

INTERNATIONAL BRAIN RESEARCH FOUNDATION

“ BRINGING BRAIN SCIENCE TO LIFE “  
Philip De Fina, Ph.D.



**Functional Imaging Neuromarkers Guide Non-Invasive  
Neuromodulation in Brain Injury:  
An Integrated Multimodal Approach to Assessment &  
Rehabilitation**

Philip A. DeFina, Ph.D.

International Brain Research Foundation, Inc.

[www.ibrfinc.org](http://www.ibrfinc.org)

### Typical “Standard” Model for Assessment/Treatment of Chronic Stage TBI

- Assorted NP test measures
- Rating scales
- Symptom monitoring
- Standard MRI, CT, EEG (limited correlation with functional recovery)
- “sit and wait”
  
- Poor predictor of outcomes
- No subtyping
- Does not translate to (guide) treatment protocol
- Administered beyond critical time window

## Neuropsychological Profile

- Neurocognitive Impairments following mTBI
  - Verbal memory
  - Verbal fluency
  - Working memory
  - Information processing (speed and ease)
  - Attention (sustained, selective, distributed, divided)
  - Memory encoding and registration of new information
  - Visual-motor processing speed
  - Concentration
  - Distractibility
- \*Often times Neuropsychological measures are not sensitive in detecting mTBI\*
- \*Cognitive sequelae are usually time limited (most disappear within 1 month post injury)\*

### Standard Model for Assessment/Treatment of Chronic Stage TBI

- Assorted NP test measures
- Rating scales
- Symptom monitoring
- Standard MRI, CT, EEG (limited correlation with functional recovery)
- “sit and wait”
  
- Poor predictor of outcomes
- No subtyping
- Does not translate to (guide) treatment protocol
- Administered beyond critical time window

### Standard Approaches to Assess BI

Method	Assess	Result
CT Scan	Potential Structural Damage	Usually negative
EEG	Atypical brain wave changes Paroxysmal Discharges	Usually negative
MRI and DTI	Potential structural Damage Damage to the white matter tracts	Usually negative
Neurological Exam	Focal neurological signs Pathognomonic BI	Usually negative
Neuropsychological Exam	Perceptual and Cognitive Sequelae Fronto-Temporal	May show signs of dysexecutive functioning, attentional deficits and working memory (usually resolved and efficiency, resolved in 1 month)
Psychiatric Exam	Emotional or behavioral changes	Increased anxiety, Increased depression, low frustration tolerance, increased behavioral disinhibition, PTSD symptoms (usually delayed onset)

## IBRF Program Goals:

- 1) Identify functional neuromarkers to establish TBI subtypes.
- 2) Comprehensively evaluate the unique patterns associated with individual TBI subtypes.
- 3) Develop integrated, multi-modal assessment that directly guides multi-modal treatment.
- 4) Predict treatment outcomes based on TBI subtypes.

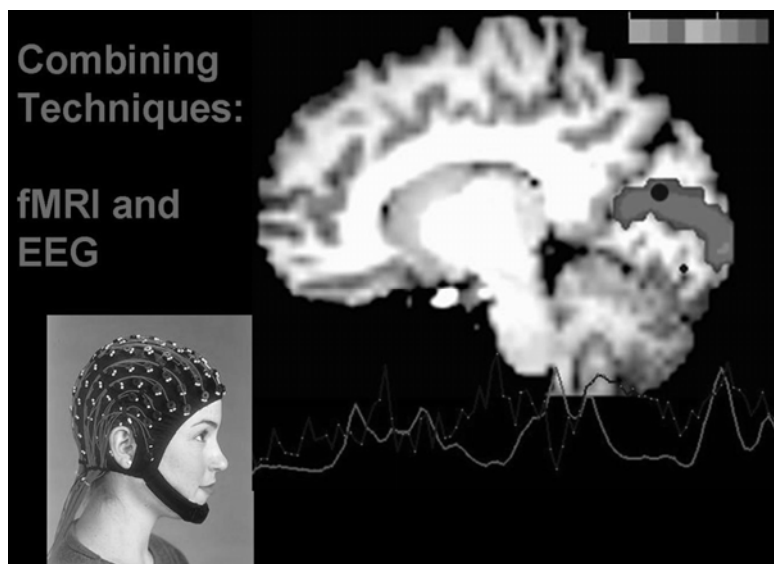
## NeuroImaging to Determine Level of Arousal

1. IF Functional MRI Scan shows:  
Brainstem activity.....but no upper brain activity:  
Vegetative State (NOT brain dead or locked-in syndrome)
2. IF Functional MRI Scan shows:  
Upper Brain activity...but no brainstem activity:  
Locked-in Syndrome (NOT brain dead or vegetative)

### IBRF Brain Injury Model Using Neuromarkers

- **Functional neuromarkers are the electrical, chemical and metabolic signatures that underlie brain injury.**
- Neuromarkers define the physiological trajectory of dysfunction while simultaneously tracking the preservation of function in brain injury. “Integrity-Deficit Matrix”

## Quantitative EEG (qEEG)



## Quantitative EEG (qEEG)

- A metric approach used to assess CNS integrity by measuring the amplitude and frequency of brain wave patterns throughout the brain.
- Connectivity is measured through a **Coherence Model** and *speed and efficiency* through **Phase Lag**. Source localization is accomplished by mathematical algorithms.
- (s/e-LORETA).

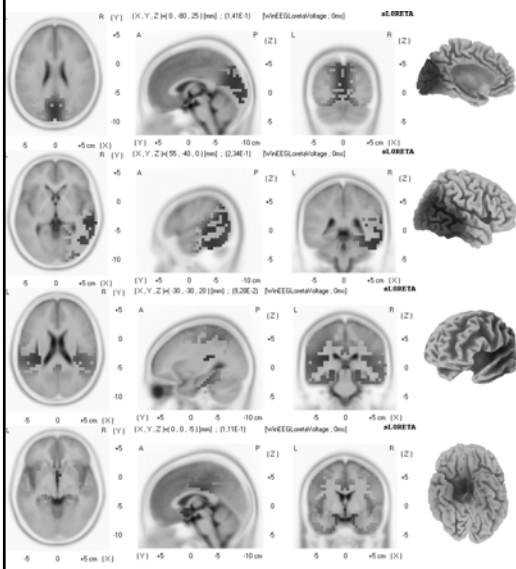
### Unique Properties of EEG as Electrophysiological Neuromarkers

- High temporal resolution (milliseconds).
- Measures electrical communication between neurons
- Measures connectivity and time-locking of connectivity between brain regions
- Allows for neural source localization of electrical signal generators

## Electrophysiological (qEEG) Neuromarkers seen in Acute mTBI

- reduced mean alpha frequency
- reduced alpha power (automaticity)
- reduced fast waves (processing)
- Hyper or hypo-coherence (connectivity)
- Reduced P300 amplitude (info processing)
- Increased P300 latency (attention)
- Cumulative effect:
  - localized dysfunction with diffuse ramifications
  - diminished information processing
  - PTSD symptoms

## Areas that are disturbed in mild TBI patients



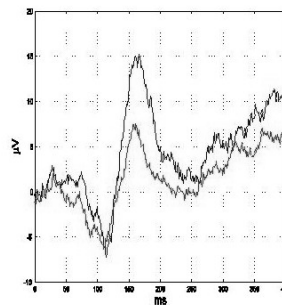
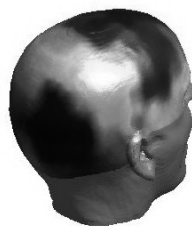
- sLORETA images of ERPs ICA components are presented.
- Each image corresponds to a endophenotype associated with a specific psychological operation
- Note that these are functional disturbances because MRI scans do not show damage in these areas.
- *Moncvol Rehabilitation Center, St.Olav's Hospital, Norwegian University of Science and Technology*

## Event Related Potentials

ERPs are electrophysiological signals that represent neural activity in response to stimulation of the auditory, visual and somato-sensory system. This neural activity is associated with perceptual processes.

More advanced protocols using P-300 and Contingent Negative Variation (CNV) paradigms measuring centro-frontal functions can assess electrophysiological aspects of cognition.

### EP, ERP (Processing Speed)

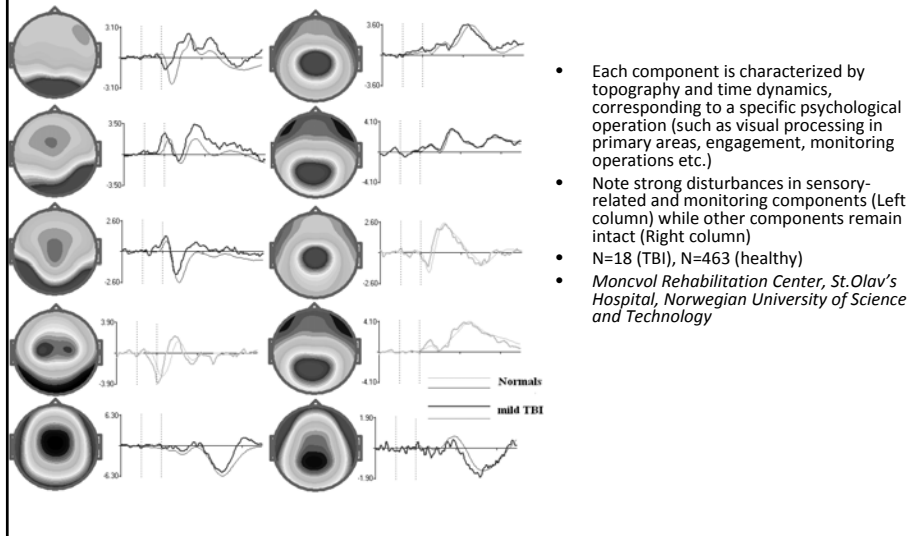


Measures	Controls	Concussed	F	P
<u>P3a</u>				
Amplitude	4.50 SD 2.32	2.94 SD 1.67	5.67	< .05
Latency	359.6 SD 35.5	387.2 SD 44.9	4.43	< .05
<u>P3b</u>				
Amplitude	5.25 SD 2.11	4.18 SD 1.99	2.57	> .05
Latency	362.9 SD 28.9	397.6 SD 57.0	5.58	< .05

**Table 2.** Between-group difference on the mean P3a / P3b components amplitude ( $\mu$ V) and latency (ms) recorded at Fz and Pz, respectively.

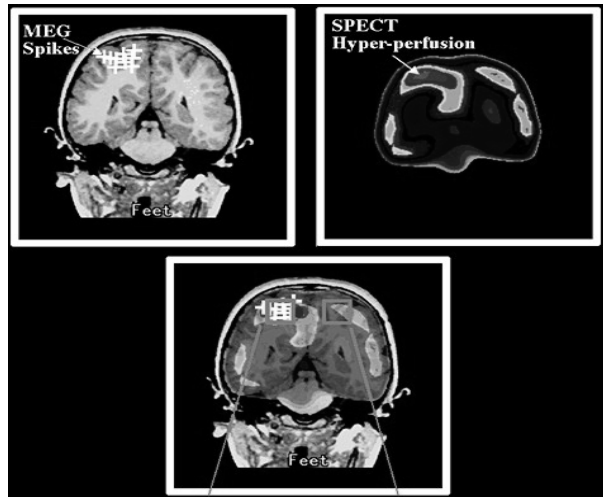


### Independent ERPs components in mild TBI patients in comparison to healthy subjects



### Magnetic Encephalography (MEG) Neuromarkers

- Thalamo-cortical dysrhythmia (between DMN and DLPFC)

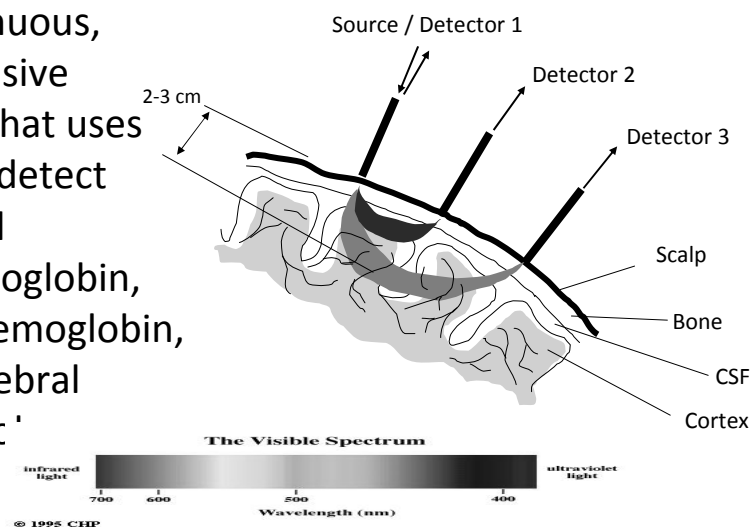


## NIRS

Near Infra-Red Spectroscopy is a method that directly assesses brain metabolic functioning through oxygen consumption with non-invasive technology.

### What is Near Infrared Spectroscopy?

A continuous, noninvasive device that uses light to detect cerebral oxyhemoglobin, deoxyhemoglobin, and cerebral blood volume



## Bedside Evaluations



## Portable fNIRS



Hoshi et al., 2001

Measurement of Brain Function with Clinical Tests  
Without Confinement



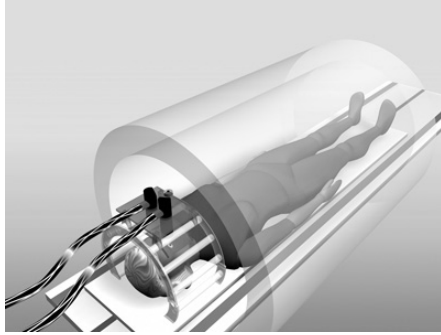
## fNIRS of Verbal Working Memory

### Objectives

- fNIRS can detect frontal lobe activation during the VWM tasks
- There is an increase in oxyHb in the TBI group compared to the HC group.



## fMRI Scanner

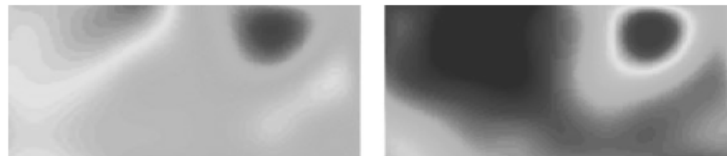


## fNIRS Scanner

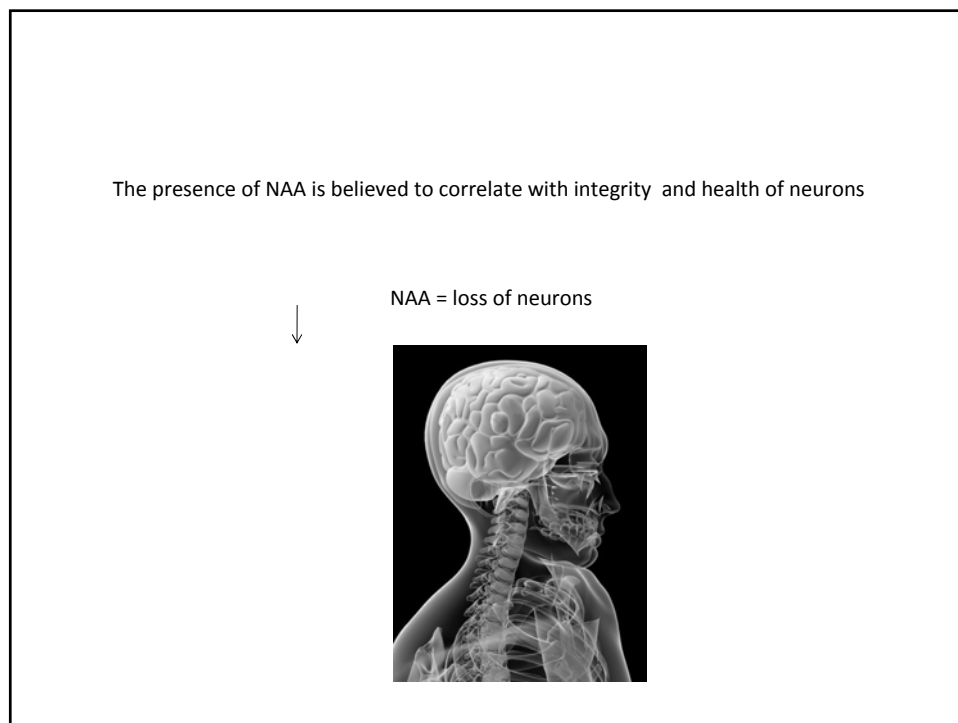
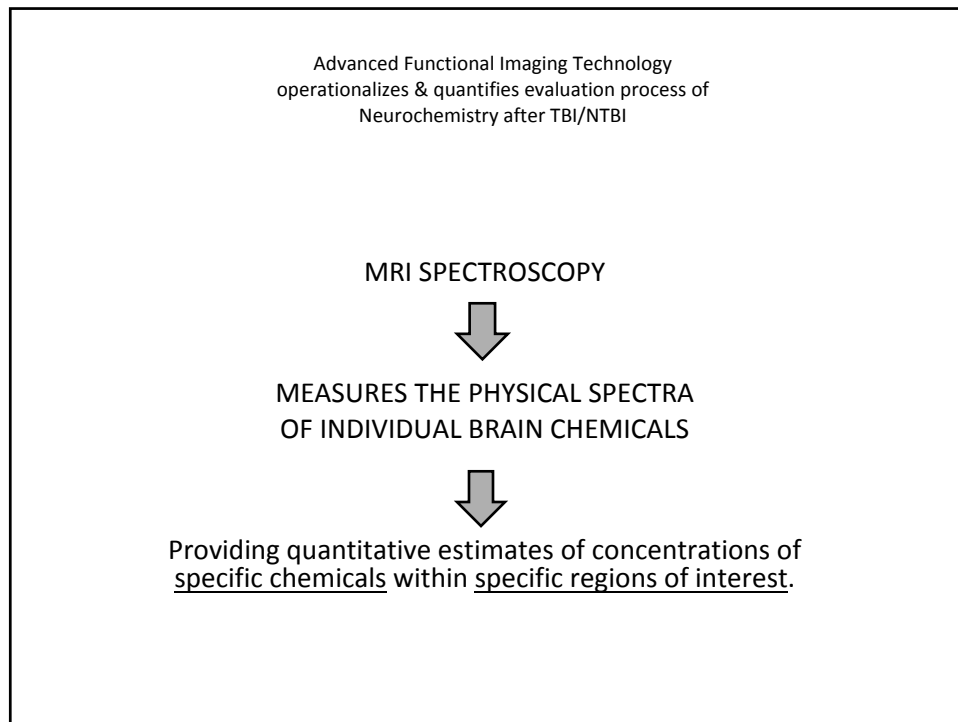


## Near-Infrared Spectroscopy (NIRS) Biomarkers

### Joint Time-Frequency Analysis (JTFA)



- Source detector matrix combined with spectral EEG
- maps hemodynamic and neural responses simultaneously (combined NIRS/EEG).
- measures oxy/de-oxy hb
- partials our increased bloodflow from increased O<sub>2</sub> consumption
- EP's give endogenous evoked responses to auditory or visual odd-ball stimulus
- adults: NIRS wavelength between 690 – 760 ms and 830 nm is optimal
- distance between emitters and detectors is 3cm



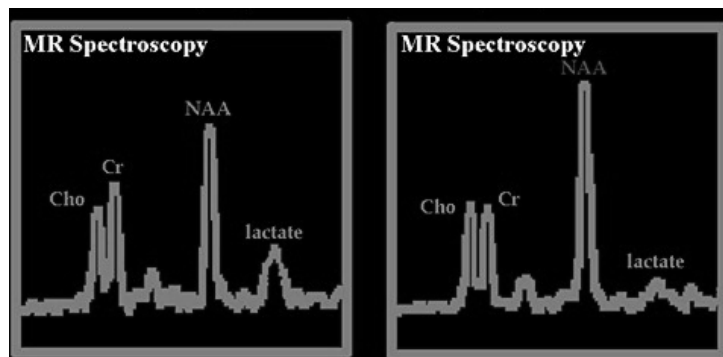
### IMPORTANT SPECTRAL INDICES

- Spectrum of creatine related to energy metabolism
- Spectrum of choline = marker of membrane metabolism
- Spectrum of NAA = marker of neuronal viability

Together with ratios of glutamate, glutamine and aspartate

### Magnetic Resonance Spectroscopy (MRS) Neuromarkers

- Single voxel localization specific to preselected ROI
- Measures metabolic concentrations of neurochemicals
- Predictive of recovery (subtyping)
- Guides pharmacological and Nutraceutical treatment regime.



## BIS Monitor = Consciousness

- An EEG algorithm has been developed to assess depth of sedation and recovery of consciousness from anesthesia in the OR.
- The BIS has been successfully applied to monitor Levels of consciousness and can be used to plot trajectories during **Emergence to Consciousness**.

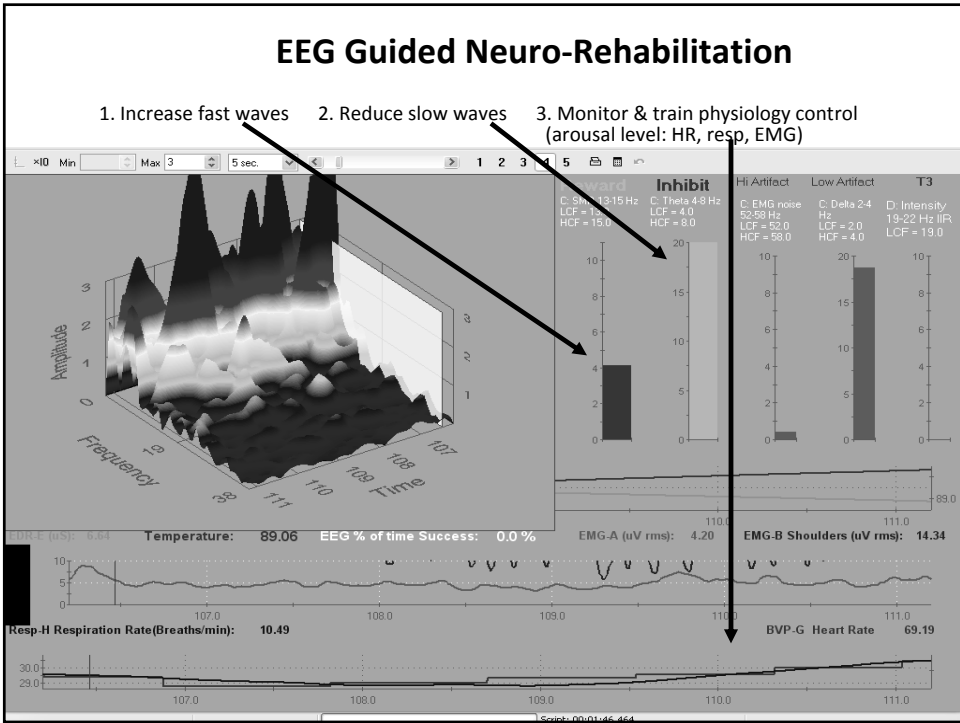
## Reprogramming The Brain

- Traumatic Brain Injury
- Anoxic Encephalopathy
- Diffuse Axonal Injury
- Stroke Syndromes



# INTEGRATED FUNCTIONAL NEUROMARKERS...

## HELP TARGET NON-INVASIVE NEUROMODULATION PROCEDURES



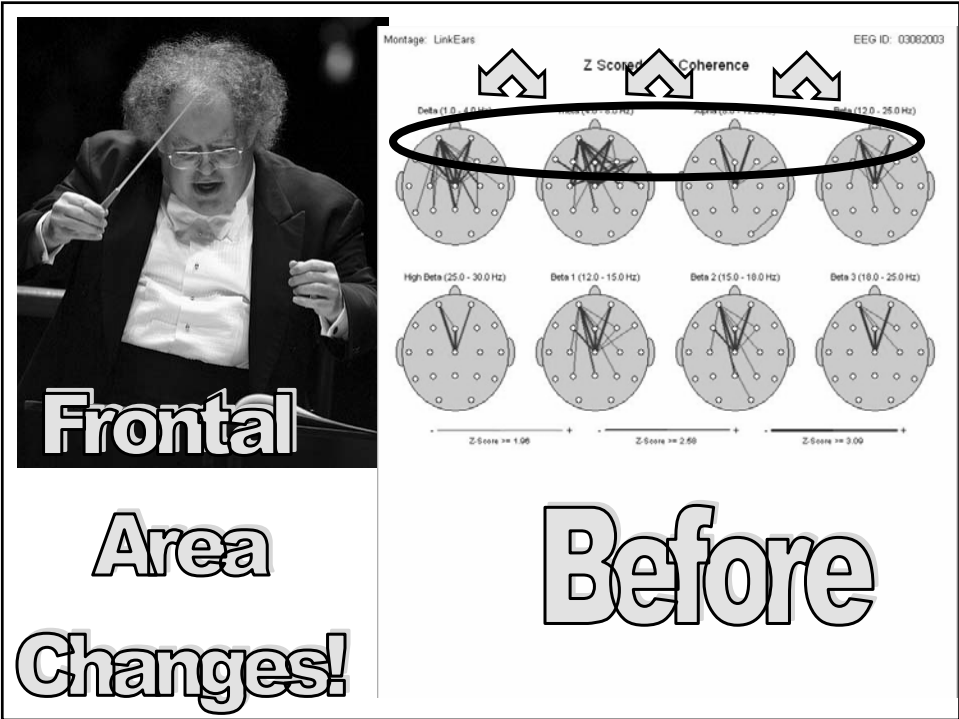
qEEG -MEG-ERP Directed  
Neuromodulation In mTBI

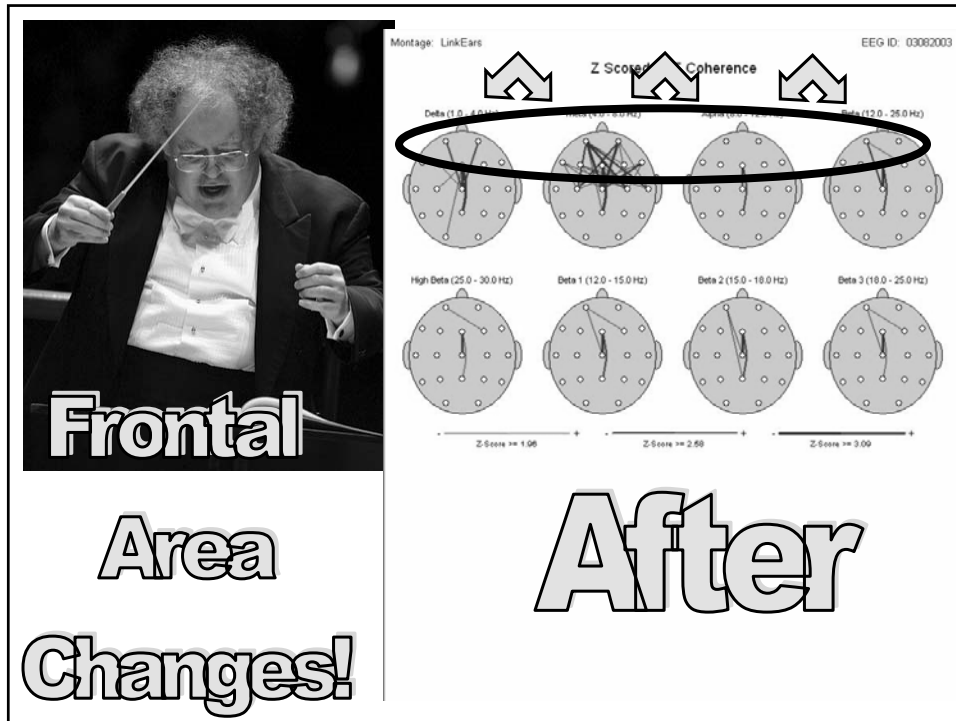
Neurofeedback/Brain Computer Interface

Cognitive enhancement software

Low level electrical stimulation

Transcranial Magnetic Stimulation



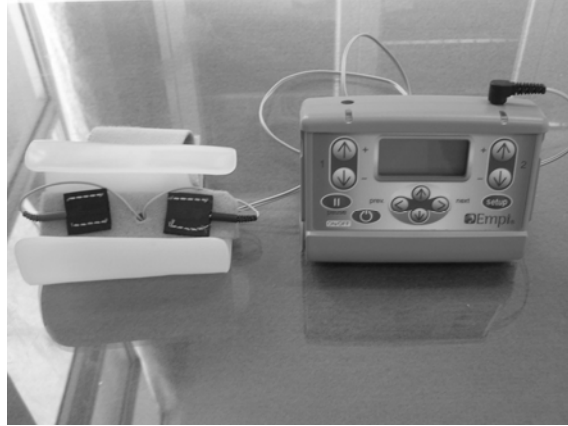


### Integrated Functional Mapping: The IBRF Approach

Combined neurologic assessment modalities: limitations of one modality are compensated for

Measure	Marker	Strengths	Associated Treatment
EEG, qEEG	electrophysiology	High temporal resolution (ms) Source localization of electrical generators in cortex	EEG brain-computer interface (BCI) training Guides DCS and TCMS
EP, ERP	electrophysiological	High temporal resolution (ms) Measure processing speed Measure intactness of sensory pathways	EEG BCI training Guides DCS and TCMS
MEG	Brain electromagnetism	High temporal resolution Subcortical structures	Guides DCS and TCMS
B.I.S. Monitor	Level of consciousness	Real-time measure of patient level of consciousness	Determine patient receptiveness to treatment
MRI w/ DTI	Structural anomalies Brain volume Brain connectivity	Guides medical and surgical interventions	Neurosurgery Pharmacotherapy
MRI Spectroscopy	Brain chemistry / metabolites	Provides chemical neuromarkers	Pharmacotherapy, nutraceuticals
PET-CT	Metabolic functions	Multiple metabolic neuromarkers	Pharmacotherapy, nutraceuticals
Near Infra-red Spectroscopy	O <sub>2</sub> concentrations/uptake	Non-invasive O <sub>2</sub> exchange method	Pharmacotherapy, nutraceuticals Median nerve stim

## 1990s – Pilot Studies of Right Median Nerve Stimulation

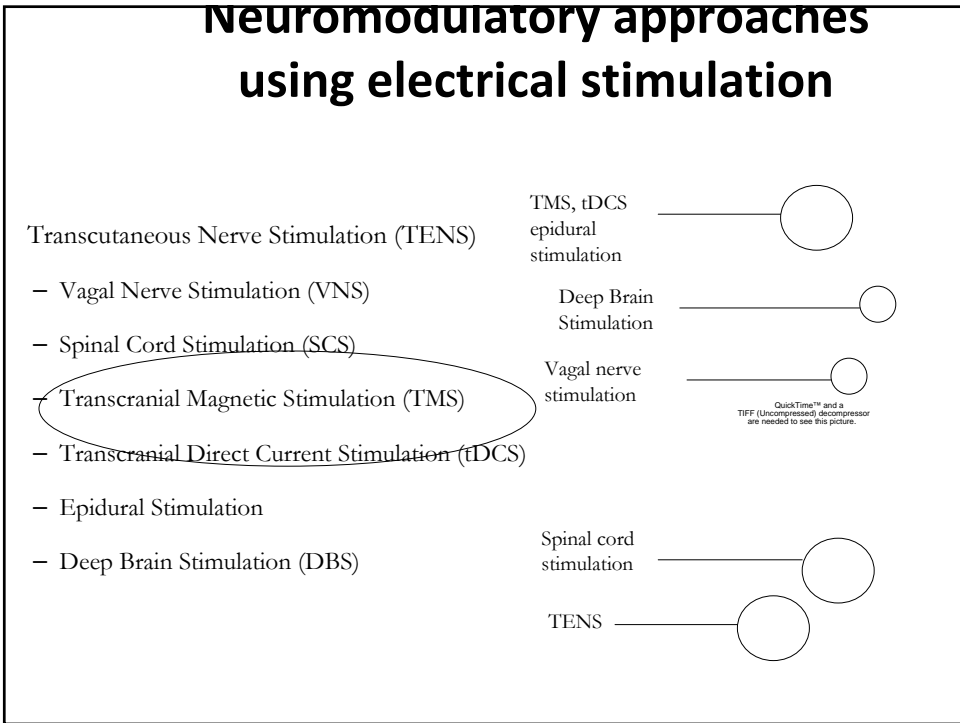


Right wrist portal to communicate with the  
injured brain

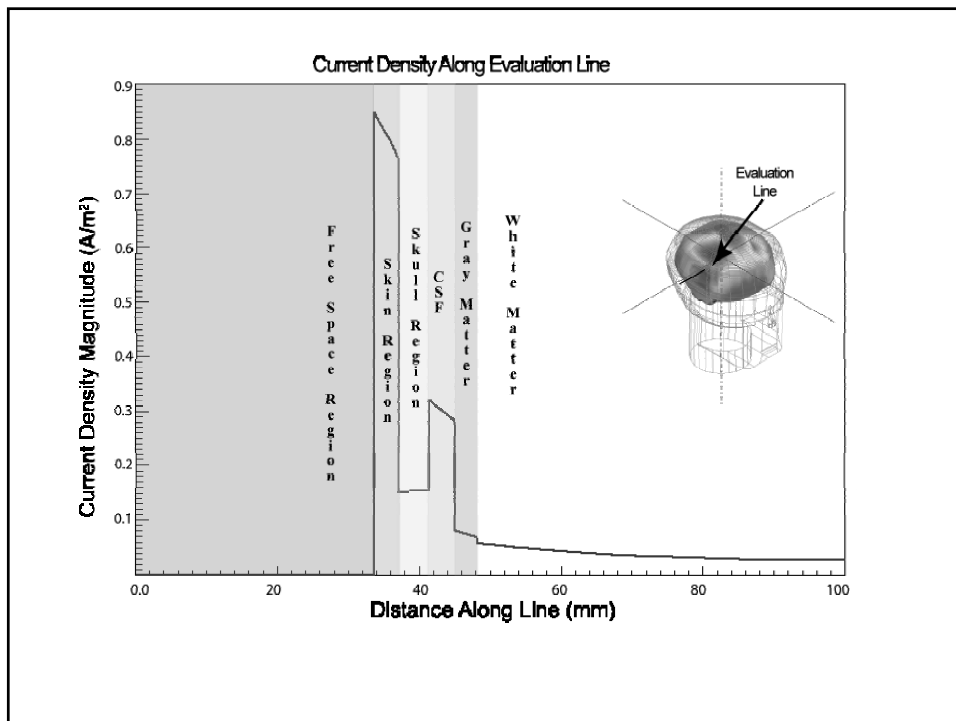
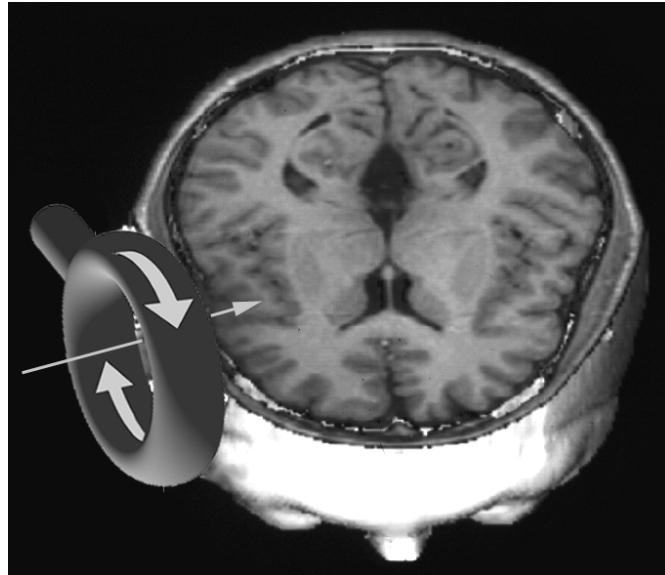
## RMNS EFFECTS

- Increased dopamine
- Increased Cerebral Blood Flow
- Result -- earlier (and better?) awakening from coma

**Neuromodulation**  
**Important Finding:**  
**CONSCIOUSNESS MAY ARISE FROM 40**  
**HZ THALAMOCORTICAL ACTIVATION**



## Transcranial Magnetic Stimulation



## What Exactly Happens In a Closed Head Injury?

- Excess Calcium Enters Cell Bodies
- Edema (swelling)
- Diffuse Axonal Injury (DAI, shearing & tearing)
- Destructive Enzymes
- Hematoma
- Hypoxia
- Cell Death

## Long Term Effects, Severe TBI Anatomy

- Corpus callosum area shown to have declined over a 3-year period in kids with severe TBI, whereas mild-mod. TBI kids showed increase (Levin et al, 2000).
- White matter degeneration, cerebral atrophy, enlarged ventricles (Bigler, 1997).
- More diffuse damage than localized damage, esp. affecting Frontal/Temporal lobes.
- Delayed cellular damage from neurotoxic cascade (Ca influx into cells, free radical damage, receptor-mediated damage, inflammation).

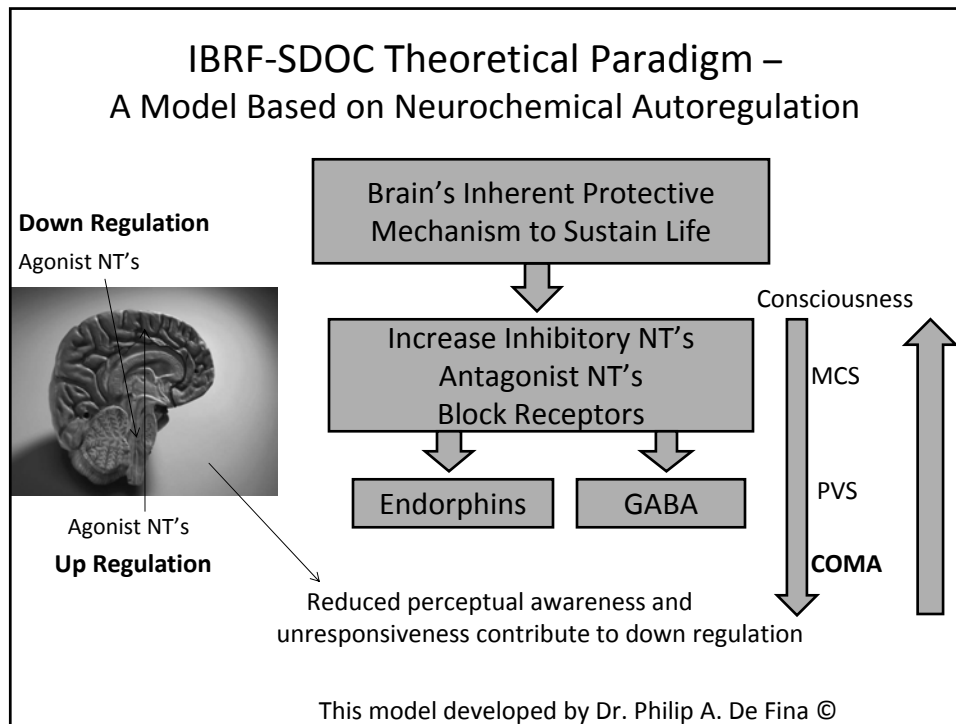
IBRF Model for Assessment/Treatment of Chronic  
Stage TBI

- Identification of Neuromarkers
- Subtyping Injury
- Predicting Recovery Timeline
- Direct relationship between assessment measures and treatment protocols
- Treatment of patient from intake through functional recovery

IBRF Brain Injury Model Using Neuromarkers

- **Functional neuromarkers are the electrical, chemical and metabolic signatures that underlie brain injury.**
- Neuromarkers define the physiological trajectory of dysfunction while simultaneously tracking the preservation of function in brain injury. “Integrity-Deficit Matrix”





## Complexity of Injuries

- Diffuse injuries may have specific focal or multi-focal symptom patterns

Whereas ...

- Focal injuries have diffuse symptom patterns (diaschisis)

Standard Approach

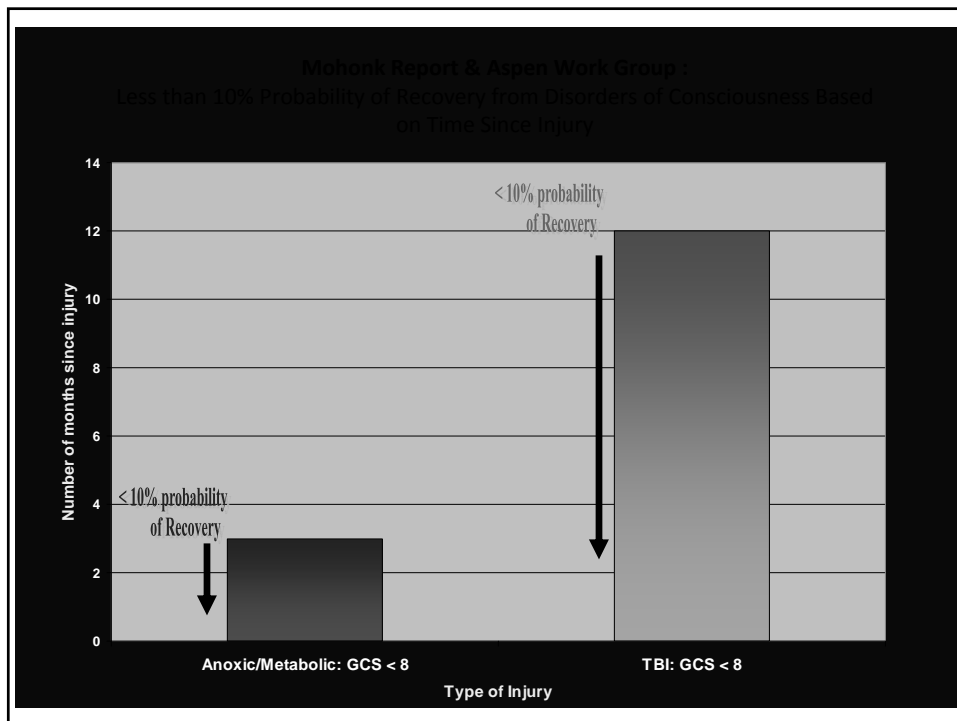
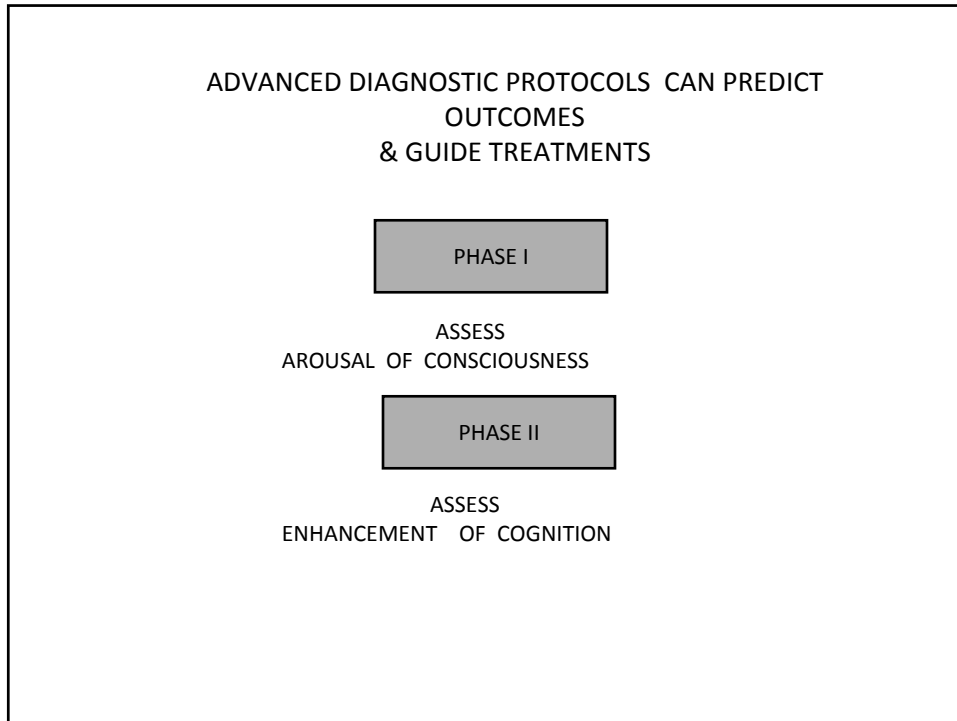
Vs.

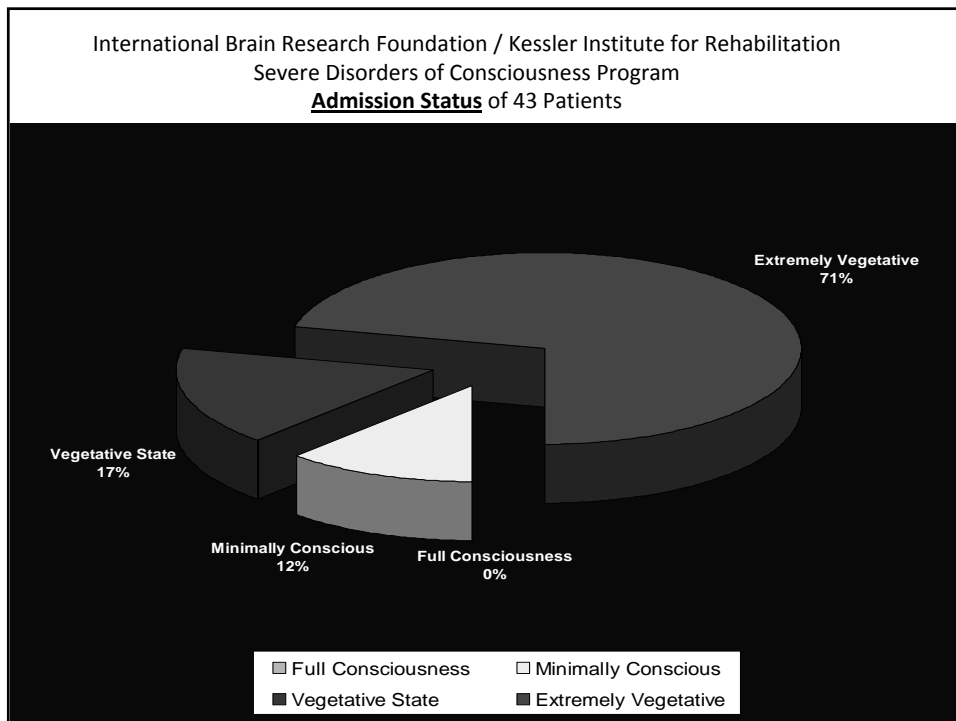
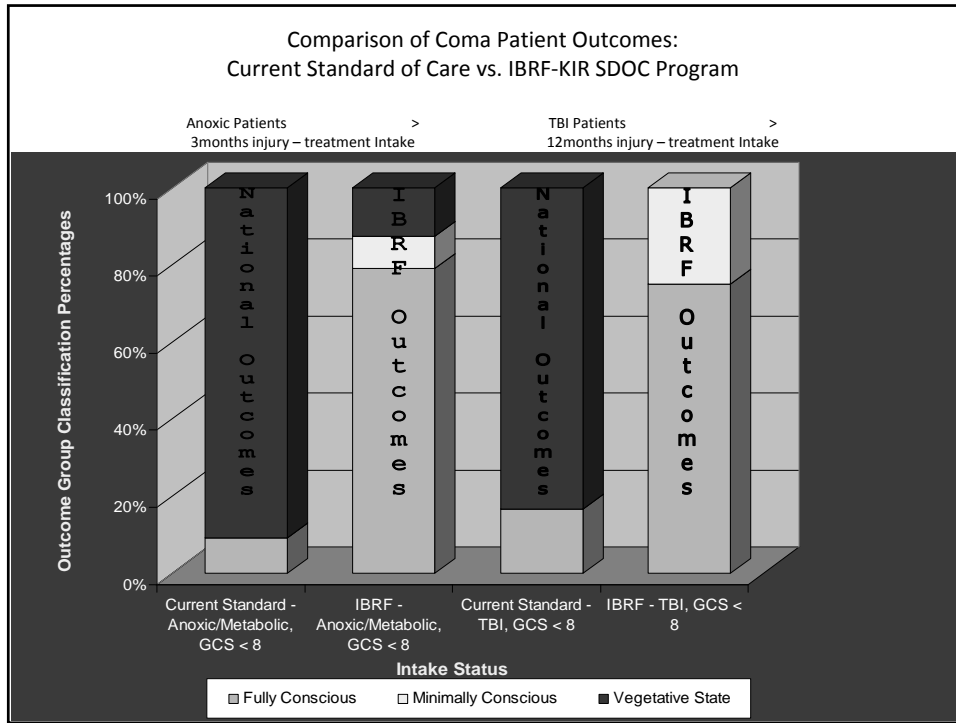
IBRF Integrated Multi-modal Approach

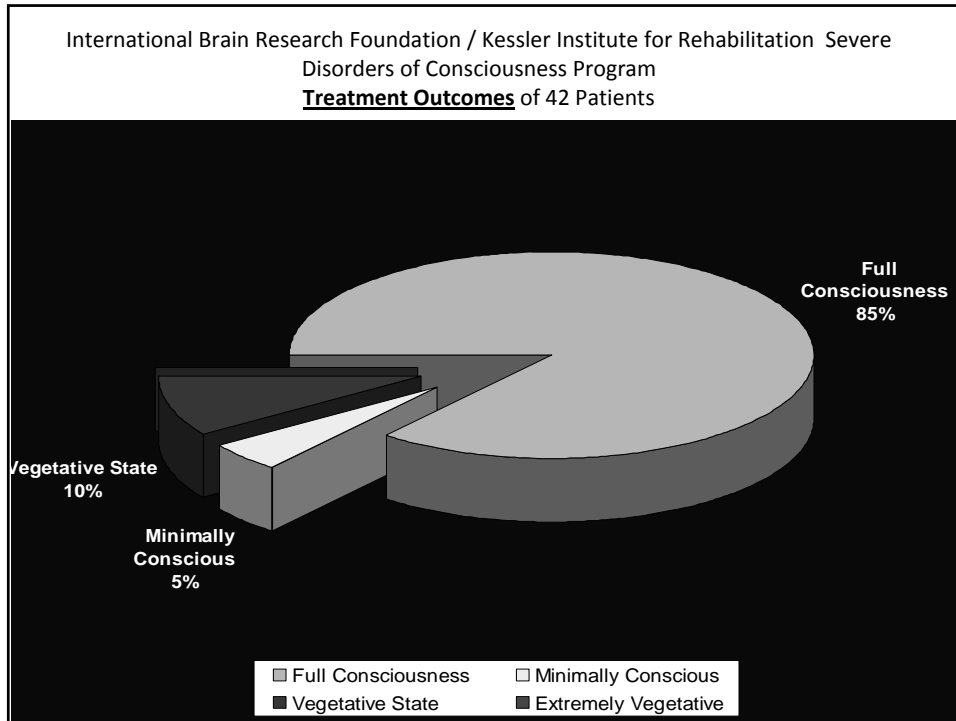
There is no magic bullet for successful  
treatment of brain injury...

*However....*

There are different weapons in the  
armamentarium of treatment, that if  
used correctly and combined  
properly, can be a very successful  
strategy for recovery.







**IBRF COMA INITIATIVES  
CONSOLIDATED OUTCOMES  
PROGRAMS I and II**

- **43 Patients successfully emerged to consciousness**
- **9 Patients remain in vegetative state**
- **4 Patients remain in minimally conscious state**
- **10 Are currently being treated as inpatients**