# Innovative Approach to Treatment for Persisting Symptoms After TBI

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No Conflicts to Disclose

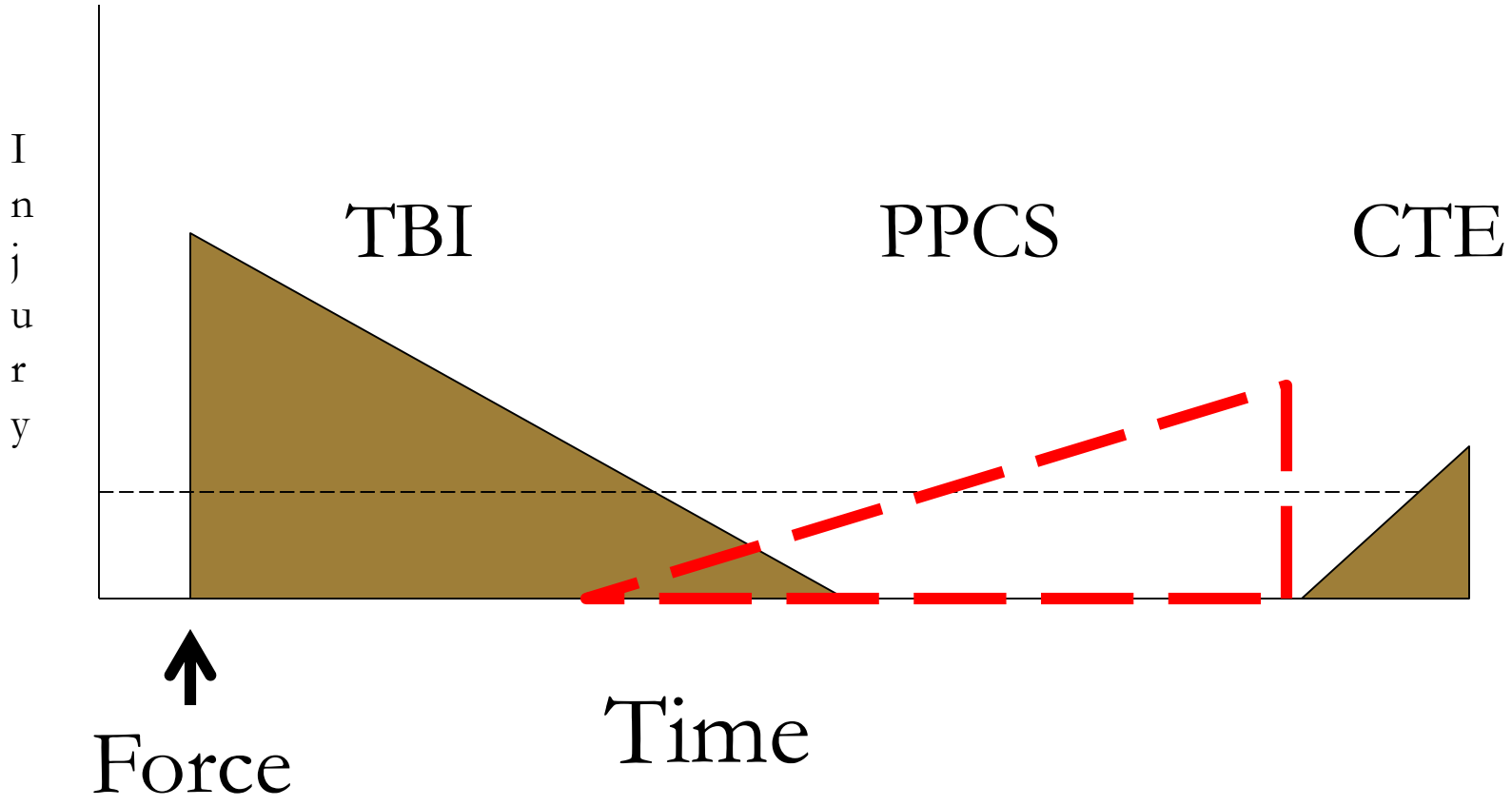
# Persisting Symptoms After Concussion

- Focus on persisting symptoms
- Review brain management of autonomic response to traumatic stress
- Overview of HIRREM
- Results with Insomnia, TBI/concussion, PTSD
- Future directions and opportunities

# Persisting Symptoms After Concussion

- Symptoms typically resolve quickly (80-90% in 7-10 days; 15-20% symptoms >21 days; 3-5% > 30 days)
- Can cause severe, long-lasting symptoms/deficits
- Brain electrical activity altered, and autonomic dysregulation recognized in TBI/concussion
- Persisting symptoms more behavioral (insomnia, depression, stress, anxiety, irritability, focus, concentration, fatigue, headache); overlap with PTSD
- Treatment is symptomatic, and lack of validated non-pharmacological strategies for behavioral symptoms, insomnia, that also improve autonomic function

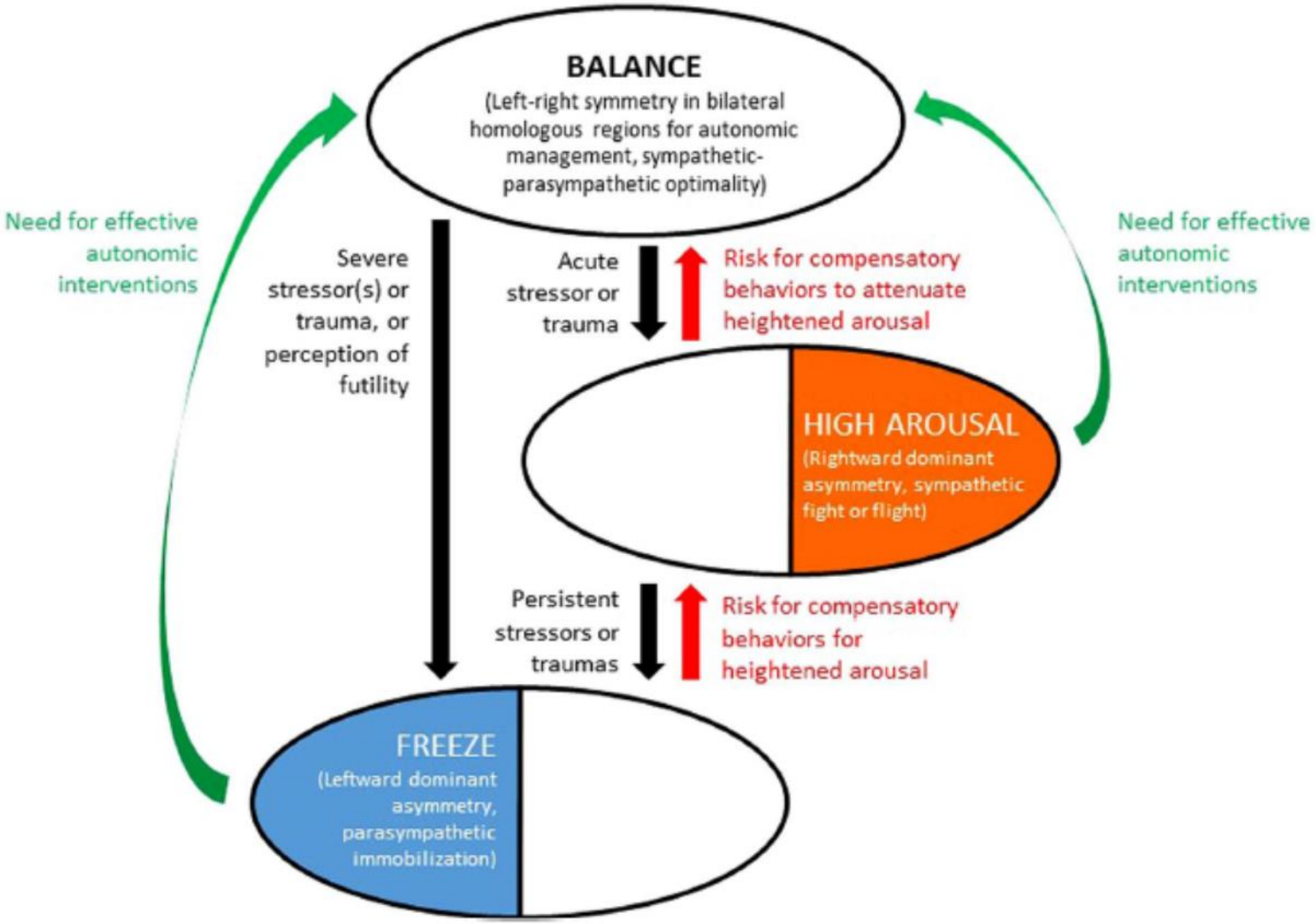
# Spectrum of TBI/Concussion



# Important Background

- Stress is killing people
- Sleep is crucial for optimal for health and healing
- Chronic stress/insomnia increase risk of adverse health outcomes; effective non-drug therapies are lacking
- Brain drives/is the organ of central command for autonomic management of “survival” responses (sympathetic/parasympathetic) to trauma or threat
- Due to plasticity, with severe or repeated traumas or threats those responses may get stuck; imbalance may lead to symptoms, diseases, impaired performance

# Bihemispheric Model for Autonomic Management of Traumatic Stress





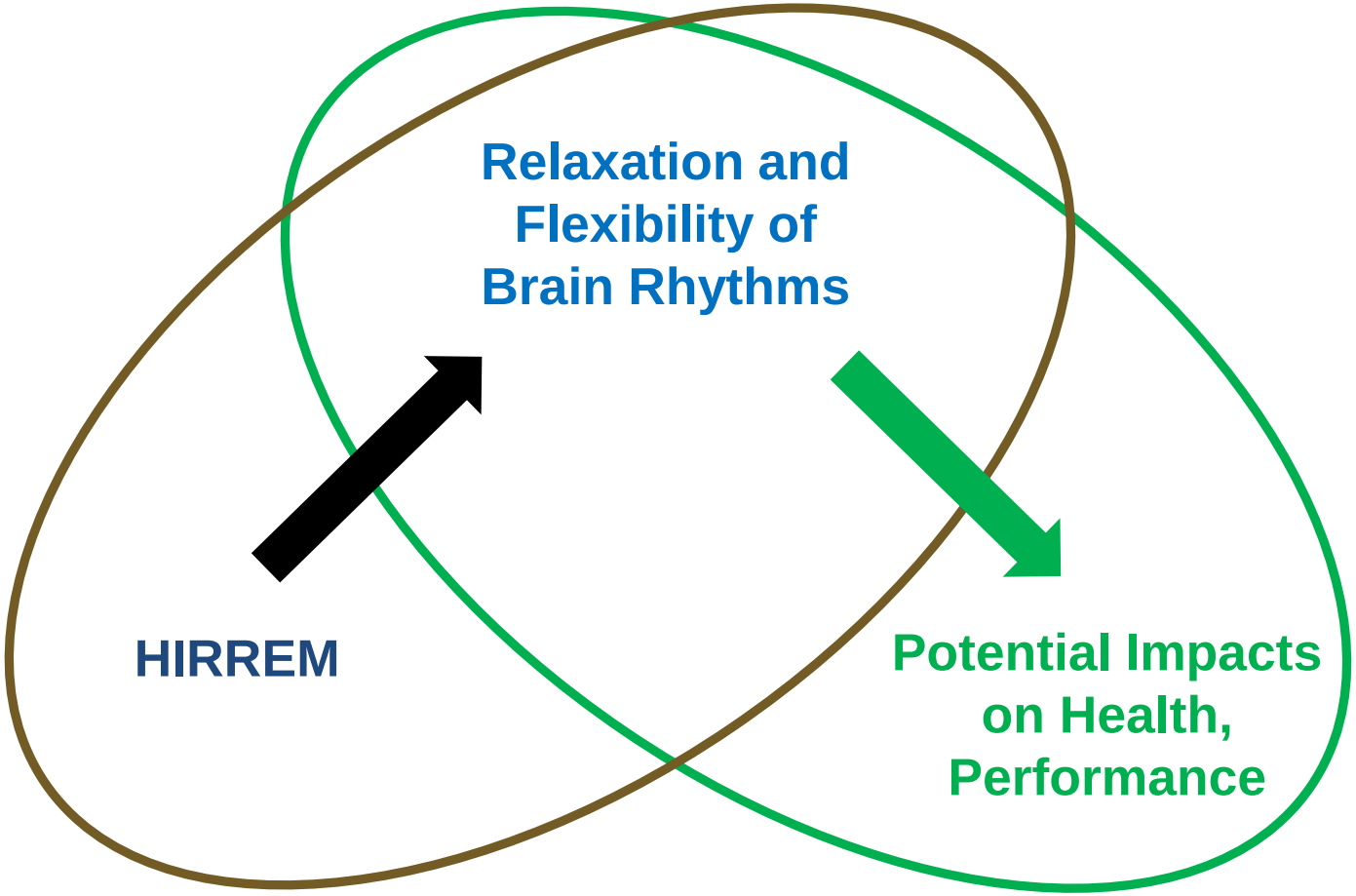

Lee et al., 2014

# High-resolution, relational, resonance-based, electroencephalic mirroring (HIRREM®)

- Noninvasive, closed-loop, frequency-based brain feedback neurotechnology (Brain State Technologies, LLC, Scottsdale, AZ)
- Scalp sensors monitor brainwaves, software algorithms translate selected frequencies into audible tones of varying pitch
- Tones are echoed back in real time via earbuds (brain listens to itself; “looks at itself” in an acoustic mirror)
- Resonance/rapid echoing on its pattern supports brain to self-adjust, relax, balance, “re-set” (like musical instrument tuning itself)
- Brain pattern shifts on its own, and on its own terms, with no conscious/cognitive activity needed, towards improved balance, reduced hyperarousal – no zapping with electricity or magnetism

# HIRREM

## Closed-loop Feedback/Echoing Technology Engages the Brain to Improve Balance, Reset, Repair on Its Own Terms

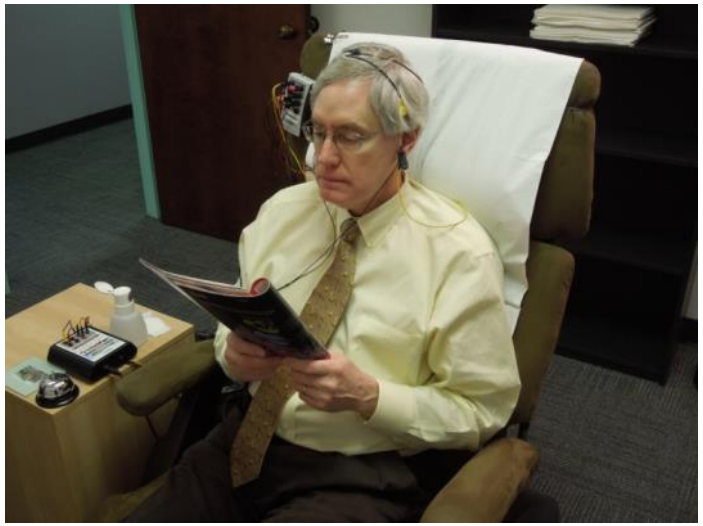


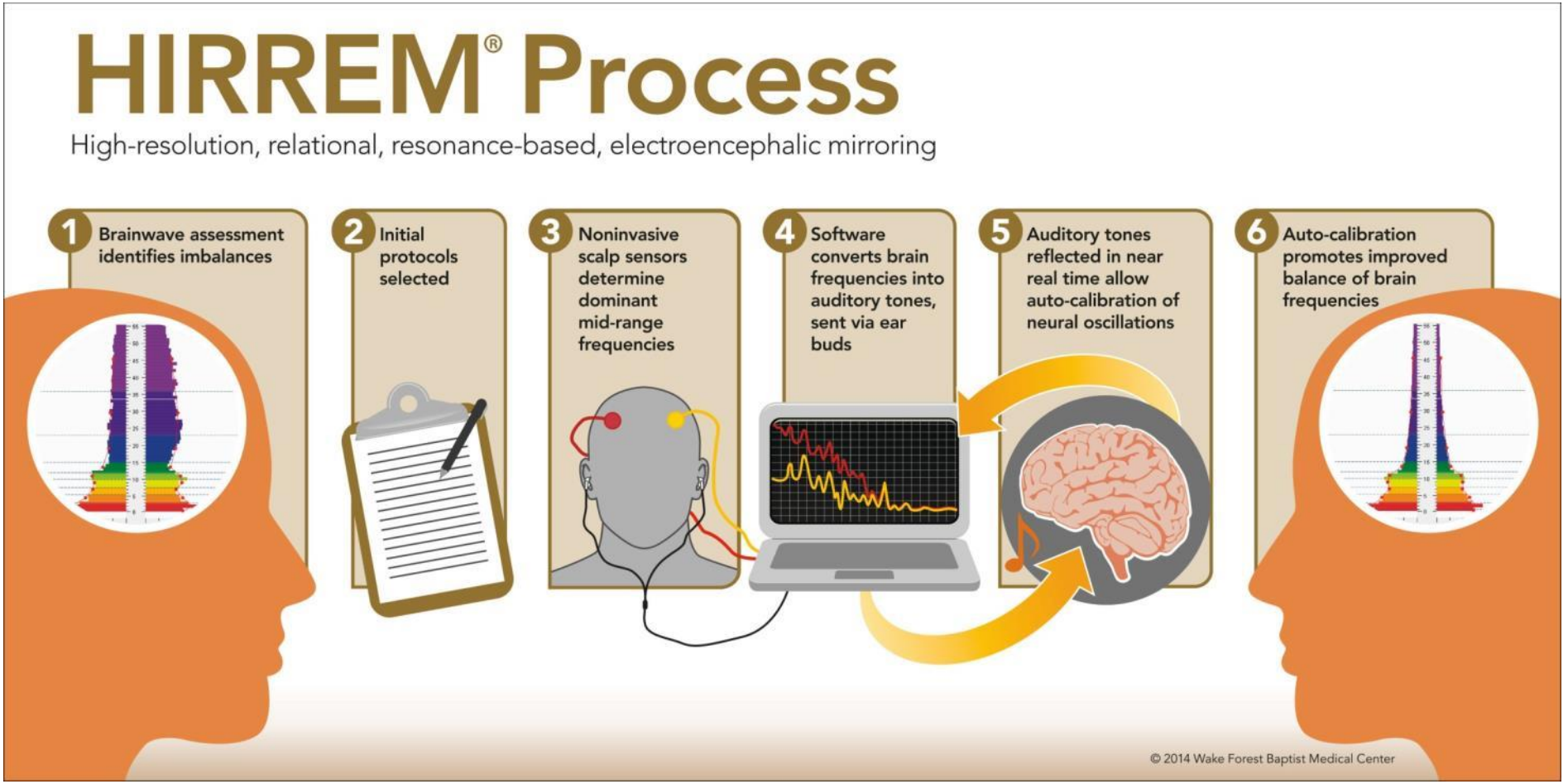

= HIRREM path to relaxation and flexibility in brain rhythms

= Recipient path from relaxation to achieving health and other objectives

# HIRREM In-Office Process

- Initial brain assessment at standard locations
- Series of sessions (90-120 minutes each):
  - 3-10 protocols (varied location and frequencies observed)
  - 6-40 minutes for each protocol
  - Data reviewed after each session
  - Some protocols done with eyes closed, others eyes open




HIRREM® Process
High-resolution, relational, resonance-based, electroencephalic mirroring
1 Brainwave assessment identifies imbalances
2 Initial protocols selected
3 Noninvasive scalp sensors determine dominant mid-range frequencies
4 Software converts brain frequencies into auditory tones, sent via ear buds
5 Auditory tones reflected in near real time allow auto-calibration of neural oscillations
6 Auto-calibration promotes improved balance of brain frequencies
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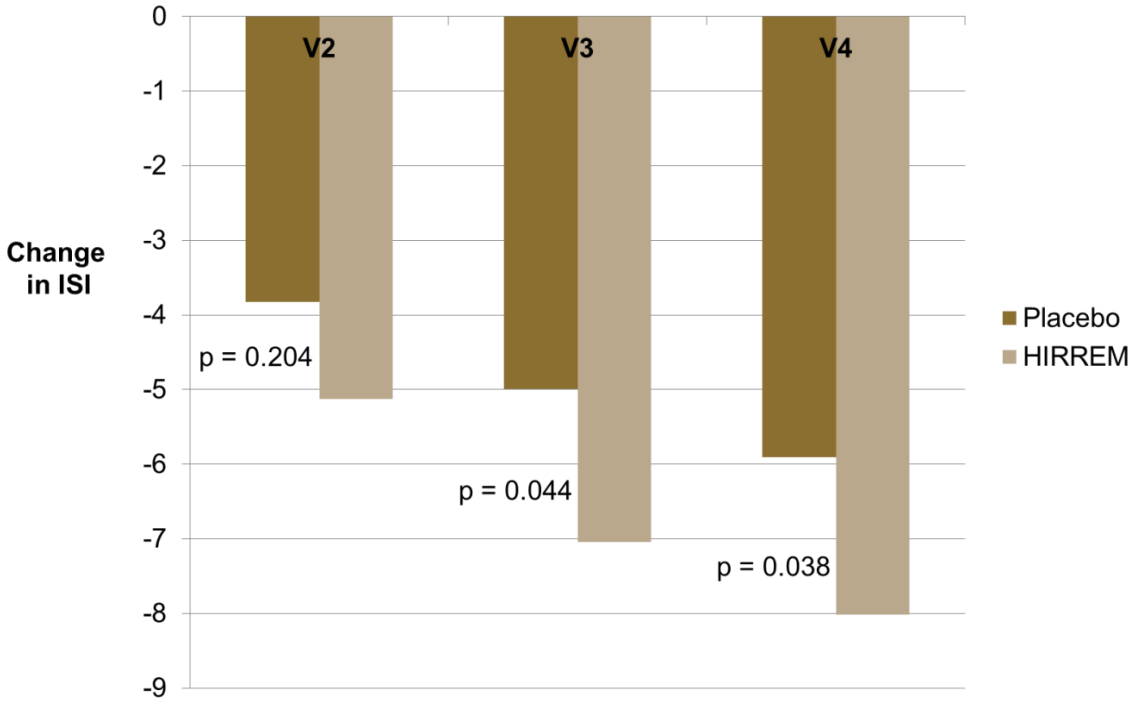
# HIRREM Research Program at WFSM

## Launched in 2011; > 500 now enrolled

- Completed studies:
  - Randomized, wait list control study for insomnia (n = 20)
  - Randomized, placebo pilot trial for migraine (n = 33)
  - Randomized, placebo trial for insomnia (n = 122)
  - Open label developmental study (n = 300)
- Ongoing studies:
  - Pilot trial for military-related traumatic stress (n = 29)
  - Randomized trials for primary hypertension (n = 2), hot flashes (n = 3)
  - Pilot placebo controlled trial of HIRREM-SOP for insomnia (n = 5)
- Supported to date by grants from foundations (SMCF), philanthropy, and DoD/US SOCOM

# Placebo-controlled Insomnia Trial

## Primary Clinical Outcome for n = 101
## Differential Change in Self-reported ISI Score



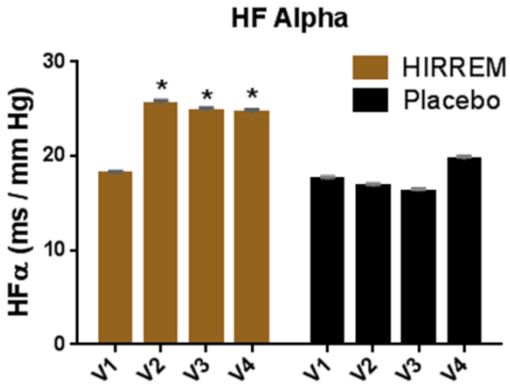

V2 = 1-7 days, V3 = 2 months, V4 = 4 months post-intervention.

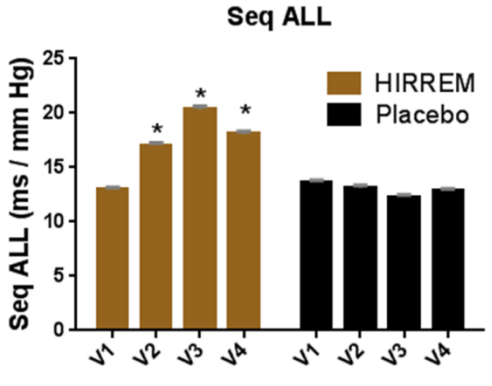
Tegeler, et al, Sleep 2017 (poster)

# Placebo-controlled Insomnia Trial

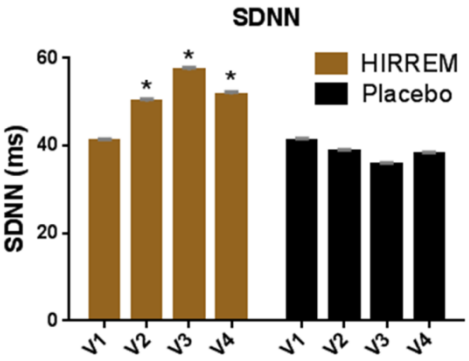
## Objective Autonomic Outcomes

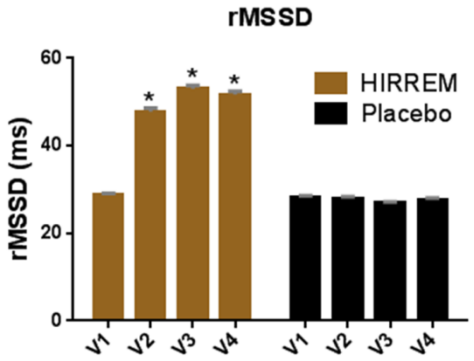
### Baroreflex Sensitivity




### Heart Rate Variability






Tegeler, et al, Sleep 2017 (poster)

# Series of Athletes with Persisting Post-Concussion Symptoms

## (n = 16, 8 female, mean age 17.9, 2.6 concussions, symptom duration 5.4 months,18.3 sessions over 27.5 days)

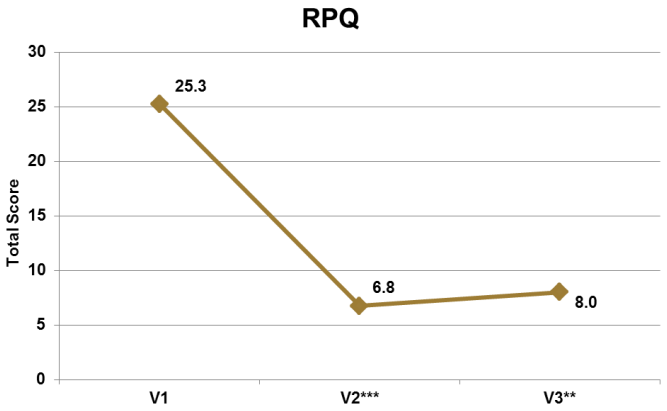
| Measure | n | Baseline Mean (SD) | Mean Change After HIRREM (SD) | Paired t-test P values | Wilcoxon P values |
|---|---|---|---|---|---|
| RPQ Concussion Score | 13 | 28 (14.3) | - 20 (11.1) | < 0.01 | < 0.01 |
| Insomnia Severity Index | 16 | 7.1 (4.3) | -3.9 (4.1) | < 0.01 | < 0.01 |
| CES-D Depression Score | 11 | 20.4 (13.6) | - 11.9 (9.5) | < 0.01 | < 0.01 |

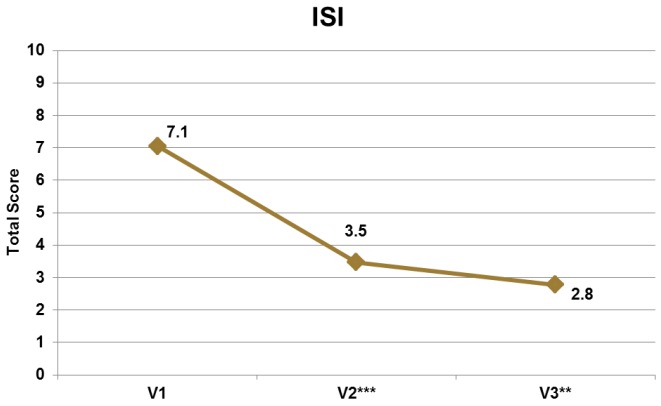
All returned to full exercise, workouts, academics, or recreational activities
11/16 returned to full participation in their athletic activity

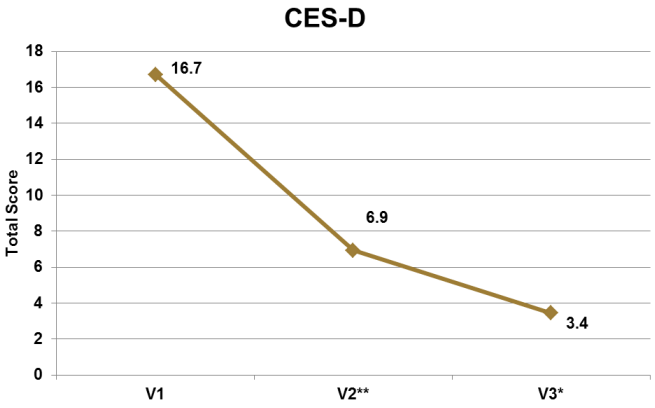


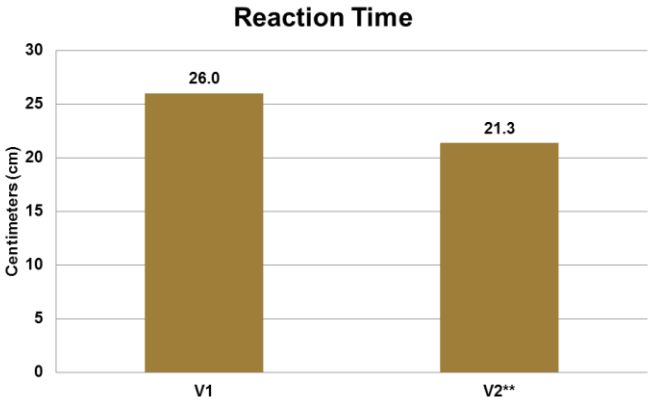
Tegeler, et al, 2016 Sports Medicine - Open

# Outcomes at Baseline, 3 Weeks, and 3 Months




AAN Sports Concussion Conference, 2017

# Series of Athletes with Persisting Post-Concussion Symptoms

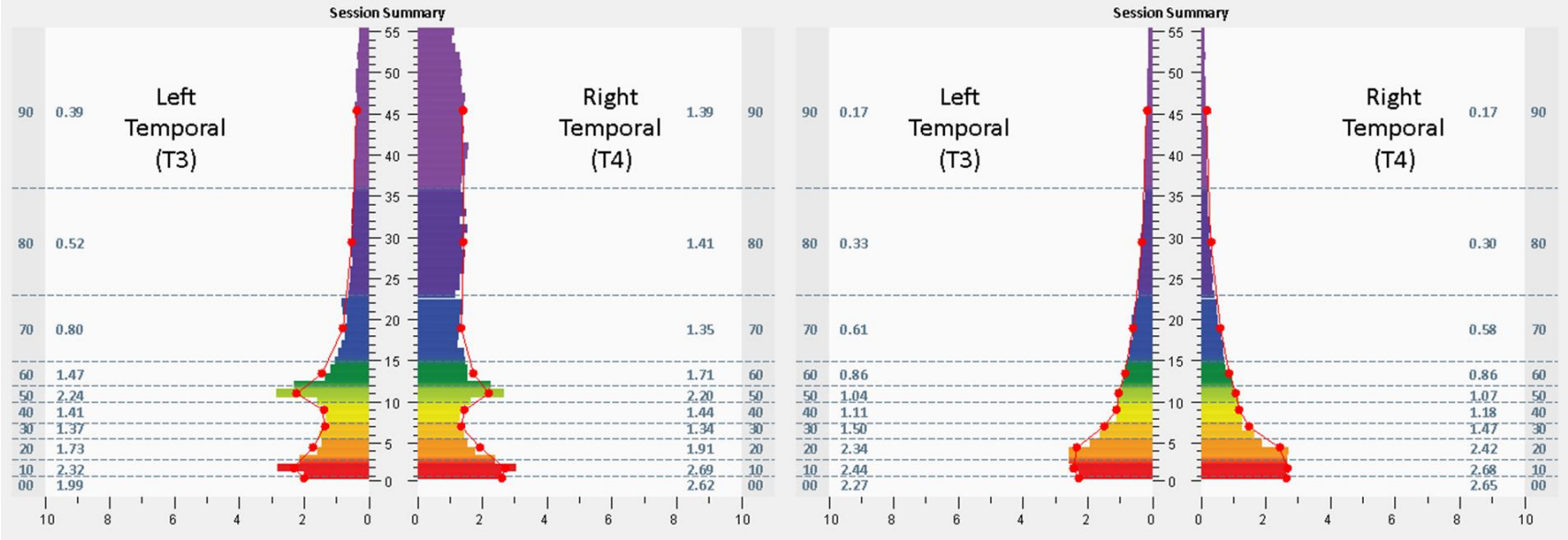
## Autonomic Outcomes

| Key Autonomic Cardiovascular Outcomes | | | |
|---|---|---|---|
| Measure (Units) | Mean Value Baseline (SE) | Mean Change (SE) at V2 | Mean Change (SE) at V3 |
| HF Alpha (ms/mmHg) | 28.1 (3.7) | + 10.9 (4.3)* | + 16.2 (6.4)* |
| Sequence Down (ms/mmHg) | 18.9 (2.2) | + 13.5 (3.5)*** | + 11.0 (3.1)** |
| SDNN (ms) | 62.9 (5.6) | +13.2 (4.9)** | + 18.6 (7.6)* |

* = $p \leq 0.05$ ** = $p \leq 0.01$ *** = $p \leq 0.001$

# Typical shifts seen with HIRREM

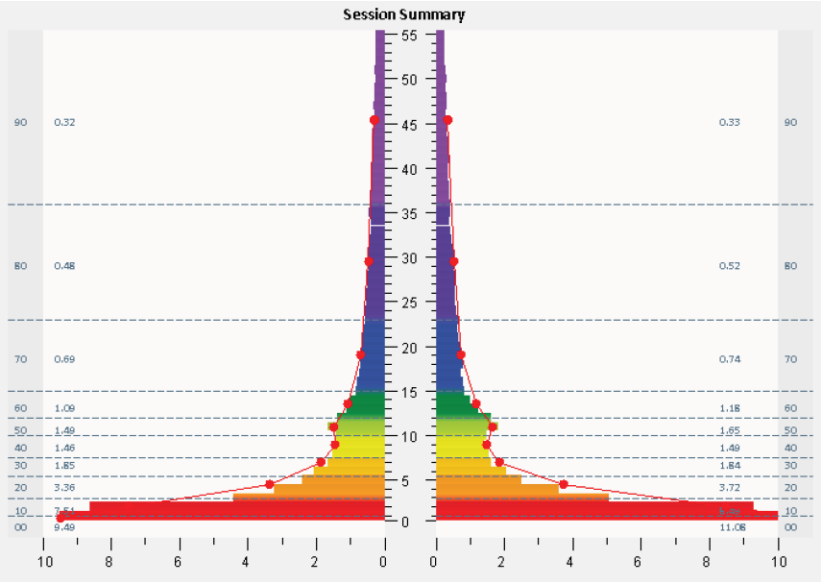
## 23 year old male athlete, T3/T4, EC



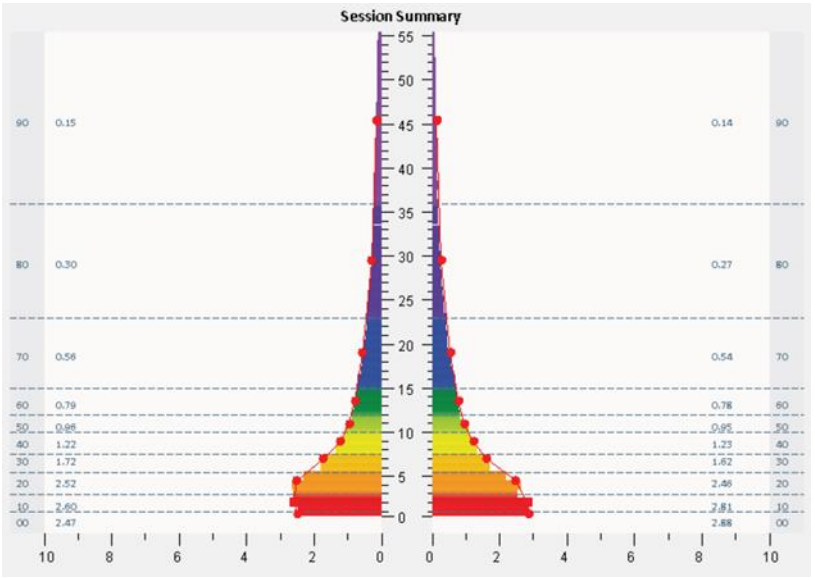

Baseline assessment

9th Session, same location/eye state

# DE 66: 20 y/o athlete, ADHD, TBI, unable to play for > 1 year, can't "see the ball," poor sleep, Adderall as needed

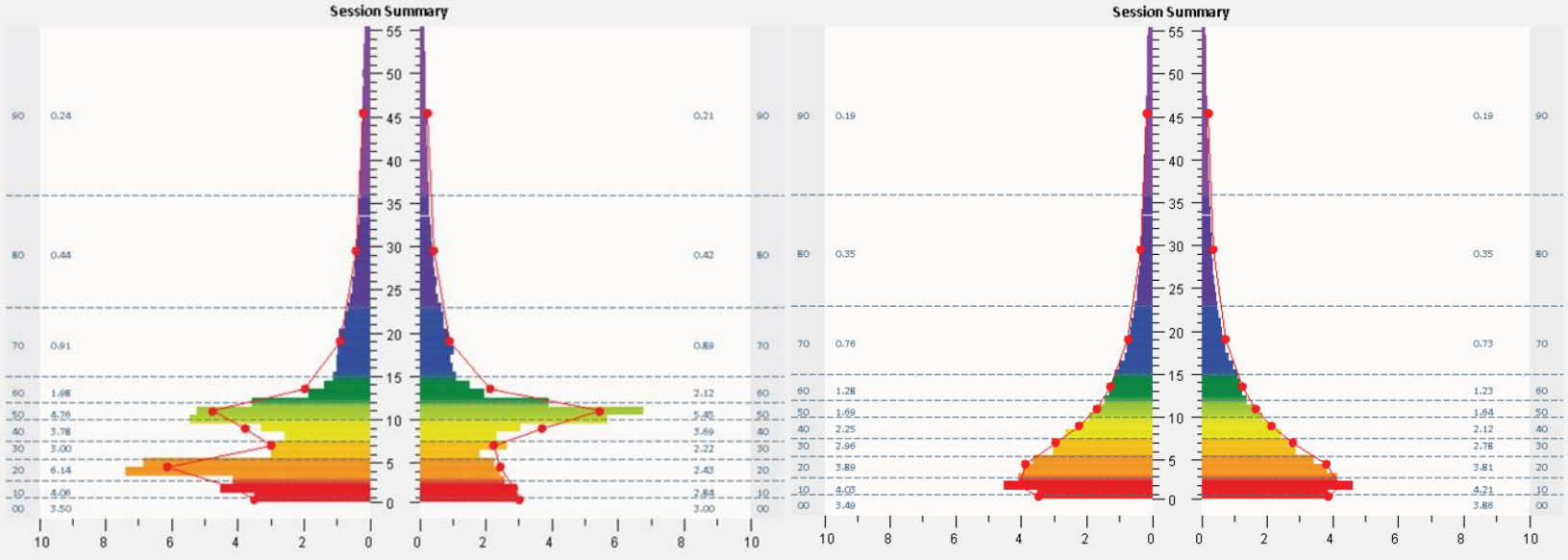



TT EC Assessment
Increased amplitudes in LF's




TT EC 21st session
Now balanced and quieted

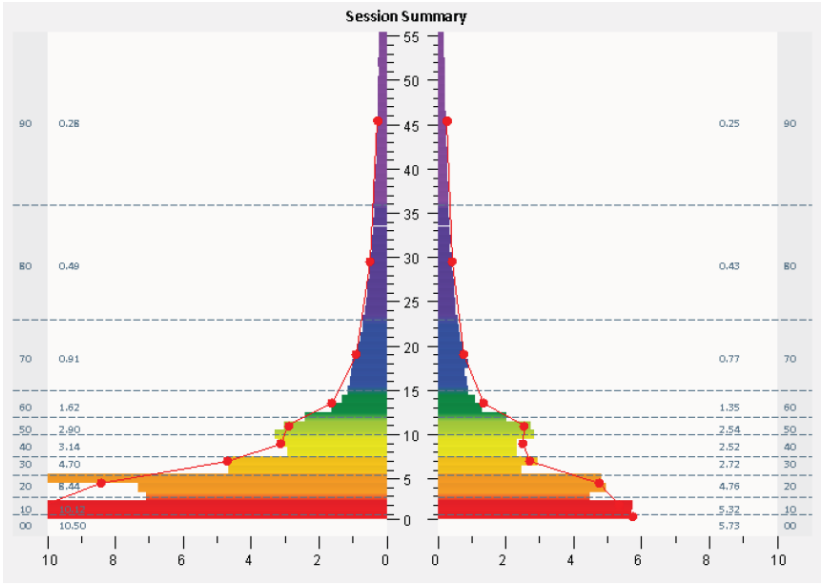
# DE 66: Post-HIRREM
# Post-HIRREM off Adderall, sleeping well, playing baseball again



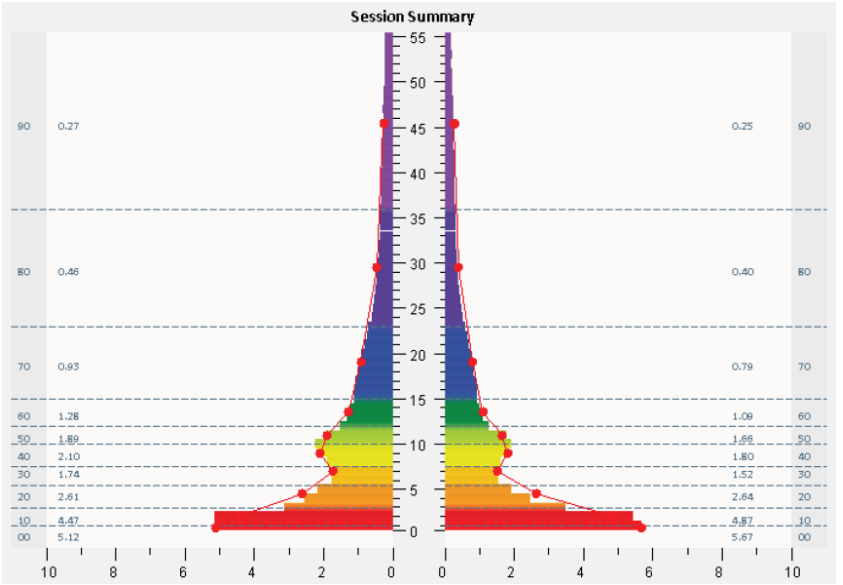

OO EC at assessment
Asymmetry low and mid frequencies

OO EC at 21st session
Balanced and quieted

# DE 66: During Sessions
# Imbalance emerged after video game binge



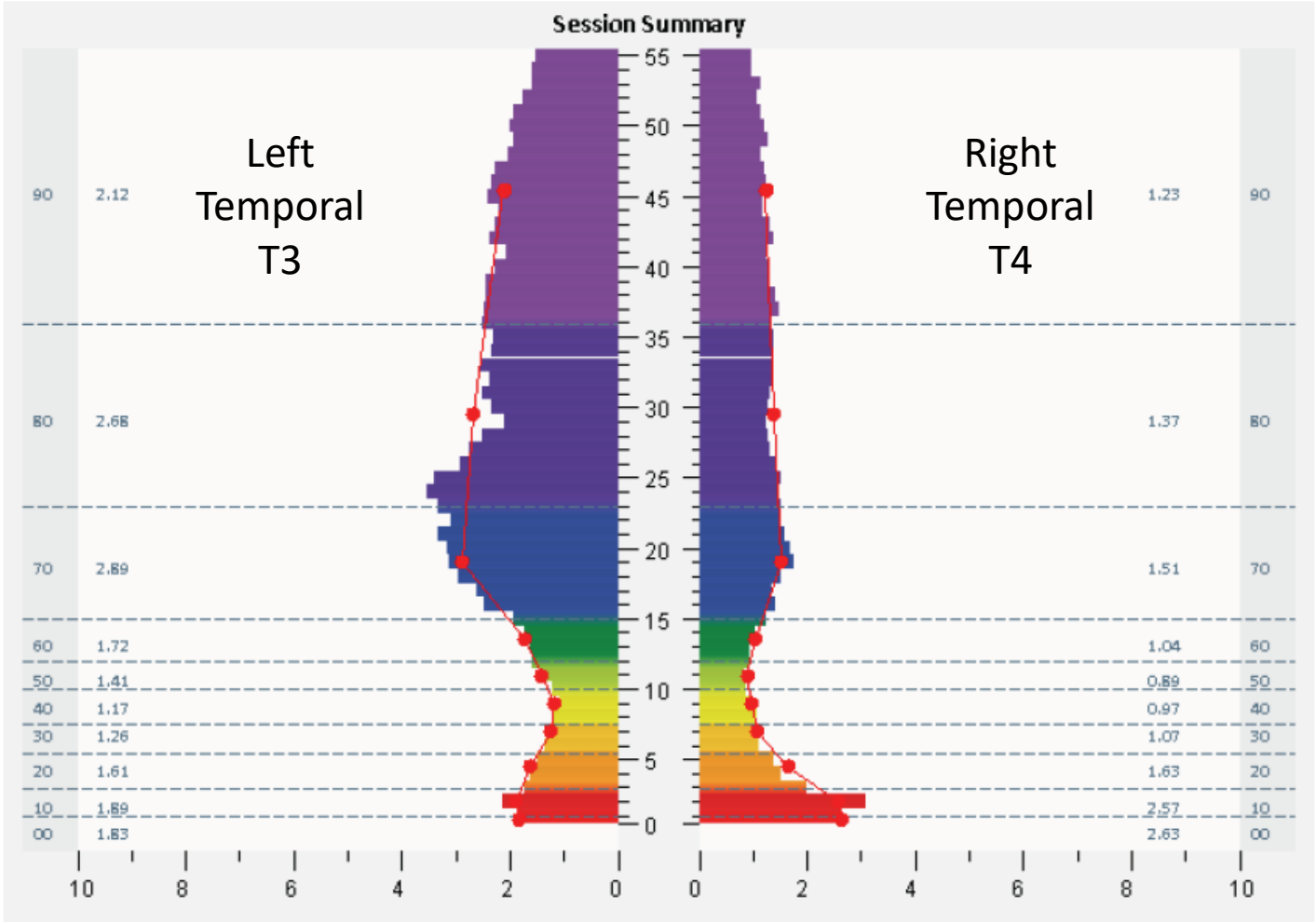

Cerebellar (CBS) 25th session
90% left dominance




Cerebellar (CBS) 29th session
Balanced (10% right dominant)

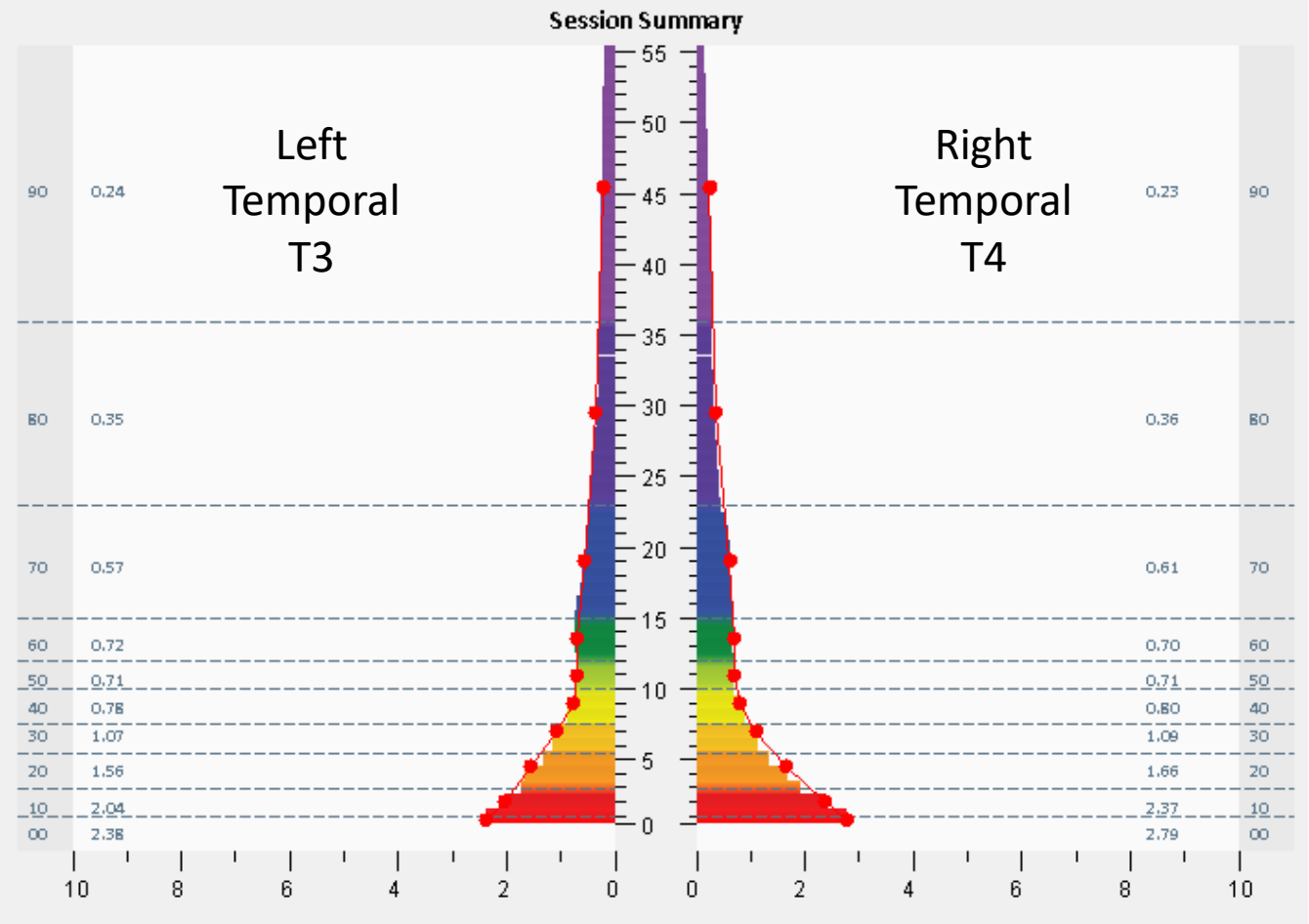
# 38 y/o male s/p IED blast in 2006 with TBI/PTSD

## Pre-HIRREM TT EC with increased HF amplitude bilaterally, and a left dominant pattern (parasympathetic)



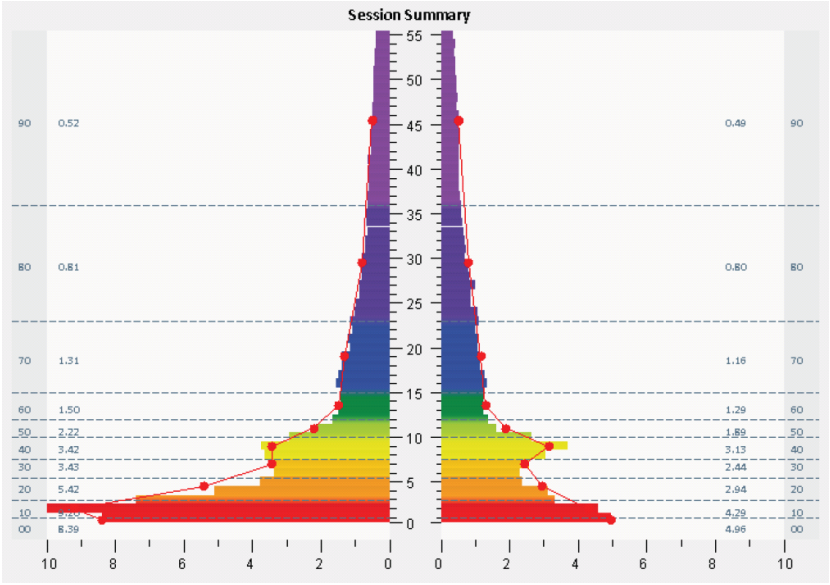
# TT EC pattern with penultimate HIRREM session

## Greatly decreased amplitudes in HF's, balanced pattern



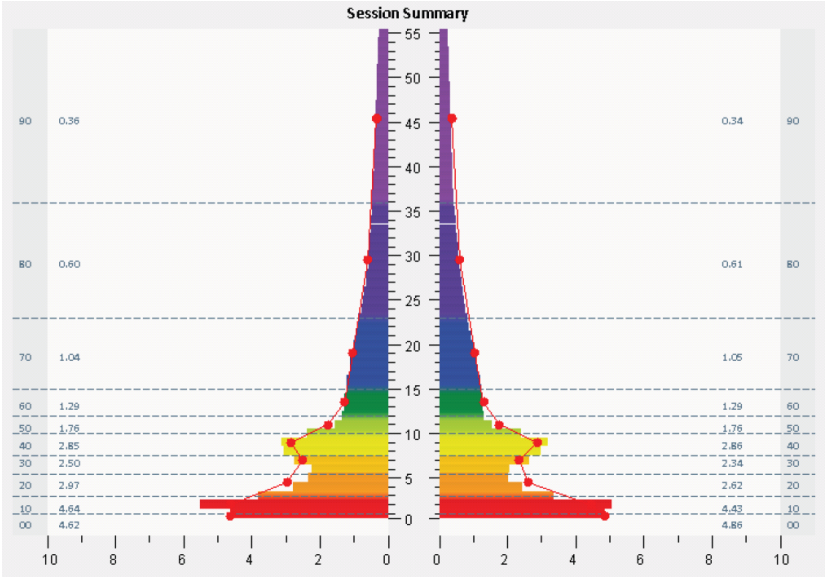
# DE 115: 50 y/o male veteran (1980's) with 1 year of persisting post-TBI symptoms (HA, insomnia, foggy, short fuse)

FPS EO at assessment




114% left dominant LF's

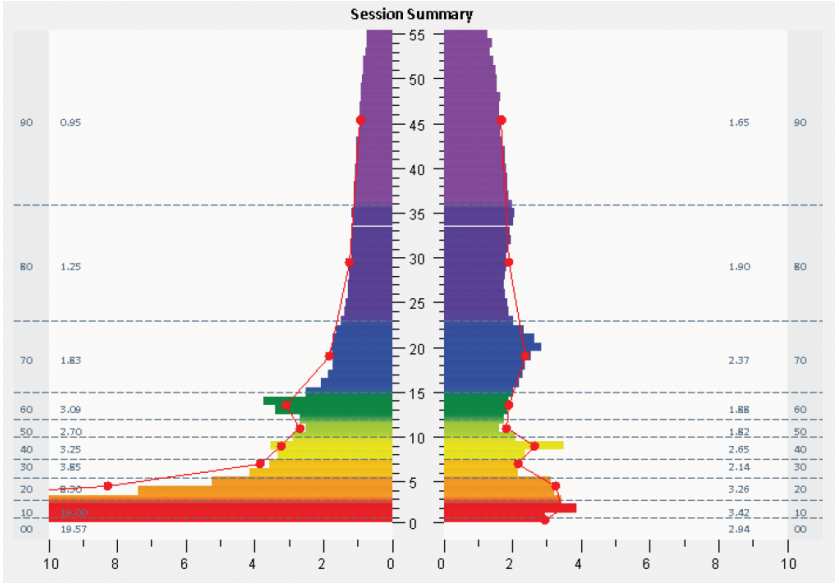
FPS EO 4th session




LF's balanced

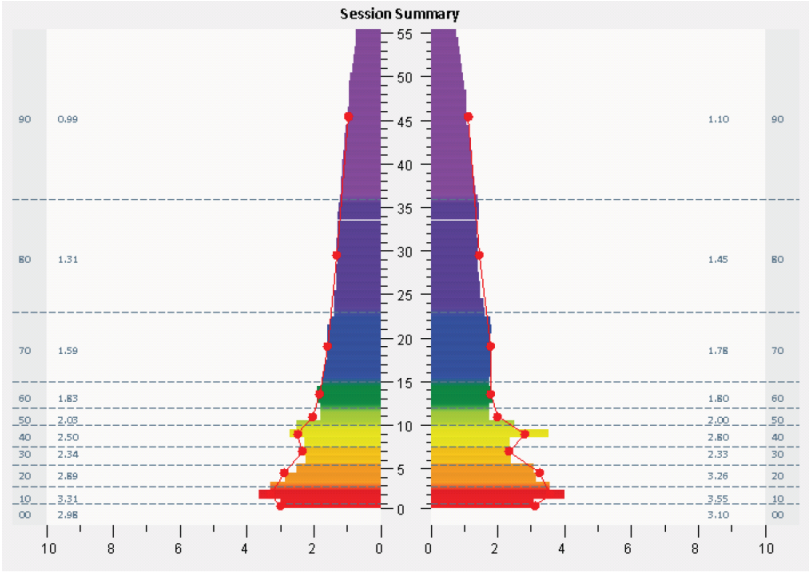
# DE 115: 50 y/o male veteran (1980's) with 1 year of persisting post-TBI symptoms (HA, insomnia, foggy, short fuse)

CC EO 1st session




564% left dominant LF's
74% right dominant HF's

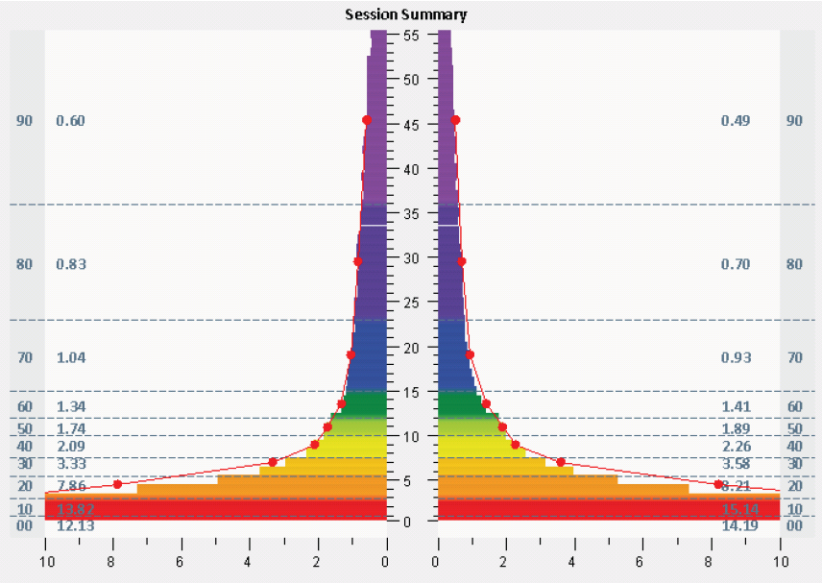
CC EO 3rd session



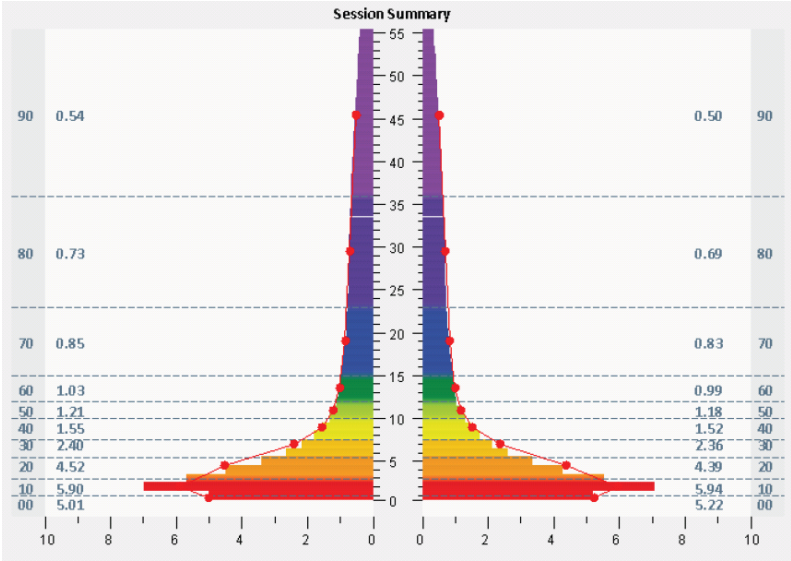

LF's and HF's balanced

# DE 130: 26 y/o male Operator with TBI and post-deployment PTSD

## Frontals, eyes open



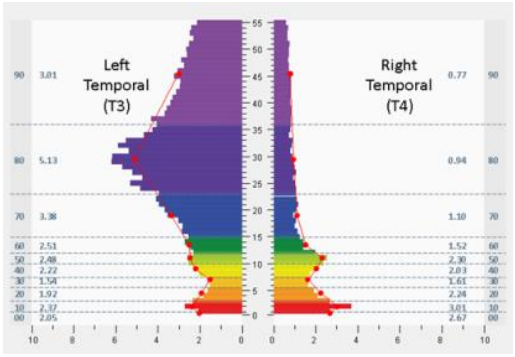

At assessment, no imbalance but hyperarousal in low frequencies (12-15 µv)



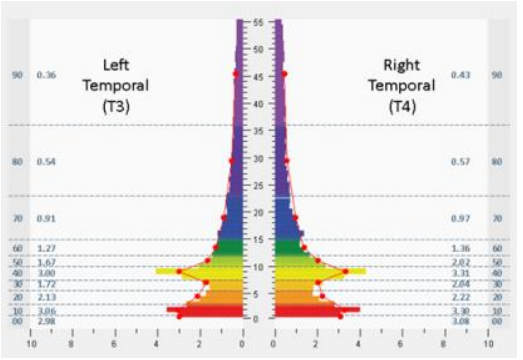

5th HIRREM session with reduced low frequency amplitudes (5 µv)

# HIRREM for Military-related PTS

- 18 participants (15 active duty, most with Navy Seals, 39.5 y/o, 20.5 years in service, 2-12 years of symptoms, 8 deployments)
- 19 HIRREM sessions over 12 days; data collection before, after, and at 1, 3, 6 months. No drop-outs, no serious adverse events
- Significant, clinically meaningful reductions in self-reported symptoms of PTSD, depression, insomnia, and anxiety, with durability to 6 months
- Significantly improved HRV and baroreflex sensitivity
- Significantly improved network connectivity on whole brain rest MRI
- Example of brain electrical pattern changes (29 year old male):




Baseline Assessment
T3/T4 EC




Penultimate Minute
T3/T4 EC 19th Session



Tegeler CL, et al., 2017

# Improved Symptom Outcomes after HIRREM for Military-related PTS

| Key Symptom Outcomes | | | | | |
|---|---|---|---|---|---|
| Measure | Baseline Mean (n=18) | V2 Post-HIRREM (n=18) | V3 1 month (n=18) | V4 3 months (n=18) | V5 6 months (n=15) |
| PCL-M | 48.4 (12.9) | -11.2 (8.2)*** | -17.7 (12.8)*** | -16 (12.5)*** | -12.9 (8.9)*** |
| CES-D | 24.7 (11.5) | -13.3 (9.5)*** | -15.1 (11.6)*** | -13.7 (11.2)*** | -10.3 (8.0)*** |
| ISI | 16.0 (5.5) | -5.4 (4.6)*** | -9.2 (5.3)*** | -5.9 (7.4)** | -5.8 (5.5)*** |
| GAD-7 | 11.6 (5.7) | -5.3 (4.4)*** | -6.2 (5.5)*** | -5.3 (7.5)** | -4.5 (6.5)** |

* = $p \leq 0.05$
** = $p \leq 0.01$
*** = $p \leq 0.001$

For PCL-M, 72% reported a Minimal Clinically Important Difference (≥ 10 point reduction) at one month, with 61% still reporting reductions reaching the MCID after 6 months



Tegeler, et.al., 2017

# Improved Autonomic Cardiovascular Regulation

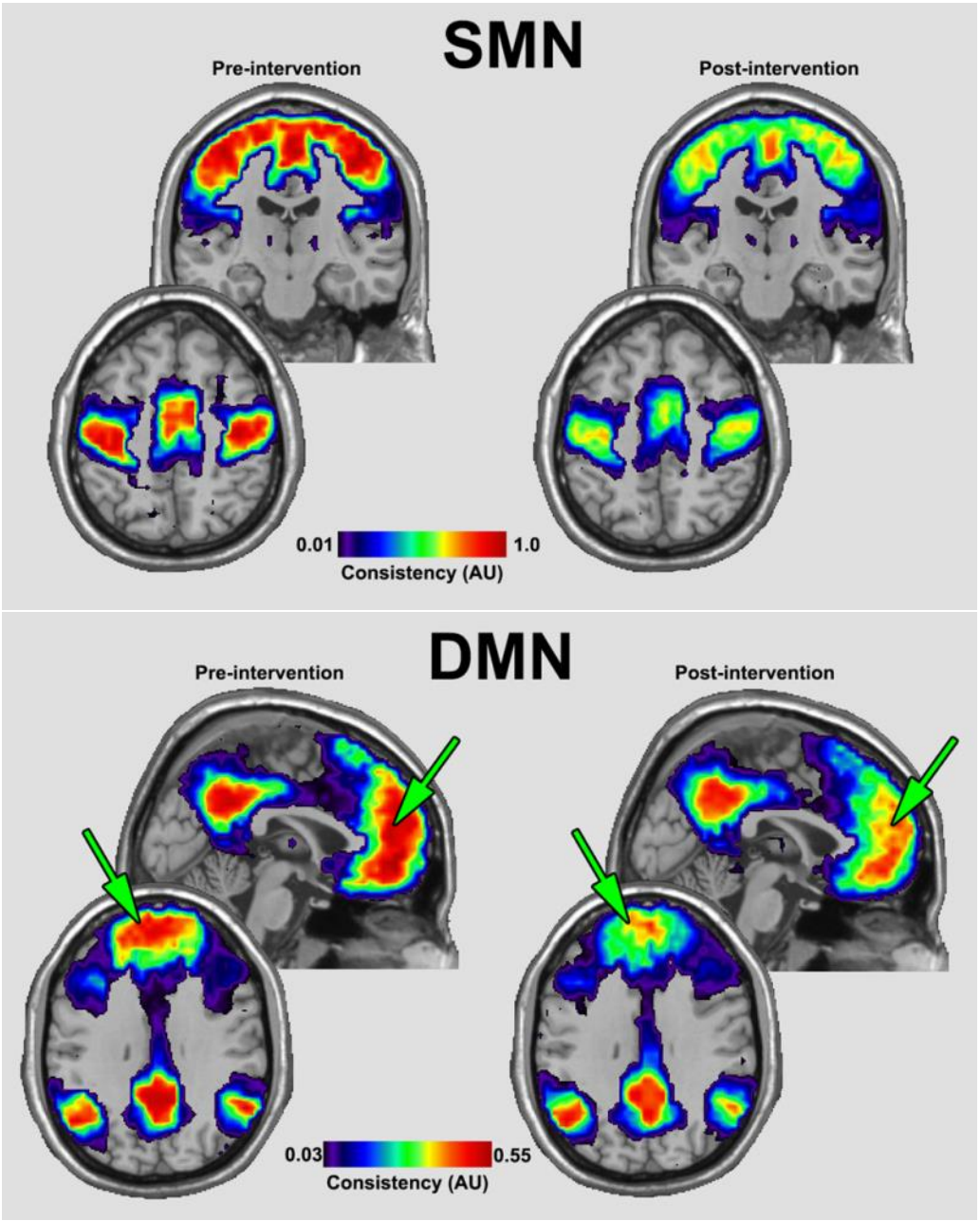
| Key Autonomic Cardiovascular Outcomes | | | | |
|---|---|---|---|---|
| Measure (Units) | Mean Value Baseline (SE) | Mean Value Post-HIRREM (SE) | Mean Change (SE) | p value |
| HF Alpha (ms/mmHg) | 17.61 (2.56) | 27.28 (3.84) | 9.67 (3.09) | p = 0.005 |
| Up SBP (ms/mmHg) | 13.06 (1.87) | 21.45 (2.99) | 8.39 (3.04) | p = 0.011 |
| Down SBP (ms/mmHg) | 14.43 (1.78) | 22.03 (2.60) | 7.61 (2.42) | p = 0.005 |
| Sequence All (ms/mmHg) | 13.75 (1.74) | 21.41 (2.37) | 7.66 (2.20) | p = 0.006 |
| SDNN (ms) | 50.98 (5.40) | 62.97 (5.23) | 11.98 (3.46) | p = 0.003 |
| rMSSD (ms) | 32.76 (4.33) | 45.98 (5.33) | 13.22 (3.00) | p < 0.001 |
| SAP (mmHg) | 131.26 (3.18) | 125.39 (2.92) | -5.87 (1.91) | p = 0.020 |



Tegeler, et.al., 2017

# Whole Brain Rest MRI
# Network Community Consistency Maps

- Pre- to post-HIRREM changes evaluated using a permutation statistic analysis
- Sensorimotor Network (SMN)
  - Baseline network hyper-connectivity significantly reduced ($p = 0.005$)
- Default Mode Network (DMN)
  - Baseline frontal hyper-connectivity significantly reduced ($p = 0.009$)
- Salience Network (SN)
  - Trends for increased connectivity for the insula bilaterally
- Central Executive Network (CEN)
  - No meaningful changes






Lee, 2018, J Neuroimaging

# Narrative Feedback Quotes
## Military Pilot Study

- MP01: *I must say though that the two weeks down there did me a world of good. Thank you again and please tell everyone "hi" for me.*
  (V5 scores; PCL-M -24, ISI -9, CES-D -23 points)
- MP20: *I feel that you have restored my hope in life and given me another shot at this world.*
  (PCL-M -27 points at V2)
- MP21: *Thanks for everything. You have given me a second chance at being happy in life!!*
  (CES-D -30 points at V2)

# HIRREM Research Program at WFSM

## Summary of Overall HIRREM Results

- Precision-guided, noninvasive, patient-centric process
- Supports the brain to balance, repair itself
- Enrolled > 500 participants in 8 clinical studies
- Observed reduced self-reported symptoms (insomnia, depression, stress, anxiety, others), including TBI
- Improved objective autonomic cardiovascular regulation (HRV, baroreflex sensitivity, BP)
- Improved brain network connectivity on MRI (military)
- No serious adverse events, very low drop out rate

# Future Directions

- Continue current studies
- HIRREM re-branded to Cereset (Cerebral Reset) – Cereset Research for our new research projects
- CR uses the same core technology, with some upgraded components, placement of 4 sensors, more standardized operating procedures
- Shorten session time, reduce number of sessions, reduce variability, and operator dependence
- Increase scalability and generalizability

# Directions in 2019

- Randomized trials to extend pilot data (mTBI, first responders, caregivers, others)
- Focus on wellness, prevention, improve sleep, mitigate impact of stress *(turn off the stress spigot before it turns into a raging torrent downstream)*
- Explore new wearable, limited scope home use device (temporal and frontal poles only)
- Focus on nurses, medical students, employees, physicians, others
- Webpage: www.wakehealth.edu/HIRREM