Neuroscience Introduces Physiological Brain Treatment to SUD and Addiction

USC Center for NeuroResoration
Newport Brain Research Laboratory
Brain Treatment Center
Strategic Partnerships

Keck Medical Center of USC
Center for Neurorestoration

Joseph Hoag Health

Hoag • Mission • St. Joseph • St. Jude
In alliance with CHOC Children's

UNIFORMED SERVICES UNIVERSITY of the Health Sciences

Rancho Los Amigos National Rehabilitation

RANCHO Research Institute

BRAIN TREATMENT CENTER
Scope of the Problem

TBI called the “signature injury” of OEF/OIF
- 33% of all patients
- 60% of patients with blast related injuries
  (Veterans Health Initiative Traumatic Brain Injury)

13.8% of Gulf War Vets suffer from PTSD
- 50% do not seek treatment
- Of the half that do, only 25% get “minimally adequate” treatment
  (Rand, Center for Military Health Policy Research)

22 suicides/day among US Military Veteran
- More active duty personnel died by their own hand than combat in 2012
  (USDVA Mental Health Services)
DoD releases 2nd quarter suicide figures

By Patricia Kline, Staff writer
9:54 a.m. EDT October 1, 2015

Suicides among active-duty service members rose by 20 percent in the second quarter of this year to 71, according to a new report released Wednesday by the Defense Department.

The Marine Corps had the highest percentage increase, 12 suicides, up from three in the previous quarter.

The Army had 28 active-duty suicides, the Air Force, 17, and the Navy, 14, according to...

(The rest of the article is obscured by an advertisement.)
VA Polytrauma Model

Prevalence of Chronic Pain, PTSD and TBI in a sample of 340 OEF/OIF veterans with polytrauma

Chronic Pain
N=277
81.5%
10.3%
12.6%
5.3%

PTSD
N=232
68.2%
16.5%
2.9%
6.8%

TBI
N=227
66.8%
42.1%

Chronic Pain and Opioids

More physician-prescribed opioid fatalities than illicit cocaine and heroin combined
Pain and Opioids

Mortality = “Tip of the iceberg”

For every 1 death there are...

- 10 treatment admissions for abuse
- 32 emergency dept visits for misuse or abuse
- 130 people who abuse or are dependent
- 825 nonmedical users

Source: CDC - Injury Prevention & Control – Prescription Pain Killer Overdoses
http://www.cdc.gov/homeandrecreationalsafety/rxbrief/
Chronic Pain and Brain Function
NIH Funded Study

• NIH-sponsored study utilizing f-MRI and diffusion tensor imaging (DTI) identified areas of the brain that may predispose individuals to chronic pain. The results, published in the journal *Pain*, support the growing idea that the brain plays a critical role in chronic pain.

• “We may have found an anatomical marker for chronic pain in the brain...Our results suggest that the structure of a person’s brain may predispose one to chronic pain. We were surprised how robust the results were and amazed at how well the brain scans predicted persistence of low back pain.”

  Vania Apkarian, Ph.D., senior author of the study and professor of physiology at Northwestern University Feinberg School of Medicine


Morphologic changes of the addicted brain are observable.

Functional MRI (f-MRI) and Addiction

The brains response to cocaine. Arrows point to the anterior cingulate area, which is activated in cocaine addicted patients (left), but not in healthy volunteers (right).

(Wexler, et al. 2001)
Functional Interaction between Medial Thalamus and Rostral Anterior Cingulate Cortex in the Suppression of Pain Affect

Steven E. Hartle, Catherine A. Spudich, and George S. Borszcz

*Chronic Pain and Fatigue Research Center, Department of Anesthesiology, University of Michigan, Ann Arbor, MI 48106, USA

Abstract

The medial thalamic parafascicular nucleus (PT) and the rostral anterior cingulate cortex (ACC) are implicated in the processing and suppression of the affective dimension of pain. The present study evaluated the functional interaction between PT and ACC in mediating the suppression of pain affect in rats following administration of morphine or carbachol (acetylcholine agonist) into PT. Vocalizations that occur following a brief noxious tailshock (vocalization afterdischarges) are a validated event-related model of pain affect, and were preferentially suppressed by injection of morphine or carbachol into PT. Vocalizations that occur during tailshock were suppressed to a lesser degree, whereas, spinal motor reflexes (tail flick and hindlimb movements) were only slightly suppressed by injection of carbachol into PT and unaffected by injection of morphine into PT. Blocking glutamate receptors in ACC (NMDA and non-NMDA) by injecting 2-[2-(2-imidazolin-1-yl)ethyl]-5-phosphonovaleric acid (AP-5) or 6-cyano-7-nitroquinolin-2-yl-2-carboxylic acid (CNQX) produced dose-dependent antagonism of morphine-induced increases in vocalization thresholds. Carbachol-induced increases in vocalization thresholds were not affected by injection of either glutamate receptor antagonist into ACC. The results demonstrate that glutamate receptors in the ACC contribute to the suppression of pain affect produced by injection of morphine into PT, but not to the suppression of pain affect elicited by intrathecal injection of carbachol.
Neuromodulation

Neuromodulation – Refers to an emerging class of medical therapies targeting the nervous system for: restoration of function, relief of pain, and/or to control symptoms of depression/anxiety.

- Invasive Neuromodulation

- Non-Invasive Neuromodulation
Surgical (Invasive) Neuromodulation . . . Deep Brain Stimulation (DBS) is a rapidly evolving area of neurosurgical intervention and is now considered “standard of care” for drug-resistant Parkinson’s and OCD.
Despite good outcomes with DBS, patients are largely unwilling to undergo brain surgery with craniotomies.

• Less than 30% of candidates eligible agree to have it performed.

Race to develop a “non-invasive” neuromodulation modality!

• Transcranial Magnetic Stimulation (TMS)
  • Magnetic energy → left dorsolateral prefrontal cortex (10 Hertz at 120% of threshold)
  • FDA approved for treatment of depression in 2008.

• EEG-guided TMS (eTMS) / Magnetic e-Resonance Therapy (MeRT)
  • Customized application / Guided by brain map (q-EEG) / personalized / precision frequency at 50-70% of threshold
  • Early Data: Almost twice as effective as TMS in head-to-head clinical trials
  • Broader application: Autism Spectrum Disorder (ASD) / PTSD, Depression/Anxiety and Addiction/Substance Use Disorder
  • Current trials: ADHD & TBI)
Neuromodulation (Non-Invasive)

Non-pharmaceutical (no systemic side effects) + Non-invasive (painless) + Similar to exposure in a standard MRI (almost no adverse events) = strong clinical efficacy
# Neuromodulation (Non-Invasive)

## Safety Profile

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Single-pulse TMS</th>
<th>Paired-pulse TMS</th>
<th>Low frequency TMS</th>
<th>High frequency TMS</th>
<th>Theta burst</th>
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</thead>
<tbody>
<tr>
<td>Impaired</td>
<td>Rare (usually protective effect)</td>
<td>Rare</td>
<td>Rare</td>
<td>Rare</td>
<td>Rare</td>
</tr>
<tr>
<td>Motor (due to direct brain effects or not)</td>
<td>Rare</td>
<td>Rare</td>
<td>Rare</td>
<td>Rare</td>
<td>Rare</td>
</tr>
<tr>
<td>Frequency</td>
<td>(see para. 3.3)</td>
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**Table 1**: Potential side effects of TMS. Consensus has been reached for this table.
Neuromodulation (Non-Invasive) Safety Profile

“In summary, based on *ex vivo* and *in vivo* studies . . . it appears that TMS can be safely applied to patients.

It is worth noting that exposure to electro-magnetic fields appears safe at levels even greater than those possible with TMS (Gandhi, 2002; Martens, 2007).”
Neuromodulation (Non-Invasive) Adverse Effects

- Temporary discomfort/pain at scalp
- Temporary headache
- Overstimulation (excitation)
- Seizure (estimate 1:100,000 – 1:500,000)
  (Note: Nintendo warns of 1:4000 seizure possibility)
Quantitative EEG (q-EEG)

q-EEG is painless and takes only 20-30 minutes.
Quantitative EEG

• Measures 6 brainwave clinical bands

• Every individual has a “cognitive fingerprint” with an intrinsic wavelength profile

• Deficits are picked up when an area of the brain deviates from the intrinsic wave signature

Major depression manifests as abnormality of the left dorsolateral prefrontal cortex (DLPFC).
Transcranial Magnetic Stimulation (TMS)

- FDA-approved for drug-resistant major depression (2008)
  - 1\textsuperscript{st} Generation – Transcranial Magnetic Stimulation (TMS)
    - Alpha wave fixed at 10.0 Hz via single coil device delivered to the LDLPFC
    - 33\% response rate for drug-resistant depression

![Diagram showing depression profile and normal brain activity with different frequency waves.](image)
Magnetic e-Resonance Therapy (MeRT)

- **2nd Generation – Magnetic e-Resonance Therapy (MeRT) / EEG-guided TMS (eTMS)**
  - Deep signal across multiple bands personalized to an individual’s intrinsic profile
  - Guided by q-EEG to specifically targeted areas (brain navigation)
PTSD Trial
Prospective/ Double-Blind/ Placebo-Controlled/ Randomized

86 subjects (77 M & 8 F) / Average Age 37.8 yrs / Moderate-Severe PTSD

Phase 1:
Random assignment into one of two treatment groups - Active MeRT Treatment or SHAM Treatment
• Technicians were blinded.

Clinical symptom severity evaluated using quantitative scale - PTSD Checklist Military (PCL-M)
  (well-recognized and validated questionnaire scoring range 0-80 used by the VA)
• Baseline symptoms varied from ‘moderate’ to ‘severe’ (38-80)
• Research clinicians were blinded.

Phase 2:
Two-week, Open-Label Trial during which all received active MeRT treatment.
Clinical Improvement in PCL-M following MeRT and Sham

Phase 1 Double Blind: Repeated Measure ANOVA $F_{1,49} = 4.65$, $p = 0.03$

Phase 2 Open Label: Single Variable ANOVA $F_{1,50} = 0.04$, $p = 0.85$
Neuromodulation (Non-Invasive) PTSD MeRT Trial

- Average 63% reduction in symptom severity (Fig.1; p<0.0001).
- EEG improvement in alpha power, coherence, and reduction in slow waves.

Figure 1. PCL-M change after MRT
Neuromodulation (Non-Invasive) TBI/PTSD MeRT Study

- Corroboration of PCL-M scores (subjective questionnaire) with q-EEG brain imaging (objective study)

Pre MRT

Post MRT
A Case . . .

Note: Jeff has provided consent to share his case
Before Treatment . . .

- **Insomnia** - “I haven’t had a good night of sleep in 11 years”
  - Medicates & drinks himself to sleep

- **Chronic Pain**
  - Failed back surgery x 2
  - 170 morphine equivalents daily
  - 20 pills/day (antidepressants, muscle relaxants, pain pills, etc)
  - Used “Every antidepressant known to man . . .”

- Utilized every available VA treatment modality for PTSD and addiction.

- Anger issues, road rage, hypervigilance in crowds, depressed mood, etc.
After Treatment . . .

After 6 weeks of MeRT treatment:
- Restful sleep
- Anger dissipated
- Upbeat mood
- Chronic pain dramatically reduced (hyperalgesia resolved)
  - Off all prescription drugs
  - Takes 1 pill/day (Vitamin D)
- Completed Masters of Social Work and Addiction Counseling Certification
- Applying for PhD programs
PTSD MeRT Trial Findings

- 63% reduction in symptom severity (PCL-M).
- 96% reported improved quality of sleep.
- VAS Pain Scores reduced from 7.4 to 2.7.
- 25% voluntarily weaned off opioids
- 86% of Veterans voluntarily decreased opioid use.
- 77% of Veterans voluntarily decreased alcohol use.

*Data points still holding at 1-year marker.*
Quantitative EEG

Pre Treatment

Post Treatment
So . . . Where are we with all of this?
Based on Veteran results . . .

- Pilot conducted through Workers Compensation for pain and opioid dependence:
  - All subjects reduced opioid dose by 50% within the first month.
  - 66% successfully weaned off opioids.
  - Remaining 33% were able to reduce to a safer, low dose, opioid regimen.
  - Subjects reported “very limited” or “no withdrawals” . . . the weaning process was characterized as a “soft landing.”

- One case went from 700 morphine equivalents daily (MED) to 80 MED’s. This patient felt well enough to find a new job and return to work after 18 years of “total disability” and unemployment.
Private Insurance Pilot Data
Neuropsych Testing

Self Regulation
Feeling
Thinking
Emotion
Public Sector
Department of Defense

• Tinker Airforce Base . . .
  Randomized, Double-Blind, Placebo-Controlled Trials now expanded within DOD

• US Special Operations Command . . .
  Two-Site Trial (CA and FL) underway by Uniformed Services for Health Sciences (USUHS)

“The USSOCOM Command Surgeon and several senior members of the Special Operations Community have witnessed some remarkable anecdotal results from the treatment provided by NBRL; some of which defy traditional medical explanation. We are excited about the opportunity to further explore this method of treatment to help our active duty and veteran teammates in DOD.”

CAPT (SEAL) J Doolittle, USN, Director, Preservation of the Force and Family (POTFF)
Department of Veteran Affairs

The No Hero Left Untreated Act

- **FINDINGS**

  Congress finds the following:

  Magnetic EEG/EKG-guided Resonance Therapy technology (in this section referred to as “MeRT technology”) has successfully treated more than 400 veterans with post-traumatic stress disorder, traumatic brain injury, military sexual trauma, chronic pain, and opiate addiction.

  Directs the Secretary of Veterans Affairs to carry out a pilot program to provide access to Magnetic EEG/EKG-guided Resonance Therapy technology to veterans.

- **PASSED THE HOUSE UNANIMOUSLY.**
- **CURRENTLY . . . IN THE SENATE COMMITTEE ON VETERAN AFFAIRS**
- **RECEIVED A LEGISLATIVE HEARING LATE AUGUST**
- **NEXT STEP: MARK-UP**
• MeRT is an innovative medical technology demonstrating strong clinical efficacy for opioid dependence.
  • Clinical efficacy is corroborated by post-treatment brain imaging.

• MeRT has an excellent safety profile.
  • Non-invasive, minimal side effects or adverse events, in an outpatient setting with the same exposure/energy of an MRI.

• MeRT is cost effective.
  • A fraction of the cost of lifetime opioid treatment for pain.
  • Lowers costs of current SUD and addiction treatment through integrative medicine.

• MeRT transforms Quality of Life factors.
  • Impossible to quantify the impact for patients and their families. Patients (and their family members) identify transformative quality of life changes
“All truth passes through three stages. First, it is ridiculed. Second, it is violently opposed. Third, it is accepted as being self-evident”

--

Arthur Schopenhauer, German Philosopher (1788-1860)
Contact . . . Dr Judi Kosterman

jkosterman@braintreatmentcenter.com
775-544-8840