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

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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

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Standard Approaches to Assess BI

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

Combining Techniques:
fMRI and EEG
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 an 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)

<table>
<thead>
<tr>
<th>Measures</th>
<th>Controls</th>
<th>Concussed</th>
<th>F</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>P3a Amplitude</td>
<td>4.50 SD 2.32</td>
<td>2.94 SD 1.67</td>
<td>5.67</td>
<td>&lt; .05</td>
</tr>
<tr>
<td>Latency</td>
<td>359.6 SD 35.5</td>
<td>287.2 SD 44.9</td>
<td>4.43</td>
<td>&lt; .05</td>
</tr>
<tr>
<td>P3b Amplitude</td>
<td>5.25 SD 2.11</td>
<td>4.18 SD 1.99</td>
<td>2.57</td>
<td>&gt; .05</td>
</tr>
<tr>
<td>Latency</td>
<td>362.9 SD 28.9</td>
<td>397.6 SD 57.0</td>
<td>5.58</td>
<td>&lt; .05</td>
</tr>
</tbody>
</table>

Table 2. Between-group difference on the mean P3a / P3b components amplitude (µV) and latency (ms) recorded at Fz and Pz, respectively.
Independent ERPs components in mild TBI patients in comparison to healthy subjects

- Each component is characterized by topography and time dynamics, corresponding to a specific psychological operation (such as visual processing in primary areas, engagement, monitoring operations etc.)
- Note strong disturbances in sensory-related and monitoring components (Left column) while other components remain intact (Right column)
- N=18 (TBI), N=463 (healthy)
- Moncval Rehabilitation Center, St.Olav’s Hospital, Norwegian University of Science and Technology

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

Hoshi et al., 2001

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.
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
- Partially our increased bloodflow from increased O2 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
Advanced Functional Imaging Technology operationalizes & quantifies evaluation process of Neurochemistry after TBI/NTBI

MRI SPECTROSCOPY

MEASURES THE PHYSICAL SPECTRA OF INDIVIDUAL BRAIN CHEMICALS

Providing quantitative estimates of concentrations of specific chemicals within specific regions of interest.

The presence of NAA is believed to correlate with integrity and health of neurons

NAA = loss of neurons
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.

MR Spectroscopy
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

EEG Guided Neuro-Rehabilitation

1. Increase fast waves
2. Reduce slow waves
3. Monitor & train physiology control (arousal level: HR, resp, EMG)
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

<table>
<thead>
<tr>
<th>Measure</th>
<th>Marker</th>
<th>Strengths</th>
<th>Associated Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>EEG, qEEG</td>
<td>electrophysiology</td>
<td>High temporal resolution (ms) Source localization of electrical generators in cortex</td>
<td>EEG brain-computer interface (BCI) training Guides DCS and TCMS</td>
</tr>
<tr>
<td>EP, ERP</td>
<td>electrophysiological</td>
<td>High temporal resolution (ms) Measure processing speed Measure intactness of sensory pathways</td>
<td>EEG BCI training Guides DCS and TCMS</td>
</tr>
<tr>
<td>MEG</td>
<td>Brain electromagnetism</td>
<td>High temporal resolution Subcortical structures</td>
<td>Guides DCS and TCMS</td>
</tr>
<tr>
<td>B.I.S. Monitor</td>
<td>Level of consciousness</td>
<td>Real-time measure of patient level of consciousness</td>
<td>Determine patient receptiveness to treatment</td>
</tr>
<tr>
<td>MRI w/ DTI</td>
<td>Structural anomalies Brain volume Brain connectivity</td>
<td>Guides medical and surgical interventions</td>
<td>Neurosurgery Pharmacotherapy</td>
</tr>
<tr>
<td>MRI Spectroscopy</td>
<td>Brain chemistry / metabolites</td>
<td>Provides chemical neuromarkers</td>
<td>Pharmacotherapy, nutraceuticals</td>
</tr>
<tr>
<td>PET-CT</td>
<td>Metabolic functions</td>
<td>Multiple metabolic neuromarkers</td>
<td>Pharmacotherapy, nutraceuticals</td>
</tr>
<tr>
<td>Near Infra-red Spectroscopy</td>
<td>$O_2$ concentrations/uptake</td>
<td>Non-invasive $O_2$ exchange method</td>
<td>Pharmacotherapy, nutraceuticals Median nerve stim</td>
</tr>
</tbody>
</table>
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

Neuromodulatory approaches using electrical stimulation

- Transcutaneous Nerve Stimulation (TENS)
  - Vagal Nerve Stimulation (VNS)
  - Spinal Cord Stimulation (SCS)
  - Transcranial Magnetic Stimulation (TMS)
  - Transcranial Direct Current Stimulation (tDCS)
- Epidural Stimulation
- Deep Brain Stimulation (DBS)

TMS, tDCS epidural stimulation
Deep Brain Stimulation
Vagal nerve stimulation
Spinal cord stimulation
TENS
Transcranial Magnetic Stimulation

Current Density Along Evaluation Line

- Current Density Magnitudes (A/m²)
- Distance Along Line (mm)
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

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IBRF-SDOC Theoretical Paradigm – A Model Based on Neurochemical Autoregulation

Brain’s Inherent Protective Mechanism to Sustain Life

Increase Inhibitory NT’s
Antagonist NT’s Block Receptors

Endorphins
GABA

Reduced perceptual awareness and unresponsiveness contribute to down regulation

Consciousness

MCS
PVS
COMA

This model developed by Dr. Philip A. De Fina ©

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.
ADVANCED DIAGNOSTIC PROTOCOLS CAN PREDICT OUTCOMES & GUIDE TREATMENTS

PHASE I

ASSESS AROUSAL OF CONSCIOUSNESS

PHASE II

ASSESS ENHANCEMENT OF COGNITION

Mohonk Report & Aspen Work Group:
Less than 10% Probability of Recovery from Disorders of Consciousness Based on Time Since Injury
Comparison of Coma Patient Outcomes: Current Standard of Care vs. IBRF-KIR SDOC Program

Outcome Group Classification Percentages

<table>
<thead>
<tr>
<th>Outcome Group</th>
<th>Current Standard - Anoxic/Metabolic, GCS &lt; 8</th>
<th>IBRF Anoxic/Metabolic, GCS &lt; 8</th>
<th>IBRF - TBI, GCS &lt; 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anoxic Patients &gt; 3months injury – treatment intake</td>
<td>IBRF - TBI, GCS &lt; 8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TBI Patients &gt; 12months injury – treatment intake</td>
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</table>

Intake Status

- Fully Conscious
- Minimally Conscious
- Vegetative State

International Brain Research Foundation / Kessler Institute for Rehabilitation
Severe Disorders of Consciousness Program

**Admission Status** of 43 Patients

- Full Consciousness 6%
- Minimally Conscious 12%
- Vegetative State 17%
- Extremely Vegetative 71%
International Brain Research Foundation / Kessler Institute for Rehabilitation Severe Disorders of Consciousness Program

**Treatment Outcomes** of 42 Patients

- Full Consciousness: 85%
- Minimally Conscious: 5%
- Vegetative State: 10%
- Extremly Vegetative

**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