BRAIN OPTIMIZATION INDEX

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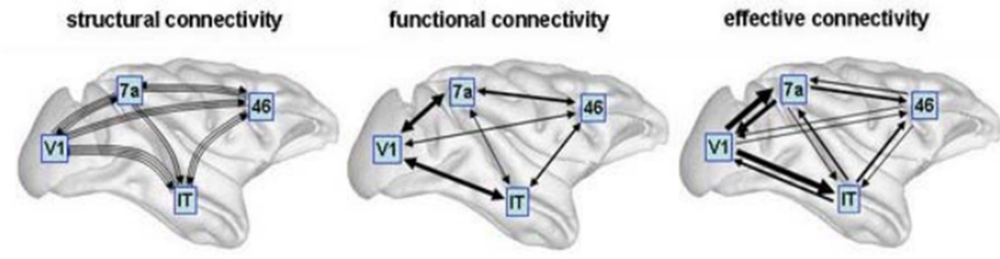
Introduction

Recent studies have shown that intelligence is related to neural efficiency defined as the capacity to rapidly recruit large numbers of neurons referred to as neural resources in local collections of neurons called "Hubs" followed by brief phase lock durations (e.g., 250 msec) during which functions are mediated. In addition, efficiency is related to the connectivity between Hubs as measured by coherence and phase delays. Hubs are organized in interconnected networks in the brain where each Hub is sending and receiving information from all other Hubs where intelligence is directly related to the capacity to efficiently process information locally and to minimize the burden on compensatory and distant Hubs (Thatcher et al, 2016; Thatcher, 2012; 2016). The goal of this document is to describe the details of how an index of optimal brain function related to intelligence and efficiency was developed, testing and cross-validated. We renamed the Brain Optimization Index (BOI) to the Brain Optimization Index (BOI) to more clearly reflect the use of the "Peak Performers"or the individuals with I.Q. scores ≥ 120 from the University of Maryland normative reference database as an optimal reference population to compute the statistical distance from using discriminant analyses (Thatcher et al, 2003; 2007; 2008). Some of the figures may still use the word "function", however, there have been no changes in the analyses. The word "optimization" better fits the purpose and original intent for the development of of a brain index.

There are three main types of brain connectivity. One is structural connectivity as measured by structural MRI and diffusion tensor imaging. This level of connectivity is the same whether one is alive or shortly after death and represents the essential structural infra-structure of the brain. The second is functional connectivity as measured by EEG coherence and fMRI correlations between brain regions. This level measures the temporal correlation between two or more brain regions and indicates functional activity shared by the correlated regions. The third level is called effective connectivity which is a measure of the magnitude and direction of information flow between two or more connected brain regions (Nolte et al, 2008a; 2008b; Ewald et al, 2013). By analogy structural connectivity is like the street connecting a parking lot to a sports stadium, functional connectivity is the correlation between changes in the two locations and effective connectivity measures the direction and magnitude of the flow of people that travel between the two locations.



From Sporns

An added factor in understanding the nature of intelligence and efficiency of information processing is the relationship between short distance connections vs long distance connections in complex networks. For example, in small-world models increased efficiency is related to increased differentiation or localization and minimization of long distance connections. Consistent with the global efficiency small-world models are studies showing weak long distance functional connectivity correlated with higher intelligence (Santarnecchi et al, 2014). A complementary finding are correlations with higher intelligence in short distance EEG electrode combinations using EEG phase reset which is also consistent with a small-world model where reduced long distance connectivity and increased short distance connectivity are correlated with higher intelligence (Thatcher et al, 2008). The EEG studies are also consistent with Graph theoretical models of intelligence using structural MRI. For example, van den Heuvel et al (2010) and Li et al (2009) found that higher I.Q. negatively correlated with path length and path length is inversely proportional to network efficiency. Thus, both structural connectivity and functional connectivity measures demonstrate a positive correlation between I.Q. and the efficiency of information processing in networks of the brain.

Recently, our laboratory published a study (Thatcher et al, 2016) showing significant correlations between intelligence and estimates of information flow using the phase slope index. While information flow was present in all subjects, a linear inverse relationship was demonstrated in which the higher I.Q. then the less the magnitude of information flow between EEG scalp locations as measured by the phase slope index (Nolte et al, 2008a; 2008b; Ewald et al, 2013). Also, the largest difference in information flow between the high and low I.Q. groups was in the frontal-parietal electrode combinations in the alpha frequency bands. This finding is consistent with EEG coherence and phase measures of intelligence published previously (Thatcher et al, 2007).

Another finding was that differences in information flow between high and low I.Q. groups were primarily in long distance inter-electrode combinations. This finding is opposite to the relationship between I.Q. scores and EEG phase reset in which short inter-electrode distances (e.g., 6 cm to 12 cm) were more strongly correlated with intelligence than the long inter-electrode distances (Thatcher et al, 2008).

Intelligence, Efficiency and Homeostatic Neuroplasticity

The finding of reduced magnitude of information flow in higher I.Q. subjects in long distance inter-electrode combinations is best interpreted in the context of other network correlations with intelligence. For example, correlations between phase shift and phase lock duration were statistically significant in short inter-electrode combinations that reflect information processing in local or segregated clusters of neurons (Thatcher et al, 2008). The longer the phase shift duration then the higher the I.Q. where phase shift duration was interpreted as a recruiting process to synchronize available neurons at a given moment of time (Thatcher, 2012; 2016). The current study when also considering the phase reset relations to intelligence indicates that the lower magnitude of information flow in high I.Q. subjects represents a more efficient local information processing where there is reduced demand for neural resources located in distant clusters of neurons. Information flow occurs in all subjects, however, the magnitude of information flow between brain regions is less in the higher I.Q. subjects as seen in figure 3. This indicates that each network hub receives and sends information to all other network hubs but if a given hub has inefficient information processing in the local domain then compensatory hubs send information to the weak hubs in order to achieve maximum efficiency of information processing in the network as a whole.

This is consistent with a homeostatic neuroplasticity model of intelligence in which maintenance of an optimal small-world dynamic involves minimizing long distance information processing and maximizing the efficiency of local information processing. [29] Phase reset operates primarily in the local hub domain to recruit and allocate resources to efficiently process information while information flow operates in the long range compartments to compensate for inefficiencies in the local domain. The greater the small-world efficiency of the global brain networks then the higher is performance on the WISC-R I.Q. intelligence test. Graph theoretical models of intelligence using structural MRI (van den Heuvel et al, 2010; Li et al, 2009) found that higher I.Q. is negatively correlated with path length and path length is inversely proportional to network efficiency. All three types of connectivity, that is, structural connectivity, functional connectivity and effective connectivity demonstrate a positive correlation between I.Q. and the efficiency of information processing in networks of the brain. Long distance information flow and local phase reset are part of the underlying dynamics in which neural resources are quickly identified and allocated in local functional clusters or hubs embedded in a small-world network with high speed homeostatic plasticity to maintain function even when there is loss of neurons (high resiliency).

Methods

Subjects

A total population of 1,015 rural and urban children ranging in age from 2 months to 17.54 years of age were recruited as part of a Department of Agricultural study of the relationship between nutrition and brain development and this is why no adults beyond the age of 17.54 were included in this study (Thatcher et al, 1983; 1987; 2003). The study was approved by a University of Maryland Institutional Review Board (IRB) and informed consent was obtained from the parents of all the subjects in this study. All methods were performed in accordance with the relevant guidelines and regulations. Two data acquisition centers were established, one at the rural University of Maryland Eastern Shore campus and one at the urban campus of the University of Maryland School of Medicine in Baltimore, Maryland. Identical data acquisition systems were built and calibrated, a staff was trained using uniform procedures and a clinical and psychometric protocol were utilized in the recruitment of subjects.

An additional group of adult peak performing and successful business leaders (N = 20) were recruited from the Arizona State University Department of Business ranging in age from 25 years to 45 years of age and also peak performing military officers at West Point (N = 25) age 35 – 40 were recruited and included in this study as part of the hi-IQ or peak performing group.

Inclusion/Exclusion Criteria

From the total of 1,015 subjects, 371 subjects ranging in age from 5 years to 17.58 years were selected. a neurological history questionnaire given to the child's parents and/or filled out by each subject, 2- psychometric evaluation of I.Q., and/or school achievement, 3- for children the teacher 9 and class room performance as determined by school grades and teacher reports and presence of environmental toxins such as lead or cadmium. A Neurological questionnaire was obtained from all of the adult subjects >18 years of age and those in which information was available about a history of problems as an adult were excluded. The inclusion criteria were: 1- no history of neurological disorders such as epilepsy, head injuries and reported normal development and successful school performance, 2- A Full Scale I.Q. > 70; 3- WRAT School Achievement Scores > 89 on at least two subtests (i.e., reading, spelling, arithmetic) or demonstrated success in these subjects and 4- A grade point average of 'C' or better in the major academic classes (e.g., English, mathematics, science, social studies and history).

Demographic Characteristics

The subjects were made up of 58.9% males, 41.1% females, 71.4% Caucasian, 24.2% African American and 3.2% oriental. Socioeconomic status (SES) was measured by the Hollingshead four factor scale. Time of day was randomized and counter-balanced with half the subjects tested in the morning and half the subjects tested in the afternoon. Testers were blind as to what the subject's I.Q. or WRAT or other inclusion criteria at the time of assignment to morning or afternoon test times. All subjects were given an eight-item "laterality" test consisting of three tasks to determine eye dominance, two tasks to determine foot dominance, and three tasks to determine hand dominance. Scores ranged from – 8 (representing strong sinistral preference or left handedness), to +8 (representing strong dextral preference or right handedness). Dextral dominant children were defined as having a laterality score of ≥ 2 and sinistral dominant children were defined as having a laterality score of ≤ -2. Only approximately 9% of the subjects had laterality scores ≤ 2 and 87% of the subjects had laterality scores ≥ 2 and thus the majority of subjects in this study were right side dominant.

As shown in Table I, age was not a confounding variable because there were no statistically significant differences in age between different I.Q. groups (low I.Q. vs hi I.Q. t = 1.949, df = 1/148, P = 0.06; low I.Q. vs middle I.Q, t = 1.787, df = 1/290, P = 0.076; hi I.Q, vs middle I.Q. t = 1.821, df = 1/298, P = 0.073). Gender was 55.6% male and 44.4% female and there were no significant differences in gender between the different I.Q. groups (t ranged from 0.059 to 0.295, P values ranged from 0.77 to 0.95). There was a significant difference in the socioeconomic status of the parents of the high I.Q. group vs the low I.Q. group (t = 5.65, P < .05) but not between the middle I.Q. group and the other two groups. The full scale I.Q. and age means, ranges and standard deviations of the subjects are shown in Table I.

Table I

Group sample sizes and age and I.Q. Descriptive Statistics

IQ Groups	N	Mean age	SD age	Age range	Mean full IQ	SD full IQ	Full IQ Range
Low IQ	71	11.31	3.08	5.02 - 17.18	82.65	6.12	70 - 90
Middle IQ	221	10.46	3.26	5.00 - 17.54	105.48	7.54	91 - 119
High IQ	79	9.50	2.85	5.14 - 15.80	128.52	7.68	120 - 154

The three I.Q. groups were selected solely based on the range of the full-scale I.Q. scores as shown in the column to the right in Table I.

Neuropsychological Measures

Neuropsychological and school achievement tests were administered on the same day that the EEG was recorded. The order of EEG and neuropsychological testing was randomized and counter-balanced so that EEG was measured before neuropsychological tests in one half the subjects and neuropsychological tests were administered before the EEG in the other half the subjects.. The Wechler Intelligence Scale for Children revised (WISC-R) was administered for individuals between 5 years of age and 16 years and the Weschler Adult Intelligence Scale revised (WAIS-R) was administered to subjects older than 16 years. The neuropsychological sub-tests for estimating full scale I.Q. were the same for the WISC-R and the WAIS and included information, mathematics, vocabulary, block design, digit span, picture completion, coding and mazes.

EEG Recording

Power spectral analyses were performed on 58 seconds to 2 minute 17 second segments of EEG recorded during resting eyes closed condition. The EEG was recorded from 19 scalp locations based on the International 10/20 system of electrode placement, using linked ears as a reference in the resting eyes closed condition. Subjects were instructed to close their eyes, relax and to try not to move their eyes during the recording. The trained EEG technicians were blind as to the subject's I.Q. or WRAT and other inclusion criteria at the time of the EEG recording. The EEG was continually monitored during acquisition and if any electrodes were bad then the recording was paused and the electrode replaced. All subjects provided 19 channels of EEG plus a bipolar eye monitor channel. Eye movement electrodes were applied to monitor artifact and all EEG records were visually inspected and manually edited to remove any visible artifact. Each EEG record was plotted and visually examined and split-half reliability and test re-test reliability measures of the artifact free data were computed using the Neuroguide software program (NeuroGuide, v2.8.9). Split-half reliability tests were conducted on the edited artifact free EEG segments and only records with > 90% reliability were entered into the spectral analyses. The amplifiers were designed and built by engineers at the NYU School of Medicine and amplifier bandwidths were nominally 1.0 to 30 Hz, the outputs being 3 db down at these frequencies. The EEG was digitized at 100 Hz and up-sampled to 128 Hz and then spectral analyzed using complex demodulation.[23-25]

Hilbert Transform of Network Connectivity Measures

After recording the EEG and artifact deleted then LORETA was computed from the center voxels of 88 Brodmann areas using the Hilbert transform to compute the cross-spectrum and coherence, phase differences and the phase slope index (xx) in 8 different frequency bands (delta, theta, alpha1, alpha2, beta1, beta2, beta3, hi-beta). The phase slope index is a measure of the magnitude and direction of information flow. For details see Thatcher, et al, 2016. Absolute or relative power were not used in these computations and instead only network connectivity analyses were conducted.

Selection of Variables for Discriminant Analyses Between High and Low I.Q. groups.

The subjects were separated into a high full scale IQ group (I.Q. ≥120) and a low full scale I.Q. group (≤ 90 I.Q.) for purposes of the full scale I.Q. analyses In order to assess possible confounding by age, t-tests were conducted of differences between age in different I.Q. groupings (low I.Q. vs. middle I.Q., low I.Q. vs. high I.Q. and middle I.Q. vs. high I.Q.). The results of the analysis showed that there were no statistically significant differences in age between any of the I.Q. groupings.

Functional Networks

Table II shows the twelve networks and the Brodmann areas that comprise each network used to compute discriminant functions. The smallest number of Brodmann areas was in the memory network (4) and the largest number were in the salience network (13).

Table II – Twelve Networks and Brodmann Areas that Comprise the Networks

Networks	Brodman Areas
Addiction	13, 24, 25, 32, 34, 44, 45, 46, 47
Anxiety	4, 6, 7, 10, 13, 21, Amygdala
Attention-Dorsal	6, 7, 8, 9, 19, 39 ,40
Attention-Ventral	10, 11, 19, 21, 37, 44, 45
Default Mode	2, 7, 10, 11, 19, 29, 30, 31, 35, 39, 40
Executive Function	7, 8, 9, 10, 11, 19, 22, 37, 40, 46
Language	22, 39, 40, 41, 42, 44, 45
Memory	28, 34, 35, 36
Mirror Neuron	1, 5, 6, 13, 27, 40, 44, 45, 46
Mood	10, 11, 13, 23, 24, 32, 33, 44, 45, 47
Pain	1, 2, 3, 4, 5, 13, 24, 32, 33
Salience	8, 9, 10, 13, 22, 23, 24, 25, 29, 30, 31, 32, 33

Results

Discriminant Analysis of High I.Q. vs Low I.Q. groups

Table IIIis a summary of the number of subjects and classification accuracy of the discriminant analyses showing a discriminant classification accuracy of 99%. The sensitivity = 97.3% and specificity = 100%. The positive predicted value (PPV) = 100% and negative predicted value (NPV) = 97.5%. An independent cross-validation test was for the intermediate I.Q. group (90 < and < 120). As shown in Table II, the independent cross-validation is where the intermediate I.Q. group was approximately evenly classified in the two extreme high vs low I.Q. groups which is expected if there is an approximate linear relationship between I.Q. and the phase slope index estimate of information flow.

Table III

Discrimintant Analysis and Jackknife Replication

Classification Accuracy = 99%

IQ GROUP	N	IQ <= 90	IQ >= 120
Full IQ <= 90	n = 71	71 (100%)	0 (0%)
Full IQ >= 120	n = 79	2 (3%)	77 (97%)
90 < Full IQ < 120	n = 221	100 (45%)	121 (55%)

Jackknifed Classification Accuracy = 94%

IQ GROUP	N	IQ <= 90	IQ >= 120
Full IQ <= 90	n = 71	66 (93%)	5 (7%)
Full IQ >= 120	n = 79	4 (3%)	75 (95%)

In addition, as shown in Table III a leave-one-out (jackknife) cross-validation was conducted between the high and low I.Q. groups. The jackknife cross-validation yielded an overall classification accuracy = 94%, sensitivity = 94.3% and specificity = 93.8%. The positive predicted value (PPV) = 93.0% and negative predicted value (NPV) = 94.9%.

Figure 1 shows the distribution of the discriminant scores. The left is a scatter plot of discriminant scores of the high I.Q. and low I.Q. groups. Right is the distribution of discriminant scores for the high and low I.Q. groups as well as the intermediate I.Q. group. The intermediate subject's distribution was midway between the high and low groups and serves as a cross-validation test. Also, the distribution supports a linear relationship between the magnitude of information flow and intelligence.

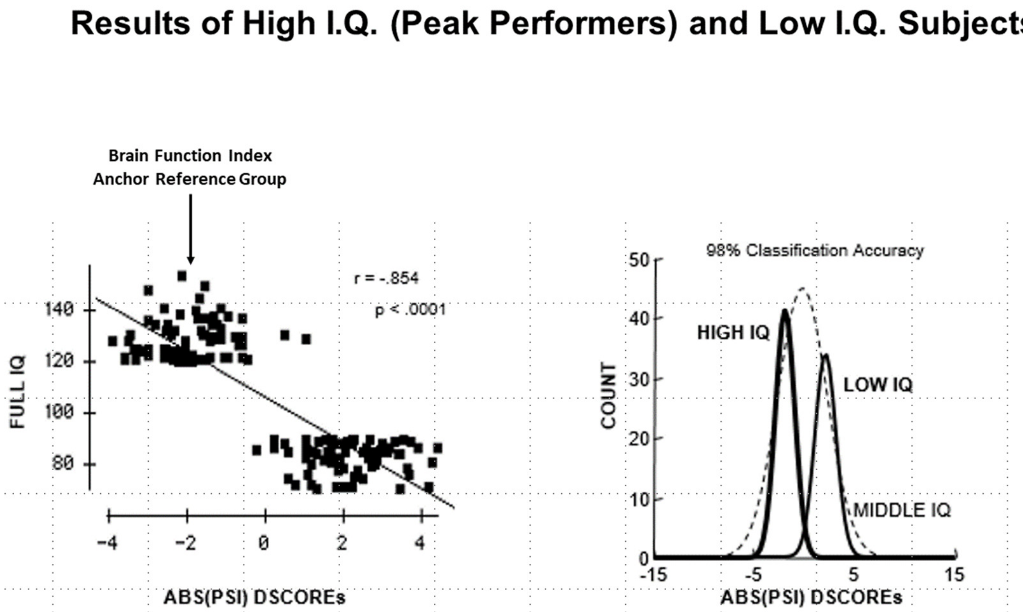


Fig. 1 – Results of discriminant analyses. Left is a scatter plot of discriminant scores of the peak performer high I.Q. and low I.Q. groups. Right is the distribution of discriminant scores for the high and low I.Q. groups as well as the intermediate I.Q. group. The intermediate subject's distribution was midway between the high and low groups and serves as a cross-validation test. Also, the distribution supports a linear relationship between the discriminant scores and intelligence.

Discriminant Scores and the Construction of a Brain Optimization Index (BOI)

The finding of a linear relationship between discriminant scores (DS) and intelligence justifies using the peak performing or Hi IQ group as an optimal reference by which discriminant scores from individuals can be used to estimate the 'distance' the individual is from the optimal peak performance group. The method of computing a Brain Optimization Index was to compute the mean and standard deviation of the Hi IQ peak performers discriminant scores (DS) for each of the 12 networks and then compute a Z score as a distance metric from the mean of the optimal group for a given subject for each of the 12 networks. The Z_{DS} score = (mean of Hi IQ DS – DS of subject/St. Dev. Of Hi IQ DS). The 12 functional networks are based on fMRI and PET scan studies in thousands of subjects which are reviewed in the "Handbook of QEEG and EEG Biofeedback" (Thatcher, 2012; 2016). The 12 functional networks are: **Addiction, Anxiety, Attention Dorsal, Attention Ventral, Default Mode, Executive, Language, Memory, Mirror Neurons, Mood, Pain, Salience.**

Examples of Discriminant Analyses using Peak Performers (High I.Q.) Subjects as the Reference to Compute Discriminant Scores (DS) and then Z Scores where Z = Mean DS Hi I.Q. – (Subject's DS/St. Dev. Hi I.Q.)

Memory Network

Discriminant Analyses: LORETA NETWORK - MEMORY
using COH_absPHASE_absPSI

LOW IQ (n=70) vs HIGH IQ (n=79) with MIDDLE IQ (n=227)

Total Vars = 121

STEP WISE BACKWARDs with TOTAL SURVIVED VARs = 60

Classification matrix (cases in row categories classified into columns)

	LOW IQ	HIGH IQ	%correct
LOW IQ	69	1	99
HIGH IQ	2	77	97
Total	71	78	98

MIDDLE IQ	107	120

Jackknifed classification matrix

	LOW IQ	HIGH IQ	%correct
LOW IQ	61	9	87
HIGH IQ	5	74	94
Total	66	83	91

Anxiety Network

Discriminant Analyses: LORETA NETWORK - ANXIETY
using COH_absPHASE_absPSI

LOW IQ (n=70) vs HIGH IQ (n=79) with MIDDLE IQ (n=227)

Total Vars = 112

STEP WISE BACKWARDs with TOTAL SURVIVED VARs = 43

Classification matrix (cases in row categories classified into columns)

	LOW IQ	HIGH IQ	%correct
LOW IQ	67	3	96
HIGH IQ	3	76	96
Total	70	79	96

MIDDLE IQ	101	126

Jackknifed classification matrix

	LOW IQ	HIGH IQ	%correct
LOW IQ	62	8	89
HIGH IQ	12	67	85
Total	74	75	87

Executive Network

Discriminant Analyses: LORETA NETWORK - EXECUTIVE
using COH_absPHASE_absPSI

LOW IQ (n=70) vs HIGH IQ (n=79) with MIDDLE IQ (n=227)

Total Vars = 68

STEP WISE BACKWARDs with TOTAL SURVIVED VARs = 36

Classification matrix (cases in row categories classified into columns)

	LOW IQ	HIGH IQ	%correct
LOW IQ	67	3	96
HIGH IQ	6	73	92
Total	73	76	94

MIDDLE IQ	113	114

Jackknifed classification matrix

	LOW IQ	HIGH IQ	%correct
LOW IQ	62	8	89
HIGH IQ	9	70	89
Total	71	78	89

The final computation for the Brain Optimization Index (BOI) is to compute the average Z score and display the average Z score for all 12 networks in a dial. In this way re-tests can be compared in a single simple display as shown in figure fig. 2

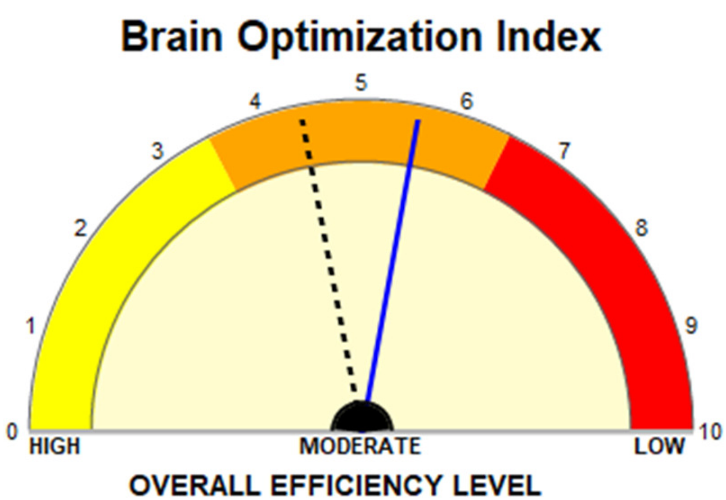


Fig. 2 – Example of the Brain Optimization Index (BOI) as the average Z score distance of 12 different functional networks for a given subject. For example, the 1st EEG recoding can be made shortly after a concussion.

Figure 3 is an example of repeated and sequential EEG recordings following a mild TBI. A discriminant score distance from the peak performing or optimal group for each of the 12 networks were first computed and then the mean Z score distance was computed and scaled from 0 to 10 on the BOI dial in figures 1 and 2.

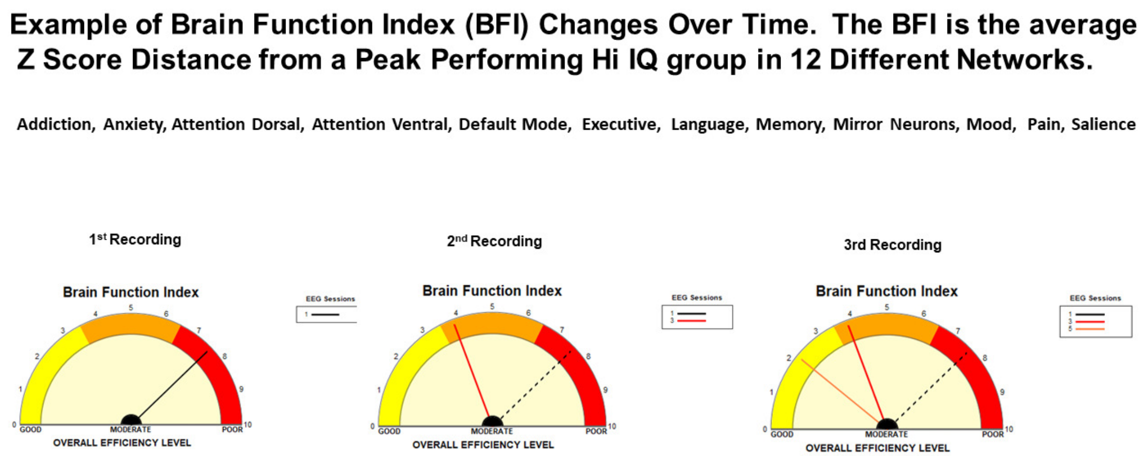


Fig. 3- A sequence of EEG recordings from the time of injury or treatment are displayed in the BOI dial. Each line is the average distance from mean of the peak performing Hi IQ reference group for each of he 12 functional networks.

A summary of the Brain Optimization Index construction is illustrated in figure 4.

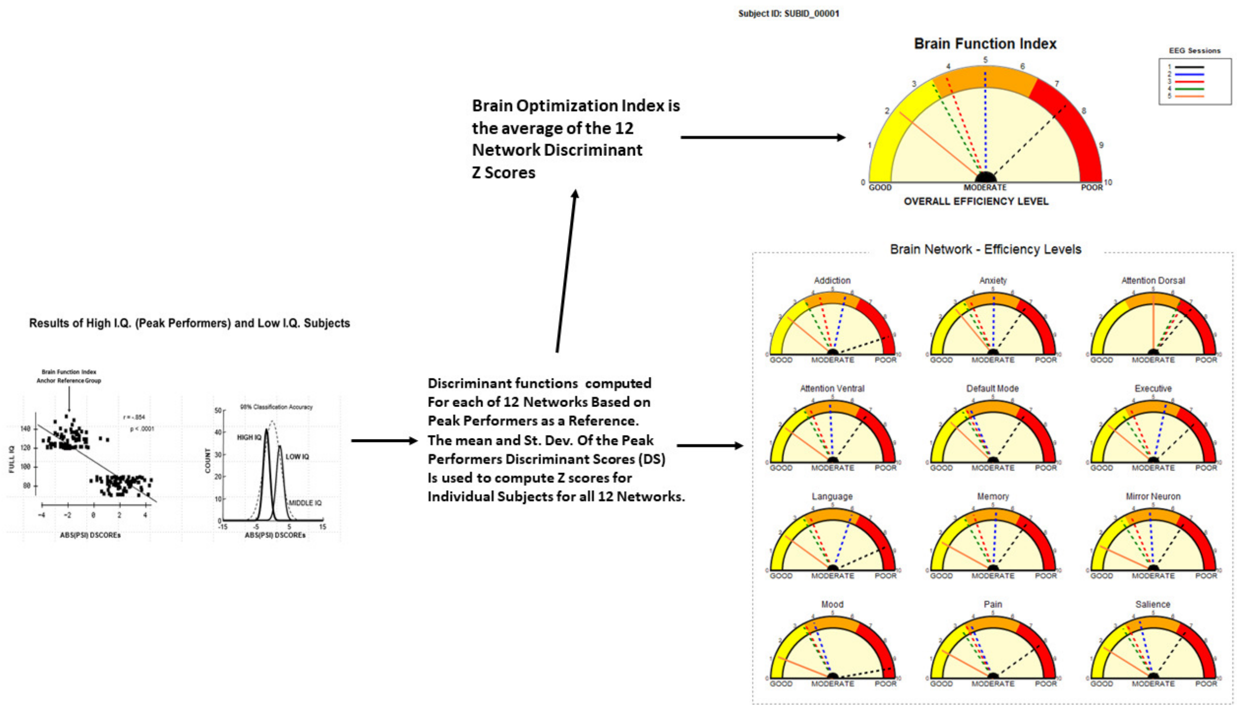


Fig. 4 – Illustration of the construction of the Brain Optimization Index (BOI). Left are the results of rhe discriminant analysis that computes the distance between Hilbert transform of EEG from the center voxels of a given functional network. The metrics were network metrics such as LORETA coherence, LORETA phase difference and LORETA phase slope index that were entered into the discriminant function. A mean and standard deviation of the Hi IQ group was computed for each of 12 functional networks. Individuals are compared to the reference peak performing group by computing the Z score distance of the individual's discriminant scores from the optimal reference group.

Here is a url to a You Tube Video that describes the Brain Optimization Index (BOI):

https://youtu.be/AY176R4p4F8

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