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LORETA Z SCORE BIOFEEDBACK AND TRAUMATIC BRAIN INJURY

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Quantitative EEG (qEEG) analysis does not provide a definitive stand alone test for traumatic brain injury nor is it a screening test for TBI. Instead, qEEG is used as an adjunct along with other tests such as clinical history, neuropsychological tests, MRIs, etc. to help a clinician to diagnosis and treat patients with a history of TBI. In the last 30 years the application of qEEG to evaluate traumatic brain injury has grown dramatically with applications in traumatic brain injury intensive care units (Buzea, 1995; Classen et al, 2000; Haug et al, 2004; Cottencea et al, 2008; Shields et al, 2007), correlation with neuropsychological tests in TBI patients (Thatcher et al, 1998a; 1998b; 2001a, 2001b), correlations with biophysical measures in TBI patients (Thatcher et al, 1998a; 1998b; 2001b), prognostication of recovery (Fabregas et al, 2004; Grindel et al, 2006; Thatcher et al, 1991; Theilen et al, 2000; Nenadovic et al, 2008), reduced connectivity in neural networks (Johnson et al, 2011; Castellanos et al, 2011) and treatment of mild to moderate TBI patients using qEEG operant conditioning (also called neurofeedback) to change the frequency and phase relationships in the brain (Thornton, 2000; Thornton and Carmody, 2005; 2008; 2009; Tinius and Tinius, 2001; Hoffman et al, 1996a; 1996b; Ham and Packard, 1996; Duff, 2004; Ayers, 1987; Byers, 1995; Schoenberger et al, 2001). Thus, there is currently a wide spectrum of clinical applications of qEEG in traumatically brain injured patients by psychiatrists, neuropsychiatrists, family practitioners, internal medicine doctors, neurosurgeons, clinical psychologists and neuropsychologists as evidenced in the vast scientific literature that has accumulated over that last 20 years[1]. For example, a survey of the National Library of Science medical database using the search words "EEG and traumatic brain injury" produced over 2,800 qEEG peer reviewed citations.

In general, the scientific literature presents a consistent and common quantitative EEG pattern correlated with mild TBI (mTBI). Namely, reduced amplitude of alpha, beta and gamma frequency bands (8 – 12 Hz, 13 – 25 Hz and 30 - 40 Hz respectively) (Mas et al, 1993; von Bierbrauer et al, 1993; Ruijs et al, 1994; Korn et al, 2005; Hellstrom-Westas, 2005; Thompson et al, 2005; Tebano et al, 1988; Thatcher et al, 1998a; 2001a; Roche et al, 2004; Slewa-Younan, 2002; Slobounov et al, 2002). Changes in EEG coherence and phase delays have also been consistently published for qEEG and fMRI (Thatcher et al, 1989; 1991; 1998b; 2001b; Hoffman et al, 1995; 1996a; Trudeau et al, 1998; Thornton, 1999; 2003; Thornton and Cormody, 2005; Johnson et al, 2011; Castellanos et al, 2011). The reduced amplitude of EEG is believed to be due to a reduced number of synaptic generators and/or reduced integrity of the protein/lipid membranes of neurons (Thatcher et al, 1997; 1998a; 2001b). EEG coherence is a measure of the amount of shared electrical activity at a particular frequency and is analogous to a cross-correlation coefficient. EEG coherence is largely amplitude independent and is correlated to the amount of functional connectivity between distant EEG generators (Nunez, 1981; 1994; Thatcher et al, 1986; Thatcher et al, 1998b). EEG phase delays between distant regions of the cortex are mediated in part by the conduction

[1] The American Academy of Neurology position paper (Nuwer, 1997) does not support the use of QEEG to evaluate TBI and thus neurologists typically do not use qEEG for this purpose For example, the author of the AAN position paper recently estimated that less than 100 neurologists use qEEG in TBI evaluations (Dr. Nuwer's April, 6, 2004 deposition in "State of Florida vs. Samuel Harris", pg. 67, lines 1 – 10.).

velocity of the cerebral white matter which is a likely reason that EEG phase delays are often distorted following a traumatic brain injury (Thatcher et al, 1989; 2001a). In general, the more severe the traumatic brain injury then the more deviant the qEEG measures (Thatcher et al, 1998a; 1998b; 2001a; 2001b).

The relatively high consistency (homogeneity) across qEEG analyses of traumatic brain injury is because of a common etiology due to the biomechanics of rapid acceleration/deceleration of the brain inside of the human skull (Ommaya, 1968; 1995; Ommaya and Hirsch, 1971; Davis, 2000). The physics of rapid acceleration/deceleration provide a deductive cross-validation of qEEG studies of traumatic brain injury based on the laws of inertia. For example, the temporal lobes and frontal lobes sit in bony "vaults" with apposition to the frontal and temporal bones and rapid acceleration/deceleration always maximally impacts these brain regions to some extent, independent of the direction of impact of a force on the skull because of the fact that the brain sits on a bony hard surface (Ommaya, 1968; 1995; Davis, 2000; Sano, 1967). In the case of closed head injuries the forces are much greater in the orbital frontal, frontal poles and anterior temporal lobes than anywhere else in dependent of the direction of the impact to the skull. In the case of whip lash, the forces are posterior to the skull and include brain stem stretching and torsion forces. In the case of IED energy forces that arise directly beneath the body the forces are direct upward through the spinal canal and brainstem resulting in sleep and anxiety problems in addition to the common frontal and temporal cortical injury. The consistency of biomechanical forces in closed head injury, in contrast to penetrating head wounds, is due to three common forces: 1- a percussion force that travels from the point of impact on the skull to the opposite side of the skull in less than 150 msec often producing a coup contra-coup pattern and disrupting protein-lipid neural membranes, 2- linear forces that are maximal in the frontal and temporal bone to brain interfaces that result in contusions of the frontal and temporal lobes and, 3- shear/rotational forces where different densities of brain tissue move at different rates (e.g., gray matter *vs*. white matter) that result in swelling of axons and diffuse axonal injury. Because of the high sensitivity of qEEG, detection and quantification of coup contra-coup patterns related to the point of impact against the skull is also a common finding. Finally, 3-dimensional electrical source localization and co-registration with MRI help to further identify the brain regions most affected by TBI and to aid in linking patient symptoms and complaints to functional specialization in the brain (Thatcher et al; 1998b; 2001; 2005; Korn et al, 2005).

qEEG Current Source Localization and TBI

In the last 15 years new advances in 3-dimensional source imaging or QEEG neuroimaging have evolved to the point of high sensitivity and high localization accuracy (Pascual-Marqui et al, 1994; Pacual-Marqui, 1999; Thatcher, 2011; Hernandez-Gonzalez et al, 2011). Low resolution electromagnetic tomography (LORETA) is easy to use, has been cross-validated in numerous studies and has high localization accuracy. There are over 750 peer-reviewed publications on the topic of QEEG and LORETA which is too extensive a literature to review here. LORETA is free at: http://www.unizh.ch/keyinst/NewLORETA/Software/Software.htm and it is also helpful in the evaluation of coup contra-coup patterns. The importance of 3-dimensional source imaging as an adjunction to the evaluation of traumatic brain injury is that it provides

clinicians with a method to link the patient's symptoms to functional localization in the brain (Thatcher et al, 2005; Korn et al, 2005; Boyd et al, 2007; Leon-Carrion et al, 2008a; 2008b). High sensitivity and specificity arises because one can test hypotheses prior to launching 3-dimensional electrical source imaging. This is done by predicting frontal and temporal lobe and network deviations from normal that are present in patients with a history of TBI and complaints such as short-term memory problem, attention and concentration problems and/or depression (see Johnson et al, 2011).

Figure one shows an example of reduced functional connectivity in the posterior cingulate part of the default mode network in a group of mild TBI patients (mTBI) in comparison to control subjects (NV). Reduced functional connectivity following

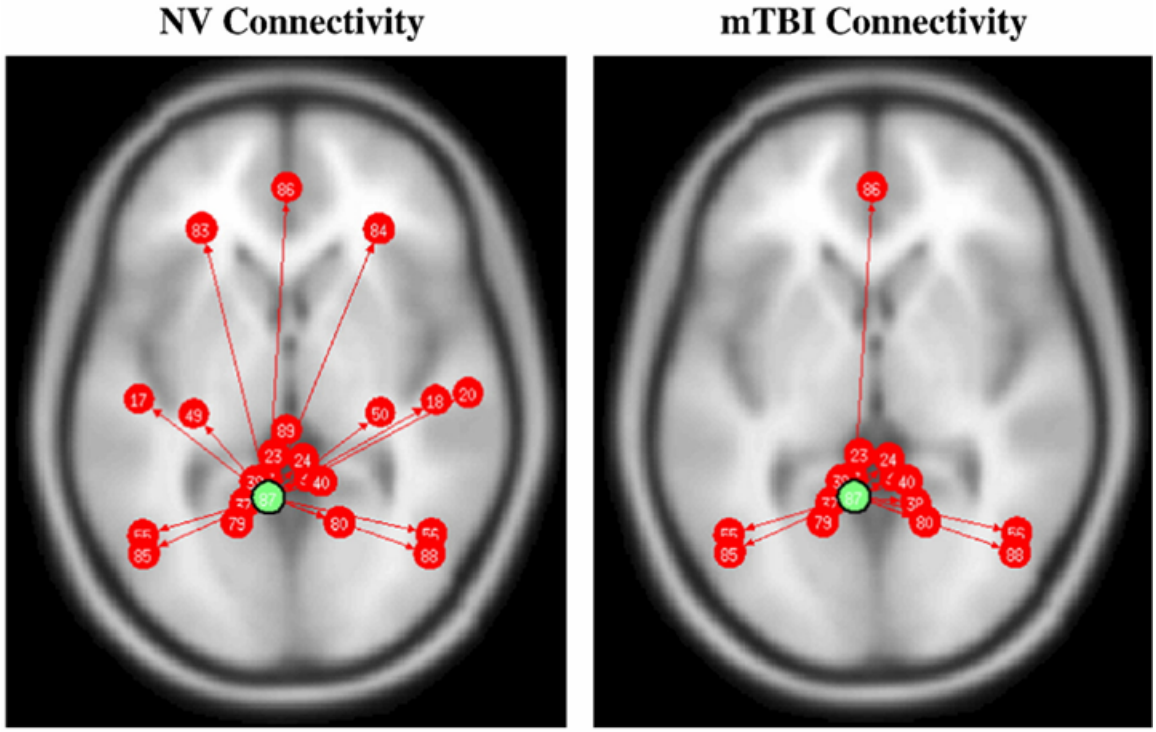

Fig. 1- Example of reduced connectivity in mTBI patients (right) in comparison to normal volunteers (NV) (left) using fMRI functional connectivity analyses (see Johnson et al, 2011 for details). A general reduced connectivity is reported in the default mode network in mTBI patients in comparison to controls (From Johnson et al, 2011).

a traumatic brain injury was reported for other parts of the default mode network (Johnson et al, 2011) as well as in surface qEEG coherence studies (Thatcher et al, 1998b). The application of LORETA coherence and LORETA phase differences between Brodmann areas provides clinicians with important tools to evaluate the affects of trauma on various networks in the brain.

Surface qEEG Biofeedback (Neurofeedback) and the Treatment of TBI

One of the earliest qEEG biofeedback studies was by Ayers (1987) who used alpha EEG training in 250 head injured cases and demonstrated a return to pre-morbid functioning in a significant number of cases. Peniston et al (1993) reported improved symptomology using qEEG biofeedback in Vietnam veterans with combat related post-traumatic disorders. More recently Hoffman et al (1995) in a biofeedback study of fourteen TBI patients reported that approximately 60% of mild TBI patients showed improvement in self reported symptoms and/or in cognitive performance as measured by the MicroCog assessment test after 40 sessions of qEEG biofeedback. Hoffman et al (1995) also found statistically significant normalization of the qEEG in those patients that showed clinical improvement. Subsequent studies by Hoffman et al (1996a; 1996b) confirmed and extended these findings by showing significant improvement within 40 sessions. A similar finding of qEEG normalization following EEG biofeedback was reported by Tinius and Tinius (2001) and Bounias et al (2001; 2002). Ham and Packard (1996) evaluated EEG biofeedback in 40 patients with posttraumatic head ache and reported that 53% showed at least moderate improvement in headaches; 80% reported moderate improvement in the ability to relax and cope with pain and 93% found biofeedback helpful to some degree. Thornton and Carmody (2005) reported success in using qEEG biofeedback for attention deficit disorders in children with a history of TBI. An excellent review of the surface qEEG biofeedback literature for the treatment of TBI is in Duff (2004).

LORETA Z Score Biofeedback

A new method of EEG biofeedback is the use of LORETA Z score biofeedback to directly train deregulated or unstable functional systems of the brain linked to symptoms that arose as a consequence of a traumatic brain injury. This new method involves the use of quantitative EEG to identify unstable or deregulated brain regions and network nodes linked to a patient's symptoms followed by LORETA Z score biofeedback to train toward improved stability and regulation in the affected brain regions. For example, short-term memory with the memory networks (anterior cingulate, prefrontal cortex, hippocampus, temporal lobes) or attention and concentration problems and the attention network (prefrontal cortex, parietal lobes, anterior cingulate, temporal lobes, default mode network) or mood dyscontrol and the mood networks of the brain (insula, medial and lateral frontal lobes, amygdala) . Once symptoms and complaints are linked to functional networks in the brain then LORETA Z score biofeedback is used for the treatment of mild to moderate TBI. The goal is to achieve consistent improved clinical outcome in fewer sessions than is possible using surface EEG biofeedback or even surface Z score biofeedback.

Z score biofeedback was first developed myself and colleagues in 2004 and is now commonly used by hundreds of clinicians and is distributed by a variety of EEG biofeedback companies (e.g., BrainMaster, Thought Technology, EEG Spectrum, NeXus, Deymed, Neurofield, Advanced Brain Monitoring and Mitsar). The ability to achieve improved clinical outcome in fewer than 20 sessions using Z score biofeedback has been documented in several publications (Collura et al; 2008; 2011; Hammer et al, 2011). Figure two illustrates how Z score biofeedback differs from raw score biofeedback by using a real-time or 'live' comparison to an age matched reference database of healthy

normal subjects (see Thatcher & Lubar, 2008). This is similar to the use of a real-time blood test where the patient's cholesterol or liver enzymes are measured instantaneously or in real-time and the clinician treats

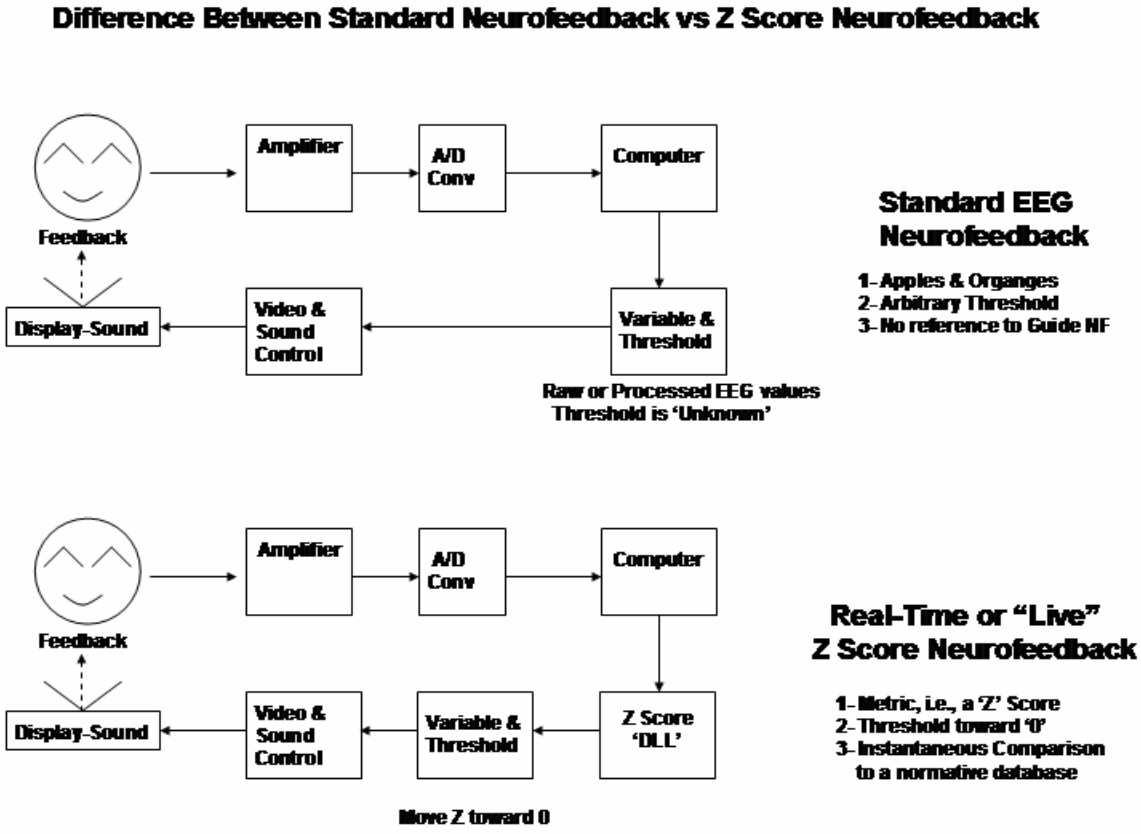

Fig. 2 – Illustration of the difference between 'raw score' EEG biofeedback (Top) and 'Z score' EEG biofeedback (Bottom). The methods are the same except that the raw scores are instantaneously transformed to Z scores with respect to the mean and standard deviation of an age-matched reference population of healthy individuals. Z score biofeedback simplifies by reducing disparate EEG metrics (abs. power, relative power, coherence, phase, phase shift, etc.) to a single common metric, i.e., the metric of a Z score. Z score biofeedback also takes the guesswork out of the process by providing the clinician with a common target toward which the brain is reinforced, i.e., the center of an age matched group of healthy individuals.

the patient by modifying the organ systems responsible for the deviant blood constituents. Z scores are a statistical measure of distance from the center of the age matched reference normal population and therefore Z scores provide a simplified 'threshold guide' in which the goal is to reinforce toward Z = 0. This is in contrast to non-Z score biofeedback or 'raw score' biofeedback in which the threshold for reward is arbitrary involving many different measures with different metrics. For example, as illustrated in the top row of Figure 2, with raw score biofeedback the clinician must guess at a threshold, e.g., reinforce if theta rhythms are less than 6 microvolts or maybe 10 microvolts or inhibit if beta is greater than 12 microvolts or should it be 10 microvolts or reinforce coherence

when it is greater than 0.3 or maybe 0.5 is the correct guess for the threshold? In contrast, as illustrated in the bottom row of figure two, Z scores simplify EEG biofeedback by using a single common metric no matter what the EEG measure, providing age and location matching and by removing the guess work because now the feedback threshold is not arbitrary but rather is uniform and always involves reinforcing toward Z = 0. This does not mean that a patient will ever attain exactly Z = 0 because none of the normal subjects are exactly at Z = 0 because this is only a statistical value that a large group of normal subjects deviate around. Instead, one is reinforcing increased stability and homeostasis in brain networks that have been damaged or have become deregulated. Z = 0 is a statistical 'ideal' just like the center of the 'normal reference' blood range when using a blood test.

LORETA Z score biofeedback differs from surface Z score biofeedback by targeting specific Brodmann areas or 3-dimensional locations of hubs and modules of networks linked to the patient's symptoms. With the surface EEG a given scalp electrode is sensing electrical potentials generated in many different parts of the brain that are mixed together at the scalp, e.g., the Cz electrode is detecting a mixture of sources from the occipital, frontal, temporal and parietal lobes. In contrast, LORETA is a mathematical method that unscrambles the mixture of electrical sources and provides a 3-dimensional depth source analysis at resolutions of less than 1 cubic centimeter (see Pascual-Marqui et al, 1994 and Pascual-Marqui, 1999 for the mathematical details and validations). The use of raw LORETA Z scores has the same limitations as the use of surface raw scores in comparison to Z scores. That is, biofeedback of raw LORETA values involves the use of an arbitrary threshold where the clinician must guess at whether or not to reinforce for current densities greater or less than a certain value. Raw LORETA phase differences and raw LORETA coherence suffer from the same complexity and arbitrariness and metric apples and organges. In contrast, LORETA Z score biofeedback removes the guess work and provides an age matched normal reference population as a guide and simplifies absolute power, relative power, coherence, phase, phase shift, phase lock, etc. to a single common metric, i.e., the metric of a Z score where one reinforces toward Z = 0 where zero is the idealized center of a group of healthy individuals.

DoD/VA LORETA Z Score Symptom Check List for TBI

The US Army has implemented LORETA Z score biofeedback as a standard clinical treatment of active duty military personnel involved in an extensive rehabilitation program (Fort Campbell Warrior Resiliency and Recovery Center or WRRC). Drs. Joel Lubar, Marc Zola and David Twilley are involved in the implementation of LORETA Z score biofeedback that follows an extensive clinical evaluation of each soldier including surface qEEG evaluations. A link of the patient's symptoms to deregulated or unstable networks of the brain known to be vulnerable to rapid acceleration/deceleration injuries is made through the use of a symptom check list that follows the 'Co-occurring Conditions Toolkit for Mild Traumatic Brain Injury and Psychological Health' or CONUS. In Neuroguide this is a tab located in the symptom check list panel for Z score biofeedback and labeled 'DoD/VA'. An example of the DoD/VA symptom checklist is shown in figure three and Table I. The upper left panel is a symptom check list based on the Defense Centers of Excellence of Psychological Health & Traumatic Brain Injury which

was established by the Department of Veterans Affairs in 2009 and incorporated into the DoD/VA clinical practice guidelines. The items in the Dod/VA tab reproduce the 2009 "Co-occurring Conditions Toolkit: Mild Traumatic Brain Injury and Psychological Health" (CONUS) for Concussion, Posttraumatic Stress, Depression, Chronic Pain, Headache and Substance Abuse Disorder. The right panel are Brodmann areas and the lower left panel are hypothesized Brodmann areas known to be related to a given symptom or assessment based on the scientific literature. The lower middle panel are the matches of deviant qEEG Z LORETA Z scores to the hypothesized Brodmann areas linked to the patient's symptoms. The lower right are the mismatches of deviant LORETA qEEG Z scores that are likely related to compensatory processes. The goal of this procedure is to separate the 'weak' systems from the 'compensatory' systems and to target the 'weak' systems for EEG biofeedback training and reinforce movement of the weak system toward Z = 0 which is the center of an age match normal population. Specific Brodmann areas can be trained such as the anterior cingulate gyrus in depression or attention deficit or the parahippocampus in attention deficit or the left angular gyurs in dyslexia, etc.

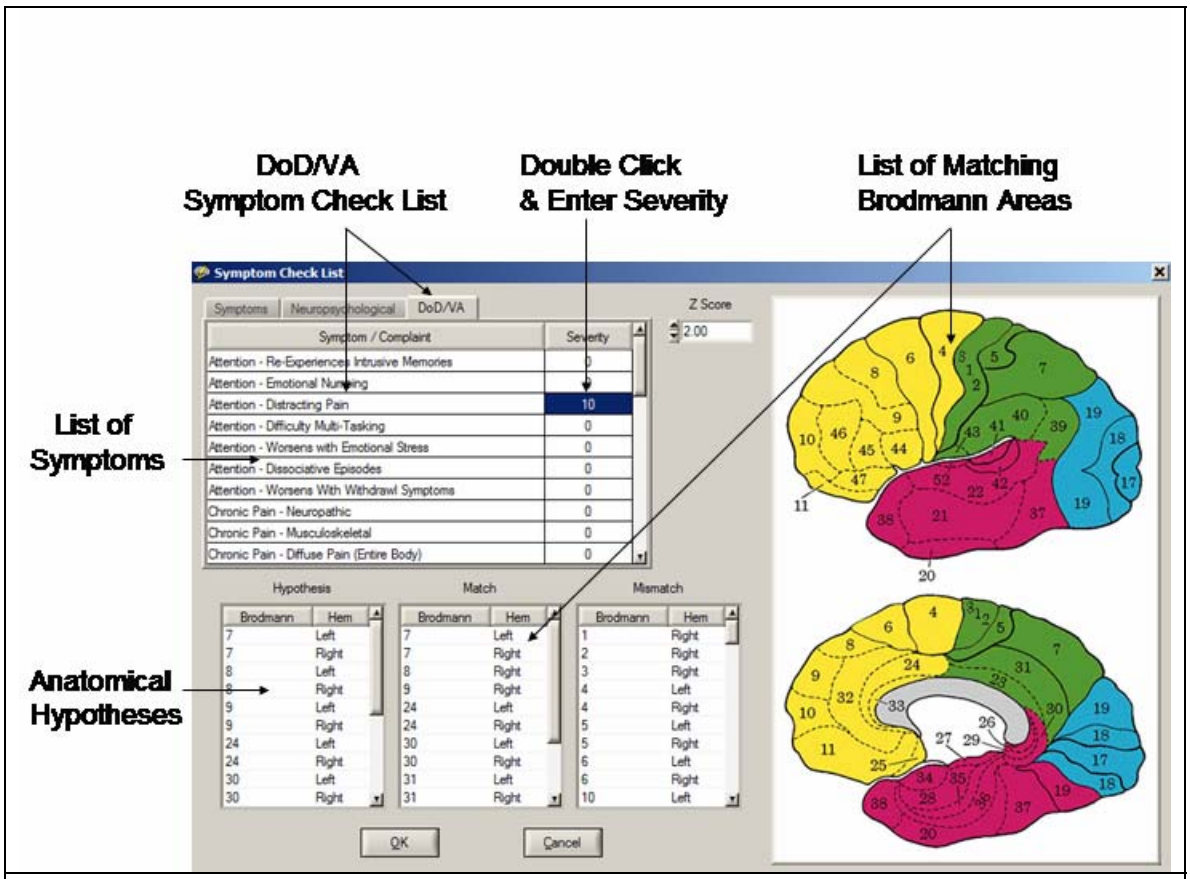

Fig. 3- EEG biofeedback of LORETA Z scores that are linked to the patient's symptoms and complaints. (From Neuroguide 2.6.9).

DoD/VA Symptom Check List – Adapted from the US Army CONUS Manual

Attention-Re-Experiences Intrusive Memories	Concussion Difficulty Multi-Tasking
Attention-Emotional Numbing	Concussion-Short-Term Memory Problems
Attention-Distracting Pain	Concussion-Difficulty Concentrating
Attention-Difficulty Multi-Tasking	Concussion-Sleep Problems
Attention-Worsens with Emotional Stress	Concussion-Balance Problems
Attention-Dissociative Episodes	Concussion-Problems Controlling Anger
Attention-Worsens With Withdrawl Symptoms	Concussion-Depressed Mood
Chronic Pain-Neuropathic	PTSD-Hyperarousal
Chronic Pain-Musculoskeletal	PTSD-Sudden Fear Reactions
Chronic Pain-Diffuse Pain (entire body)	PTSD-Excessive Sleep-Lethargic
Chronic Pain-Pain Triggers Memories of Trauma	PTSD-Difficulty Falling Asleep due to Rumination
Mood-Emotional Numbing	PTSD-Mood Disorders
Mood-Irritability	Sleep-Fear of Sleep Due to Nightmares
Mood-Emotional Fatigue	Sleep-Difficulty Falling Asleep due to Rumination
Mood-Physical Fatigue	Sleep-Difficulty with Sleep Due to Withdrawl Symptoms
Mood-Lack of Enjoyment of Daily Activities	Sleep-Early AM/Night Time Awakening (unexplained)
Mood-Impulsivity	
Mood-Activities Driven by Medication Needs	
Mood-Hyperarousal	

Table I – Symptom list from the US Army CONUS manual which is used inside of Neuroguide for the purposes of Z score biofeedback where symptoms are linked to networks in the brain.

Z score LORETA biofeedback includes current density and coherence and phase differences between Brodmann areas and network nodes. The goal is to identify the network nodes linked to the patient's symptoms and then to reinforce toward Z = 0 which is the center of a group of age matched and healthy individuals with no history of trauma, no history of neurological disorders and no history of psychological/neuropsychological problems. The project at Fort Campbell involves careful monitoring of all soldiers and extensive behavioral and psychological evaluation prior to implementing LORETA Z score biofeedback and pre *vs.* post treatment assessment at various stages of the rehabilitation program. The LORETA Z score symptom checklist is specially adapted from the Defense Centers of Excellence of Psychological Health & Traumatic Brain Injury manual. The items in the DoD/VA tab reproduce the "Co-occurring Conditions Toolkit: Mild Trauamtic Brain Injury and Psychological Health" (CONUS) for Concussion, Posttraumatic Stress, Depression, Chronic Pain, Headache and Substance Abuse Disorder. The selected network Brodmann areas related to different symptoms and clinical history of soldiers that suffered a TBI are based on a survey of the National Library of Medicine database using search terms such as 'fMRI and traumatic brain injury' or 'PET and traumatic brain injury' or 'EEG and traumatic brain injury.' A list of brain networks associated with TBI and that are consistently reported in the scientific literature were used to determine the Brodmann areas to target for LORETA Z score

neurofeedback. A qEEG assessment is used to rank order the most deviant nodes and hubs of the networks most commonly associated with TBI and follow-up pre vs post qEEG analyses are used to assess the progress of treatment. The US Army program is just getting started and is scheduled to continue for the next five years during which extensive pre vs post treatment assessment and statistical analyses will be conducted.

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FIGURE LEGENDS

Figure One: Fig. 1- Example of reduced connectivity in mTBI patients (right) in comparison to control subjects (NV) (left) using fMRI functional connectivity analyses (see Johnson et al, 2011 for details). A general reduced connectivity is reported in the default mode network in mTBI patients in comparison to controls (From Johnson et al, 2011).

Figure Two: Illustration of the difference between 'raw score' EEG biofeedback (Top) and 'Z score' EEG biofeedback (Bottom). The methods are the same except that the raw scores are instantaneously transformed to Z scores with respect to the mean and standard deviation of an age matched reference population of healthy individuals. Z score biofeedback simplifies by reducing disparate EEG metrics (abs. power, relative power, coherence, phase, phase shift, etc.) to a single common metric, i.e., the metric of a Z score. Z score biofeedback also takes the guess work out of the process by providing the clinician with a common target toward which the brain is reinforced, i.e., the center of an age matched group of healthy individuals.

Figure Three: EEG biofeedback of LORETA Z scores that are linked to the patient's symptoms and complaints. The upper left panel is a symptom check list based on the Defense Centers of Excellence of Psychological Health & Traumatic Brain Injury. The items in the Dod/VA tab reproduce the "Co-occurring Conditions Toolkit: Mild Trauamtic Brain Injury and Psychological Health" (CONUS) for Concussion, Posttraumatic Stress, Depresson, Chronic Pain, Headache and Substance Abuse Disorder. The right panel are Brodmann areas and the lower left panel are hypothesized Brodmann areas known to be related to a given symptom or assessment based on the scientific literature. The lower middle panel are the matches of deviant qEEG Z LORETA Z scores to the hypothesized Brodmann areas linked to the patient's symptoms. The lower right are the mismatches of deviant LORETA qEEG Z scores that are likely related to compensatory processes. The goal of this procedure is to separate the 'weak' systems from the 'compensatory' systems and to target the 'weak' systems for

EEG biofeedback training and reinforce movement of the weak system toward Z = 0 which is the center of an age match normal population. Specific Brodmann areas can be trained such as the anterior cingulate gyrus in depression or attention deficit or the parahippocampus in attention deficit or the left angular gyurs in dyslexia, etc. (From NeuroGuide 2.6.9).

TABLE LEGENDS

Table I – Table I – Symptom list from the US Army CONUS manual which is used inside of Neuroguide for the purposes of Z score biofeedback where symptoms are linked to networks in the brain.