PNES.

Although there is an MMPI-2 revised, for the purpose of the current study we focus on the MMPI-2 as that is what is used in our unit.

Patient	# AED's at admission	# AED's when discharged
1.	2	0
2.	0	0
3.	3	0
4.	0	0
5.	1	0
6.	1	0
7.	2	0
8.	1	0
9.	1	0
10.	2	0
11.	2	0
12.	2	0

Table 1: Twelve patients with PNES from the current study and the number of antiepileptic medications upon epilepsy monitoring unit admission and upon epilepsy monitoring unit discharge

1.1.2 The Minnesota Multiphasic Personality Inventory 2 (MMPI-2) as an adjunct to confirm the diagnosis of PNES

The Minnesota Multiphasic Personality Inventory 2 (MMPI-2) is a psychological test that assesses personality traits and psychopathology (Graham, 1990). It is predominantly used to test people who are suspected of having psychological health problems and/or disorders. The MMPI-2 is the most commonly studied psychological measure in the differential diagnosis of epileptic seizures and PNES (Cragar et al., 2003). The MMPI-2 consists of 567 items and 10 clinical scales measuring different psychopathologies. The MMPI-2 has been shown to be a good predictor of PNES as indicated by scores of hysteria, hypochondriasis and depression that have a predictive value of 90% (Derry & McLachlan, 1996). Patients with PNES typically show a conversion disorder type pattern that demonstrates clinically meaningful MMPI-2 t-score elevations following a 3-1-2 pattern with highest scores on hysteria, hypochondriasis and depression, respectively. When differentiating between epilepsy and PNES the MMPI-2 is highly considered and the typical conversion disorder pattern consisting of highest scores on hysteria, hypochondriasis and depression, respectively, is assessed. Although the MMPI-2 aids in the diagnosis of PNES, video-EEG remains the gold standard (McGonigal et al., 2002). However, as previously mentioned many issues surround the use of video-EEG with patients suffering as a result.

1.1.3 Problems with the diagnosis of PNES

PNES is a difficult disorder to diagnose and treat due to the many different causes and reasons for the manifestations. Both patients and physicians find it very challenging to fully comprehend how a physical manifestation such as the spells experienced by patients with PNES can be caused by or are a result of psychological and/or emotional troubles (Mcsweeney, Reuber & Levita, 2017). As a result, patients feel misunderstood and do not fully accept their diagnosis making the duration and severity of their condition worse. In a study by Wasserman and Herskovitz (2017) investigating the ability of health care professionals to correctly differentiate between epileptic seizures and PNES, they showed that most health care professionals including emergency nurses, internal medicine physicians and emergency physicians had a low rate of successfully differentiating between epileptic seizures and PNES. They also found that epileptologists, general neurologists and neurology nurses had the highest success rates of successfully differentiating between epileptic seizures and PNES with epileptologists having the highest success rates (87.5%). Unfortunately, patients wait years before being admitted into the epilepsy monitoring unit for a proper diagnosis. In a study by Ristić et al., (2004) looking at the phenomenology and psychiatric origins of PNES they found that the time from onset of spells to the actual diagnosis of PNES was four years. Additionally, the average time of use of antiepileptic drugs (AEDs) due to inaccurate diagnosis was two years with 20% of patients treated with more than two AED's. Given the nature of the disorder it is crucial that patients with PNES be seen by epileptologists and/or specializing

neurologists for proper diagnosis. Once patients have been properly diagnosed as having PNES, appropriate treatment regimes can be implemented depending on the unique circumstances of the individual.

1.1.4 Treatment of PNES

Treatments will differ depending on the unique circumstances regarding the patient diagnosed with PNES. Some patient's spells lessen in frequency and sometimes disappear by simply becoming aware of their diagnosis (Lesser, 2003). Patients are referred to a clinical psychologist and/or a psychiatrist for certain therapies and medications to help improve the spells. Patients are put on other medications to help treat the existing psychiatric condition that occasionally improves spells. Treatments are uniquely given to each individual to help resolve emotional and psychological causes. Most patients diagnosed with PNES also have other psychiatric health conditions such as anxiety, depression, personality disorders, bipolar disorders and many others. Cognitive behavioral therapy has been shown to be very effective in the treatment of PNES and in some circumstances more effective than standard medical care such as medication (Goldstein et al., 2010). In a study by Goldstein et al., (2010) it was found that patients who participated in cognitive behavioural therapy were more likely to have seizure freedom upon a three-month follow-up. In another study by LaFrance Jr et al., (2009) patients with a confirmed diagnosis of PNES were enrolled in a 12-week cognitive behavioural therapy group of which 21 patients were enrolled and 17 patients completed

the intervention. Eleven of the 17 patients who completed the program reported no spells by their final session with improvements on depression, anxiety and quality of life making this an effective treatment approach. It appears that psychotherapy including cognitive behavioural therapy shows significant success in the improvement and reduction of spells. Although certain treatments are available and help in some cases, there are still several patients who continue to have spells that increase in frequency and duration as PNES has many different origins (Lesser 2003). In a study by Lesser (2003) different causes and explanations for the development of PNES were discussed. Firstly, PNES may occur as a result of disturbing personal interactions that the patient may have had with others throughout life resulting in spells that occur due to anger and hostility towards others. Spells may also originate due to emotional problems or internalized conflicts. Alternatively, people with cognitive difficulties or a history of head trauma may be more likely to develop PNES as evident by frontal lobe impairment among patients who have a confirmed diagnosis of PNES. Ultimately, there is no single one treatment approach that works best for patients with PNES, rather there are many different approaches dependent on the circumstances of the individual which is why it is so important to better understand all aspects of the disorder. Additionally, cognitive behavioral therapy can be tailored to patients with PNES if we better understand exactly how the brain has changed its functional architecture by use of functional magnetic resonance imaging (fMRI).

1.2 Functional Magnetic Resonance Imaging (fMRI)

Functional magnetic resonance imaging (fMRI) is a functional neuroimaging procedure that measures brain activity by detecting changes associated with cerebral blood flow and oxygenation (Huettel, Song & McCarthy, 2004; Buxton et al., 2004). Specifically, fMRI relies on the blood oxygen level dependent signal (BOLD) as a measure of neuronal activity. It has been shown that when blood and any tissue near vessels are in the presence of deoxyhemoglobin this changes the proton signal from water molecules that surround a blood vessel in gradient-echo MRI which produces the BOLD signal (Ogawa et al., 1990). The BOLD signal relies on fluctuations in deoxyhemoglobin acting as an endogenous paramagnetic contrast agent which allows changes in the local deoxyhemoglobin concentration in the brain to alter the MRI signal (Kim & Ogawa, 2012). As described in an article by Mathews and Jezzard (2004) the contrast in a magnetic resonance image which determines what we see, depends entirely on how it is obtained. When adding radio frequency or gradient pulses one can investigate different features of the tissue being acquired. The useful contrast in MR images comes from differences in fundamental nuclear magnetic processes or relaxation. Three relaxation times that are primarily used in MRI are T1, T2, and T2*. T1 relaxation is the time for the return of the magnetization to equilibrium along the static magnetic field and T2 and T2* represent the time associated with loss of signal once the magnetization has been sampled (Mathews & Jezzard, 2004). T2 AND T2* relaxation times are used when exploring brain function through fMRI. fMRI has been used to recognize brain networks in healthy

individuals and patients with various neurological disorders including epilepsy (Zhang et al., 2010). fMRI allows us to study the on-going communication between brain regions and within certain networks to get a better understanding of function and disrupted function in the case of diseased human brain states (Glover, 2011). Communication between brain regions can be looked at in the presence of a task to stimulate certain responses or in the absence of a task in the resting state when no specific response is warranted to understand how brain regions communicate.

1.2.1 Resting- state fMRI

Resting state fMRI (rs-fMRI) examines the temporal correlations in the blood-oxygen-level-dependent (BOLD) signal in the absence of a specific task (Biswal et al., 2010). rs-fMRI is based on the spontaneous low frequency fluctuations in the BOLD signal which allows us to study correlations between these signal fluctuations to evaluate regional interactions that occur when a person is not performing an explicit task (Raichle & Abraham, 2007). The person is simply lying down instructed to keep their eyes open or closed and they are not being stimulated by any task. In a study by Patriat et al., (2013) it was found that when looking at resting-state functional connectivity measures in the motor, visual, auditory, attention and default-mode network there are significantly higher connectivity measures in the auditory network when participants are instructed to keep their eyes closed. No significant differences were found in connectivity strength in the default mode, attention, visual and motor networks when comparing eyes closed and eyes

open conditions. For the purpose of the current study participants were instructed to keep their eyes closed. rs-fMRI has been used in many different studies to better understand cognitive disorders including Alzheimer's disease, Attention Deficit Hyperactivity Disorder (ADHD), Amyotrophic Lateral Sclerosis (ALS), Parkinson's disease and many others (Luo et al., 2012; Baudrexel et al., 2011; Yu-Feng et al., 2007; Wang et al., 2007).

Our brain is organized into networks composed of functionally and structurally joined regions with the functional communication between regions being of high importance to examine complex cognitive processes and diseased human brain states (Sporns, 2013). Many different brain networks have been explored and established through rs-fMRI. Consistent resting-state networks have been identified that include anatomically separate brain regions that are functionally connected to one another (De Luca et al., 2006). A review article by Cole, Smith and Beckman (2010) showed that resting state networks can be reliably and reproducibly uncovered at both the individual and group subject levels across a wide variety of analysis techniques. The most commonly studied resting state brain networks include the default mode network, the sensorimotor network, the auditory network, the executive control network, the fronto-parietal network and the newly researched salience network (Smith et al., 2009). The salience brain network is a newly recognized network that is often found altered in psychiatric conditions such as bipolar disorder, schizophrenia and posttraumatic stress disorder (Sripada et al., 2012; Palaniyappan & Liddle, 2012). The salience network is

composed of the anterior cingulate cortex (ACC) and parts of the insula and is involved in emotional regulation and processing.

1.2.2 Measuring functional connectivity

There are many different ways to evaluate functional connectivity between brain regions. One common measure of functional connectivity is through the use of independent components analysis (ICA). ICA is a statistical method to reveal hidden factors that underlie sets of random variables, measurements, or signals (Hyvärinen et al., 2004). ICA takes into consideration all voxels at once and uses a mathematical algorithm to separate the dataset into individual networks that are correlated in their fluctuations but are also independent in the spatial domain (Fox & Greicius, 2010). This method can be applied to rs-fMRI to look at how different brain networks are functionally connected to one another by separating data into spatially independent patterns of activity (McKeown & Sejnowski, 1998). Specifically, this approach examines how different brain regions within a network or different brain regions between other networks communicate with one another. It is a common approach for exploratory data when one does not have an *a priori* hypothesis or assumption. Another common measure of functional connectivity is region of interest analysis or “ROI” analysis that involves the extraction of signal from identified regions of interest with a map created for the purpose of computing the correlation between the extracted signal and other brain voxels (Poldrack, 2007). ROI analysis can be used to explore the functional connectivity or communication between

brain regions based on *a priori* hypotheses or assumptions about how and why certain brain regions would be connected.

1.3 The default mode human brain network

The default mode brain network is a frequently studied network that consistently shows greater activation during resting state than during other mental tasks (Greicius et al., 2003). This network consists of regions such as the medial prefrontal cortex (MPFC) and posterior cingulate cortex (PCC), which are involved in emotional processing. The default mode network in the healthy brain is linked with self-reflection and task absent thought processing with the default mode network suppression being associated with increased performance on tasks that demand attention and effort (Whitfield-Gabrieli & Ford, 2012). The default mode network is altered in many different cognitive disorders. Specifically, Alzheimer's disease is one of the most studied brain disorders when examining alterations between regions of the default mode network (Broyd et al., 2009). In a review by Broyd et al., (2009) patients with Alzheimer's disease typically exhibited decreases in functional connectivity between regions of the default mode network specifically between the posterior cingulate cortex and other regions of the brain. Additionally, patients with epilepsy were shown to exhibit decreases in functional connectivity between regions of the default mode network specifically between the posterior cingulate cortex and other regions as related to interictal epileptiform discharges in temporal lobe epilepsy. Alterations between regions of the default mode network have

also been shown in patients with anxiety disorders, depression and many other neuropsychiatric conditions (Zaho et al., 2007). Research examining the relationship between default mode network connectivity and the severity of post-traumatic stress disorder (PTSD) symptoms in traumatized patients shows that resting state connectivity of the posterior cingulate cortex with the perigenual anterior cingulate and the right amygdala is associated with current PTSD symptoms (Lanius et al., 2010). Furthermore, a study examining default-mode network connectivity in depression using a seed region of interest analysis showed significantly reduced functional connectivity between the posterior cingulate cortex and the bilateral caudate in patients with depression compared to healthy participants (Bluhm et al., 2009). Alongside the study by Bluhm et al., (2009) a study by Zhu et al., (2012) examining default mode network connectivity in patients with treatment-naïve major depression showed that patients with major depressive disorder have decreased functional connectivity in the posterior medial cortex specifically in the posterior cingulate cortex and precuneus compared to healthy participants. Additionally in a study by Stern et al., (2012) examining resting state functional connectivity between the fronto-parietal and default mode networks in people with obsessive-compulsive disorder (OCD) they found that people with OCD which is a type of anxiety disorder exhibited altered connectivity between the fronto-parietal network primarily the anterior insula and the default mode network including the posterior cingulate cortex and medial frontal cortex. As shown, the default mode network has been regarded as disrupted and altered in

many different mental health disorders including dementia, schizophrenia, OCD, anxiety disorders, depression, autism and attention deficit hyperactivity disorder.

1.4 The salience human brain network

Very little research has been done exploring altered functional connectivity between regions within the salience network in patients with PNES. The salience network is responsible for prepping the brain for action, emotional processing and regulation as well as coping (White et al., 2010). The salience network is altered in many cognitive and psychiatric disorders such as schizophrenia, bipolar disorder, depression and anxiety. The salience network is comprised of the anterior cingulate cortex as well as insular sub-regions (Menon & Uddin, 2010). In a review by Palaniyappan and Liddle (2012) investigating the salience network and the role it plays in psychosis they concluded from many imaging studies that patients with schizophrenia show insular dysfunction with an emphasis on alterations between regions of the salience network as a whole. Specifically, they found that patients with schizophrenia have abnormalities in the functional activation of the insula and anterior cingulate cortex compared to healthy participants. In a study investigating resting state networks in patients with posttraumatic stress disorder (PTSD) it was found that resting-state functional connectivity in patients with PTSD is stronger between the right basolateral amygdala and the dorsal anterior cingulate cortex compared to healthy participants (Brown et al., 2014). Additionally, in a study using both task and resting-state data looking at the salience network in patients with major depressive

disorder it was found that the dorsal part of the anterior cingulate cortex and bilateral anterior insulae were altered (Yang et al., 2016). Another study looking at resting-state functional connectivity in patients diagnosed with panic disorder used a seed regions-of-interest analysis to look at regions of the limbic network, the default mode network and the salience network (Pannekoek et al., 2013). Specifically, they placed seeds in the bilateral dorsal anterior cingulate cortex of the salience network. The bilateral dorsal anterior cingulate cortex of the salience network was shown to have altered connections with the frontal and parietal areas. Most patients diagnosed with PNES also have a comorbid diagnosis of other neuropsychiatric conditions providing reason to believe that patients with PNES may also have alterations between regions of the salience network (Mökleby et al., 2002).

1.5 Altered brain networks in PNES

Resting state fMRI has been used to identify altered functional connectivity between brain regions in patients with many neurological disorders but has been used in few studies to address PNES. In a study by van der Kruijs et al., (2014) examining brain networks in patients with PNES using rs-fMRI they looked at four relevant networks associated with executive control, fronto-parietal, sensorimotor and default mode activation. The data was analyzed using ICA with dual regression to identify the networks in all participants and spatial maps of the four relevant networks of interest to compare patient participants with healthy participants. They found that patients with PNES had

increased contribution of the orbitofrontal, insular and subcallosal cortex in the fronto-parietal network, the cingulate and insular cortex in the executive control network the cingulate gyrus, superior parietal lobe, pre- and postcentral gyri and supplemental motor cortex in the sensorimotor network, and the precuneus and para-cingulate gyri in the default mode network. The underlying assumption was that when patients with PNES are faced with a stressful situation their brain dissociates or disconnects from reality as a coping mechanism due to past traumatic experiences. This study focused on four relevant networks associated with dissociation but did not explore the salience network as a whole which is needed to fully understand PNES given the relevance it has on emotional processing and regulation (Barrett & Satpute, 2013). In another study by Ding et al., (2013) alterations of topological organization of whole-brain functional and structural connectivity networks in patients with PNES were explored using graph theoretical analysis. They found that patients with PNES have a decreased coupling strength of functional-structural connectivity and high sensitivity and specificity to distinguish PNES patients from healthy participants which may be a central characteristic in reflecting the mechanisms of PNES. In addition, regional characteristics were altered in structural connectivity networks explored by diffusion tensor imaging (DTI) that involved attention, sensorimotor and subcortical and default mode networks likely reflecting disease-specific pathophysiology in PNES. In another study by Li et al., (2015) they combined resting state fMRI with fractional amplitude of low-frequency fluctuations and functional connectivity based on a seed voxel linear correlation method to examine alterations of

regional and inter-regional network cerebral functions in PNES. They reported significantly stronger functional connectivity between insular sub regions and the sensorimotor network, lingual gyrus, superior parietal gyrus and putamen, suggesting a hyperlink pattern of insular sub regions involved in abnormal emotion regulation, cognitive processes and motor function in patients with PNES compared to the healthy participants. This implies that patients have altered attention, emotion and sensorimotor systems. In a review by Mcsweeney, Reuber and Levita (2017) an extensive literature search was done for all neuroimaging studies on patients with PNES. They found 17 relevant research articles of which nine were selected for the meta-analysis as the remaining eight studies were either not empirically sound, not studied on an adult population, not an actual imaging study, not in English language and 1 had a very small sample size. There were a total of 6 rs-fMRI studies that included the use of ICA, ROI analysis and graph theoretical analysis. None of these studies investigated the salience network as a whole in patients with PNES. Additionally, all of these studies used the 1.5T or 3T MR to look at brain networks/regions in patients with PNES with no such study looking at brain networks using the 7T MR. Many of these studies had similar limitations that included a small sample size, no control of other psychiatric/psychological diagnoses and weak correlations. This review signifies the need for additional research on brain networks in patients with PNES while controlling for other psychiatric/psychological health diagnoses to ensure the condition is truly what is being assessed as oppose to other psychological health disorders.

1.6 Motivation for the current study

The diagnosis and treatment of Psychogenic Non-Epileptic Seizures (PNES) is challenging and patients are suffering as a result of poor treatment options and delayed diagnosis. Currently the gold standard of diagnosis is video-EEG that is problematic with the biggest issue being waiting periods before patients are admitted into the unit and examined. Upon arrival there is no guarantee that patients will receive a definitive diagnosis and treatment regime, as they may not have any spells during their stay. Many patients are diagnosed as having epilepsy before being admitted into the unit and prescribed anti-epileptic medications, which may cause further complications and health problems. Our health care system is also being affected as patients with PNES visit many different neurologists that in turn send them for different tests to figure out the cause of the spells. This can be costly for both our health care system as well as frustrating for patients who are unable to work, drive and take part in various other everyday tasks that are effected by this disorder.

Modern neuroimaging techniques such as resting state fMRI can further our understanding of what is going on in the brain of patients with PNES. Specifically, fMRI allows us to study the communication between different brain regions and networks that are implicated in this disorder. This will contribute to a better understanding of the brain function/circuitry in patients with PNES, with the hope that such research may help with diagnosis and differentiation in the future. Research looking at other psychological and

psychiatric health conditions such as schizophrenia, bipolar disorder, generalized anxiety disorder and PTSD, have shown alterations between the default mode network and the salience network. PNES are considered psychological in nature leading us to believe that the salience network and/or the default mode network may also be altered in this condition. There has been very limited research studying the salience network in patients with PNES. This study attempts to address the question whether regions that belong to the salience network and the default mode network show altered functional connectivity or altered communication. We hypothesized that because psychogenic seizures are elicited by past traumatic experiences and psychological triggers as shown by previous literature, then the default mode network and the salience network which both play a role in the development and progression of psychological disorders should show altered brain function. This will lead to a better understanding of how the salience network and the default mode network communicate and contribute to our understanding of brain function/circuitry in patients with PNES. Furthermore, independent components analysis (ICA) and whole brain functional connectivity analysis (ROI-ROI analysis) was used to study the salience network and the default mode network. By using ICA to study the default mode network and the salience network this will allow us to examine the networks as a whole and assess activation across all participants, with a region of interest approach allowing us to make group inferences of whether or not altered functional connectivity exists between regions of the brain in patients with PNES compared to healthy control participants. This study was performed using resting state fMRI with the 7 Tesla MR

benefiting from the increased signal-to-noise ratio (SNR) leading to a clearer and more accurate depiction of the brain. Our patient population included patients with mild anxiety and depression as these are not possible to completely remove and excluded patients with severe mental health disorders to better control our ability to study brain networks in patients with PNES as oppose to studying other mental health disorders that may be associated with PNES.

Chapter 2

2.0 Materials & Methods

2.1 Participants

Twelve patients were recruited from the epilepsy-monitoring unit at University Hospital in London Ontario Canada. Patients with a video-EEG confirmed diagnosis of PNES as screened by their treatment team (consisting of a clinical psychologist and neurologist) were included. It is common for patients with PNES to have serious psychological and/or psychiatric comorbidities such as, mood disorders, schizophrenia, bipolar disorder, personality disorders ext., but for the purpose of the current study patients with such serious comorbid diagnoses were excluded for better control. Patients were also excluded if they had a combined diagnosis of PNES and epilepsy. At the time of participation patients were not on any medication. Twelve healthy control participants were recruited by advertisement. Before recruiting healthy control participants we asked if they had any known neurological health conditions, psychological health conditions

and/or any other known conditions that could influence or impact the results of the study. Control participants also indicated that they were on no medications a month prior and at the time of study participation. All participants signed an informed consent and were well aware of what to expect in the study before participating. This study received ethics approval from the office of human research ethics at the University of Western Ontario.

2.2 Minnesota Multiphasic Personality Inventory 2 (MMPI-2)

Patient participants completed the Minnesota Multiphasic Personality Inventory 2 (MMPI-2) as standard protocol to assist with the diagnosis of PNES. A trained clinical psychologist administered and scored all patient questionnaires. We obtained completed MMPI-2 scores and looked for the typical 3-1-2 clinically meaningful t-score patterns of elevation with hysteria, hypochondriasis and depression, respectively, that is typically used to assist in the diagnosis of PNES (Derry & McLachlan, 1996) (Table 2). Normal scores or scores that represent an absence of PNES or other psychological disorders that can be assessed by using the MMPI-2 are any scores below a *t* score of 65. We also obtained 6 healthy control participant's hysteria, hypochondriasis and depression scales from the MMPI-2 as well as all other clinical scales to ensure that healthy control participants do not show the same typical 3-1-2 clinically meaningful t-score patterns of elevations that are looked for to confirm PNES or any other pattern that is typical of someone who has other psychological disorders (Table 3). The 6 healthy control participant's scores that we have reported were participants who were willing to complete

the MMPI-2 measure. The remaining six healthy participants were not interested in completing the measure.

Scale 1: Hysteria	Scale 3: Hypochondriasis	Scale 2: Depression
59	89	74
78	77	75
65	77	51
71	59	57
69	94	86
70	92	64
70	94	55
56	73	66
61	58	64
89	99	83
78	54	90
65	59	84

Table 2: Twelve Patient's with PNES MMPI-2 Scores

Hs	D	Hy	Pd	Mf	Pa	Pt	Sc	Ma	Si
59	44	63	35	62	52	35	48	41	47
42	45	50	55	56	39	52	55	58	42
44	34	51	41	40	45	39	42	58	36
57	47	42	77	52	64	61	60	76	41
37	44	45	47	50	39	44	39	36	53
41	44	51	47	57	45	43	48	58	32

Table 3: Six healthy control participants MMPI-2 clinical Scores. (HS: Hypochondriasis. D: Depression. Hy: Hysteria. Pd: Psychopathic Deviate. Mf: Masculinity-Femininity. Pa: Paranoia. Pt: Psychasthenia. Sc: Schizophrenia. Ma: Hypomania. Si: Social Introversion)

2.3 Imaging Protocol

All measurements were performed on a 7 T neuro-optimized MRI scanner (Siemens MAGNETOM, Erlangen, Germany) using an in-house built 8-channel transmit, 32-channel conformal receive head coil at the Western University Centre for Functional and Metabolic Mapping. High resolution 3D T1-weighted coronal anatomical images were obtained with a gradient echo (MP2RAGE) sequence with inversion times (TI) of 850 ms and 2750 ms, repetition time (TR) 6000 ms, echo time (TE) 2.83 ms, flip angles of 5° and 4° with 240 mm field of view (FOV), 0.8 x 0.8 x 0.8mm voxel size and 208 contiguous slices. Functional MRI data were acquired for two sessions both lasting for 6 minutes and 40 seconds with a multiband (MB) echoplanar imaging (EPI) sequence, MB factor 2 with a 1250 ms TR, 20 ms TE, GRAPPA factor of 3, 208 mm FOV, 45° flip angle, 2.0 x 2.0 x 2.0 mm voxel size and 60 contiguous slices. We choose two shorter resting state scans as oppose to one longer resting state scan to make the scan time shorter and more bearable for patients. Patients may have spells or may not be as comfortable remaining completely still for the duration of a long scan.

2.4 Independent Components Analysis (ICA) Image Processing

Anatomical and functional images were individually brain extracted using the BET brain extraction tool within the FSL toolbox (Jenkinson et al., 2012; Woolrich et al., 2009; Smith et al., 2004). Images were further pre-processed using fMRI Expert Analysis Tool (FEAT) which consisted of motion correction using FMRIB'S Linear Image

Registration Tool (MCFLIRT), spatial smoothing with a Gaussian Kernel of full-width-at-half-maximum (FWHM) of 4 mm, high-pass temporal filtering at 100 s (0.01 Hz), intensity normalization, and affine registration to the Montreal Neurological Institute 152 standard space standard template. Resting state fMRI analysis was performed using Multivariate Exploratory Linear Optimized Decomposition into Independent Components (MELODIC; FMRIB's Software Library, <http://fsl.fmrib.ox.ac.uk/fsl>). The pre-processed data were temporally concatenated across subjects and sessions to create a 4D data set, which represents large-scale patterns of co-activating voxels consistent over participants with the consideration of statistically independent sources of variation in the fMRI signal (van der Kruijs et al., 2014). We used MELODIC'S probabilistic group ICA with IC map thresholds set at 0.99 to control for false-positives. Using variance normalise time course we set the output components to 20 (Schöpf et al., 2010). From these, we identified 9 components that corresponded to brain networks (Smith et al., 2009).

2.5 Whole Brain Functional Connectivity Analysis (ROI-ROI Analysis)

Whole brain functional connectivity analysis on the resting state data was assessed using the CONN toolbox for SPM (<http://www.nitrc.org/projects/conn>; Whitfield-Gabrieli and Nieto-Castanon, 2012). There were a number of preprocessing steps that took place on both the functional and structural images that included, subject motion estimation and correction, skull stripping, spatial smoothing (4 mm FWHM Gaussian kernel) segmentation of the brain into grey matter, white matter and cerebral spinal fluid (CSF) and normalization to a template brain (MNI 152). Global signal from white matter, grey

matter and cerebrospinal fluid were included as regressors to correct for noise. We utilized aCompCor a default method built into the conn toolbox to correct for and remove additional noise. This is used to remove global effects from the signal in order to get the cleanest and most meaningful functional connectivity measures. Specifically, this method constructs a representative noise signal from white matter, CSF, motion and scrubbing (which removes those potential effects of outlier scans) and removes anything that correlates with those noise components from the BOLD signal for every voxel (Figure 1). This is done in a single linear regression step, which gives you a clean signal without the effect of all of the potential noise effects. We utilized the 91 cortical regions of the Harvard-Oxford probabilistic brain atlas (<http://www.fmrib.ox.ac.uk/fsl/>; Desikan et al., 2006) as seed regions to evaluate altered functional connectivity between patients with PNES and healthy control participants. Specifically, we examined brain regions associated with the default mode network and the salience network. We evaluated seeds in the medial prefrontal cortex, posterior cingulate cortex, precuneus gyrus, anterior cingulate cortex, right and left prefrontal cortex and right and left anterior insula. Average timeseries from the spatial maps from 91 seed regions were extracted from the functional data separately for each participant. Connectivity (evaluated as bivariate correlation coefficients) was examined between pairs of seed regions for each individual. We performed group level analyses to examine functional connectivity differences between patients with PNES and healthy control participants. We controlled for multiple comparisons over the multiple t-tests performed

for each analysis using the false discovery rate (FDR) correction with a threshold set a $p < 0.05$. Between subject's analyses were conducted on the resting state data comprising independent-samples t-tests which compared patient participants and healthy control participants (Patients with PNES > Controls) on the connectivity coefficients for all pairs of the 91 cortical regions.

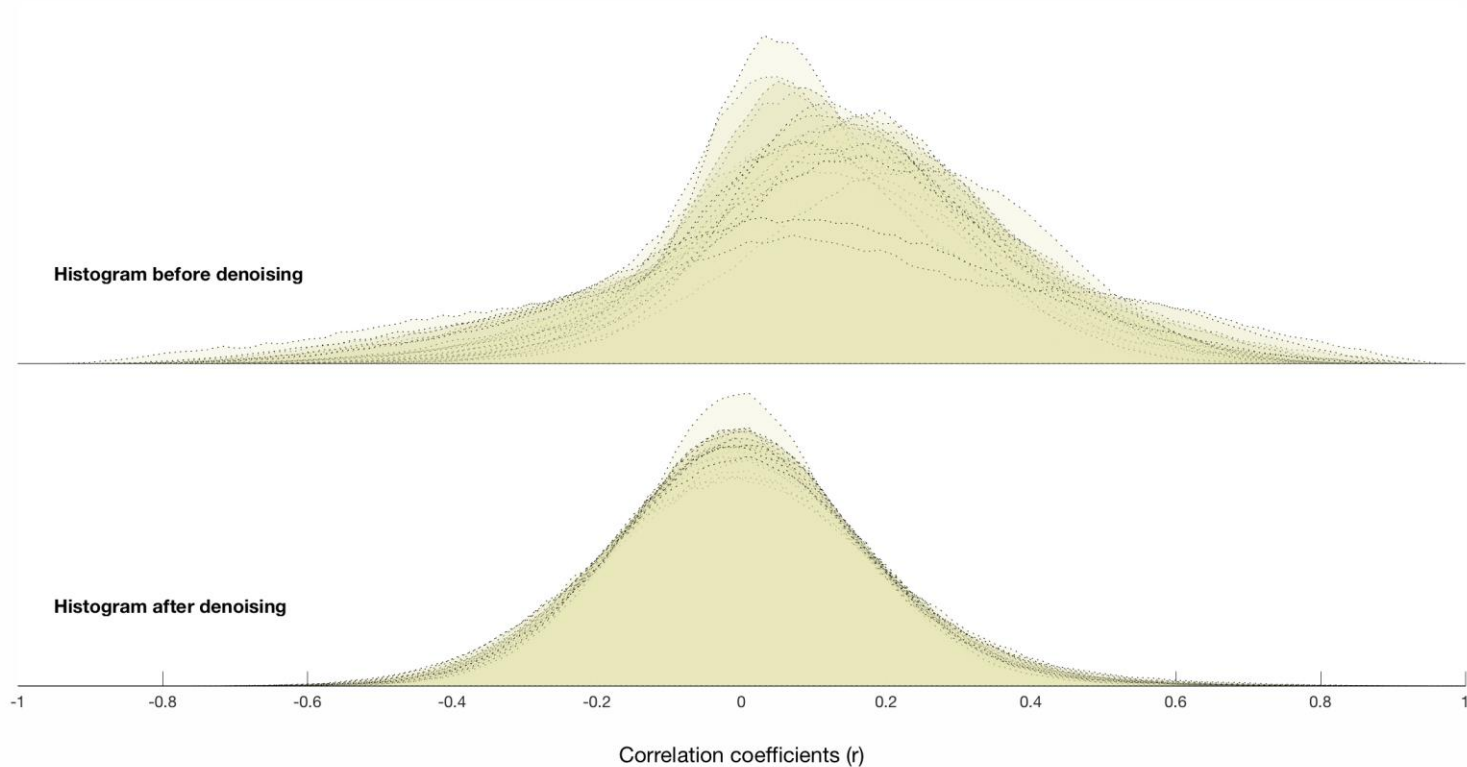


Figure 1: Two histograms depicting before and after denoising using aCompCor a method to remove anything that correlates with the noise components from white matter, CSF, motion and scrubbing from the BOLD signal for every voxel. These histograms represent the distribution of voxel-to-voxel measures before removal of potential confounding variables and after removal of these effects. In the histogram before denoising there is a more wide distribution of connectivity values before the preprocessing took place and a more centered and narrower distribution after the removal of confounding effects (Whitfield-Gabrieli, S., and Nieto-Castanon, A. (2012). *Conn: A functional connectivity toolbox for correlated and anticorrelated brain networks*. *Brain Connectivity*. doi:10.1089/brain.2012.0073).

Chapter 3

3.0 Results

Twelve patients diagnosed with Psychogenic Non-Epileptic Seizures (PNES) and twelve age- and gender-matched healthy control participants were recruited and enrolled between May 2016 and May 2017 (Table 4). The ages of patients with PNES ranged from 18-56 years with healthy participants ages ranging from 18-59 years. The average age of onset for patients with PNES was 29.1 years with the average duration of spells being 7.3 years and the average age at admission 35.4 years. There were no between group differences in demographic information. Seven of the 12 patients with PNES had clinical records indicating spell types, medication history and other existing psychological disorders (Table 5). We did not have detailed clinical records indicating spells types, medication history and other psychological disorders for the other 5 patients with PNES. All patients were on medications prior to being admitted into the epilepsy monitoring unit and participating in the study however were taken off all medications when admitted into the epilepsy unit and remained off medications when participating in the current study. Patients would have been taking medications between one to three months prior to scan time. Patients with PNES differed on their medication history, the types of spells that they experienced and other existing psychological disorders.

	PNES patients (n = 12)	Controls (n = 12)	<i>p</i>
Age (Years, range)	36 (18-56)	32 (18-59)	.158
Female (%)	(8) 72%	(6) 50%	.136
Age at onset (Years)	29.1		
Duration of PNES (Years)	7.3		
Age at Admission (Years)	35.4		

Table 4: PNES Patient's Demographics

	Spell Types	Medication History (Taken between 1-3 months prior to scan time)	Psychological Disorders (Diagnosed by a psychiatrist during previous treatment)
Patient One	Light headedness, clammy hands, numbness of hands & legs, palpitations	Carbamaepine Lorazepam	Anxiety
Patient Two	Loss of strength in left side, tremor-like movement in left arm & left leg, slurred speech, numbness in left side of body	Seroquel Sertraline Perindopril	Anxiety
Patient Three	Spells triggered by perfume, sweating and sharp pain in body, loss of voice & movement, body shaking	Topamax Amitriptyline Maxalt	Anxiety
Patient four	Rising sensation from abdomen, rapid movements, déjà vu, smell hallucinations	Levetiracetam Keppra	Conversion disorder tendencies
Patient five	Increase in heart rate, unconscious, shaking	Keppra	Somatoform disorder tendencies
Patient six	Generalized body shaking and jerking	Seroquel Mirtazapine Lamotrigine	Anxiety Depression
Patient seven	Staring	Lamotrigine Clobazam Citalopram	Anxiety Depression

Table 5: Seven Patients Spell types, medications & other psychological disorders

3.1 Independent Components Analysis (ICA)

Independent components analysis (ICA) was used to examine which brain networks were activated across participants. MELODIC in the FSL toolbox was used and we identified 8 components previously identified in the literature (Smith et al., 2009). Specifically, MELODIC uses ICA to decompose a single or multiple 4D data sets into different spatial and temporal components. Threshold IC maps were set at 0.99 to decrease the chance of generating false positives. Six out of the eight spatial and temporal components identified included the occipital pole of the visual network, the sensorimotor network, the medial visual network, the lateral visual network, the right fronto-parietal network and the left fronto-parietal network. Two of the components identified are directly related to the current study and are shown as the default mode network (Figure 2) and the salience network (Figure 3), which we further explore in our whole brain functional connectivity analysis. The regions shown in red are correlated with one another. We choose the ICA method as a starting point to confirm activation of the salience network as well as the default mode network across all participants. Once we confirmed activation of the default mode network and the salience network we went on to further explore group comparisons through the use of whole brain functional connectivity to evaluate any potential differences in functional connectivity between patients with PNES and healthy control participants.

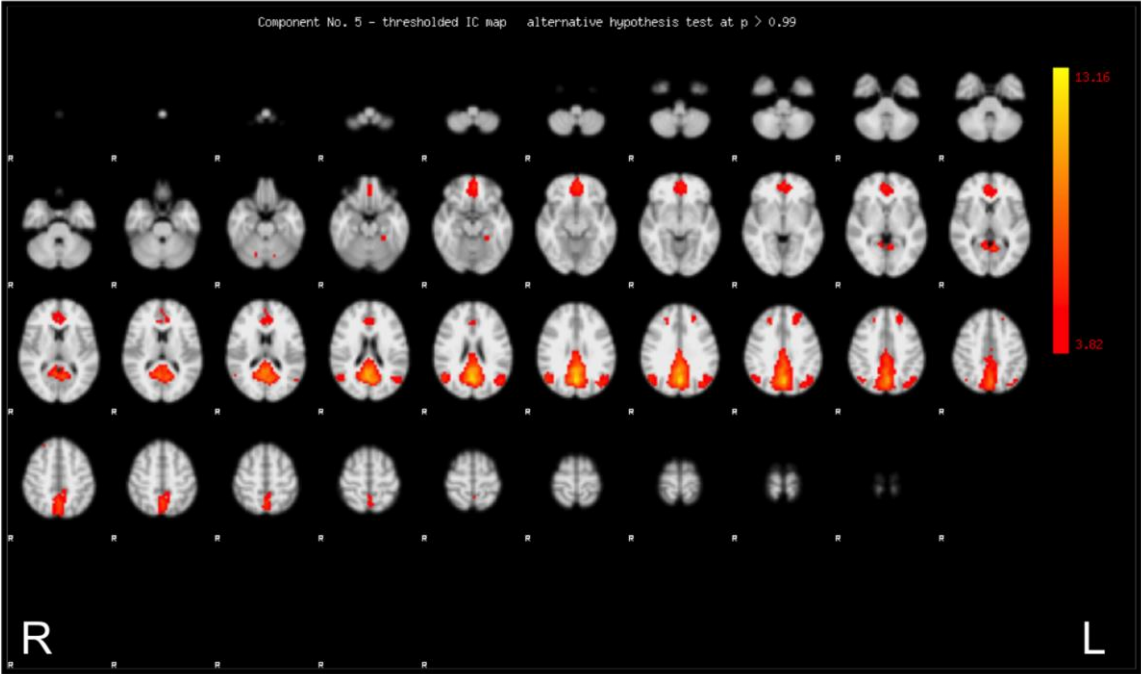


Figure 2: Component six from the independent component analysis included the Default Mode Network (DMN)

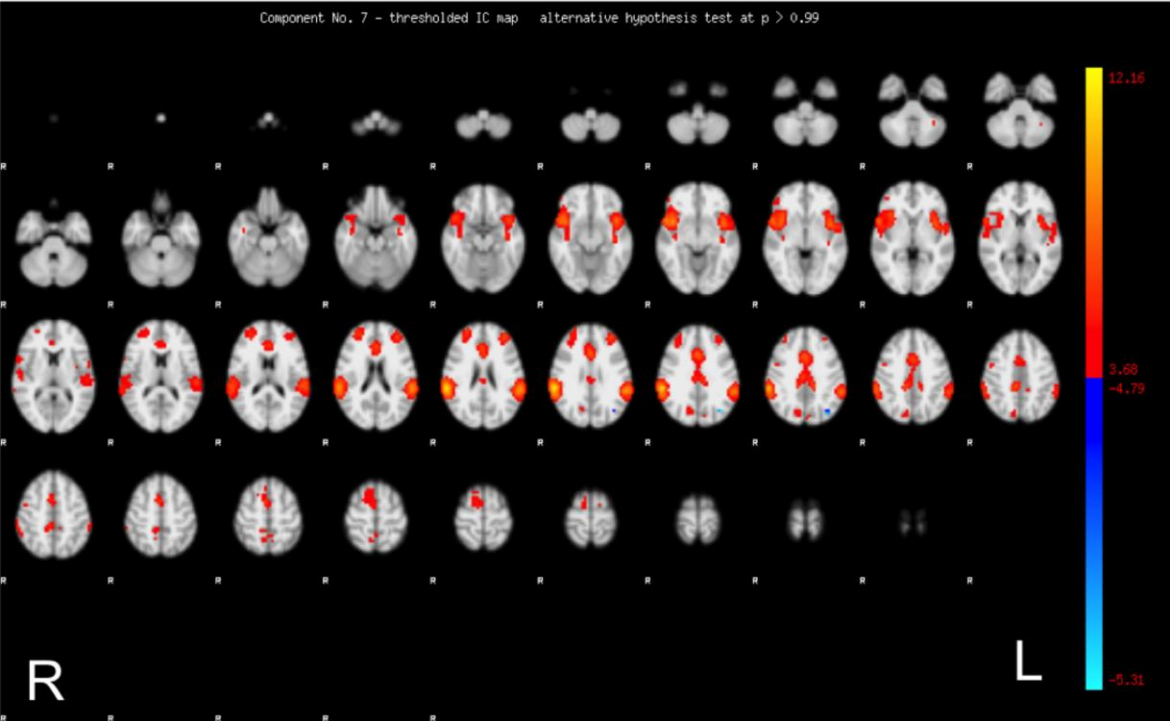


Figure 3: Component seven from the independent component analysis included the Salience Network (SN)

3.2 Exploratory Whole Brain Functional Connectivity analysis

Group comparisons of whole brain functional connectivity were made using the CONN toolbox in SPM. We compared the connectivity values across 91 cortical regions from the Harvard-Oxford atlas between patients with PNES and healthy control participants.

Fisher-transformed bivariate correlation coefficients between two regions of interest (ROI BOLD timeseries) were computed by averaging voxel timeseries across all voxels within each ROI. Specifically, we examined ROI's in the salience network and the default mode network while taking into consideration other potential regions that may be altered in PNES given the nature of the exploratory analysis. We examined potential functional connectivity alterations with seeds placed in the medial prefrontal cortex, posterior cingulate cortex and precuneus of the default mode network as well as the anterior cingulate cortex, left and right anterior insula, and right and left rostralateral prefrontal cortex of the salience network. Relative to controls, patients with PNES did not exhibit any significant differences in functional connectivity between regions in the default mode network and other areas of the brain (Figure 4). Relative to controls, patients with PNES did not exhibit any significant differences in functional connectivity between regions in the salience network and other areas of the brain (Figure 5). No other significant differences in functional connectivity were found when comparing PNES patients with healthy participants.

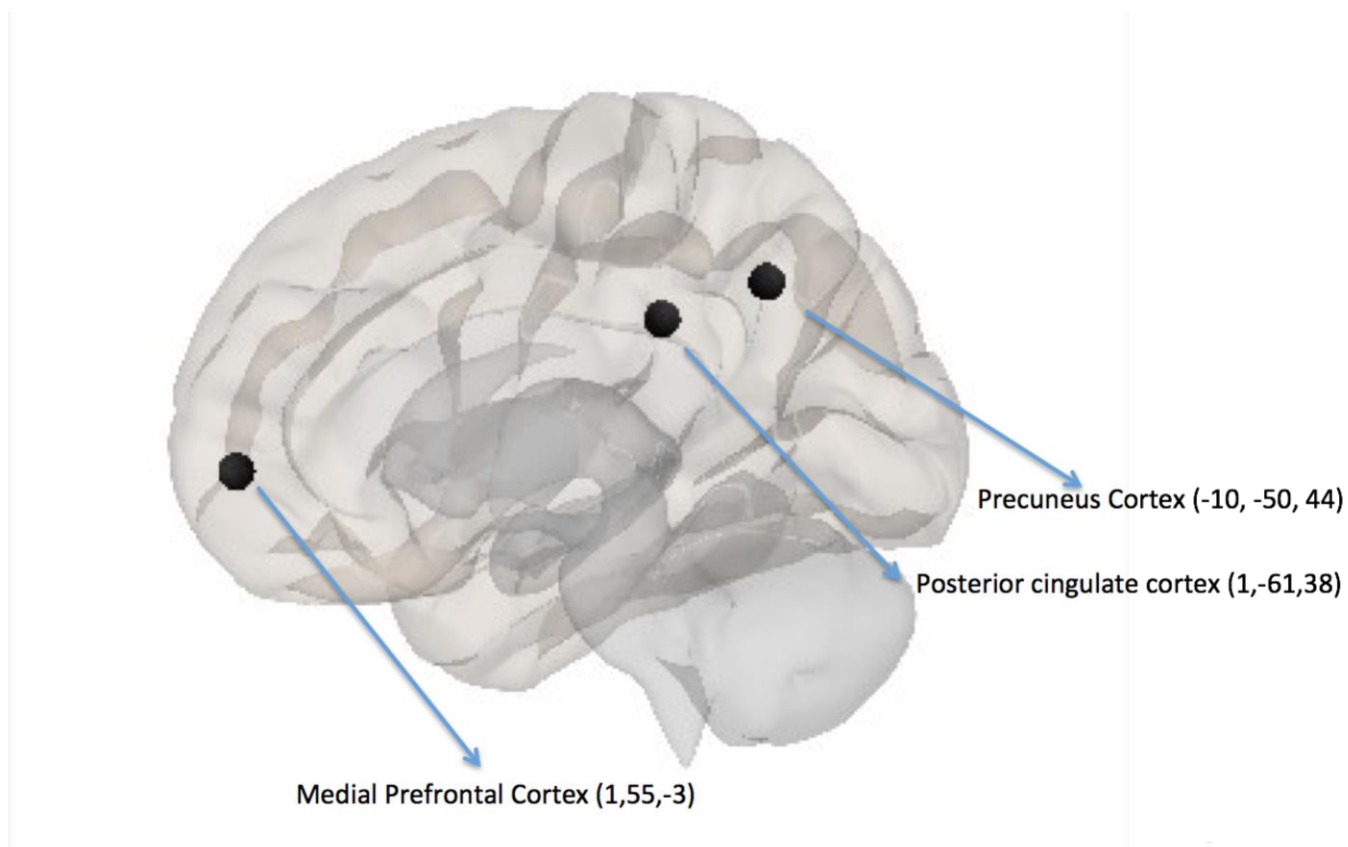


Figure 4. ROI-to-ROI analysis. No Significant differences found in functional connectivity between the default mode network (DMN) and other regions of the brain in patients with PNES relative to healthy control participants in a right medial view of the brain. The black spheres represent the regions of interest that include the precuneus cortex, posterior cingulate cortex and medial prefrontal cortex.

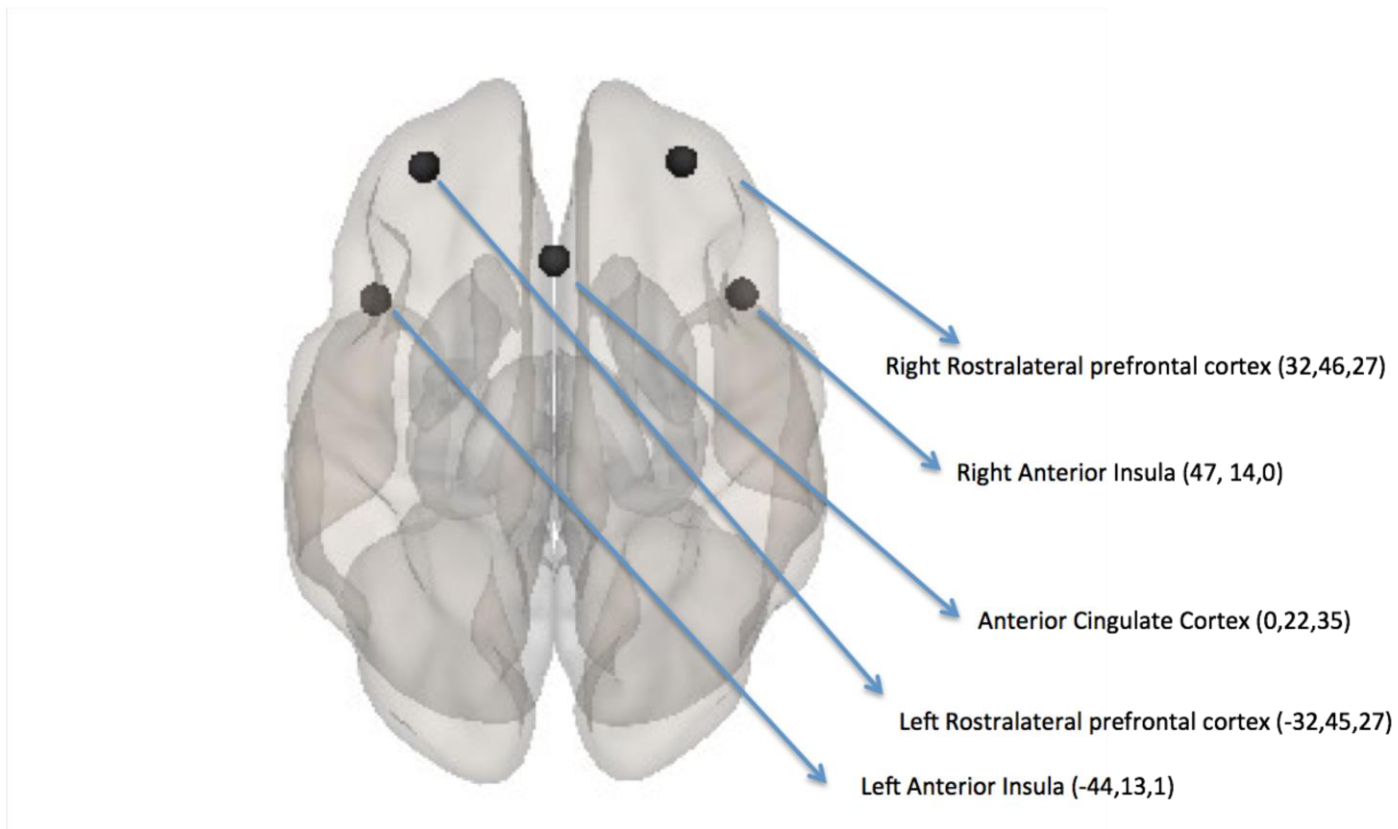


Figure 5. ROI-to-ROI analysis. No Significant differences were found in functional connectivity between the salience network and other regions of the brain in patients with PNES relative to healthy control participants in a superior view of the brain. The black spheres represent the regions of interest that include the right and left rostralateral prefrontal cortex, the right and left anterior insula and the anterior cingulate cortex.

Chapter 4

4.0 Discussion

This is the first study to explore altered brain networks in patients with PNES using the 7-tesla fMRI magnet. Additionally, the aim of this study was to understand and explore the default mode network as well as the salience network and the implications these brain networks have on PNES. Our goal was to add valuable information to the understanding of brain networks in patients with PNES and how networks communicate with one another. Although our resting state group analysis did not reveal connectivity alterations among regions between the default mode network and the salience network limitations and future directions will be discussed.

4.1 Whole Brain Functional Connectivity Analysis (ROI-ROI analysis)

A whole brain functional connectivity analysis was used to better understand alterations within the brain of patients with PNES. Our exploratory analysis which made use of the 91 cortical regions from the Harvard-Oxford atlas allowed us to investigate altered communication between multiple brain regions in patients with PNES relative to healthy control participants. Specifically, we focused on examining altered communication between regions from the default mode network by examining regions such as the medial prefrontal cortex, posterior cingulate cortex and precuneus as well as the salience network examining regions such as the anterior cingulate cortex, left and right anterior insula, and right and left rostralateral prefrontal cortex. We did not find any

significant differences in functional connectivity between regions in the default mode network as well as the salience network in patients with PNES relative to healthy control participants. We will evaluate potential drawbacks and limitations of the current study as the posterior cingulate cortex has been shown to be altered in many different psychological and cognitive disorders including depression, post traumatic stress disorder, attention-deficit hyperactivity disorder, Alzheimer's disorder, stress disorders and schizophrenia (Wang et al., 2008; Leech & Sharp, 2013; Bluhm et al., 2009; Garrity et al., 2007; Davey et al., 2012). Furthermore, the salience network has seldom been explored in patients with PNES. To fully understand PNES and the implications that surround this disorder it was critical to evaluate the salience network as it is often disrupted or altered in many psychiatric conditions including schizophrenia, anxiety disorders, personality disorders and more (Manoliu et al., 2014; Etkin et al., 2009; Daniels et al., 2010). The salience network is known for the involvement and implications it has on many neurological and emotional processes (Bush, Luu & Posner, 2000). Patients with PNES have been shown to have problems with emotional processing, regulation and coping. Ultimately, investigating the default mode network and the salience network is critical in adding valuable information to the understanding of PNES.

4.2 State Disorder vs. Trait Disorder

A potential challenge to consider when studying the brain of patients with PNES is that PNES may actually be more of a state disorder rather than a trait disorder. There is

some evidence to support the idea that psychological disorders including depression and anxiety reflect both state and trait qualities. In a study by Abrams et al., (2004) the authors evaluated the trait/state issues of harm avoidance in patients with depression to predict potential responses to medication. Harm avoidance was a reliable predictor for medical treatments in patients with depression and harm avoidance was shown to be both trait-and state-dependent in patients with depression. In another study by MacLeod and Rutherford (1992) they examined whether patients with anxiety disorders demonstrate a cognitive bias that selectively favours the processing of threat related information using a well-established colour naming paradigm to address relevant issues concerning the nature of this anxiety linked pattern of selective processing. It was shown that different patterns of anxiety linked selective processing happened when presenting stimuli to patients consciously and outside of conscious awareness. This demonstrates that the roles were played by state and trait variables and the degree to which these effects were influenced by personal relevance of the stimulus materials. In the current study patients with PNES were not scanned during a spell rather, they were scanned in between spells. It is possible that the brain is not disrupted during normal periods when the patient is not experiencing a spell or a PNES and that we would only find disruptions in brain communication between regions when testing a patient during a spell. For future directions it may be relevant to scan patients with PNES during spells to address the question whether PNES is more of a state disorder rather than a trait disorder.

4.3 Healthy Control Sample

Another potential shortcoming of why no differences were found in functional connectivity between patients with PNES and healthy control participants may be because our healthy control sample was not as clean as it could have been. As indicated by our healthy control participants MMPI-2 scores (Table 3), one participant showed an exaggeration on the psychopathic deviate measure as shown by a *t-score* of 77, as a normal score or the absence of any exaggerated psychopathologies being reflected by a *t-score* of 65 or below. Additionally, we were not able to get detailed clinical information or MMPI-2 measures on six of our 12 healthy control participants that further support the idea that our healthy control sample may not have been the cleanest or best sample to serve as a comparison to our patients with PNES. Not only were our healthy control participants potentially not the cleanest sample to compare with our patients with PNES, but they may not have been the best sample to compare to our patients to begin with. It may have been better to compare our patients with PNES to an epilepsy patient group as this is what is normally done in the epilepsy monitoring unit. This would have made for a more generalizable experiment and differences may have been found in functional connectivity between patients with epilepsy and patients with PNES that would have been directly applicable and beneficial in the realm of diagnostics. Lastly, it would have also been beneficial to include a psychiatric population group to compare with our patients to examine the differences in brain functional connectivity between different types of

psychological disorders and PNES to examine similarities as well as differences between the disorders.

4.4 PNES are not a single entity disorder

PNES are not a single entity disorder, rather, a whole host of symptoms, psychological disturbances and causes of the disorder make studying the disorder challenging and need to be considered when examining PNES. In a comparative study of trauma and PTSD prevalence in epilepsy patients and patients with PNES it was shown that PNES diagnosis is related to PTSD, many lifetime traumatic experiences and abuse traumas (Rosenberg et al., 2005). In another study by Reuber et al., (2011) looking at PNES spell manifestations it was reported that patients with PNES describe spell types as varying in the way spells present themselves. There seems to be a wide spectrum of how some patients experience spells with some losing total consciousness and others completely conscious with some abnormal physical manifestation appearing such as, teeth chattering, eye twitching or body movements. This supports the idea that there are many different causes and physical manifestations of spells which make studying PNES difficult as many different factors need to be considered. Additionally, for the current study, our patient population had been on medications one to three months prior to being tested which could have influenced or interfered with the results of the functional brain scans.

4.5 Duration of fMRI time series

There is a debate in the literature regarding scan length for reliable resting-state fMRI connectivity estimates. One study by Birn et al., (2013) examining the effects of scan length on the reliability of resting-state connectivity shows that reliability improves for increasing scan lengths, but plateaus at 12 minutes or longer. They show that reliability and similarity can be greatly improved by increasing scan lengths from five minutes up to thirteen minutes. Another study by Murphy, Bodurka and Bandettini (2007) examining the relationship between fMRI temporal signal to noise ratio and necessary scan duration found that scan duration of 10 minutes or more is necessary for an accurate temporal signal to noise ratio. These two studies provide evidence for why it is important to have longer resting state scan times. Another study by Tomasi et al., (2016) on temporal evolution of brain functional connectivity metrics found that the necessary scan time was dependent on connectivity metrics with local functional connectivity showing the most reliability with the shortest scan time (7 minutes) followed by spatial independent component analyses (10 minutes) and functional connectivity (11 minutes). This provides reason for why local functional connectivity may be most appropriate for pediatric and patient populations who are unable to tolerate long scans. There is also research supporting the idea that shorter resting state scan times are just as reliable and accurate. In a study by Van Dijk et al., (2010) looking at intrinsic functional connectivity as a tool for human connectomics, it was found that two concatenated scans of six minutes provided virtually identical results when compared to a continuous run of twelve minutes. For the current study two resting state scans both lasting six minutes and forty

seconds were acquired for each participant. The literature provides mixed results for whether longer or shorter scans are appropriate. We choose to have two scans both lasting upward of six minutes as we wanted to gather as much reliable data while ensuring that patients could remain calm and comfortable throughout the duration of the scan.

4.6 7T Dataset

One distinct feature about our study is that we acquired our data through the 7-tesla MR. Very few studies have used the 7-T MR to study brain disorders with no such study using the 7-T MR to study brain networks in patients with PNES. The 7-tesla MR is highly regarded for its high signal-to-noise ratio (SNR) and contrast-to-noise ratio (CNR) compared to lower field strength magnets as well as shorter T2* relaxation times (van der Kolk et al., 2013). The images acquired have a much higher resolution allowing us to capture more accurate and clear depictions of the brain. In certain diseases the 7-T MR in comparison to lower field strength magnets can acquire more pathophysiological details. Additionally, both sensitivity and spatial specificity of the BOLD response are increased when using higher field strength magnets making this a benefit for functional mapping in human brains (Kraff et al., 2015). Alongside the benefits of using a high field strength magnet to investigate diseased human brain states comes potential limitations. One potential drawback to consider when using the 7-T MR is the small space inside the magnet making it uncomfortable and problematic for vulnerable populations and people with claustrophobia. Another potential drawback for using the 7-T MR as compared to

lower field strength magnets is the cost, which can be comparatively more and something researchers should consider when selecting appropriate methodology for the issue under investigation. The 7-T MR may also elicit more temporary side effects such as dizziness compared to lower field strength magnets (Theysohn et al., 2014). Perhaps the biggest implication to consider when using the 7-T MR is that this magnet is more sensitive to motion artifacts and has greater interference by physiological noise (Hutton et al., 2011). In addition to standard preprocessing methods that include de-noising and the removal of motion artifacts from functional data, we used *acompcor* methodology provided by the *conn* toolbox for any additional interference by physiological noise and motion. We can ensure that our data was as clean as possible with the use of this feature. Ultimately, one should consider both strengths and weaknesses of using higher field strength magnets.

4.7 Future Directions

Overall, patients with PNES did not show altered functional connectivity between regions in the salience network as well as the default mode network. For future directions we would consider recruiting more participants for a larger overall sample size. A larger sample size would be ideal to continue exploring brain networks in patients with PNES. Additionally, a major complication of the current study is that patients with PNES were compared to healthy control participants. For future directions patients with PNES should be compared to patients with epilepsy for a more generalizable comparison as this is who we are trying to differentiate patients with PNES from in the epilepsy monitoring unit. We

would also consider adding a psychological control group for a direct comparison to patients with PNES to examine similarities and differences between the disorders. It may also be worth exploring longer scan times to see if results fluctuate as the literature is mixed on how long fMRI scan times should be for reliable results. Lastly, it may be useful to use other methodology such as diffusion tensor imaging (DTI) to explore structural abnormalities to see whether patients with PNES exhibit any differences compared to healthy participants.

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Appendix A



Research Ethics

Western University Health Science Research Ethics Board HSREB Delegated Initial Approval Notice

Principal Investigator: Dr. Seyed Mirsattari
Department & Institution: Schulich School of Medicine and Dentistry/Clinical Neurological Sciences, London Health Sciences Centre

Review Type: Delegated
HSREB File Number: 107203
Study Title: Altered connectivity networks in patients with psychogenic non-epileptic seizures
Sponsor:

HSREB Initial Approval Date: February 17, 2016
HSREB Expiry Date: February 17, 2017

Documents Approved and/or Received for Information:

Document Name	Comments	Version Date
Advertisement	Advertisement Healthy Clean	2015/11/12
Advertisement	Advertisement Patient Clean	2015/11/12
Data Collection Form/Case Report Form	Minnesota Multiphasic Inventory version II	2015/05/05
Instruments	WAIS Test 1 (Received 14Jan16)	
Instruments	WAIS Test 2 (Received 14Jan16)	
Instruments	RAVLT Test (Received 14Jan16)	
Instruments	RVDLT Test (Received 14Jan16)	
Letter of Information & Consent	LOI Patient Clean	2016/02/05
Letter of Information & Consent	LOI Health Clean	2016/02/05
Instruments	Beck Depression Inventory (Received 14Jan16)	
Western University Protocol	Received 14Jan16	

The Western University Health Science Research Ethics Board (HSREB) has reviewed and approved the above named study, as of the HSREB Initial Approval Date noted above.

HSREB approval for this study remains valid until the HSREB Expiry Date noted above, conditional to timely submission and acceptance of HSREB Continuing Ethics Review.

The Western University HSREB operates in compliance with the Tri-Council Policy Statement Ethical Conduct for Research Involving Humans (TCPS2), the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Guideline for Good Clinical Practice Practices (ICH E6 R1), the Ontario Personal Health Information Protection Act (PHIPA, 2004), Part 4 of the Natural Health Product Regulations, Health Canada Medical Device Regulations and Part C, Division 5, of the Food and Drug Regulations of Health Canada.

Members of the HSREB who are named as Investigators in research studies do not participate in discussions related to, nor vote on such studies when they are presented to the REB.

The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

Ethics Officer, on behalf of Dr. Marcelo Kremenchutzky, HSREB Vice Chair

Ethics Officer to Contact for Further Information: Erika Basile ___ Nicole Kaniki ___ Grace Kelly ___ Mina Mekhail ___ Vikki Tran 

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CURRICULUM VITAE

EDUCATION

2015- 2018 Masters of Science in Neuroscience (MSc)

Clinical Neurological sciences, Western University, London, Ontario, Dr. Seyed Mirsattari, Dr Ravi Menon

Altered brain networks in patients with Psychogenic Non-Epileptic Seizures (PNES) Using Ultra High Field MRI

2012-2015 Honours Specialization in Psychology (BA) Brescia University College, London, Ontario, Dr John Mitchell, Dr Anne Barnfield

Exercise as a protective factor against immediate stress-induced responses

RESEARCH and SCHOLARLY ACTIVITIES

September 2015-2016 National Epilepsy Research Day

London, Ontario

Altered brain networks in patients with Psychogenic
Non-Epileptic Seizures (PNES) using ultra high field
MRI (Abstract & Poster Presentation)

March 2017

London Health Research Day

London, Ontario

Altered brain networks in patients with Psychogenic
Non-Epileptic Seizures (PNES) using ultra high field
MRI (Abstract & Poster Presentation)

April 2017

Clinical Neurological Sciences Research Day

London, Ontario

Altered brain networks in patients with Psychogenic
Non-Epileptic Seizures (PNES) using ultra high field
MRI (Abstract & Poster Presentation)

SERVICE to COMMUNITY

2014-2016	Crisis/Distress Call Center Responder London & District Distress Centre London, Ontario
2013-2016	Friendly Visitor/Role-Model Children's Aid Society London Ontario
2012-2014	Hamper Program Volunteer The Salvation Army London Ontario
2011	London Optimist Volunteer London Optimist Centre

AWARDS, HONOURS and ACCOLADES

2012,2014,2015	Awarded Undergraduate Entrance Scholarship for high GPA
2012-2015	Recognition on the dean's honour role list
2015	Graduated with Honours (BA)