CLINICAL APPLICATIONS OF THE QUANTITATIVE ELECTROENCEPHALOGRAPH

by

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Abstract

Clinical psychology is a discipline that assesses and treats individuals experiencing a variety of psychological disorders; including brain injuries. Employing neuroimaging tools can reveal biological correlates that have not been previously studied in detail. The quantitative electroencephalograph (QEEG) is a dynamic neuroimaging tool that allows for the measurement of brain activity. QEEG source localization analysis has provided additional construct validity for neuropsychological tests by revealing increased activation in the associated brain regions. In addition, differences in resting brain activity have been found depending on the severity of neuropsychological impairment. Finally, enhancement of memory in normal individuals is shown by applying a weak physiologically-patterned electromagnetic field over the left hemisphere. Therefore, by integrating the QEEG with elements of clinical psychology it is possible to provide construct validity to neuropsychological tests, show differences in brain activation depending on the severity of neuropsychological impairment, and study emerging therapeutic techniques that could enhance memory.

Keywords

Quantitative electroencephalograph y, source localization (sLORETA), neuropsychological tests, mild traumatic brain injury, applied electromagnetic field, memory

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Chapter 1: Introduction

1.1 The Importance of Simultaneous Measurements in Applied Psychology

Clinical or applied psychology is a discipline that involves two distinct phases; assessment and treatment. The American Psychological Association has stated that clinical psychology attempts to better understand, predict, and alleviate "intellectual, emotional, biological, psychological, social, and behavioral aspects of human functioning across the life span, in varying cultures, and at all socioeconomic levels" (APA Society of Clinical Psychology, 2007). In order to help individuals recover from or adapt to acquired cognitive impairments it is imperative that they are first assessed using relevant tools that have been norm referenced on the population. By interpreting the assessment results clinicians are able to formulate either a diagnosis or a hypothesis regarding the individual's mental status so that a treatment plan can be created and implemented. This treatment plan is designed specifically for the individual to help them recover or adapt to daily life.

Neuropsychology is subdivision of clinical psychology that focuses on the study of the brain's structure and function and how they relate to psychological processes and an individual's behaviours. Based on this premise, measurement tools have been developed in order to assess an individual's brain functioning based on the normal population. It is the results of these assessments that determine if the individual has sustained significant neuropsychological impairment, the location of that impairment, and the severity. In order to test the lateralization and localization of a potential brain lesion the psychological tests developed by Halstead (1947) and modified by Reitan (1966) have been used as tools to aid in the assessment of neuropsychological impairment. These tools were each individually designed to assess the

functioning of specific regions of the brain however, there are conflicting reports with respect to the efficacy of many of the tests (Demakis, 2004). Even with conflicting evidence and the advances in neuroimagining technology there have been very few studies that have assessed the construct validity of the measures that are being used to evaluate one's neuropsychological functioning.

Research into the validity of neuropsychological tests has primarily been examined through two types of methodology. First, consistency between different measures has been examined in order to determine how the test correlates with other measures designed to assess similar functioning (D'Amato, Gray, & Dean, 1986). The second type of study that aims to validate neuropsychological tests are lesion studies where neuropsychological tests are administered to individuals with a specific (and confirmed) injury and their results on the tests are compared to the results of healthy controls (Dronkers, Plaisant, Iba-Zizen, & Cabanis, 2007). However, despite converging results, both these research methodologies neglect the importance of simultaneous measurement. Few studies have aimed to assess neuropsychological tests using simultaneous measurement and of those studies that have been conducted the most frequently employed neuroimaging technique is the fMRI (functional magnetic resonance imaging) where many of the original tests have had to be modified.

Neuroimaging studies that have attempted to validate neuropsychological tests primarily involve the use of the fMRI. As an example, of the classical neuropsychological tests the trail making test is one of the most frequently studied. This test is a neuropsychological test that aims to assess visual attention as well as task switching. This test is comprised of two parts (A and B) and has classically been associated with functioning of the right and left frontal regions respectively. Zakzanis et al. (2005) attempted to validate the classic trail making test using an

fMRI. Even after modifying the test, when Trail Making B was compared to Trail Making Test A it was found that Part B showed activation in the left frontal regions including the dorsolateral prefrontal cortex and regions involved with motor control. However, other regions of activation were found that would not be classified as traditional and this would lend support to the need for further validation of these tests. Other tests have also been studied in this manner namely the stroop test (Gruber et al., 2002; Adleman et al., 2002), toe graphaesthesia test (Persinger, Webster, & Tiller, 1998), as well tests like the California verbal learning test (Johnson, Saykin, Flashman, McAllister, & Sparling, 2001). However, very few studies have been conducted using electroencephalography.

The use of neuroimaging techniques including the quantitative electroencephalograph (QEEG) has grown with respect to clinical practice. The QEEG has been used to evaluate and research correlates of a wide range of cognitive disorders (Saleteu, Anderer, & Saletu-Zyhlarz, 2010; Doege et al., 2009) as well as mild to severe traumatic brain injuries in correlation with neuropsychological tasks (Thatcher, Biver, Camacho, McAlaster, & Salazar, 1998a; Thatcher, Biver, McAlaster, & Salazar, 1998b; Thatcher et al., 2001a; Thatcher et al., 2001b). However, even with this increase in popularity it is still not possible to use the QEEG as the sole diagnostic tool for mental disorders or traumatic brain injury. Given that neuroimaging tools have been shown to accurately evaluate correlates associated with mental illnesses (Kopecek et al, 2008) the next step is to ensure that the tools being used to assess these illnesses or injuries are valid through simultaneous measurements. Flskov & Goldstein (1974) stated that “accuracy in prediction is the hallmark of a good diagnostic instrument” and by validating the tools being used one can be more certain when diagnosing and developing treatment plans.

Through the use of electroencephalography it has been found that researchers can reliably use the results to correlate cognitive phenomena including clinical signs and symptoms. However, very few studies have explored correlations between psychological or neuropsychological tests and results from resting neuroimaging measurements. Even fewer studies have explored the direct relationship between the two by having the participants perform the psychological tests while concurrently being measured with a neuroimaging tool. If these measurements are going to be used to evaluate neuropsychological functioning and the technology exists to evaluate the construct validity of the tests then it seems logical to assess the brain regions activated while these tests are being performed.

1.2 Electroencephalography

An electroencephalograph (EEG) is a tool that uses sensors to record the voltage fluctuations occurring from along the cortex. These voltage fluctuations are due to the ionic current flows within the neurons of the brain (Niedermeyer & de Silva, 2005). Since the EEG was first used by Hans Berger to measure humans in 1924 the tool has been verified and electroencephalography has been employed in both experimental and clinical contexts in order to determine correlates between brain activity and behaviour. Traditionally, these recorded signals are transmitted from the sensors to an EEG system and recorded on a paper chart, however, with technological advancements classic electroencephalography has given way to quantitative electroencephalographic (QEEG) recordings which has significantly increased the options for analysis thereby increasing the inferences that can be made by researchers. In addition, the EEG is a highly temporally sensitive tool that has been consistently employed for diagnostic purposes. The primary diagnostic application of the EEG is to detect epilepsy, since epileptic activity creates abnormalities in EEG recordings due to the abnormal electric activity (Abou-Khalil &

Misulis, 2005). It has also been used for the diagnosis of tumors (Murugesan & Sukanesh, 2009) and sleep disorders (Belo, Coito, Paiva, & Sanches, 2011). However, with the advances of spatially sensitive tools like the MRI the use of EEGs as a diagnosis tool has decreased.

1.2.1 Spectral Analysis

Since the introduction of QEEG there have been many advances in the analyses that have been developed to study brain activity. Probably the most traditional method of analysis is Fast Fourier analysis. Fast Fourier analysis decomposes the QEEG time series into a power spectrum with power being the square of the EEG magnitude microvoltage time series of the QEEG (or microvolt^2/Hz). Throughout the literature spectral analysis has been employed in a number of clinical studies in order to assess individuals who had sustained a brain injury as well as those with varying types of mental illness. Goldfine and colleagues (2011) have shown that by using EEG spectral analysis individual's with a traumatic brain injury demonstrated widespread changes in EEG power on motor imagery tasks which was able to differentiate them from the healthy controls. In addition, EEG spectral power has also been used to predict human movement intention in patients with stroke and motor neuron disease indicating that this tool can be used as a diagnostic method as well as a therapeutic intervention to facilitate communication (Bai et al., 2007).

1.2.2 Standardized Low Resolution Brain Electromagnetic Tomography

Standardized low resolution brain electromagnetic tomography or s-LORETA (Pascual-Marqui, 2002; Pascual-Marqui et al., 2002) is a 3-dimensional source imaging of the human brain. s-LORETA is a type of statistical analysis that has been used to compute statistical maps of the brain from EEG data. This tool can be used to indicate the locations of the underlying sources of activation (Wanger, Fuchs, & Kastner, 2004). Therefore, this analysis technique computes a

three dimensional distribution of electrical neuronal activity from EEG electric potential differences.

This method of analysis has been employed in both experimental and clinical paradigms in order to explore differences between varying experimental conditions or mental illnesses. Within experimental paradigms s-LORETA technology has been employed to explore mental time travel (Lavallee & Persinger, 2010) as well as for tasks like mental arithmetic (Theodoropoulous et al., 2011). In addition, as a result of using this type of analysis, differences in the pattern of activation has been found between clinical populations. Dementia (Nishida et al., 2011), Huntington's disease (Painold et al., 2011), and depression (Saletu et al., 2010) have all been explored using LORETA technology and each study has found a different pattern of activation depending on the population.

1.2.3 Microstate Analysis

Microstate analysis developed by Dietrich Lehmann and Thomas Koenig allows researchers to investigate dynamic processes that are ongoing within the brain (e.g. cognitive, emotional). Electroencephalographic recordings allow for the continuous monitoring of brain activity that is highly temporally sensitive. Each of these time points allows the data to be organized to show the potential distribution across the surface of the head (Lehmann, 1971). Koenig and colleges (2002) have demonstrated consistent microstates with durations that are approximately 80 to 120 msec. These microstates have been defined as periods of quasi-stable topographical maps of the overall scalp's electric field (Lehmann, Pascual-Marqui, Strik, & Koenig, 2010). This research has revealed that there are four major stable microstates maps (Figure 1) that have been determined to account for almost three-quarters of the variance in voltage fluctuations. It has also been found that these four microstates are consistent across age groups with varying durations

and proportions (Koenig et al., 2002). Based on this information it has been hypothesized that microstates represent the basics of information processing (Lehmann et al., 2010) or the millisecond fluctuations between environmental information, pervious knowledge, and the person's internal state (Lehmann, 1990). In a healthy population microstates have been known to show relatively stable spatial distributions however abnormal microstate patterns have been found in individuals with disorders that affect cognitive functioning like dementia (Dierks et al., 1997) or schizophrenia (Koenig et al., 1999). Thus, exploring the changes in this fundamental and stable process after individuals have sustained a closed head injury could give further insight into how the brain is affected after a substantial impact.

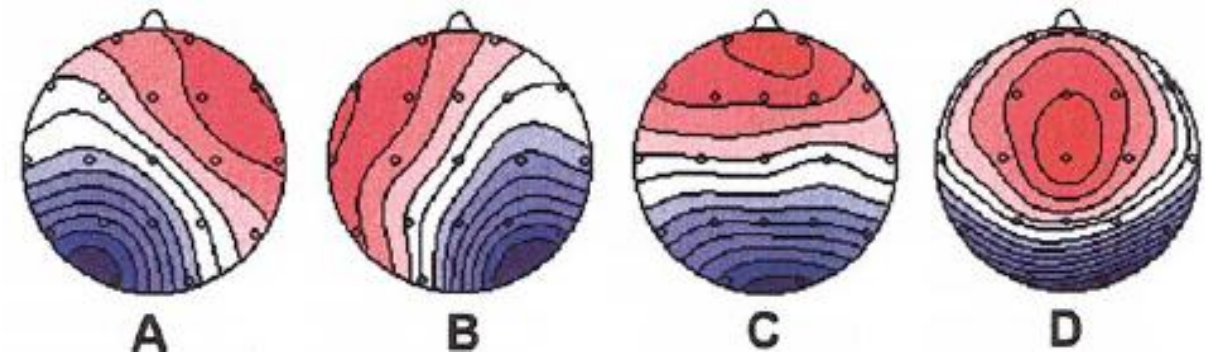

Figure 1. Contour maps of the four classic microstates

1.3 Therapeutic uses of Electromagnetic Fields

There are multiple types of magnetic field application devices currently being used as a treatment to help individuals who have been diagnosed with a disorder of cognitive functioning. Transcranial Magnetic Stimulation (TMS) is a noninvasive method that uses a changing magnetic field to induce electric currents within the brain. TMS and repetitive TMS involves the application of strong (1.5-2 Tesla; Wassermann, 1998) magnetic currents to the skull. Research

has suggested that there are some therapeutic benefits for using this technology specifically to help individual's suffering from major depression (Slotema, Blom, Hoek, & Sommer, 2010; Marangell, Martinez, Jurdi, & Zboyan, 2007). In contrast however, research executed by the Food and Drug Association indicated that repetitive TMS was not efficacious in a study of individuals with major depression who had not benefitted from prior treatments (antidepressants) (Scudiero, 2007). In addition, there have been reports of significant adverse effects after the use of this method including generalized or partial seizures (Wassermann, 1998; Rossi, Hallett, Rossini, & Pascual-Leone, 2009), syncope, headaches, cognitive changes, and mania in patients with depression (Rossi et al., 2009).

In contrast to TMS, Transcerebral Magnetic Stimulation (TCMS) involves the application of weak, complex, physiologically-patterned electromagnetic fields (Figures 2 & 3; St-Pierre, Mazzuchin, & Persinger, 2008) at strengths that are approximately one million times less intense (1 microTesla) than TMS (Baker-Price & Persinger, 2003). Researchers that employ this technique hypothesize that it is not the strength of the field applied but the information coded within the applied signal that is of key importance (Baker-Price & Persinger, 1996). TCMS has been found to influence electrical activity within the brain (as measured using electroencephalography), and in turn produce a variety of effects dependent on the pattern of magnetic field applied (Persinger, 1995; Persinger, Richards, & Koren, 1997; Richards, Koren, & Persinger, 2002; Booth, Koren, & Persinger, 2008). Within a clinical context, research has supported that these magnetic fields also can improve clinical depression in patients who had sustained a closed head injury (Baker-Price & Persinger, 1997; 2003) as well in normal volunteers (Tsang, Koren, & Persinger, 2009). However, like with TMS, there have also been critics of this work that has called into question the effectiveness of these patterned fields

(Granqvist et al., 2005) and some researchers have hypothesized that the achieved effect is specific to the equipment being used.

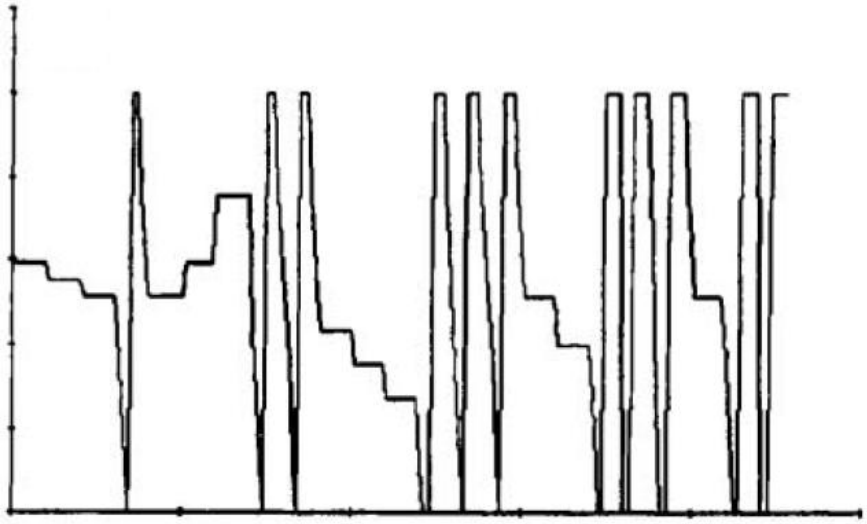

Figure 2. Burst-firing magnetic field pattern

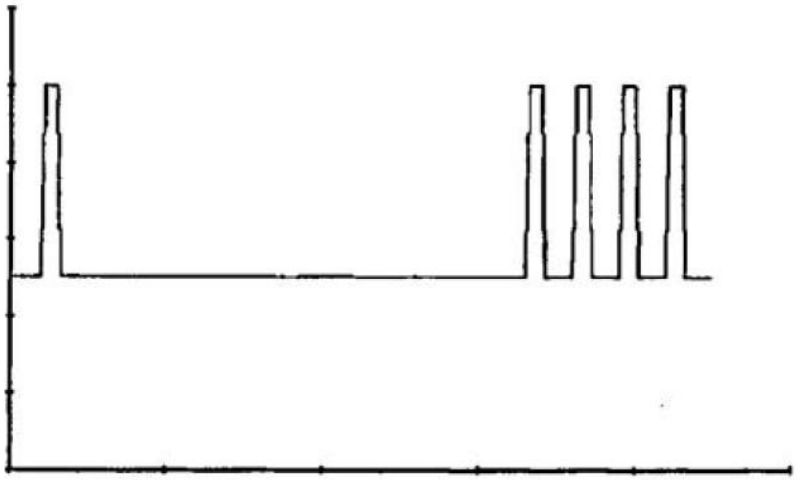

Figure 3. LTP or long-term potentiation (positive polarity only) magnetic field pattern

Since it has been hypothesized that it is the pattern of the fields that is the critical factor in producing these effects and that the effects are not reliant on the equipment being used then by keeping the characteristics of the patterns intact but changing the method of application should produce similar results. There has been research conducted using different devices to apply these

magnetic fields such as the Koren Helmet (Cook & Persinger, 1997) or the Octopus (Tsang et al., 2009) that have achieved comparable results. Additional research, by a separate laboratory, using different equipment has revealed similar results (Sandyk, 1995). In addition, Professor Todd Murphy (working in collaboration with Dr. Michael Persinger) has created variations of this equipment that has been named the Shakti and Shiva helmets (Figure 4). These helmets use the same patterned fields that have shown the results, but through a novel application method. The patterned waveforms are converted into audio files and delivered to the solenoids on the helmet from USB soundcards (Saroka, Mulligan, Murphy, & Persinger, 2010). The solenoid then delivers a weak-intensity magnetic field (microTesla range). This method of field application has also been found to be effective at producing changes in QEEG results (Tsang, Koren, & Persinger, 2004) and in replicating research using other methods of field application (Saroka et al., 2010). Based on these results, it is plausible that this technology is a viable option for treatment for individuals who are afflicted with a variety of "mental illness".

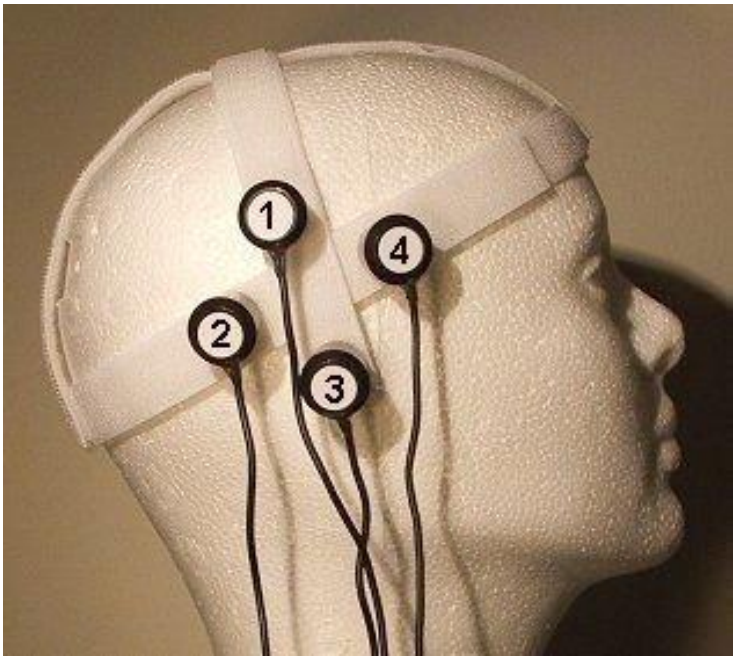

Figure 4. Shiva solenoid placement over right hemisphere

1.4 Current Studies

The studies that will be discussed in the upcoming chapters follow the traditional sequence of patient care in the field of clinical psychology. The initial study aimed to provide construct validity for traditional neuropsychological tests. By simultaneously measuring normal individuals with a highly temporally sensitive tool while they are engaged in these tasks makes it possible to determine the ongoing electrical processes within the brain. This study was designed in order to add to the literature with respect to the construct validity of these tasks and determine if the traditional regions of the brain associated with these tasks are the primary regions involved in their completion. In addition, this experiment will reveal if there are also nontraditional regions of the brain required to complete the tests. By validating traditional behavioural tests clinicians can be confident in their assessment of their patients which will provide better care for these individuals.

The second study involved the collection of data from the patients who were referred for a complete neuropsychological assessment due to a brain injury or other related aliment. These patients were all assessed between January, 2010 and April, 2013. The purpose of this study was to explore whether an individual's resting brain activity is consistent with classical neuropsychological test results. All patients who underwent a neuropsychological assessment over the approximately 3.3 years were assessed in five domains; intellect, memory, academic achievement, neurofunctioning, personality, as well as electroencephalographic measurements. By compiling this database and examining the electroencephalographic results using a variety of analysis techniques (i.e. spectral analysis, s-LORETA, and microstate analysis) it will be possible to determine if there is an evident relationship between the brain's electrical activity and the severity the individual's acquired brain injury.

The final experiment was designed to add to the current literature with respect to magnetic field treatments as an effective intervention technique. The experiment was modified from a study by Richards, Persinger, & Koren (1996) that tested the effects of the LTP field, using different application geometries, on memory. The results of the previous experiment found that there was approximately a doubling in the number of accurate details recalled by the group exposed to the field from the left hemisphere 10 days later. The current experiment used the Shiva patterned hippocampal field. This pattern was selected because it is modeled after the LTP field used in the Richards (1996) study. The purpose of the experiment was to test the effects of the field on memory while concurrent QEEG measurements were recorded however, the field was not applied over both hemispheres concurrently. Participants were either exposed to a sham field condition (no field), left hemispheric field exposure only, or right hemispheric field exposure only. The goal of this experiment was to help determine the validity of transcerebral magnetic stimulation as a genuine therapeutic treatment for individuals with brain injuries.

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Chapter 2: S-LORETA Validity of Classic and Novel Performance-Based Neuropsychological Tests: The Future of Clinical Assessment?

Submitted to *Clinical Neurophysiology*

2.1 Abstract

The validity of neuropsychological tests is essential for their perspicacious application and interpretations. Our study was designed to discern the regions of the cerebral volume that displayed specific changes in power in normal volunteers as measured by s-LORETA (standardized Low Resolution Electromagnetic Tomography) in real time for both traditional and novel neuropsychological tests that are employed to infer localized brain injury. Normal men and women's quantitative electroencephalographic activity (QEEG) were measured while performing three components of the Halstead-Reitan Battery: the Category Test, Speech-Sounds, and Seashore Rhythm Test, and four newer tests: Design Fluency, Conditioned Spatial Association, Toe Gnosis, and Toe Graphaesthesia. The data were analyzed by s-LORETA for peak power within different frequency bands. Conspicuous alterations in power occurred within various regions of the right prefrontal region during performance of the Category, Design Fluency and Conditioned Spatial Association Test, the prefrontal medial surface during Toe Graphaesthesia, the caudal medial surface during Toe Gnosis, the left temporal region during Speech-Sounds, and within the right retrosplenial-parahippocampal region for Seashore Rhythms. Results support known the well established regional association with the classic neuropsychological tests, verifies the cerebral localization with more recent procedures, and emphasizes the utility of modern real-time cerebral imaging procedures. The conspicuous nature of the changes in power

within specific frequency bands and regions in real time during performance of classic and novel neuropsychological tests reiterate their validity but also suggests procedures such as LORETA could be employed in the future to extract immediate information regarding cerebral anomalies.

2.2 Introduction

The performance-based procedures ("tests") by which clinical neuropsychologists infer the integrity of neuronal function within regions of the human cerebrum have progressed through several stages of construct-validity. During the late 19th century and early 20th century the association between behaviour and conspicuous structural alterations within the cerebrum was confounded often by years between the observation and the post-mortem examination. The development of CT (Computerized Tomography) and MRI (Magnetic Resonance Imaging) permitted more temporarily contiguous comparisons between quantitative measurements of specific behaviours and more detailed alterations of signal organization within the cerebral volume. However concurrent measurements of the specific class of behaviours and the activity within correlative regions within the cerebrum required the development of the functional tools of imaging such as fMRI, PET (positron emission tomography) and SPECT (Single Photon Emission Computer Tomography). Although remarkably precise in their differential of the location of cerebral activity, reflecting perfusion or a highly correlated metabolic product of neuronal and glial activity during specific tasks, the equipment is largely static, cumbersome and expensive (Collura, 2012).

The development of neuroimaging tools has afforded researchers the opportunity to validate neuropsychological tests that are used to infer cerebral functioning. However, few studies have been conducted and even fewer studies employ the use of electroencephalography. Zakzanis et al

(2005) attempted to validate the classic trail making test using an fMRI. Results from this study indicated that even after modifications were made to the testing procedure there was significant activation in the left frontal regions including the dorsolateral prefrontal cortex and regions involved with motor control. In addition to the trail making tests common neuropsychological tests that have been studied in the manner include the Stroop test (Adleman et al., 2002; Gruber et al., 2002), the toe graphaesthesia test (Persinger, Webster, Tiller, 1998), and the California verbal learning test (Johnson el al., 2001) however, given the technology available further research in this area is required.

The convergence of quantitative electroencephalographic technology with algorithms employed to infer activity within the cerebral volume has allowed a more versatile and dynamic paradigm by which the power within the patient's cerebral activity over incremental bands of classical EEG ranges can be imaged within computerized representations of the three axis of the human cerebrum. One of these procedures, s-LORETA (standardized Low Resolution Electromagnetic Tomography), promises substantial utility within experimental and clinical settings for monitoring the fluidity of changing behaviours within specific contexts (Pascual-Marqui, 2002; Pascual-Marqui et al., 2002). Although the spatial resolution for the simplest of configurations is in the order of 5 mm, the access to power measures across a range of discrete frequency bands is still revealing and is strongly correlated with the task-specific regions measured by fMRI (Mulert et al., 2004; Vitacco et al., 2002) and PET (Dierks et al., 2000; Pizzagalli et al., 2004; Zumsteg et al., 2005). Here we present compelling evidence that s-LORETA profiles of normal volunteers engaging in different classic neuropsychological, performance-based procedures, supports the construct validity of these tests and reveals a realistic perspective of the volume and variations involved with task execution.

2.3 Materials and Methods

2.3.1 Subjects

This study was based upon the results of two sets of five volunteers. The Category Test, Seashore Rhythm Test, Speech-Sounds Perception Test, Conditioned Spatial Association Test, and Design Fluency Test were completed by 3 men and 2 women whose mean age was 24.6 years (SD=1.8). The final two tests, Toe Gnosis and Toe Graphaesthesia tests, were performed by five additional participants (3 men and 2 women) whose mean age was 26.0 years (SD=2.5). All ten individuals were attending university and did not display neuropsychological evidence of hypofunction or deficits.

2.3.2 Neuropsychological Tests

Seven neuropsychological tests, frequently employed for clinical assessments, were selected. There were three classic tests from the Halstead-Reitan Battery: Category Test, Seashore Rhythm Test, Speech-Sounds Perception Test, and, four more recent tests: Conditioned Spatial Association, Design Fluency, Toe Gnosis, and Toe Graphaesthesia. According to traditional interpretations the accuracy or speed, compared to normative data, by which a subject completes each tests reflects integrity of function within the right prefrontal (dorsal convexity) for the Category Test (Adams et al., 1995; Fisher et al., 2007), the right superior temporal cortices for the Seashore Rhythm Tests (Lezak, 1983), the left superior temporal cortices for the Speech Sounds Test (Bornstein and Leason, 1984; Reitan and Wolfson, 1985), the right orbital frontal region for the Conditioned Spatial Association Test the right more rostral prefrontal region for the Design Fluency Test (Jones-Gotman and Milner, 1977). Toe gnosis is more associated with medial (paracentral) lobule of the parietal lobe while the rostral medial surface has been shown

by SPECT (single photon emission computerized tomography) to be activated during Toe Graphaesthesia (Persinger et al., 1998).

Our rationale for selecting three tests that traditionally involve the right prefrontal region was to discern the spatial or frequency-dependent differential capacity of s-LORETA within the same gross volume. We reasoned it could be possible for tasks involving the same cerebral region to be dominated by different frequency bands of power as discerned from the QEEG. The two temporal lobe tasks would be considered gross reference measures to reflect the construct validity as well as the face validity of both the "left" (Speech Sounds) and "right" (Seashore Rhythm) bias for these tests.

The Category Test involves the subject selecting from four options various patterns that reflect a spatial configuration concept (Reitan & Wolfson, 1993) while the Design Fluency is a time-dependent task that requires the subject to generate as many different four component combinations of novel patterns using two basic shapes (Jones-Gotman & Milner, 1977). Conditioned Spatial Association requires the subject to learn which blue light of six identical and proximally clustered blue lights are associated with a specific number from 1 to 6 when on of those lights is activated (Milner, 1982). The learning is by trial and error. The Speech Sounds Test requires the subject to pair a phoneme with the accurate grapheme contained within four different options (Reitan &Wolfson, 1990) while the Seashore Rhythm task tests the capacity for the subject to discern if two sequences of tones are the same or different (Reitan & Wolfson, 1989).

Historically there has been a relative paucity of tests, except for those by which corpus callosal function are inferred, concerning the integrity of the medial surface of the cerebral hemispheres.

Yet the rostral region of this area is serviced primarily by an arterial system, the Anterior Cerebral Artery, that is particularly prone to the torsional effects from the asymmetrical impact of mechanical energies to the two hemispheres. This is particularly relevant considering that about 20% of the population display only a single ACA from which the component to the contralateral hemisphere is derived.

Toe gnosis, like finger gnosis, involves identification of which toe on each foot is touched (dorsal surface) lightly with a stylus without the benefit of visual feedback (Richards & Persinger, 2004). The order of the toe stimulation employs the same order that is applied to fingers. Each toe is stimulated five times. Toe Graphaesthesia, like finger Graphaesthesia, involves printing with a stylus either the number 3, 4, 5, or 6 on the ventral surface of each toe. Each toe is stimulated five times. The normative information has been published for children (Knights & Norwood, 1980; Richards & Persinger, 2004) and adults (Richards & Persinger, 1992).

2.3.3 Data Collection

While the participants were engaging in the specific neuropsychological tasks brain activity was measured concurrently by a Mitsar-201 portable QEEG system that was connected to a 19-channel electrode cap (Electrode-Cap International) that contained the 10-20 Standard Electrode Placement. Electrode site include Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, T6, O1, and O2 that were linked to the ears (A1 and A2) for monopolar recordings. Impedance of all channels was less than 10 kOhm. Data were acquired using WinEEG v2.84.44 software with a sampling rate of 250 Hz. A 50 Hz to 70 Hz notch filter was used in the WinEEG software for all subjects in order to filter high frequency noise during recording. The EEG record was

inspected for movement artifacts; the principal component analyses (PCA) method of artifact correction within WinEEG software was employed where appropriate.

2.3.4 Source Localization

Source localization analyses were completed by standardized low-resolution electromagnetic tomography (s-LORETA; Pascual-Marqui, 2002; Pascual-Marqui et al., 2002) on 10 samples of EEG recorded from the 19 channels during periods when the individuals were participating in the neuropsychological tests. The time each test was presented (and engaged) was recorded on the EEG record and employed as an aid for determining where the appropriate segments were extracted. Eyes open and eyes closed baseline data were also collected.

These epochs were divided into 2 s segments that did not overlap for the purposes of analyses. Cross-spectral analyses were completed on all epochs. Independent t-tests without normalization were utilized within s-LORETA to discern source localization throughout the telencephalon for each of the software's defined frequency bands which included delta (1.5-4 Hz), theta (4-7.5 Hz), alpha-1 (7.5 to 10 Hz), alpha-2 (10-13 Hz), beta-1 (13-20 Hz), beta-2 (20-25 Hz), beta-3 (25-30 Hz) and gamma (30 to 40 Hz).

2.4 Results

When compared to baseline measurements for each individual before the standardized neuropsychological tests were initiated the changes within the software-inferred cerebral space were consistent with the traditional interpretations of test functions as well as the inferences of where any damage or hypofunction might be when standardized tests scores were below normal. The specific patterns of change were extraordinarily similar for all participants. For the sake of

brevity and clarity only exemplary profiles for each test are shown. Within the figures yellow indicates marked increase in activation while red indicates less increase in activation for the indicated frequency band. For this procedure blue, which was not produced during these tasks, indicates diminished activity. Table 1 shows the primary frequency band in which power was increased during the tasks as well as the Brodmann (BA) area and the centroid for the Montreal Neurological Institute (MNI) coordinates.

Table 1: Summary of significant findings, outlining neuropsychological test, spectral band, cortical regions, and Montreal Neurological Institute (MNI) co-ordinates

Neuropsychological Test	Frequency	Region	X	Y	Z
Conditioned Spatial	Gamma	BA10	35	40	25
Design Fluency	Alpha2	BA11	20	60	15
Speech Sounds	Theta	BA39	-40	-55	25
Category Test	Alpha1	BA10	5	45	-25
Seashore Test	Beta1	BA30	10	-50	0
Right Toe Gnosia	Alpha1	BA31	-10	-25	40
	Alpha1	BA7	-10	-54	45
Right Toe Graphaethesia	Delta	BA9	-6	35	22
	Gamma	BA9	-10	40	25

Figure 1 shows the increased activation during the execution of the Conditioned Spatial Association Test. According to software-indicators, the marked increased in gamma frequency power ($t=3.49$, $p < .05$) was localized to the right middle prefrontal gyrus (BA 10). The profiles indicate that the area of marked activation (yellow) occurred within the right prefrontal region, particularly within the orbital region. During the Design Fluency test individuals showed increased activation and power within the alpha-2 band within the right frontal gyrus (BA 11) in comparison to baseline ($t=4.24$, $p < .01$).

To illustrate that the tasks requiring integration of auditory and cognitive processing were location appropriate, Figure 3 shows the increased activity compared to baseline ($t=4.24$, $p < .01$) during the Speech Sounds Test. Interestingly the increased activity and power was within the theta band within the left superior temporal and adjacent area 39. The generalized activation of the visual cortical area and parietal regions is also noted. The low-level generalized activity within the visual cortices was noted for all tests.

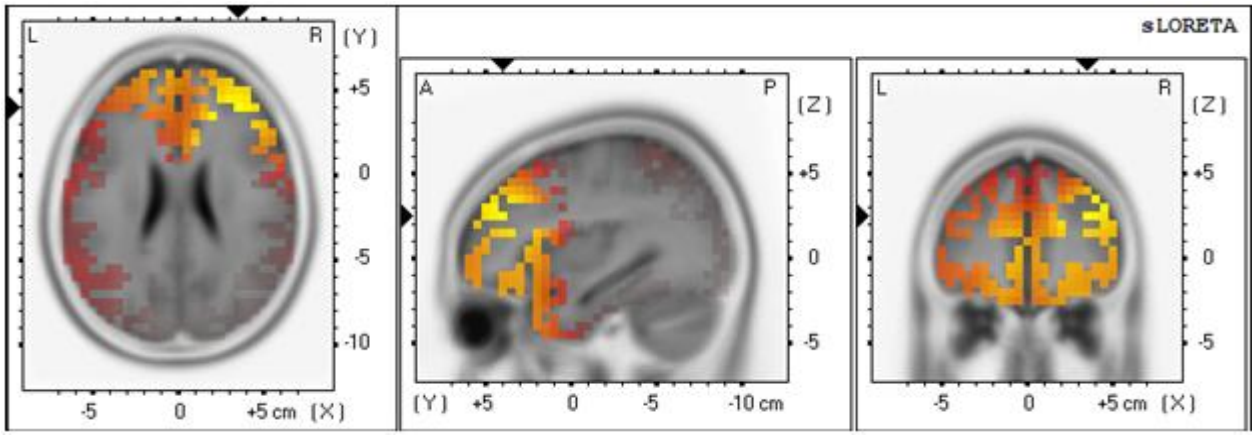

Figure 1. Increased activation compared to baseline recordings during the conditioned spatial association task in the right middle frontal gyrus (BA 10) in the gamma frequency band

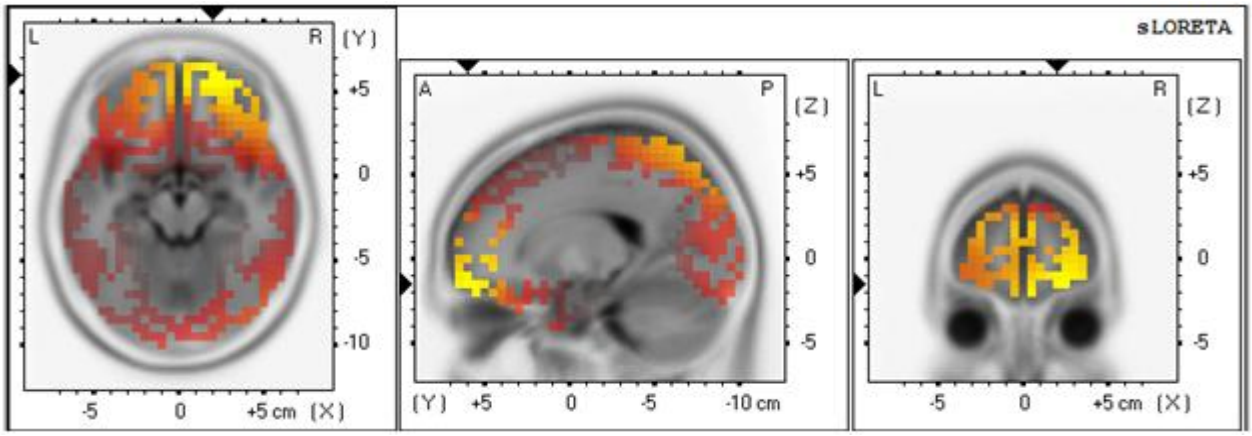

Figure 2. Increased activation compared to baseline recordings during the design fluency test in the right superior frontal gyrus (BA 11) in the alpha-2 frequency band.

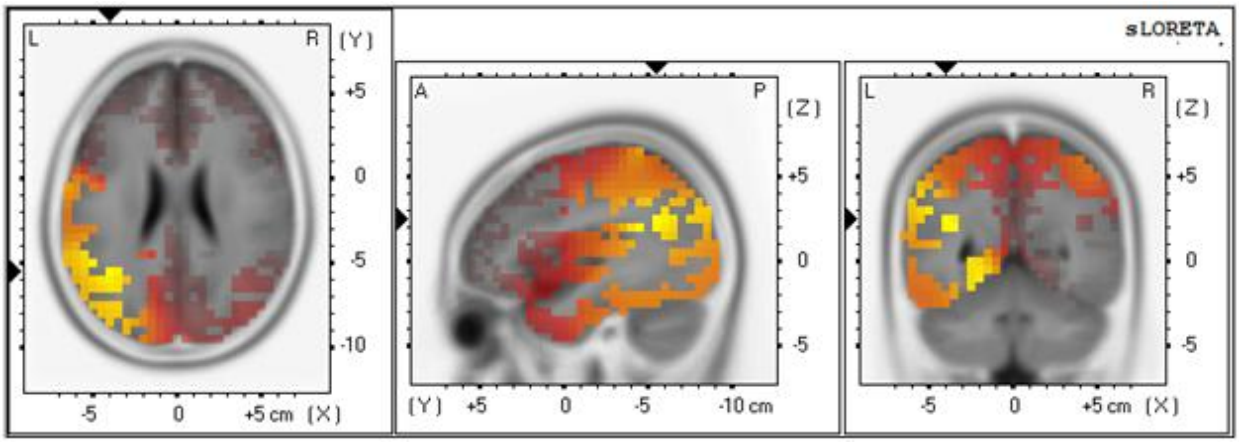

Figure 3. Increased activation compared to baseline recordings during the speech sound test in the left superior temporal gyrus (BA 39) in the theta frequency band.

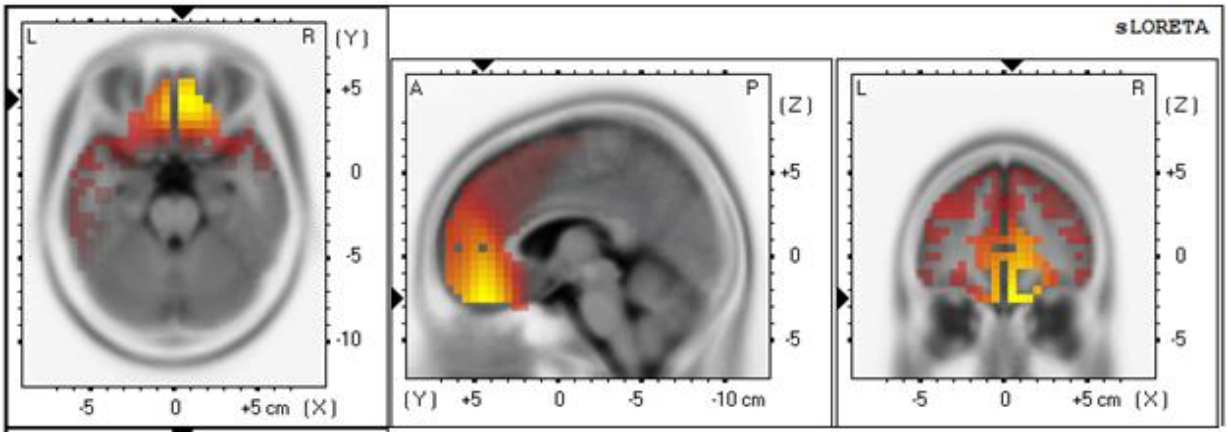

Figure 4. Increased activation compared to baseline recordings during the category test in the right orbital gyrus (BA 11) in the alpha-1 frequency band.

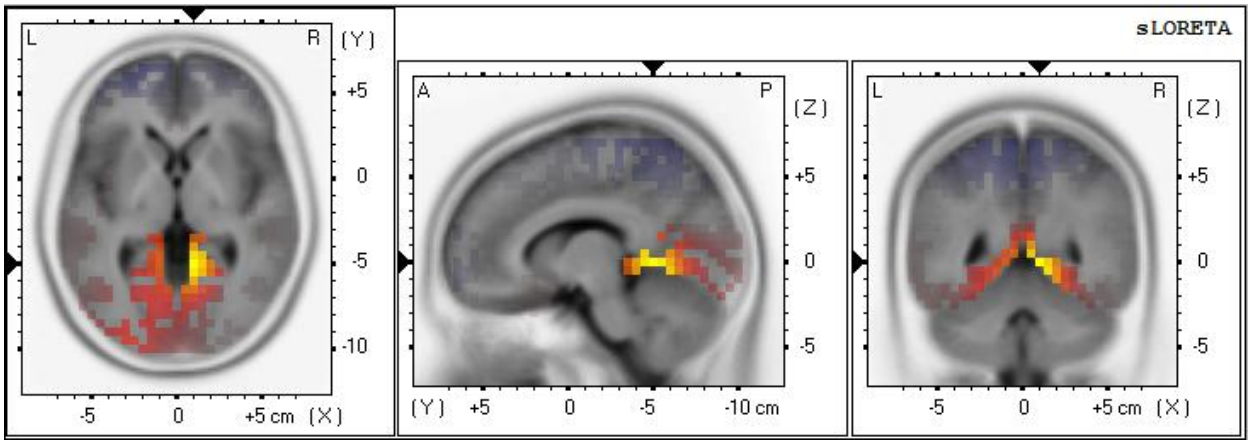

Figure 5. Increased power within the beta 1 range localized primarily within the right Brodman area 30 region (retrosplenial, parahippocampal region) during the Seashore Rhythm test.

Figure 4 is an example of the profile while subjects engaged in the Category Test. The markedly increased activation in power ($t=6.99$, $p < .01$) within the alpha-1 band occurred within BA-11 according to the software. However the sagittal profile indicates a much larger region of the prefrontal cortices was involved with the neurocognitive processing associated with this test compared to the Design Fluency and Conditioned Spatial Association tasks. Within the various subtests (5) of the Category Test, there was a common pattern of secondary increased activation and power within beta range that was most prominent in the left inferior parietal lobe, particularly within the area of the supramarginal gyrus (BA 40).

Figure 5 shows the profile for the Seashore Rhythm Test. Compared to baseline the significant increase in power ($t=6.81$, $p < .01$) within the beta-1 band was primarily within the right hemisphere not in the temporal cortices. Instead source localization indicated it was within the region of the retrosplenial and parahippocampal region. The general area of activation was the smallest of all of the tasks.

Figure 6 shows the profile obtained for toe gnosis. As predicted, the greatest change in activity occurred along caudal medial surface. There were significant differences ($t=9.68$, $p < .001$) found in the left posterior cingulate (BA 31) and left precuneus (parietal lobe: BA 7) region ($t=7.87$, $p < .001$) during the right toe gnosis task for the low-alpha frequency band. The MNI coordinates were: left cingulate: X=-10, Y=-25, Z=40; left precuneus: X=-10, Y=-54, Z=45. For the toe Graphaesthesia tasks (Figure 7) the statistically significant differences were found in the left medial frontal gyrus (BA 9) during the right toe stimulation for both the delta ($t=4.66$, $p < .001$) and gamma ($t=4.41$, $p < .001$) frequency bands.

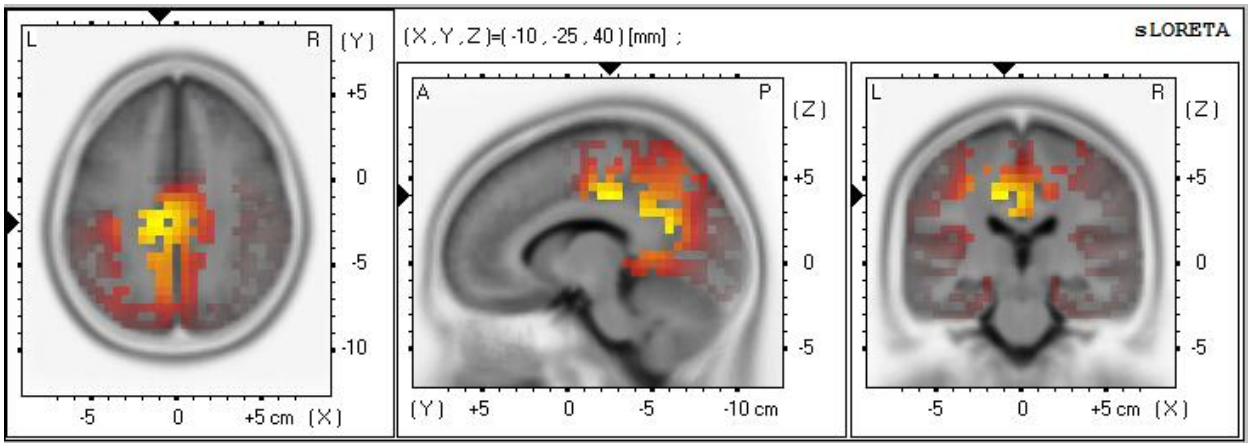

Figure 6. Increased activation compared to baseline recordings during the right toe agnosis test in the left posterior cingulate gyrus (BA 31) adjacent to paracentral medial surface and left precuneus (BA7) in the alpha-1 frequency band

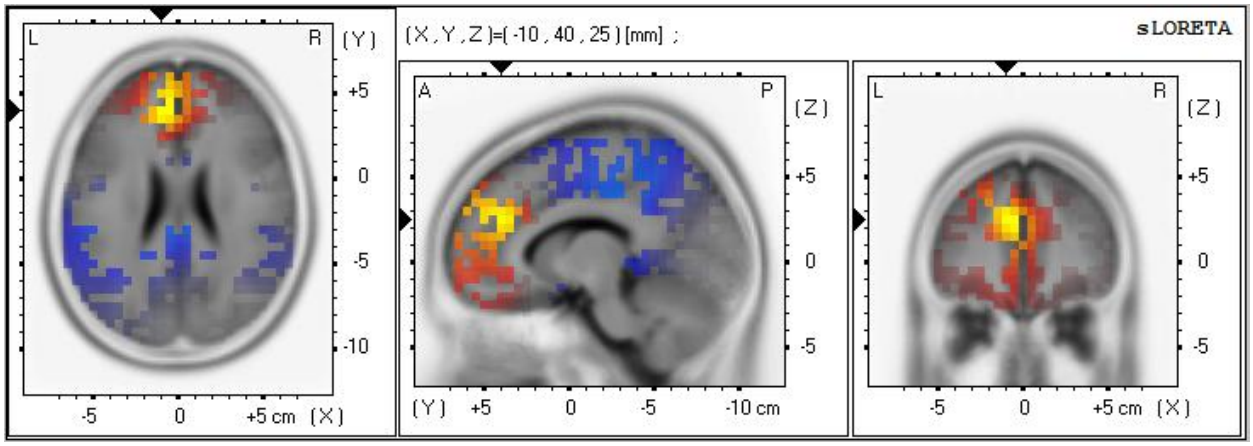

Figure 7. Increased activation compared to baseline recordings during the right toe graphaesthesia test in the left medial frontal gyrus (BA 9) in the gamma frequency band

2.5 Discussion

The results of direct, real time, measurements of brain activity and source localization for seven different neuropsychological tests that are often employed to discern or infer acquired brain injury supports the traditional interpretation of the functions and the integrity of brain regions these tests are assumed to represent. The three tasks that have been inferred to be involved with right prefrontal function, as reflected in patients with CT-verified, MRI-verified or strongly suspected injury in this region, were associated with conspicuous increases relative to baseline of power within frequency bands (alpha to gamma) associated with information processing.

The Category Test has often been considered an excellent indicator of diffuse injury within the right prefrontal region (Adams et al., 1995; Fisher et al., 2007). The s-LORETA profiles confirmed the greater involvement of this area during the execution of the task. The area activated most significantly was larger than the areas involved with the other two prefrontal tasks. The Conditioned Spatial Association Task showed only activation in the right prefrontal region while the Design Fluency test, which required recognizing patterns of shapes and placing them over the surface of a paper, also involved the parietal region.

On the other hand the task (Speech Sounds) that have been attributed to left superior temporal lobe functions (Bornstein and Leason, 1984; Reitan and Wolfson, 1985) was associated with activation in these respective areas. From our experiences the increased power within theta bands for the Speech Sounds Task is consistent with the over-learned nature of the process associated with this process even though the manner in which the detailed stimuli (the graphemes and phonemes) were presented may have been partially novel.

The absence of enhanced activity within the right temporal region while normal subjects listened to the Seashore Rhythm Task is consistent with the observation that this procedure, of all of the tasks, is most vulnerable to distraction (Hom & Reitan, 1990). In fact in traditional clinical neuropsychology practice, the attribution of abnormal scores for task to damage or dysfunction within the right temporal lobe is considered a "weak" hypothesis. Consequently relatively large lesions in the right temporal lobe, such as those often involved with the population involved with the validation of this test in the original Halstead series, would be required before the adverse affect influenced the region we measured (Halstead, 1947).

The caveat to our observations is that the participants were normal, university students. If the brain behaves as a matrix whereby different functional volumes within the cerebrum can be combined in different manners to produce the same behaviour then different areas would be activated in response to environmental demands for different types of brain injuries. However the long history of general correlations between specific task deficits and brain injury locations indicate a stability of these associations. If it were otherwise, the classic neuropsychological tests would not continue to be valuable inferences of locations of brain damage or hypofunction.

We suggest that more quantitative exploration of this procedure of measuring during active engagement of tasks could reduce the inferential errors when the clinician is dependent completely upon standardized scores and current norms. The simultaneous activation or diminishment of other areas not typically associated with the task might reveal compensatory responses within the cerebrum or even the idiosyncratic organization of functional responses. Changes in power within *different* frequency bands could be potentially important for estimating the degree to which the area, activated by specific tasks, is displaying characteristics of novelty

or well-acquired profiles. All of these possibilities would be expected to increase the accuracies of inference and consequently facilitate the application of more appropriate interventions.

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Chapter 3: Use of Spectral Power, Source Localization (s-LORETA) and Microstates to Quantify Chronic Deficits from "Mild" Closed Head Injury: Correlation with Classic Neuropsychological Tests

Submitted to *Brain Injury*

3.1 Abstract

Primary objective: To explore the quantitative relationship between neuropsychological impairment and spectral QEEG power, source localization (s-LORETA) and microstate duration in patients who "fail to adapt" years after mild closed head injury. *Methods and procedures*: Differences in classic psychometric measures, QEEG measures, s-LORETA indicators and microstate durations were compared for three levels of neuropsychological impairment approximately (average) 6 years after injury. *Results*: Patients who displayed the moderate to severe neuropsychological impairments typical of mild TBIs exhibited shorter microstates, less power within the alpha band and lower power within the theta and delta bands within caudal regions. There were conspicuous differences in the configurations of microstates, their source localizations and frequency bands. *Conclusions*: The systematic relationship between neuropsychological impairment as inferred by classic psychometric measures that can require tens of hours to collect and modern configurational analyses of brain activity that requires 30 min suggests that the latter might be useful in discerning the area of dysfunction and potential focus of treatment for closed head injury patients years after the event.

3.2 Introduction

Closed head injury is associated with a rapid change in acceleration of pressures or force per unit area that distributes mechanical energy through the cerebral volume. Although the long-term effects of severe brain injuries are often evident by direct neurological and computerized imaging, the long-term consequences of mild Traumatic Brain Injuries (mTBI), often described as "mild" closed head or concussive injuries, are often ambiguous (Cooper, 1993). Until recently the primary method of inference required standardized scores from performance-based neuropsychological test batteries such as the Halstead-Reitan Impairment Index (Reitan & Wolfson, 1985) or means of standardized scores from aggregates of performance-based tests whose integrity are strongly dependent upon a particular cerebral region. Quantitative electroencephalography (QEEG) and the source localization algorithms derived from these data, such as standardized low resolution electromagnetic tomography (s-LORETA), added an addition level of resolution.

Quantitative Electroencephalography (QEEG) has been shown to discern changes associated with the post-concussion syndrome and to predict the level of improvement one year later (Nuwer, Hovda, Schrader, & Vespa, 2005). It can distinguish normal patients from those with mild traumatic brain injury (Thatcher, Walker, Gerson, & Geisler, 1989) and the later from more severe forms (Haneef, Levin, Frost, & Mizrahi, 2013). Recently Naunheim et al (2010) developed a QEEG algorithm for inference of brain injury for an Emergency Department setting that revealed 90% specificity.

The changes in pattern, localization and amplitude within different frequency bands after a closed head injury are time-dependent. Shortly after the impact there are usually reductions in

power within alpha frequency but increased theta and delta power. Within the alpha range the power within 8 to 10 Hz increases while the faster alpha interval decreases. Some variation of this pattern can be maintained for weeks to months. Thatcher et al (1997) reported that increased frontal and temporal coherence with less temporal difference between the two regions, increased differences in rostral-caudal amplitudes, and reduced posterior power allowed moderately accurate classification of individuals with mild TBI compared to controls. This configuration was relatively stable six months after the injuries.

Classic neuropsychological test batteries often reveal standardized quantitative deficits whose profiles are commensurate with the reported or observed behavioural alterations subsequent to mild TBI. In a series of validation analyses for various test batteries for mild TBI patients Persinger and his colleagues (Tiller, St-Pierre, & Persinger, 2013; Persinger & Richards, 1995; Persinger, 2003) found that amount of z-score discrepancy between standardized scores for a composite of intelligence and memory and the aggregate score for neuropsychological tests was strongly related (phi=0.85) to inferred brain damage. Repeated assessments one year and two years after a mild TBI indicated no significant change in several indices of neuropsychological impairment (Tiller et al., 2013). A non-linear relationship between severity of impairment and scores for the Depression scale from the Minnesota Multiphasic Personality Inventory (Persinger, 1997) the complex partial epileptic-like experiences profile (Persinger, 2000) indicated mild TBI patients displayed the most extreme scores.

Although the general consensus has been that mild TBI is associated with short-term cognitive deficits that resolve within about three months after the injury, the assumption may not be accurate. About 15% of this population develops a post-concussion syndrome that can be incapacitating for years (Walker & Tesco, 2013). Many of these patients report complex partial

epileptic-like experiences but without classic or overt electroencephalographic correlates (Gorham & Persinger, 2012). The convergence of information regarding the results from traditional neuropsychological assessments that require tens of hours to administer and QEEG profiles that require less than an hour to obtain would facilitate cross-validity and potentially alter methods of assessment for patients who despite the "mild" nature of the initial injury cannot adapt to the premorbid vocational or familial demands. We reasoned that discerning the quantitative relations between neuropsychological impairment and measures from the most modern QEEG technology and applications would yield valuable information. We also assumed that if the effects were to clinically useful, the effects should be clearly evident and reliable and internally consistent within a small population of patients.

3.3 Materials and Methods

3.3.1 Subjects

The database was created by extracting QEEG data and neuropsychological data from every patient (n=26) who had undergone full neuropsychological assessments over and approximately three year period (January 2010-April 2013). Their mean age was 40 years (SD=16.3 years). The mean and standard deviations for the delays between the mechanical impacts to the skulls and the assessments were 5.6 and 5.2 years, respectively (range 0.3 to 16 years). All of them had been referred by external agencies subsequent for a full neuropsychological assessment to discern the level of functioning following a closed head injury due to an impact of concussive force or mechanical energies. They all met the criteria of mTBI on the bases of either a GSC of >13 or a suspension of consciousness of less than 20 min. All patients were administered our standard battery of intellectual, memory, academic achievement, classic (Halstead-Reitan

Battery) and novel (e.g. Conditioned Spatial Association Test) neuropsychological, personality, and quantitative electroencephalographic measurements (Gorham & Persinger, 2012). On the bases of the Russell et al (1970) ordinal categories (in parentheses), subjects were assigned to one of three groups: no impairment (0 or 1), mild impairment (2) and moderate to severe impairment (3-5). They were partitions of the original Halstead-Reitan Impairment Index between 0 and 1 such that 0 to 0.1=0, 0.2 to 0.3=1, 0.4 to 0.5=2, 0.6 to 0.7=3, 0.8 to 0.9=4, and 1.0=5. There were 9, 8, and 9 patients in each group respectively.

3.3.2 Procedure

Each assessment required two full days. Testing occurred between 10 hr and 18 hr. The QEEG data were collected in the final hour of the first day and required 45 min. Descriptions of the tests employed have been published elsewhere (Tiller et al., 2013; Persinger & Richards, 1995; Persinger, 1995). During the QEEG the patient sat in a comfortable chair in a dimly lit acoustic chamber. The patient was informed that the QEEG assessment was not the same as an EEG performed by a neurologist and was utilized to help validate the results of the standard psychometric tests. The patient could communicate at any time with the EEG technicians through a microphone and speaker system.

The first phase of the QEEG collection was an eyes-open baseline (10 min). The patient was asked to pick a spot on the wall in front of them and focus on that spot. They were told they could blink as much as needed but to try and remain as still as possible throughout the duration of the testing. The patient was then asked to close the eyes and to relax; the lights were dimmed. After the eyes-closed portion the patient was asked to keep the eyes closed and breathe deeply but very slowly for approximately 45 seconds. After the 45 seconds they told they could relax keeping the eyes closed. After 30 seconds of relaxation they were again asked to deep breathe for

45 seconds at a slightly increased pace and then they were asked to relax. Finally they were asked to breathe deeply a third time again at a slightly increased pace for 45 seconds before relaxing. The patient was then disconnected from the EEG and this concluded day 1 of testing.

Table 1: Clinical EEG Testing Procedure

Clinical EEG Testing Procedure		
1	10 minutes	Eyes-open baseline
2	10 minutes	Eyes-closed baseline
3	45 seconds	Deep breathing (slowest speed with eyes closed)
4	30 seconds	Relax with eyes closed
5	45 seconds	Deep breathing (middle speed with eyes closed)
6	30 seconds	Relax with eyes closed
7	45 seconds	Deep breathing (fastest speed with eyes closed)
8	30 seconds	Relax with eyes closed

3.3.3 Quantitative Electroencephalographic Equipment

Brain activity was measured by a Mitsar-201 portable QEEG system that was connected to a 19-channel electrode cap (Electrode-Cap International) that contained the 10-20 Standard Electrode Placement. Electrode site include Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, T6, O1, and O2 that were linked to the ears (A1 and A2) for monopolar recordings. Impedance of all channels was less than 10 kOhm. Data were acquired using WinEEG v2.84.44 software with a sampling rate of 250 Hz. A 50 Hz to 70 Hz notch filter was used in the WinEEG software for all subjects in order to filter high frequency noise during recording. The EEG record was inspected for movement artifacts; the principal component analyses (PCA) method of artifact correction within WinEEG software was employed where appropriate.

3.3.4 Analysis of QEEG Data

All QEEG data was analyzed using three different methods; spectral power, standardized low resolution brain electromagnetic tomography (s-LORETA), and microstate analysis. Spectral analysis was computed utilizing WINEEG software and further statistical analysis was completed using SPSS software. Spectral analysis was performed on 30 seconds of artifact-free EEG recorded from the 19 channels during periods when the individuals were relaxing with their eyes closed.

3.3.5 Source Localization

Source localization analyses were completed by standardized low-resolution electromagnetic tomography or s-LORETA (Pascual-Marqui, 2002; Pascual-Marqui et al., 2002) the same 30 second sample that was used to compute the spectral power was used for source localization. All 84 regions of interest (ROI), 42 from each hemisphere, for each of the software's defined frequency bands [delta (1.5-4 Hz), theta (4-7.5 Hz), alpha-1 (7.5 to 10 Hz), alpha-2 (10-13 Hz), beta-1 (13-20 Hz), beta-2 (20-25 Hz), beta-3 (25-30 Hz) and gamma (30 to 40 Hz)] were computed. The analysis calculated the activation of a single voxel at ROI centroid. Results were then extracted and exported into SPSS for statistical analysis. Finally, the regions were then summed based on their location (rostral, caudal, or limbic).

3.3.6 Microstate Analysis

Koenig et al (2002) have demonstrated consistent microstates whose durations are approximately 80 to 120 msec. These microstates have been defined as periods of quasi-stable topographical maps of the overall scalp's electric field (Lehmann et al., 2010). This research has revealed that there are four major stable microstates maps that have been determined to account for close to 80% of the variance in voltage fluctuations. It has also been found that these four microstates are consistent across age groups with varying durations and proportions (Koenig et al., 2002). Based on this information it has been hypothesized that these microstates could reflect a type of information processing (Lehmann et al., 2010).

The microstates were computed from 40 seconds of artifact-corrected EEG records taken from the 19 channel EEG during the eyes-closed baseline. The epochs were analyzed using the procedures outlined by Koenig (Koenig et al., 2002) except that all patients were analyzed in one analysis and the data was then individually exported for statistical analysis. The characteristics of the cumulative microstates of all patients were mapped and the durations were then analyzed with respect to impairment index. Additionally, to discern if the *qualitative* configuration of the microstates differed between the patients who displayed no neuropsychological impairment and those that displayed moderate to severe impairment (mild TBI), averaged microstates for both populations were extracted separately.

3.4 Results

3.4.1 Distribution of Neuropsychological Impairment

The Halstead Impairment Index was employed as the reference inference for brain dysfunction or injury. The Impairment Index is derived from seven scores from the battery and ranges from 0 to 1 with intermittent decimals. In this study we divided the ranges according to Russell et al (1970) into increments of no impairment (0,1), mild impairment (2), and moderate-severe impairment (3+) . The proportion of the patients assessed that were included in each of these three groups were 35%, 30%, and 35%, respectively which also reflects the approximate proportion for the last ~800 patients assessed over the last 25 years.

3.4.2 Other Global Indicators

In both clinical practice and following experimental analyses we have found that toe graphaesthesia, which involves activity within the medial prefrontal lobe according toe SPECT analyses (Persinger, Webster, & Tiller, 1998) also reflects general impairment when the medial surface is involved. There was a significant difference in toe graphaesthesia errors as a function of the three groups of Halstead-Reitan defined impairments [$F_{(2,21)}$=5.00, p=.018, eta^2=0.34]. Post hoc analysis indicated that patients with the most severe neuropsychological impairment displayed more toe graphaethesia errors. The groups differences were still present when the data were analyzed by the Kruskal-Wallis test (χ^2=6.74,p =.034). The results are shown in Figure 1.

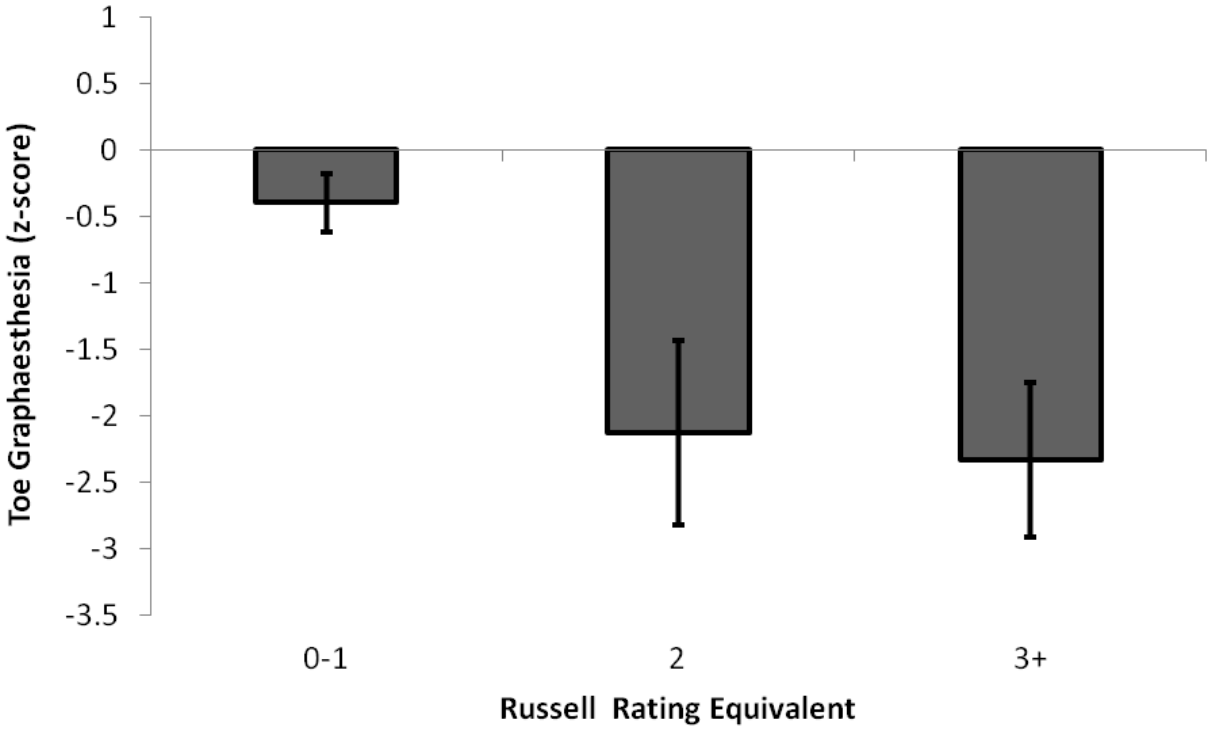

Figure 1. Standardized differences in scores for toe Graphaesthesia for groups with different levels of impairment. Vertical bars indicate SEMs.

3.4.3 Personal and "Electrical Lability" Differences

The results from the 16PF indicated that individuals who displayed mild or greater neuropsychological impairment were intrinsically lower on the liveliness factor (Figure 2) than those who sustained an impact and displayed no neuropsychological impairment [$F_{(2,\ 18)}$=5.71, p=.013, eta^2=0.42].

Only one scale Pt, or psychasthenia, from the 10 clinical scales of the MMPI-168 displayed significant group differences. Individuals with a moderate-severe impairment scored significantly higher on this scale than those with no impairment [$F_{(2,21)}$=5.27, p=.015, eta^2=.36] (Figure 3). This result indicates that those individuals with a moderate-severe impairment have significantly more worry, anxiety, and tension than those with no impairment.

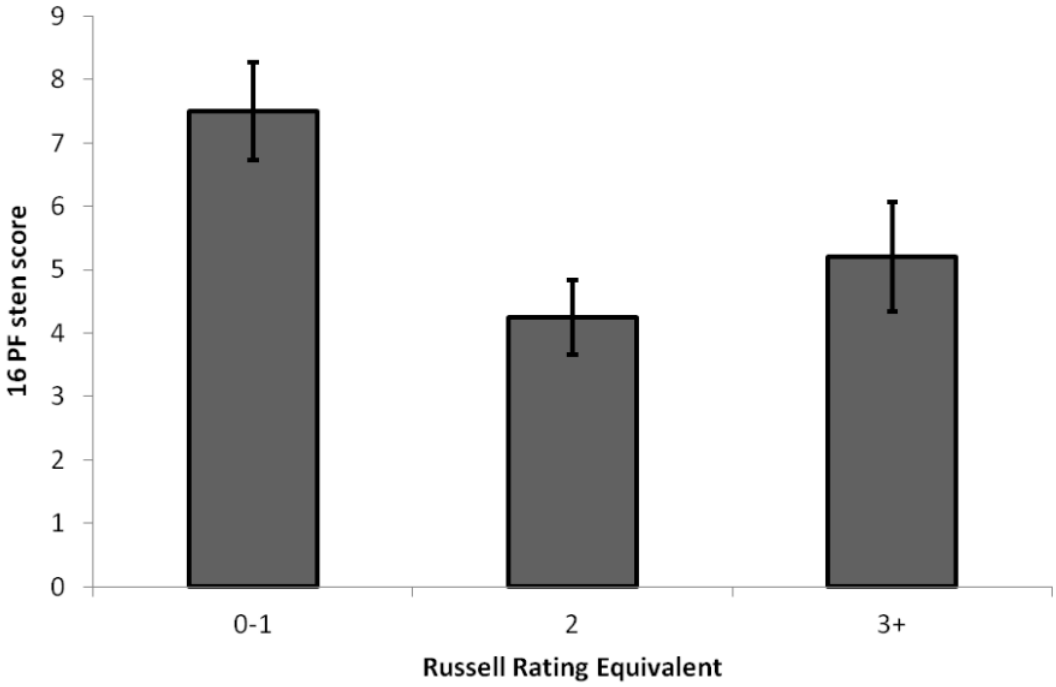

Figure 2. Sten scores for the "lively" factor on the 16PF for groups with different degrees of neuropsychological impairment. Vertical bars indicate SEMs.

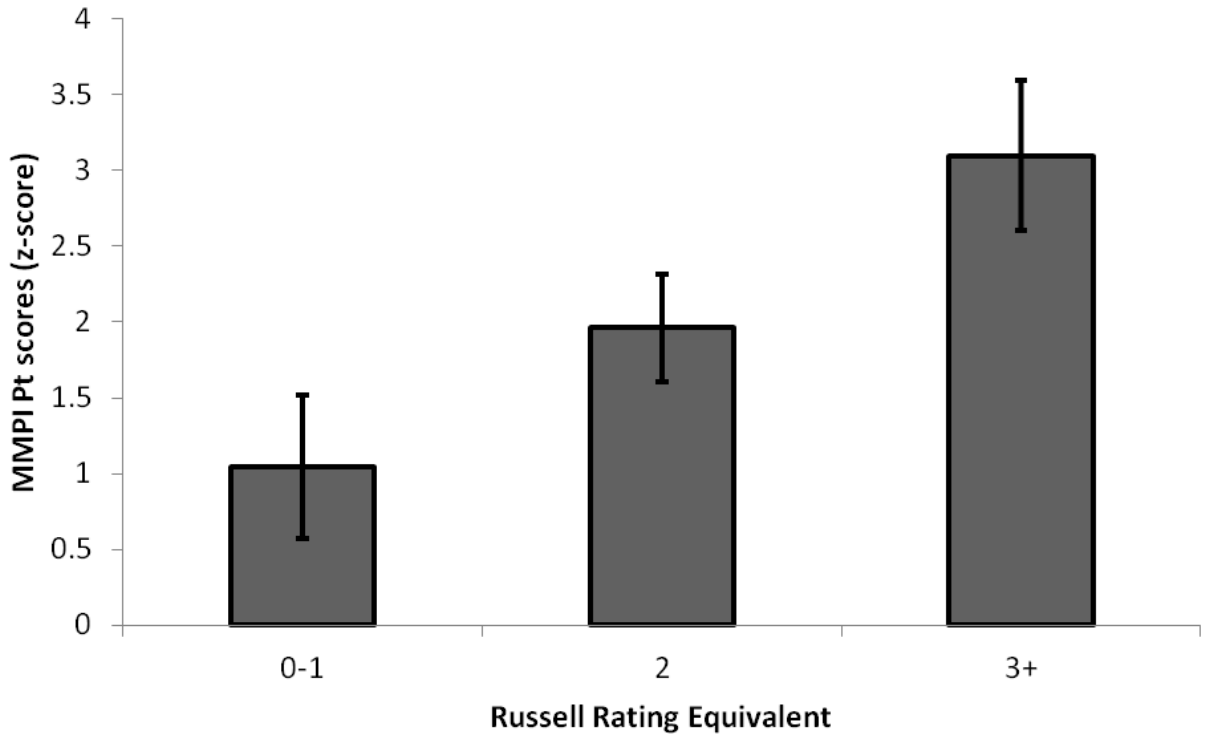

Figure 3. Means and standard error of the mean for the psychasthenia ("ruminative anxiety") scale of the MMPI for patients who displayed different severities of neuropsychological impairment.

The Roberts et al (1994) CPES inventory assesses the temporal incidence partial complex seizure-like symptoms and signs based upon subjective reports. The group who was measured to have moderate-severe impairment reported they experienced significantly elevated scores on this test [$F_{(2,20)}$=3.546, p=.050, eta^2=0.28]. The results are shown in Figure 4. It is interesting to note that even those individuals with no impairment displayed a mean score in the above average (z >1) range for experiencing these symptoms (Gorham & Persinger, 2012).

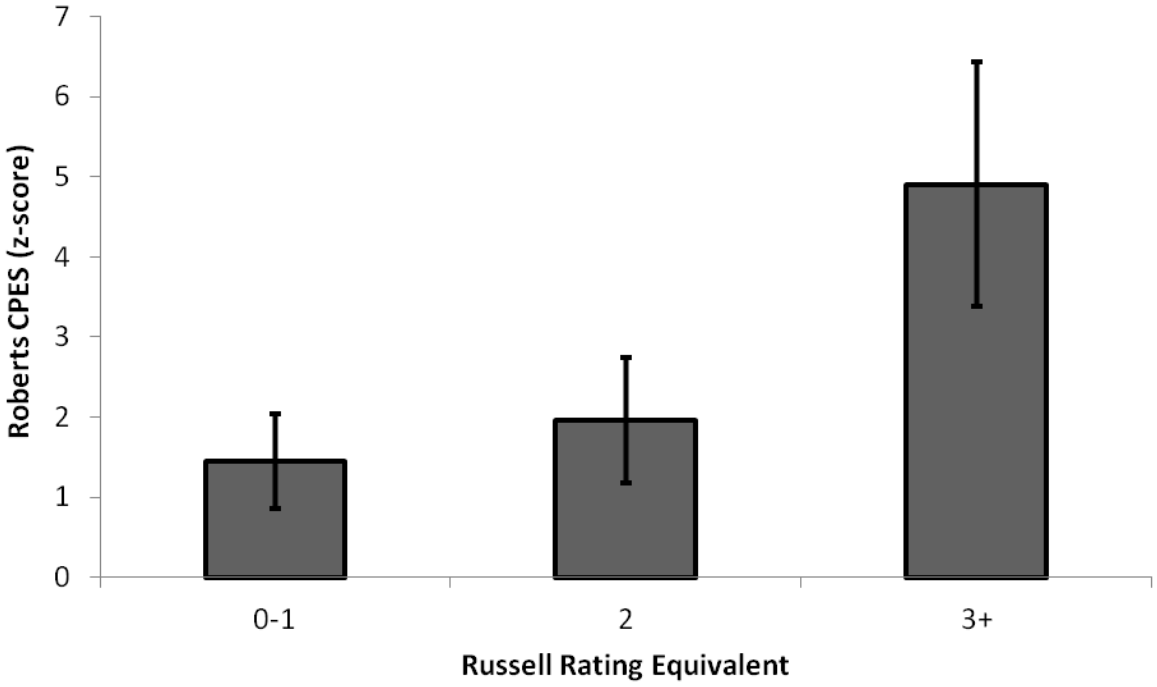

Figure 4. Means and SEMs for the Roberts' Inventory for Complex Partial Epileptic Symptoms for patients whose Impairment rating indicated no, mild, or moderate to severe dysfunction

3.4.4 Spectral Power

Spectral power of QEEG activity was computed for each individual and analyzed as a function of the degree of neuropsychological impairment. In order to determine general trends within the data all the spectral power for each frequency band was summed. Results of these analyses revealed that global alpha power was significantly different between groups [$F_{(2,23)}$=3.69, p=.042, eta^2=0.26]. *Post hoc* analysis shows that the moderate-severe group had significantly less global alpha power than the other groups (Figure 5). A non-parametric Kruskal-Wallis test confirmed the group differences (χ^2=6.47, p< .05).

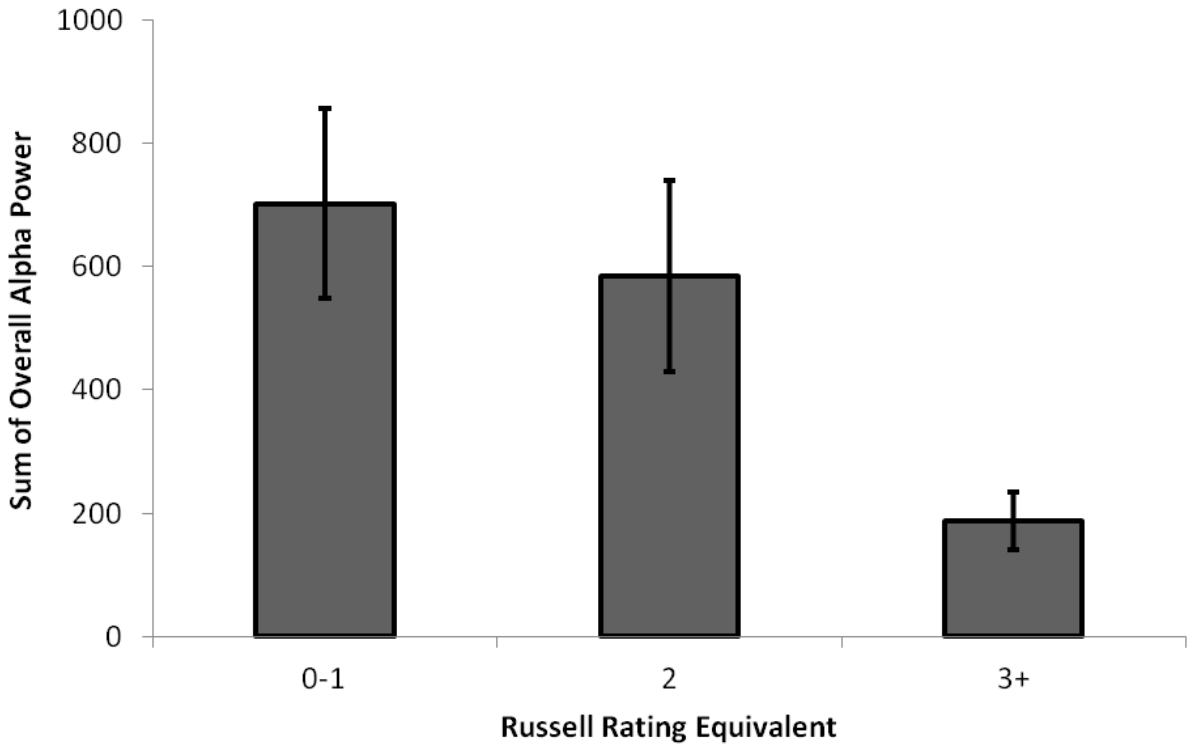

Figure 5. Means and SEMs for the sums of the global alpha power from QEEG measurements as a function of the degrees of neuropsychological impairment

The results of comparing the spectral data with respect to rostral (frontal channels) and caudal (temporal, parietal, occipital regions with central regions excluded) were also revealing. Analyses (Figures 6 and 7) revealed that the sums of the caudal delta [$F_{(2,23)}$=4.46, p=.024, eta^2=0.30] and theta [$F_{(2,23)}$=4.93, p=.018, eta^2=0.32] power were significantly reduced in individuals whose impairment was considered moderate-severe compared to those individuals who had no impairment.

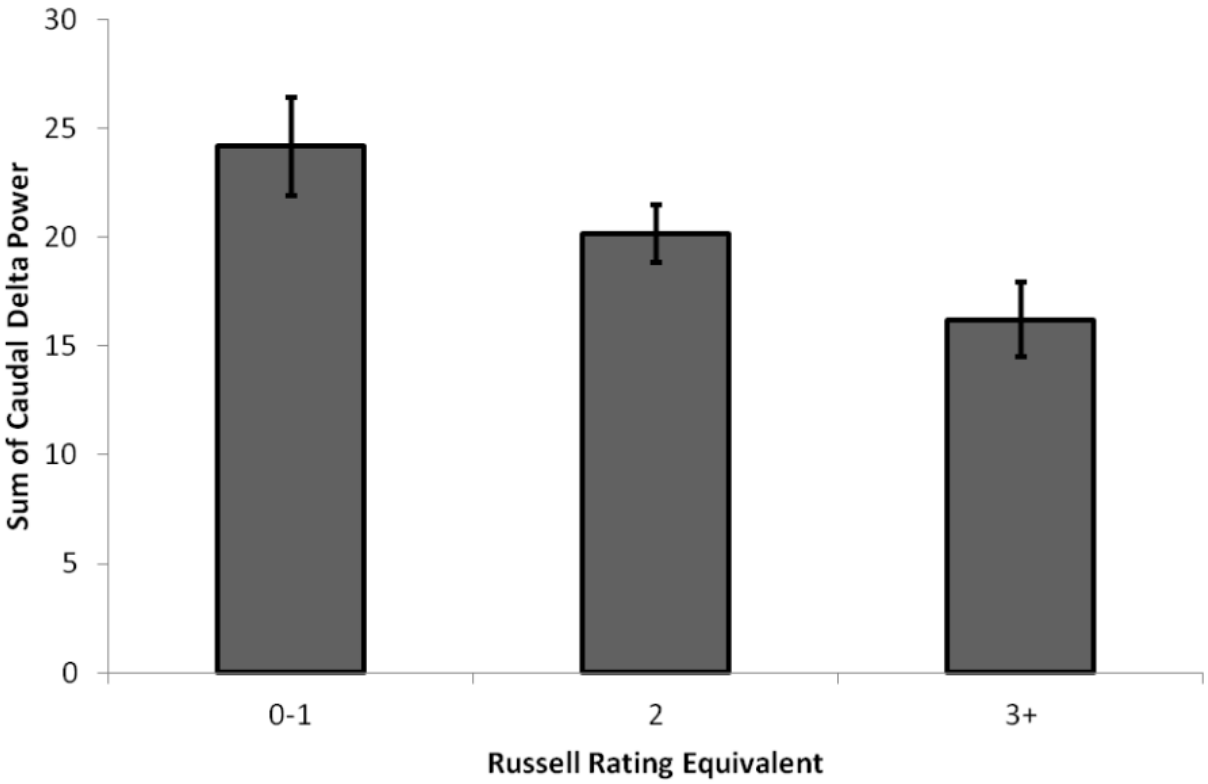

Figure 6. Means and SEMs for the sum power within the caudal cerebral regions as a function of the degree of neuropsychological impairment

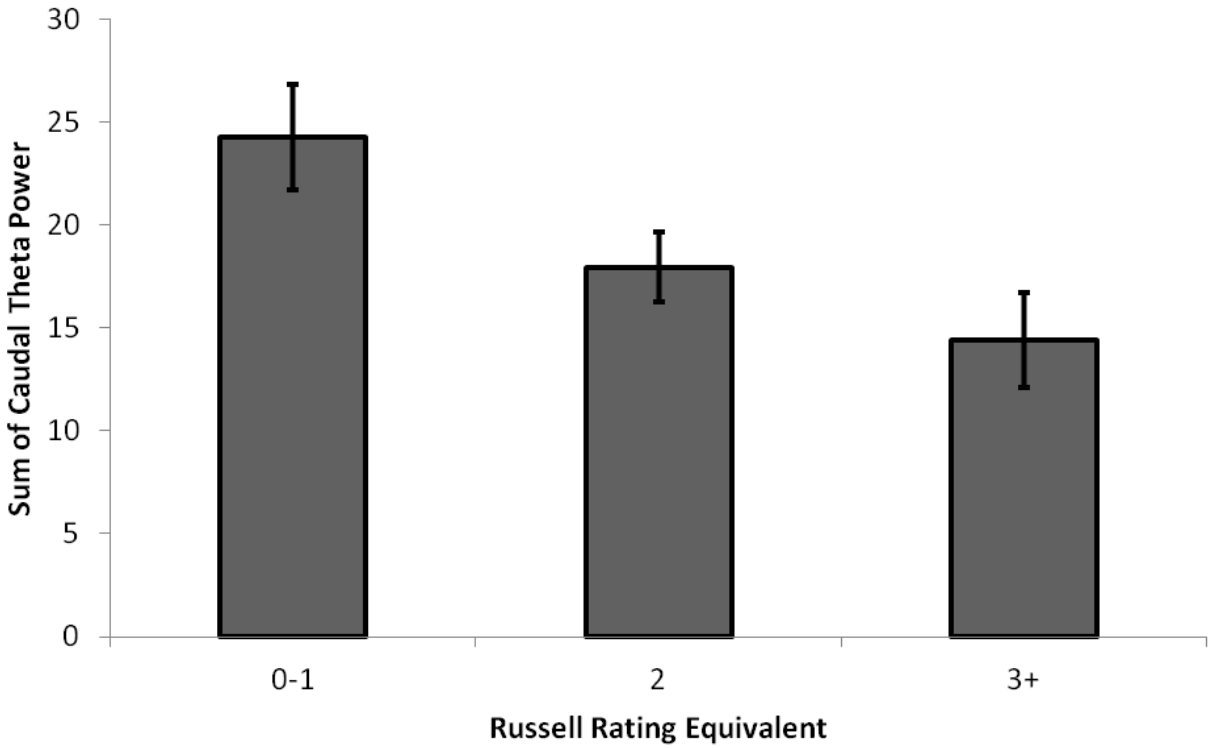

Figure 7. Means and SEMs of the sum of power within the theta band for patients as a function of the degree of neuropsychological impairment

3.4.5 s-LORETA or Source Localization

s-LORETA analyses were completed where regions of interest (Brodmann areas) were selected individually and analyzed for activation. The s-LORETA activation scores were summed based upon three regions (i.e. rostral, caudal, and limbic) regardless of hemisphere. These regions were analyzed with respect to the Halstead Impairment Index.

Analyses of variance revealed that activation in the caudal and limbic regions differed as a function of the level of impairment. *Post hoc* analysis revealed that, for the most part, the group who was assessed to have a moderate-severe neuropsychological impairment showed significantly reduced caudal activation in the theta band compared to the group with no impairment [$F_{(2,23)}$ = 3.901, p=.036, eta^2=0.27] as well as decreased activation in the limbic region (in theta) [$F_{(2,23)}$ = 7.676, p=.003, eta^2=0.42]. There was also decreased caudal and limbic activation in the low alpha band [$F_{(2,23)}$ = 4.631, p=.022, eta^2=0.31; $F_{(2,23)}$ = 6.288, p=.007, eta^2=0.37] as well as decreased gamma activation in the limbic region [$F_{(2,23)}$ = 3.670, p=.043, eta^2=0.26]. Within the limbic and caudal cortical regions the moderate-severe group showed significantly lower activation in the theta band than compared to the other two groups (Figures 8 and 9).

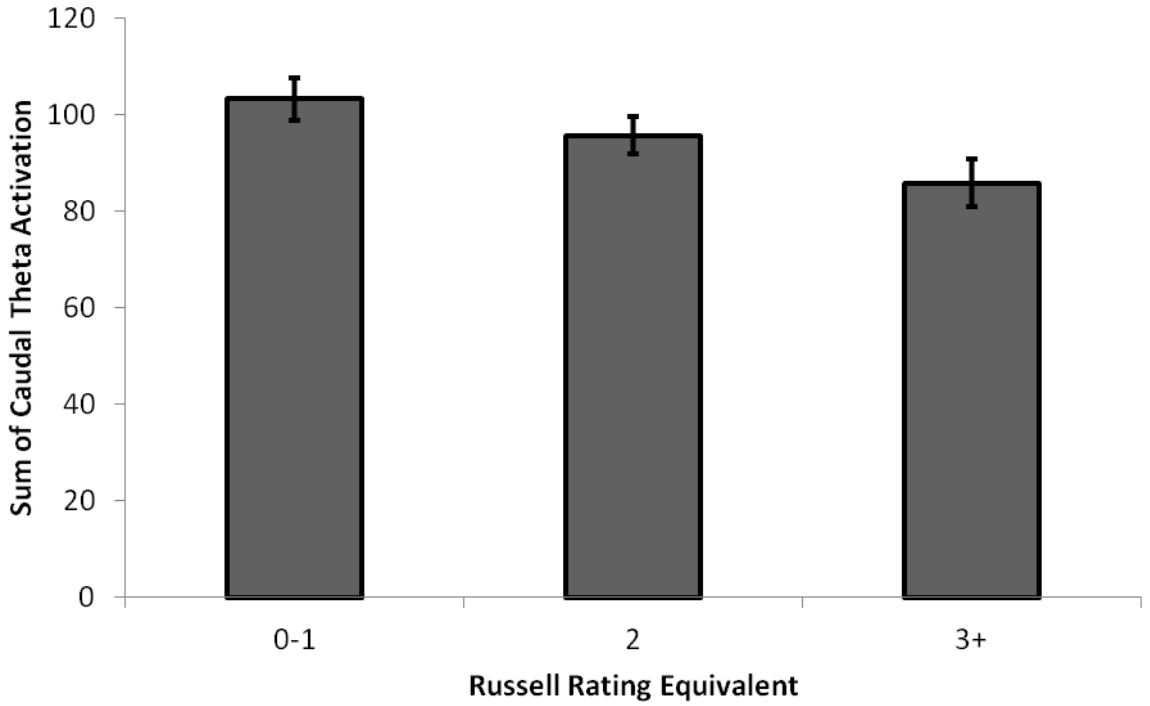

Figure 8. Decreased caudal theta activation for individuals in the moderate-severe impairment group compared to individuals with no impairment

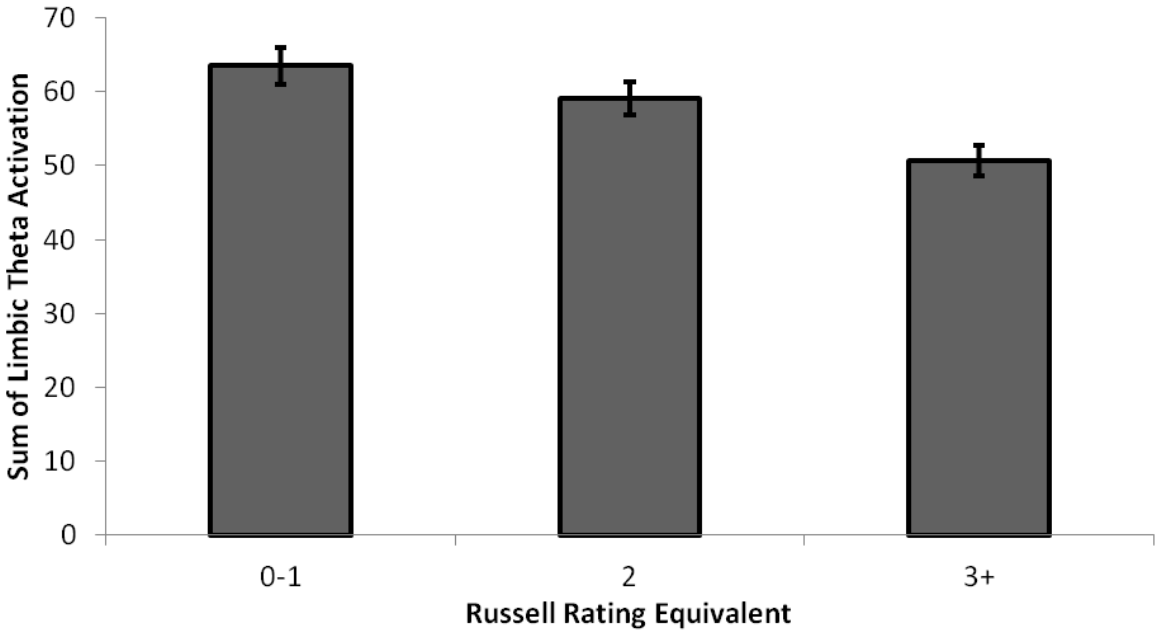

Figure 9. Decreased limbic theta activation for individuals in the moderate-severe impairment group compared to individuals with no impairment and individuals with a mild impairment

3.4.6 Microstate Analysis

Microstate analysis was performed on the entire database of patients producing four microstates that explained 58% of the variance. Although the variance explained was considerably less than that typically reported in the literature (Koenig et al., 2002) the global structure of the four microstates produced from this database were consistent with those previously identified (Figure 10). The red and blue reflect relatively similar magnitudes but of opposite polarities.

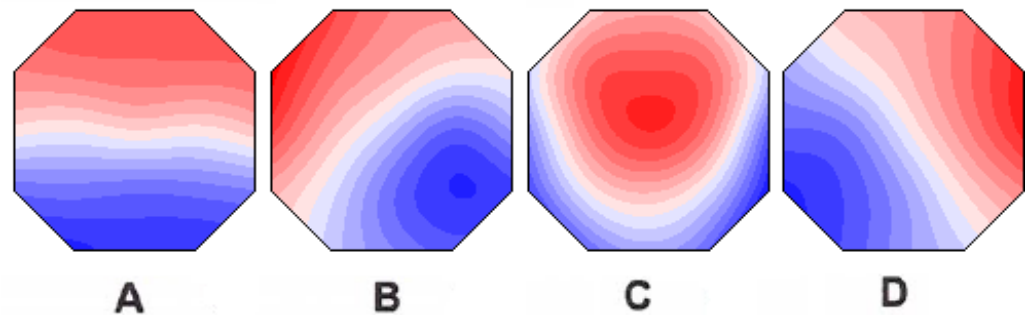

Figure 10. Average patterns for the four microstate maps obtained from the patient's global EEG activity

Results of the analyses of the individual microstates for each patient that were combined indicated a conspicuous relationship with the degree of neuropsychological impairment. The mean durations of the four microstates were negatively correlated with the impairment index (rho=-0.541, $p<.01$; r=-0.573, $p<.01$). This indicated that as the neuropsychological impairment of the individual increased the mean durations of the four microstates decreased (Figure 11).

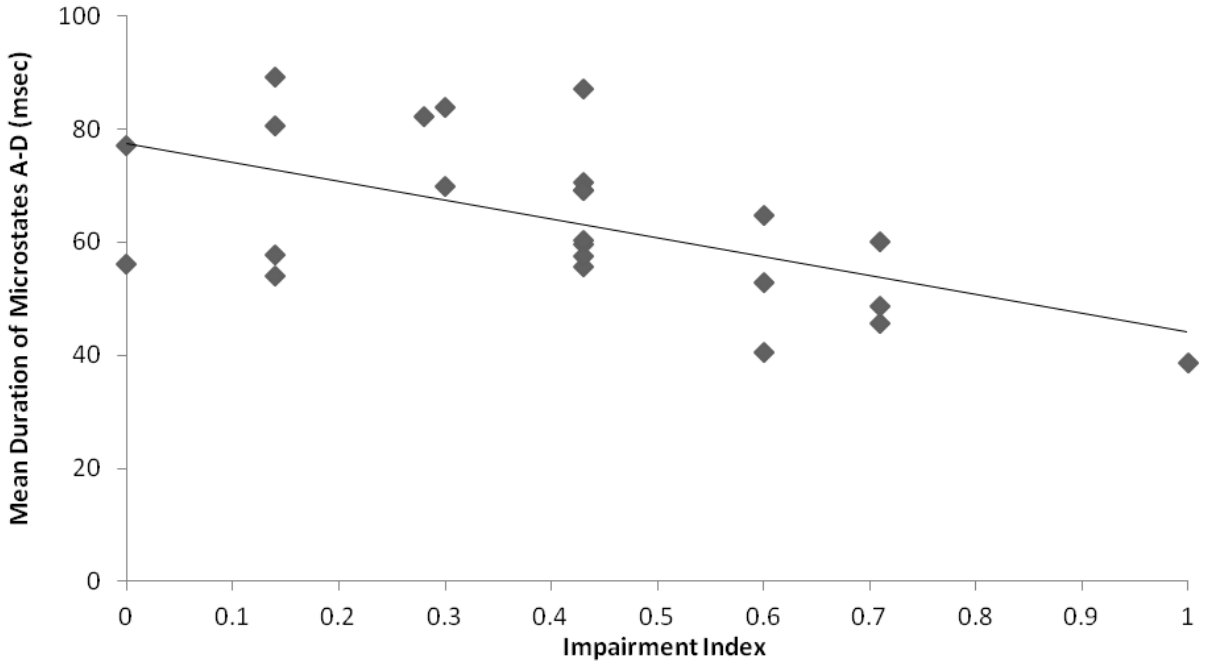

Figure 11. Correlation between the mean microstate durations and the individual's impairment index

Group differences were analyzed for each individual microstate (class A-D). The durations of microstates A (rho=-0.462, p<.05; r=-0.491, p<.05), C (rho=-0.612, p<.05; r=-0.475, p<.05), and D (rho=-0.514, p=.01; r=-0.536, p<.01) were all significantly negatively correlated with the impairment index. Because age positively correlated with the impairment index (rho=.522, p<.01) age was also explored within this analysis. Results revealed that the class B microstate was negatively correlated with age (rho=-.501, p=.01).

Exploration of the literature showed that as healthy individuals age the asymmetrical microstates (classes A and B from Figure 10) decrease in duration while the symmetrical microstates (classes C and D from Figure 10) increase. Although these results were not completely replicated it should be noted that the population being explored has sustained a significant brain injury. Perhaps these results indicate that the pattern of the class B microstate duration is the most stable over time even after sustaining a significant injury.

Finally, global field power peaks significantly differed between groups of impairment for microstates A [$F_{(2,23)}$=4.48, p=.024, eta^2=.30] and D [$F_{(2,23)}$=4.18, p=.029, eta^2=.29]. Post-hoc analyses indicated that patients who displayed moderate-severe impairment displayed greater power than those with no impairments or mild impairments. The results are shown in Figure 12.

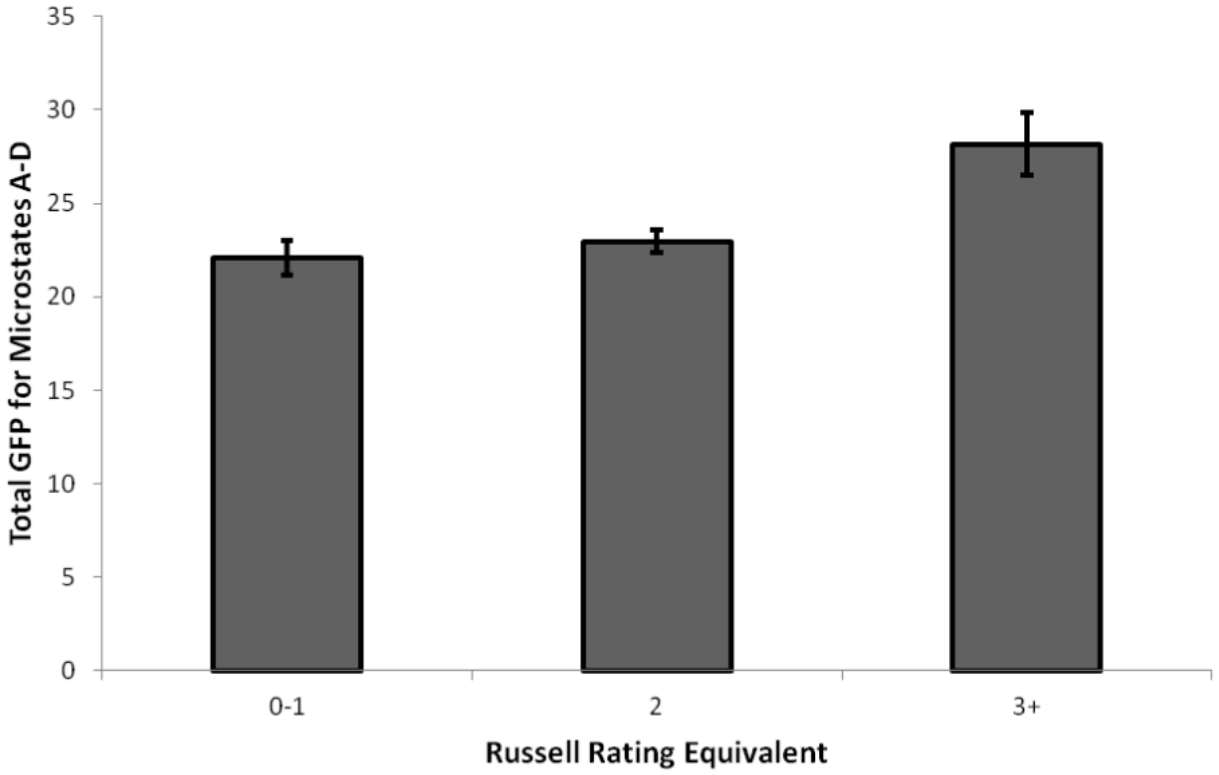

Figure 12. Total GFP for microstates A through D as a function of the different groups of neuropsychological impairments

3.4.7 Qualitative Differences in Microstate Configurations for Impaired and Non Impaired Groups

In order to discern potential persistent differences in microstate configurations as well as the source locations for the configurations, microstates were computed for the patients who displayed no impairment compared to the group who displayed moderate to severe neuropsychological impairment. The four microstates displayed for each group are shown in Figures 13 and 14. The configurations for the non-impaired group were similar to normal individuals. Three of the four configurations for the impaired group were similar. However their microstate C displayed the source of the opposite polarity within the same (right) hemisphere.

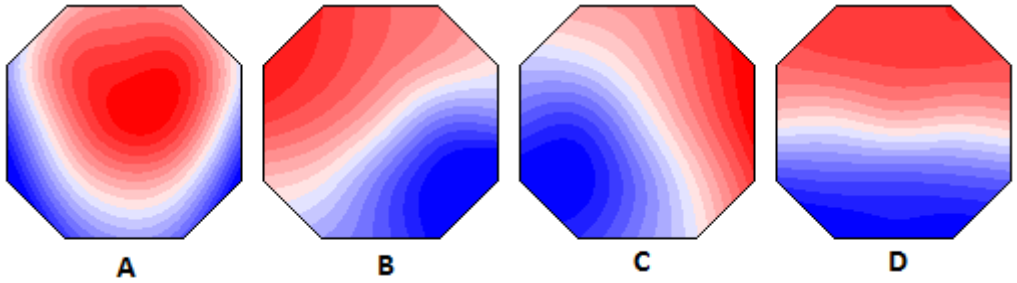

Figure 13. Microstate classes calculated for the group of individuals who were determined to have no impairment. The calculated microstates explained 60.8% of the variance

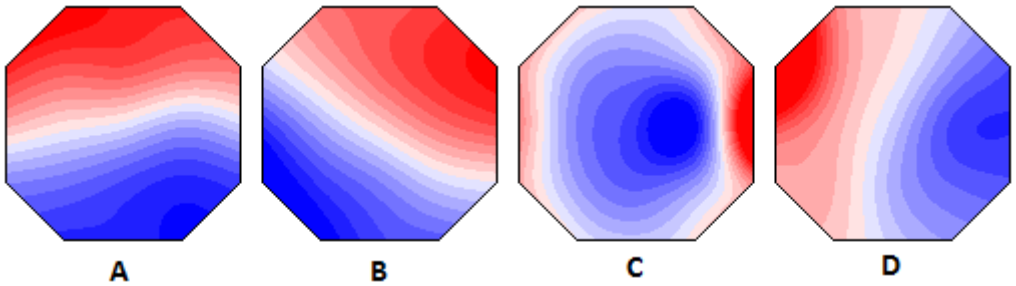

Figure 14. Microstate classes calculated for the group of individuals who were determined to have a moderate to severe impairment. The calculated microstates explained 52.1% of the variance

3.4.8 Relationships between Global Power for Each Microstate and Source Localization Activation

GFP or average global peak power can be considered a measure of the stability of the microstate. The primary sources of the correlations between each of the four microstates for the patients who displayed no neuropsychological impairment and for each of the four microstates for patients who displayed impairments consistent with mTBI are shown in Figures 15-22, respectively. In order to simplify and organize the large numbers of ROIs involved the data were grouped according to region. The solid rectangles indicate significant negative correlations with the average global field power (GFP) peaks while dotted rectangles indicate positive correlations with average GFP peaks. The colors represent the frequency band, which were: green (delta), red (theta), blue (alpha), beta (grey) and gamma (black).

One parsimonious interpretation of the relationship between activation within the source localization (clusters of ROIs) and GFP is the following. For negative correlations, an increase in the stability of the peak power of the microstate is associated with decrease activation of s-LORETA. Functionally this is similar to a diminished variability of standard deviation of scores for power across the different correlated ROIs. On the other hand positive correlations between GFP peaks and source localization indicates that as the activation scores increase ("variability" increases) the stability of the peak power of that specific microstate decreases.

For the group who displayed no formal neuropsychological impairment the stability of microstate A was related to less activation in the limbic and caudal regions within both hemispheres. For microstates B, only the left limbic region contributed in this manner. The classic microstate C, which relates the right prefrontal coherence with the left caudal region,

exhibited the typical rich association between less activation within the delta, theta, alpha and gamma bands within the left temporoparietal region and for all but theta activity in the left limbic structures. All other areas also contributed. On the other hand increased activation contributed to the GFP stability for microstate D.

The most conspicuous pattern for the group who displayed moderate to severe neuropsychological impairments typical of mild TBI was the relative absence of strong correlations between the clustered areas of interest and GFP stability. Except for the negative correlation between theta and gamma activity and the stability of microstate A within the rostral and caudal regions of the right hemisphere and the higher frequencies in the caudal regions of the left hemisphere there were no consistent associations.

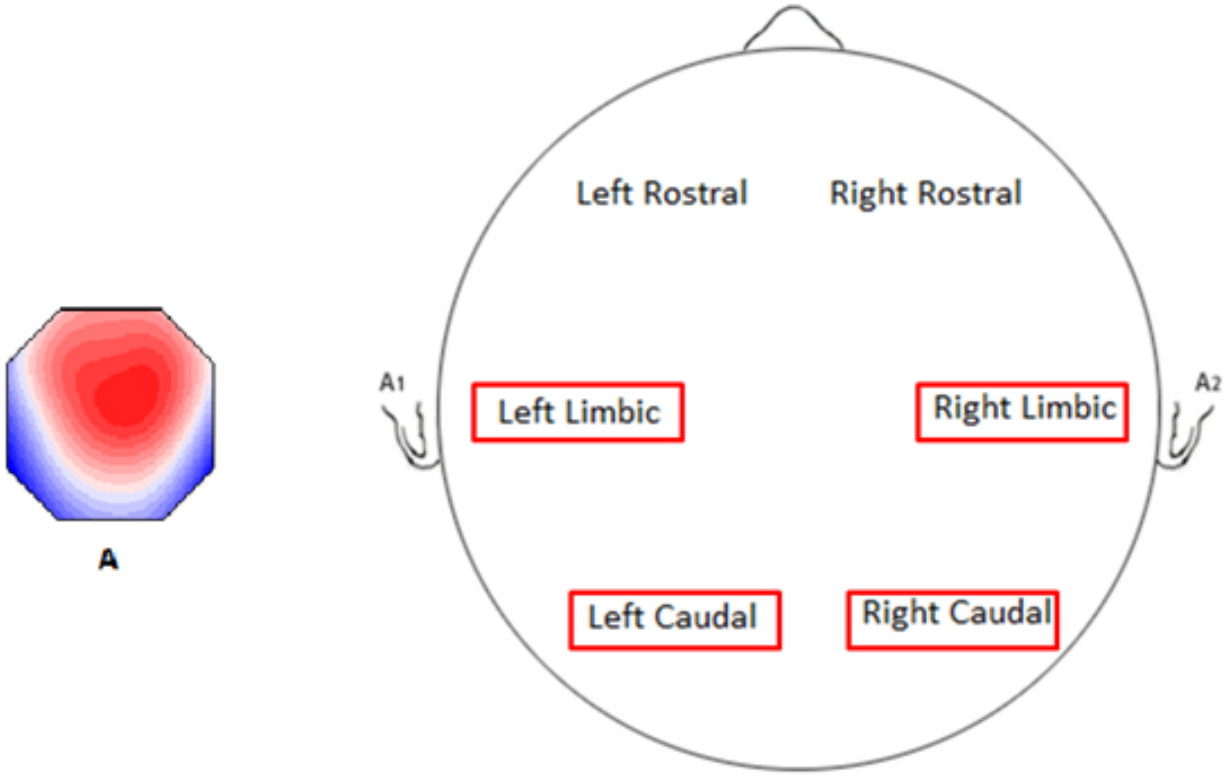

Figure 15. Average global field power (GFP) peaks for individual's with no impairment for microstate A are negatively (solid line) correlated with source localization theta (red) activation in the left and right limbic regions and left and right caudal regions

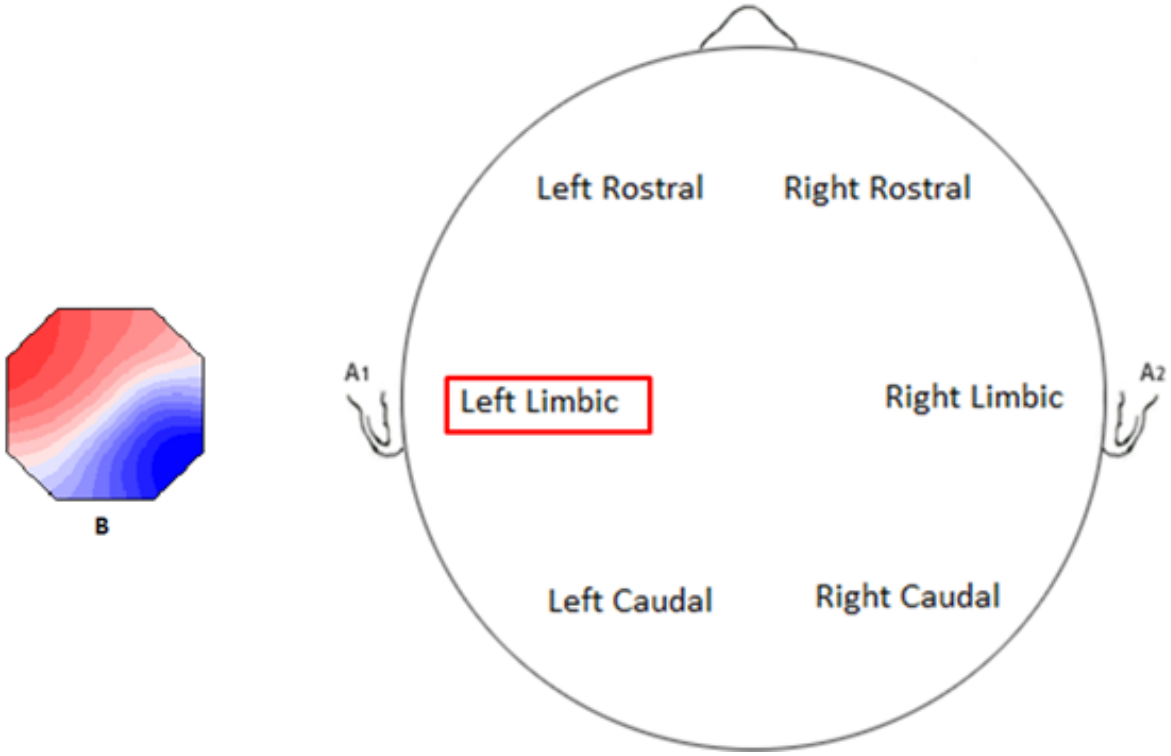

Figure 16. Average global field power (GFP) peaks for individual's with no impairment for microstate B are negatively (solid line) correlated with source localization theta (red) activation in the left limbic region

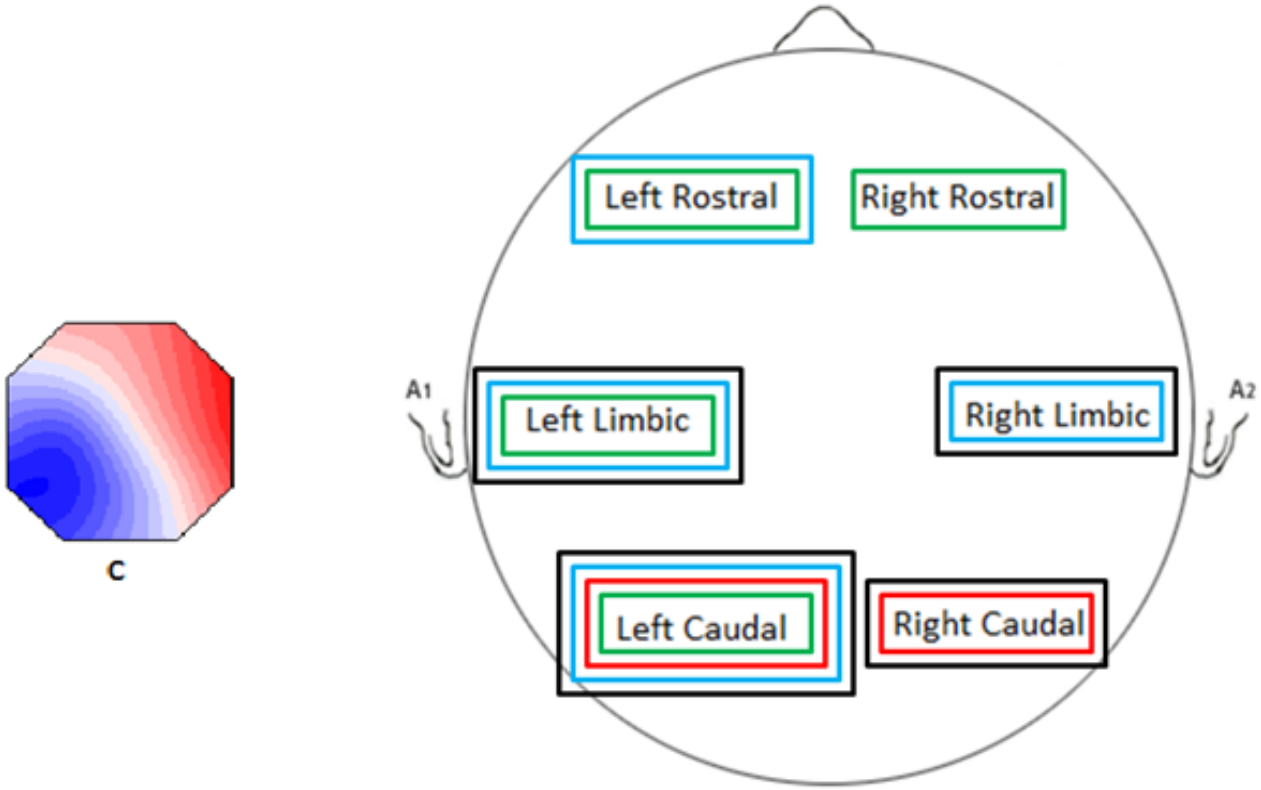

Figure 17. Average global field power (GFP) peaks for individual's with no impairment for microstate C are negatively (solid line) correlated with source localization delta (green) activation in the left and right rostral region, left limbic region, and left caudal region; theta (red) activation in the left and right caudal regions; alpha (blue) activation in the left rostral region, left and right limbic regions, and left caudal region; gamma (black) activation in the left and right limbic regions and left and right caudal regions

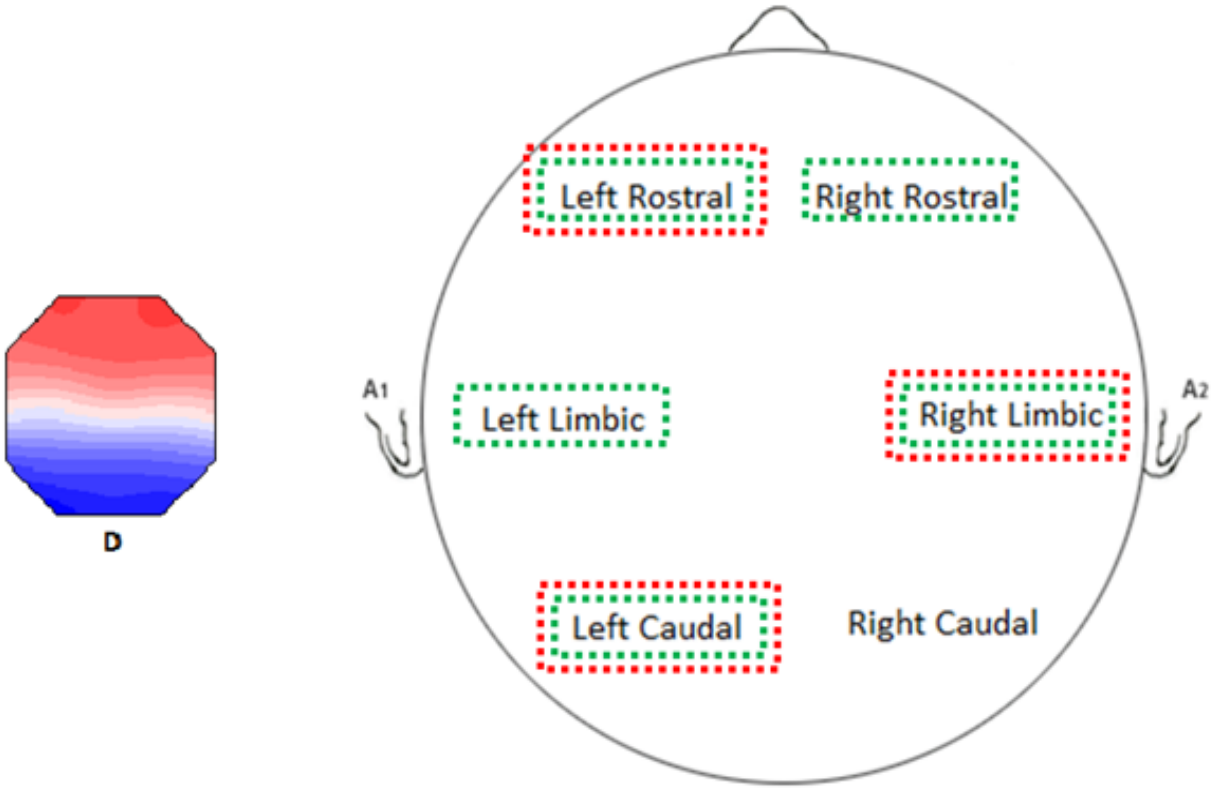

Figure 18. Average global field power (GFP) peaks for individual's with no impairment for microstate D are positively (dotted line) correlated with source localization delta (green) activation in the left and right rostral region, right and left limbic regions, and left caudal region; theta (red) activation in the left rostral region, right limbic region, and left caudal region

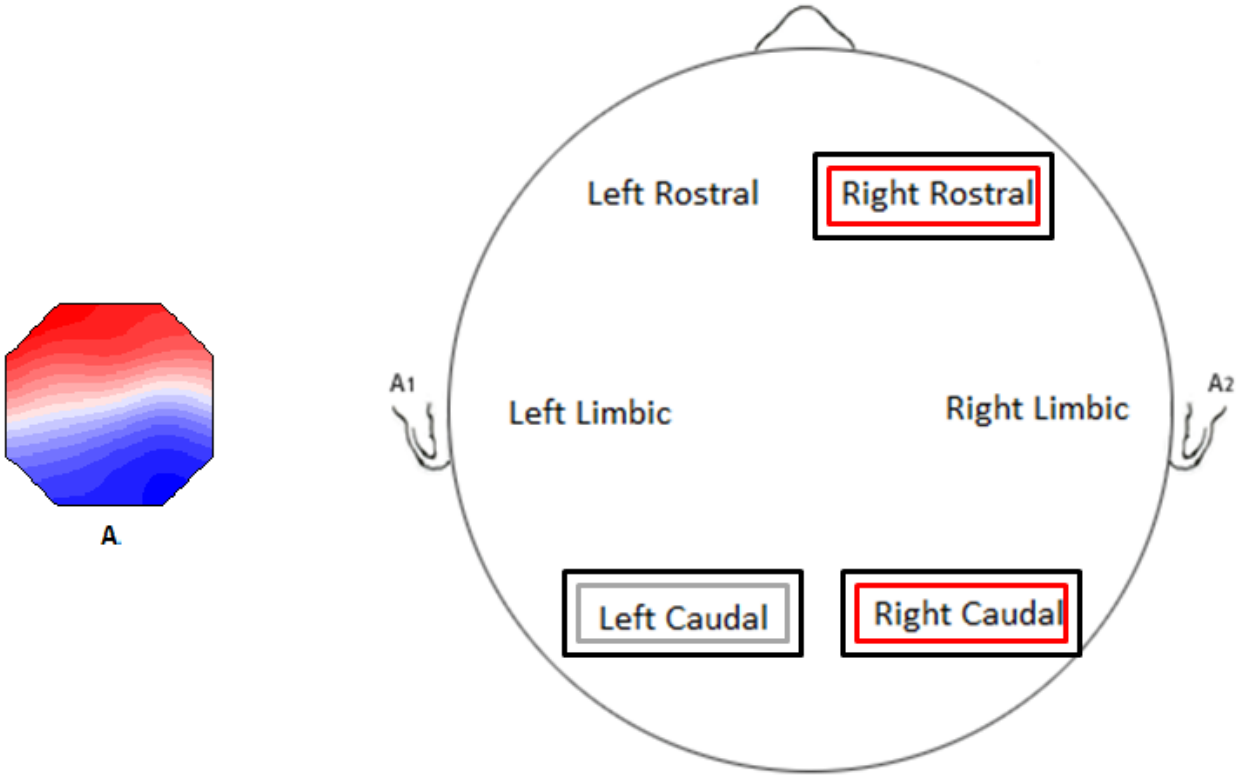

Figure 19. Average global field power (GFP) peaks for individual's with a moderate to severe impairment for microstate A are negatively (solid line) correlated with source localization theta (red) activation in the right rostral region and right caudal; beta (gray) activation in the left caudal region; gamma (black) activation in the right rostral region and left and right caudal region

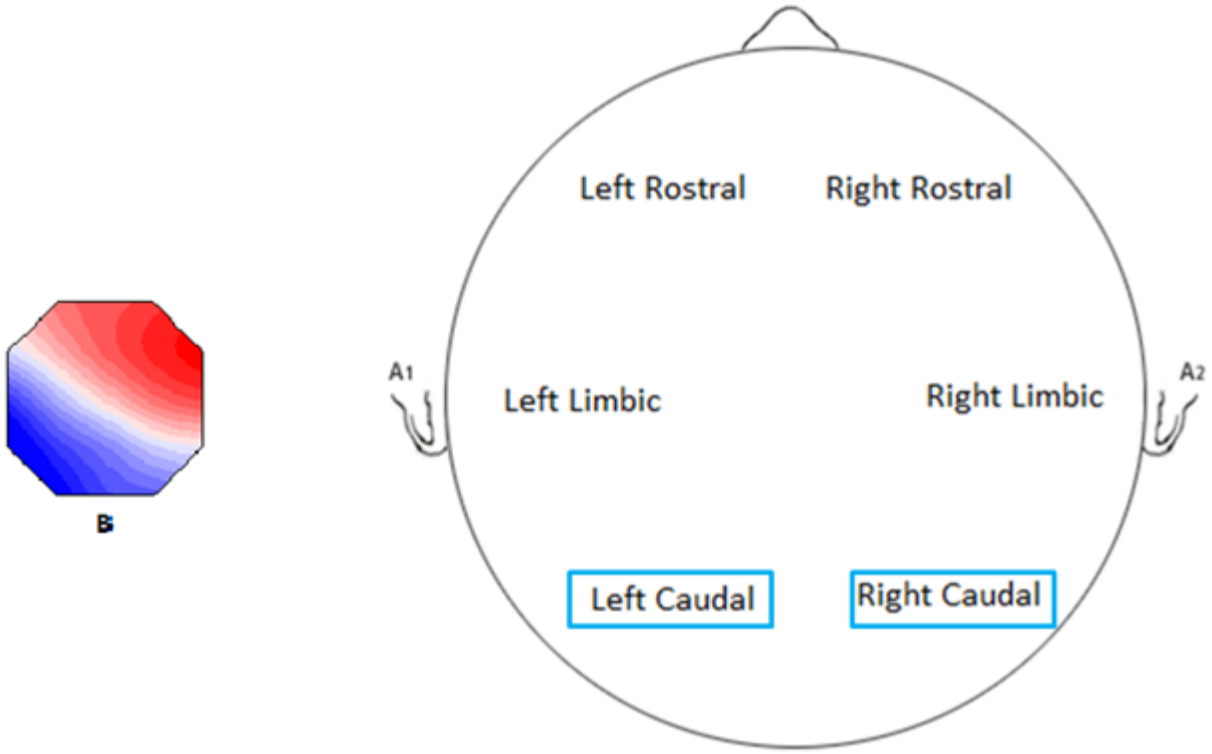

Figure 20. Average global field power (GFP) peaks for individual's with a moderate to severe impairment for microstate B are negatively (solid line) correlated with source localization alpha (blue) activation in the left and right caudal regions

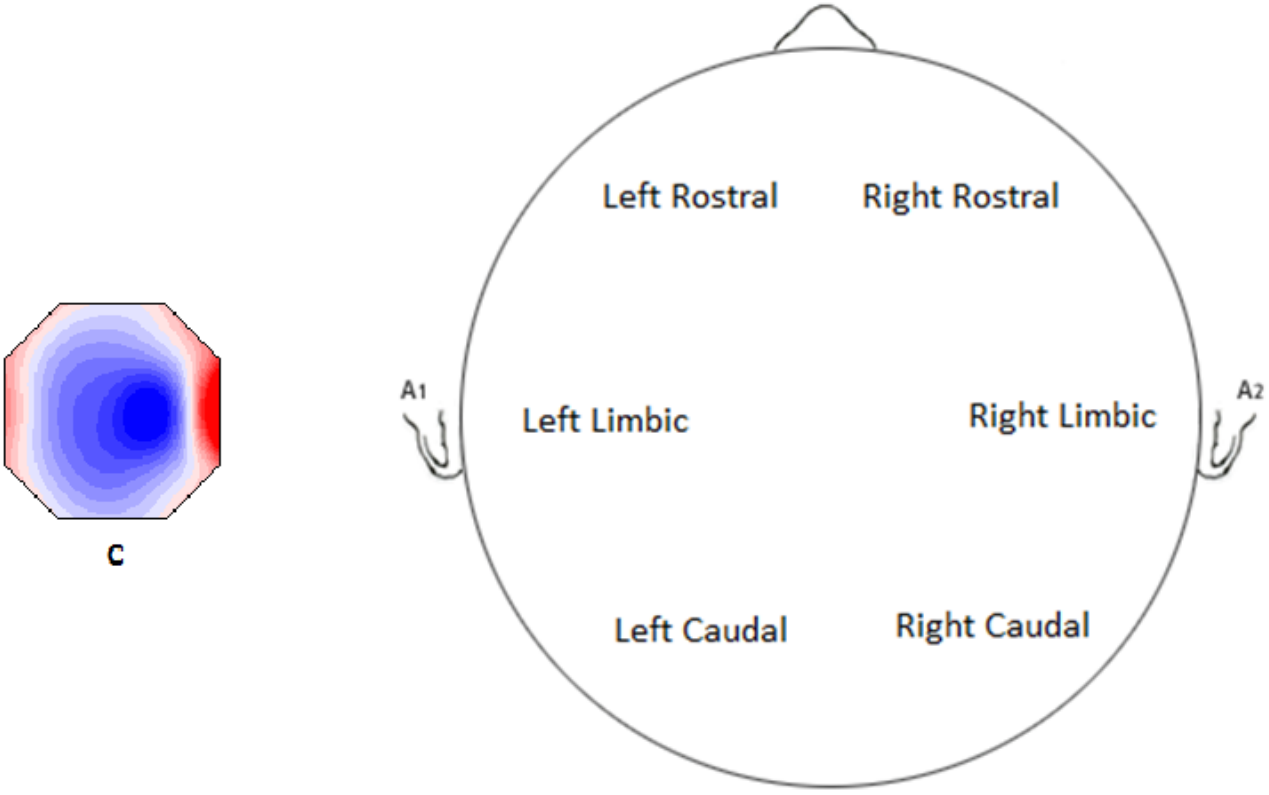

Figure 21. Average global field power (GFP) peaks for individual's with a moderate to severe impairment for microstate C is not significantly correlated with any of the computed regions

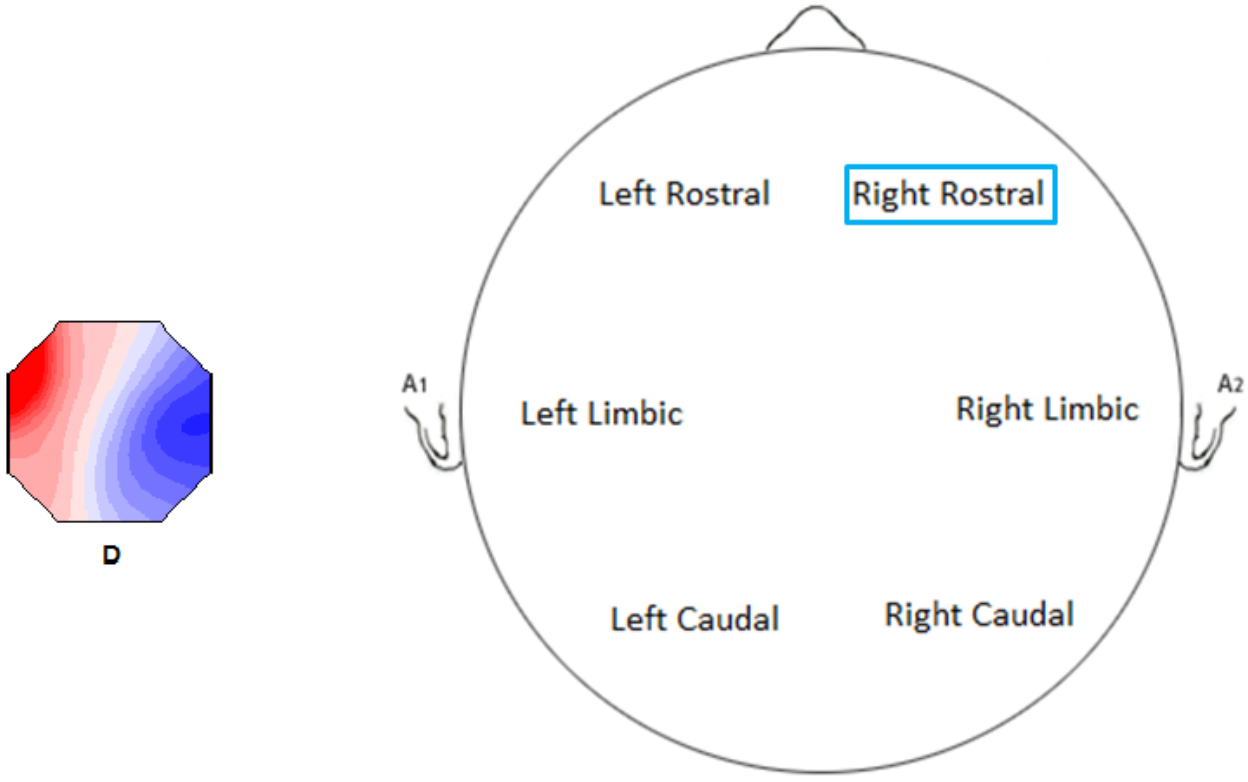

Figure 22. Average global field power (GFP) peaks for individual's with a moderate to severe impairment for microstate D is significantly negatively (solid line) correlated with the alpha (blue) activation in the right rostral region

3.4.9 Delay Since the Injury and Source Localization

The time between the mechanical impact and the neuropsychological assessment was not significantly correlated with the Halstead-Reitan Impairment Index; there was also no significant difference between the three groups for the latencies. However the duration of time that had elapsed between the incidents and the QEEG measurements was revealing. As the time since the injury increased the source localizations for higher beta activity within the *left* temporal region (rho=-0.56, p <.01) and insular (rho=-0.45, p <.01) decreased. A similar inverse relationship was note in the left temporal lobe for beta-3 band.

3.5 Discussion

Although many patients who sustained mTBIs do not appear to display long term dysfunctions or difficulties adapting, the scientific literature and clinical experience indicate there is a substantial subset of the population who do not easily adapt to the post-injury environment and exhibit the post-concussion syndrome or its many variants. Accurate and valid diagnosis of these patients is clearly important. However what may be equally relevant is discerning the source localization and cerebral dynamic processes that may be contributing to their disability. More than one locus within the cerebral volume that exhibit mild dysfunctions and display the capacity to interact and transiently enhance each others' anomalies, like the summation and cancellation of multiple wave systems, could contribute to the often phasic incapacitation of patients for decades. Accurate isolation could be instrumental for designing treatments to at least partially compensate for the deficits. This study was designed to explore the utility of modern QEEG applications, particularly s-LORETA and microstates, to address these challenges.

We reasoned that to be clinically useful and practical, any patterns should be discernable within a small sample of patients as long as they exhibited the characteristics of the more general population. The empirical measurements from the patients assessed in this study were the first 26 to whom we have extracted QEEG data of sufficient quality to apply to the various algorithms that define spectral, s-LORETA, and microstates. They were representative of the approximately 800 patients we have assessed thoroughly over the last 25 years without the benefit of QEEG technology. For example, the proportion of no impairment, mild, and moderate to severe impairment were comparable. The primary differentiating psychometric indicators between levels of impairment, such as toe Graphaesthesia (Persinger, 1995), the personality factor: liveliness (Varney, Hines, Bailey, & Roberts, 1992), the MMPI scale for ruminative anxiety (Persinger, 1997) and the elevated complex partial epileptic-like signs scores (Persinger, 2000; Gorham & Persinger, 2012) were similar to what has been measured in our previous assessment of the major population.

The general patterns that emerged from the present study were very clear and relevant to mTBI. First, for almost all measures the classic EEG indicators (such as the sum of power within the alpha frequency band) the patients within the group who displayed moderate to severe neuropsychological impairment (which constitutes the majority of patients who overlap with the mild TBI diagnosis in our experience) differed from the group of patients who displayed no neuropsychological impairment. The mildly neuropsychologically impaired group occupied an intermediate level or did not differ significantly from the no impairment group.

Like many other groups who have employed electroencephalographic measurements as collateral or correlative data for validating and facilitating interpretation of standardized scores from formal psychometric tests and neuropsychological test batteries, we have observed the

conspicuous rostral-caudal division in coherence of similar activity. This was evident even in the days of strip-chart recordings (Niedermeyer & Lopes da Silva, 1987) and is now quantitatively clear with QEEG. However unlike other approaches which show changes within frontal cortical parameters (Nuwer et al., 2005), we found the major differentiating indicators (power, i.e., $\mu V^2 \cdot Hz^{-1}$) for sustained neuropsychological impairment years after the injury was lower frequency (delta and theta) power within the caudal hemisphere. Clustered frontal indicators did not differ between the impairment groups. This difference could suggest that the more immediate sequealae to mTBI are frontal disruptions involving organization of stimuli and behaviour while residual effects years later involve the (caudal) regions involved with sensory and perceptual organization and processing.

The results from the two newer technologies we applied in this study were quite revealing. The s-LORETA activation scores or theta activity within the caudal regions and the limbic areas was significantly less in the neuropsychologically impaired group compared to the patients whose assessments did not indicate impairment approximately six years after the TBI. The specificity of this frequency band is relevant because theta activity is well known to be associated with the proficiency and efficiency of memory (Lisman & Idiart, 2009; Ahmed & Mehta, 2009). "Memory", particularly for new information acquired since the injury, is one of the major complaints of these patients. Even at the most fundamental cellular level at which the variety of different durations of long-term potentiation (LTP) operates, the theta frequency range is critical for optimal consolidation of new experiences (Adams & Sweatt, 2002).

Perhaps the most useful tool for ascertaining the global and dynamic frequency-dependent differences in patients who display maintained neuropsychological impairment compared to those who do not was the microstates analyses. This technology may be one of the most

comprehensive global vector measures we have available. Wackermann (1999) has extracted single indicators to represent global activity, much like a single fractal number can be employed to describe a very complex and irregular geometric shape, that include three states: Sigma: a measure of global field strength in μV, Phi: a measure of global frequency of field changes in Hz, and Omega: a measure of spatial complexity (dimensionless). As superbly demonstrated by Koenig et al (2002) four microstates, that accommodate about 70% of the variance in QEEG activity as transient episodes of coherence over relatively large cerebral areas, are remarkably stable over people's life times. Their average durations, which range from 80 to 120 ms, or on average would reflect the classical power peak of the cerebral output (10 Hz), are within the range of the percept. Assuming 4 fundamental states and an average of 100 ms per state there would be 4^{10} combinations or about 1 million (1 MHz) variations per s. As suggested by Lehmann et al (2010) these microstates could be the "building blocks", analogous to the base nucleotides for DNA sequences, for consciousness and information processing.

In the present study the microstates were representative of the general population. The group that displayed the most severe neuropsychological impairment exhibited significantly shorter average durations of microstates compared to the patients who did not display impairment. The approximate diminishment of duration for the impaired group was about 10 to 20 ms per microstate which is within the range of the phase shift duration and recursive rostral-to-caudal cerebral fields associated with consciousness (Llinas & de Pare, 1991). Decreased durations of microstates have been reported for populations of patients exhibiting dementia (Strik et al., 1997) and within groups of schizophrenics (Lehmann et al., 2005). Enhanced dementia-like symptoms and schizotypal behaviours, often indirectly reflected in increased incidence of complex partial epileptic-like syndromes, are common correlates of patients who display protracted difficulties

subsequent to closed head injuries and mTBI (Gorham & Persinger, 2012). The latter "schizotypal" symptoms include persistent sensed presences, sudden shifts in states of consciousness, and experiences of mystical states; they also have more direct neuroscientific explanations (St-Pierre & Persinger, 2006).

The results from the calculation of microstates for the non-impaired and most neuropsychologically impaired groups were both confirming and revealing. The spatial configurations of the non-impaired patients displayed the classic four shapes that are reported for normal individuals including our non-patient population. The configurations for the group displaying neuropsychological impairments were anomalous, particularly one state that showed both polarities in the same hemisphere. We have seen such peculiarities in a single exceptional case where a right parietotemporal anomaly, likely from early childhood, was sufficient to be discerned as perfusion (SPECT) uptake anomalies as well (Roll, Persinger, Webster, Tiller, & Cook, 2002). The remarkable diminishment of correlations between the source location activation scores and the global power measurements for the impaired group in this study, if interpreted simplistically, would suggest these patients are impaired because of a dissociation or disconnection between coherence localization activity and the integration of microstates with which both consciousness, the sense of now, and information processing are associated.

From our approach the most effective treatments of mTBI must accommodate the physical, physicochemical, and electromagnetic substrates to the symptoms. There are a myriad of mechanisms that have been individually pursued. They include accumulations of amyloid precursor protein, amyloid-beta peptide, neurofibrillary tangles and hyperphosporhylated tau (a microtubule associated protein), an enhanced disequilibrium of intracellular calcium (Walker &

Tesco, 2013) as well as multiple biomarkers that include S100B calcium-binding proteins, neuron-specific enolase, and activated calpain/caspase (Jeter, Hergenroeder, Hylin, Redel, Moore, & Pramod, 2013). Neurofibrillary tangles and amyloid-beta pathology occur in approximately one-third of patients who sustained a single TBI 1 to 47 years later (Breunig, Guilot-Sestier, & Town, 2013). However the primarily histopathological correlate of mTBI in rodents that would not be easily discernable with the contemporary resolution of MRI are the scattered distributions of conspicuous shrunken, darkly stained neuronal soma that appear below the impact site of the mechanical force (Lado & Persinger, 2008). These cells remain there for months after the injury (rather than fragmenting) and are correlated with the severity of structure-specific behaviours (Lado & Persinger, 2012). The numbers of these dark stained neuronal somas below the impact site and at countercoup areas can be reduced by continuous post-impact exposure to weak, physiologically-patterned magnetic fields that contain components known to enhance long-term potentiation (Cheung, Lado, Martin, St-Pierre, & Persinger, 2010).

Employment of quantitative EEG measurements and extended algorithms to discern if patients reporting difficulties following mTBI are displaying neurocerebral anomalies in addition to those inferred from full neuropsychological assessments could be very useful for designing individual-based treatments. Although pharmacological approaches can be useful, they are often diffuse and not localized. Recent technology that employs computer-generated signals and engineering strategies to apply regional, physiologically-patterned, weak magnetic fields might be one solution to help these patients with apparently intractable dysfunctions to partially adapt (Baker-Price & Persinger, 2003). Very weak magnetic fields rotating around the skull with specific rates of change in angular velocity produce marked enhancements of gamma activity over the frontal and occipital regions when the average field velocity is ~4 to 5 $m \cdot s^{-1}$ or about 7 to 8 Hz. This

resonant frequency is also the solution (Tsang, Koren, & Persinger, 2004) based upon cortical grey matter inductance (permeability and capacitance (permittivity). In animal studies we have found that brief, daily application of a patterned magnetic field to rats with brain injury resulted in persistent normalization of their behaviours (Martin, Koren, & Persinger, 2004). One recent animal study (Arendash et al., 2010) demonstrated that daily exposure to typical-intensity cell phone frequencies reduced the incidence of amyloid markers. Considering the increased proportion of patients who have sustained a closed head injury and earlier onset of dementia, these treatments may be relevant. There is now clear evidence of a biophysical linkage between EEG coherence and structural (MRI) measurements for TBI patients (Thatcher, Biver, McAlaster, & Salazar, 1998). For human patients by knowing where within cerebral space and which frequency bands are most anomalous, custom-designed and compensatory magnetic fields could be applied.

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Chapter 4: Facilitation of Declarative Memory and Congruent Brain States By Applications of Weak, Patterned Magnetic Fields: The Future of Memory Access?

Submitted to *Memory Studies*

4.1 Abstract

Modern communication and electronic technology have produced a complex secondary electromagnetic environment within which we are all immersed. Ultimately patterns will be generated that are intimately congruent with those generated by the human brain during memory consolidation. Human volunteers exposed to a weak patterned magnetic field whose electrical equivalent produces long-term potentiation or memory enhancement in a variety of contexts, showed a significant increase in the retention of narrative details 20 min after the field was applied over the left temporal lobe but not the right temporal lobe; scores for the latter group did not differ from sham-field subjects. The effect size of the memory enhancement was sufficiently large, accommodating 60% of the variance, to have clinical and practical applications. The changes required about 15 minutes to be apparent and were related to the expected quantitative changes in brain activity. These results, which replicate previous experiments, indicate there is a potential technology that could be developed to enhance memory capacity for individuals following mild traumatic brain injury and vocational advantages for the average person in the 21st century.

4.2 Introduction

Memory is the representation of experiences within cerebral space. Classical approaches to the taxonomy of human memory have differentiated different types of memory that involve non-awareness and awareness (Squire, 1986; Tulving, 1983). The latter is dependent in large part upon language processing. Declarative memory has been dichotomized into semantic and episodic forms. For most human experiences declarative memory is the form that defines the individual's memories concerning knowledge in general (semantic) and with whom, where, and when (episodic) this knowledge was acquired.

Although there are pharmacological enhancements for some populations who exhibit deficiencies in memory, particularly for the elderly, facilitation of retrieval accuracy for normal individuals with average memory has been more variable. However within an expanding age of information processing and successful access to vocational opportunities that is contingent upon "how much" one knows, even small increases in retention rates can be advantageous. Within the near future one would expect a technology to emerge and be to be required to enhance memory capacity in order to adapt to the greater demands and challenges of competition. One promising non-pharmacological technology involves applying weak, physiologically-patterned magnetic fields while the person is engaging in acquisition of information.

If individual memory is experience represented within brain space, then stimuli that have the capacity to penetrate this volume could potentially enhance, diminish or even alter (Healy and Persinger, 2001) the details or themes of memories. The 21st century environment is replete with myriad weak electromagnetic fields from electronic equipment and communication technology that have the capacity to interact with the microstructure of brain tissue. Effectively most human

beings are now exposed to a complex matrix or "secondary" field of electromagnetic signals that have the potential to contain rich information capable of modifying the chemistry that is strongly correlated with memory consolidation (Whissell & Persinger, 2007). That weak, physiologically-patterned magnetic fields can penetrate easily through the skull and brain with minimal attenuation has been shown experimentally (Persinger & Saroka, 2013; Saroka & Persinger, 2013). Weak, complex-patterned applied electromagnetic fields may not necessarily be deleterious. Arendash et al (2010) found that long-term exposure of mice to cell-phone fields reduced the chemical markers associated with Alzheimer's disease.

For the last two decades we have been investigating the facilitatory effects of physiologically-patterned magnetic fields on human volunteers (Michaud & Persinger, 1985; Richards, Persinger, & Koren 1996). Several experiments have shown enhancement of the details of brief (a few minutes) complex narratives if biofrequency weak magnetic fields were applied across the brain at the level of the temporal lobes (Richards et al., 1996). The enhancement is usually in the range of 20 to 40% compared to control or reference conditions. There is also evidence that strategic application of very weak, patterned magnetic fields over the left prefrontal region will increase the person's likelihood of accepting a false statement as true (Ross & Persinger, 2008). The left prefrontal region is involved with decision-making and the perception of "choice".

Here we present results of an experiment that was modified from the procedure first reported by Richards, Persinger, & Koren (1996). Unlike other studies the shape of the applied magnetic field was designed after a specific pattern that was demonstrated to evoke Long Term Potentiation in slices of hippocampal tissue ("the gateway to memory") and to be associated with intrinsic processes coupled to the transition from short-term to intermediate and long term

memory. In the Richards study the numbers of accurate details recalled by the group who listened to a narrative while they were being exposed to this field applied over the left hemisphere but not the right hemisphere were twice that of the sham-field group approximately 10 days later. In the present study we expanded this procedure to include additional measurements of mood and subjective experience as well as the ongoing (real-time) quantitative electroencephalographic activity during the field exposure and consolidation period. We reasoned that if the treatment promised any practical or clinical effects, the effect size (eta^2 or the amount of variance explained) should be at least 40% and would therefore require a small sample size to be statistically significant. We also concluded that the subject as well as the person interacting with the subject and scoring the results should be blind to the experimental condition.

4.3 Materials and Methods

4.3.1 Subjects

A total of 12 university men and women volunteered to participate in the experiment. Their ages ranged from 20 to 27 (mean age of 22.5 years; standard deviation of 2.6 years). Eight of the participants (2 males and 6 females) were exposed to the magnetic field condition with 4 participants (4 females) exposed to the field over only the left hemisphere and 4 participants (2 males and 2 females) were exposed to the field over only the right hemisphere. In addition, 3 subjects (1 male and 2 females) were exposed to the sham condition. In the sham field condition all procedures were identical but no magnetic field was applied. One individual was excluded from the analysis after the study was completed because a field not designated for this study had been applied.

4.3.2 Procedure

The protocol was first approved by the university's Research Ethics Board. Each participant was told that he or she may or may not receive a weak intensity magnetic field. The participant was seated in a comfortable chair in a darkened, shielded acoustic chamber to minimize extraneous sounds and visual stimuli. An ELECTRO-Cap international electrode system with 19 AgCl sensors was placed over the head and referenced to the ears for collecting monopolar EEG data. Impedance under 10 kOhms was verified and maintained for each sensor. The EEG cap was connected to a portable laptop outside the chamber employing a Mitsar 201 amplifier system. WinEEG version 2.84.44 working in Microsoft Windows XP was used to collect the EEG data.

A baseball cap was placed over the EEG cap. Over the surface of the hat there were 8 solenoids. The 8 solenoids were arranged with four over each temporal lobe in (Figure 1). The Shiva Neural Stimulation Software (Todd Murphy) was used to apply the magnetic field to the appropriate solenoids through USB audio devices. The software was custom-designed by Todd Murphy to deliver weak-intensity (1 μT) magnetic fields to each of the solenoids at specific times. This intensity is comparable to that generated by some electronic sound sources that are placed within the ears.

The signals generated from the Shiva software were audio derivatives of patterns converted into magnetic fields. For this experiment the Shiva patterned hippocampal field was selected given that it is modeled after the LTP (long-term potentiation) field (see Figure 2). The purpose of the experiment was to discern the effects of the field on memory while concurrent QEEG measurements were recorded. To ensure specificity the field was not applied over both hemispheres concurrently. Participants were either exposed to a sham field condition (no field), left hemispheric field exposure only, or right hemispheric field exposure only. Within the

treatment conditions the magnetic field would rotate to each solenoid individually (clockwise if the exposure was over the left hemisphere and counter-clockwise if the exposure was over the right hemisphere).

Figure 1. Participant in the acoustic chamber wearing the magnetic field application device

Prior to the experiment participants were administered the short form of Profile of Moods States (McNair et al, 1992) as a pre-test as well as two memory tests that. All memory tests were counterbalanced in their administration. The first memory test involved the immediate (within 15 s of completion of reading the stories or words) recollection of two stories from the Wide Range Assessment of Memory or WRAML2 (Adams, 2003) as well as the Rey's (1958) auditory verbal learning test (AVLT) which involves the recollection and recognition of lists of 15 words. Baseline EEG recordings consisting of 2 minutes of eyes open and 2 minutes of eyes closed EEG

conditions before the experiment began. The participants were instructed to keep their eyes closed during the next portion of the experiment.

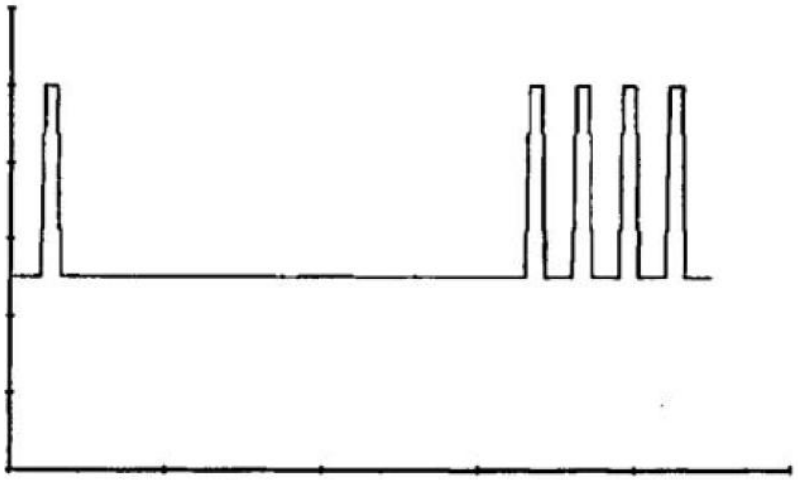

Figure 2. The pattern of LPT (long Term Potentiation) that was applied as a weak magnetic field over either the right or left temporal lobe during the interval of memory consolidation. The x axis represents time in 1 ms intervals while the amplitude indicates values between 127 and 256 which were transformed to the magnetic field pattern. The time between the primer pulse and subsequent 4 pulses was 150 ms.

The participants were then exposed to one of the three magnetic field conditions for 20 minutes while QEEG activity was measured. After the treatment period a second set of baseline recordings were obtained. The participants were then asked to recall both stories from the WRAML2 as well as the wordlist from the AVLT. After the delayed recall participants were then asked to immediately recall two additional stories from the Wechsler memory scale (Wechsler, 1945) and the test of verbal learning (from the WRAML2) as analogues to the first two memory tests presented in counterbalanced order. The information was reported by the subjects through the lapel microphone while they were still sitting comfortably within the chamber and recorded on standardized tests sheets.

Each subject was then administered the post-test POMS as well as an exit questionnaire for experiences within the chamber during the 20 min exposure period. This questionnaire listed

items of common experiences reported by approximately 500 subjects exposed to variations of these weak magnetic fields over the last 15 years (see, Persinger & Saroka, 2013). Each item was ranked according to the frequency of these experiences (0=no experience, 1=happened once, 2=occurred frequently). These experiences referred to visual, auditory, tactile, vestibular and spatial anomalies as well as the sensed presence, out-of-body experiences, and a variety of emotions including fear and sadness. The timeline of the experiment is presented in Table 1.

Two experimenters were responsible for the experimental procedure. One of the experimenter's was responsible for the control of the magnetic field equipment and the other for the administration and scoring of the psychological tests. Given that there is an element of subjectivity required for the scoring of the psychological tests the experimenter responsible for the scoring was blind to the field conditions until after all participants had completed the paradigm and the psychological data were scored and entered into an SPSS data file.

Table 1: Procedure timeline

Timeline
POMS(sf) Pre-Test
Stories 1 & 2 and AVLT in counterbalanced order (administration and recall)
Baseline Recordings
Field Exposure
Baseline Recordings
Stories 1 & 2 and AVLT in counterbalanced order (delayed recall)
Stories 3 & 4 and Verbal Learning in counterbalanced order
POMS(sf) Post-Test & Experiences Questionnaire

4.3.3 Electroencephalographic Recordings

Brain activity was measured by a Mitsar-201 portable QEEG system that was connected to a 19-channel electrode cap (Electrode-Cap International) that contained the 10-20 Standard Electrode Placement. Electrode site include Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, T6, O1, and O2 that were linked to the ears (A1 and A2) for monopolar recordings. Impedance

of all channels was less than 10 kOhm. Data were acquired using WinEEG v2.84.44 software with a sampling rate of 250 Hz. A 50 Hz to 70 Hz notch filter was used in the WinEEG software for all subjects in order to filter high frequency noise during recording. The EEG record was inspected for movement artifacts; the principal component analyses (PCA) method of artifact correction within WinEEG software was employed where appropriate.

4.3.4 Statistical Analysis

Raw spectral power was extracted from the EEG data within the WinEEG software. Two, 30 second, artifact-free sample was extracted for each individual during a pre- and post-baseline, during all memory tasks (both pre- and post-field exposure), and at 5, 10, 15, and 20 minutes after the start of the treatment or sham field procedure. The spectral analyses partitioned the EEG data into delta (1.5-4 Hz), theta (4-7 Hz), alpha (7-14 Hz), beta 1 (14-20 Hz), beta 2 (20-30 Hz), and gamma (30+ Hz) bands. All statistical analyses involved SPSS 19.0 operating using Windows 7.

4.4 Results

4.4.1 Quantitative Memory Increase But No Mood Changes

The means of the z-scores for the immediate recall of the two stories were between 0.1 and 4 (SD=0.8) for all three groups combined indicating that the population was representative of the average person. Because persistent rather than brief memory enhancement was the focus of the study, the differences in z-scores 20 min after the stories (average of the two) were first recalled and after 20 min of treatment were subtracted from the immediate z-scores for the stories. Analysis of variance revealed strong and statistically significant differences between the three treatment conditions (sham or no field, left hemisphere application, right hemisphere

application). As shown in Figure 3 the z-scores for the stories (delay recall – immediate recall) was significantly [$F_{(2,10)}$=6.02, p<.05, eta^2=0.60] higher for the group exposed to the left hemispheric field application compared to the no field condition.

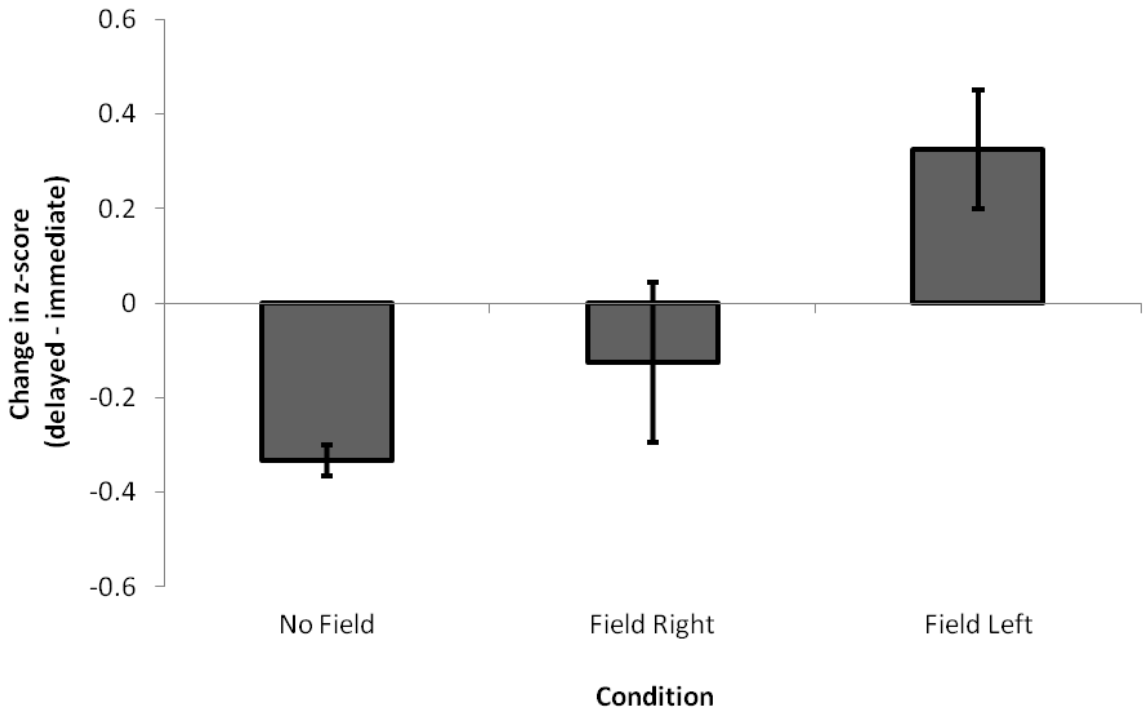

Figure 3. Change in z-scores between delayed and immediate recall of the narratives (stories) for groups exposed to the no field or to the field applied over the right or left temporal lobe region. Vertical bars indicate SEMs.

As shown in Figure 4 a general magnetic field effect was evident for the two tests that required recall of a list of un-related words (AVLT). The change in total z-score for the pre-treatment first word list test (AVLT) to the post-treatment verbal learning test showed that the change in z-score (post-treatment word total – pre-treatment word total) was significantly improved for the group of participants exposed to a field (regardless of exposure hemisphere) compared to controls [F-$_{(1,10)}$=5.28, p<.05, eta^2=0.37]. Analyses of variance demonstrated no significant difference in

mood scores for any of the six domains for the groups. The grand means and standard deviations for each domain were: tension (2.0, 3.7), depression (1.9, 1.8), anger (0.5, 0.9), vigor (6.6, 4.8), fatigue (5.2, 3.5), and confusion (0, 1.7, negative scores are possible for this scale).

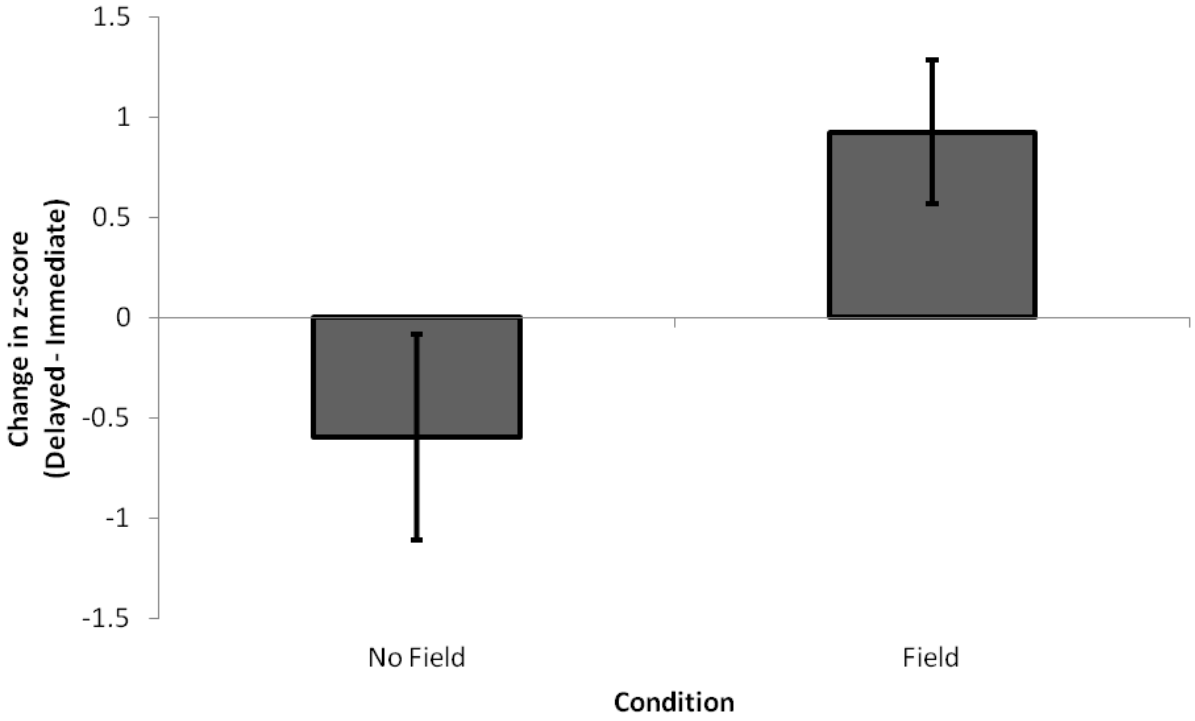

Figure 4. Change (improved) in z-scores for unrelated word recall for individuals exposed to the no field (sham) or no field (regardless of hemisphere) conditions. Vertical bars indicate SEMs.

4.4.2 Quantitative Electroencephalographic Results

QEEG data were collected for the entire duration of the field or sham-field exposures. Initial analysis of brain activity was examined over the temporal lobes during the 5th, 10th, 15th, and 20th minute of exposure. A significant 4-way interaction between condition, time, hemisphere and anterior/posterior portion of the cerebrum was found [$F_{(6,57)}$=2.34, $p<.05$, partial eta^2=.20] for power within the alpha range only (Figure 5). *Post hoc* analysis revealed that the left-hemispheric exposure group had significantly more relative alpha power over the *right posterior temporal region* than the sham group at approximately 15 minutes after the initiation of the field exposure.

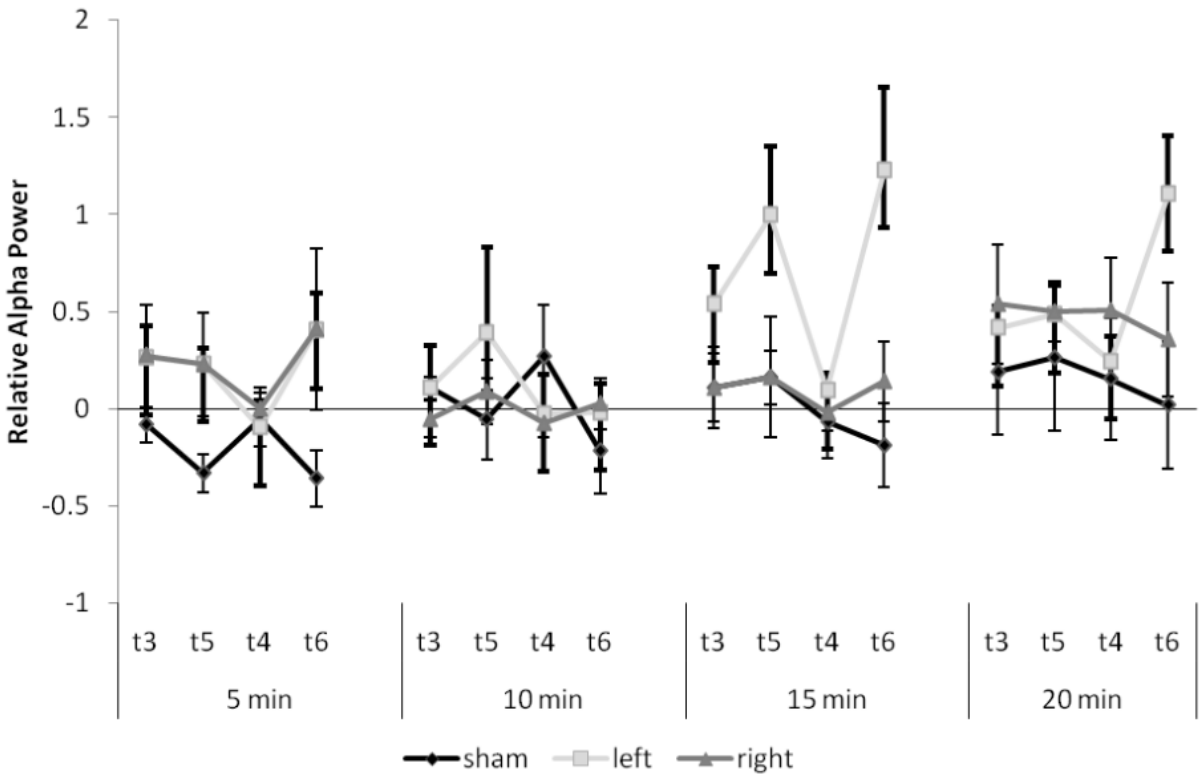

Figure 5. Relative temporal alpha power during different periods for the three treatments: sham, field over the left temporal lobe, field over the right temporal lobe. Vertical bars indicate SEMs

The relative temporal alpha power measurements over the left posterior alpha channel increased around 15 minutes for the participants in the group exposed to the left hemispheric application of the LPT magnetic field. In order to explore this further the posterior temporal channels were summed (regardless of hemisphere). Results revealed that there was significantly more relative alpha power at 15 minutes after the initiation of the field exposure for individuals in the left-hemispheric group compared to the sham group [$F_{(2,21)}$=4.462, p=.026, eta^2=0.32] (Figure 6).

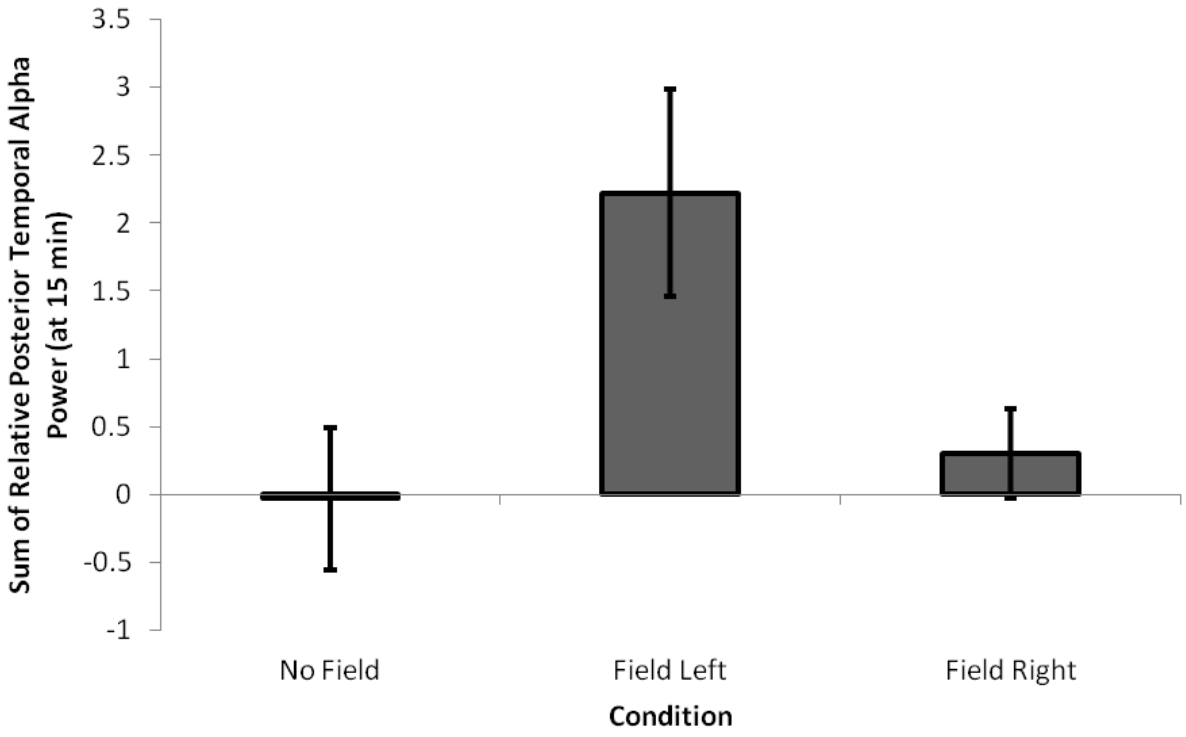

Figure 6. Sum of relative posterior temporal alpha power after 15 min of treatment. Vertical bars indicate SEMs

Correlation analyses were employed to relate the QEEG results ($\mu V^2\ Hz^{-1}$) with results obtained from the memory tasks. Analyses revealed that the magnitude of the posterior alpha power was significantly correlated with the change in story memory scores (z-scores) only after 5 minutes of exposure (rho=.522, p=.013; r=0.507, p=.016). When the posterior temporal channels were combined, significant correlations, depending on the order of the test administration, were found. If the individuals had been given the stories as the second test performed (5 minutes into the field exposure and approximately 13 minutes after they were presented the stories to be recalled) significant correlations were found after 5 (rho=.598, p=.040; r=.754, p=.005), 15(rho=.598, p=.040), and 20 minutes (rho=.669, p=.017; r=.692, p=.013). These results indicated that after 5, 15, 20 minutes of field exposure there were moderately strong correlations between the strength of posterior alpha activity and how well the participants *would* later recall the details of the stories.

4.4.3 Intrinsic Validation from Non-Memory Mood and Subjective Experiences

Although there was no significant changes in various mood scores between the sham and two field exposed groups, we discerned if there were any non-memory related associations between mood, subjective experiences associated with sitting in the chamber, and QEEG patterns. Results indicated that participants who rated themselves as "feeling dizzy or odd" throughout the experiment as inferred by their responses on the Exit Questionnaire endorsed items indicative of more global mood disturbance between the pre- and post-treatment conditions [$F_{(2,10)}$=5.41, p<.05, eta^2=0.57] regardless of condition. *Post hoc* analysis indicated that the greater the increase in negative mood, the more dizzy or odd the participants reported feeling throughout the experiment.

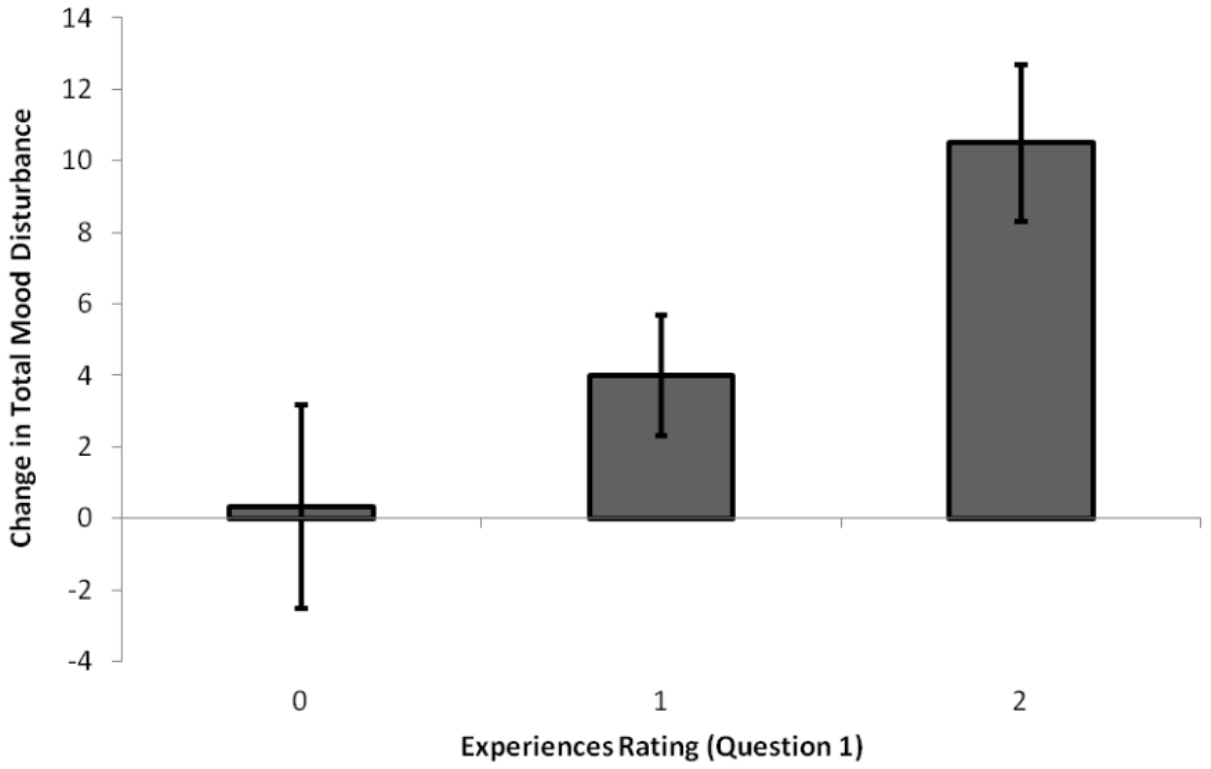

Figure 7. Average change in total mood scores for groups of individuals who reported various frequencies of feeling dizzy or odd frequently during the experiment

Correlation analyses were performed in order to determine if there was a relationship between the change in total mood disturbance scores and relative spectral power in electroencephalographic activity. The relative power scores were correlated with change in mood. Only one relative power score was significantly associated. The "I felt dizzy or odd" item score was correlated with power within the beta frequency band over the central parietal region after 15 minutes into exposure (rho=-.771, $p<.01$; r=-.785, $p<.01$). The association suggests that as the relative beta power in the central parietal channel decreased (around 15 minutes) the dizzier or odder the participants later reported they felt and the more disturbed the general mood was endorsed. Given that many neuroimaging studies have localized some vestibular functioning

to parietal (intraparietal sulcus) regions it is not surprising that this region could be involved with this sensation and facilitated the change in mood.

4.5 Discussion

The presentation of a patterned weak electromagnetic field along the left hemisphere during the consolidation of declarative memory had been shown previously to facilitate the accuracy for a narrative (5 minutes in length) when it is recalled around 10 days after the initial presentation (Richards et al., 1996). Consolidation of declarative memory is a process within the human brain that requires both chemical and electromagnetic factors to facilitate long-term potentiation (LTP). The "hippocampal field" which was the applied magnetic field employed in the present study was the exact pattern that when applied to hippocampal slices evoked protracted alterations in neuronal thresholds after about 10 to 15 min, the time usually required for spine formation on dendrites. The LTP field was based on the algorithm for induction of LTP (Rose, Diamond, Pang, & Dunwiddie, 1988) within the hippocampus.

In the present study participants who had been exposed to the hippocampal field over the left hemisphere for 20 minutes recalled two-thirds of a standard deviation (almost 25%) more details from the stories compared to the immediate recall than the participants who were exposed to the sham field condition. The effect size also indicated that the experimental treatments accommodated 60% of the variance in the number of memories. This effect size was within the range reported by Richards et al (1996) and is well within the range of having practical applications. In the present study we also ensured that the person interacting with the subjects and scoring the data were not aware ("blind") to the field treatments so that subtle influences

would have been eliminated even though the responses were collected by intercom between where the subjects were sitting and the experimenter recorded their comments.

The specificity for the hemisphere of application for the stories but not for the unrelated list of words is congruent with the differences between the left and right hemisphere. As reported by Budzynski (1986), the right hemispheric exhibits the semantic capacity of a young adolescent but the syntactic capacity of a six year old. Consequently for unrelated words, such as the word list, stimulation of the right hemisphere should have produced the same effect as stimulation of the left hemisphere. This was observed. On the other hand verbal memories depending upon syntax, such as the stories was not facilitated by right hemispheric stimulation but was enhanced by left hemispheric stimulation. We appreciate there may be other explanations.

Given such strong and hemispheric specific treatment effects evident from the behavioural results one would expect easily discernable quantitative measures within concurrent brain activity within classically associated regions. Analysis of the QEEG data revealed that the posterior temporal (specifically the within the right hemisphere) regions displayed increased power (μV^2) after approximately 15 minutes of the field exposure for individuals that received the treatment over the left hemisphere. The intricate and strongly correlated coupling between verbal memory and left temporal lobe function is pervasively documented within both experimental and clinical historical literature (e.g., Kolb and Whishaw, 2003). References to the role of alpha activity over the temporal lobes during memory tasks are also replete within the scientific literature. That increases in alpha power over the posterior temporal region are related to improvements in memory has been demonstrated by Jensen et al, (2002), Lisman (2002), and Meeuwissen et al (2011).

Interestingly, the condition that produced the effect was application of the LTP magnetic pattern over the left hemisphere whereas the QEEG spectral power differences were noted primarily over the homologous region of the right hemisphere. This may not be contradictory. Enhanced alpha activity over the right temporal lobe, (which is often the initial processing region for novel information) could reflect diminishment of input from this novelty processing into the left hemisphere so that verbal representations within left temporparietooccipital tertiary areas are less disrupted. This would later increase the accuracy of the verbally labeled and cognitively reconstructed information during the recall tasks.

This supposition is consistent with results for individuals who have reportedly enhanced visual 'eidetic' memory. Brang and Ramachandran (2010) studied an individual who reported grapheme-colour synesthesia and a seemingly separate ability for visual imagery/memory, i.e., eidetic memory. They found the subject exhibited a right-hemispheric bias in his grapheme-colour synesthesia. Assuming eidetic memory is predominantly associated with visual/spatial stimuli it is not unlikely that the right hemisphere plays a dominant role in this ability considering its propensity for visual/spatial processes. Because the task that showed the difference in this study was the recollection of details in stories it is likely that individuals use imagery as a tool to enhance their memory and then when the field was applied over the left hemisphere the transference from verbal (left hemisphere) to visual (right hemisphere) could have been facilitated.

The results of this study support the results found in previous work indicating that the pattern not necessarily the intensity of the applied magnetic field produces the largest effects (Sandyk, 1995). If this feature of physiologically-patterned magnetic fields is generally valid, then more

precise and individualized patterns of applied magnetic fields across the temporal lobes might be employed as an adjunct facilitator for memory consolidation when maximum information is required. This application might be particularly helpful for the millions of individuals within the contemporary population who compose the "silent epidemic" of mild closed head injury from concussive forces and energies. Many individuals who have sustained "mild" traumatic brain injuries consistently report difficulties with memory that can adversely affect their adaptation for years. Perhaps by simulating the neuronal patterns that mediate memory these fields could be used not only to enhance the accuracy and details of their reconstructions of experience.

From a societal perspective and considering the rapid growth and proliferation of complex patterns of electromagnetic fields that penetrate the body and brain from countless sources of communication, electronic, and computer-based technologies, the subtle effects of certain patterns that can occur as *synergisms* or emergent phenomena (Whissell & Persinger, 2007) upon human behaviour in a rapid-demanding memory-based future could be considered. The technological precision of many of the most effective circuits that now constitute computers, solid-state processors, and electronic tunneling junctions are approaching the spatial dimensions of the neuronal synapse. Although the carrier waves may be generated within the upper MHz and lower GHz range there are innumerable variations in modulation of subharmonics. The "beats" from superimposition of these fields with much lower base frequencies and irregular shapes approach the capacity for complete resonance with those generated with the brain.

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Chapter 5: Discussion

Applied psychology is a discipline where practitioners are committed to helping individual's recover or adapt after experiencing mental illness or a traumatic brain injury. Accurately assessing these individuals is imperative so both the severity and type of mental illness can be determined and treated. In order to effectively assess these individuals there is a need for reliable measurement tools that accurately and efficiently assess for disorders of mental illness because it is based on the results of these assessments the individual's treatment plan is developed. By incorporating a dynamic neuroimaging tool, like the quantitative electroencephalograph (QEEG) into standard assessment can provide clinicians with additional data that can help determine the location of the impairment as well as the intensity of the anomaly compared to a normative database. By consistently incorporating the QEEG into the assessment protocol the amount of data that the practitioners have access to will increase which will allow them to make increasingly accurate hypotheses about the individual's injury and a more effective treatment plan can be formulated. The data presented throughout these three experiments has effectively demonstrated the capabilities and benefits of the QEEG and has shown the possible future clinical applications of this tool. By using neuroimaging tools in applied psychology we will be able to bridge the gap between experimental and clinical work and use all the available tools to the advantage of the patients.

5.1 S-LORETA Validity of Classic and Novel Performance-Based Neuropsychological Tests

Very few studies have examined the construct validity of classical neuropsychological tests. These tests have been employed for decades to infer the lateralization and localization of brain

injuries. With the advancements in dynamic neuroimaging techniques researchers have been given a unique opportunity to study the dynamic brain activity of participants. The source localization analyses performed were the results of direct, real time, measurements of brain activity while individuals are engaged in neuropsychological testing. Employing the QEEG in this study allowed for the neuropsychological tests to be performed, without modification, while simultaneous measurement was ongoing and the results support the traditional interpretation of the functions of these tests. In addition, given that the participants were normal, university students who were, in some cases, not naïve to these tasks is an indication of the robustness of these tasks.

The three tasks that were performed that have been inferred to be involved with right prefrontal function were associated with increases, relative to baseline power, within the alpha to gamma frequency bands (bands that are typically associated with higher level information processing). For the remainder of the tests there were also evident elevations in activation compared to baseline measurements within various regions of the brain typically associated with the respective test. During the Toe Graphaesthesia test the prefrontal medial surface showed this increased activation, the caudal medial surface during Toe Gnosis, the left temporal region during Speech-Sounds, and within the right retrosplenial-parahippocampal region for Seashore Rhythms. Overall these results support the traditionally established regional relationships with these classic neuropsychological tests. The changes in activation within the specific regions and frequency bands add to the validity of not only these tasks but also that the s-LORETA technique is an analysis that can be employed to measure the ongoing activation within the brain.

5.2 Use of Spectral Power, Source Localization (s-LORETA) and Microstates to Quantify Chronic Deficits from "Mild" Closed Head Injury: Correlation with Classic Neuropsychological Tests

By incorporating dynamic neuroimaging tools like the QEEG into the standard neuropsychological assessment it was possible to combine all the acquired data and analyze the population as a whole. By combining the data into one functional database it was possible to determine what regions of the brain are more susceptible to dysfunction after a significant brain injury. By using more than just traditional behavioural or pencil and paper tests to assess the significance of an individual's brain injury clinicians can better treat individuals based on both the behavioural and neuroimaging data. Using a direct measure of brain activity has shown, through this study, to be effective at differentiating between varying severities of neuropsychological impairment. Using a more quantitative method of exploration could increase the effectiveness of clinicians to assess the intensity of the brain injury as well as localize the region that has been most significantly affected. Interestingly, the results of this study have revealed consistent results regardless of the location of the initial injury. Patients who displayed the more severe neuropsychological impairments displayed less power within the lower frequency bands in the more caudal aspects of the brain as well as shorter microstate durations. In addition, there were clear differences in the microstate configurations and source localization activation. It is therefore possible that this study has revealed the relative vulnerability in the electrical stability of the brain after a brain injury.

In the future, it is possible that the QEEG or other neuroimaging technique could be used as a prescreening measure to determine the affected region(s) and analyze the severity. Using neuroimaging tools in this way could allow clinicians to focus their assessments on the regions

of the brain identified by the QEEG or verify the findings of the traditional behavioural tools. Not only could this allow the clinicians to save time by determining where the majority of their focus should be but it could allow them to predict symptoms that may emerge later in the individual's life and help prepare them for those transitions. The use of this tool would not only benefit the clinicians but it would be extremely valuable for the patients as well. After having experienced a traumatic brain injury it can be extremely taxing for the patient to undergo hours of behavioural testing. The use of a dynamic quantitative tool could increase the efficacy of the testing procedures.

5.3 Facilitation of Declarative Memory and Congruent Brain States By Applications of Weak, Patterned Magnetic Fields: The Future of Memory Access?

Treating individuals who are experiencing mental illness or helping individuals who have sustained a traumatic brain injury adapt and function in everyday life can be a challenge. In addition, given the law of diminishing returns, certain individual's are likely not going to respond to the commonly available treatments. At strengths approximately one million times less intense (1 microTesla) than transcranial magnetic stimulation (Baker-Price & Persinger, 2003), transcerebral magnetic stimulation (TCMS) has been shown to produce a variety of effects dependent on the pattern of magnetic field applied (Persinger, 1995; Persinger, Richards, & Koren, 1997; Richards, Koren, & Persinger, 2002; Booth, Koren, & Persinger, 2008). This method involves the application of weak, complex, physiologically-patterned electromagnetic fields (St-Pierre, Mazzuchin, & Persinger, 2008) in order to achieve results. Previous studies have shown that this technology has the ability to aid individuals with mental illness, specifically

depression in individuals who had sustained a closed head injury (Baker-Price & Persinger, 1996; 2003).

The results from this study support the results from previous work by revealing not only changes in the electrical activity within the brain as measured using the QEEG but also that these fields can produce significant behavioural differences. The significant improvement in memory for individuals exposed to the left hemispheric condition indicate that the application of weak-intensity physiologically patterned electromagnetic fields is a potential treatment for individuals who have sustained memory impairments due to brain injury or other ailment. These results, in addition to other research using similar methodology and equipment have shown memory benefits for both humans (Sandyk, 1995) and animals (Arendash et al., 2010). The current study adds to the body of evidence that supports the use of this technology to enhance memory processes.

5.4 Conclusion

In conclusion, whether it be for validating assessment tools, finding correlates between behavioural data from a brain injured population and their brain activity, or assessing the efficacy for an emerging therapeutic technique the quantitative electroencephalograph is a valuable tool that can be beneficial for patients and practitioners in the field of applied psychology. Throughout these studies the QEEG has shown to be a versatile tool that can be used for more than classical neurological examinations and laboratory experimentation. In addition, given that this neuroimgaing technique has evolved from a qualitative research tool to a quantitative tool the methods of analyses have become, not only more precise, but also much more diverse allowing for a greater ability to discern subtle differences between populations.

There is still more research to be completed with respect to quantitative electroencephalography in applied psychology however, based on the results of the presented studies this tool has proven to be a valuable resource that can offer insight into the brains of patients that classical behavioural tests cannot provide.

5.5 References

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