NEURAL NETWORK INJURY INDEX

Thatcher, R.W. North, D.M., Zhou, L. and Biver, C. J.

EEG and NeuroImaging Laboratory, Applied Neuroscience Research Institute, 8200 Bryan Diary Road, Suite 315, Fl 33777

Send Reprint Requests To:
Robert W. Thatcher, Ph.D.
NeuroImaging Laboratory
Applied Neuroscience Research Institute
St. Petersburg, Florida 33777
(727) 244-0240, rwthatcher2@yahoo.com

1- Introduction

A concussion is a traumatic brain injury that alters the way your brain functions. Effects are usually temporary but can include headaches and problems with concentration, memory, balance and coordination. Although concussions usually are caused by a blow to the head, they can also occur when the head and upper body are violently shaken. These injuries can cause a loss of consciousness, but most concussions do not. Because of this, some people have concussions and don't realize it.

Concussions are common, particularly if you play a contact sport, such as football. But every concussion injures your brain to some extent. This injury needs time and rest to heal properly. Most concussive traumatic brain injuries are mild, and people usually recover fully.

The Neural Network Injury Index (NI) is a EEG measure of the extent and severity of a traumatic brain injury that is characterized by having a concussion. The NI is an extension and refinement of the 2004 FDA 510k registered Mild Traumatic Brain Injury Discriminant Function but adds changes in the connectivity between EEG produced in Brodmann areas and connectivity measures at the scalp surface (see Thatcher, et al, EEG discriminant analyses of mild head trauma. EEG and Clin. Neurophysiol., 73: 93-106, 1989 and Thatcher, et al, An EEG Severity Index of Traumatic Brain Injury, J. Neuropsychiatry and Clinical Neuroscience, 13(1): 77-87, 2001). However, here we refer to the discriminant function as a Network Injury Index (NI) and not a concussion index because the EEG was often measured months and years after the concussion. The NI is not based on the time interval immediately after a concussion and then repeat tests following a concussion and nor are the vast majority of QEEG studies on TBI. Such data are very rare and difficult to obtain and are seldom if ever reported in the scientific literature. Instead, the NI discriminant function compares the EEG recorded from severe TBI confirmed by Glasgow Coma Scores (GCS), post traumatic amnesia and age matched normal subjects with no history of TBI and then is cross-validated by an independent group of subjects and mild and moderate TBI patients. The NI does not include EEG power or current density measures and only includes connectivity measures. As explained in Thatcher et al (1989; 1991; 2001; 1998) stretching of axons and dysregulation of nodes of networks is a common consequence of rapid acceleration deceleration injuries which forms the rationale for the NI.

2.0 – Methods

2.1 Subjects

A total of 250 normal control subjects were included in this study (age from 15 to 30 years). The normal control subjects had no history of neurological disorders such as epilepsy or concussions and performed within the normal range on the WISCR-R neuropsychological tests and were part of the normative database produced at the University of Maryland (Thatcher et al, 1987; 2003; 2007). A total of 348 age matched subjects with a history of concussion were included in the study. All of the concussion subjects participated in the Department of Defense and Head Injury Program (DVHIP) (Thatcher et al, 1998a; 1998b; 2001; 2003). The concussion subjects were categorized into three groups: 1- Mild (N = 88) defined by a Glasgow Coma Scale (GCS) 13-15, Post Traumatic Amnesia (PTA) < 1 hour and either no loss of consciousness (LOC) or less than 20 minute LOC; 2- Moderate (N = 138) defined by a GCS 10-12, PTA 1 hour to 6 days and LOC 1 hour to 24 hours and, 3- Severe (N = 122) defined by a GCS < 7, PTA > 7 days and LOC > 23 hours. The time between injury and EEG test varied from 2 months to 4 years.

2.2 EEG Recording

The EEG was recorded from 19 scalp locations based on the International 10/20 system of electrode placement, using linked ears as a reference. Eye movement electrodes were applied to the inner and outer

canthus to monitor artifact and all EEG records were visually inspected and manually edited to remove any visible artifact. Two five minutes of EEG was recorded in the eyes closed and in the eyes open condition. The order of recording for the eyes open followed by closed conditions and vice versa was counter-balanced across subjects. Each EEG record was plotted and visually examined and split-half reliability and test re-test reliability measures of the artifacted data were computed using the Neuroguide software program (NeuroGuide, v2.8.0). The amplifier bandwidths were nominally 1.0 to 30 Hz, the outputs being 3 db down at these frequencies and the EEG was digitized at 100 Hz. Analyses were performed on 58 seconds to 2 minute 17 second segments of EEG. Split-half reliability tests were conducted on the edited EEG segments and only records with > 90% reliability were entered into the spectral analyses.

2.3 – Cross-Spectral Analysis and LORETA computation

The edited EEG was saved in which the 19 channels were columns and the 256 time points as rows. In order to minimize windowing effects 75% overlapping 256 point segments were used according to the procedure described by Kaiser and Sterman (2001). The LORETA analyses were limited to the center voxels of the Brodmann areas that comprise eight different functional networks as described in section 2.4. For each center voxel cross-spectral analyses using the Hermitian matrix for LORETA implementation were computed according to standard procedures for LORETA frequency analyses (Gomez and Thatcher, 2001; Frei et al, 2001; Pascual-Marqui, 2003). A cosine taper windowing was performed using the cross-spectral FFT on each 256 point data sample. The cross-spectra were averaged across the overlapping windows which yielded a total of 61 frequencies from 0.5 Hz to 30 Hz. The spectral resolution was 0.5 Hz, however, adjacent frequency bands were averaged to produce a 1 Hz resolution thus yielding a total of 30 frequency bands from 1 to 30 Hz. The Key Institute software was used to compute the T matrix according to the Talairach Atlas coordinates of the Montreal Neurological Institute's MRI average of 305 brains (Pascual-Marqui, 1999; 2003; Talairach and Tournoux, 1988). The computations were restricted to the cortical gray matter according to digitized probability atlases (Mazziota et al, 1995). The spatial resolution is 7 mm for each of the Brodmann area center voxels. The cross-spectral values were computed at 8 frequency bands (Delta 1-4 Hz; Theta 4-8 Hz; Alpha1 8-10 Hz; Alpha2 10-12 Hz; Beta1 12-15 Hz; Beta2 15-18 Hz; Beta3 18-25 Hz and Hibeta or Gamma 25 – 30 Hz). Hz frequency band were multiplied by the T matrix which is a 3-dimensioinal matrix of x, y and z current source moments in each of the 2,394 gray matter voxels. The resultant current source vector at each pixel was computed as the square root of the sum of the squares for the x, y & z source moments for each 1 Hz frequency band for each subject. The log transform of the current density values was computed but similar statistical findings with nearly identical effect sizes were observed with or without log transform. Therefore, for simplicity only the untransformed current source vectors are used in the present study.

2.4 Functional Networks

Convergent evidence from different imaging modalities has demonstrated that the human brain is a network organized by "Nodes" with linkages and clustering of connections defined as "Modules" based on the density of synaptic connections and constituting "Functional Networks" (Achard et al, 2006; Sporns et al, 2004; Raichle, 2010; Etkin et al, 2009; Petersen and Posner (2012). Based these studies and reviews of functional brain networks we selected a sub-set of eight functional networks that are most likely affected by a concussion. The selected networks were: Anxiety (Etkin et al, 2010); Dorsal & Ventral Attention (Petersen & Posner, 2012; Default Mode (Raichle, 2010: Sridharan et al, 2009); Language (Mesulam, 2000) Memory (D'Ardenne et al, 2012); Mood (Jacobs et al, 2014) and Pain (Simonsa et al, 2014; Stern et al, 2006). These particular functional networks are also reviewed in Thatcher, 2012).

Table I shows the Brodmann areas that were selected for the eight functional networks in which the LORETA coherence and phase differences were computed from the time series of current density produced by the center voxel of each of the 8 functional networks.

Table I -

LORETA Networks:	Brodmann Areas	Total Brodmann Pairs	Total Coherence & Absolute Phase Variables	*T* tests p < .05	Varimax Factor Analyses > .8 Final Reduction
Anxiety	4,6,7,10,13,21,Amygdala	42	672	265 (39%)	20
Attention Dorsal	6,7,8,19,39,40	30	480	119 (25%)	14
Attention Ventral	10,11,19,21,37,44,45	42	672	246 (37%)	19
Default Mode	7,10,11,19,22,29,30,31,35,39,40	110	1760	454 (26%)	24
Language	22,39,40,41,42,44,45 Left Hemisphere only	21	336	87 (26%)	11
Memory	7,9,24,30,31,32,33,40,Hippocampus	72	1152	436 (38%)	25
Mood	10,11,13,23,24,32,33,44,45,47	90	1440	452 (31%)	23
Pain	1,2,3,4,5,13,24,32,33	72	1152	398 (35%)	26

The Network Injury Index (NI) provides a mathematical scaling to show the severity of a concussion between normal subjects with no history of head injury to subjects with severe head injuries. Similar to Thatcher et al (1989; 2001) the NI is based on EEG discriminant analyses of 248 subjects (age of 18 - 30 years) between normal and severe TBI groups. The other groups (N = 366) utilized for cross-validation are from other normal, mild TBI, moderate TBI and other severe TBI subjects included in the Thatcher et al (1989; 1998a; 1998b; 1998b; 2001).

2b- Creation of the Test Discriminant Function

Figure 1 shows the qEEG measures included in the surface EEG discriminant function, i.e., amplitude asymmetry, coherence, absolute phase, instantaneous connectivity, and lagged connectivity. Each measure using the 19 electrode locations on the International 10/20 system using eyes closed linked ears as a reference with 8 frequencies (Delta, Theta, Alpha1, Alpha2, Beta1, Beta2, Beta3 and Hi-Beta). The total number of qEEG variables a given surface EEG connectivity measure such as coherence, amplitude difference and phase differences. Each category involved 177 electrode combinations with 10 frequency bands resulting in a total of

6,840 veriables per subject. Each surface EEG connectivity variable was further classified by anatomical hemisphere and cross-hemisphere of right, left, homologous, diagonals, and midline.

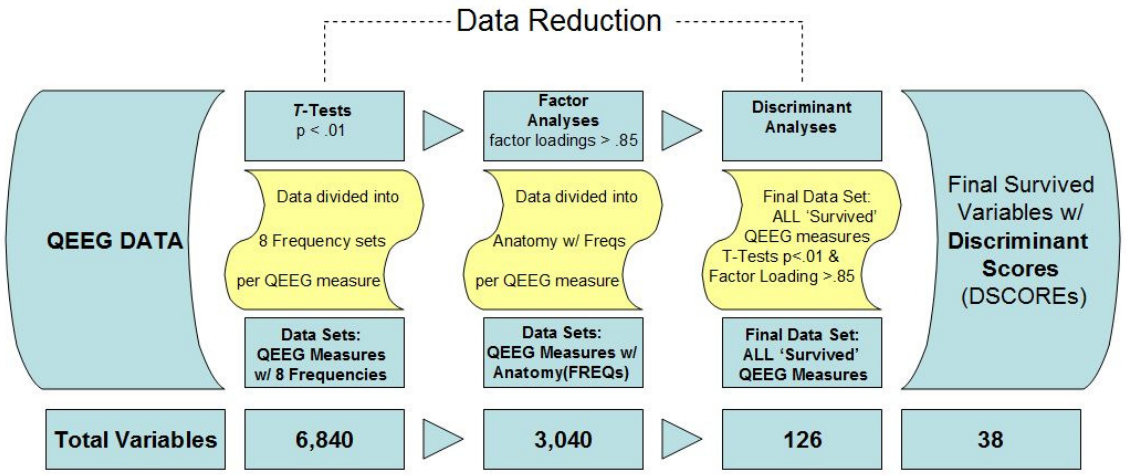

Fig. 1- Data reduction procedures of computing T-tests between the normal vs severe group and then selecting variables that were significant at P < .01 to be entered into factor analyses to reduce the data set by selecting variables that loaded > 0.85 on a given factor to then enter into a step-wise discriminant analysis.

Surface EEG connectivity data reduction process consisted of using *T*-tests of p < .01 and varimax factor analyses with factor loadings of > .85. *T*-tests showed a 44% difference (3,040 variables) in qEEG data between normal subjects with the severe TBI group. After *T*-tests, the varimax factor analyses were performed to reduce the data from 3,040 variables to only 126 variables from factor loadings of > .85. After data reduction, the step-wise forward discriminant analysis was performed. This resulted in a final reduction of 38 total survived variables. Table II shows the results of the test or initial discriminant analysis with a 99% classification accuracy.

Table II – Discriminant Test Classification matrix

Groups:	SEVERE TBIs	NORMALs	% Correct
SEVERE TBIs (82)	80	2	98%
NORMALs (166)	0	166	100%
Total	80	168	99%

2c- Cross-Validation of the Discriminant Function

Two separate cross-validation tests were performed: 1- A leave-one-out or Jackknife procedure and 2- An independent cross-validation using the unclassified mild and moderate TBI

subjects. The leave-one-out cross-validation involved each individual subject being removed from the analysis and then the analysis repeated and the subject removed was classified as a member of either the normal control group or the severe TBI group. Table III shows that the leave-one-out replication had an overall classification accuracy of 97%. This analysis showed high test re-test reliability of the discriminant function.

Table III - Jackknifed classification matrix

Groups:	SEVERE TBIs	NORMALs	% Correct
SEVERE TBI (82)	78	4	95%
NORMAL (166)	3	163	98%
Total	81	167	97%

The independent cross-validation involved the use of the initial discriminant function equation to classify the moderate TBI subjects that were not used in the initial discriminant function. If the effects of rapid acceleration/deceleration on the brain is a linear function of the magnitude of the force then the mild and moderate subjects will be located intermediate between the extreme of normal and severe TBI and the mild will be closer to the normal than the moderate TBI subjects. The results of the independent cross-validation is shown in Table IV and also in the distributions in Figure 3. These analyses supported both the validity of the discriminant function or concussion index and the presence of linearity relating the magnitude of forces imparted to the brain and the EEG.

Table IV – Independent Cross-Validation classification matrix

Ungroups:	SEVERE TBIs	NORMAL TBIs	% SEVERE TBIs	%NORMAL TBIs
NORMAL (84)	4	80	5%	95%
SEVERE TBI (40)	35	5	88%	12%
MODERATE TBI (125)	122	33	79%	21%
MILD TBIs (88)	61	27	69%	31%

3- Results:

3a – Figure two are the distributions of the various groups that were used to produce and cross-validate the NI. The y-axis are the percentage of subjects in a given group and the x-axis are discriminant scores that ranged between -7 & +7. This range was then scaled to range from 0 and 10 as shown in figure one.

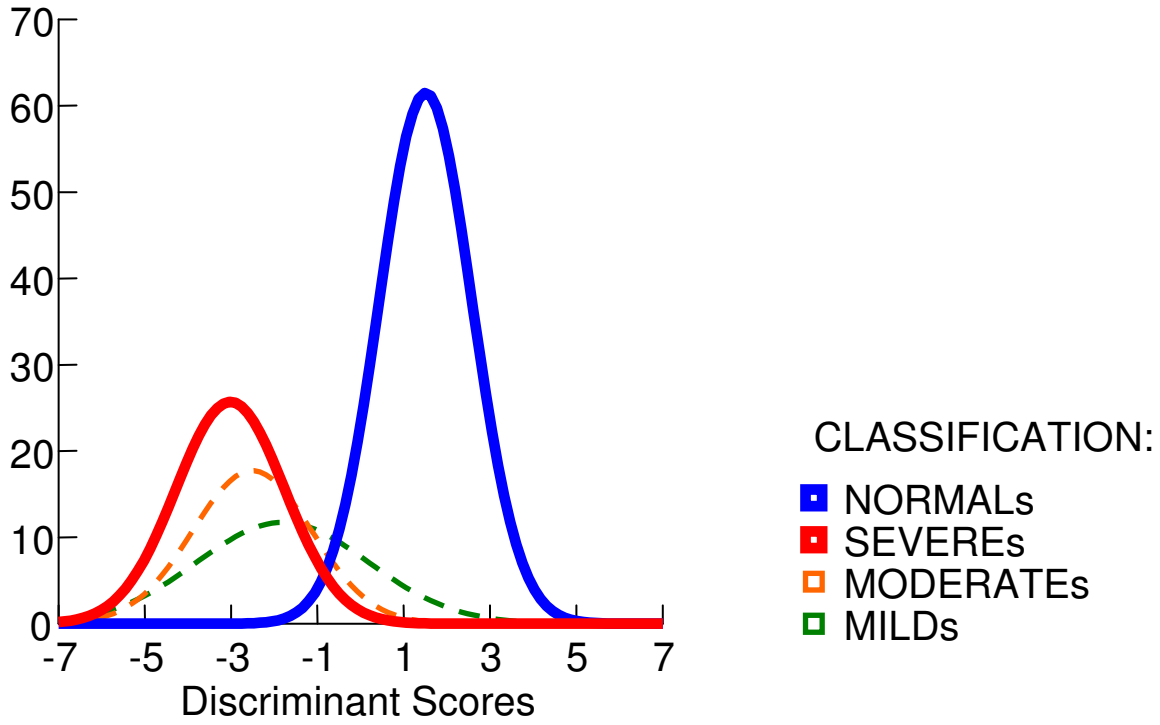

Fig. 2 - The y-axis are the percentage of subjects in a given group and the x-axis are discriminant scores that ranged between -7 & +7. This range was then scaled to range from 0 and 10 as shown in figure one.

Figure three is an example of the NI in which 1 to 3 minutes of artifact free EEG is submitted to the discrimant function and scaled between 0 = normal and 10 = severe TBI with the mild and moderate discriminant scores falling between normal and severe. The overall classification accuracy with cross-validations was 99%.

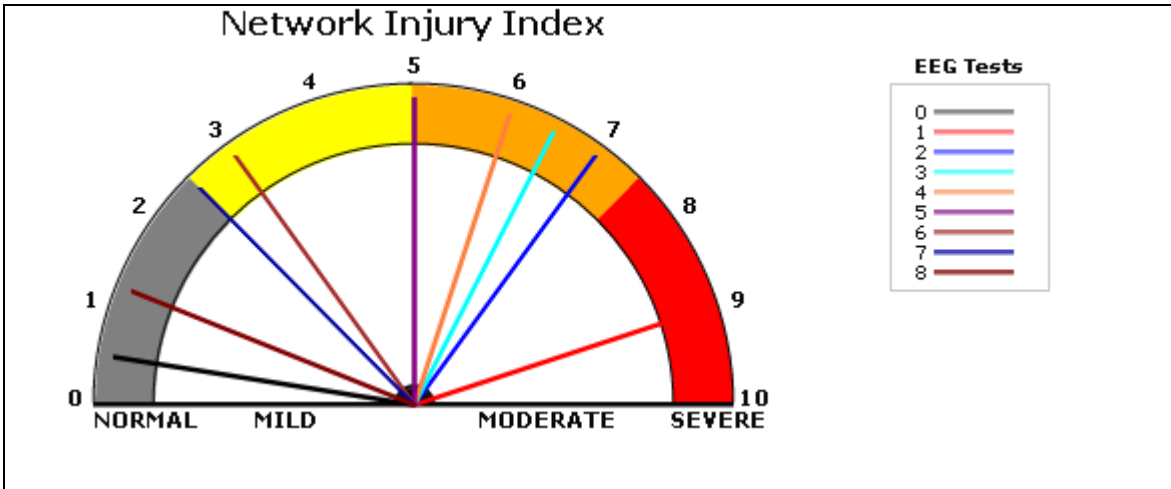

Fig. 3 – Example of the Network Injury Index (NI) where the range of discriminant scores vary from zero for normal control subjects and 10 for severe TBI subjects. The normal range is 0 to 3.5, mild is 3.51 to 6.5 and severe is 6.51 to 10.0. The line drawn

from the origin indicates the discrimiant score for a given EEG recording. Multiple lines are drawn for multiple EEG recordings to allow one to view the time course of recovery from a TBI over successive EEG recordings.

3c- Predicting LORETA Networks using Z-scores

An approximate linear relationship was present in the cross-validation analyses in which the scalp surface discriminant function was normal > mild > moderate > severe. A separate discriminant analysis was also conducted but using LORETA Z scores from the Brodmann areas constituting the ten networks shown in Table V. Only LORETA network measures were included in the LORETA discriminant scores similar to the scalp surface discriminant function. A list of the LORETA coherence and phase variables used in the discriminant function are in Table V. The same procedures used in Thatcher et al (1989; 2001) for data reduction were *T*-tests ($p < .01$) and varimax factor analyses (> .8 loading factors). *T*-tests showed a 36% difference (11,267 variables) between normal subjects and the severe TBI group. After *T*-tests, the varimax factor analyses were performed to reduce the data from 11,267 variables to only 127 variables from factor loadings of > .80. After data reduction, the step-wise forward discriminant analysis of the LORETA connectivity measures was performed. Results showed a final reduction of 32 total survived variables. The overall classification is 98% of discrimination between normal and severe TBI groups.

The LORETA discriminant analysis showed essentially the same discriminant accuracy as the surface discriminant function and also was significantly correlated with the scalp surface EEG discriminant scores. Therefore, a linear multivariate regression analysis was conducted where the LORETA discriminant function was the dependent variable and the LORETA network Z scores were the independent variables. The variables and results of the multivariate linear regression are shown in Table VI.

Figure four are the standard Brodmann Areas used for the network analyses. Each variable was classified by anatomical lobe(s) of frontal (F), temporal (T), parietal (P), and occipital (O) with the following different combinations of Brodmann pairs: (*F_F, F_T & T_F, F_P & P_F, F_O & O_F, T_T, T_P & P_T, T_O & O_T, P_P, P_O & O_P, O_O*).

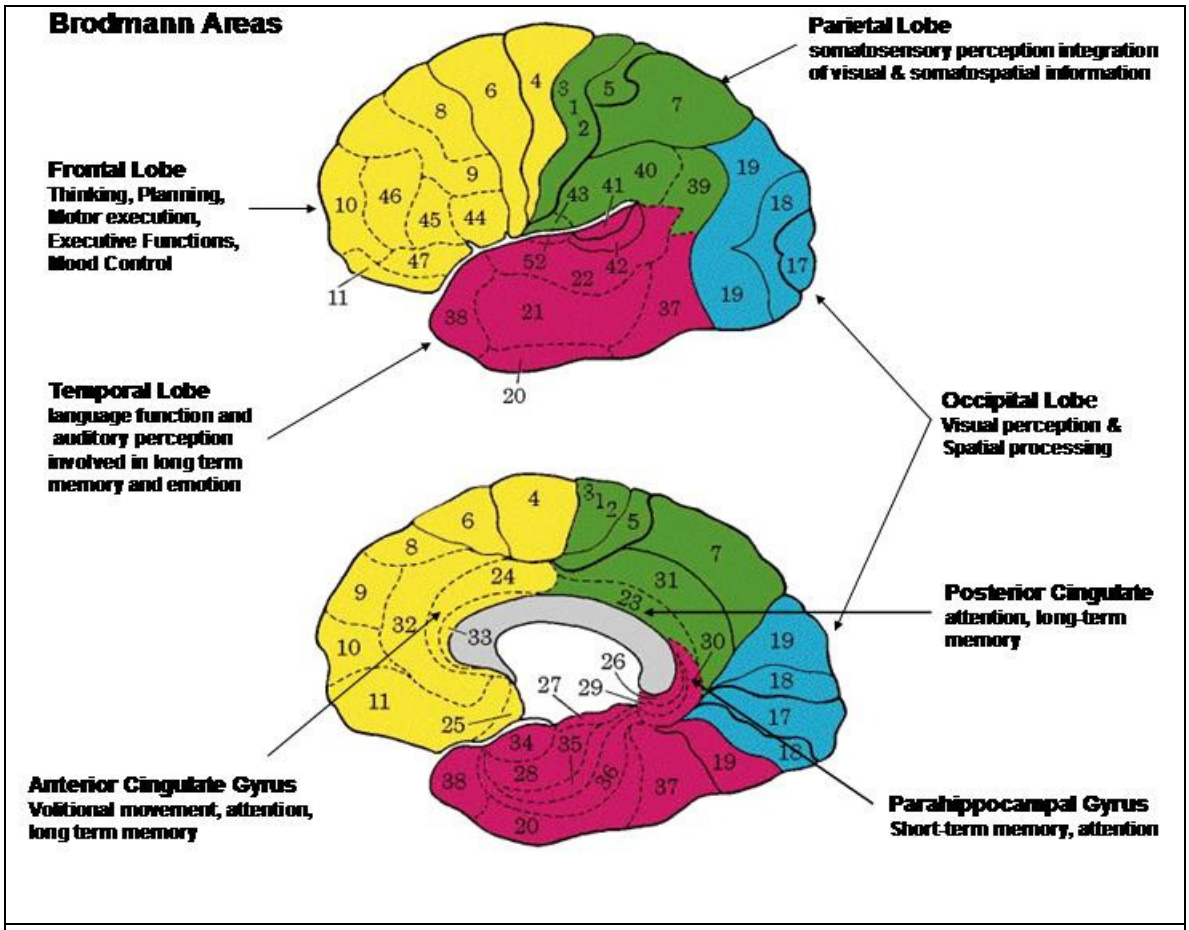

Fig. 4 – Standard Brodmann areas

The LORETA Brodmann area functional variables were the independent variables that were independently predicted based on the functional categories of anxiety, attention dorsal, attention ventral, default mode, language, memory, mood, and pain. The Brodmann pairs for each network consisted of z-scores from coherence and absolute phase between the center voxels of each Brodmann area. Below is Table V that shows the details of the network statistical predictions

Table V -

LORETA Networks:	Brodmann Areas	Total Brodmann Pairs	Total Coherence & Absolute Phase Variables	*T* tests p < .05	Varimax Factor Analyses > .8 Final Reduction
Anxiety	4,6,7,10,13,21,Amygdala	42	672	265 (39%)	20
Attention Dorsal	6,7,8,19,39,40	30	480	119 (25%)	14

Attention Ventral	**10,11,19,21,37,44,45**	**42**	**672**	**246 (37%)**	**19**
Default Mode	**7,10,11,19,22,29,30,31,35,39,40**	**110**	**1760**	**454 (26%)**	**24**
Language	**22,39,40,41,42,44,45 Left Hemisphere only**	**21**	**336**	**87 (26%)**	**11**
Memory	**7,9,24,30,31,32,33,40,Hippocampus**	**72**	**1152**	**436 (38%)**	**25**
Mood	**10,11,13,23,24,32,33,44,45,47**	**90**	**1440**	**452 (31%)**	**23**
Pain	**1,2,3,4,5,13,24,32,33**	**72**	**1152**	**398 (35%)**	**26**

The discriminant scores showed separation between normal and severe TBI groups and were utilized as the dependent variable in the multiple regression analyses for the prediction of the LORETA networks.

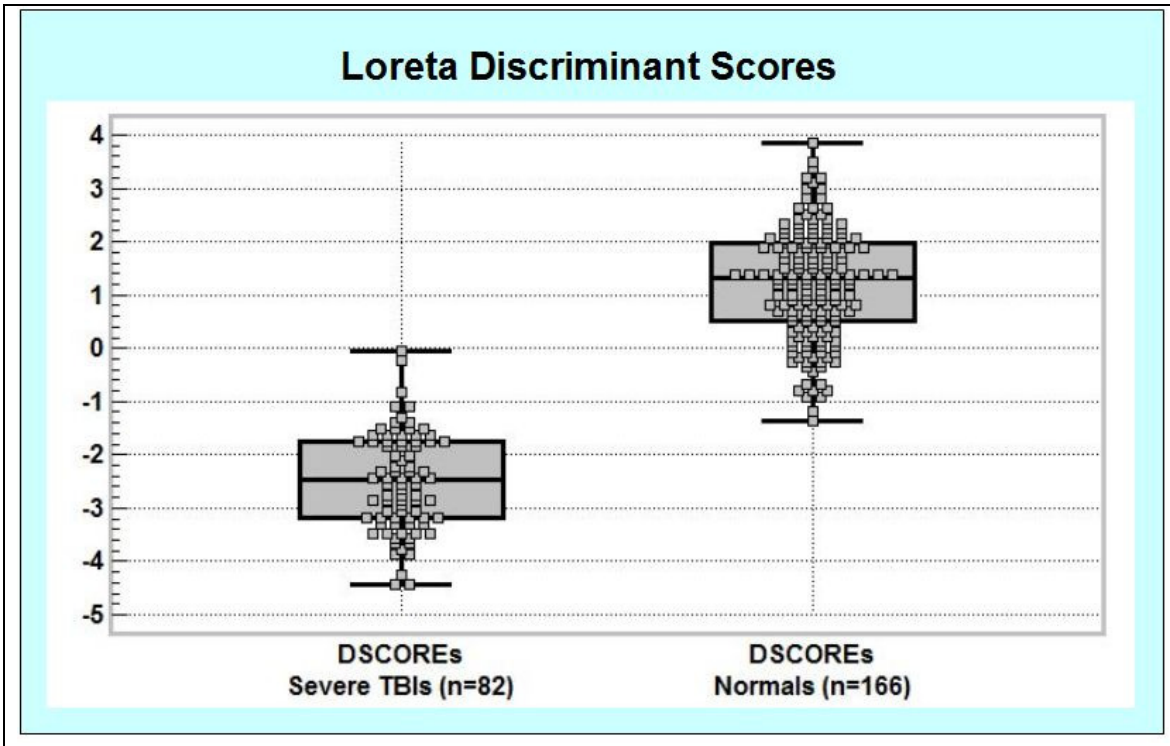

Fig. 5 Distribution of neural network discriminant scores of severe TBI vs. age matched normal controls

After conducting the data reduction process for the center voxel of each LORETA network, the discriminant scores of the normal and severe TBI groups were correlated with the surviving

LORETA network Brodmann pairs of z-scores from LORETA coherence and absolute phase differences. The results produced mostly a high correlation (p <= .0001) between the discriminant scores with each LORETA network Brodmann pair z-scores of coherence and absolute phase. After conducting the correlation procedure, multiple regression analyses were conducted in which the LORETA discriminant scores were the dependent variables and the survived z-scores from each Loreta network Brodmann pairs of coherence and absolute phase were the independent variables. As seen in table VI the multiple regression analyses produced highly predicted equations for the LORETA networks using Brodmann pair z-scores for coherence and absolute phase differences.

Table VI - Multiple Regression Analyses: Normals vs Severe_TBIs (n = 248) Dependent Variable: DScores (LORETA Discriminant Function 19-Channels). Independent Variables: Z-Scores Network Loreta Brodmann Pairs (Coherence & absPhase Differences)

Loreta Networks:	Probability Value	Multiple R	Squared Multiple R	Adjusted Squared Multiple R	Standard Error
Anxiety	p <= 0.000	0.793	0.628	0.596	1.279
Attention Dorsal	p <= 0.000	0.711	0.506	0.476	1.456
Attention Ventral	p <= 0.000	0.751	0.564	0.528	1.382
Default Mode	p <= 0.000	0.781	0.610	0.568	1.322
Language	p <= 0.000	0.693	0.481	0.457	1.483
Memory	p <= 0.000	0.866	0.750	0.722	1.061
Mood	p <= 0.000	0.793	0.629	0.591	1.286
Pain	p <= 0.000	0.832	0.692	0.656	1.180

Predicted Networks Using Z-Scores

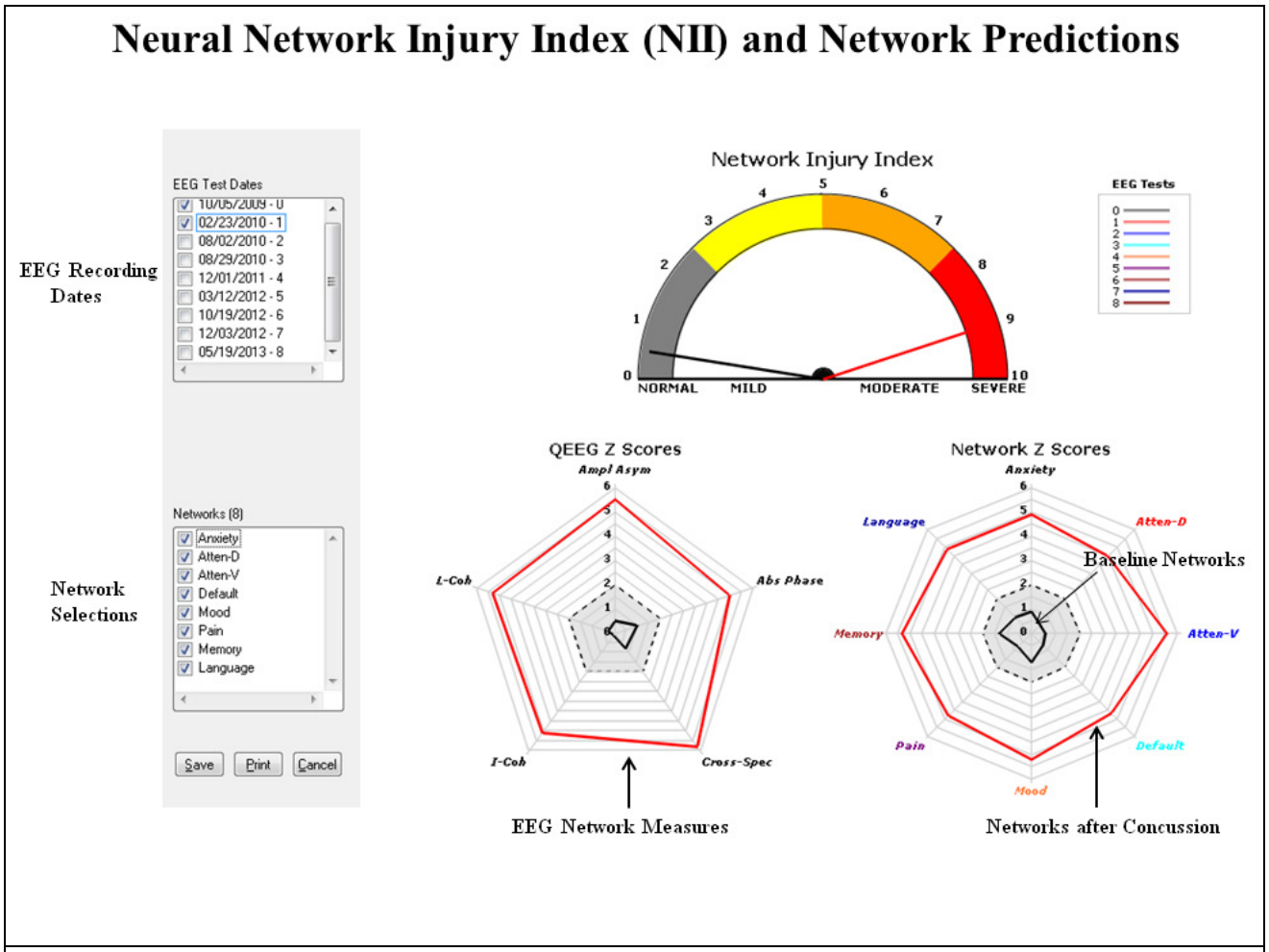

Fig. 6 – Example of Neural Network Injury Index controls on the left and the Network Injury Index discriminant function on the top. Bottom left are the surface QEEG measures used in the discriminant function and bottom right are the LORETA neural network discriminant Z score predictions.

Post Injury Changes over Time

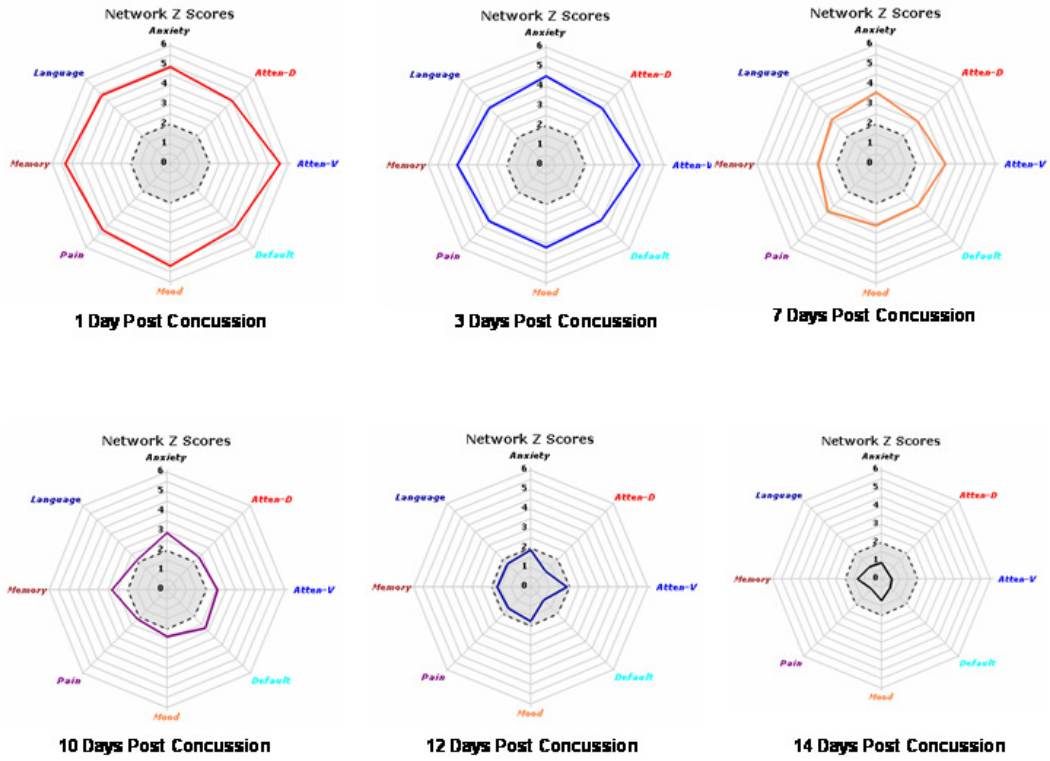

Fig. 7 – Example of changes in Network Z scores after injury in successive EEG recordings.