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RE-TRAINING THE INJURED BRAIN: A CASE SERIES IN sLORETA NEUROFEEDBACK AS AN ACUTE CONCUSSION INTERVENTION IN YOUTH

By

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THESIS APPROVAL PAGE

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Abstract

RE-TRAINING THE INJURED BRAIN: A CASE SERIES IN sLORETA NEUROFEEDBACK AS AN ACUTE CONCUSSION INTERVENTION IN YOUTH

Paul David Ims, III

Concussion incidence rates are at epidemiological levels and rising (Giza & Hovda, 2001). Concussion symptoms caused by underlying cortical deregulation and functional disturbances (McCrory et al., 2017), which can be measured by quantitative EEG (Rapp et al., 2015), interrupt the daily functioning of the injured person. The principle investigator hypothesized that neurofeedback would reduce symptoms and improve recovery time compared to rest and recovery alone. Concussed youth completed a series of QEEG-guided neurofeedback sessions. QEEG measurements, cognitive scores, and symptoms were tracked from injury to recovery and compared to individuals not receiving neurofeedback. This pilot study revealed a potential non-invasive treatment option for concussion which warrants further study.

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INTRODUCTION

In 2011, the Center for Disease Control (CDC) estimated 1.6 - 3.8 million sport- or recreation- related concussions occur per year (Daneshvar et al., 2011). Concussion rates are increasing in the adolescent population (Zhang et al., 2016). Current concussion recovery guidelines emphasize the reduction of symptom-provoking behaviors promote recovery (McCrory et al., 2017). Electrophysiological assessment after concussion injury demonstrate measurable differences in cortical functioning (Rapp et al., 2015). Dysfunctional patterns of brain activity related to concussion injury persist beyond concussion recovery defined by current evidence-based guidelines (Kerasidis & Ims, 2017). Neurofeedback is the operant conditioning of brain waves as measured by the electroencephalogram (EEG) to promote neuroplasticity and self-regulation of brain activity (Collura, 2014), and stands to be investigated as an intervention for acute sport- and recreation-related concussion in adolescents and children.

The paper will begin by providing an operant definition of concussion injury, description of the mechanism of concussion injury, and current evidence-based concussion management practices. Electroencephalogram (EEG) and quantitative EEG analysis techniques and metrics, including the relationship between brain activity and concussion, will be outlined, followed by an explanation of neurofeedback approaches and procedures. Subsequently, the hypothesis, study methods, and results will be presented for each case study. Finally, implications of the results will be discussed, limitations outlined, and conclusions drawn.

Psychology and Brain Injury

As the brain is the physical medium to mental processing, impairment to neurophysiology exerts an effect on psychological functioning. Concussion presents acute and

chronic mental health challenges (Broglio et al., 2016). In the days or weeks following injury, individuals with severe post-concussion symptoms are advised to rest and reduce cognitive and physical activity that provokes symptoms (McCrory et al., 2017). Functional disturbances due to injury in brain regions associated with emotional regulation may be directly responsible for changes in mood or emotional lability. Unable to attend school or other social events, withdrawal from society for extensive time during recovery may contribute to depression (Broglio et al., 2016). For student athletes with intense academic workloads, anxiety may increase as time out of the classroom as past-due assignments build. Insomnia secondary to anxiety may impede sleep important to recovery, and concussion cases with sleep disturbance symptoms further complicate efforts to rest. With make-up schoolwork mounting and interruptions in activities of daily living, feelings of hopelessness may creep into the mind of concussed youth. In the PI's clinical experiences, conversations with injured patients often include descriptions of "feeling crazy" because "life is out of control" and "wondering how to get back to normal."

The long-term effects of concussion may be seen in a host of psychological disorders. Personality, sleep, cognitive ability may be negatively influenced by brain injury, increasing the risk for suicide, PTSD, depression, and anxiety (Peskind et al., 2013). This comorbidity between brain injury and mental illness is compounded by the fact that many concussions are underreported, a symptom of the culture surrounding brain injury in sport or military service, or undiagnosed (Buck, 2011). As the PI has worked with individuals struggling with different psychological conditions, a suspect and undiagnosed concussion frequently lurks in the past, often forgotten by the patient or their parents.

Throughout history, several historical figures suffered head injuries, which appear correlated with erratic personality and behavioral changes when evaluated in hindsight (Esty & Shifflet, 2014). When Phineas Gage famously survived a tamping rod blasting through his left frontal and temporal region in 1848, ensuing changes in Gage's behavior after the destruction of specific brain regions offered unique insight to the impact of brain on psychology which are routinely discussed in modern psychology classes. One high profile figure was King Henry VIII of England, famous for a series of failed marriages, two of which ended in beheadings, and separating England from the Catholic Church. Beloved as a young man, historical records note two major head injuries as an adult during two separate jousting accidents approximately twelve years apart and ensuing problems of severe migraine headaches, impulsive spending, and emotional lability. Over the years, King Henry transformed from a handsome and benevolent gentleman to a greedy and temperamental ruler. Similarly, the lives of Mary Lincoln, Elvis Presley, and Howard Hughes spiraled out of control after each suffered documented head injuries and related symptoms that contributed to dramatic changes in behavior and personality which contributed to their demise. Although the injuries were noted in time, past scientific understanding of the relationship between brain and behavior limited the connection between the injuries and the individuals' behavioral changes. Modern neuroscience and psychology have investigated the correlation between brain structure and function and related deficits when cortical function is lost to varying degrees of brain injury.

Concussion Defined

According to the Fifth International Conference on Concussion in Sport in Berlin, Germany in October, 2016, "concussion is a brain injury and is defined as a complex

pathophysiological process affecting the brain, induced by biomechanical forces" (McCrory et al., 2017). When a secondary concussion injury occurs before the brain recovers from the primary injury, the athlete is at risk for second impact syndrome which may lead to brain herniation in severe cases (Tator, 2013). Over time and many repeat concussions, post-traumatic degeneration of the brain may develop into a condition known as chronic traumatic encephalopathy (CTE).

Concussion involves a direct blow to the head or transmission of force from elsewhere on the body (McCrory et al., 2017). The primary injury is known as the coup impact; contra-coup impact occurs when momentum from the primary impact leads to impact on the opposite internal wall of the skull as the brain rocks back-and-forth inside the skull. Neurological impairment may develop immediately after injury or in the hours or days following injury. Clinical symptoms reflect functional disturbance rather than structural injury and typically resolve in a sequential course. Concussion symptoms may include headache, cognitive impairment, emotional dysregulation, and sleep disturbances, and loss of consciousness; however, concussion may occur without loss of consciousness.

The term mild traumatic brain injury (mTBI) is often used interchangeably with concussion (McCrory et al., 2017), but may not describe the same clinical syndrome that is concussion injury as defined by the fifth consensus statement on concussion in sport. Rather, mTBI typically refers to a broader context of brain injury. Sport- and recreation- related concussion is the focus of the present study, but the term mTBI may be used at times in review of relevant past research. The present study defines developmental time frames as the consensus statement on concussion by McCrory et al.: adults as individuals over the age of 18, adolescents as individuals between ages 13-18, and children as individuals under the age of 13.

Mechanism of Concussion Injury

Concussion results in damage to the neuronal membrane, impairment of neuronal functioning, and ensuing disturbance of regional brain function (Giza & Hovda, 2001). Diffuse axonal injury is a proposed mechanism of concussion injury. Rapid acceleration, deceleration, or rotation of the brain compromises the integrity of the neuronal membrane. The axon, the projection from the neuronal cell body to the terminal, twists, stretches, or shears as a result of biomechanical injury. This physical insult leads to an ionic, metabolic, and physiologic chain reaction within the affected neuron or population of neurons.

Trauma to the cerebral cortex induces unrelenting action potentials and the release of excitatory neurotransmitters, namely glutamate (Giza & Hovda, 2001). Due to the compromised integrity of the neuronal membrane; the sodium, potassium, and calcium electrochemical gradients cannot be appropriately maintained. This results in a massive efflux of intracellular potassium. Membrane ion pump activity, specifically the sodium potassium (Na-K) pump, increases to compensate for the potassium efflux and restore the ion gradients. The Na-K pump requires energy in the form of adenosine triphosphate (ATP) to export three sodium ions out of the neuron and import two potassium ions. With membrane Na-K pump activity in overdrive, cellular ATP requirements increase dramatically and an energy crisis ensues as neuronal mitochondria are unable to keep up with the increased demand for ATP.

Mitochondria produce ATP via cellular respiration and the citric acid cycle, otherwise known as the Krebs cycle (Stanfield & Germann, 2009). The citric acid cycle is the second step of cellular respiration, the first step being the anaerobic process of glycolysis. Although glycolysis does not require oxygen, ATP is required to complete the process and produce the

reactants for the citric acid cycle. Deregulation of the transmembrane ionic gradient results in increased intracellular calcium, and increased intracellular calcium concentration impedes mitochondrial production of ATP (Giza & Hovda, 2001). Therefore, physical insult impairs the neuronal capacity for energy production and restoration of the ion gradient necessary to assume normal neuronal functioning. As concussion impact occurs on the order of large brain regions rather than a single neuron, this process affects massive populations of neurons.

On a larger scale, regional cerebral blood flow (CBF) to the affected area decreases (Giza & Hovda, 2001), resulting in decreased glucose and oxygen delivery and waste removal. Positron emission tomography (PET) scans after concussion injury demonstrate decreased glucose uptake that can last 2-4 weeks after injury (Giza & Hovda, 2001). Concussion injury leaves the brain gasping for air, craving energy to restore homeostasis, and less able to receive the oxygen and glucose required for recovery. The energy crisis caused by biomechanical injury to the brain results in impaired neuronal functioning, and functional brain deficits related to the location of neurological impairment result in concussion related symptoms.

Concussion in the Developing Brain

Healthy brain development through childhood and adolescence has been studied extensively with neuroimaging techniques. As the neuro-typical brain develops, highly used functional connections are strengthened while less utilized neural pathways undergo synaptic pruning, especially in the frontal lobe (Sowell et al., 2001). White matter volume increases with age as myelination improves speed of transmission and connectivity necessary for efficient neuronal communication (Geidd & Rapoport, 2010). Given the typical pattern of cortical development, external factors which alter development are of particular concern.

Studies have demonstrated that biomechanical injury to the developing cortex and subcortical structures may have persistent effects on brain function and structure (Toledo et al., 2012). Rat studies demonstrate that injury to the developing brain may lead to long term impairment, although there may be minimal evidence of deficit at the time of the injury (Giza & Hovda, 2001). Human studies have demonstrated that concussion during adolescence may alter the trajectory of maturation by impairing plasticity and cortical excitability (Meehan et al., 2017). In children, the effect of concussion on CBF may be more global compared to adults (Churchill, Hutchinson, Graham, & Schweizer, 2017). Although post-concussion metabolic changes may be shorter in the immature and developing brain than adult brain, effects of undermined plasticity and axonal integrity may be more dominant in the young brain (Giza & Hovda, 2014). Taken together, concussion injury to the young brain disrupts cortical plasticity and functioning which impair brain function, albeit subtle in some cases, as development continues.

Current Approaches for Concussion Recovery and Rehabilitation

The expected time frame of normal clinical recovery from concussion and related symptoms is 10-14 days in adults and 4 weeks in children, and symptoms that extend past these respective time points are labeled persistent symptoms (McCrory et al., 2017). Growing empirical evidence suggests that some youth, high school, and collegiate athletes require longer than 10 days to recovery and return to sport (McCrory et al., 2017). Variability of concussion recovery time and necessity for diverse approaches to rehabilitation is exemplified in the 2.5% of concussed individuals who remain symptomatic 45 days after injury although objective measures

indicate recovery; meanwhile, 80-90% of individuals recover within 14 days without intervention (Broglio et al., 2016).

According to a recent review of rehabilitation interventions for concussion, physical and cognitive rest are the most commonly used interventions (Broglio et al., 2016). The rationale behind rest focuses on reducing concussion-related symptoms to reduce discomfort. Although rest is widely recommended, empirical support for rest versus an early return to light physical activity is wanting. Previous research suggests some athletes may benefit from rest while others may respond to light physical activity after injury. Due to the heterogeneity of concussion, Broglio et al. recommend a case by case approach regarding rest. The details of physical and cognitive rest plans suggested by McCrory et al. in the consensus statement will be described below.

Vestibular and oculomotor rehabilitation therapies have been increasingly investigated as interventions for concussion and appear useful for concussed athletes whose symptoms involve these systems (Broglio et al., 2016). If concussion disrupts normal vestibular sensory processing, vestibular problems may ensue, such as benign paroxysmal positional vertigo, vestibulo-ocular reflex impairment, visual motion sensitivity, balance dysfunction, cervicogenic dizziness, and exercise-induced dizziness (Broglio et al., 2016). Impaired oculomotor function may play a role in concussion symptoms like blurred vision, difficulty reading, headache, and reading problems (Broglio et al., 2016). Interventions that target specific vestibular or oculomotor deficits have enhanced recovery from concussion injury, but further research is needed to evaluate the efficacy such therapies (Broglio et al., 2016).

Over-the-counter (OTC) or prescription medications are commonly used to treat concussion related impairment and symptoms past of the acute phase (Broglio et al., 2016).

Normal concussion recovery lasts 10-14 days, but studies demonstrate pharmacological intervention for concussion usually begins at day 10 (Broglio et al., 2016). Medication treatment is designed to address the athlete's clinical subtype of concussion related symptoms. Examples of targeted medication intervention include stimulants to address cognitive problems or fatigue; tricyclic antidepressants for anxiety or mood problems; tricyclic or SSRI antidepressants, anticonvulsants, beta-blockers, or triptans for headaches or vestibular disturbances; and melatonin for sleep problems.

Physical Rest and Graduated Return-To-Play Protocol

The International Consensus of Concussion in Sport recommends a graduated return to play protocol to gently rehabilitate a concussed athlete back to normal game play (McCrory et al., 2017). This protocol describes a stepwise progression of increasing levels of physical exertion while the athlete remains symptom free. The athlete abstains from physical activity to rest and recover in the first stage. Once the athlete is symptom free at rest, light aerobic exercise (i.e., walking) is introduced to increase heart rate. Successive stages progressively increase across five exertion levels through sport-specific exercise, non-contact training drills, and full contact practice until the athlete is cleared for normal game to exit the protocol (see Table 1).

Table 1 Graduated return-to-sport (RTS) strategy

Stage	Aim	Activity	Goal of each step
1	Symptom-limited activity	Daily activities that do not provoke symptoms	Gradual reintroduction of work/school activities
2	Light aerobic exercise	Walking or stationary cycling at slow to medium pace. No resistance training	Increase heart rate
3	Sport-specific exercise	Running or skating drills. No head impact activities	Add movement
4	Non-contact training drills	Harder training drills, eg, passing drills. May start progressive resistance training	Exercise, coordination and increased thinking
5	Full contact practice	Following medical clearance, participate in normal training activities	Restore confidence and assess functional skills by coaching staff
6	Return to sport	Normal game play	

Table 1 – Graduated Return-To-Play Protocol provided in McCrory et al. (2017)

A critical aspect of the return to play protocol is that the athlete remains symptom free during a given level of exertion before graduating to the next level of exertion. Protocol guidelines recommend each step lasts approximately 24 hours, with completion of the full protocol requiring around one week. If concussion symptoms are experienced during exertion, the athlete returns to the previous level of exertion and re-attempts progression after 24 hours of rest. The athlete gradually works up to exertion levels of normal game play while monitoring symptoms. The athlete is cleared of the program when he or she is symptom free at full exertion.

Concussion management programs exist to provide integrated care of concussed athletes. XLNTbrain Sport is comprehensive concussion management program developed by neurologist Harry Kerasidis, M.D., and was utilized in this study. The technology-based program fully integrates the following components of concussion management: education, baseline testing, balance testing, sideline assessment tools, post-injury assessment, monitoring, and recovery guidance (Kerasidis, 2015). Within the program, athletes undergo a pre-season baseline cognitive test, repeat the cognitive test upon injury, track symptoms and cognitive scores throughout recovery, and finally repeat the cognitive test again once medically cleared from acute concussion.

Cognitive Rest and Return to School Protocol

Younger people may be more vulnerable to concussion injury and take longer to recover (Tator, 2013). According to the most recent consensus statement on concussion, symptoms are expected to last four weeks in children (McCrory et al., 2017). Increased cognitive load may exacerbate concussion-related symptoms, which poses a dilemma regarding the academic expectations of children, adolescents, and college-age young adults. To address this problem,

McCrory et al. encourage schools to offer a Return-to-School program to support students recovering from concussion (Table 2). There is consensus among concussion experts who advise cognitive rest and academic accommodations; such as excused absences, shortened school days, reduced classwork, or extended due dates or exam times; to mitigate symptoms that would otherwise negatively impact academic performance (Broglio et al., 2016).

Consensus statement

Table 2 Graduated return-to-school strategy

Stage	Aim	Activity	Goal of each step
1	Daily activities at home that do not give the child symptoms	Typical activities of the child during the day as long as they do not increase symptoms (eg, reading, texting, screen time). Start with 5–15 min at a time and gradually build up	Gradual return to typical activities
2	School activities	Homework, reading or other cognitive activities outside of the classroom	Increase tolerance to cognitive work
3	Return to school part-time	Gradual introduction of schoolwork. May need to start with a partial school day or with increased breaks during the day	Increase academic activities
4	Return to school full time	Gradually progress school activities until a full day can be tolerated	Return to full academic activities and catch up on missed work

Table 2 – Return-to-School Protocol (McCrory et al., 2017)

The Electroencephalogram

The electroencephalogram (EEG) measures the electrical discharges of regional populations of neurons (Collura, 2014). Post-synaptic potentials of pyramidal neurons in layer IV of the cerebral cortex are the largest generators of the electrical activity seen on the EEG. The EEG was first discovered by Richard Caton's research with small mammals in the late 1800s, but German neuropsychiatrist Hans Berger is credited with acquiring the first human EEG in 1924 (Niedermeyer & Schomer, 2011). Traditional EEG signals were put to paper by an oscilloscope, similar to a galvanometer that measures earthquakes. Present day EEG acquisition utilizes digital amplifiers and data processing made available by computers.

The clinical standard for EEG electrode placement is known as the International 10-20 System, which places nineteen electrodes on the scalp in a grid relative to the size of the

subject's head. The 10-20 System uses measurements of the subject's head circumference, distance from inion to nasion, and pre-auricular points to determine the placement of electrodes (Trans Cranial Technologies, 2012). The numbers "10" and "20" originate from the distances between the electrodes, which are 10% or 20% of the transverse or longitudinal distance of the skull. Electrodes are named alphanumerically to indicate location on the scalp. The letter refers to hemisphere or lobe location: frontal (F), temporal (T), parietal (P), occipital (O), and central (C). Numbers designate electrode positions with even numbers indicating right hemisphere locations and odd numbers for left hemisphere. Frontal lobe activity is monitored by seven electrodes, two electrodes record from each hemisphere's temporal lobe totaling four temporal lobe sites, three electrodes measure parietal lobe activity, two electrodes measure activity from the occipital lobe, and three electrodes measure from the sensorimotor strip at the frontal parietal junction. The signal is processed by digital filters to remove artificial signals caused by modern technology, then manually inspected for biological artifacts caused by the subjects' movements such as eye blinks.

The EEG plots voltage against time (Chang, Schomer, & Niedermeyer, 2011). EEG amplitude is measured in microvolts (uV), while the unit Hertz (Hz) describes the number of cycles per second. The clinically relevant EEG frequency spectrum ranges from 0.3 Hz to 70 Hz because frequencies above 70 Hz are reduced due to effects of EEG filtering (Chang, Schomer, & Niedermeyer, 2011). Similar to white light passing through a prism broken down into component wavelengths and corresponding visible colors, the broad EEG frequency spectrum is divided into component frequency bands. Greek letters classify the EEG signal into generally defined frequency bands; although, specific definitions of frequency ranges are somewhat blurry between researchers. This discrepancy does not speak so much to the function of the band and

refers more to EEG nomenclature. The frequency bands were named in the order they were discovered and do not follow the logical sequence of the Greek alphabet. Delta activity generally ranges from 0.3-4 Hz, theta from 4-7 Hz, alpha from 8-13 Hz, beta from 13-35 Hz, and gamma from 30-80 Hz. Wave amplitude, frequency, morphology, spatial distribution, and physiological or psychological meaning more accurately describe the frequency bands (Collura, 2014; Chang, Schomer, & Niedermeyer, 2011).

The alpha wave was the first wave visualized by Berger, whom subsequently named the waveform alpha (Rivello, Douglas, & Niedermeyer, 2011). Alpha activity typically ranges from 8 to 13 Hz, is posteriorly dominant, waxes and wanes, and increases when the eyes are closed (Collura, 2014). The adult mean alpha rhythm frequency is around 10 Hz, which is usually reached in the maturing brain between ages 10-15 (Rivello, Douglas, & Niedermeyer, 2011). Alpha represents oscillatory communication between the thalamus and cortex, known as thalamo-cortical communication (Collura, 2014). Synchronous oscillations in the alpha range are generated by thalamic pacemaker neurons that project to the cortex (Hughes & John, 1999). Alpha activity is associated with wakeful relaxation and is readily generated when the eyes are closed, while alpha is suppressed with higher alertness or opened eyes (Chang, Schomer, & Niedermeyer, 2011). Visual processing in the occipital cortex requires high frequency activity when the eyes are open, but closing the eyes decreases visual processing and leads to an increase in alpha activity in posterior regions as visual processing cortices decrease in activity and "rest." Alpha may be divided into fast and slow alpha ranges, oscillating at 10-13 and 8-10 Hz, respectively, which have different properties. According to Collura (2014), fast alpha, sometimes referred to as alpha2, is considered the occipital idling rhythm and is related to

background memory processing, and slow alpha, or alpha1, is located in more frontal regions and has been implicated in emotional processing.

The beta frequency range begins where alpha ends and was the second frequency named by Berger. According to Chang, Schomer, and Niedermeyer (2011), beta begins at 13 Hz with an open-ended upper limit; although, 30 Hz is a common upper limit of the frequency band. Collura (2014) defines beta as ranging from 12-35 Hz broken into three sub-frequencies: low beta (12-15 Hz), beta (15-20 Hz), and high beta (20-30 Hz). Beta may be found in various cortical regions, but serves different purposes in normal conditions (Chang, Schomer, & Niedermeyer, 2011). Fast thalamocortical and cortico-cortical communications produce beta activity, which indicates active, local cortical functioning (Hughes & John, 1999; Collura, 2014). Low beta, associated with a relaxed and attentive state, is also the resting rhythm of the motor cortex and is thus referred to as the sensorimotor rhythm (SMR) when found in the somatosensory cortex (Collura, 2014). In posterior regions during eye closure, beta activity in the range of 13-15 Hz suggests a fast version of the alpha rhythm (Chang, Schomer, & Niedermeyer, 2011). Higher beta frequencies are associated with increased levels of awareness and alertness (Collura, 2014).

Delta waves are the slowest of the EEG frequencies, ranging from 0.5 to 4 Hz according to Collura (2014), and is considered the sleep rhythm in healthy humans. The reticular activating system, located in the midbrain, modulates the production of delta activity by oscillator neurons in the thalamus and deep layers of the cortex (Hughes & John, 1999). Delta activity is typically widespread and indicates lower levels of arousal (Collura, 2014). Excess, local delta activity in the wakeful condition may suggest injury, perhaps by trauma or toxicity (Collura, 2014), and insinuate less efficient cortical processing.

EEG activity between 4-8 Hz is deemed theta activity (Chang, Schomer, & Niedermeyer, 2011). Theta reflects communication at the subthalamic level in the ascending brainstem (Chang, Schomer, & Niedermeyer, 2011; Collura 2014). Hughes and John (1999) assert that theta is the effect of the nucleus reticularis on the thalamus slowing the alpha rhythm into lower frequency theta activity. Theta holds many properties, some pathological and some natural. The theta frequency range sits above delta and as such is related to drowsiness and early stages of sleep. Theta has been connected to inwardly focused processing, memory integration, creativity, and an overall dreamlike state; however, theta is also related to distractibility and cortical dysregulation (Collura, 2014).

EEG frequencies above beta, typically in the range of 30-80 Hz, are referred to as gamma (Chang, Schomer, & Niedermeyer, 2011). Collura (2014) defines gamma from 35-45 Hz, while other researchers define different but similar ranges of the EEG spectrum as gamma. Gamma is considered to be a binding frequency that recruits different cortical areas for synchronous information processing (Singer & Grey, 1995). With a mean frequency in vivo of 35 Hz, gamma activity reflects cortical activation and the balance of excitation and inhibition rather than a specific cognitive activity (Merker, 2016). Localized gamma activity is associated with high-level information processing (Collura, 2014).

De-Artifacting the EEG

As EEG recordings pick up brain-generated electrical signatures from scalp electrodes, non-brain generated signals are also acquired on the recording (Hammond & Gunkelman, 2011). Non-brain generated signatures, called artifacts, are inherent to EEG recordings and must be removed from the EEG before analysis in a process called artifacting. Movements of the eyes

are a major artifact generator and different types of artifact arise from eye blinks (see Figure 1), lateral eye movements, and eye roll or flutter when the eyes are closed. Electromyelographic (EMG) artifact appears in the EEG when muscles are activated. EMG artifact typically occurs in the frontal regions due to muscles under the forehead or temporal regions when the jaw is tightened. Glossokinetic artifact occurs when the tongue moves inside the closed mouth. EEG equipment sometimes picks up electrocardiographic activity generated by the heart, known as EKG artifact. Technical problems during EEG acquisition may also lead to artifacts, such as improperly applied electrodes leading to poor quality signals during recording.

Artifacts included in the EEG data selected for analysis skew results of QEEG maps. If included in the selection, the quantitative analysis package classifies the artefactual EEG signal into a corresponding frequency band, which is then incorporated into the brain maps. Eye blink artifact (Figure 1) is low frequency by default and most prominent at frontal electrode sites. If included in the EEG selections for analysis, eye blink artifact data analyzed by a QEEG package results in artificially elevated frontal delta activity that disappears from the brain maps when the eye blink artifact is removed from the selections. Since artifacts skew the data, they must be edited from the record prior to analysis.

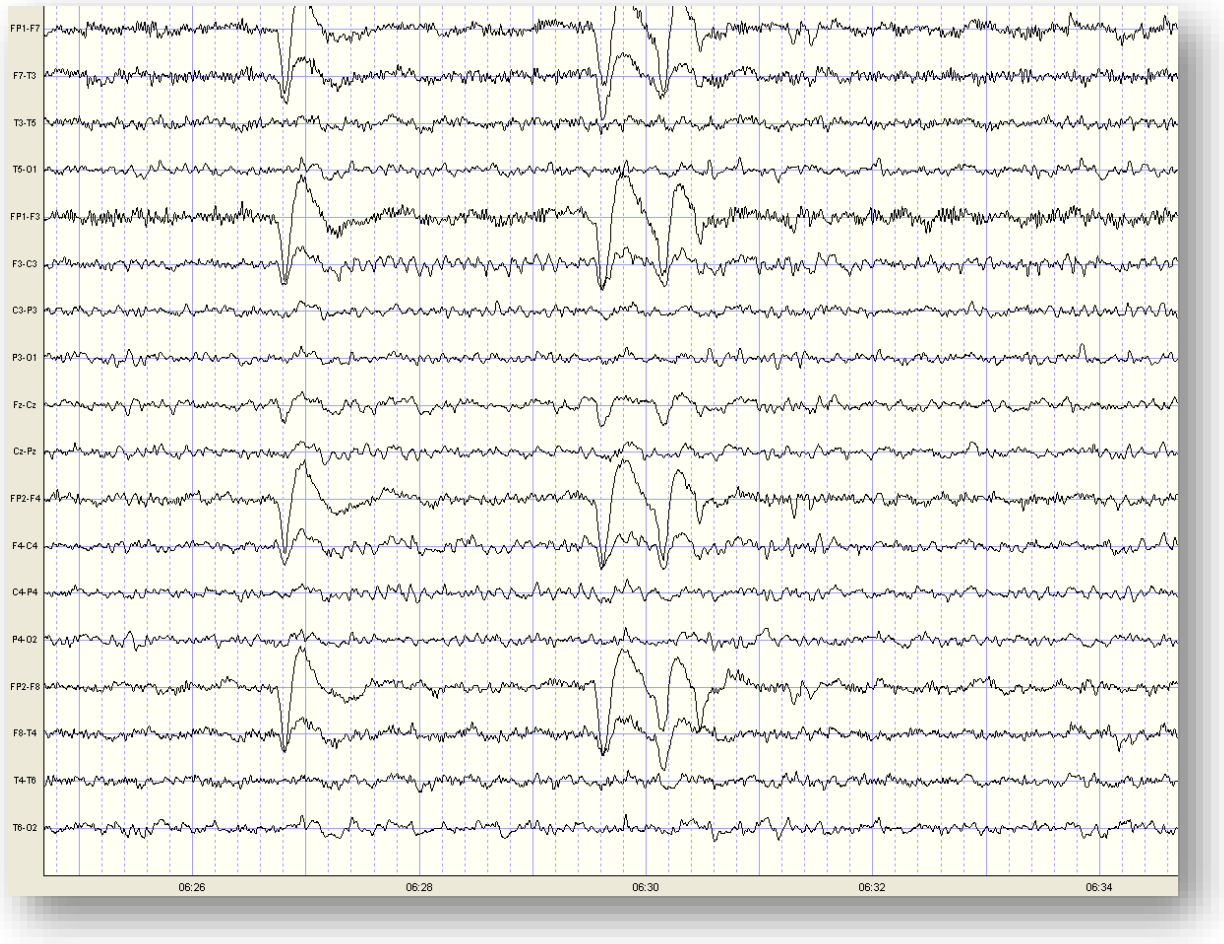


Figure 1 – Eye blink artifact during an eyes open EEG recording.

There are several approaches to clip artifacts from the EEG. Perhaps the most widely used type of approach is manual artifact removal whereby a human physically inspects the full EEG recording for artifacts and manually selects segments of EEG to be included or excluded from the analysis (Hammond & Gunkelman, 2011). Computerized automatic artifacting software may be used to detect and remove artefactual EEG from the recording. The QEEG Professionals database package offers a Standardized Artifact Rejection Algorithm (S.A.R.A.) which automatically deartifacts an entire EEG in four steps: “epileptiform episode detection, filtering, detection/rejection/interpolation of noisy channels, and detection/rejection of EEG-

segments containing artifacts" (pg. 3, Keizer, 2014) before performing the QEEG analysis. Automatic Z-score artifact rejection and selection automatically selects EEG data based off instantaneous Z score deviations equal to or less than a given threshold – i.e., activity within 1.5 standard deviations is selected (Thatcher, 2015). Template matching automatic artifacting allows the user to manually select short, artifact free template sections of data (i.e., 10 seconds) and automatically select all other segments of the EEG recording that match the template (Thatcher, 2015). Thatcher recommends visually examining the automatically selected data when using employing Z-score and template matching artifacting methods to ensure that the automatic artifacting methods did not select artefactual data. Independent component analysis (ICA) is an artifacting method that uses signal processing techniques to reconstruct the EEG signal with the artifact removed (Kroptov, Thatcher, Kerasidis, & Cantor, 2017). While this technique successfully deletes the artifact from the record, the authors note signal reconstruction alters the coherence and phase properties of the waveform that compromises the reliability of processing ICA de-artifacted data.

Quantitative EEG

Quantitative EEG (QEEG) analysis compares acquired EEG samples to a normative database of EEG data, producing Z scores for various EEG metrics (Collura, 2014). Once artifacts are removed from the record, the remaining data is essentially compressed into inferential statistics about the EEG sample. QEEG enhances the clinical utility of the EEG by identifying statistical patterns of abnormalities of patients through comparison to age matched normative data in a cost-effective method (Prichep, 2005). Commercially available QEEG reference database packages allow users to compare EEG data acquired in the clinic to the

database. Examples of commercially available QEEG database packages are Applied Neuroscience, Inc. (Largo, FL), BrainDx (Suwannee, GA), and QEEG-Professionals (Eindhoven, Netherlands). Results of QEEG analyses depict Z-scored brain activity in color coded brain maps. Brain maps may be topographic or three dimensional depending on the QEEG technique employed. Brain regions functioning within mean ranges (i.e., +/- 1.5 Zs) are often shaded neutrally (green or grey), while regions above the average range are shaded warmer colors (yellow, orange, red) and regions below the average range are shaded cooler colors (teal, blue, purple).

Due to the heterogeneity of EEG activity, QEEG results are applied to the patient relative to his or her clinical presentation because similar brain activity patterns may be present in different disorders (Rapp et al., 2015). For example, excess beta activity denoted as a positive Z score may be seen in anxiety, insomnia, migraines, over-focused or OCD-like tendencies, or a combination of these symptoms. Specific EEG characteristics may be associated with a given pathology, but the pathology does not dictate a specific EEG profile. Therefore, QEEG reflects underlying brain function and results are considered within the context of the patient's symptoms.

Common QEEG measures are absolute power, relative power, amplitude asymmetry, coherence, and phase lag (Collura, 2014). Absolute power measures the total amount of an EEG frequency band that is present in a given channel or region (Hughes & John, 1999). Relative power measures the amount of an EEG band present compared to the total of all EEG bands (Collura, 2014). Amplitude asymmetry measures the ratio of EEG frequency between channels or regions (Hughes & John, 1999). Statistically normal asymmetry indicates a typical balance of EEG frequency, while abnormal asymmetry reflects an imbalance. Atypical frontal lobe alpha

asymmetry is often implicated in cases of depression (Collura, 2014). Coherence measures synchronization between EEG electrodes that reflects the amount of cortical connectivity and processing (Collura, 2014; Hughes & John, 1999). Hypercoherence suggests too much information sharing while or hypocoherence indicates deficient information sharing. Phase measures the speed of information sharing between cortical regions, which may be too fast or slow (Collura, 2014). See Figure 2 for a sample topographic brain map from the BrainDx QEEG database.

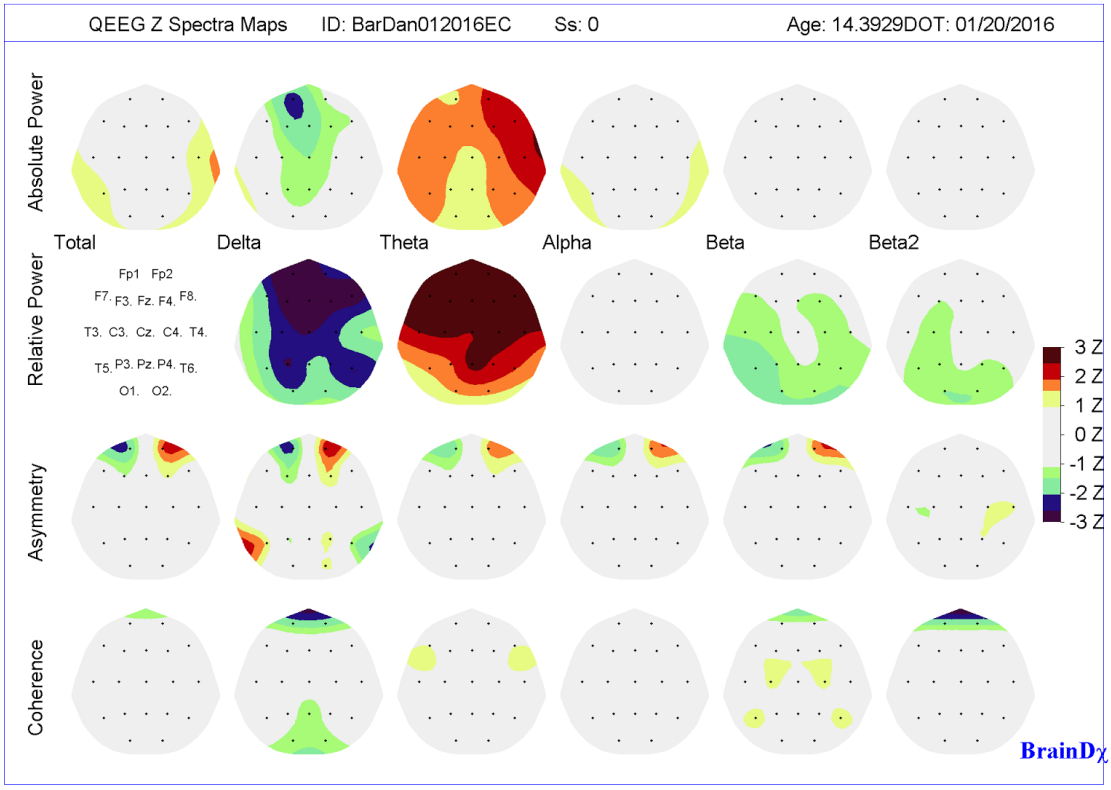


Figure 2. Sample BrainDx QEEG Topographic Map depicting absolute power, relative power, amplitude asymmetry, and coherence across delta, theta, alpha, beta, and beta2 frequency bands (Phase not shown).

QEEG highlights atypical brain activity in the tails of the Gaussian distribution beyond a theoretical Z score significance threshold. The clinician interpreting QEEG data must decide where natural variation stops and deviant, clinically relevant data begins. Too high of a threshold may exclude clinically relevant data while too low of a score risks ascribing pathology to otherwise naturally variable EEG activity. Basic principles of statistics suggest a significance threshold of +/- 1 Z considers EEG activity outside of 68.3% of the population, a threshold of +/- 2 Z considers EEG activity outside of 95.5% of the population as clinically relevant, and a threshold of +/- 3 Z refers to deviant activity outside of 99.7% of the population (Field, 2009). Discussions with clinicians at neurofeedback and QEEG conferences revealed an array of preferences for different QEEG relevance thresholds, but most clinicians choose to use a significance threshold of 2 or 3 Z scores.

QEEG data is described with terms that indicate the directionality of the QEEG metric. Data in the right tail of the distribution with positive Z scores greater than the defined Z score threshold are described as increased or excessive to communicate a finding that is above the expected normal range. Data in the opposite tail with Z scores less than the negative counterpart of the Z score threshold are decreased or reduced to suggest a finding of less of a specific EEG frequency than is expected. In many cases, simpler terms as “higher” or “lower” may be used. This language does not communicate hyperactivity or hypoactivity of a particular brain region; rather, it is an indication of the degree a QEEG frequency is present or absent.

Discussion of activation levels of brain regions requires consideration of the nature and level of conscious awareness characteristic of different EEG frequency bands in order to relate QEEG findings to function and related activation. For example, alpha activity is related to a state of wakeful rest and relaxation, beta indicates active processing, and delta is the natural

sleep EEG rhythm but indicates dysfunction in the wakeful state. QEEG results that demonstrate increased alpha, beta, or delta in the frontal lobe denoted by a Z scores of +3 Z suggest different levels of frontal lobe activation. Of the three findings in this example, increased frontal lobe beta activity indicates the greatest level of activation, and increased delta activity suggests the lowest level of activation. If the directionality of the findings were reversed to a Z score of -3 Z for each sample frequency, completely different levels of activation would be implicated with decreased beta suggesting the lowest activation of the three examples. Thus, it is critical to consider EEG frequency and Z score direction before drawing conclusions on cortical activation based on the QEEG.

QEEG Database Parameters

The statistical values used in QEEG metrics are derived from sample populations where EEG data is collected from individuals across the lifespan to gather differences in the EEG that vary by age. The EEG is broken into target metrics through a Fourier transform or joint time-frequency analysis (JTFA) that computes means and standard deviations on the metrics based on brief variations in the target values to create a spectrum of EEG power across the entire EEG frequency spectrum (Thatcher et al., 2003; Collura, 2014; Hughes & John, 1999). Different QEEG databases have been created from different populations and methods, resulting in a large degree of overlap in QEEG results but differences do exist between database results. The purpose of the following section is to describe the construction of three popular QEEG databases: BrainDx (Suwannee, GA), Applied Neuroscience, Inc. (Largo, FL), and QEEG-Professionals (Eindhoven, Netherlands).

The NYU database used in BrainDx is composed of 154 adults and 310 children between ages 6-90 (BrainDx, 2016; Prichep, 2005). Individuals with normal developmental, medical, and psychosocial histories were selected for analysis. Adults were excluded for a history of drug use, head injury or loss of consciousness, previous EEG or neurological examination, or febrile convulsions (BrainDx, 2016). Children were excluded for the presence of extreme prenatal or perinatal trauma, extreme febrile illness, loss of consciousness related to head injury or convulsions, extreme behavior problems, school failure at any level, or Wide Range Achievement Test score below 90 on any index. EEG data was recorded in 20-30 minute recordings in the eyes closed state. A split-half regression method was used to construct the Z score norms from one half of the data, independently replicated on the second half, then combine the halves. Subjects were added to the test population until the addition of a new subject did not alter the regression model. BrainDx worked with Pascual-Marqui in the construction of sLORETA Z scores. Using the same dataset and methodology as before, sLORETA normative data was constructed by computing voxel norms and age regression equations were used to standardize the measures. The frequency bands defined by BrainDx are as follows: delta (1.5-3.5 Hz), theta (3.5-7.5 Hz), alpha (7.5-12.5 Hz), beta (12.5-25 Hz), and beta2 (25-35 Hz). Z scores are calculated for the frequency bands and in 0.3 Hz increments. The NYU/BrainDx database will be the focus of the present study. Other databases are presented for alternative perspective offered by additional database packages.

The ANI database is constructed of 678 individuals ranging from two months of age to 82 years of age (Thatcher, 2015). Individuals were screened based on medical, psychosocial, and neurological history, as well as neuropsychological batteries (Thatcher et al., 2003), similar to the BrainDx database. Subjects were organized into 22 age groups with six-month age

overlaps to produce age matched norms by calculating two year means with a sliding average. A Fourier transform was applied to the EEG data to extract the EEG variables and establish a Gaussian distribution (Thatcher et al., 2003). EEG metrics are classified into broad frequency bands for delta (1-4 Hz), theta (4-8 Hz), alpha (8-12 Hz), beta (12-25 Hz), and high beta (25-30 Hz) (Thatcher, 2015). Z scores are available for the broad frequency bands and single hertz bins.

The QEEG Professionals (QEEG Pro) database uses subjects age 1 through age 75 from a clinical population, using 1,482 subjects in the eyes closed condition and 1,231 subjects in the eyes open condition (Keizer, 2014). This database differs in that it was constructed from a clinical population, compared to a population constructed of individuals that passed exclusion criteria whom are deemed healthy norms. Clients that presented to the Neurofeedback Institute Netherlands were evaluated with a clinical EEG and questionnaire. The CNC1020 Questionnaire (EEG Professionals; Eindhoven, Netherlands) assessed 47 DSM psychopathologies with 292 Likert scale items. Nineteen channel EEGs were recorded on clients and artifact was removed from the EEGs using S.A.R.A., QEEG Pro's automatic artifacting algorithm. The total 1,482 individuals were divided into 150 subgroups each consisting of 200 individuals whose ages were closest to the age bin in question. Keiser (2014) performed a regression analysis of the log-transformed QEEG metrics and log-transformed questionnaire data for 47 psychopathologies. Means and standard deviations for all QEEG metrics were calculated from the residuals of the regression equation, which represent variance in the EEG data unaccounted for by any psychopathology to be taken as normal cortical functioning (Keiser, 2014). These population statistics are applied in all QEEG Pro topographic or sLORETA maps for single hertz bins and broad frequency bands. The broad frequency bands defined are delta

(1-3 Hz), theta (4-8 Hz), alpha (8-12 Hz), beta (15-20 Hz), and gamma (35-54 Hz) (Keizer, 2014).

Standardized Low Resolution Electromagnetic Tomography

Low Resolution Electromagnetic Tomography (LORETA) is the application of the inverse problem to estimate the location of electrical generators in the brain by measuring the electrical fields at the scalp (Pascual-Marqui et al., 1994). As LORETA was subject to localization error, standardization of the measurements eliminated localization error and resulted in standardized LORETA (sLORETA; Pascual-Mariqui et al., 2002). LORETA images brain activity in 2,394 voxels at 7 mm spatial resolution, while the improved sLORETA images 6,430 voxels at 5 mm spatial resolution (Collura, 2014). Given that sLORETA is an approximation, the depicted electrical source is blurred and not a fine point; although, the three-dimensional distribution maximizes the similar orientations and magnitudes of neighboring neuronal populations to improve accuracy.

Source localization using sLORETA applies electrodynamics to electrophysiological and neuroanatomical measures to approximate the location and current density of post-synaptic potentials generated by pyramidal neurons (Pascual-Marqui et al., 2002). sLORETA calculations require, at minimum, nineteen channels of EEG data to estimate cortical activity in internal brain space, giving rise to the concept of the density of electrical current generated from a discrete source. This is otherwise known as current source density (CSD). It is important to distinguish between amplitude and current density. Given that amplitude refers to the height of a wave in two dimensions, CSD may be conceptualized as a three-dimensional version of amplitude. In terms of EEG measured at a point on the scalp, amplitude depicts the electrical

energy generated by the cerebral cortex below the recording electrode. When discussing three-dimensional brain activity, the terminology must be adjusted to reflect electrical activity a volume of a brain region. Since sLORETA requires at least nineteen channels to compute source localization, amplitude is inaccurate in 3D space because amplitude describes a wave at one channel. Therefore, the term current source density refers to the density of electrical current generated by a certain source and describes the magnitude of an EEG frequency band in a volumetric brain region.

Group statistics provided by QEEG database packages may be combined with sLORETA properties to generate Z scores of CSD and quantify the source localization findings by comparison to normative data. Z score data for sLORETA allows the user to quantify how far from the norm a given region of interest is functioning. Z score sLORETA data is readily available for CSD only; there are presently not sLORETA Z scores for connectivity or asymmetry metrics although these tools are in development. See Figure 3 a-d for examples of sLORETA imaging from two different databases depicting the same EEG sample.

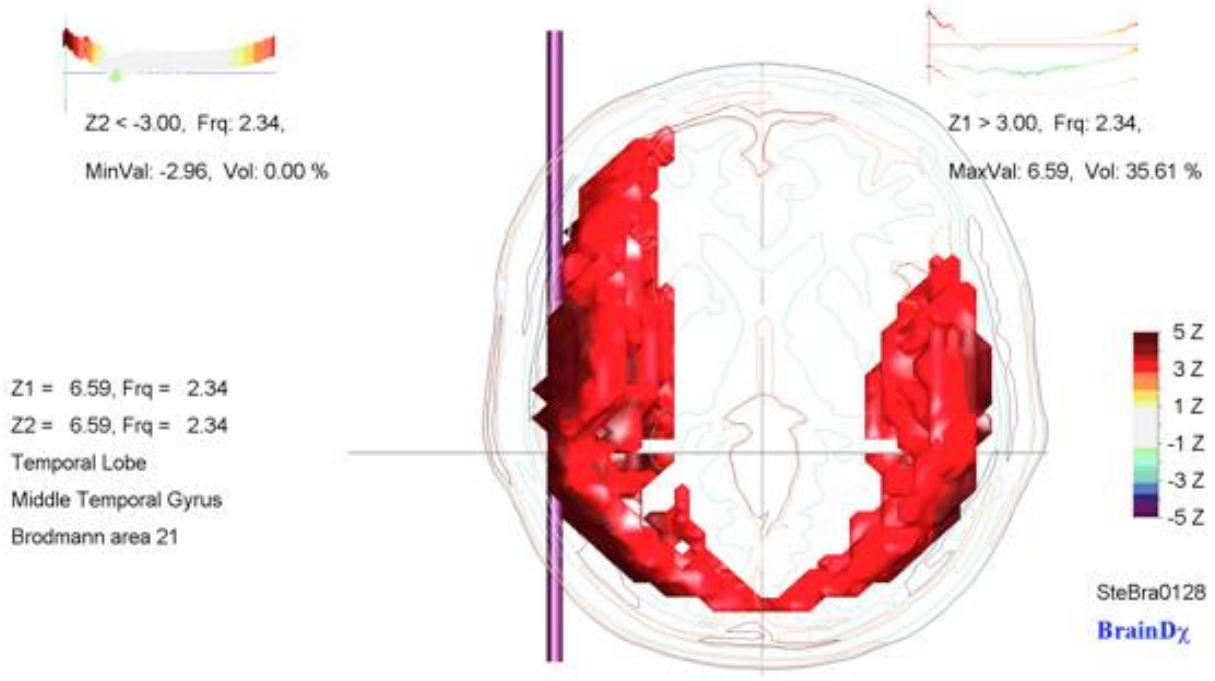


Figure 3a. sLORETA imaging from BrainDx QEEG database comparison depicting 2.34 Hz delta activity in the temporal, occipital, and left frontal lobes with a maximum Z-score of 6.59 located in the left temporal lobe, middle temporal gyrus, Brodmann area 21; seen from a superior perspective.

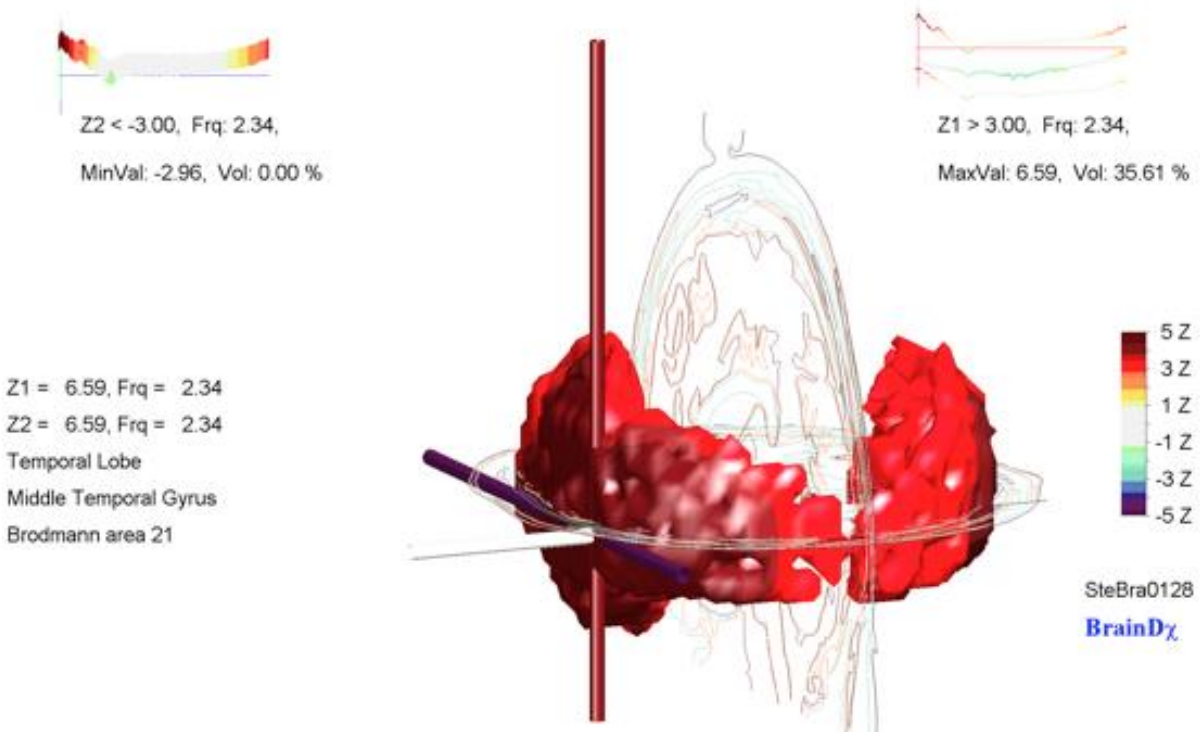


Figure 3b. Alternate view of BrainDx sLORETA imaging from Figure 3a; seen from left posterior region looking forward from behind the imaginary left ear.

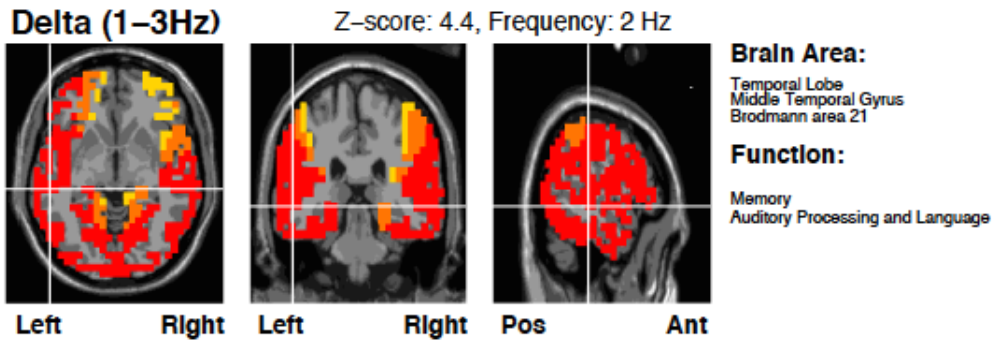


Figure 3c. Summarized sLORETA imaging from QEEG Pro depicting delta activity; maximum Z score is 4.4 for 2 Hz located in the left temporal lobe, middle temporal gyrus, Brodmann area 21.

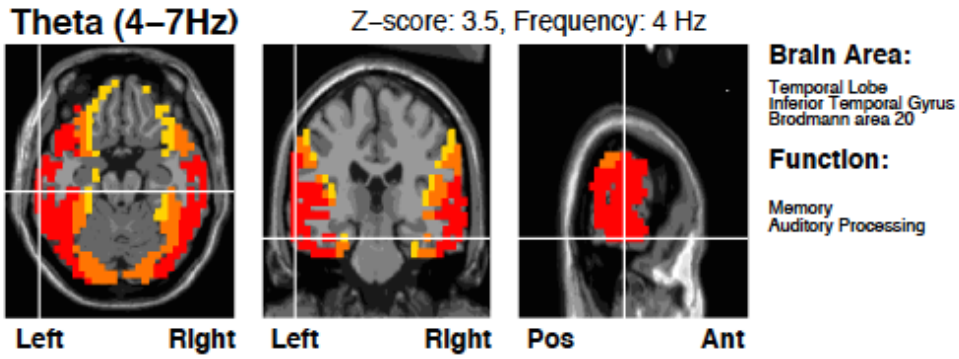


Figure 3d. Summarized sLORETA imaging from QEEG Pro depicting theta activity; maximum Z score is 3.5 for 4 Hz located in the left temporal lobe, middle temporal gyrus, Brodmann area 20.

The BrainDx Report Generator (BDxRG) applies the normative database from the NYU QEEG database and was the sLORETA processing software utilized in the present study. The sLORETA volumetric display in the BDxRG displays activity above or below a user-defined threshold with no scores from the middle of the distribution displayed. An image of brain volume above or below a positive or negative Z score threshold, respectively, at a given EEG frequency is depicted on a 3D head map. The head map indicates the cortical lobe (i.e., temporal lobe), sub-lobar structure (i.e., middle temporal gyrus), and corresponding Brodmann Area (i.e., BA 21) of the maximum or minimum Z score displayed and a value for the percent of grey matter volume above or below the defined Z score threshold. The process differs from topographic QEEG maps, which display data for all points along the Gaussian distribution where Z scores towards the center of the distribution are typically indicated by grey or light colors, while scores approaching the tails are increasingly darker shades of blue or red.

The defined Z score threshold for viewing EEG data in the sLORETA volumetric display is an informed decision of personal preference for the user. The clinic where the study was conducted utilizes a Z score viewing threshold of 2.5 Z, illustrating EEG activity outside of

98.8% of the population. Clinical use of a viewing threshold of 2.5 Z developed through the collaboration of the PI with the neurologist and medical director of Chesapeake Neurology Associates. Initially, we employed a threshold of 3 Z but after several months of use we felt that useful information within three standard deviations was missed. However, there were concerns that a reduced threshold of 2 Z would include neurotypical EEG activity due to natural variability. This led to compromise on a threshold of 2.5 Z to image activity that is further than two and a half standard deviations from the mean. Although anecdotal, viewing sLORETA QEEG data less than -2.5 Z and greater than 2.5 Z has consistently proven useful in identifying clinically relevant information about a patient's brain physiology in cases of concussion injury, as well as ADHD, depression, anxiety, and other neurological or psychological disorders where QEEG data are applied at Chesapeake Neurology Associates. It is important to note that cases where a patient presents for treatment but QEEG analysis at +/- 2.5 Z fails to reveal cortical deregulation measured by sLORETA due to the heterogeneity of EEG. That is, application of the standard 2.5 Z threshold masks deregulated brain activity underlying the disorder. Such cases benefit from reduction of the Z score threshold (i.e., +/- 2 Z) to image potentially useful data relevant to the presenting problem.

sLORETA-based current density Z-scores and affected brain volumes are the focus of the present study, which seeks to add to the current literature on concussion injury, QEEG, and neurofeedback. mTBI results in changes in EEG power, coherence, and phase depicted by topographic maps (Thatcher, 1989; Thatcher, 2006). Past research using EEG source localization to analyze brain injury demonstrated EEG changes, specifically increased low frequency activity in frontal and temporal regions (Ponamarev et al., 2010; Thatcher, 2011). A recent literature review of QEEG and brain injury by Rapp et al. (2015) omitted LORETA and

sLORETA analysis, suggesting room for additional research in the field of EEG source localization and brain injury.

Source localization analysis extracts useful data where topographic QEEG mapping fails to demonstrate significant cortical deregulation. Anecdotal experiences in the clinic yield cases where topographic brain mapping after concussion did not reveal clinically relevant findings, but sLORETA analysis of the same data unmasked significant cortical deregulation. As stated previously, the BDxRG was the QEEG package applied the current study. The BDxRG is the only QEEG software with sLORETA capability that provides a discrete value for percent of grey matter volume deviant beyond a specific, user-defined threshold. Other packages provide data about the percentage of deviant brain volume, but the data are visualized in a continuous scale less ideal for graphical or statistical analysis. Coherence measures will not be included in the present study because sLORETA measures of coherence are not offered by the BDxRG package, although such methods pose a useful tool in the study of concussion and other brain injuries and warrant further study.

Neurofeedback: EEG Biofeedback

The Association for Applied Psychophysiology (AAPB), the Biofeedback Certification International Alliance (BCIA), and the International Society for Neurofeedback and Research (ISNR) define biofeedback as:

> *…a process that enables an individual to learn how to change physiological activity for the purposes of improving health and performance. Precise instruments measure physiological activity such as brainwaves, heart function, breathing, muscle activity, and skin temperature. These instruments rapidly and accurately "feed back" information to the user. The presentation of this information – often in conjunction with changes in thinking, emotions, and behavior – supports desired physiological changes. Over time, these changes endure without continued use of an instrument (AAPB, 2011 -* http://www.aapb.org/i4a/pages/index.cfm?pageid=3678*).*

The typical biofeedback training loop involves an instrument recording a discrete biological activity of interest, the trainee receiving reinforcement for achieving a desired activity level and resulting awareness and possible volitional control of the biological activity (Demos, 2005). Neurofeedback, also known as EEG biofeedback, is biofeedback of brain activity generated by grey matter of the cerebral cortex. Brain activity information is fed back to the user in real time in the form of audible tones or computer games that indicate when the user's brain waves meet the training criteria. This process allows for learned self-regulation as the individual passively trains their brain to produce more efficient EEG patterns. Self-regulation is learned through a series of sessions over several weeks to reinforce optimal brainwave patterns that persist after the end of an individual training session and the termination of treatment. Neurofeedback capitalizes on the principle of neuroplasticity, that the dynamic brain fluctuates in response to input from the external world, to promote change in electrophysiologic functioning by operant conditioning (Collura, 2014).

The separate efforts of Joe Kamiya and Barry Sterman are largely credited in the discovery of neurofeedback (Demos, 2005). Kamiya explored human conscious awareness of brain activity, pioneering alpha enhancement training to enter a state of emotional learning and psychological growth (Demos, 2005). In 1970, Nowlis and Kamiya used a neurofeedback system to play an audible tone when the user's alpha activity increased above a given threshold. Subjects were instructed to increase or decrease the occurrence of the tone at different times when their eyes were open or closed. This revealed a difference in the user's subjective experience during a given task. When instructed to increase the alpha tone with the eyes closed, the user felt more relaxed, while decreasing the alpha tone during eyes open led to feelings of

attentiveness. Nowlis and Kamiya concluded that humans can control their alpha rhythm and the alpha rhythm impacts conscious awareness (Nowlis & Kamiya, 1970).

Sterman determined that cats can regulate the production of the sensorimotor rhythm (SMR; 12-15 Hz) by using a neurofeedback loop to condition increased SMR amplitude in the cats (Demos, 2005). Shortly thereafter, exposure to rocket fuel became a suspected causal factor for seizures when NASA employees working with rocket fuel began to suffer seizures. NASA commissioned Sterman to investigate the relationship between rocket fuel exposure and seizures. In his research, Sterman exposed cats, some of which were from his previous SMR research, to rocket fuel and observed increases in seizure activity in the animals. Cats trained to increase SMR amplitudes from the previous neurofeedback research demonstrated greater resistance to seizures upon exposure to rocket fuel compared to the other felines because of the inhibitory regulation provided by the SMR activity (Sterman, 1996). This suggested that self-regulation of brain activity provided physiological benefit. Presently, SMR neurofeedback is widely used in the treatment of pediatric attention deficits, seizures, and insomnia (Collura, 2014).

Traditional neurofeedback protocols involve the enhancement or inhibition of EEG amplitudes at specific electrode sites on the scalp (Demos, 2005). To reinforce the desired brain state, a tone sounds when a given EEG condition is met. Examples of common traditional protocols are alpha enhancement in posterior regions, SMR enhancement in the somatosensory region, or theta inhibition in frontal regions. Multiple frequency bands may be trained simultaneously to achieve the desired effect. Rewarding SMR, the resting rhythm of the motor system as discussed above, and inhibiting theta, a rhythm associated with distractibility, in the somatosensory region theoretically increases brain wave patterns that are intrinsically calming to

that brain region. These training protocols seek to encourage or discourage the presence of the respective EEG frequency, thereby affecting the electrophysiology of the trained region.

The advent of z-scored QEEG databases allowed for the introduction of z-score neurofeedback, where feedback is contingent on comparison to population statistics rather than thresholds for raw amplitudes (Collura, 2014). Feedback is provided when QEEG metrics are within a desired z-score range, such as below +2 Zs or within +/- 1 Zs. Adaptations of z-score neurofeedback allow for reinforcement when a percentage of z-scores are within a desired range, known as PZOK for "percent of Z scores OK" (Collura, 2014). Reinforcement of a range of Z scores allows some scores to remain outside of the target range, allowing individual differences within the subject's EEG to endure as the overall EEG is trained towards the middle of the bell curve (Collura, 2014). For example, PZOK neurofeedback may reward when 70% of z-scores are within +/- 1 Z. This training was first performed with four electrodes and gradually evolved to include more electrode sites. Z-score neurofeedback is not an attempt to "normalize" the brain; rather, the goal of Z-score neurofeedback is to provide a reference point for the brain and allow variability as percentages of Z sores in statistically optimal ranges are reinforced and the brain is guided towards more advantageous and efficient patterns of cortical processing (Collura, 2014).

Application of sLORETA technology to neurofeedback protocols enables more precise neurofeedback training. Three-dimensional brain structures may be targets for training, such as the entire frontal lobe or the posterior cingulate cortex. Training on brain regions of interest (ROIs) may proceed with or without Z scores. Current source density (CSD) may be rewarded or inhibited in a specific direction. This is conceptually similar to standard amplitude training where the EEG feedback occurs when the amplitude is above or below threshold. In terms of

CSD, feedback is provided when the CSD in the target ROI meets the threshold criteria. QEEG packages that apply population statistics to sLORETA allow Z score training of regions of interest similar to Z-score neurofeedback methods described above.

Neurofeedback is implemented in clinical settings as a noninvasive intervention for various neurological or psychological problems as indicated above by Collura (2014). The American Academy of Pediatrics recognizes neurofeedback as a treatment for ADHD that provides sustained benefits for at least 6 months after intervention (Steiner et al., 2014). Neurofeedback has been used as an intervention for traumatic brain injury but requires further investigation as an evidence-based practice. Neurofeedback is currently ranked as "Level 3 - Probably Efficacious" by the statement of efficacy on evidence-based practice in biofeedback and neurofeedback by the Association for Applied Psychophysiology and Biofeedback (AAPB; Yucha & Gilbert, 2004). A pilot study by Kerasidis and the PI demonstrated that excessive slow wave activity is related to the presence of concussion related symptoms (Kerasidis & Ims, 2017). The purpose of the current study is to investigate neurofeedback as an intervention for acute sport-related concussion and contribute to the literature regarding concussion and neurofeedback.

Neurofeedback Protocol Design

Concussion leads to functional disturbance that underlie concussion related symptoms (McCrory et al., 2017) demonstrated by sLORETA measurements (Kerasidis & Ims, 2017). Due to the diversity of concussion injury, subsequent symptoms, and electrophysiological deregulation following concussion, a universal approach to neurofeedback training is not ideal. Clinical presentation, QEEG data, neurocognitive test results, and concussion symptoms inform neurofeedback protocol design.

Deregulated brain regions of interest indicated by statistically deviant EEG patterns are typically selected for training using Z-score and CSD neurofeedback training methods. If highly symptomatic, neurofeedback sessions may provoke symptoms or fatigue the patient. To mitigate the balance of providing challenging neurofeedback without overworking the patient's brain, the PI developed methods of reducing the demands of the neurofeedback protocol through years of experience with neurofeedback. Applying simultaneous Z-score and CSD neurofeedback on a symptomatic individual typically intensified symptoms and patient discomfort. Removal of CSD training criteria offered more gentle neurofeedback training through Z-score methods that the patient tolerated without abreaction. After several sessions of surface and sLORETA Z-score neurofeedback, reintroduction of the CSD criteria did not provoke abreaction and contributed to lessening the patient's symptoms compared to Z-score training alone. With information from QEEG assessment guiding the neurofeedback protocol, the patients' condition at session provides vital information for protocol decision making on the day of a given session.

Neurofeedback Session Structure

At the beginning of the first neurofeedback session in a series of neurofeedback treatment, the session administrator, often a neurofeedback technician, outlines the neurofeedback process and provides the patient with instructions for the sessions, such as remaining still to reduce EEG signal artifact and passively observing the auditory or visual neurofeedback rewards. Patients are advised that auditory or visual feedback events are decided more by the training settings and less by his or her conscious control. Subsequent neurofeedback sessions begin with dialogue between the patient and session administrator regarding symptom

changes since the previous session. Reminders for session instructions are frequently provided to the patient.

With the patient seated, the technician cleans electrode sites and applies the electrode cap, ear-clip reference electrodes, and conductive electrode gels. At CNA, a computer with two monitors is used to administer the session. The neurofeedback administrator views a primary computer screen, which is not visible to the patient, while the patient was sits in a reclining chair in front of a secondary computer screen. EEG signal quality is assessed with an on-screen impedance meter and visual inspection of the raw waveform. Once the signal is appropriate, headphones are placed on the patient's head and the session begins. On the primary screen, the session administrator monitors EEG signal quality and reward success outputs. The technician adjusts training thresholds if necessary to maintain a reward rate of approximately 50-70%, meaning the neurofeedback training criteria are met 50-70% of the time.

Visual and auditory feedback is provided if training in the eyes open condition, but if the eyes are closed then only auditory feedback is provided. The patient watches the auxiliary screen, which displays a neurofeedback game or DVD movie chosen by the trainee. Visual feedback is provided by modulating game progress or movie screen brightness. Most patients watch a movie, where the trainee watches the movie play continuously without interruption and the movie is more visible when the trainee's brain meets criteria and less visible when not. Audible reward tones play on the headphones when the trainee meets criteria. When a movie is displayed on screen for visual feedback, the audio feedback tones play at a reduced volume in the background of the normal movie sound effects. After the allotted session time passes, the patient is disconnected from the equipment and leaves the appointment.

QEEG, Neurofeedback, and Brain Injury

Decades, if not centuries, of brain research have revealed the correlation between brain regions and psychological functioning. The work of scientists like Paul Broca, who correlated a region of the left frontal lobe with verbal expression after observing a patient with a lesion to the left frontal cortex (Kerasidis, 2015). Present understanding of concussion injury posits that concussion symptoms reflect functional disturbance caused by biomechanical injury rather than structural injury (McCrory et al., 2017). Modern neuroimaging technologies provide insight to the structure and function of the brain in high resolution.

In the field of magnetic resonance imaging (MRI), related techniques like diffusion tensor imaging (DTI), arterial spin labeling (ASL), functional MRI (fMRI), and blood oxygen level dependence (BOLD) map grey and white matter functioning and may be used to investigate changes in brain function related to concussion (Churchill et al., 2017). The results of this study depicted changes in brain function related to injury, but heterogeneity of concussion and variance of findings complicated the Churchill et al.'s abilities to draw clear conclusions on the effect of concussion on various MRI measurements. Measures of CBF following concussion show differences in CBF between concussed subjects and non-concussed controls, as well as different CBF patterns between distinct concussion symptom clusters (Churchill, Hutchison, Graham, & Schweizer, 2017). In a MRI study of collegiate athletes at post-injury and recovery, brain regions affected by concussion were involved in visual and sensory integration and cognitive response, and deficits in these functions were often reflected in post-concussion symptoms (Churchill et al., 2017). Churchill et al. (2017) also demonstrated the brains of the athlete subjects were continuing to recover although the athletes were cleared of concussion and had successfully returned to play, which bears relevance to the present study.

Electrophysiology provides an alternative perspective on brain function. A recent literature review of mild traumatic brain injury (mTBI) detection using electrophysiological techniques found that mTBI injury results in measurable EEG and QEEG abnormalities (Rapp et al., 2015). In cases of mild traumatic brain injury (mTBI), high frequency amplitudes typically decrease, especially in frontal regions, low frequency amplitudes increase, and coherence patterns change (Thatcher et al., 1999). Out of the limited available research applying sLORETA to concussion, Ponamarev et al. (2010) used sLORETA to assess patients with post-concussion syndrome compared to healthy subjects and measured increased delta, theta, and alpha, especially in the frontal and temporal lobes.

However, similar electrophysiologic abnormalities may be present in other neuropsychiatric disorders and additional assessments should be included in conjunction with EEG in the evaluation of mTBI. This sentiment was summarized by Rapp et al., who concluded the clinical utility of the electrophysiology in mTBI assessment was not invalidated by the non-specific nature of QEEG, and this assessment of brain injury is best used as part of a discriminant analysis rather than isolated spectral analysis (Rapp et al., 2015). This supports the findings of Thatcher et al., who used a discriminant analysis to successfully discriminate between mTBI patients from healthy controls with greater than 90% accuracy (Thatcher et al., 1989), albeit the mTBI patients in Thatcher's study were more severely injured compared to a typical concussion case. QEEG is not a perfectly specific assessment of concussion, but it does provide useful information to complement the clinical picture despite the lacking specificity (Rapp et al., 2015) whereas standard neuroimaging techniques fail to detect abnormalities (McCrory et al., 2017).

Kerasidis and Ims (2017) tracked sLORETA QEEG data on athletes from concussion injury to medical clearance and found increased amplitudes of low frequency activity following

concussion injury. Data from the QEEGs acquired after clinical recovery from concussion demonstrated a reduction in the low frequency amplitudes; however, statistically abnormal activity (i.e., Z-score > +/- 3) persisted beyond clinical recovery albeit the patient was free of concussion-related symptoms. See Figure 4 for comparison of post-concussion and post-recovery QEEG data on a subject who suffered a head injury after colliding with a concrete wall while sledding. The QEEG study by Kerasidis and Ims was similar to the MRI study by Churchill et al. (2017), both of which revealed brain alterations following concussion injury that endured past clinical recovery. The data from this pilot study comprises the control group of the present study and will be described further in Methods.

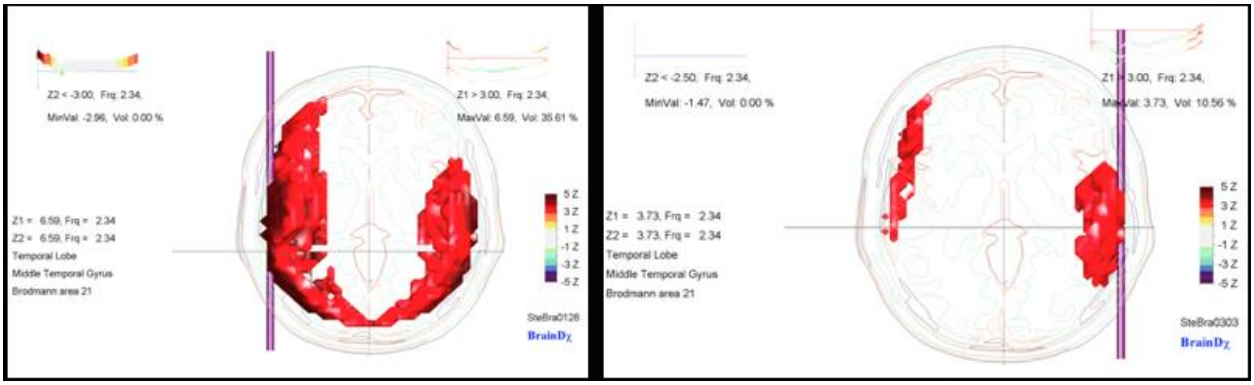


Figure 4. Post-concussion injury sLORETA QEEG data depicting elevated delta activity (left image); post-recovery sLORETA QEEG data depicting reduced, yet elevated, delta activity.

Although concussion reflects functional disturbance, there is typically no structural injury observed on traditional imaging methods (McCrory et al., 2017). Judicious QEEG methods extract useful information from the background rhythm of the digital EEG through application of group statistics to suggest how far findings deviate from the mean range. The heterogeneity of both concussion and EEG demands scrutiny and modesty when discussing the effect of head injury on electrophysiologic measures of the brain. EEG variability exists in healthy and

disordered patients alike (Nuwer, 1997), and QEEG abnormalities present in concussion are similarly observed in other neuropsychiatric disorders (Rapp et al., 2015; Nuwer, Hovda, Schrader, & Vespa; 2005). Therefore, activity at the extremes of the distribution that is further from the mean is less likely due to natural variation and suggests regional dysfunction which may be considered within the clinical context of the patient's presenting problem and symptoms. Because EEG serves as a reflection of the brain physiology underlying cognitive, physical, and emotional functioning, neurofeedback should enable the concussed patient to reinforce optimal EEG activity in regions disrupted by injury, potentially improving recovery time and cortical functioning.

HYPOTHESIS

The principle investigator hypothesizes:

(1) Post-concussion EEG testing using sLORETA source localization will demonstrate elevated delta and theta activity in accordance with previous research;

(2) Cortical recovery from concussion injury will be indicated by normalization of sLORETA Z score measurements and reduction in the percent of affected grey matter volume;

(3) Neurofeedback interventions to reinforce optimal EEG frequencies, especially a reduction of low frequency delta and theta EEG activity, will reduce the presence of concussion related symptoms;

(4) Because sLORETA QEEG, as well as MRI, have shown brain abnormalities persist past clinical concussion recovery, concussed subjects treated with neurofeedback will demonstrate fewer abnormalities after recovery;

(5) And, use of the intervention will decrease recovery time compared to natural recovery and/or treatment according to recommended clinical guidelines.

MATERIALS & METHODS

Subject Population and Clinical Care

The study was performed at Chesapeake Neurology Associates (CNA) in Prince Frederick, MD, where the principle investigator, a graduate student at Towson University, is the full-time supervisor of the QEEG, Neurofeedback, and TMS Laboratory. CNA provides clinical concussion management to the regional population of Southern Maryland, and actively utilizes neurofeedback in the treatment of many neurological and psychological disorders, including ADHD, anxiety, depression, insomnia, dementia, and brain injury. The present research functioned within the normal workflow of clinical care at CNA, and data was collected as soon as logistically possible. The evaluation and treatment of acute concussion is a priority at CNA, and emergency patient appointment times are held to accommodate concussed patients that present for treatment. The present study and related informed consent forms were ethically approved by the Towson University independent review board.

In accordance with the 5th Consensus Statement on Concussion in Sport by McCrory et al. (2017), medical providers at CNA prescribed physical and cognitive rest to concussed individuals. Patients were instructed to avoid physical activity until free of concussion symptoms at rest, at which point the athlete began the five-step progressive exertion outlined in the Return-To-Play protocol by McCrory et al. (2017). At the attending provider's instruction, over-the-counter or prescription pharmacological interventions were used to manage persistent concussion related symptoms and documented in the case studies. QEEG and XLNTbrain

computerized neurocognitive tests were administered to all individuals as close to the injury date as possible and after clinical recovery. Clinical recovery was defined as the athlete remaining free of concussion-related symptoms, including cognitive impairment, at physical rest and after completion of the 5-step, progressive exertion Return-to-Play protocol as outlined by McCrory et al (2017).

Cases to be reviewed in the case series received neurofeedback treatment during recovery until cleared from concussion. Cases treated with neurofeedback were compared to the control group consisting of individuals treated with the same recovery standards with the exception of any neurofeedback treatment during recovery. Data was collected from three child and adolescent patients presenting to the neurology clinic for the evaluation and treatment of acute concussion related to sport or recreational activity. The subjects were age 9, 16, and 17; there was one female and two males. Following concussion injury, patients autonomously presented to a primary care provider or emergency room physician for medical evaluation of concussion injury who then refers the patient to CNA for neurological evaluation. One subject was a past patient of CNA and presented directly to CNA. Neurological evaluation for concussion was performed by the attending medical provider. CNA employs a neurologist, nurse practitioner, physician assistant, or licensed athletic trainer, all of whom evaluate patients for concussion as part of a team. With a completed neurological assessment, the patient entered the concussion management protocol and completed the QEEG and neurocognitive testing.

During the concussion evaluation appointment, the medical provider, aware of the study and familiar with neurofeedback, presented the study to potential subjects. Medical providers were not provided a script to explain the study and often described neurofeedback for acute concussion as analogous to “physical therapy for the brain.” The provider supplied informed

consent forms if the patient agreed to participate in neurofeedback treatment. If the patient opted out of the study, clinical care continued as normal without the use of neurofeedback. The PI was not present when the study was presented to potential subjects to reduce the risk of coercion. Patients that consented to the study were contacted by the neurofeedback lab coordinator to schedule neurofeedback appointments.

Data collection occurred as soon as possible after evaluation. QEEG data was processed and analyzed immediately for use in neurofeedback protocol decision making. Subjects were scheduled to begin neurofeedback as quickly as possible following the EEG collection. Patients completed two neurofeedback sessions per week until symptom free and cognitively normal at rest and full athletic exertion. The PI discussed changes in concussion related symptoms with the patient at each neurofeedback appointment. Subjects were encouraged to use the XLNTbrain, Inc. symptom tracker to monitor change in symptoms over time. Once the patients were free of symptoms and cleared from concussion, neurofeedback sessions ceased and QEEG and computerized neurocognitive testing were repeated immediately.

QEEG Data Collection and Analysis

QEEG data was recorded on a BrainMaster Technologies, Inc. (Bedford, OH) Discovery 24E amplifier using ElectroCap International, Inc. (ECI; Eaton, OH) electrode caps to collect EEG activity from 19 channels according to the International 10-20 system. Electrode sites were prepped with NuPrep Abrasive Skin Prep. Conductive gel from ElectroCap International, Inc. was applied at each cap electrode site for EEG signal conduction. Ten20 Conductive EEG Paste by Weaver and Company (Aurora, CO) was used on ear clip reference electrodes. The QEEG

data was acquired in BrainAvatar by BrainMaster Technologies, Inc. The same set up from the EEG acquisition process and software was used to administer neurofeedback sessions.

Template matching artifacting was combined with manual selection to remove artifact from the EEG recordings. The investigator's primary method of artifacting over 5 years of QEEG experience is a combination of manual selection and template matching artifacting. Alternative artifacting methods were excluded from the study. On occasion, automatic artifacting algorithms select healthy, yet abnormal, sleep EEG patterns for quantitative analysis that result in highly abnormal QEEG maps. For this reason, the automated artifacting algorithm was not employed in the present study. ICA remains a controversial topic within the field of QEEG and will also not be used to remove artifact from the data. The science of ICA is well founded, but transformations in the EEG traces created by ICA adjustment distort QEEG maps (Kroptov, Thatcher, Kerasidis, and Cantor, 2017). Therefore, manual artifacting and template match artifacting were used to remove artifact from EEGs for the present study.

NeuroGuide by Applied Neuroscience, Inc., was used for manual and template selection artifacting methods. QEEG analysis was performed with the BrainDx Report Generator (BDxRG) for to calculate sLORETA source localization. Maximum and minimum peak Z score variation from the mean, PZV_{max} and PZV_{min}, respectively, and percent increased or reduced volume of grey matter activity deviant from Z = +/- 2.5, PIGMV and PRGMV, respectively, were calculated for each of 5 frequency bands. Frequency bands were defined as follows: Delta = <4 Hz, Theta = 4-8 Hz, Alpha = 8-13 Hz, Beta = 13-30 Hz, and Beta-Gamma (Bamma) = 30-35 Hz.

Cognitive Testing

The XLNTbrain cognitive test, developed from research on the cortical origin and electrophysiology of specific cognitive event related potentials (Kerasidis, 2015), was used to assess cognitive ability of concussed subjects. The test measured subjectively reported concussion symptoms, reaction time, attention, inhibition, impulsivity, working memory, information processing efficiency, and executive functioning. Results of the cognitive testing, provided in spider charts, depicted the patient's reported symptoms and accuracy and efficiency results in measures of verbal processing, verbal memory, nonverbal processing, nonverbal memory, attention, and emotional reactivity (Figure 5). The test is age normed for individuals from 11-50 years-old.

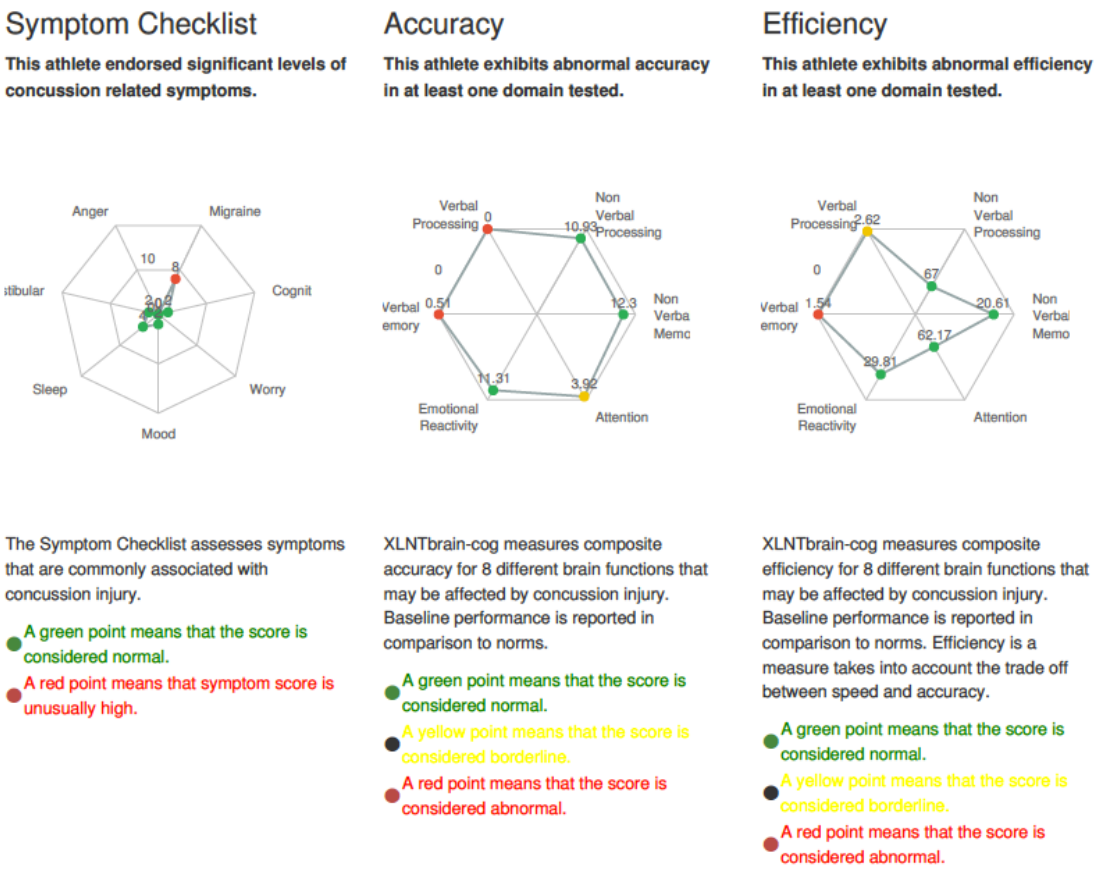


Figure 5. Sample of XLNTbrain Cognitive Test Results

Every subject used a personalized password protected account login to the secure XLNTbrain website to take the test. The cognitive test takes approximately 35 minutes and is taken in a distraction free environment. The test consists of 10 sections: symptom checklist, word task, emotional identification task, finger tapping, time estimation task, stop-go task, one back test, sentence task, facial recognition task, and verbal memory task. The subject was instructed to respond as quickly and accurately as possible for all sections except the symptom checklist. Below are detailed descriptions of each section of the XLNTbrain cognitive test.

Section 1: Symptom Checklist

Subjects indicated the frequency of concussion related symptoms experienced over the last 24 hours as never, sometimes, often, or very often. The symptoms assessed in the checklist were related to migraines, cognition, worry, mood, sleep, vestibular, and anger.

Section 2: Word Task

The word task tested the subject's ability to memorize a list of 15 words. Words were presented one at a time with three chances to view the list. After the list of words was presented, pairs of words were displayed next to each other on the screen. One word was from the list and one was not. If the word from the list was on the left the subject pressed the left arrow key, and if the word from the list was on the right the subject pressed the right arrow key.

Section 3: Emotional Identification

The emotional identification task tested the subject's ability to recognize emotion in other people's faces. Different emotions were expressed by different pictures of human faces. The subject pressed the spacebar as quickly as possible after each photograph except for a designated target emotion. The test was repeated for five target emotions: happy, sad, afraid, angry, and neutral/no emotion.

Section 4: Tapping

Tapping measured how fast the subject tapped the spacebar using their dominant hand. The subject was instructed to tap the spacebar with the same hand with which he or she writes. The user had a three second countdown to prepare for the test, then tapped spacebar for thirty seconds.

Section 5: Time Estimation

The time estimation task asked the subject to estimate the passage of a target time-period without using a time measuring tool (i.e., clock or watch). The subject pressed the spacebar to start the time and pressed the spacebar again when they felt the target time had passed. Target times included 30 seconds and 90 seconds.

Section 6: Stop or Go Task

The stop or go task consisted of two parts. The word "Go" or "Stop" was displayed on the screen in blue or red print in both parts. During the first part, the subject tapped spacebar if the

word “Go” appeared but did not tap if “Stop” appears. During the second section, the subject tapped the spacebar if the color of the word was blue, but not if the color of the word was red.

Section 7: One Back Task

A series of photographs was presented during the one-back task. The subject tapped spacebar after each new photograph and abstained from tapping if the photograph was the same as the previous photograph.

Section 8: Sentence Task

The sentence task presented five-word sentences one word at a time. If the last word in the sentence fit the context of the sentence and makes sense, the subject tapped the right arrow key. The subject tapped the left arrow key if the last word in the sentence did not fit the context.

Section 9: Facial Recognition Task

The facial recognition task tested the subject’s ability to remember faces presented earlier in the test during the Emotional Identification Task. Pairs of faces were presented side-by-side. One face was presented earlier during the Emotional Identification Task and the other was not. The subject tapped the right arrow key if they recognized the face on the right or left if they recognized the face on the left.

Section 10: Word Memory Task

The word memory task tested the subject’s ability to remember words displayed earlier in the test battery during the Word Task. The word list was not presented again during the Word

Memory Task. Word pairs were presented side-by-side. One word was presented during the Word Task and the other was not. The subject tapped the right arrow key if they remembered the word on the right or left if they remembered the word on the left.

Neurofeedback Sessions

Neurofeedback was administered by the PI using BrainAvatar neurofeedback software by Brainmaster Technologies, Inc. (Bedford, OH). The principle investigator consulted with attending neurologist, Harry Kerasidis, M.D., to design the neurofeedback training protocols specific to each subject. Neurofeedback protocols utilized a combination of scalp or surface Z-score training, sLORETA Z-score training, and raw (un-Z-scored) CSD training. Brain regions that displayed deregulated activity on the sLORETA analysis that matched symptom presentation were selected for Z score training. ROIs that demonstrated severely deregulated activity were selected for CSD training.

The neurofeedback sessions were performed in the eyes open or eyes closed conditions, or a combination of the two. Eye condition selected for the training depended on the protocol chosen and patient preference and tolerance of session demands. In the eyes open condition, one audio feedback tone was presented when the sLORETA Z score and CSD components met criteria, and a second tone was presented when the surface Z score criterion were met. Some neurofeedback sessions incorporated eyes closed alpha training after eyes open Z-score based neurofeedback. The alpha training protocol played a first tone when the alpha activity in the cingulate gyrus, precuneus, and occipital lobe increased above threshold. A second and third tone played when theta and beta (20-35 Hz) activity decreased below threshold, respectively. Feedback was adjusted so the trainee met criteria at a rate varying between 50-70%.

Patients received neurofeedback two times per week. The appointments were scheduled as soon as logistically possible given the clinic's and patient's schedules and availability. Neurofeedback protocol settings remained as constant as possible, although subject to change based on patient symptom reporting. Symptom changes and any adjustments made to the protocol were documented throughout neurofeedback treatment.

RESULTS

Case Study #1 – JR

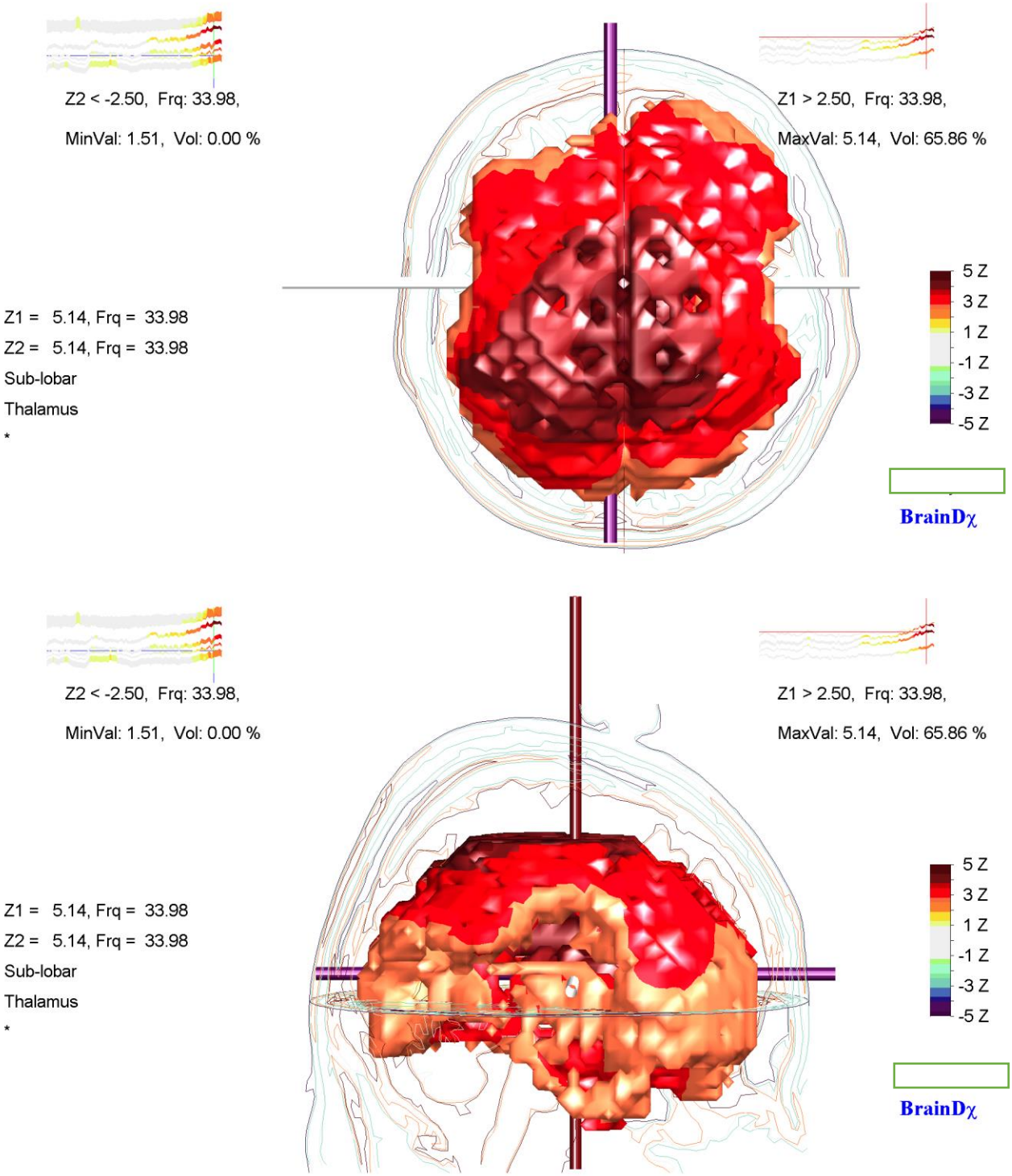
JR, a nine-year-old male, suffered a concussion when he was tackled to the ground during football practice. He maintained consciousness when he hit the back of his head while wearing his helmet. After the concussion, he experienced light sensitivity and daily headaches of varying severity that were sometimes accompanied with nausea and stomach aches. This was his second concussion; the first occurred last football season and without prolonged concussion-related symptoms. Two days after injury, JR was neurologically evaluated. EEG data was collected four days after injury. When he presented to the neurology clinic, JR's chief complaint was concussion-related headaches. He described the head pain as a pressure or stabbing sensation in the frontal region. His case was managed with medication and neurofeedback. Under the direction of the medical provider, JR was treated with imipramine and diclofenac potassium to manage concussion-related symptoms.

Cognitive testing after JR's injury was collected 2 days after injury with the WebNeuro Focus Report by Brain Resource Company. JR was ineligible for XLNT Brain cognitive testing, which is intended for use with individuals between age 11 to 50 (Kerasidis, 2015). The Brain Resource WebNeuro Focus Report evaluates subjects on the domains of thinking, emotion, self-

regulation, and feeling. Domains consist of groups of markers. Thinking is measured by tests of sustained attention, impulsivity, intrusions, inhibition, and response variability. A test of emotional identification comprise the emotion domain. Self-regulation is evaluated with markers for negativity bias, emotional resilience, and social skills. Depression, anxiety, and stress are measured under the feeling domain. The computer-based test takes approximately 30 minutes to complete. The test format includes self-report items on a Likert scale and objective tasks. Markers are given a score on a 0-10 scale and normative Z-scores. Percent change between testing sessions are calculated for each marker if available. Statistically meaningful change consists of a raw score change of 1 or more, and clinically meaningful change is reflected in percent change scores greater than or equal to 50%. Testing demonstrated atypical findings for the thinking domain, specifically on markers of inhibition, impulsivity, and response variability.

QEEG analysis of JR's post-concussion EEG data collected four days after injury indicated deregulation in the bamma frequency range primarily. In the frontal and parietal regions, bamma activity was elevated to a PZVmax of 5.14 Z with a PIGMV of 92.73% (Figure JR.1). Beta activity was slightly elevated with PZVmax of 2.75 Z and PIGMV of 1.51%. Metrics for all other frequency bands were located centrally on the bell curve with Z-scores within 2.5 standard deviations and thus no percent affected grey matter. Given the elevated bamma activity and absence of additional QEEG abnormalities measured by sLORETA source localization, excess bamma activity was deemed the primary EEG deregulation potentially related to JR's symptoms.

Figure JR.1: Post-Concussion sLORETA Imaging – Bamma Activity: f = 33.98 Hz; Max Z-score = 5.14; PIGMV = 65.86%



JR completed ten neurofeedback sessions before he was symptom free and cleared of his concussion six weeks after injury. Neurofeedback training began four days after injury. The protocol rewarded decreased bamma and theta activity and increased alpha activity. The cingulate gyrus, precuneus, and occipital lobe were targeted for training due to the close relationship between these regions and generation of the alpha rhythm, roles in cognitive and sensory processing, and close proximity to the thalamus, the primary generator of the alpha rhythm. Theta activity was included in JR's neurofeedback because of elevated relative theta power in the frontal regions depicted in topographic mapping. Although not a focus of the present study, the neurofeedback protocol reinforced optimal EEG connectivity by rewarding coherence Z-scores within the defined training range of one standard deviation.

Neurofeedback sessions were approximately twenty minutes and performed in the eyes closed condition. At the first two sessions, JR reported reduced head pain at the end of the session compared to the beginning of the session but his head pain returned several hours later. In addition to alpha training, the third session included 13 minutes of Z-score training combined with CSD training in the eyes open condition to reward decreased delta, theta, and beta activity. The goal was to reinforce optimal functioning in the eyes open condition to extend the effects of the first two sessions. When JR returned for the fourth session, he recounted more head pain following session three. Given the only protocol adjustment made in session three was Z-score training with CSD training, only alpha training was performed. JR returned for the fifth session without a headache and described fewer overall headaches. From this point in treatment, his headaches at rest had resolved. He was intermittently sensitive to auditory or photic overstimulation which provoked headaches. He reported situations where bright lights and

echoed sounds intermittently provoked headaches as he neared full recovery. Forty-two days after sustaining his injury JR, was cleared of his concussion.

JR's cognitive testing at recovery demonstrated clinically and statistically significant changes in the thinking domain, which was the most abnormal and relevant domain on JR's post-concussion testing. Impulsivity improved by 433%, inhibition by 117%, and response variability by 25%. Sustained attention decreased by 10% and intrusions by 25%. Per the test-maker's standards included in the report, improvements in impulsivity and inhibition were statistically and clinically meaningful and the decline in intrusions was statistically meaningful. In the self-regulation domain, improvement in negativity bias was statistically and clinically significant. Results of JR's testing indicated improved cognitive function at recovery compared to post-injury. See Table JR.1 for results from JR's cognitive testing from both time points.

Marker	Post-concussion	Post-recovery	% Change
Domain: Thinking			
Sustained Attention	5	4.5	-10%
Impulsivity	**1.5**	**8**	**+433%**
Intrusions	4	3	-25%
Inhibition	**3**	**6.5**	**+117%**
Response Variability	2	2.5	+25%
Domain: Emotion			
Emotion Identification	5	5	0%
Domain: Self-Regulation			
Negativity Bias	**5**	**8.5**	**+70%**
Emotional Resilience	10	6.5	-35%
Social Skills	9.5	9	-5%
Domain: Feeling			
Depression	7.5	7.5	0%
Anxiety	7	7	0%
Stress	6	8	+33%

Table JR.1 – Results from JR's WebNeuro Focus Test. Bolded rows indicate markers that demonstrated statistically and clinically meaningful change.

JR's post-recovery EEG was recorded five days before meeting with the medical provider to be formally cleared of injury. Bamma PZVmax was 5.11 and PIGMV of 57.45% (Figure JR.2). Comparison of bamma activity from post-concussion and post-injury EEG data demonstrated a minimal change in PZVmax and more substantial change in PIGMV. PZVmax after injury measured 5.14 Z, .03 Z greater than the second EEG. Post-concussion PIGMV was 92.73%, indicating a 35% difference in PIGMV (Table JR.2). At recovery, PZVmax for delta (Z = 2.5) theta (Z = 2.16) were further from the center of the distribution compared to post-concussion values which both measured below 2 SD. Alpha activity remained unchanged. Deregulation in the beta frequency range was present at recovery with PZVmax of 3.06 and

PIGMV of 4.41%, reflecting increases from post-concussion values of 2.75 Z and 1.51%, respectively. The data from EEG1 and EEG2 are depicted in Graphs JR.1-JR.4.

Per the attending neurologist, high frequency EEG activity is related to active cognitive processing, excessive amounts may be related to over-focused tendencies, anxiety, insomnia, or headaches. The literature on electroencephalographic findings during migraine and other types of headaches is mixed with an array of findings of normal and abnormal brainwave patterns for individuals with headaches (Niedermeyer & Schomer, 2011). Other EEG patterns, such as theta bursts, may be related to migraines or headaches, but the literature is inconclusive (Niedermeyer & Schomer, 2011).

Decreased bamma activity correlated with the reduction in JR's headaches as he recovered from his concussion. The presence of headache with an EEG profile consisting of excess fast activity in absence of other significant abnormalities suggests a relationship between the headaches JR experienced after injury and bamma activity. As JR recovered from his concussion, Z-scores for bamma activity were relatively constant but the percent of grey matter volume showing elevated bamma activity declined by approximately 35%. Alternatively, beta activity increased as JR's headaches decreased. The increase in beta activity potentially indicated a return to normal neurological functioning or the establishment of a new brain state as posited by Thatcher et al. (1989).

When considering JR's clinical presentation and EEG findings, certain characteristics distinguished this case from others. Frontal headaches were JR's primary complaint after concussion. He reported no cognitive and emotional symptoms related to concussion injury, although cognitive testing markers suggested dysfunction in impulse control and inhibition, both of which may be classified as frontal lobe functions. Quantitative analysis of the EEG recorded

after the concussion did not show elevated delta or theta activity above 2.5 standard deviations. Only high frequency ranges demonstrated substantial abnormalities distributed globally, rather than focally. This finding contradicts the hypothesis which predicted local dysfunction indicated by increased slow wave activity would be related to concussion symptoms.

MRI studies by Churchill et al. (2017) have suggested the heterogeneity of concussion contributes to the variability of brain-based findings, although distinct symptom subgroups of concussion demonstrate specific patterns of CBF changes. Electrophysiologic findings of the current case, which presented with primarily somatic symptoms, differed from QEEG findings seen in other cases that often include deregulation of low frequency EEG activity. A possible explanation for this difference may be in a similar vein to the findings of Churchill et al. (2017) – specific patterns of electrophysiology seen after concussion may better describe subgroups within concussion.

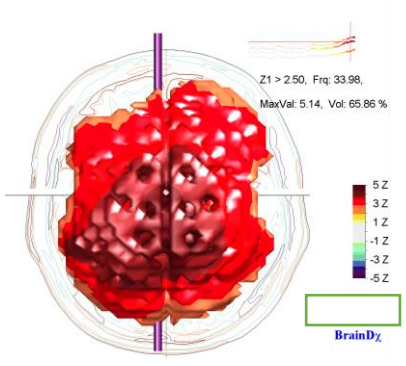
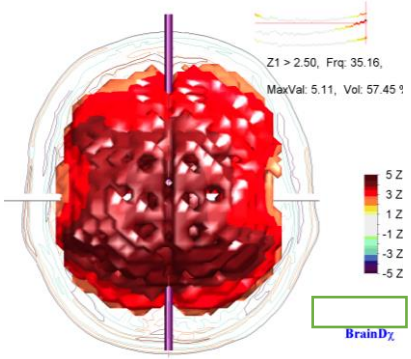
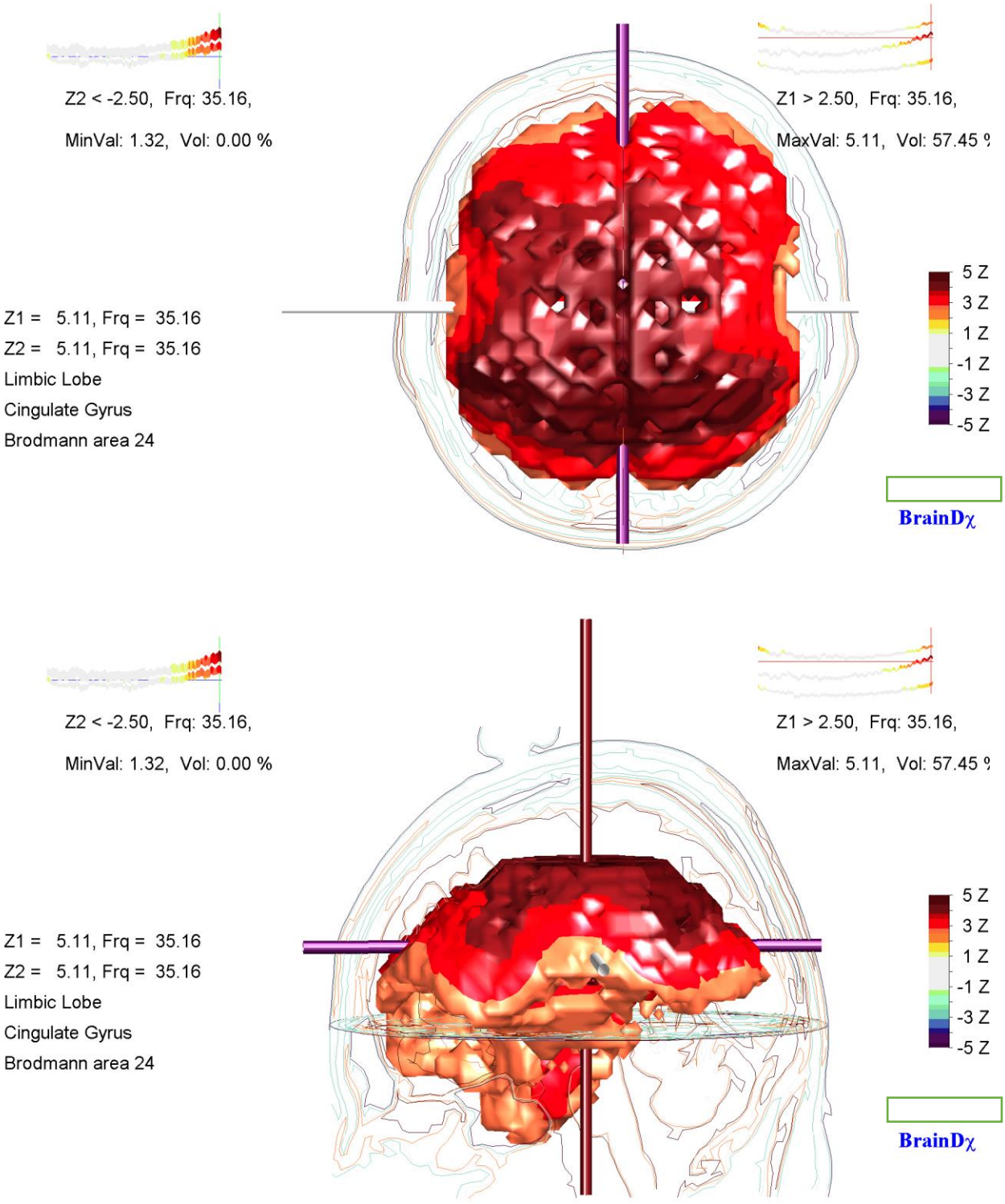
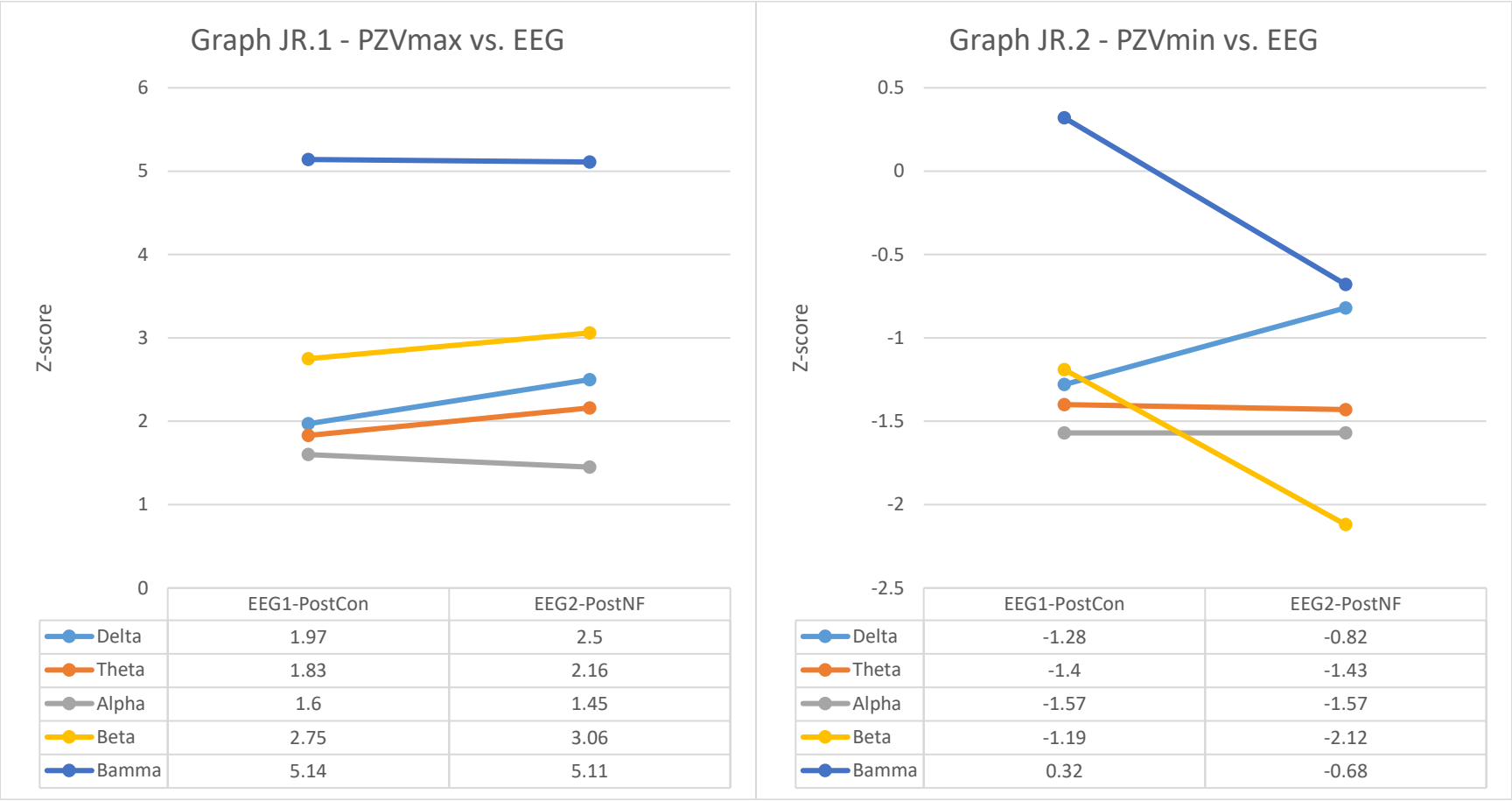
Table JR.2	Post-Concussion QEEG	Post-Recovery QEEG
Days From Injury	4	37
Bamma		

Table JR.2 depicts side by side images of bamma activity above 2.5 Z-scores at post-concussion and post-recovery time points.

Figure JR.2: Post-Recovery sLORETA Imaging – Bamma Activity: f = 35.16 Hz; Max Z-score = 5.11; PIGMV = 57.45%

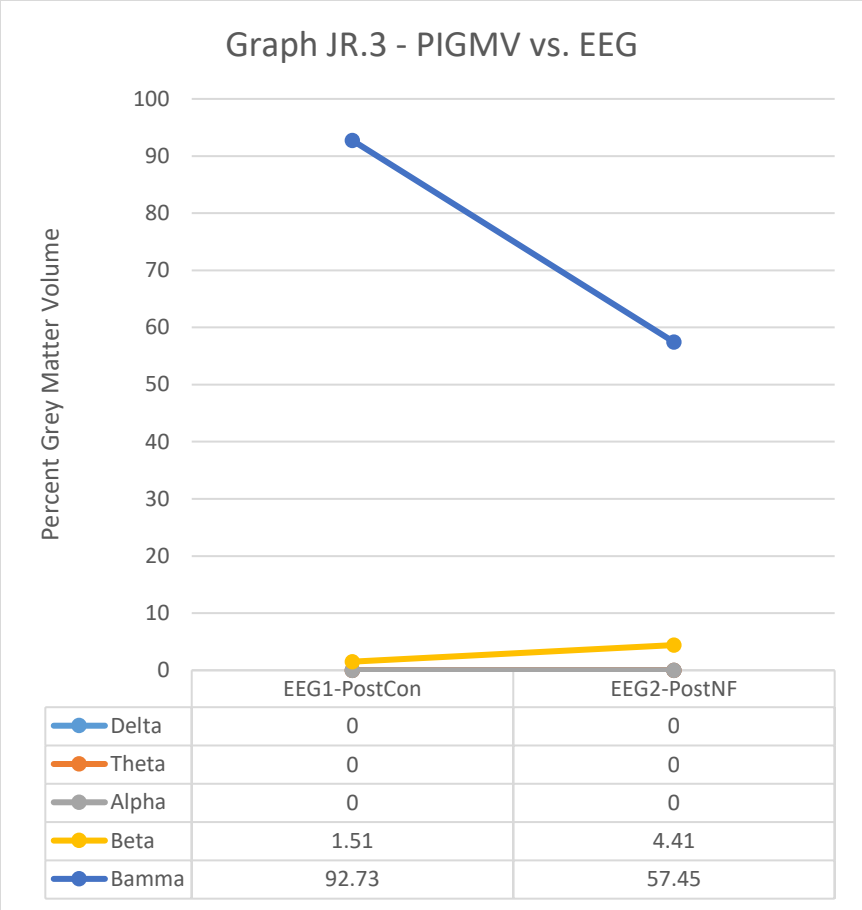


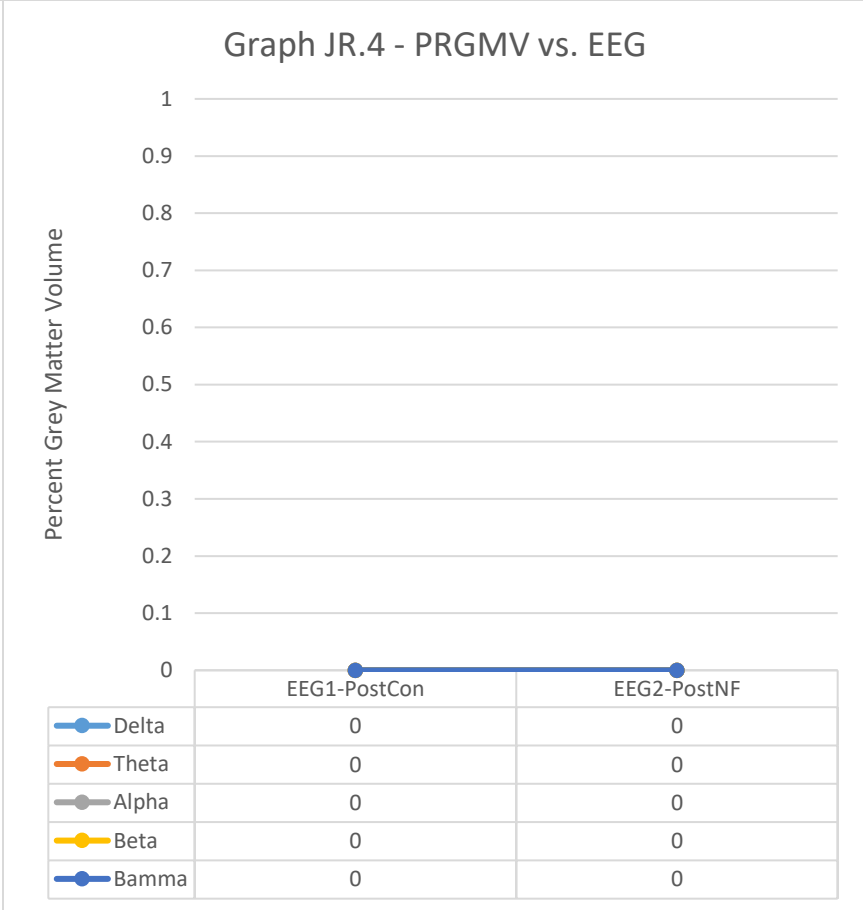


	EEG1-PostCon	EEG2-PostNF
Delta	1.97	2.5
Theta	1.83	2.16
Alpha	1.6	1.45
Beta	2.75	3.06
Bamma	5.14	5.11

	EEG1-PostCon	EEG2-PostNF
Delta	-1.28	-0.82
Theta	-1.4	-1.43
Alpha	-1.57	-1.57
Beta	-1.19	-2.12
Bamma	0.32	-0.68

Graph JR.1 depicts PZVmax for each of the 5 frequency bands across EEG time points 1 and 2. Graph JR.2 depicts PZVmin. EEG1 = post-concussion EEG, EEG2 = post-recovery with neurofeedback.





Graph JR.3 depicts PIGMV for each of the 5 frequency bands across EEG time points 1 and 2. Graph JR.4 depicts PRGMV. EEG1 = post-concussion EEG, EEG2 = post-recovery with neurofeedback.

Case Study #2 – RH

RH, a varsity football quarterback, hit the back of his head on the ground when he was tackled during football practice. He was wearing a helmet at the time and maintained consciousness but noted a mild headache immediately after impact. After the concussion, he withdrew from the rest of practice. The following day, his symptoms included headache, difficulty focusing, blurred vision, mental fogginess, light sensitivity, and feeling more tired than usual.

Post-injury cognitive testing was completed with the XLNTbrain Cognitive Test. RH had completed a pre-season baseline cognitive test to which the post-injury scores were compared. Baseline scores were indicated by the blue shaded region. On the Symptom Checklist, RH endorsed migraine symptoms but no other symptom domains. The score in the migraine domain was deemed unusually high by XLNTbrain standards of comparison and denoted by a red dot (See Figure RH.1). Accuracy and efficiency scores for cognitive items on the evaluation were within normal ranges for the XLNTbrain test but indicated deviant scores compared to baseline.

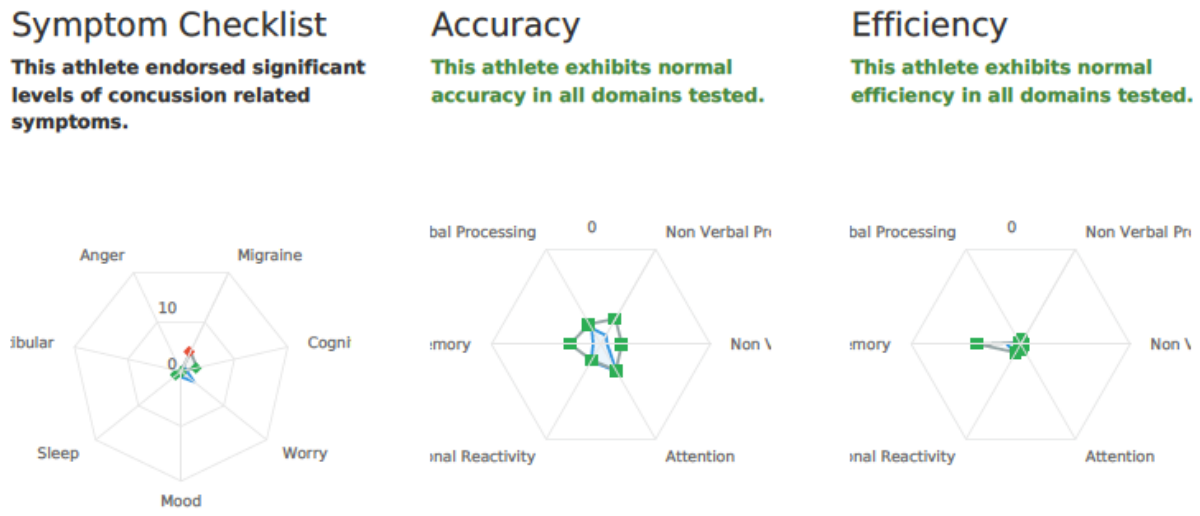


Figure RH.1 – XLNTbrain cognitive test scores collected 3 days after injury. The blue shaded area represents scores from the preseason baseline test.

Neurological evaluation occurred three days after injury and EEG data was collected the following day. QEEG data analysis revealed delta activity elevated to 2.7 Z with 1.23% of grey matter volume affected in the right temporal lobe. There was increased 12 Hz alpha activity in posterior regions with a PZVmax of 4.74 Z and PIGMV of 38.14%. Alpha PZVmin of -2.65 and PRGMV of 0.2% indicated reduced 8 Hz alpha activity. Beta activity was elevated in the parietal lobe with a PZVmax of 4.74 and PIGMV of 29.39%. Bamma activity was globally elevated to a PZVmax of 7.69 Z with 100% of grey matter affected.

Figure RH.2 – Post-Concussion sLORETA Imaging – Delta Activity: f = 3.13 Hz; Max Z-score = 2.70; PIGMV = 0.57%

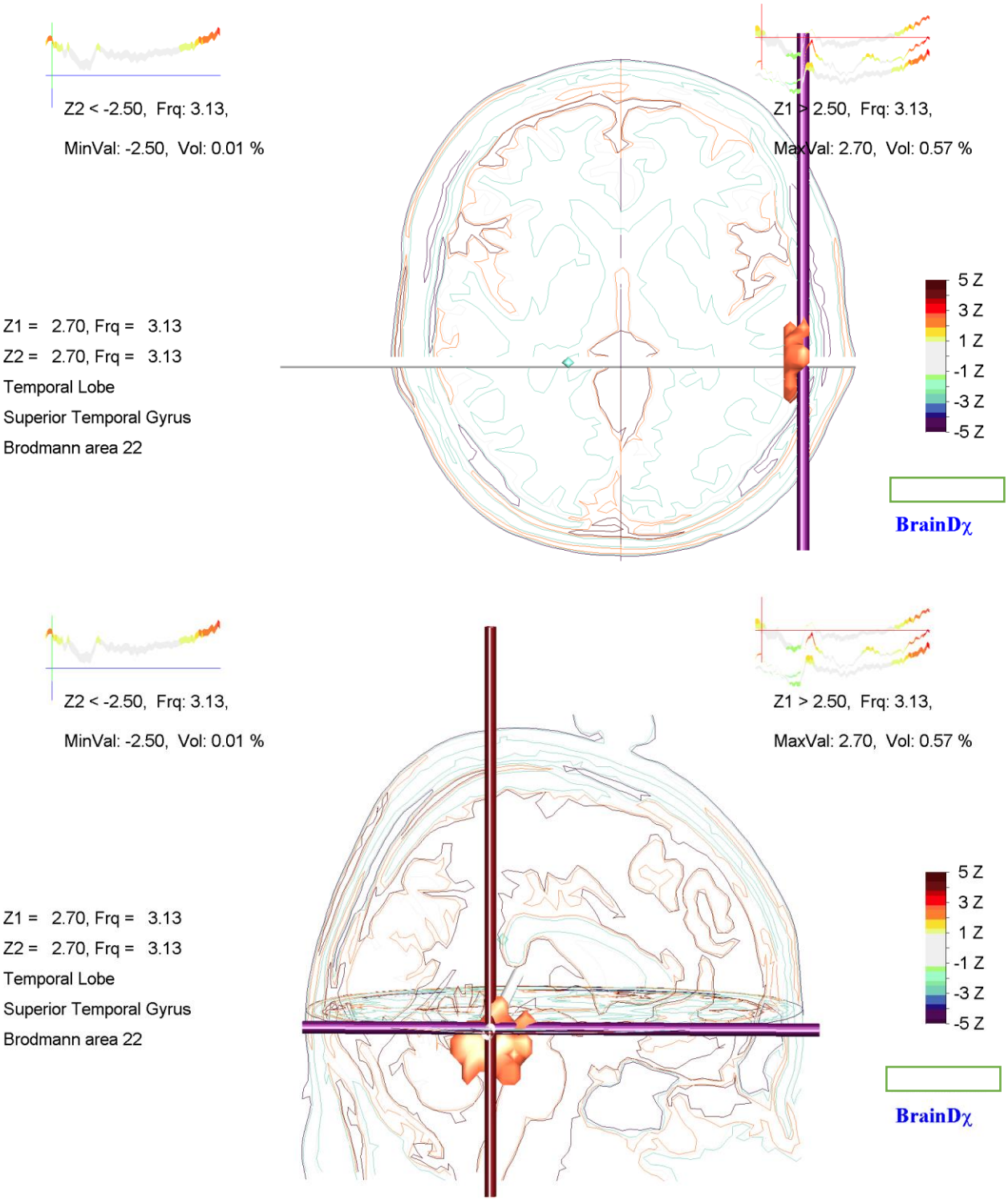


Figure RH.3 – Post-Concussion sLORETA Imaging – Alpha Activity: f = 12.89 Hz; Max Z-score = 4.74; PIGMV = 38.14%

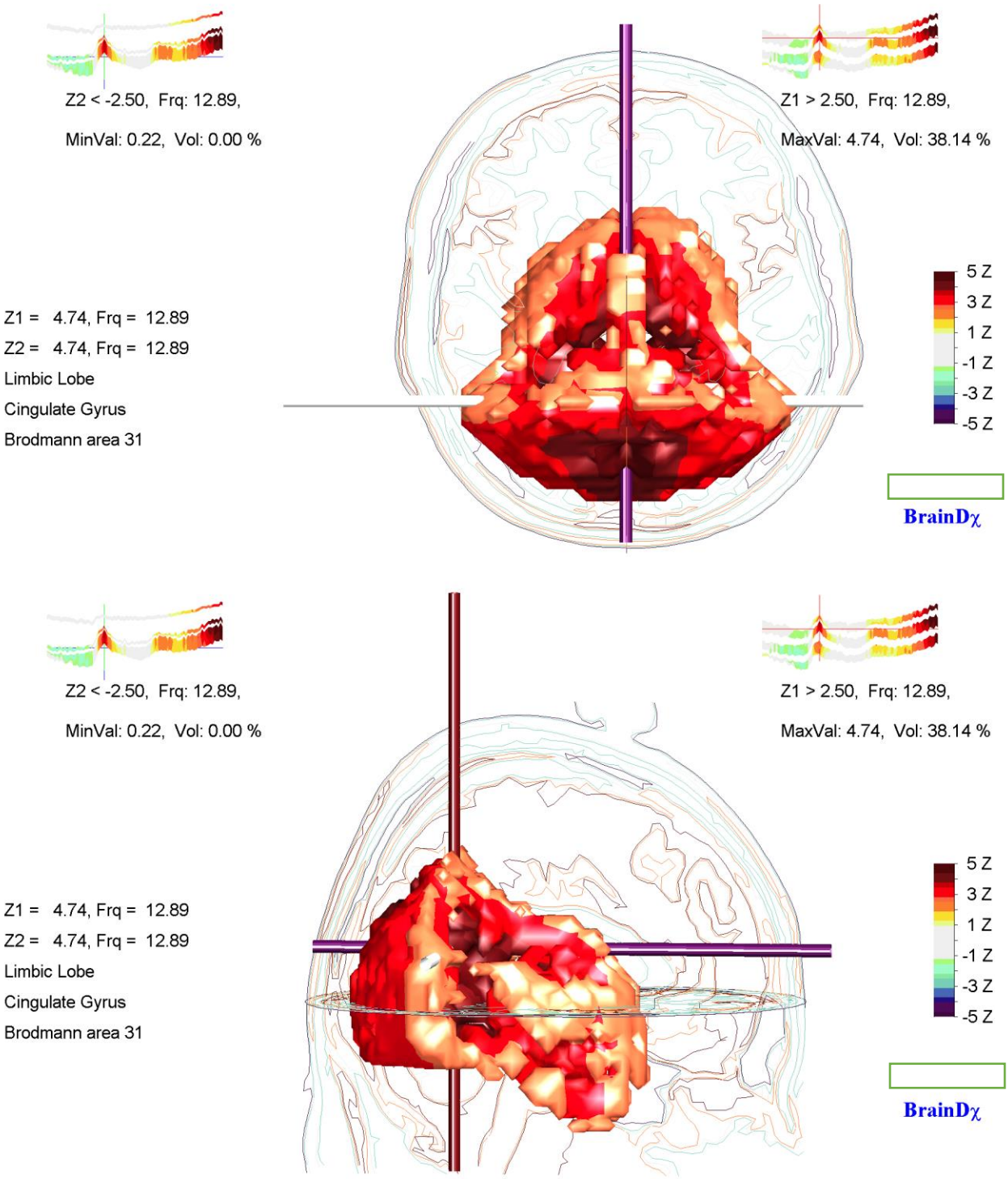
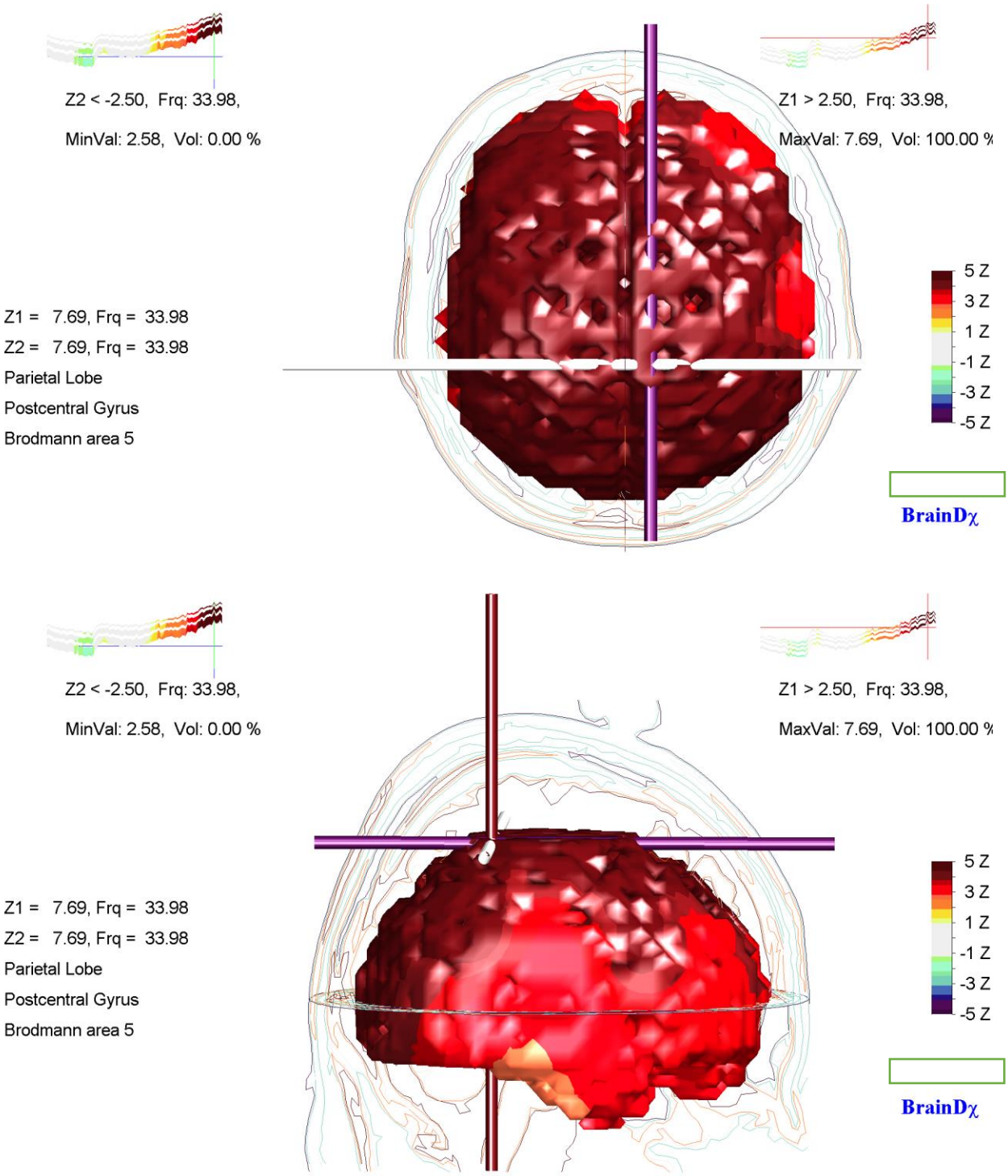


Figure RH.4 – Post-Concussion sLORETA Imaging – Bamma Activity: f = 33.98 Hz; Max Z-score = 7.69; PIGMV = 100.00%



As RH's data was reviewed in preparation for neurofeedback training, visual inspection of the Z-scored EEG spectrum hinted at pertinent Z-score deviations below the cutoff of 2.5 standard deviations (Figure RH.5). Similar to the tip of an iceberg concealing the majority of mass below the water's surface, a reduced cutoff of 2 SD unveiled findings that were otherwise hidden from analysis. With the cutoff adjusted, the elevated delta activity previously located solely in the right temporal lobe expanded to include the left frontotemporal region (Figure RH.6), and newly emergent elevated theta activity appeared in the bilateral frontal regions (Figure RH.7). While values less than 2.5 standard deviations were not included in the percent of affected grey matter calculations, they presented relevant information about RH's regional cortical functioning that potentially contributed to his presenting symptomatology.

sLORETA analysis of the QEEG results informed the neurofeedback protocol design. Regional dysfunction in the frontal and temporal lobes were the primary focus of neurofeedback. Frontal lobe dysfunction, indicated by increased delta and theta activity, was hypothesized to be related to RH's symptoms of headache and difficulty focusing. sLORETA Z score training for all frequency bands was applied to the frontal and temporal lobes. CSD inhibits were included to reduce the elevated delta and theta activity in these regions.

Figure RH.5 – Delta Activity Figured at Z-score = 2.5

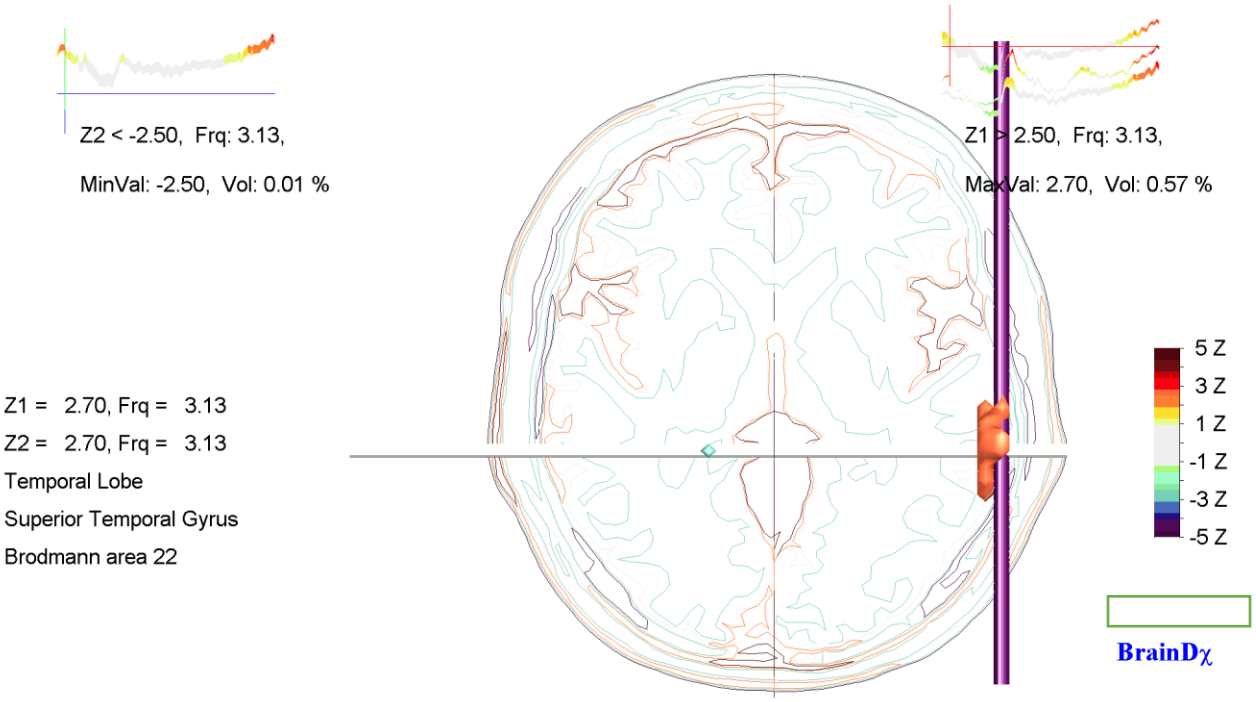


Figure RH.6 – Delta Activity Figured at Z-score = 2.0

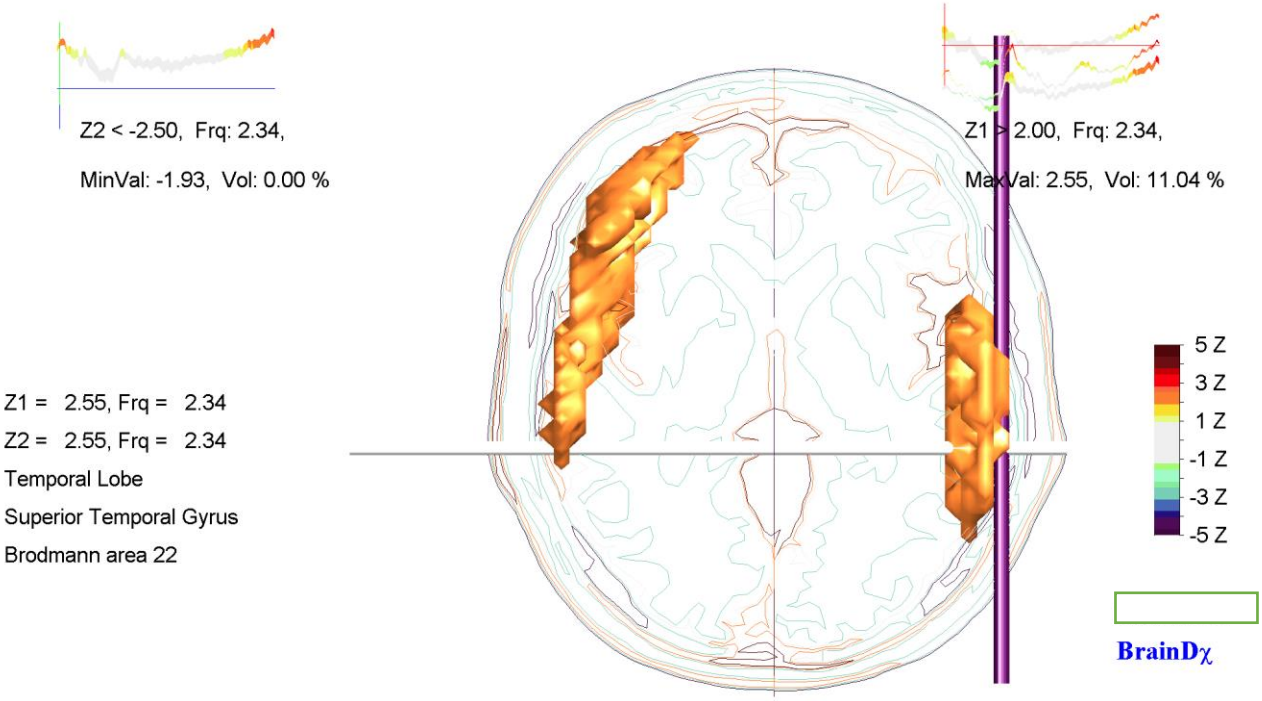
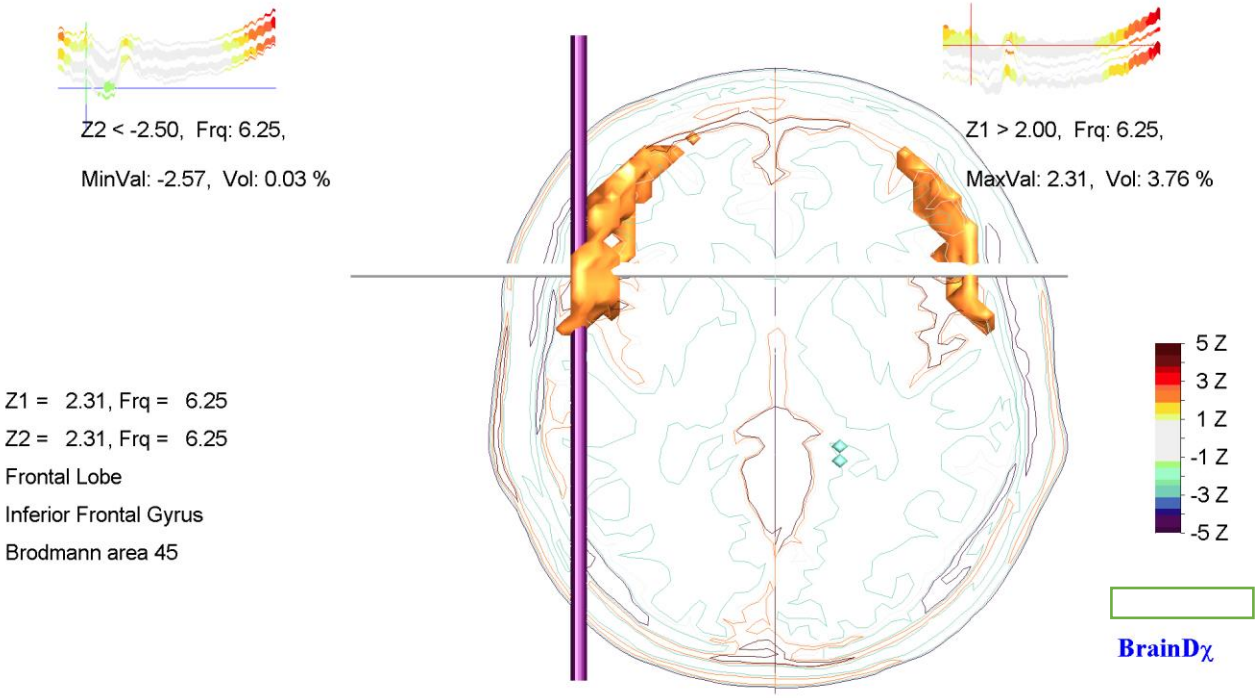


Figure RH.7 – Theta Activity Figured at Z-score = 2.0



RH was treated with the same neurofeedback protocol for three neurofeedback sessions, each lasting twenty minutes. The first session was eight days after injury. Intermittent, minor headaches and difficulty focusing in class were his primary complaints, although RH reported he was largely symptom free and on the third step of the progressive exertion at the first session. His second session was approximately one week later, at which point he had cleared the progressive exertion and participated in a full football practice without provoking symptoms. At session two, he reported experiencing a dull headache for several hours following the first session that disappeared by the following morning. The headache was different from those triggered by the concussion and described it as similar to fatigue after physical exercise. He noted improvements in his ability to focus in class. His third session and QEEG were twenty-two days after injury. Although cleared of concussion before his final session, RH chose to

proceed with the session because of the benefits he noticed from training. At the final session, RH denied experiencing headaches and endorsed improvements in his ability to focus.

RH's symptom checklist measured concussion-related symptoms during recovery. Figure RH.9 demonstrates the decline in symptoms. The first data point represents symptoms at the baseline cognitive test. The second data point was self-report by the subject the day after injury. The fourth data point represents symptoms reported at the post-injury cognitive test three days after injury. The last data point reports symptoms at the post-exertion cognitive test. All other data points were self-reported by the subject. Post-recovery cognitive test results (Figure RH.10) indicated overall reduction in symptoms and shifts in RH's accuracy and efficiency cognitive scores. All scores measured in the normal range, but some scores demonstrated improvements from post-injury testing while other trends indicated declines in cognitive abilities.

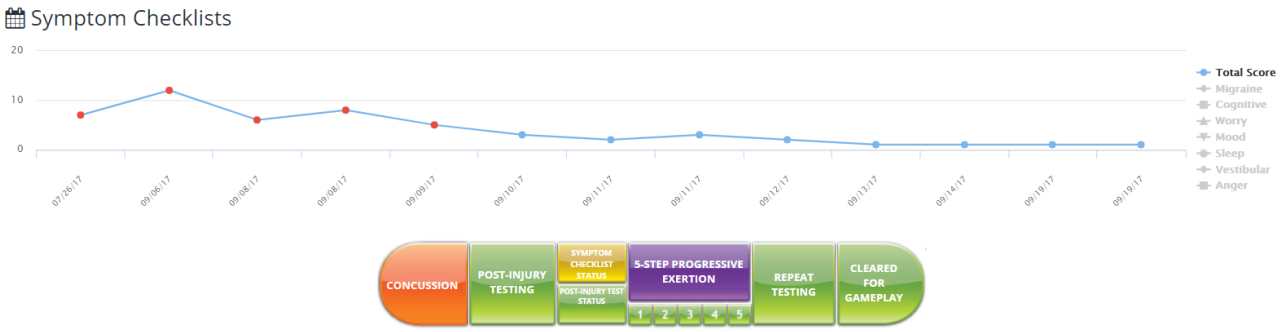


Figure RH.8 – XLNTbrain Symptom tracker for Case RH.

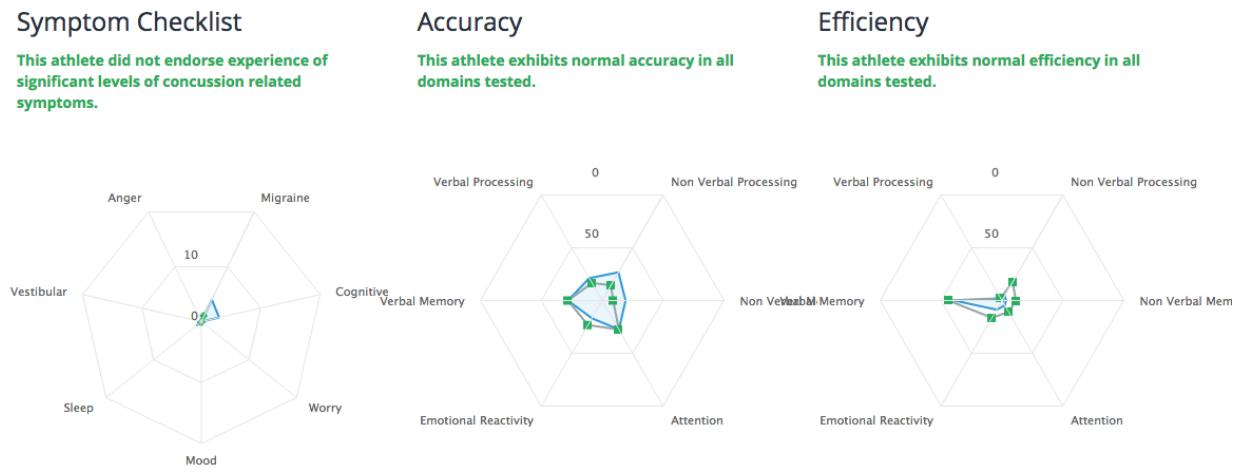


Figure RH.9 – Post-recovery cognitive test results and reported symptoms. Post-injury results are indicated by the blue shaded area.

QEEG data collected after RH was cleared of his concussion indicated delta activity with a maximum Z-score of 2.11, which occupied 0.16% grey matter volume above two standard deviations in the left temporal region. Theta activity was slightly decreased in medial occipital regions. Low alpha activity – approximately 9 Hz – was decreased in the occipital region, while high alpha activity – approximately 12.5 Hz – was increased in posterior regions. RH's peak frequency increased to 11.7 Hz compared to the post-concussion measurement of 11.3 Hz. This change in peak frequency likely contributed to the increased high alpha activity in posterior regions and will be discussed later. There was increased beta activity in the occipital lobe and posterior cingulate gyrus. Bamma activity was elevated with a PZVmax of 5.19 Z covering 85.93% of the grey matter volume.

Figure RH.10 – Post-Recovery sLORETA Imaging – Delta Activity: f = 2.34 Hz; Max Z-score = 2.11; PIGMV (< 2.5 Z) = 0.00%

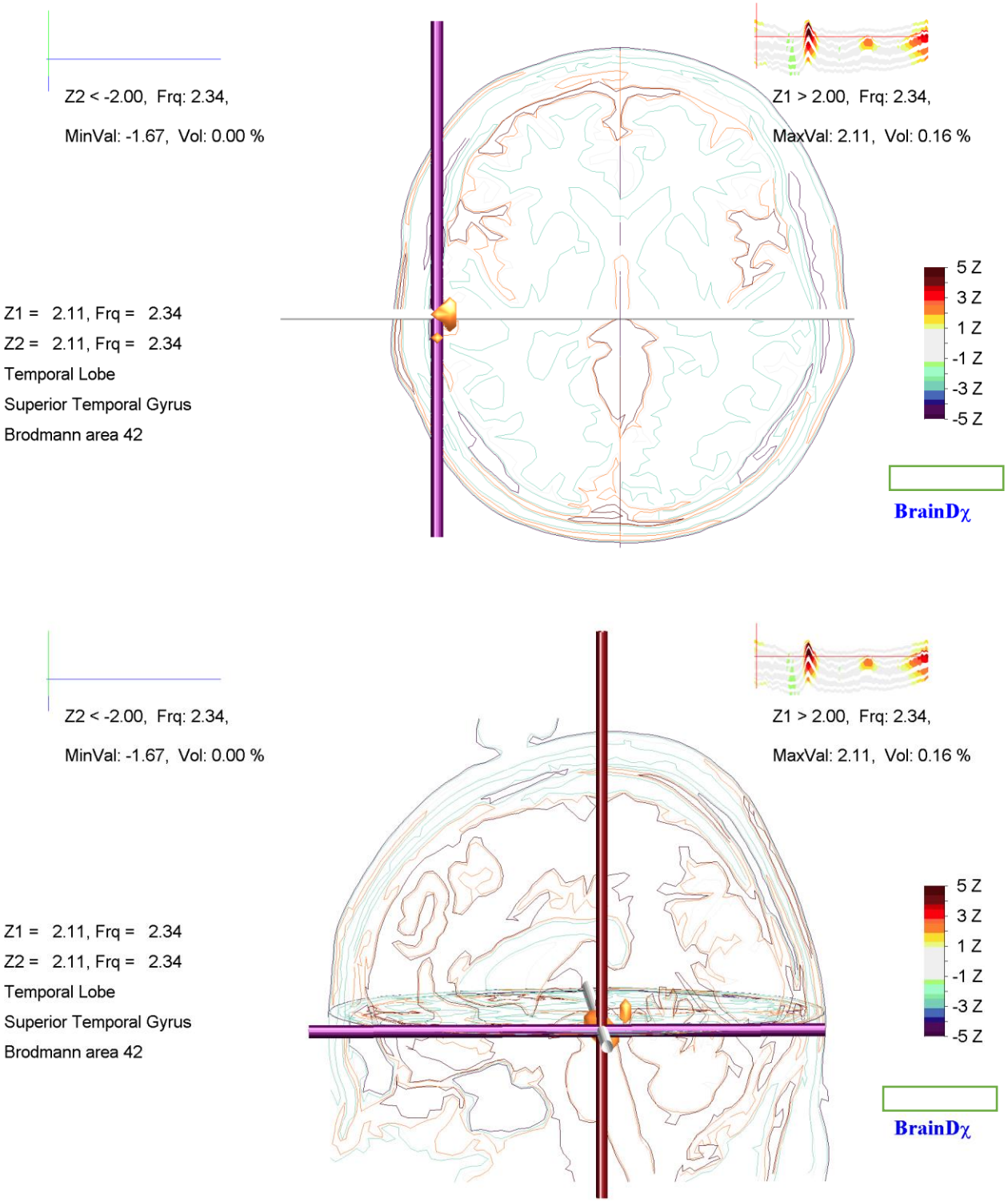


Figure RH.11 – Post-Recovery sLORETA Imaging – Alpha Activity: f = 9.38 Hz; Min Z-score = -2.34; PRGMV (< -2.5 Z) = 0.00%

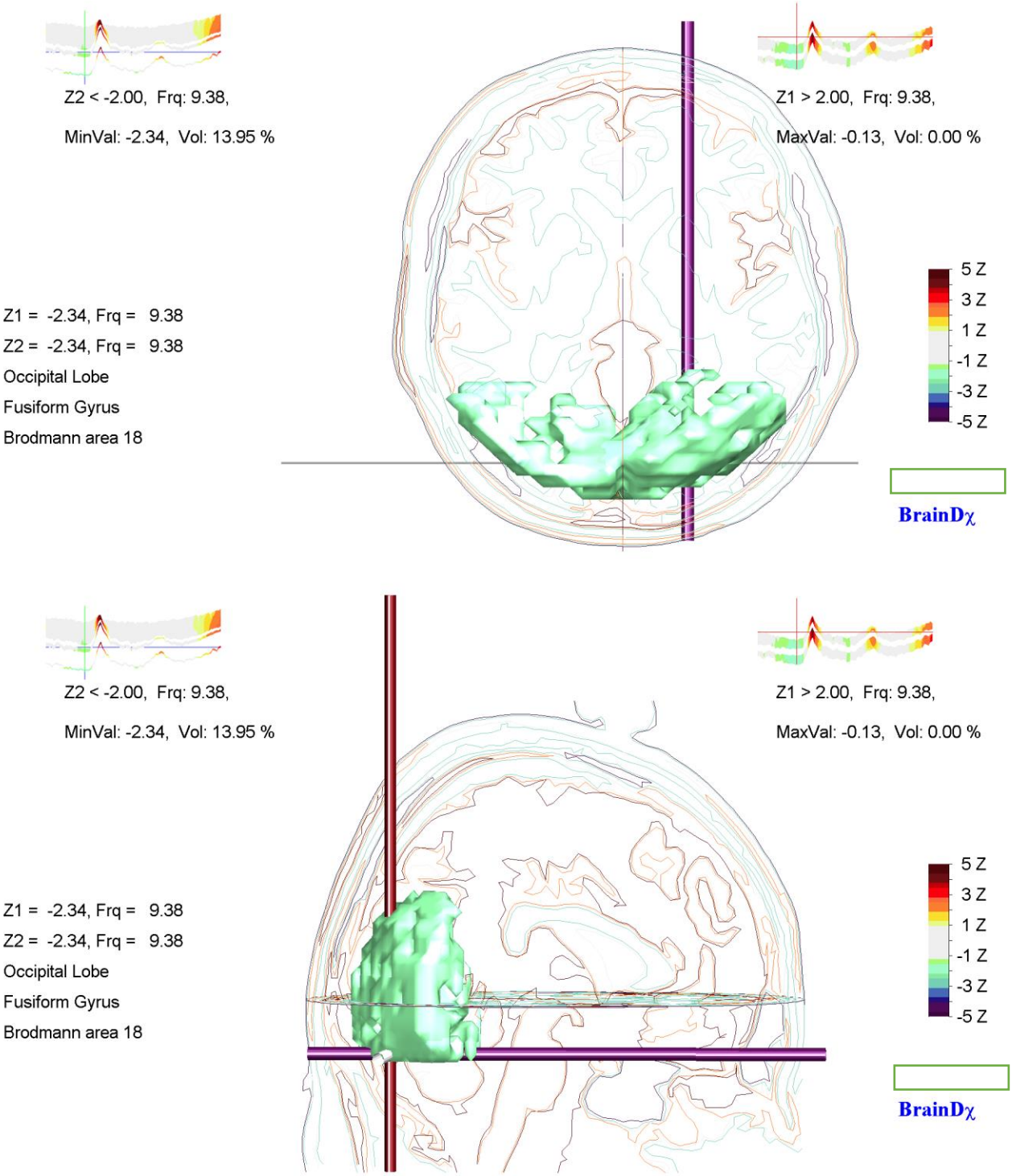


Figure RH.12 – Post-Recovery sLORETA Imaging – Alpha Activity: f = 12.50 Hz; Max Z-score = 6.76; PIGMV = 67.87%

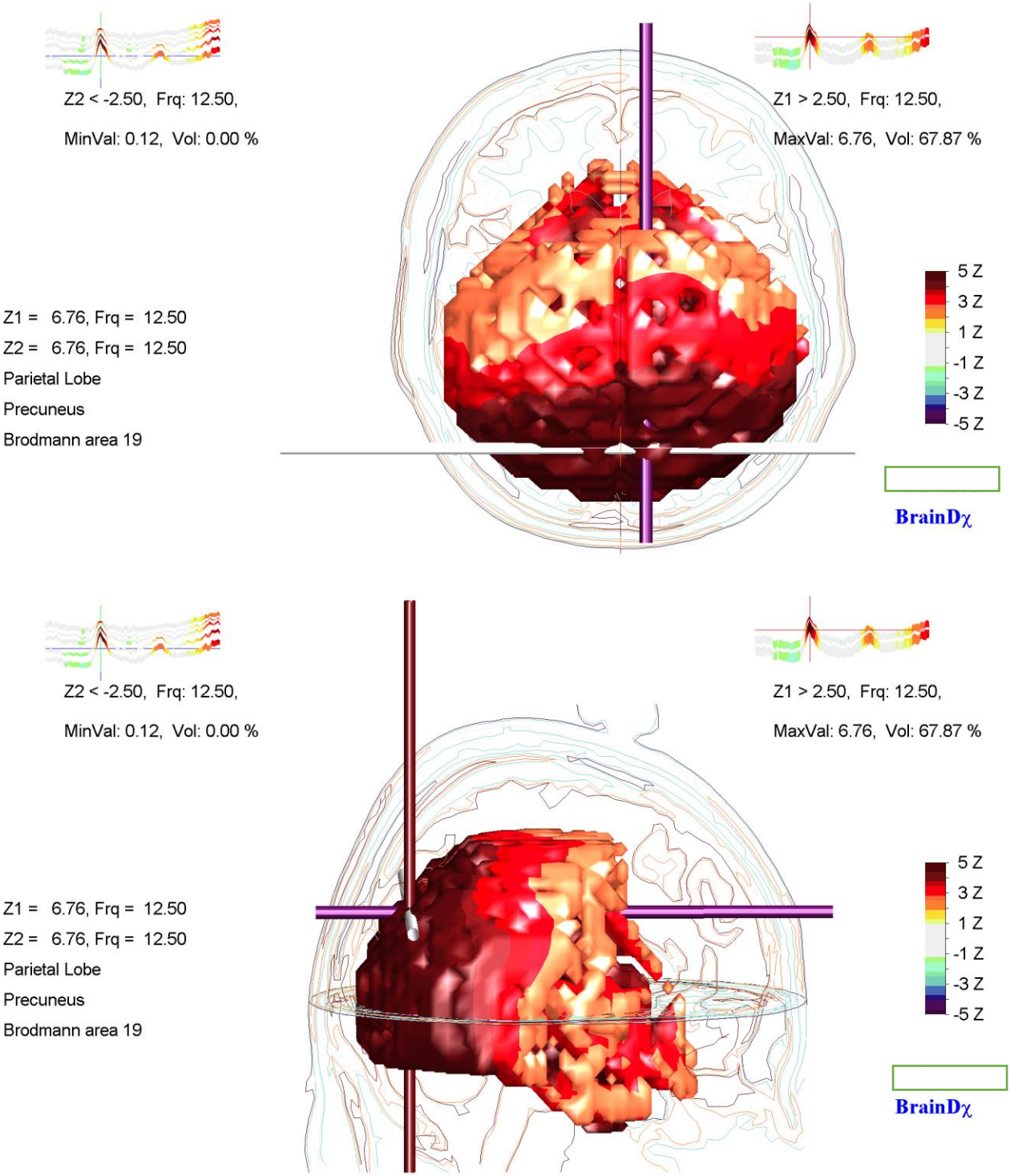


Figure RH.13 – Post-Recovery sLORETA Imaging – Beta Activity: f = 23.83 Hz; Max Z-score = 4.11; PIGMV = 13.28%

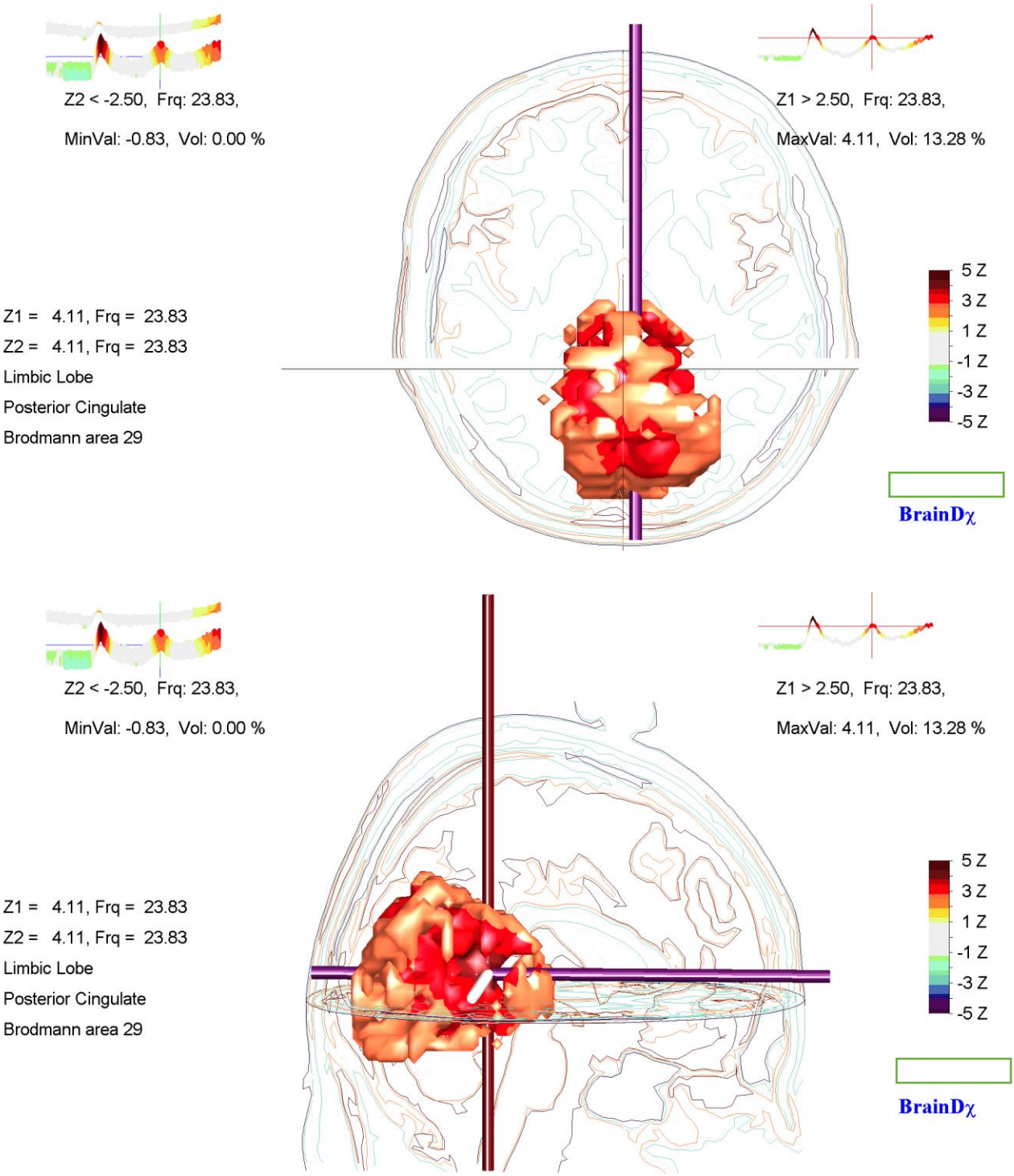
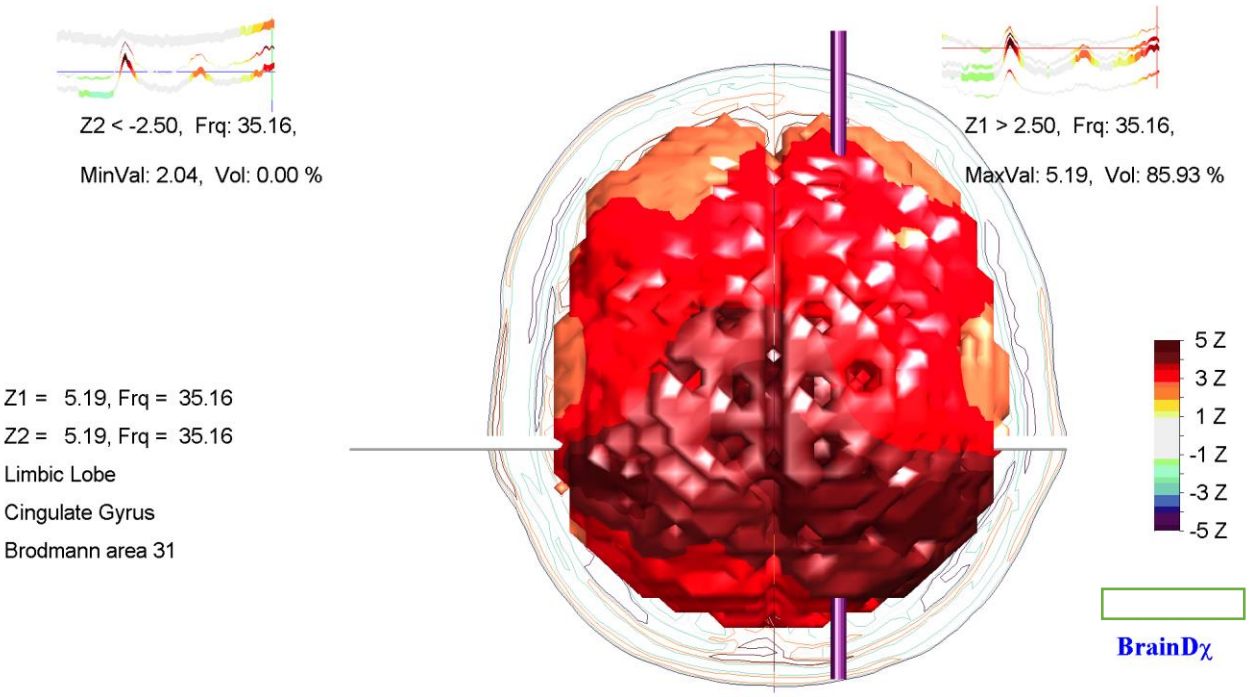
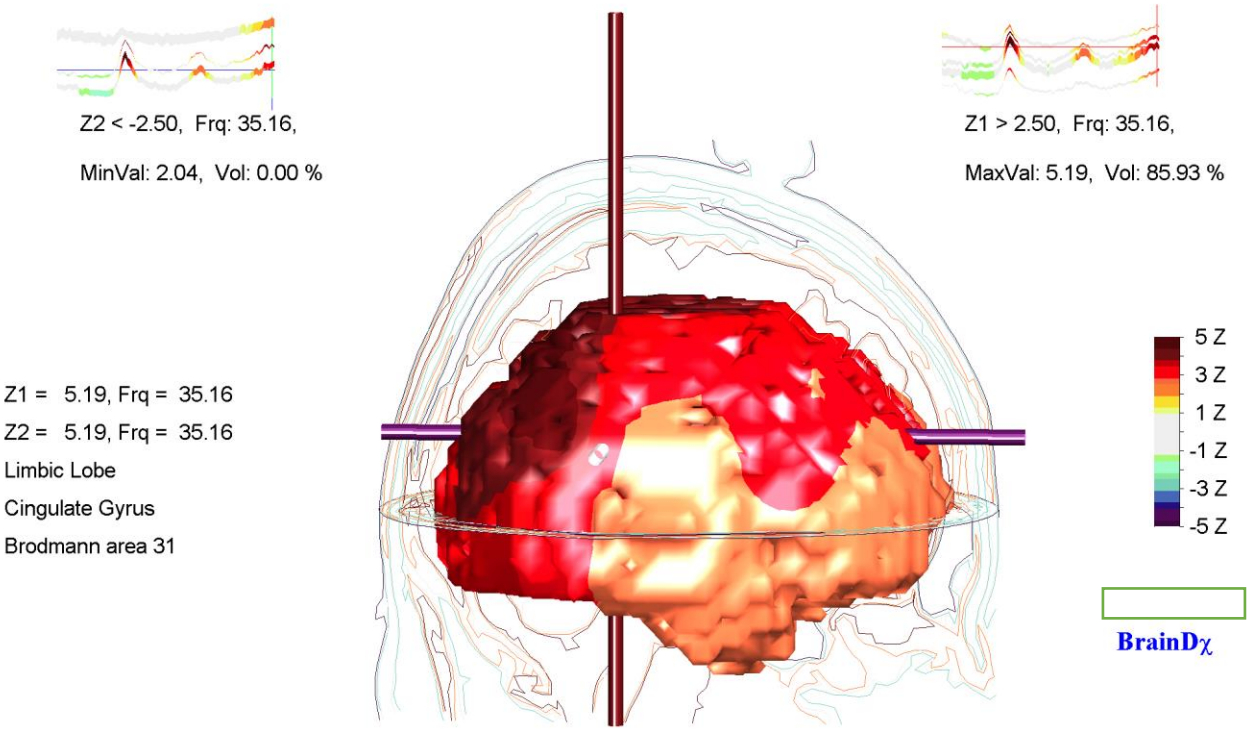


Figure RH.14 – Post-Recovery sLORETA Imaging – Bamma Activity: f = 35.16 Hz; Max Z-score = 5.19; PIGMV = 85.93%





EEG data collected after recovery compared to data after injury suggest some metrics approached statistical normality during recovery while other measurements moved away from center and into the tails of the distribution. Delta, theta, and bamma values for PZVmax and PIGMV at recovery were reduced from post-injury values, representing improvement in cortical functioning. Post-concussion EEG testing indicated elevated delta and theta activity in frontal and temporal regions, as well as reductions in central regions. PZVmax and PZVmin scores from the post-recovery EEG for delta and theta bands indicated all scores moved towards the center of the distribution. After injury, percent grey matter volumes, both increased and reduced, were minimally elevated above the standard cutoff for this study. Upon recovery, 0% grey matter volume was affected in the delta and theta bands. These data suggest improved cortical functioning as RH recovered from his concussion. Elevated delta and theta activity in the wakeful state suggest inefficient cortical processing, as slow oscillations interfere with the corticocortical communication required for regional activation and functionality. Improvements in RH's mental fog and ability to focus in class was supported by the decrease in low frequency EEG waves associated with inefficient cortical processing.

Alpha activity moved away from the center of the distribution, likely due to changes in RH's posterior dominant frequency. Mean posterior dominant rhythm frequency registers at approximately 10.2 Hz in healthy individuals above age 10 (Chang, Schomer, & Niedermeyer, 2011). For RH, large amounts of 11 Hz activity, due to a posterior dominant rhythm of 11 Hz, resulted in large Z-scores and PIGMV for alpha activity between 10-13 Hz in post-concussion and post-recovery EEG analyses. As RH healed, Z-scores and PRGMV for low alpha grew more negative and greater in volume, respectively. The opposite trend occurred for high alpha – Z-scores were increasingly positive and more grey matter was affected when RH was cleared from

injury. Peak frequency increased from 11.3 Hz to 11.7 Hz during RH's recovery, suggesting a faster posterior dominant rhythm when healthy. The alpha Z-score values appeared abnormal, but when considered in the context of the posterior dominant rhythm they likely reflect normality in this case. Although the absence of baseline QEEG testing prevents knowledge of RH's EEG distribution before injury, this illuminates a possible shadow of RH's pre-concussion functioning.

Beta activity is often associated with anxiety, insomnia, over-focused thoughts, or headaches. In this study, the beta frequency band ranged from 13-30 Hz. Frequencies from 30-35 Hz were defined as bamma, a hybrid between beta and gamma coined by the author due to discrepancies in the literature as to where beta ends and gamma begins. As RH recovered, his headaches reduced and bamma activity declined. Comparison of QEEG data from injury and recovery indicated a relative reduction in bamma PZVmax (EEG1 = 7.69 Z; EEG2 = 5.19 Z) and PIGMV (EEG1 = 100%; EEG2 = 86.15%). Bamma PZVmax at RH's recovery remained in the right tail of the normative distribution, albeit less deviant by approximately 2.5 SD, and affecting 13.85% less volume of the cerebral cortex. Decreased bamma activity may have reflected changes in cortical functioning associated with decreases in RH's headaches. With bamma values persistently elevated above statistically normal levels and free of concussion related symptoms, RH was cleared from concussion injury.

Beta patterns from EEG1 and EEG2 showed a particular regional increase in beta activity at 25.78 Hz and 23.83 Hz, respectively. Both elevations occurred in the posterior regions, localized to the parietal lobe and underlying structures such as the posterior cingulate gyrus. PIGMV of this beta pattern is 7.29% on EEG1 and 13.28% on EEG2. These findings may have indicated a true elevation of beta activity that increased during recovery and is related to regional

corticocortical communications. More likely, the effects of wave harmonics related to the previously described 12 Hz alpha activity might be generating increased amounts of beta activity at a frequency roughly double that of 12 Hz.

There are several additional possible explanations for the overall maintenance of such bamma and beta patterns. Despite clearance from injury, is it reflects RH's new normal electrophysiological functioning as his brain habituates to life after the concussion. Thatcher posits cortical functioning adapts to a new state after injury, leaving previous normal functioning in the past. The continued increase in bamma activity may be a reflection of the new cortical state. Another possible explanation is RH's bamma activity was originally elevated prior to injury, increased after injury, and subsequently revolved back towards pre-injury functioning. This speculation highlights the appeal of baseline QEEG testing in the context of concussion injury regardless of the use of neurofeedback as a possible intervention.

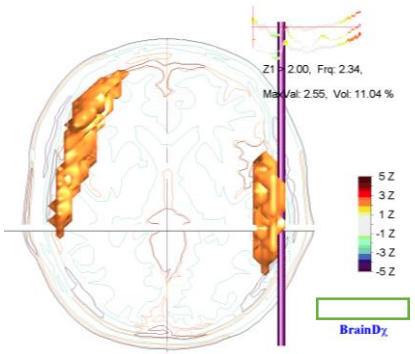
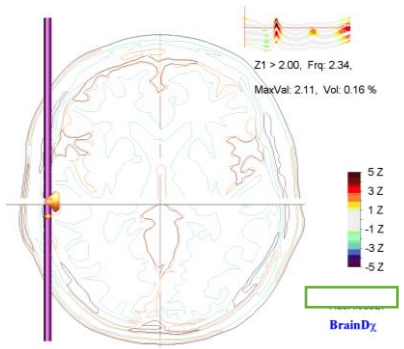
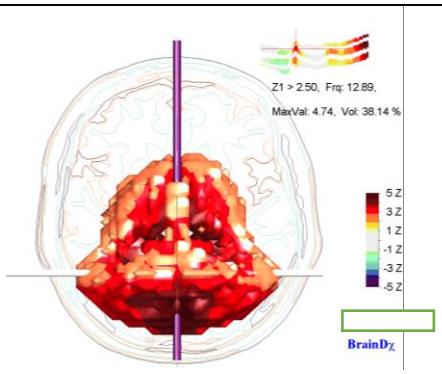
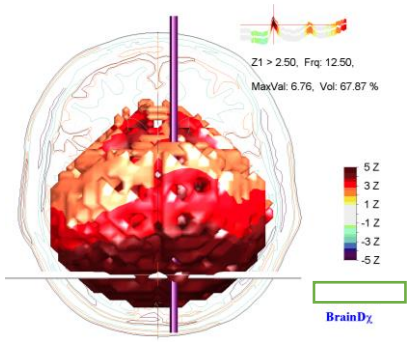
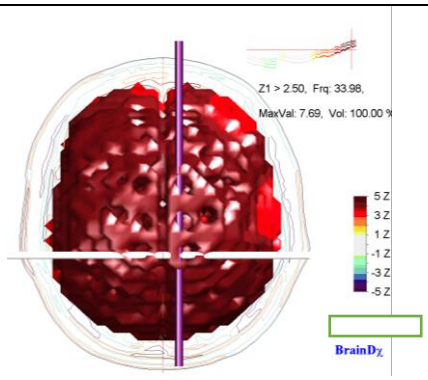
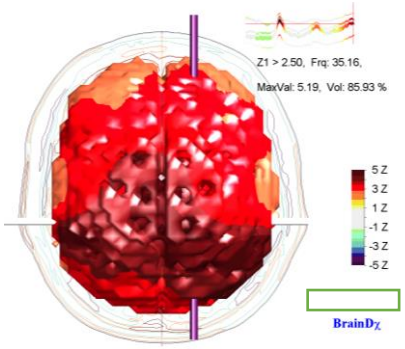
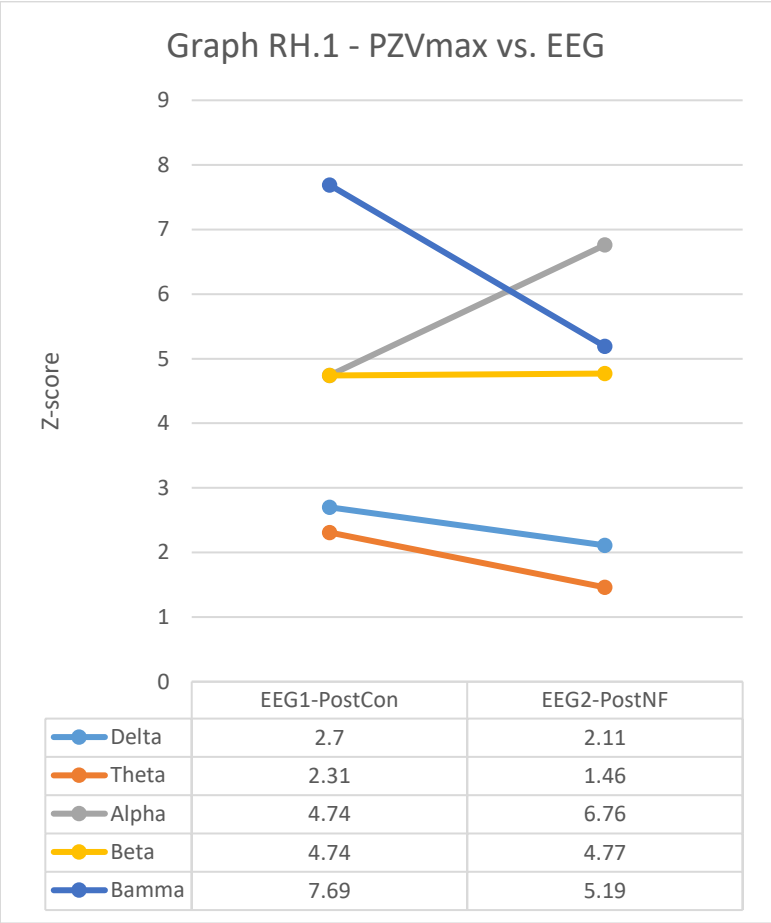
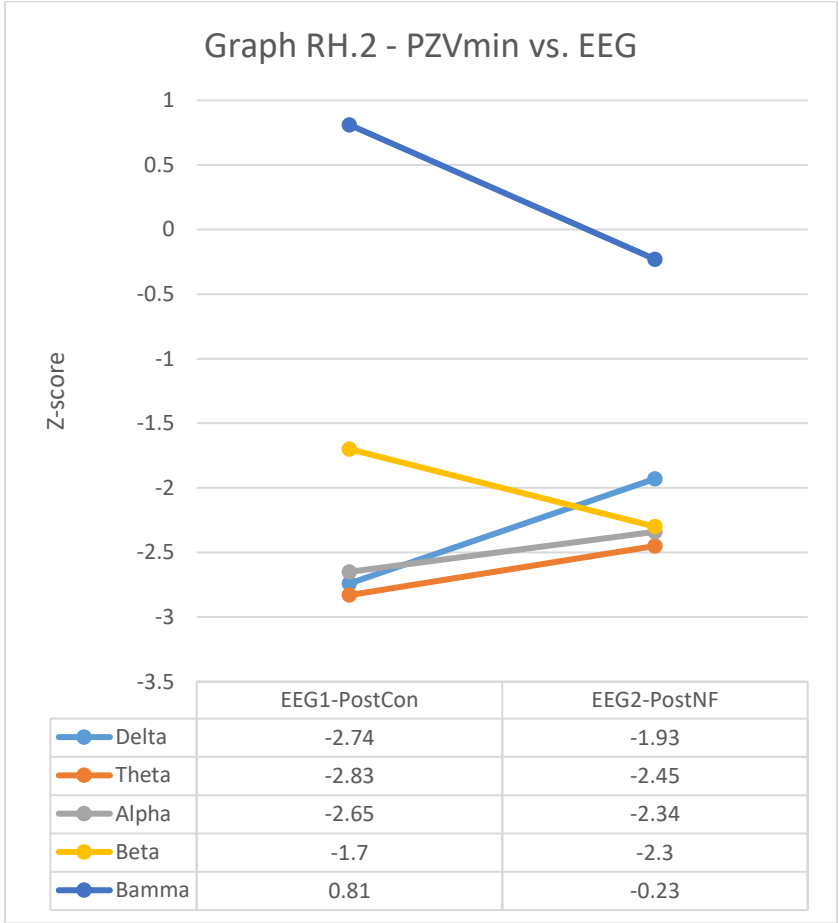
Table RH.1	Post-Concussion QEEG	Post-Recovery QEEG
Days From Injury	4	22
Delta (Cutoff Z-score = 2)		
Alpha - Increased		
Bamma		

Table RH.1 displays sLORETA QEEG images for deviant frequency bands of interest. The cutoff Z-score threshold is 2.5 Z unless otherwise noted

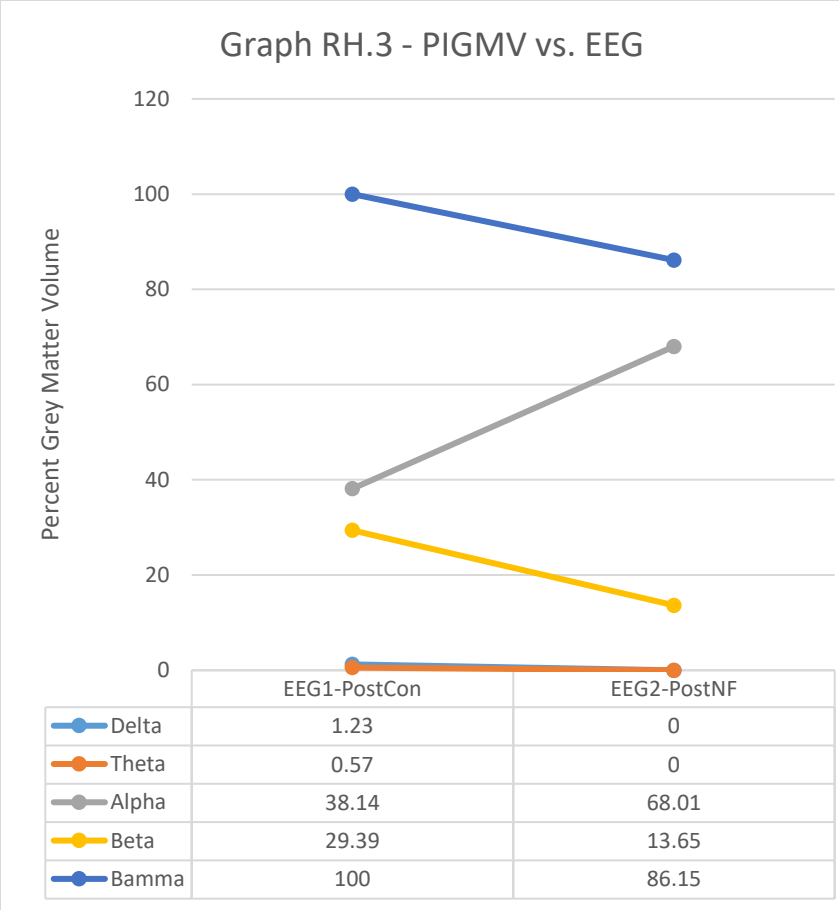


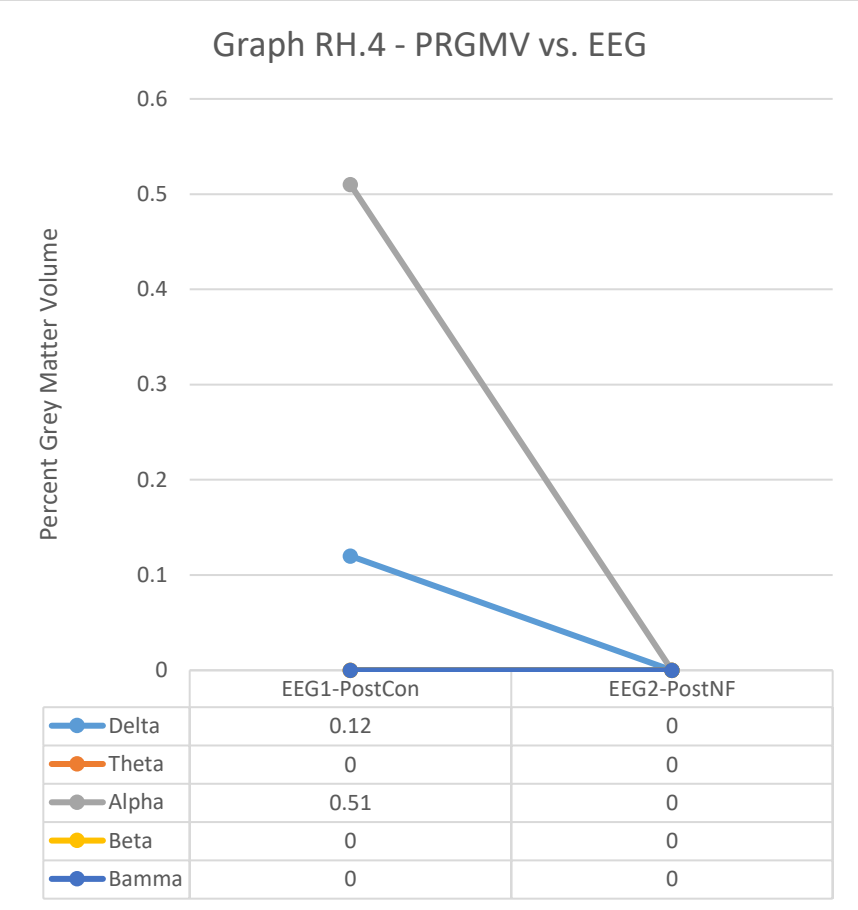
	EEG1-PostCon	EEG2-PostNF
Delta	2.7	2.11
Theta	2.31	1.46
Alpha	4.74	6.76
Beta	4.74	4.77
Bamma	7.69	5.19



	EEG1-PostCon	EEG2-PostNF
Delta	-2.74	-1.93
Theta	-2.83	-2.45
Alpha	-2.65	-2.34
Beta	-1.7	-2.3
Bamma	0.81	-0.23

Graph RH.1 depicts PZVmax for each of the 5 frequency bands across EEG time points 1 and 2. Graph RH.2 depicts PZVmin. EEG1 = post-concussion EEG, EEG2 = post-recovery with neurofeedback.





Graph RH.3 depicts PRGMV for each of the 5 frequency bands across EEG time points 1 and 2. Graph RH.4 depicts PIGMV. EEG1 = post-concussion EEG, EEG2 = post-recovery with neurofeedback.

Case Study #3 – BN

Subject BN was a volleyball player with no history of concussion hit in the face by a spiked volleyball. She did not lose consciousness but was dazed and confused shortly after the injury. Her immediate symptoms following injury were headache, nausea, and blurred vision. One year before her injury, BN underwent neurofeedback treatment for chronic migraines. The PI administered the neurofeedback that consisted of SMR training at electrode C4 and deep states training at Pz. She experienced migraines all her life, and they worsened during stormy weather patterns and the winter months. BN's migraines responded well to the neurofeedback and did not experience any headaches until her concussion that led to her consent to the study. Compared to the other cases, this case provides a unique perspective because past EEG testing from previous neurofeedback treatment provide a healthy EEG baseline for comparison to the EEG recorded after concussion injury. At the time of her baseline EEG, GN was not experiencing headaches. By the time she presented to the clinic for her post-concussion EEG, she was experiencing daily headaches in frontal regions. Enduring a full day of school and related classwork was a struggle for BN and attempting her assignments provoked headaches.

Figure BN.1 depicts BN's cognitive testing after injury. XLNTbrain post-injury cognitive testing revealed disturbances in several measures of cognitive functioning. Verbal memory accuracy and efficiency was abnormal. Verbal processing accuracy was abnormal but efficiency was borderline abnormal. Non-verbal memory accuracy was borderline abnormal. Scores for non-verbal processing, attention, and emotional reactivity were within normal limits. BN's symptom checklist indicated abnormally high reporting for symptoms in domains for migraine, cognitive, and vestibular.

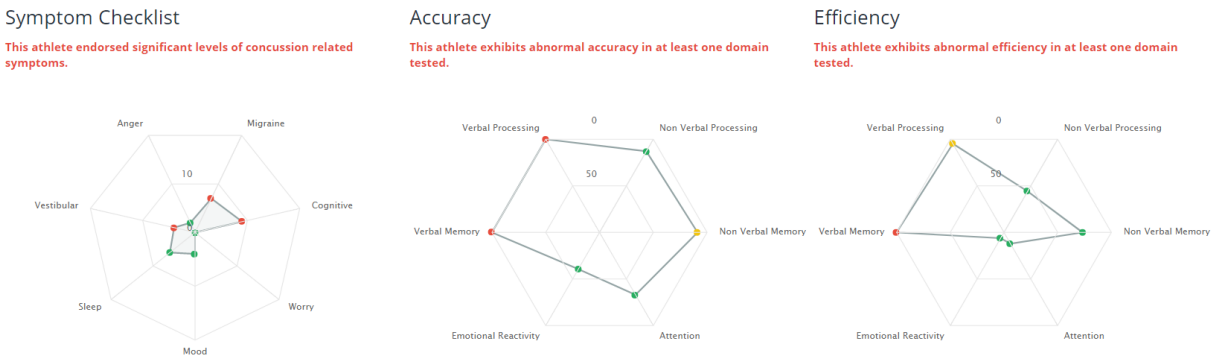


Figure BN.1 – XLNTbrain Cognitive test scores collected one day after injury. Normal scores are marked green, abnormal are marked red, and borderline are yellow.

The EEG collected after injury (EEG1) demonstrated frontal and temporal lobe deregulation. sLORETA findings indicated increased delta and theta activity in the bilateral frontal and temporal regions. There was decreased alpha activity in posterior regions, namely the occipital lobe. There was increased alpha activity in frontal regions. Neurofeedback training focused on these EEG deregulations found on BN's post-concussion EEG which demonstrated differences from her past EEG from one year prior to injury and will be detailed later. Figures depicting deviant Z scores outside of 2.5 standard deviations of the norm from BN's post-concussion EEG analysis may be found on the following pages.

Figure BN.2 – Post-Concussion sLORETA Imaging – Delta Activity: f = 2.34 Hz; Max Z-score = 4.42; PIGMV = 41.98%

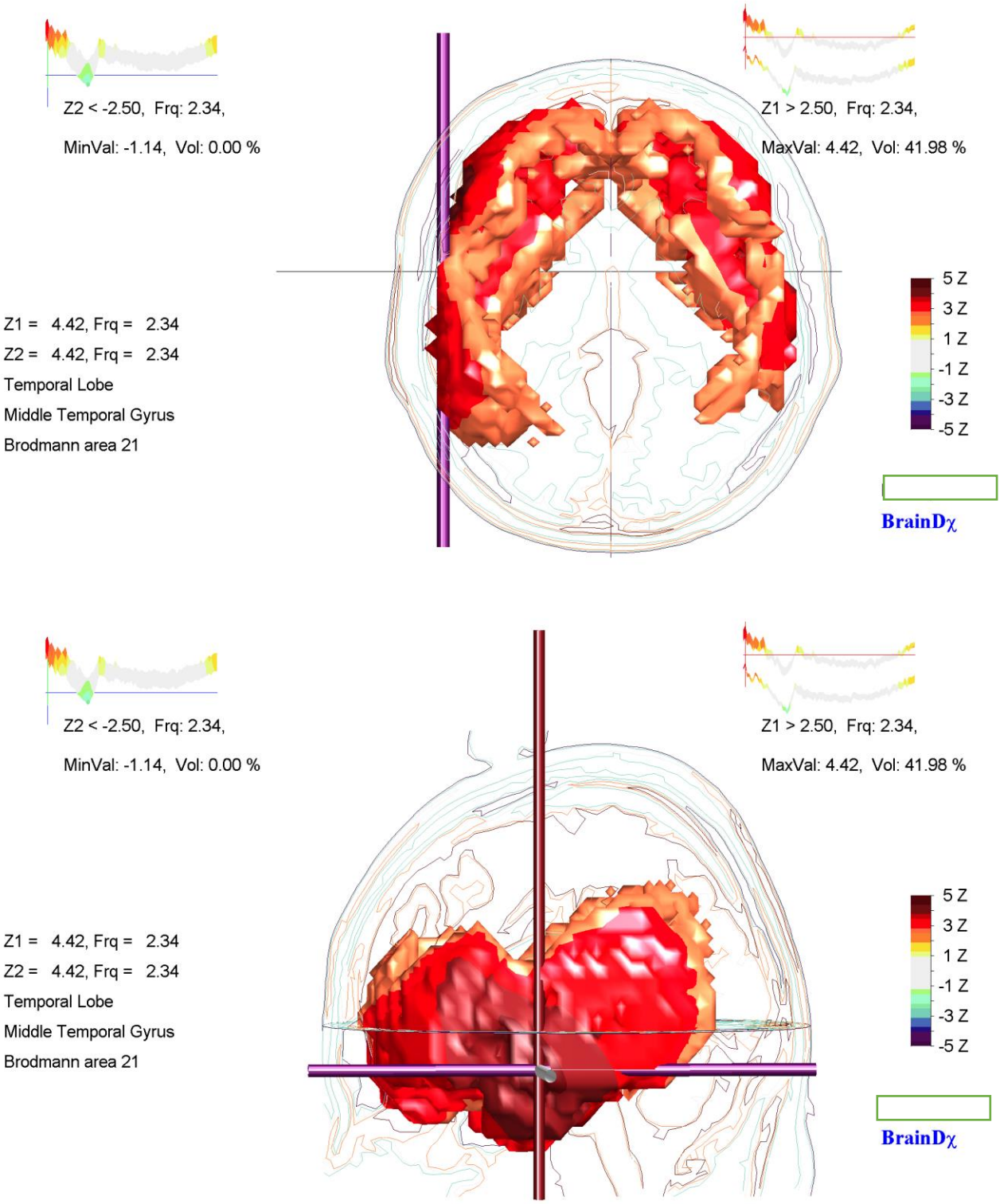


Figure BN.3 – Post-Concussion sLORETA Imaging – Theta Activity: f = 5.86 Hz; Max Z-score = 3.43; PIGMV = 7.77%

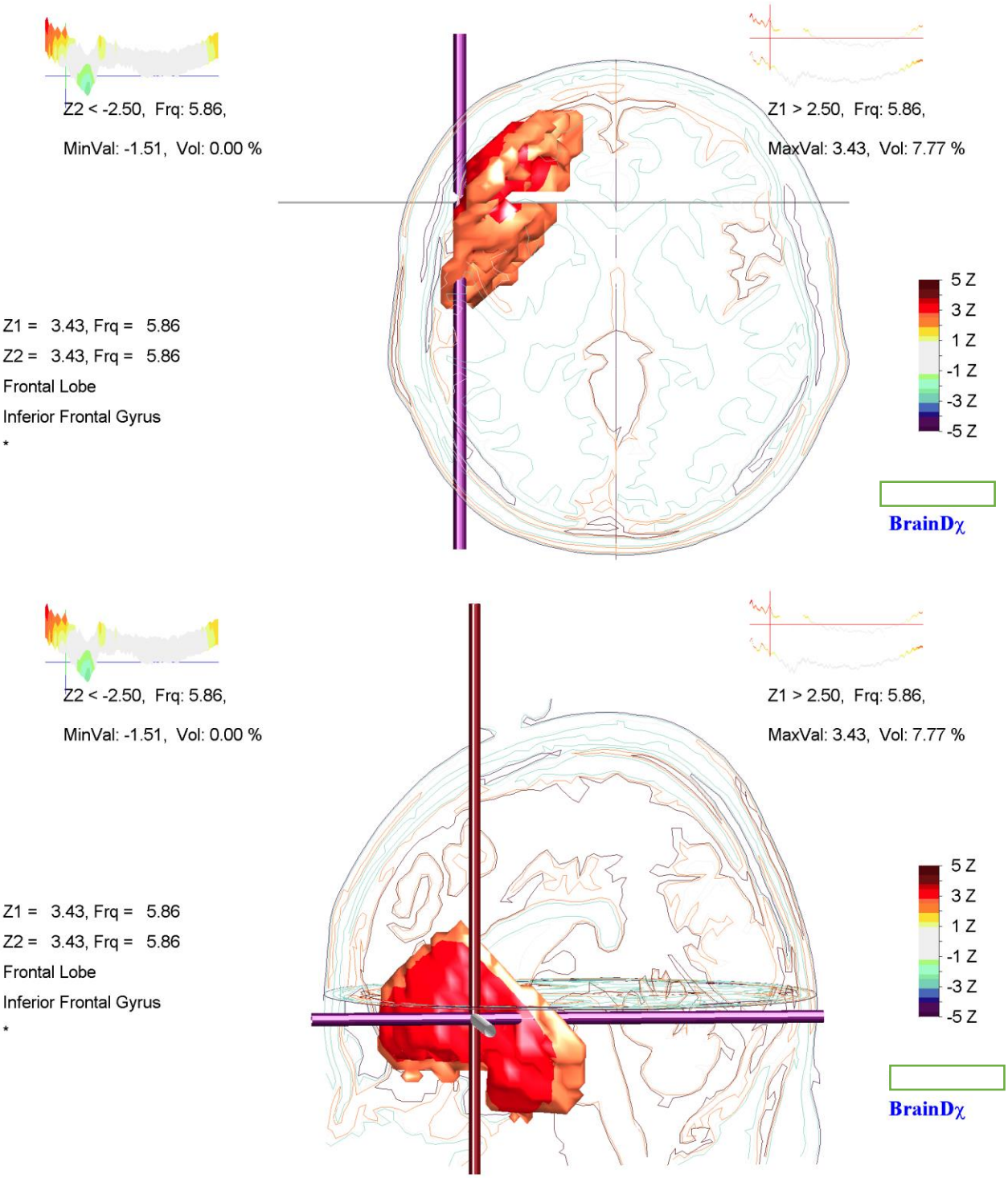


Figure BN.4 – Post-Concussion sLORETA Imaging – Alpha Activity: f = 10.16 Hz; Max Z-score = -3.95; PRGMV = 43.40%

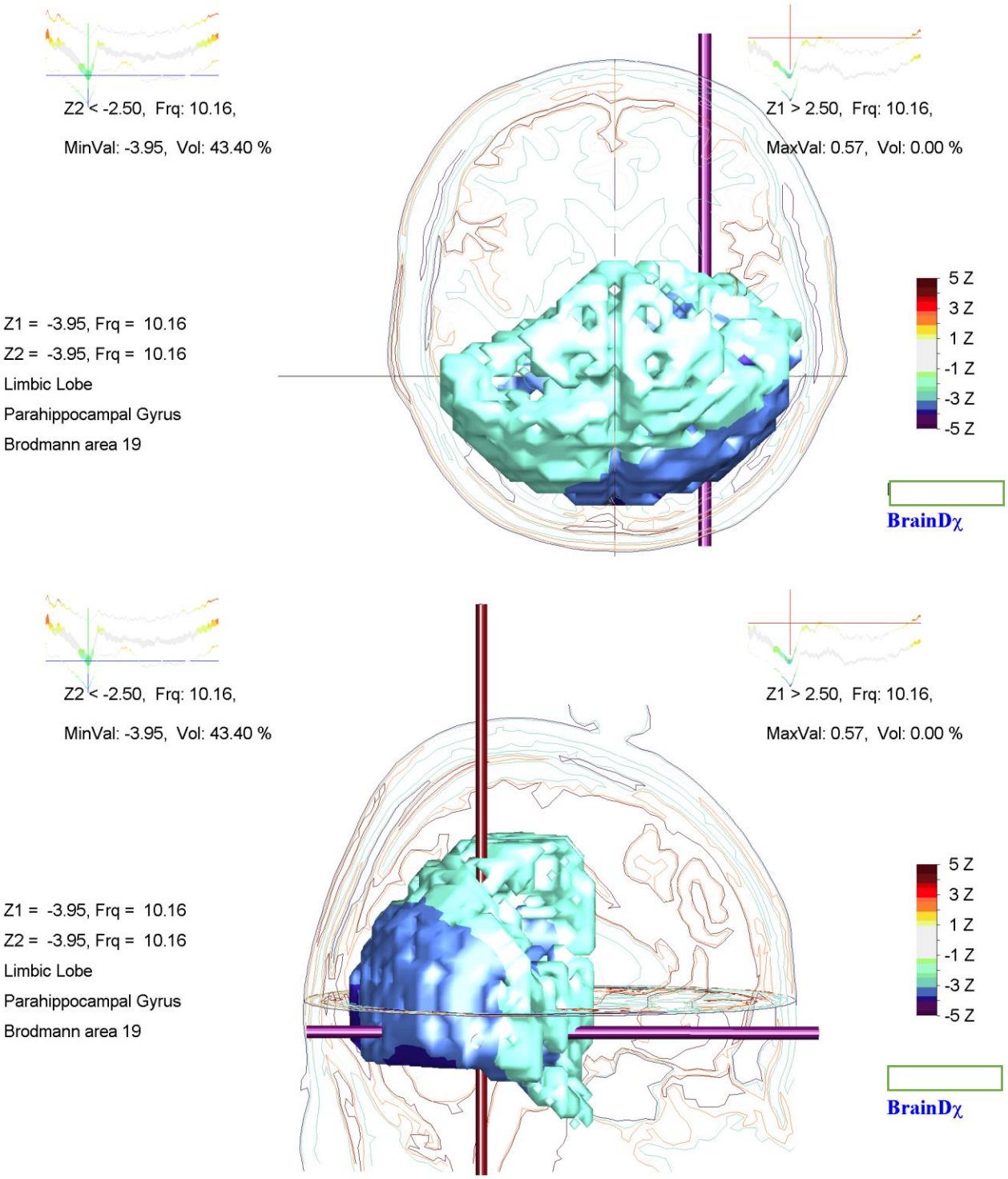
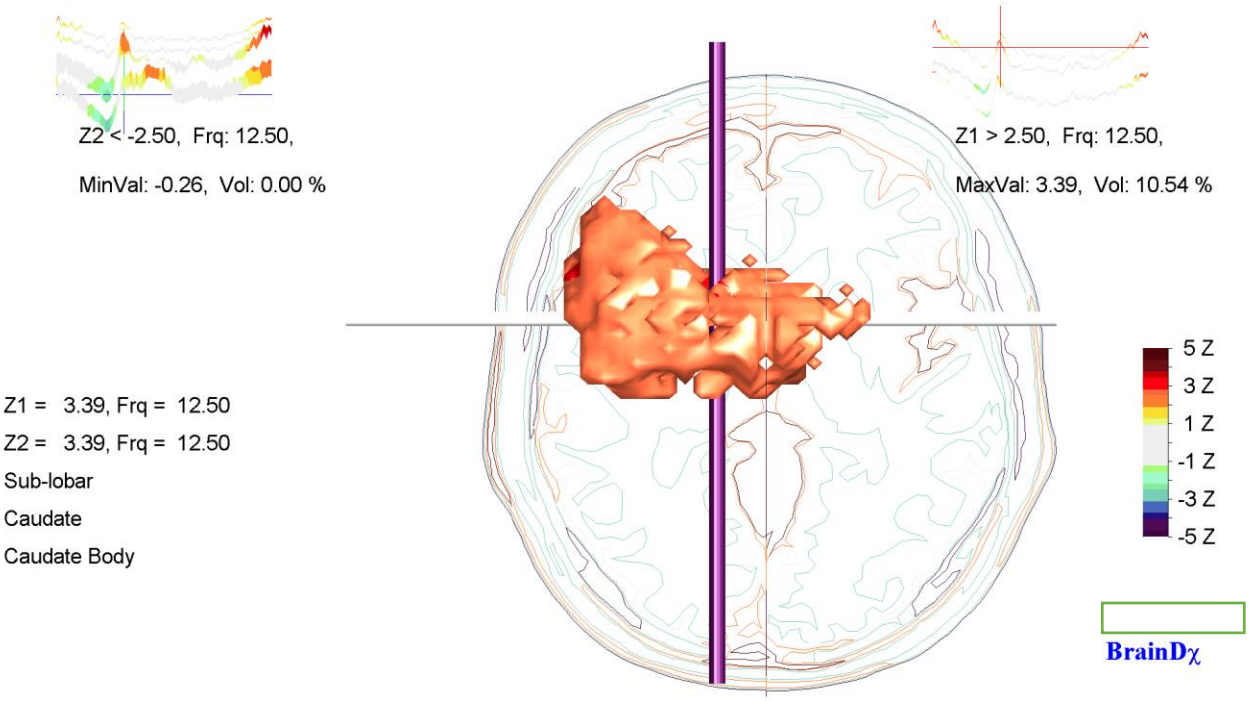


Figure BN.5 – Post-Concussion sLORETA Imaging – Alpha Activity: f = 12.50 Hz; Max Z-score = 3.39; PIGMV = 10.54%



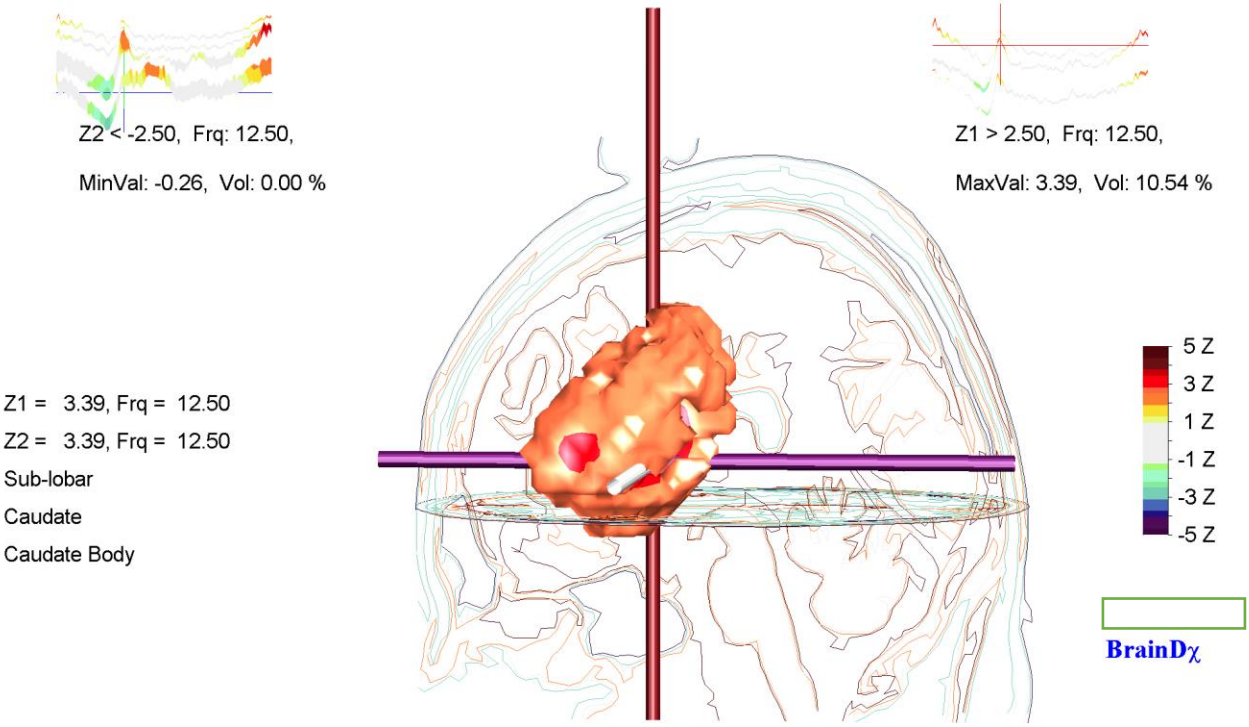


Figure BN.6 – Post-Concussion sLORETA Imaging – Beta Activity: f = 16.41 Hz; Max Z-score = 2.77; PIGMV = 2.77%

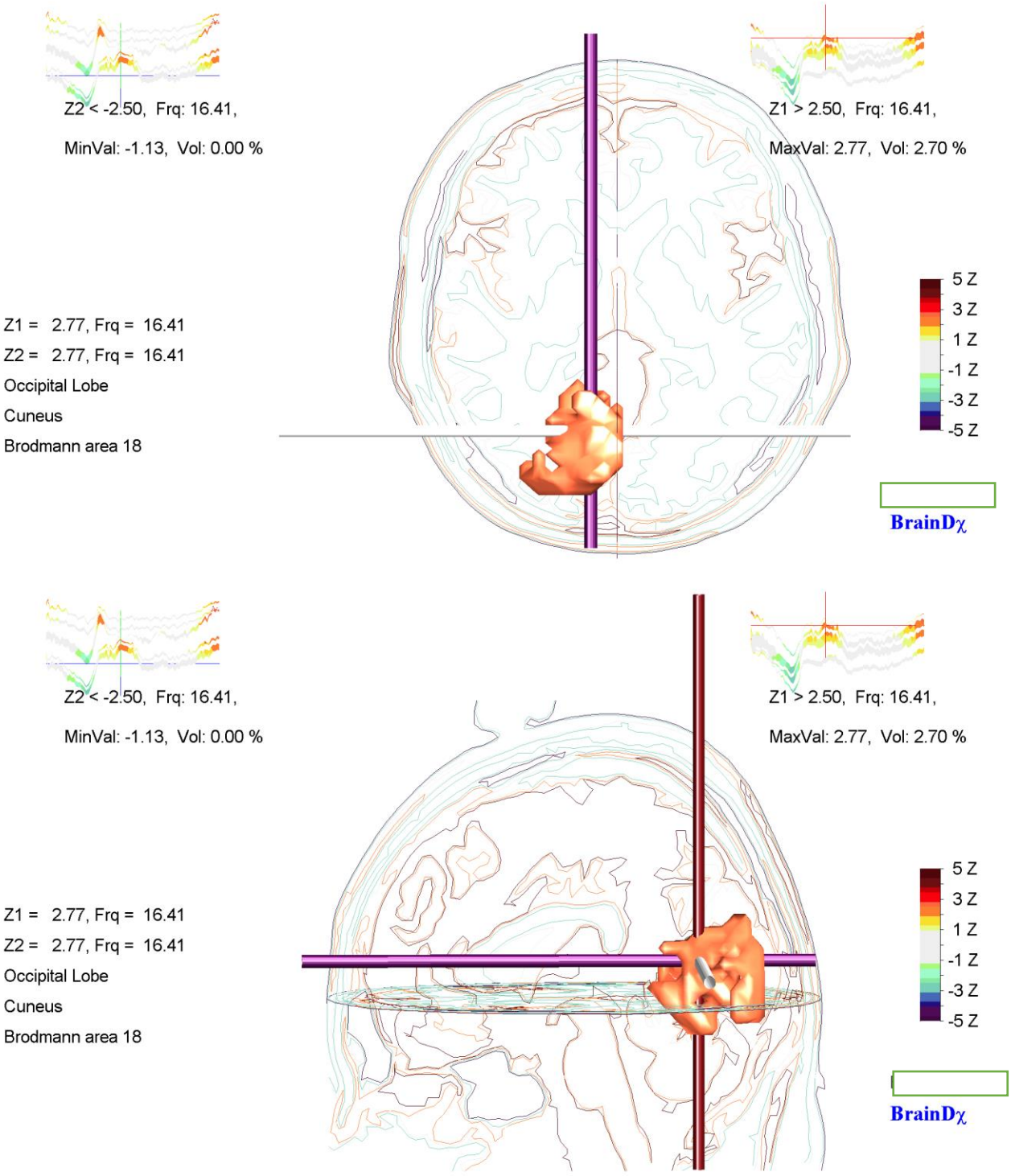
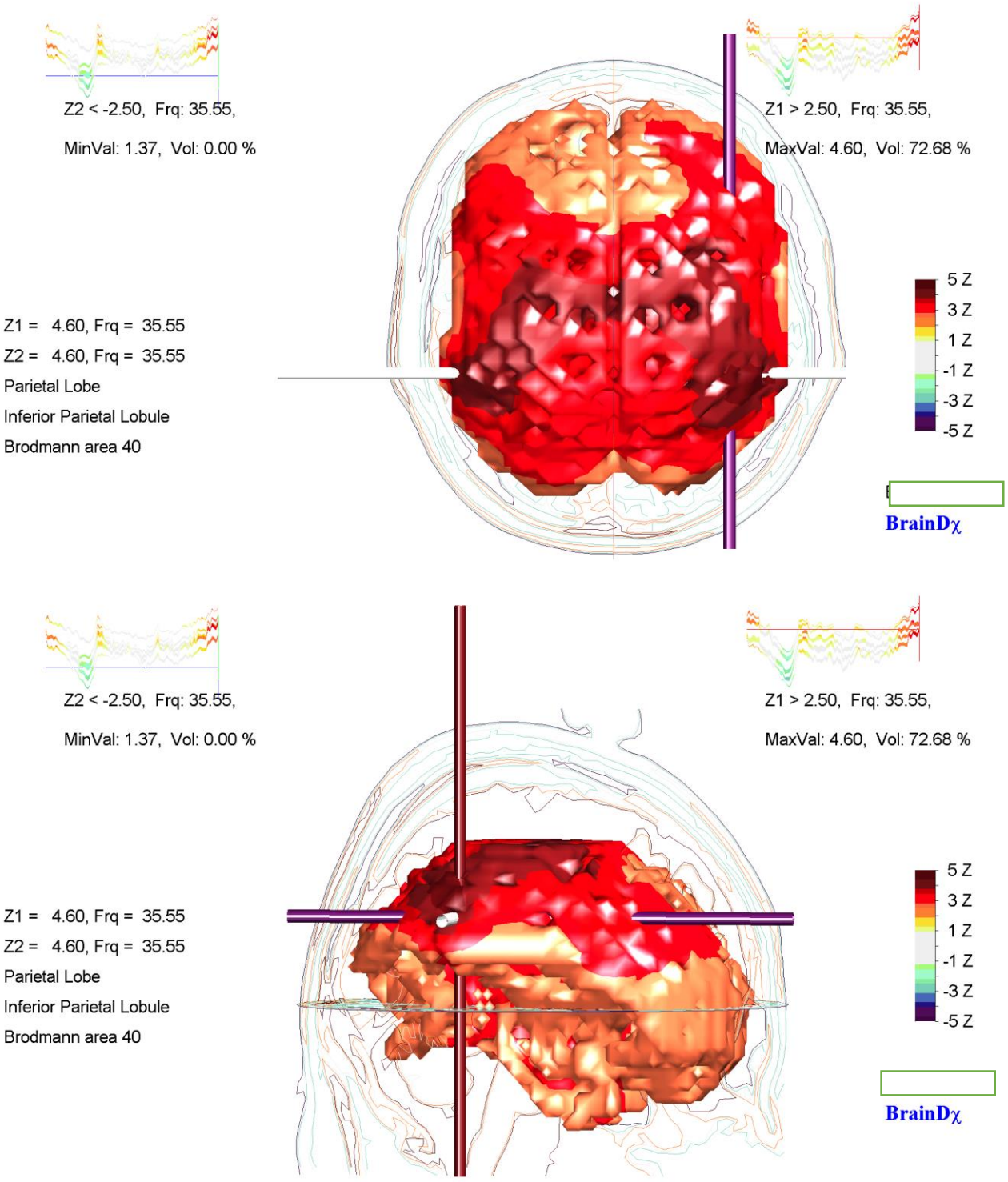


Figure BN.7 – Post-Concussion sLORETA Imaging – Bamma Activity: f = 35.55 Hz; Max Z-score = 4.60; PIGMV = 72.68%



BN's neurofeedback session consisted of two types of training protocols performed sequentially. The first neurofeedback protocol applied Z-score neurofeedback to BN's frontal and temporal regions to encourage statistically normal Z-scores for all frequency bands spanning 0.5-35 Hz. Raw, non-Z-scored CSD in the delta and theta bands were inhibited in the frontal and temporal lobes to emphasize the reduction of the deviant slow-wave EEG patterns likely related to BN's recent concussion. This protocol was performed in the eyes open condition as the patient watched a DVD movie for visual feedback and received simultaneous auditory feedback that quietly played in the background of the movie audio. The second protocol applied alpha training at the following sLORETA regions of interest: anterior cingulate gyrus, middle cingulate gyrus, posterior cingulate gyrus, precuneus, and occipital lobe. As alpha was rewarded in these structures, theta and beta2 were inhibited in the same structures.

BN was treated with 8 neurofeedback sessions in total. After the first session, she experienced a dull headache which dissipated by the following morning. Her headaches at rest gradually decreased but were consistently provoked by increased cognitive load associated with schoolwork. The subject presented to the 4th session having experienced a significant headache while doing schoolwork over the weekend. The intensity of the headache decreased immediately after the session, especially after the alpha protocol.

When BN presented for the 5th session, she described her experience after session 4. The headache had dissipated after the neurofeedback session but returned and intensified on her drive home from the session. The headache was located in posterior regions. She vomited when she arrived home and did not attend school or volleyball practice the following day, remaining home fatigued and battling the headache. To gather updated EEG information considering this change in BN's headache, an EEG was recorded at the beginning of this session. BN completed 20

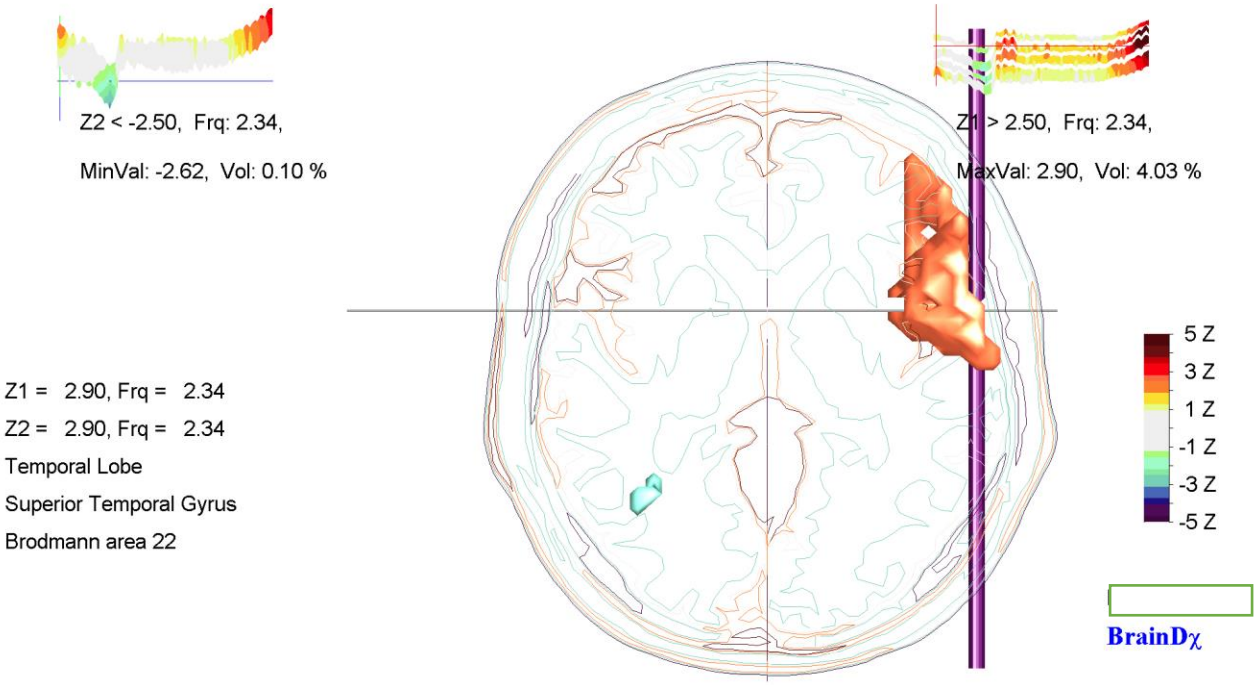
minutes of alpha training. The PI processed the new EEG data during the alpha protocol, which demonstrated decreased delta PZVmax and elevated posterior beta patterns similar to the patient's past EEG. Upon discussion of the data after completion of the alpha training, the patient explained the recent, severe headache reminded her of last year's migraines, which were typically located in posterior regions. Her post-concussion headaches originated frontally. Nausea, vomiting, and fatigue were symptoms she experienced during past migraines. The patient's protocol from previous migraine neurofeedback treatment, SMR training at electrode C4, was introduced after the discussion which had differentiated the new head pain from the concussion head pain. The patient rated her pain at a 6/10 before SMR training and 2/10 afterwards. The final 3 sessions consisted of BN's old protocol to reduce migraine-type headaches.

As BN's headaches shifted towards what she used to experience during migraine headaches, she was clinically cleared from her concussion injury 13 days after the EEG2. The post-recovery EEG demonstrated reductions delta and theta PZVmax and PIGMV and increases in high alpha/alpha2 and beta patterns. In contrast to the post-concussion EEG, the newly emergent patterns more closely matched her old EEGs from prior neurofeedback treatment. Data from EEG2 is located below, followed by comparison to past EEG data from earlier neurofeedback treatment.

Analysis of EEG2 suggested altered cortical functioning compared to EEG1. Delta and theta activity decreased indicated by Z-scores approaching statistical normality and reductions in deregulated grey matter volume during concussion recovery. Delta activity changed from 4.42 PZVmax with 41.98% PIGMV to 2.90 PZVmax with 4.03% PIGMV, and theta from 3.43 PZVmax with 15.44 PIGMV to 2.17 PZVmax with 0% PIGMV. Low alpha activity decreased

away from the normal range as the already minimum -3.95 PZVmin with 43.40% PRGMV measured more negative on the second EEG at -4.36 PZVmin with 50.90% PRGMV. High alpha activity with Z-score of 3.39 PZVmax with 10.54% PIGMV increased after neurofeedback to a Z-score of 3.89 PZVmax with 39.33% PIGMV. Beta activity on EEG2 demonstrated a generalized increase around 13 Hz and an increase in the frontal region around 20 Hz. Bamma activity increased from PZVmax of 4.60 with 72.68% PIGMV to PZVmax of 7.35 with 100.00% PIGMV.

Figure BN.8 – Post-Neurofeedback sLORETA Imaging – Delta Activity: f = 2.34 Hz; Max Z-score = 2.90; PIGMV = 4.03 %



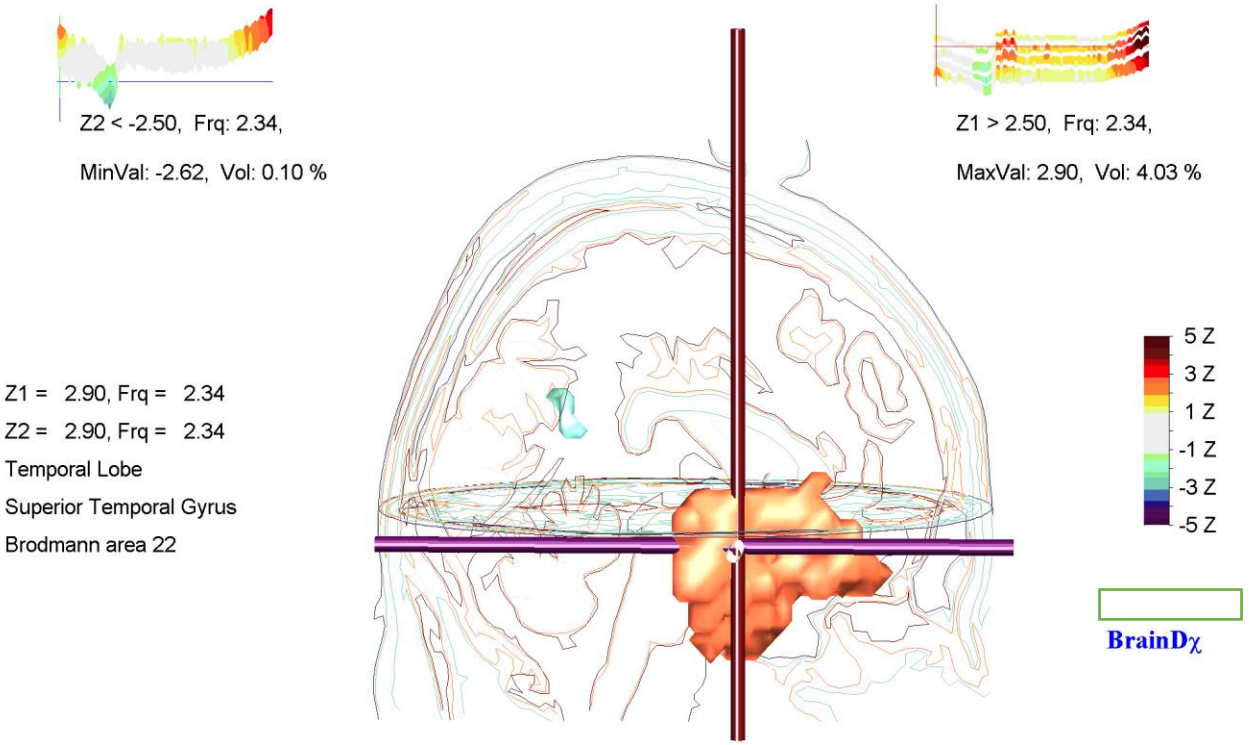


Figure BN.9 – Post-Neurofeedback sLORETA Imaging – Alpha Activity: f = 10.16 Hz; Max Z-score = -4.36; PIGMV = 50.90 %

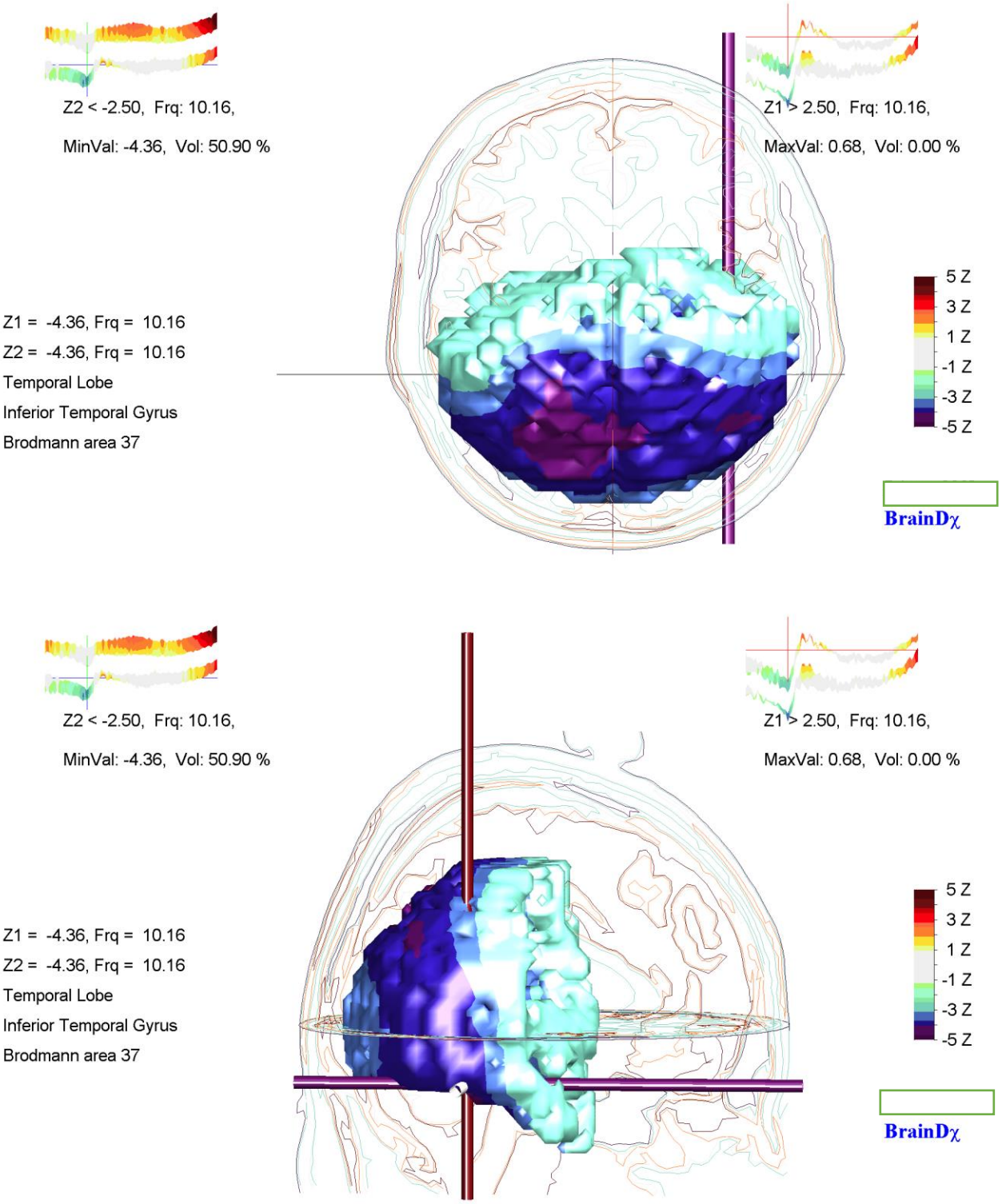
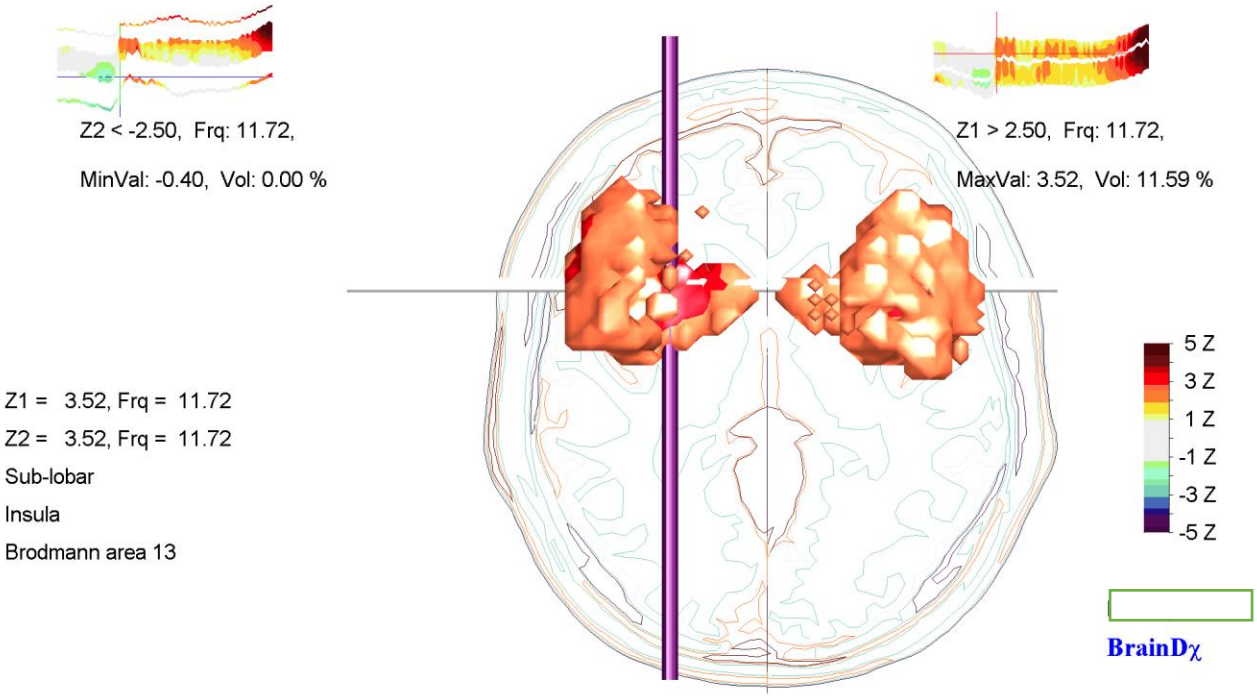


Figure BN.10 – Post-Neurofeedback sLORETA Imaging – Alpha Activity: f = 11.72 Hz; Max Z-score = 3.52; PIGMV = 11.59 %



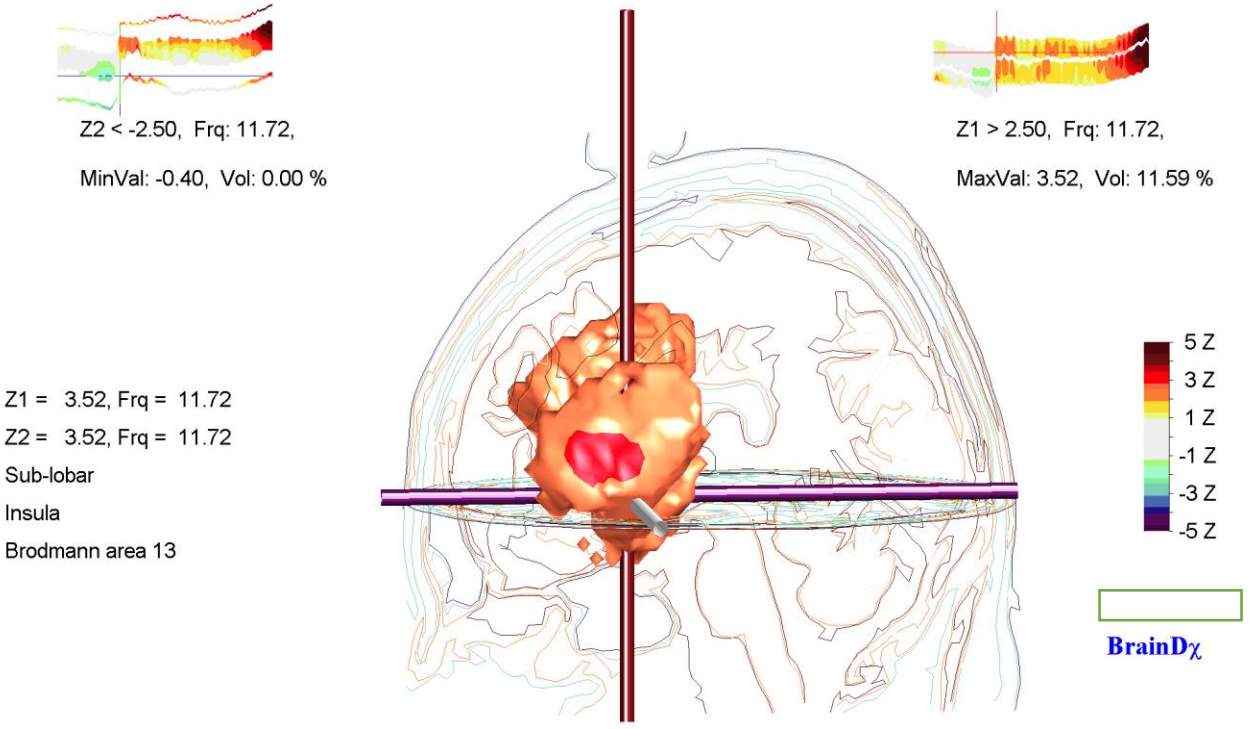
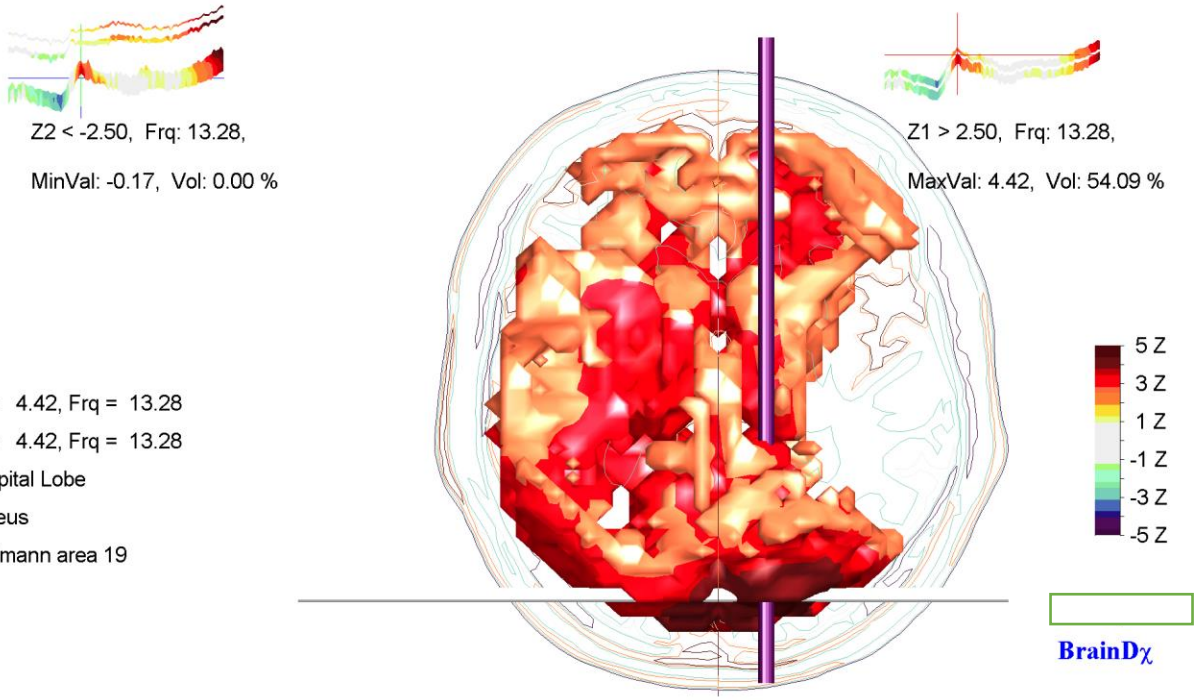


Figure BN.11 – Post-Neurofeedback sLORETA Imaging – Beta Activity: f = 13.28 Hz; Max Z-score = 4.42; PIGMV = 54.09 %



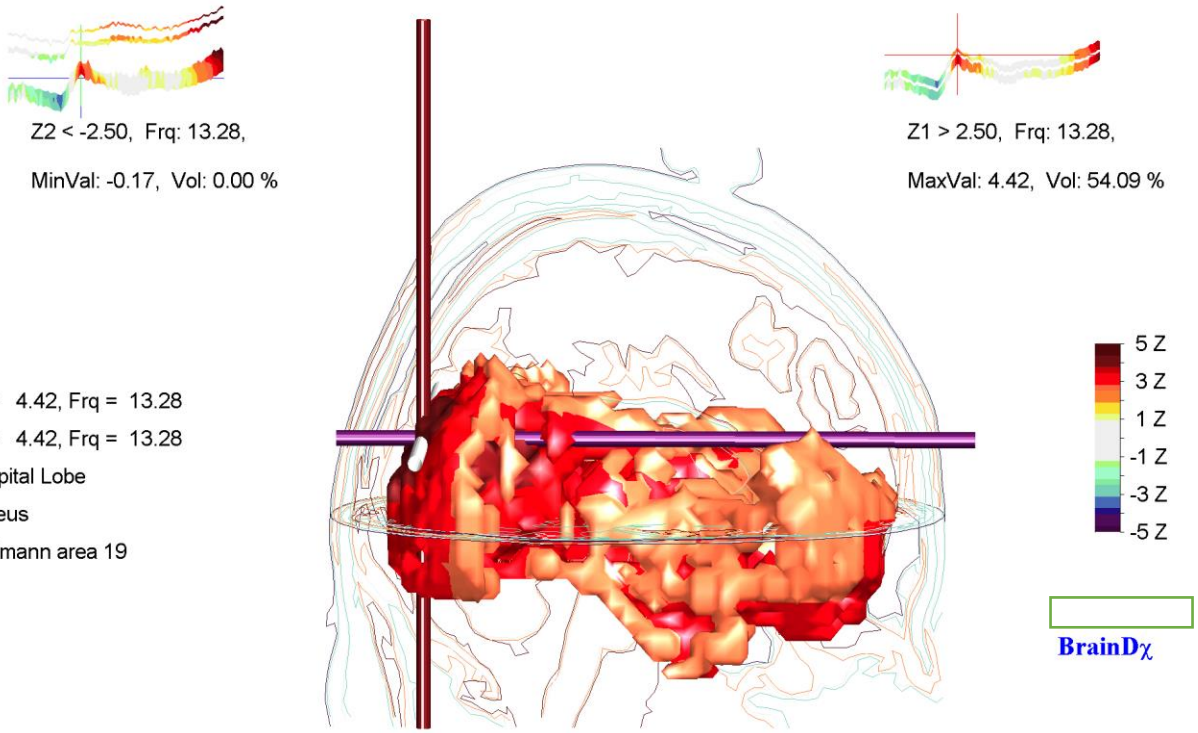
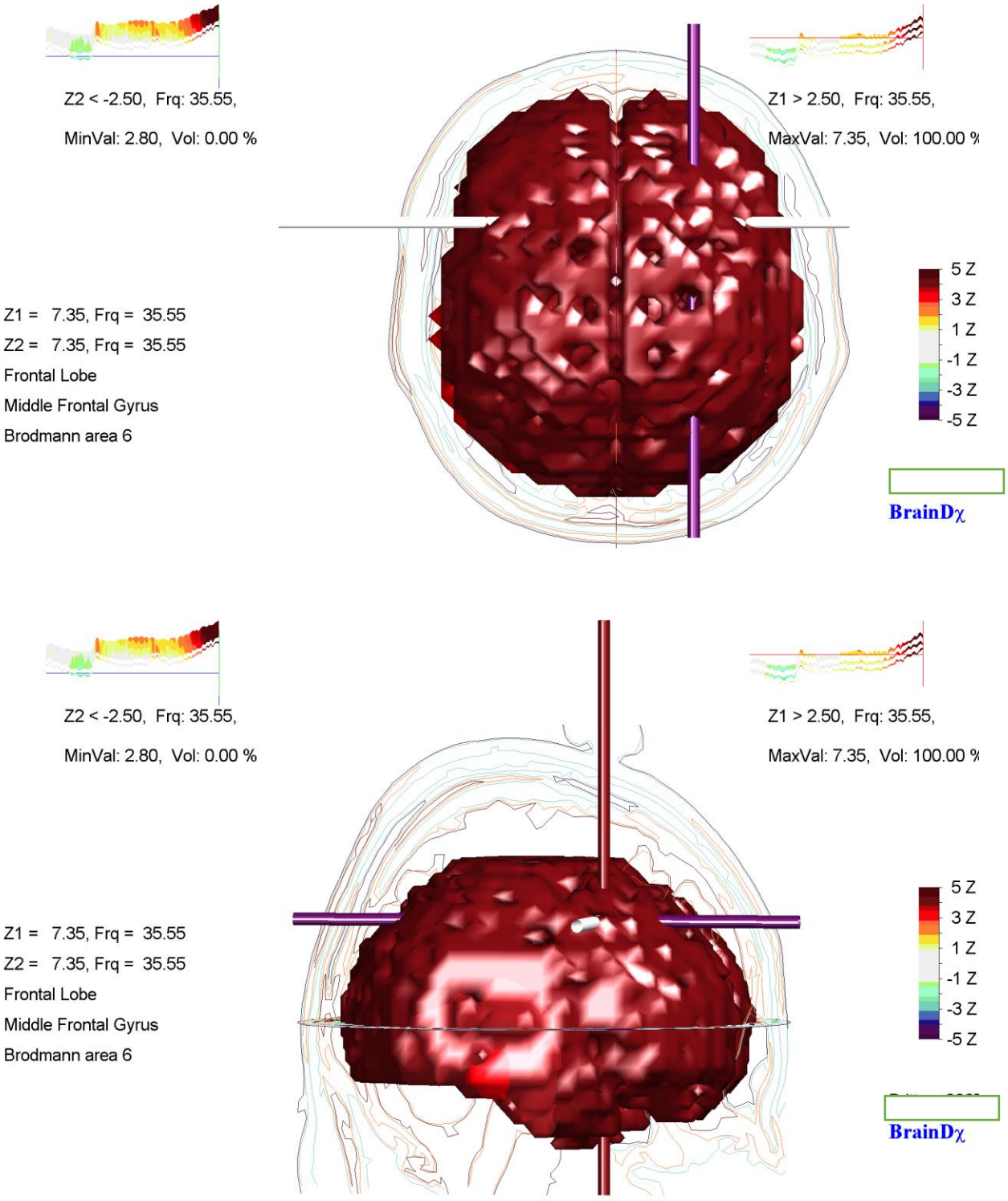


Figure BN.12 – Post-Neurofeedback sLORETA Imaging – Bamma Activity: f = 35.55 Hz; Max Z-score = 7.35; PIGMV = 100.00 %



XLNTbrain cognitive testing repeated after BN was cleared of her concussion demonstrated improvements in self-reported symptoms and cognitive measures (Figure BN.13). Colorful markers connected by grey lines indicate scores from the post-recovery cognitive test, and the blue shaded area on the test results indicate scores from the first cognitive test. On nearly all measures, scores decreased from post-concussion levels to values within the normal range and more centered on the spider chart. BN's endorsement of migraine symptoms at recovery remained elevated from normed ranges, but showed a relative decrease compared to post-concussion migraine levels.

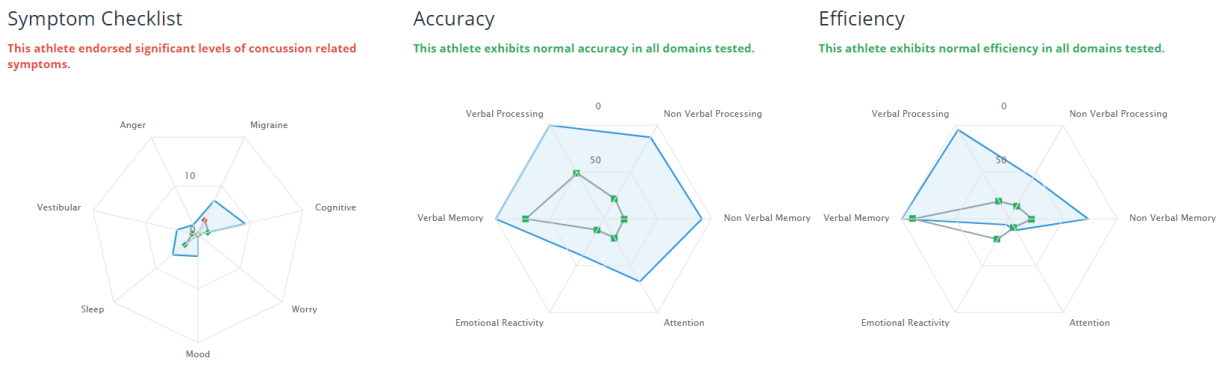


Figure BN.13 – XLNTbrain cognitive testing collected after recovery from concussion injury. The blue shaded area represents BN's scores from post-concussion cognitive testing.

BN's EEG data demonstrates a quantifiable change in electrophysiological activity related to a concussion. In this rare case, an EEG baseline was established due to BN's prior clinical concussion management at CNA. When BN was injured playing volleyball, the entire EEG profile shifted away from her baseline and subsequently returned to near-baseline, if not improved from baseline, upon clinical recovery. In Table BN.1, baseline EEG findings are depicted in the left column, post-concussion findings in the middle column, and post recovery data are in the right column. The post-neurofeedback baseline EEG appears similar to the right-

most column for post-recovery EEG when compared to the middle column depicting the data collected after concussion injury. The picture suggested by this data is that BN's cortical functioning after injury slowed compared to baseline, then demonstrated a relative increase in speed and functioning with recovery.

This was evident in the change in delta activity. BN's baseline EEG demonstrated slightly increased delta activity in the right frontal region. Roughly eleven months after the baseline EEG and seven days after injury, regional increases in delta were evident in the frontal and temporal lobes. After 15 days, during which BN underwent 5 neurofeedback sessions, the frontotemporal regions demonstrated a dramatic reduction in delta activity to Z-score and volume measurements lower than baseline values found in the same right frontal region. Maximum Z-scores of theta activity showed a similar pattern as baseline theta was elevated in the right frontal region, increased and lateralized to the left frontal region after injury, and finally reduced to lower measurements in the right frontal region after recovery from concussion.

BN's minimum theta values depicted an increase in theta activity from baseline to concussion, indicated by the decreased blue volume on the post-concussion image, followed by a reduction of theta activity at post-recovery. While the PZVmin and PRGMV values consistently suggested atypical minimum theta activity compared to the normative database, considering only the direction of change relative to BN communicates movement away from baseline after injury then back towards baseline during recovery. The minimum values for alpha activity told a similar story. BN's baseline EEG suggested decreased alpha activity (PZVmin = -4.52) compared to the normative database, which remained low after injury (PZVmin = -3.95) but was less statistically deviant from the normal distribution. After recovery from concussion related symptoms, BN's alpha activity registered further left from center with a PZVmin of -4.36. This

suggested BN's alpha activity returned towards baseline, pre-concussion levels, albeit statistically abnormal compared to normative database.

Measurements of fast wave activity depicted a similar change over time. Beta and bamma Z scores and volumes were elevated prior to concussion. After the volleyball accident, fast wave activity declined relative to the baseline EEG but was still elevated above 2.5 standard deviations. Fast waves increased and returned to near baseline levels that were similarly elevated above the normal range. Bamma activity was greater than 6 SD on the first EEG and decreased to just below 5 SD after concussion injury before increasing to greater than 7 SD on the final EEG.

Analysis of BN's alpha and low beta activity warrants further discussion of peak frequency (f_{peak}) from what was covered in the case of RH above. Peak frequency typically refers to the posterior dominant rhythm of an individual's EEG spectrum measured during the eyes closed condition and is identified as a high point in the frequency spectrum (Collura, 2014). The posterior dominant rhythm waxes and wanes during the eyes closed, responds to eye closure, and is found in posterior regions of the cortex. This activity often falls in the alpha frequency band range, but is not operationally defined as alpha activity. Peak frequency increases through childhood. Average adult peak frequency falls within the 8-12 Hz alpha range, and children typically achieve this peak by age 8-10 (Collura, 2014).

Individuals with peaks below 8 Hz (i.e., 7 Hz) or above 12 Hz (i.e., 13 Hz) present a confounding situation for QEEG database comparison. Although the 7 or 13 Hz peak frequency is normal for the presenting individual, the pattern tricks the quantitative database which depicts the increased theta or beta activity as a gross abnormality on the brain maps. A hypothetical adolescent subject with f_{peak} of 7 Hz would show high amplitudes of 7 Hz activity in posterior

regions that technically falls within the theta frequency range. QEEG analysis on this subject would generate brain maps with positive theta Z-scores located in the occipital and parietal regions. While the elevated theta looks highly abnormal on the QEEG maps, this is the norm for the subject in question because of their known f_{peak}.

The data on BN represent a similar pattern. BN's f_{peak} at baseline was 12.1 Hz, decreased to 11.7 Hz after injury, and increased to 12.9 Hz after clinical recovery. This change in f_{peak} was likely related to the changes in alpha and low beta (approx. 13 Hz) depicted on BN's QEEG analyses. BN's f_{peak} at baseline was at the upper end of the typical peak frequency range, resulting in elevated beta activity and corresponding reduced alpha activity at baseline. After the concussion injury and associated electrophysiological changes, BN's f_{peak} slowed by 0.4 Hz. The changes in the QEEG maps are the by-product of this slowing. The 0.4 Hz decrease in f_{peak} tilted her posterior EEG functioning towards the alpha range as depicted by the increase in alpha activity and decrease in beta relative to baseline. By recovery, the subject's f_{peak} increased to 12.9 Hz, and the corresponding alpha Z-scores decreased and beta Z-scores increased. Thus, while the QEEG findings depicted clear changes in cortical functioning, accurate interpretation of the alpha and beta measurements depends on the subject's peak frequency.

Compared to data collected after concussion injury, BN's sLORETA QEEG Z-score and percent changed grey matter volume (PIGMV/PRGMV) measurements upon recovery approached baseline measurements. BN recovered in 35 days, 7 days greater than the expected recovery time for concussed adolescents (McCrory et al., 2017), and 12 days less than the average recovery time of the non-treatment control group. Several factors may have played a role in BN's recovery from her concussion. BN reported no prior history of concussion, which is related to increased susceptibility to concussion injury and increased recovery time (McCrory et

al., 2017). The subject had a documented history of migraine headaches, and concussion recovery is typically longer for people with pre-existing history of migraine headaches (Kerasidis, 2015). Despite this history of migraines, BN recovered quickly. The PI posits that the past neurofeedback treatment influenced BN's recovery. Given neurofeedback that applies neuroplasticity to retrain brain function and BN had past experience with neurofeedback, the subject's brain was potentially more receptive to both neurofeedback-reinforced change and natural recovery due to her increased neuroplastic potential. However, the trajectory of BN's specific recovery without neurofeedback is unknown and support of this position requires further study. It is impossible to infer causality of neurofeedback given the current study design and limited research on the present topic, but this case is of particular interest because of pre-concussion data collection and treatment.

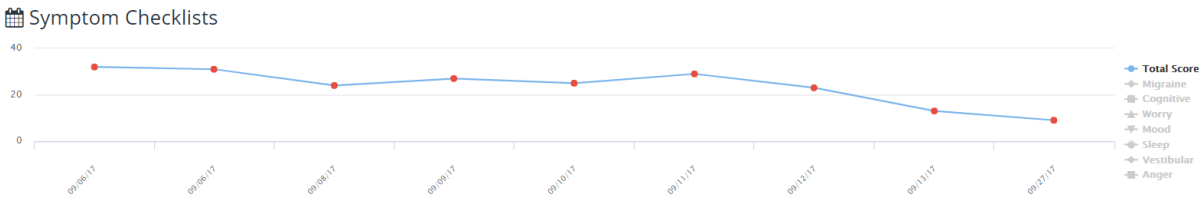
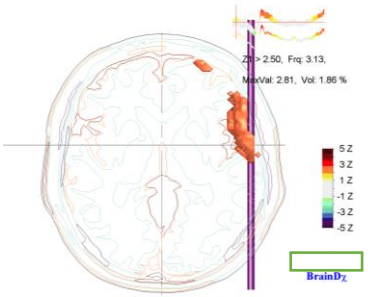
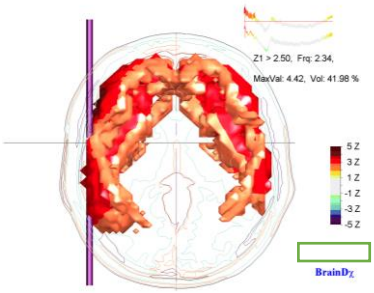
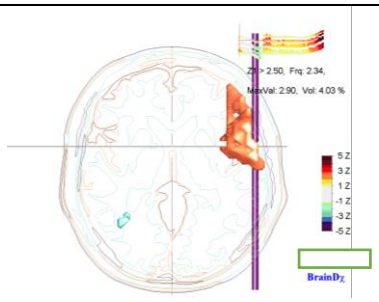
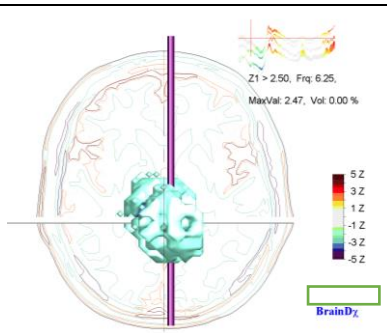
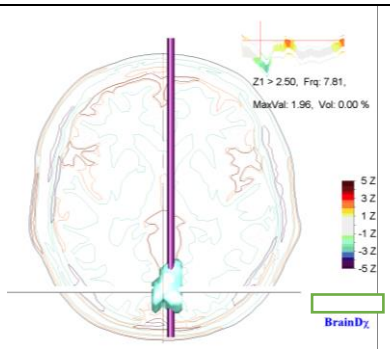
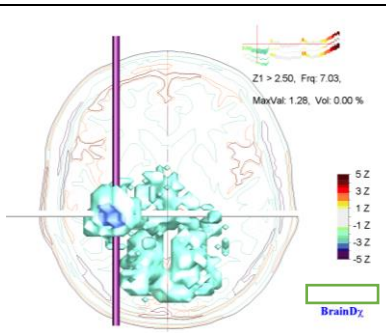
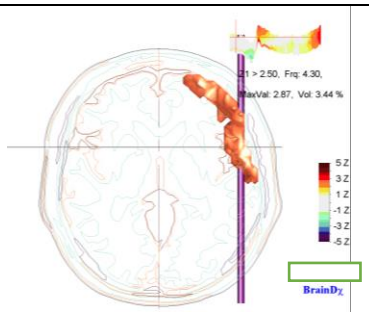
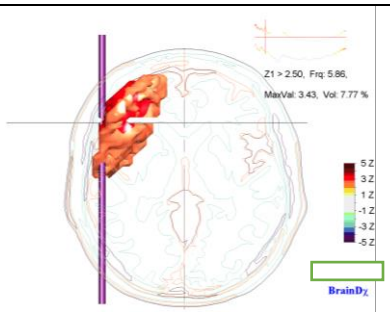
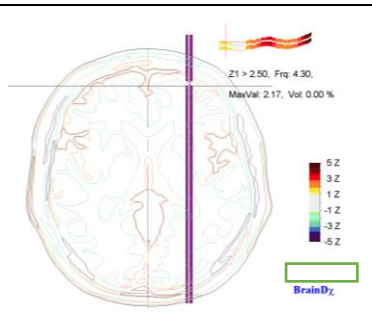
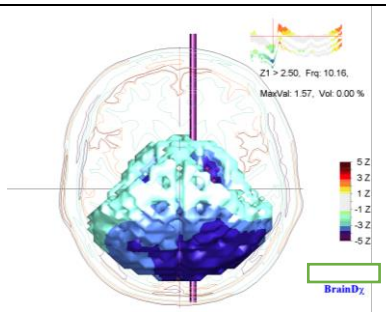
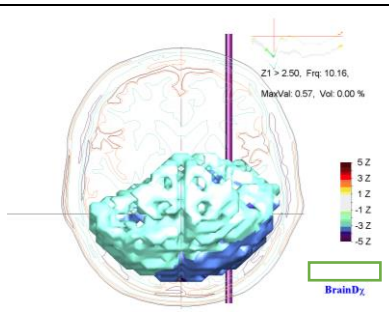
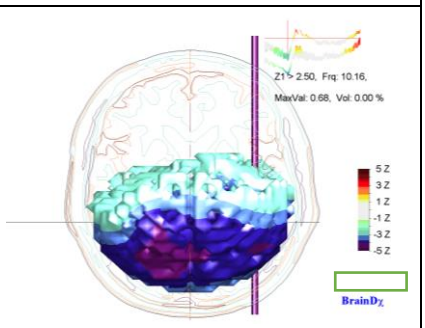


Figure BN.14 – Symptom tracking during BN's recovery.

Table BN.1	Post-Neurofeedback Baseline QEEG	Post-Concussion QEEG	Post-Recovery QEEG
Days From Injury	-339	7	22
Delta			
Theta – Reduced			
Theta – Increased			
Alpha – Reduced			

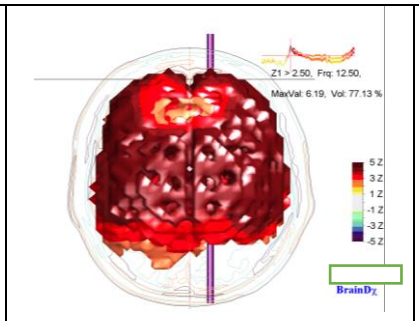
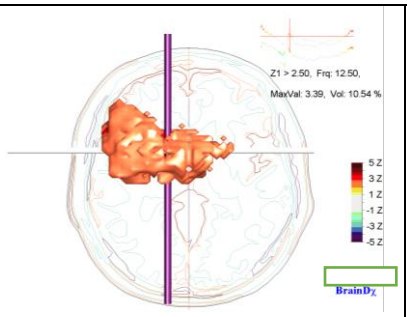
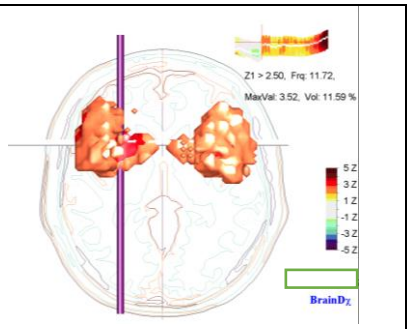
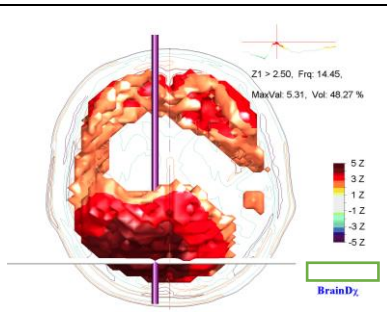
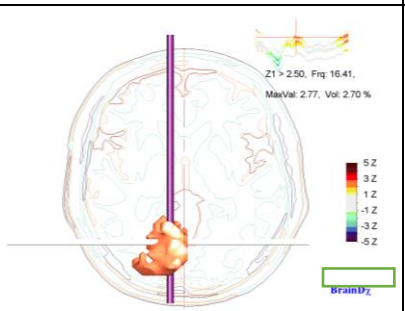
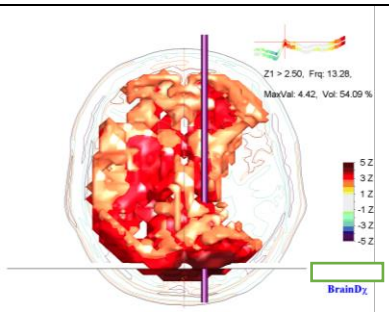
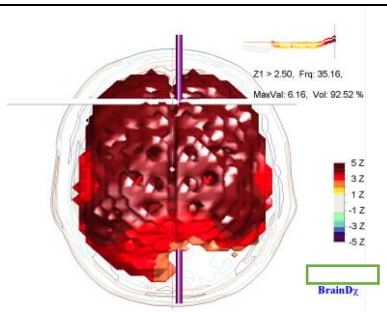
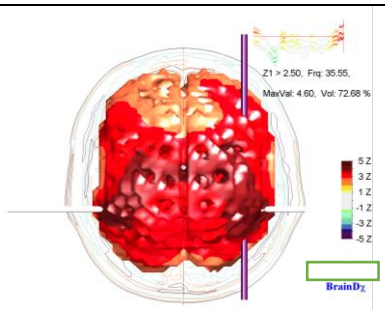
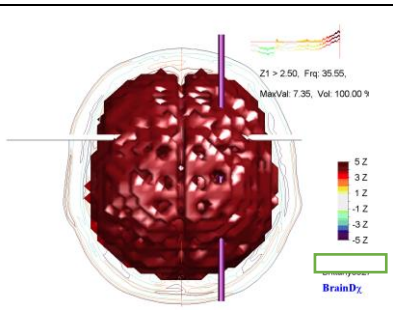
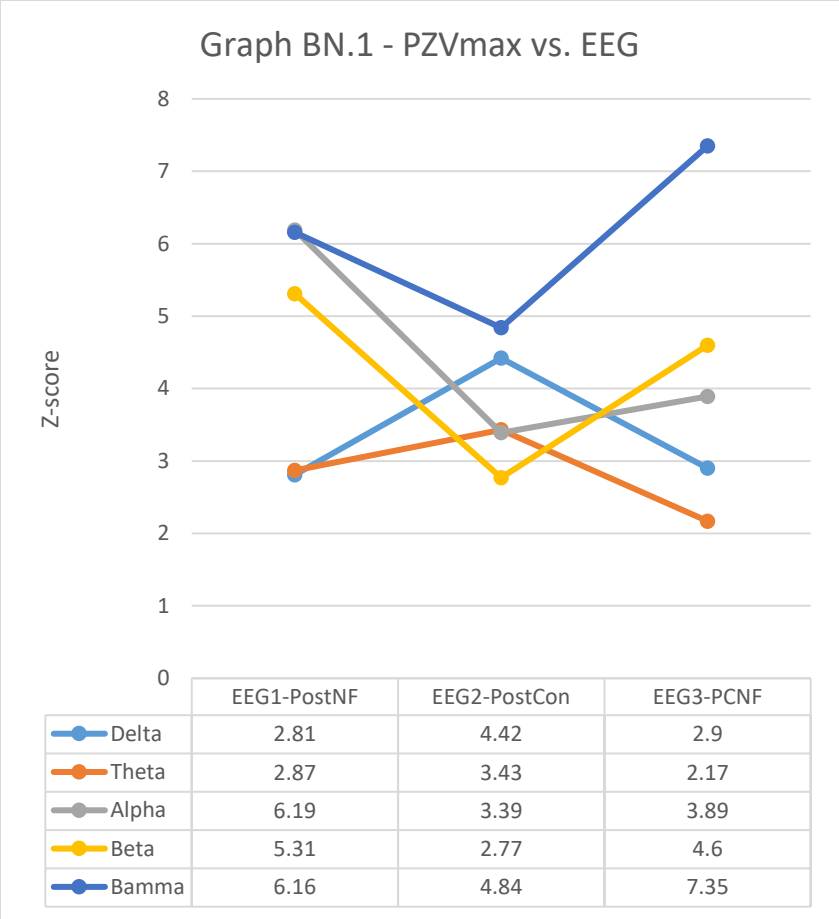
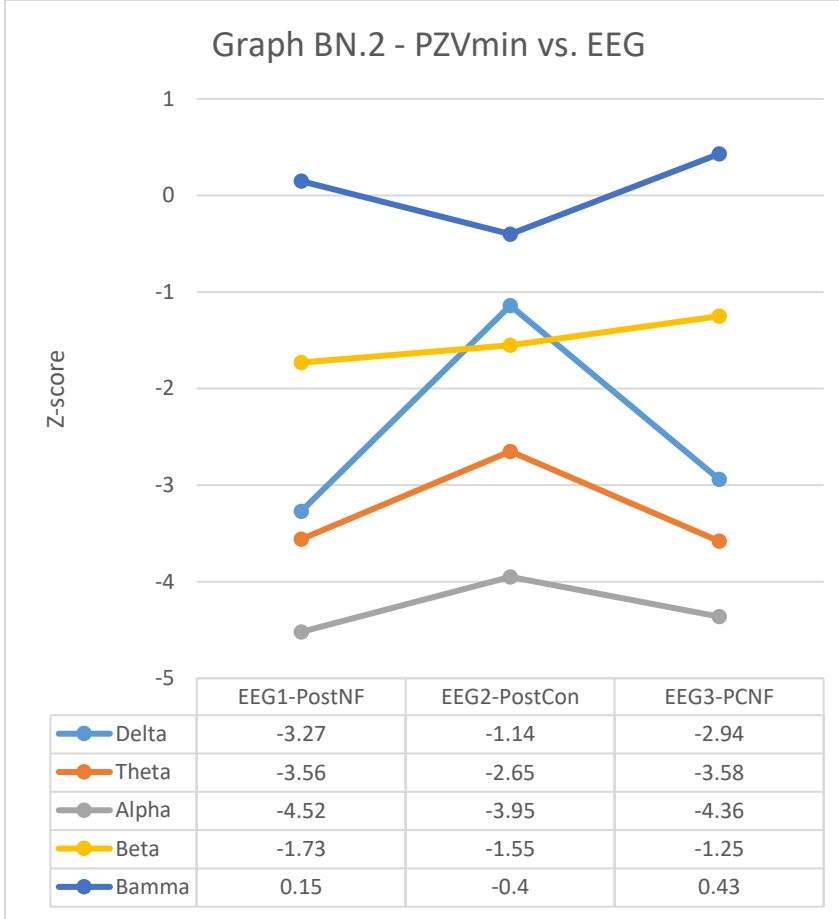
Alpha - Increased			
Beta			
Bamma			

Table BN.1 displays Z-score sLORETA QEEG images for each frequency band across all time points. Data displayed is above/below +/- 2.5 Z scores



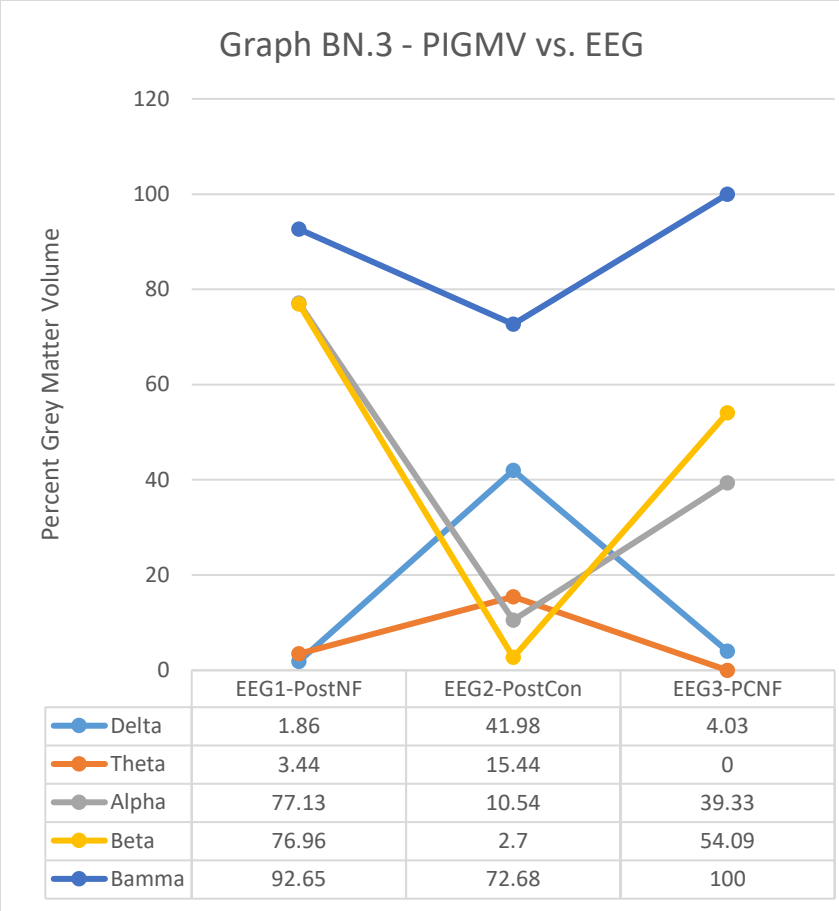
	EEG1-PostNF	EEG2-PostCon	EEG3-PCNF
Delta	2.81	4.42	2.9
Theta	2.87	3.43	2.17
Alpha	6.19	3.39	3.89
Beta	5.31	2.77	4.6
Bamma	6.16	4.84	7.35



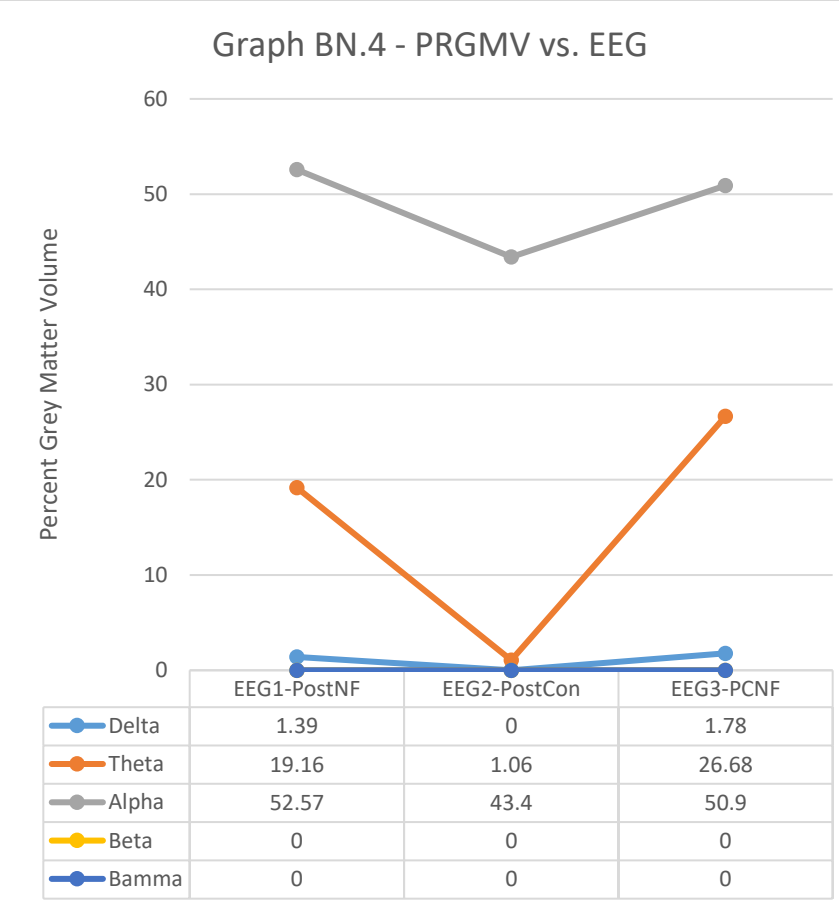
	EEG1-PostNF	EEG2-PostCon	EEG3-PCNF
Delta	-3.27	-1.14	-2.94
Theta	-3.56	-2.65	-3.58
Alpha	-4.52	-3.95	-4.36
Beta	-1.73	-1.55	-1.25
Bamma	0.15	-0.4	0.43

Graph BN.1 depicts PZVmax for each of the 5 frequency bands across EEG time points 1, 2, and 3. Graph BN.2 depicts PZVmin.

EEG1 = baseline EEG, EEG2 = post-concussion EEG, EEG3 = post-concussion with neurofeedback.



	EEG1-PostNF	EEG2-PostCon	EEG3-PCNF
Delta	1.86	41.98	4.03
Theta	3.44	15.44	0
Alpha	77.13	10.54	39.33
Beta	76.96	2.7	54.09
Bamma	92.65	72.68	100



	EEG1-PostNF	EEG2-PostCon	EEG3-PCNF
Delta	1.39	0	1.78
Theta	19.16	1.06	26.68
Alpha	52.57	43.4	50.9
Beta	0	0	0
Bamma	0	0	0

Graph BN.3 depicts PRGMV for each of the 5 frequency bands across EEG time points 1, 2, and 3. Graph BN.4 depicts PIGMV.

EEG1 = baseline EEG, EEG2 = post-concussion EEG, EEG3 = post-concussion with neurofeedback.

Control Group

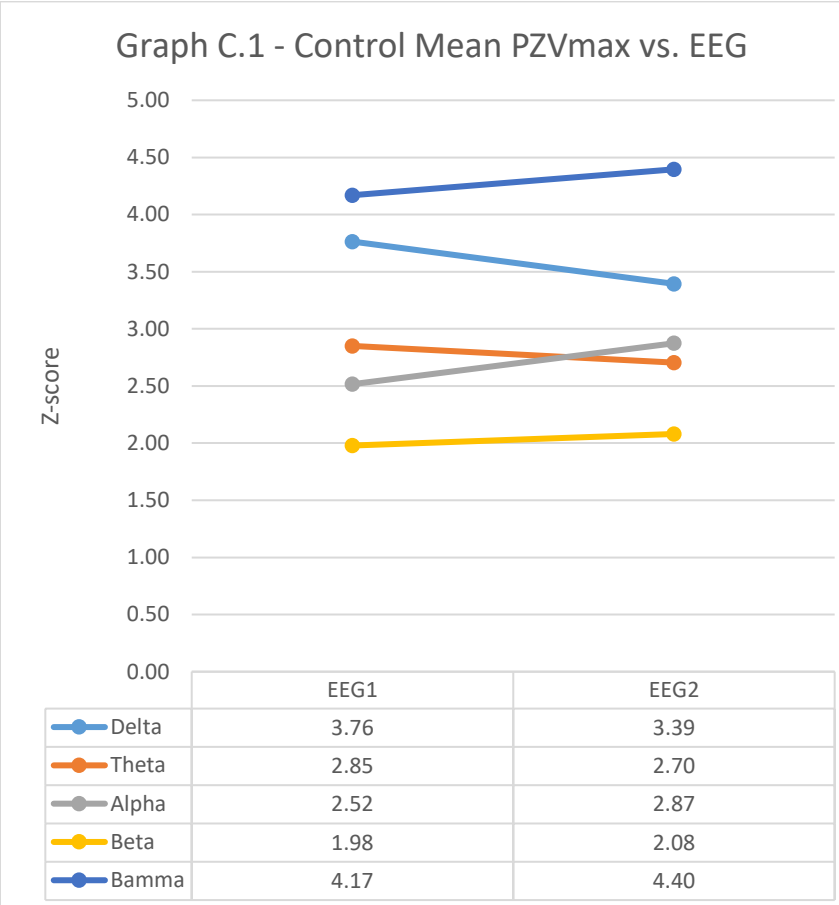
The control group consisted of nineteen concussed high school athletes who presented to the neurology clinic shortly after sustaining a concussion. These athletes were treated in accordance with the clinical concussion management guidelines until they were symptom free and back to cognitive baseline. Cognitive and QEEG testing was completed shortly after concussion injury and repeated once the athletes were cleared of concussion. QEEG data was analyzed in the BDxRG in identical fashion to the cases presented above. For every individual in the control group, PZVmax, PZVmin, PIGMV, and PRGMV were calculated for each frequency band. Paired t-tests were used to test for significant differences between each variable at EEG1 and EEG2, but no significant differences emerged for any variable. Means for each variable were calculated and graphed to observe the changes over time for each variable (Graphs C.1-C.4). Significance testing was calculated in IBM SPSS Statistics Version 24.

Variable	T score	P-value
Delta PZVmax	-1.154	.264
Delta PZVmin	.467	.646
Theta PZVmax	-.710	.487
Theta PZVmin	-.093	.927
Alpha PZVmax	1.770	0.94
Alpha PZVmin	-1.124	.276
Beta PZVmax	.609	.550
Beta PZVmin	1.938	.068
Bamma PZVmax	1.211	.241
Bamma PZVmin	1.598	.128

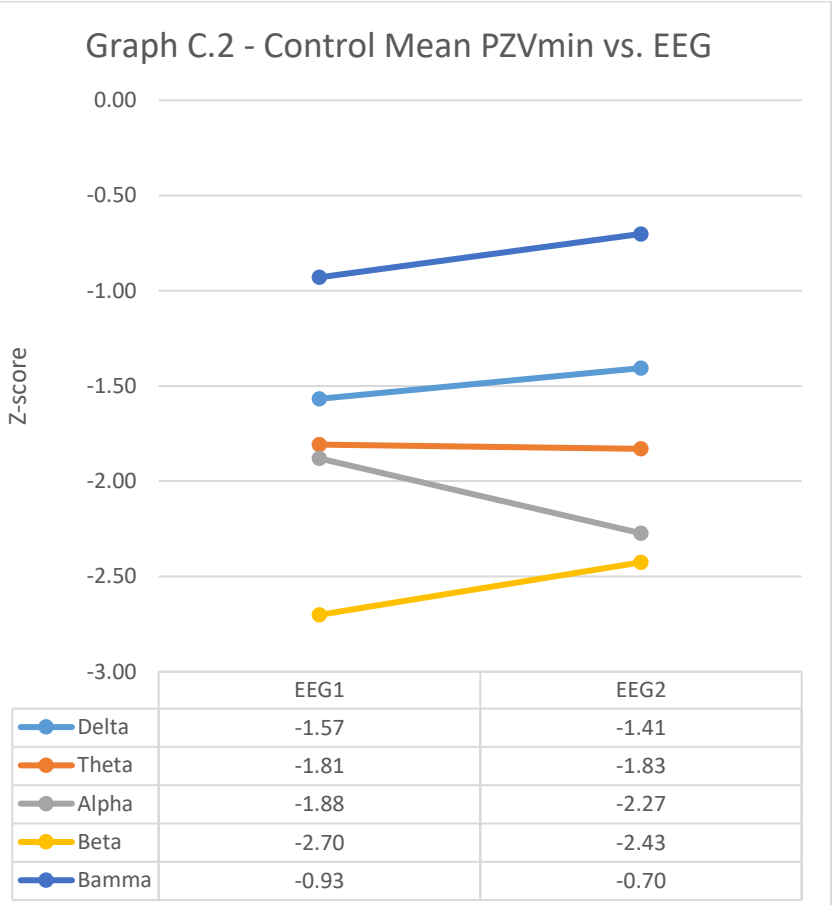
Table 3 – Paired t-test results for PZV of control group.

Variable	T score	P-value
Delta PIGMV	-1.162	.261
Delta PRGMV	-1.009	.326
Theta PIGMV	-1.272	.219
Theta PRGMV	-1.236	.232
Alpha PIGMV	1.250	.227
Alpha PRGMV	-.253	.803
Beta PIGMV	-.701	.492
Beta PRGMV	-1.321	.203
Bamma PIGMV	.420	.680

Table 4 – Paired t-test results for control group percent changed grey matter volume. Because Bamma PRGMV was not reduced for any subject, no scores were provided for Bamma PRGMV.

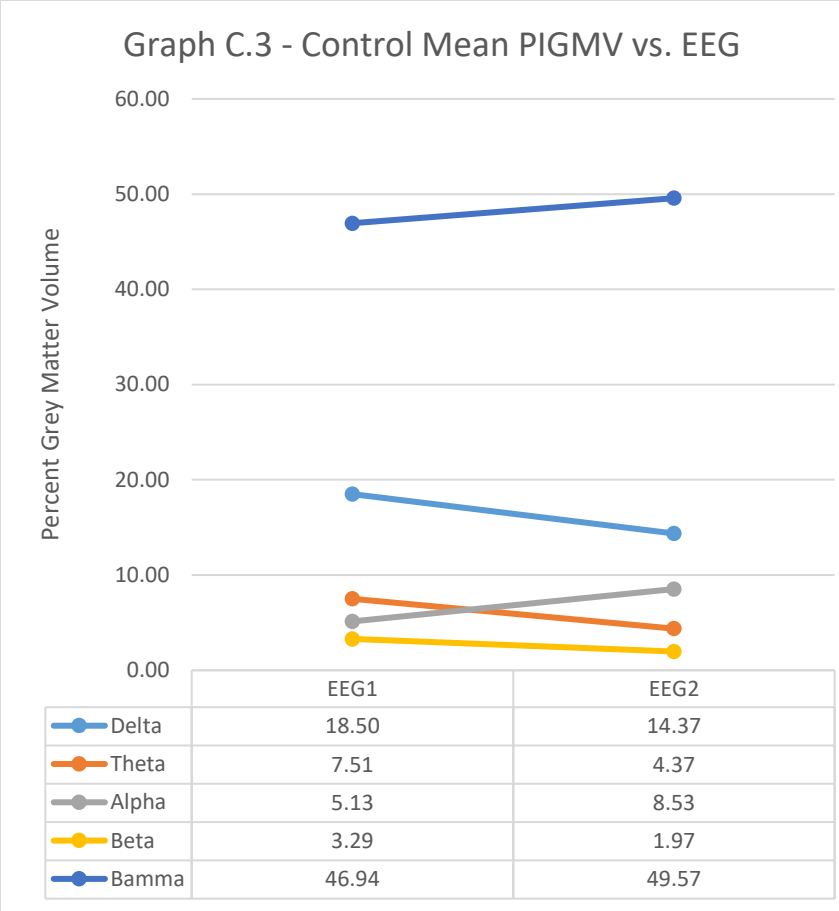


	EEG1	EEG2
Delta	3.76	3.39
Theta	2.85	2.70
Alpha	2.52	2.87
Beta	1.98	2.08
Bamma	4.17	4.40

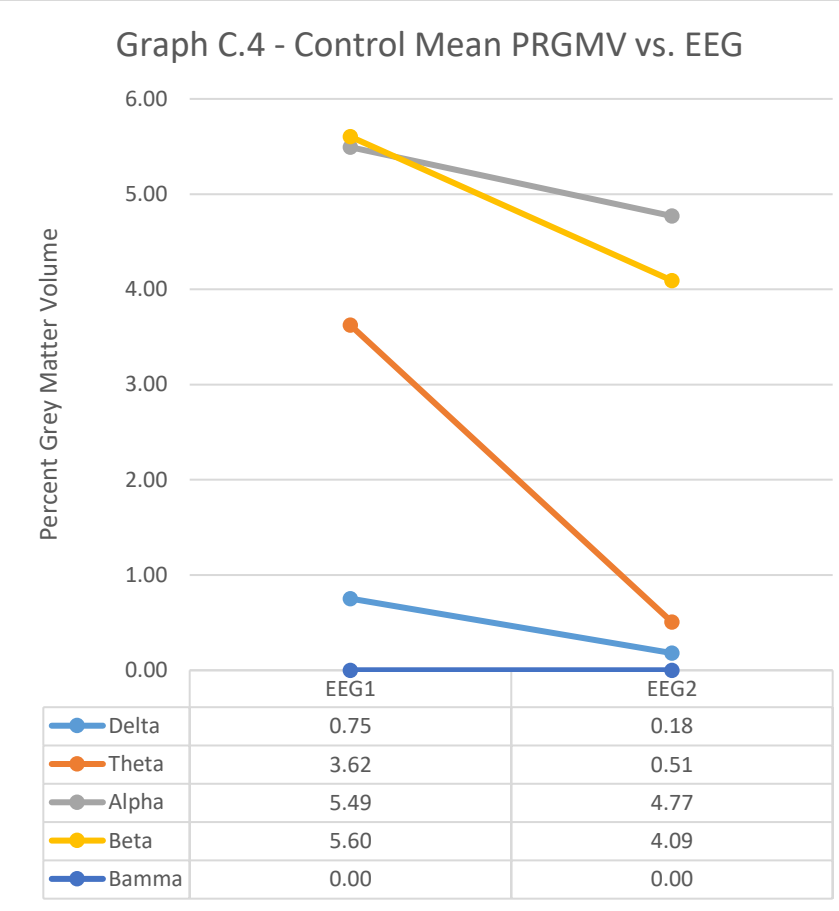


	EEG1	EEG2
Delta	-1.57	-1.41
Theta	-1.81	-1.83
Alpha	-1.88	-2.27
Beta	-2.70	-2.43
Bamma	-0.93	-0.70

Graph C.1 depicts mean PZVmax for the control group at EEG1 and EEG2. Graph C.2 depicts mean PZVmin.



	EEG1	EEG2
Delta	18.50	14.37
Theta	7.51	4.37
Alpha	5.13	8.53
Beta	3.29	1.97
Bamma	46.94	49.57



	EEG1	EEG2
Delta	0.75	0.18
Theta	3.62	0.51
Alpha	5.49	4.77
Beta	5.60	4.09
Bamma	0.00	0.00

Graph C.3 depicts mean PIGMV for the control group at EEG1 and EEG2. Graph C.4 depicts mean PRGMV.

To compare the abnormalities for subjects treated with neurofeedback to subjects in the control group, EEG data for the control group at injury and recovery were assessed. Averages for PZVmax, PZVmin, PIGMV, and PRGMV were calculated for individuals in the control group. Paired samples t-testing was used to compare means for each variable per band at EEG time points for injury and recovery (EEG1 and EEG2). Statistical testing failed to demonstrate significant differences between time points for any variable. Despite the lack of statistical significance, graphical analysis yielded apparent trends in the data. To further describe the data, the directionality of PZV and percent of grey matter volume (GMV) change from EEG1 to EEG2 was determined and displayed in the table below. Green cells with a "+" indicate PZV movement away from the normal range or increased GMV deviant of 2.5 SD; red cells with a "–" indicate PZV movement towards the normal range or decreased GMV.

Of the twenty metrics for the five frequency bands calculated for four variables PZVmax, PZVmin, PIGMV, and PRGMV, thirteen variables remained abnormal at recovery. These variables were marked in the chart with a blue slash through the cell. Abnormal was defined as PZV with deviance outside of 2.5 Z-scores or GMV greater than 0%. Individuals about which the case studies were written were compared to this reference point of thirteen abnormalities at recovery based off averages for the control group. The data collected from this control group also suggests comparative trends in changes in QEEG activity during recovery from concussion injury. Subjects treated with neurofeedback were compared to the trend as well as the abnormality of finding.

Control Group Change Scores				
Band	PZVmax	PZVmin	PIGMV	PRGMV
Delta	–	–	–	–
Theta	–	+	–	–
Alpha	+	+	+	–
Beta	+	–	–	–
Bamma	+	+	+	No Δ

Legend	
–	Decrease PZV towards center; or GMV
+	Increased PZV away from center; or GMV
	Abnormal scores > +/-2.5 Z-scores

Table 5 – Control group change scores for each variable and frequency band.

DISCUSSION

Elevated Delta and Theta After Injury

Elevated delta and theta activity suggests deregulated cortical activity and impaired regional functioning. In the case of JR, this hypothesis was not supported. Delta and theta activity was within two standard deviations after injury. On post-injury cognitive testing, findings demonstrated abnormalities in cognitive properties although JR had not subjectively endorsed disturbances in cognitive functioning after injury. The test findings possibly reflected cognitive functioning that was present before the concussion, but without pre-season baseline cognitive testing JR's cognitive functioning before injury is a mystery.

This case highlights the variance of electroencephalographic findings in concussion, a point made by Rapp et al. (2015). The EEG frequency pattern that was elevated on JR's post-injury testing was bamma activity, which was potentially related to his post-concussion symptomatology consisting largely of headaches. Elevated high frequency activity may be seen in cases of headache. The absence of elevated slow wave activity agreed with the patient's symptom report that failed to include cognitive disturbances. Therefore, QEEG analysis yielded potential physiological evidence for the headaches the patient was experiencing. It is possible that the abnormalities on JR's cognitive test were related to his experienced head pain distracting him from the task.

QEEG data collected after RH sustained a concussion at football practice demonstrated elevated delta and theta activity and supported the hypothesis that delta and theta activity increase after concussion injury. Delta activity was above 2.5 Z-scores at 2.7 PZVmax, while theta measured less than 2.5 Z-scores at 2.31 PZVmax. Both values decreased and moved towards the center of the distribution as the subject recovered from injury, although the absence of a baseline QEEG assessment prevents objective comparison to pre-concussion brain functioning. In the other tail of the distribution, RH's PZVmin values for delta and theta frequencies were outside of negative 2.5 Z-scores, suggesting atypically decreased slow wave activity that increased towards the center of the distribution with recovery.

Compared to the calculated norms for the XLNTbrain cognitive test, RH's cognitive testing indicated normal functioning in spite of his recent concussion injury. However, RH's condition after concussion motivated neurological evaluation. Therefore, his subjective experience after injury must have been noticeably different relative to his normal functioning to warrant evaluation, albeit his cognitive scores did not demonstrate significant findings. If significantly elevated slow wave activity may reflect impaired cortical functioning expected in cases of poor scores on neurocognitive testing, the minimal disturbances in RH's measured cognitive functions were likely reflective of delta and theta Z-scores that measured slightly above the 2.5 Z-score border of abnormal cortical functioning. Lending further evidence to the heterogeneity of concussion injury, the present case demonstrated deviant slow wave activity after injury, although deviations in cognitive testing and QEEG metrics were minimal and the subject recovered in a mere 14 days.

BN's case presented a unique perspective on cortical function after concussion injury and recovery as measured by QEEG. Coincidentally, baseline QEEG testing for this case existed

because of past clinical care at CNA, allowing for comparison of BN's post-concussion and post-recovery EEG data to a baseline. BN's QEEG recorded after concussion indicated increased delta and theta activity in frontal and temporal regions and supported the hypothesis predicting elevated delta and theta activity after injury. QEEG testing after concussion injury demonstrated increased delta and theta activity measured by PZVmax and PIGMV after injury compared to the baseline data. Unlike the other cases in the study which infers change in cortical functioning based on changes in EEG during recovery, this case provided evidence that supports the hypothesis claiming that delta and theta activity increase after concussion injury because of baseline EEG data.

Recovery Indicated by Normalization of Z-scores and Reduction in Affected Grey Matter Volume

Comparison of JR's post-concussion and post-recovery QEEG demonstrated some Z-score metrics moved towards the center of the distribution while others moved away from center, suggesting this hypothesis was partially supported. Z-scores that moved toward center were delta PZVmin, alpha PZVmax, and bamma PZVmax. Delta PZVmax, theta PZVmax, beta PZVmax, beta PZVmin, and bamma PZVmin moved away from center. PZVmin for alpha and theta remained unchanged from post-injury to post-concussion EEG recordings. Bamma PIGMV decreased from approximately 93% to 58% during recovery, while beta PIGMV increased slightly from 2% to 4%.

In summary, three out of ten peak Z-score variation metrics moved towards center, five away from center, and two remained unchanged. The majority of PZV measures did not approach the center of the distribution when neurofeedback training was applied during concussion recovery. Delta and theta activity measures moved away from center as JR

recovered, essentially contradicting the first hypothesis that expected increased delta and theta after injury. Actual values demonstrated delta and theta were not elevated after injury and trended towards statistical deviance as measured by PZV at recovery, further rejecting the hypotheses which placed emphasis on slow wave activity in concussion. As JR's headaches reduced during recovery, PIGMV for bamma trended in the expected direction, decreasing by nearly 30% PIGMV albeit PZVmax for bamma remained outside of 5 standard deviations.

This hypothesis was largely supported by the data from RH's case, although some measures of RH's QEEG data demonstrated increases in PZV and affected GMV. The majority of RH's PZVmax and PZVmin scores trended towards the center of the distribution. Affected GMV decreased as less grey matter was functioning outside of 2.5 Z-scores at recovery. Alpha and beta PZVmax and beta PZVmin were more statistically deviant at recovery than after injury. Alpha PIGMV increased during recovery. At recovery from concussion, all other measures were within 2.5 Z-scores and affected GMV had decreased or remained at 0% affected GMV as after injury. Changes in alpha and beta activity were related to changes in the subject's peak frequency.

This hypothesis was not supported by the QEEG data in BN's case. Some of BN's QEEG metrics followed the expected pattern of the hypothesis and approached the center of the distribution, but the majority of metrics were further from center at recovery. However, comparing the post-recovery QEEG to the baseline data indicated the subject's brainwave patterns returned to baseline functioning, which was similarly deviant from the center of the Gaussian distribution. This data indicated a return to normal electrophysiological functioning specific to this subject. Although the Z-scores and affected GMV remained statistically abnormal compared to the QEEG database, the patient was healthy and free of concussion

symptoms when the recovery data was collected. This suggested healthy cortical functioning of this subject included QEEG metrics statistically deviant from the normative database, exemplifying the point that normalized Z-scores are not required for normal functioning. Rather, normal functioning must be defined relative to the specific individual in question.

Neurofeedback Intervention Contributed to Reduce Concussion Related Symptoms

According to subjective reporting of concussion symptoms, JR noticed reduced head pain following individual and cumulative neurofeedback sessions. Headaches at the end of the neurofeedback session were rated less painful than at the beginning of the session on several occasions. JR reported his headaches returned several hours after the session, but as neurofeedback treatments continued during JR's recovery the overall presence of headaches declined. It is critical to acknowledge that in the case of natural concussion recovery without treatment or intervention, decreases in headaches are expected as the brain recovers through natural healing processes. Although it is impossible to define a causal relationship due to the study design in this case, JR's observed decrease in head pain during a twenty-minute neurofeedback session suggests a possible effect of the neurofeedback treatment.

JR described auditory and photic hypersensitivity after his injury, and overstimulating environments often contributed to his headaches. During recovery, JR did not report any significant changes in sensory processing that he related to treatment. Bright lights and echoed sounds intermittently provoked headaches towards the end of his recovery. Given this information, it is inconclusive, if not unlikely, as to whether any change in JR's hypersensitive sensory processing was related to neurofeedback.

Although RH reported subjective improvement in his ability to focus in class after the first neurofeedback session, the natural trajectory of the athlete's recovery complicates inferences about the role of neurofeedback in changes in his symptoms. When RH presented for his first neurofeedback session, he had nearly recovered from his concussion and experienced minimal symptoms. Neurofeedback targeting the frontal and temporal lobes, the ROIs that demonstrated the most significant deregulation on the QEEG. The frontal and temporal lobes are implicated in tasks such as executive functioning, planning, decision making, attention, memory, and emotional regulation. RH's expressed improvement in his ability to focus in class agreed with the expected outcome of the neurofeedback training, but his condition was improving before neurofeedback was introduced to his clinical care.

Simultaneously, RH described a dull headache in the hours after the first session. The headache, described as similar to muscle fatigue after physical exercise, pained him in a different manner than headaches he experienced after his concussion but disappeared the next morning, whereas the post-concussion headaches persisted. In a situation where the subject would have desired to feel better with less head pain, the fact that subject experienced a headache after the session communicates the ability of neurofeedback to influence the symptomatology of concussion in the negative direction. It is therefore possible that neurofeedback may have affected symptoms, such as focus in class or headaches, in a positive direction, but it is difficult to draw an objective conclusion based on subject report when the patient's condition and tracked symptoms and cognitive scores were already improving without neurofeedback treatment.

For the third case, it remains difficult to arrive at an objective decision about the role of neurofeedback on concussion symptoms. BN reported decreased symptoms as she recovered from her concussion, which was to be expected in the process of natural recovery from

concussion injury. The reduction of symptoms was supported by improvements on her XLNTbrain symptom checklist, and cognitive scores indicated return to normal cognitive functioning. She described reduced headaches immediately after the sessions on several occasions, although she described a dull headache after the first session that had disappeared by the following morning. She experienced relief from a major headache after the fourth session, which was present before the session, but the headache amplified several hours later and included nausea and vomiting. She described this headache as similar to the migraine headaches she used to experience that led her to seek treatment in the past before she suffered a concussion. Application of BN's old neurofeedback protocols used to address her migraine headaches saw her headaches improve immediately. Therefore, it is likely BN's symptoms benefitted from neurofeedback treatment but an overstatement to claim that her improvement in symptoms were caused by neurofeedback.

Reduced Number of Abnormalities at Recovery in Subjects Treated with Neurofeedback

QEEG data collected on JR was compiled in a chart similar to the chart that described the control group findings. Cells depicting data where the findings at clinical recovery remained abnormal are indicated by a blue slash. Cells with an asterisk indicate a finding that matched the trend in the control group. The table below demonstrates five QEEG abnormalities persisted past clinical recovery, eight fewer abnormal findings than the averages of the control group. Four metrics from JR's data matched the PZV and GMV trends established by the control group. Therefore, this case agreed with the hypothesis that subjects treated with neurofeedback will have fewer QEEG abnormalities after recovery from concussion.

JR Change Scores				
Band	PZVmax	PZVmin	PIGMV	PRGMV
Delta	+	– *	No Δ	No Δ
Theta	+	+ *	No Δ	No Δ
Alpha	–	No Δ	No Δ	No Δ
Beta	+ *	+	+	No Δ
Bamma	–	+	–	No Δ *

Legend	
–	Decrease PZV towards center; or GMV
+	Increased PZV away from center; or GMV
	Abnormal scores > +/-2.5 Z-scores
*	Score matches trend of control group

Table 6 – JR change scores for each variable and frequency band.

Comparing RH's change scores to those of the control group demonstrated six abnormal QEEG scores at recovery from concussion. This is less than the thirteen abnormal scores measured in the control group at recovery, supporting the hypothesis that the subject treated with neurofeedback had fewer abnormalities at recovery than the subjects in the control group. Thirteen out of twenty metrics tracked during concussion recovery matched the trends of the control group metrics, indicating similar change in QEEG patterns between RH and the controls during recovery from concussion.

RH Change Scores				
Band	PZVmax	PZVmin	PIGMV	PRGMV
Delta	– *	– *	– *	– *
Theta	– *	–	– *	No Δ
Alpha	+ *	–	+ *	– *
Beta	+ *	+	– *	No Δ
Bamma	–	– *	–	No Δ *

Legend	
–	Decrease PZV towards center; or GMV
+	Increased PZV away from center; or GMV
	Abnormal scores > +/-2.5 Z-scores
*	Score matches trend of control group

Table 7 – RH change scores for each variable and frequency band

Assessment of BN's change scores do not support the hypothesis that neurofeedback contributes to less abnormalities on post-recovery QEEG testing compared to controls. At recovery, BN's QEEG data indicated one more abnormality than that of the controls. Over half of her metrics followed the trends of QEEG changes demonstrated by the control group.

BN Change Scores				
Band	PZVmax	PZVmin	PIGMV	PRGMV
Delta	– *	+	– *	+
Theta	–	+ *	– *	+
Alpha	+ *	+ *	+ *	+
Beta	+ *	– *	+	No Δ
Bamma	+ *	+	+ *	No Δ *

Legend	
–	Decrease PZV towards center; or GMV
+	Increased PZV away from center; or GMV
	Abnormal scores > +/-2.5 Z-scores
*	Score matches trend of control group

Table 8 – BN change scores for each variable and frequency band

Length of Recovery Time for Individuals Treated with Neurofeedback

According to McCrory et al. (2017), children and adolescents are expected to recover from concussion within four weeks of injury. JR's 42-day recovery was 6 days shorter than the control group mean recovery time of 48 days. This case supports the hypothesis that individuals who undergo neurofeedback may have shorter recovery time than the control group. The length of time JR required to recover from injury when neurofeedback was used as an intervention was 12 days longer than the expected recovery time for children of 28 days.

RH recovered from his concussion in 14 days, which was remarkably less than the 48-day mean recovery time for the control group. The recovery time of this individual supported the hypothesis. This subject's recovery fell well within the expected recovery time of four weeks supported by the International Consensus Statement on Concussion.

BN's recovery time lasted 35 days, which was 13 days less than the recovery time of the control group. Her recovery was one week longer than the four-week period during which most

adolescents recover from concussion according to McCrory et al. The results of this hypothesis should be interpreted loosely. The unique nature of all concussions, neurobiology of the injured, and environmental factors could contribute length of recovery. Results from each case in the context of the five hypotheses are summarized in Table 9.

Hypothesis	**Case JR**	**Case RH**	**Case BN**	**Overall**
1) Elevated Delta and Theta (D-T) After Injury	Not supported – D-T activity was within two Z-scores after injury	Supported – D-T PZVmax measured above 2 Z-scores	Supported – D-T PZVmax was increased from baseline	Partially supported
2) Recovery Indicated by Normalization of Z-scores and Reduction in Affected Grey Matter Volume	Partially supported – majority of PZV did not move centrally albeit few did; marked decrease in bamma PIGMV	Supported – majority of PZV moved towards center, GMV reduced with recovery	Not supported – PZV and GMV largely remained deviant/elevated but similar to pre-injury baseline values	Partially supported
3) Neurofeedback Intervention Contributed to Reduce Concussion Related Symptoms	Partially supported – headaches improved, sensory hypersensitivity did not	Limited support, patient largely recovered when NFB began, reported improved focus after NFB	Supported – headaches improved	Cautiously supported; future study required for comparison to natural recovery
4) Reduced Number of Abnormalities at Recovery in Subjects Treated with Neurofeedback	Supported – 8 fewer QEEG abnormalities than control group	Supported – 7 fewer QEEG abnormalities than control group	Not supported – 1 more QEEG abnormality than control group	Partially supported
5) Length of Recovery Time for Individuals Treated with Neurofeedback	Supported – recovered in 42 days	Supported – recovered in 14 days	Supported – recovered in 35 days	Supported – all cases recovered in fewer days than the 48 days of the control group

Table 9 – Summary of results for each case per hypothesis.

LIMITATIONS

The design of the present study failed to address several variables which would hold bearing on the outcome of the study. 1) EEG recordings after concussion injury were conducted on a loosely controlled timeline that did not gather EEG data immediately after injury. Due to the clinical nature of the study, EEGs were recorded as close to injury as logistically possible. This improves the generalizability of the study results in clinical settings but disrupts the relationship between injury and EEG findings. Per McCrory et al., most individuals recover within 10-14 days of injury (2017); therefore, an EEG recorded one week after injury does not capture as much deregulation as an EEG recorded the day after injury. As an individual naturally heals from concussion injury, EEGs recorded further from the injury date may not be an accurate reflection of concussion induced cortical deregulation. Efforts to evaluate EEG as a measurement of cortical deregulation resulting from concussion would benefit from recording at a predetermined time point following injury, i.e., 2 days post-injury.

2) Neurofeedback sessions commenced as quickly as possible after the EEG recording and analysis rather than in a controlled fashion, i.e., 2 days after the baseline EEG1 recording. Scheduling conflicts interfered with how quickly neurofeedback sessions began following injury. Since the present study was conducted within the pre-existing clinical framework of CNA, specific appointment times were reserved for the present study but these times did not always match the subject's availability. Additionally, concussed subjects were often expected to attend school or athletic practice, despite their concussion injury prevented their full participation, which limited their availability to attend neurofeedback appointments. Beginning neurofeedback at a controlled time point after injury and continuing treatment at a regular interval would be advantageous for future studies.

3) Treatment subjects had a past history of concussion. Such subjects were included in the present study due to the already small sample of possible subjects. Research has demonstrated that past injury may be related to greater sensitivity to concussion symptoms and prolonged recovery (Kerasidis, 2015). Past concussion injury is a risk factor for future concussions (McCrory et al., 2017), so it is unsurprising that subjects presenting for treatment experienced an injury prior to the event under study. This contributes to the generalizability of the present study, but presents a confounding element to the recovery timeline if past injury increases recovery time. Future research should consider excluding cases with past history of concussion to control for this variable.

4) The treatment group represented a heterogeneous mixture of concussion injury types. Future studies might restrict treatment subjects to a specific type of concussion injury, such as relating to a specific sport or activity (i.e., football, snowboarding).

5) The specific neurofeedback training protocol differed from patient to patient and was not consistent across the treatment group. The neurofeedback protocols were implemented within a constant training paradigm, but specific aspects of the protocol were customized to the patient receiving treatment based on data collected after injury. Therefore, the specific neurofeedback protocol varied between patients and was not held constant across the treatment group in order to address the specific needs of the patient. However, a central tenant of QEEG-guided neurofeedback remains that neurofeedback protocols supported by QEEG data match the patient, so standardization of neurofeedback protocols may not be appropriate in the treatment of concussion with neurofeedback. Neurofeedback must “treat the patient.”

6) Aside from the single case which coincidentally included a baseline EEG prior to injury, the study did not include baseline EEG testing collected prior to injury. The absence of

baseline QEEG and cognitive testing limits the interpretation of data collected during concussion management.

7) The present study did not include randomization or blinding, preventing conclusions of causality regarding neurofeedback as an intervention for concussion. The present study sought to be as unambiguous as possible to show change in the tracked variables without stating causality. Randomized and blinded assignment of subjects to treatment groups would reduce researcher or subject bias in the results and enable more conclusive results.

8) Because the current study was a case series, the sample size was too small for statistical tests of significance and could only assess trends in Z-scores and PIGMV/PRGMV. The size of the control group was inadequate for statistical testing. Future studies with larger sample sizes would allow for tests of significance.

CONCLUSIONS

Although the research design of the prevents conclusions of causation regarding the role of neurofeedback in concussion rehabilitation, conclusions which might guide future research may be drawn:

1) Tracking changes in QEEG metrics during concussion recovery clearly suggests that concussion injury results in measurable change in brain function as measured by sLORETA source localization techniques. This finding agrees with past research conducted by Rapp et al. that suggested QEEG provides a useful measure of brain function worth considering in cases of mTBI/concussion.
2) In agreement with Churchill et al., the brain continues to change and show signs of recovery as the athlete remains free of concussion related symptoms to be clinically

clear of concussion injury. Results from the control group and cases studied with neurofeedback support this finding.

3) Although subjects recovered from their concussions, QEEG abnormalities persisted past recovery. Additionally, there were varied findings in the data collected after injury that did not support an expected or specific trend of findings of the effects of concussion on the brain. These abnormalities may have been related to pre-concussion functioning as suggested by the case of BN. However, the QEEG results align with another point made by Churchill et al.: the heterogeneity of concussion injury impedes the ability to make specific statements on the effects of concussion on brain injury. Due to this heterogeneity, each concussion appears to act differently on the brain of the injured person, despite measurement with fMRI or sLORETA QEEG. Classification of concussed individuals into symptom-subtypes, as suggested by Churchill et al., may improve the diagnosis and treatment of concussed individuals.
4) Baseline QEEG testing, as seen in the case of BN, is of upmost importance in the objective assessment of cortical function in concussion injury. Data collected on BN demonstrated the clinical utility of baseline QEEG for comparison of post-injury and post-recovery brain function measured by electroencephalography, especially in cases where normal, baseline functioning does not align with the QEEG database package used as a reference. The author strongly advocates QEEG be integrated to the pre-season physical assessment that is mandatory for participation in most athletic organizations.
5) Neurofeedback seemed to influence concussion-related symptoms in the cases studied but cannot be solely credited with causing improvements in symptoms out of concern

for Type I Error. The goal of the present study was to provide a detailed narrative of how neurofeedback might be introduced to clinical concussion management. MRI investigation on the effect of neurofeedback for sustained attention evidenced changes in white and gray matter microstructure although the specific mechanism of action remained unknown (Ghaziri, et al., 2013). These findings support potential brain changes due to neurofeedback. In the context of concussion, where brain function is disrupted due to injury, the prospect of improving brain function with neurofeedback appears promising and offers a solution to the growing concussion conundrum. Further study, especially that including MRI, is required to build the body of evidence surrounding the use of neurofeedback in concussion.

The field of concussion assessment and treatment offers an array of treatment modalities as outlined by Broglio et al., all of which deserve further investigation. Physical and cognitive rest and recovery are the current gold standard, and vestibular and ocular therapies appear to provide benefit. Pharmacological interventions may offer utility, but the medications prescribed in the treatment of concussion, such as stimulants, may not comply with regulations by governing athletic bodies (Broglio et al., 2015). Neurofeedback offers a possible treatment method which truly targets brain function, a quality often missing from current concussion rehabilitation strategies. In QEEG, there is a brain-based assessment tool significantly more affordable than standard neuroimaging techniques, not to mention sophisticated fMRI studies, which typically fail to demonstrate neurological abnormality in concussion (McCrory et al., 2017).

Passive guidance offered by the neurofeedback paradigm provides recommended boundaries for brain function based on statistical analysis and sophisticated EEG source localization techniques. The author conceptualizes neurofeedback in the management of concussion as similar to casting a broken arm. While the arm will likely heal by natural causes, healing without intention or guidance provided by a cast may result in further deformity and impaired functioning of the arm. Unprotected and improper healing in turn disrupts the present and future daily functioning of the individual. Much the same, neurofeedback, in theory, may serve as the cast for cortical recovery, providing the brain a supportive reference point on the road to recovery.

Appendix

Date: May 8th, 2018

Office of Sponsored
Programs and Research

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NOTICE OF APPROVAL

TO: Paul David Ims, III ***DEPT:*** Psychology

PROJECT TITLE: ***Re-training the Injured Brain: QEEG-Guided Neurofeedback as an Intervention for Concussion***

SPONSORING AGENCY: N/A

APPROVAL NUMBER: 1704019565

The Institutional Review Board for the Protection of Human Participants has approved the project described above. Approval was based on the descriptive material and procedures you submitted for review. Should any changes be made in your procedures, or if you should encounter any new risks, reactions, injuries, or deaths of persons as participants, you should notify the Board.

A consent form	☑	is required of each participant
	☐	is not
Assent	☑	is required of each participant
	☐	is not

This protocol was first approved on 08/30/2017.
This research will be reviewed ***every year*** from the date of first approval.

Elizabeth Katz, Chair
Towson University Institutional Review Board, IRB

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Curriculum Vitae

Paul David Ims, III

Education:

08/2015-Present	Candidate for M.A. in Psychology, Clinical Concentration Towson University; Towson, MD Master's Thesis (In Progress): *Re-Training the Injured Brain: sLORETA Neurofeedback as an Acute Concussion Intervention*
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Professional Experience:

03/2013-Present	QEEG, ERPs, Neurofeedback, & pEMF Laboratory Supervisor & Chief Technician; Chesapeake Neurology Associates; Prince Frederick, MD
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10/2012	Live Z-Score, Percent ZOK Z-Plus (4-19 Channel) Training for Beginners-Intermediate-Advanced; Stress Therapy Solutions; Cleveland, OH
07/2012	Neurofeedback Bootcamp for Beginners; Stress Therapy Solutions; Cleveland, OH

Awards:

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09/2017	Deep States NeuroMeditation: New Innovations and Implications Based on Psychedelic Science; Conference Workshop at International Society for Neurofeedback and Research (ISNR) 25th Annual Conference; Mashantucket, CT

01/2017	The Effect of Concussion on Brain Activity; The Calverton School; Prince Frederick, MD
12/2016	Brain Imaging in Psychology; Calvert High School; Prince Frederick, MD
09/2016	Riding the Wave to Recovery: sLORETA QEEG in Sport-Related Concussion; Plenary Presentation at International Society for Neurofeedback and Research (ISNR) 24th Annual Conference; Orlando, FL
06/2016	Private QEEG & Neurofeedback Instruction Course; Aspire Academy; Doha, Qatar
03/2016	QEEG & Behavior: The Relationship Between Brain Activity and Behavior; Towson University (Undergraduate & Graduate Student Audience); Towson, MD
04/2015	Basic EEG Instrumentation and Electronics; BCIA Didactic Course – Neurofeedback Bootcamp for Beginners; Prince Frederick, MD
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Research:

07/2017	Ims. P.D., Kerasidis, H. (2018). Re-Training the Injured Brain: A Case Series in sLORETA Neurofeedback as an Acute Concussion Intervention in Youth. Calvert Memorial Hospital Center for Neuroscience. Presented as a poster at the Association for Applied Psychophysiology and Biofeedback Conference in Orlando, FL.
07/2017	Kerasidis, H., Ims. P.D. (2017). sLORETA Quantitative EEG Analysis Demonstrates Persistent EEG Changes Beyond Clinical Recovery from Sport Concussion in High School Athletes: A Volumetric Study. Calvert Memorial Hospital Center for Neuroscience. Presented as a poster at the American Academy of Neurology Sport Concussion Conference in Jacksonville, FL.