“Integrative Management of Sensitized Chronic Pain with Autonomic Self-Regulation”
 Presenter: JP Ginsberg, PhD
 Date: Thursday, October 19, 2016
 09:00A-04:30P

I. Sensitized Chronic Pain (SCP) and Autonomic Self-Regulation (ASR) 09:50A-10:50A

II. Research in Application of ASR for SCP 01:45P-02:30P
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Disclaimer and Disclosure

• Not expert in cardiology, pain, or medication
  • Neuropsychologist with some specialization in cognitive psychophysiology

• No conflicts of interest, affiliations, or product endorsements

• Slides are original or freely available from internet with acknowledgment
Prelude
The Opioid Epidemic in the U.S.

In 2015...

12.5 million
People misused prescription opioids

2.1 million
People misused prescription opioids for the first time

33,091
People died from overdosing on opioids

2 million
People had prescription opioid use disorder

15,281
Deaths attributed to overdosing on commonly prescribed opioids

828,000
People used heroin

9,580
Deaths attributed to overdosing on synthetic opioids

135,000
People used heroin for the first time

12,989
Deaths attributed to overdosing on heroin

$78.5 billion
In economic costs (2013 data)


Updated May 2017. For more information, visit: http://www.hhs.gov/omi/
PAIN MEDICATION ADDICTION

<table>
<thead>
<tr>
<th>Negative Punishment</th>
<th>Negative Reinforcement</th>
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<tr>
<td>Suspension</td>
<td>Medication</td>
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<td>‘Time-out’</td>
<td>Self-Medication</td>
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<td>Positive Punishment</td>
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<td>Fines</td>
<td>Honors</td>
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<td>Shocks (experimental)</td>
<td>Addiction</td>
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PAIN MEDICATION ADDICTION INCLUDES SUFFERING DUE TO STRESS AND DEPRESSION IN ADDITION TO UNRELIEVED PAIN AND THE BEHAVIORAL DYSFUNCTION OF ADDICTION – NEED TO REPLACE POSITIVELY REINFORCING CHARACTERISTICS OF MEDICATION.
The Backfire Effect
I. **Sensitized Chronic Pain (SCP) and Autonomic Self-Regulation (ASR)** (60 minutes)

- Define SCP and ASR
- Shared physiological basis of SCP and ASR
- How ASR reduces SCP
Sensitized Chronic (Nociceptive) Pain: Stress and Depression
Not all pain is the same: The pathophysiology of painful diseases

**Nociceptive pain**
Caused by activity in neural pathways in response to potentially tissue-damaging stimuli

- Postoperative pain
- Mechanical low-back pain
- Sports/exercise injuries
- Arthritis
- Sickle cell crisis

**Neuropathic pain**
Initiated or caused by a primary lesion or dysfunction in the nervous system

- Neuropathic low-back pain
- Diabetic neuropathy
- Central post-stroke pain
- Postherpetic neuralgia
- Peripheral neuropathy
- CRPS
- Trigeminal neuralgia

**Mixed**

Rollin Gallagher, MD, MPH
dhss.delaware.gov/dsamh/files/2007gallagherii.pps
Understanding Pain and Pain Amplification. Robert Benett, MD.
http://www.myalgia.com/Pain_amplification/Overview.htm
C Fiber

1. Peripheral tissues
2. Spinal cord

Nociceptive Pain

C Fiber

Sub P → NK1

Glut

NMDA → AMPA
Nociceptive Pain

C Fiber

= STRESS

1. Peripheral tissues

2. Spinal cord

3. Brain

Sub P → NK1

NMDA → AMPA

Glut
To Whom It May Concern:

C Fiber

Descending Modulation of Pain Influences from brainstem nuclei and forebrain on spinal transmission of incoming peripheral pain signals:

- periaqueductal gray in upper brain stem
- serotonergic from nucleus raphe magnus
- adrenergic from locus coeruleus
- dopaminergic from ventral tegmental area and hypothalamus
A. Antidepressants (e.g. amitriptyline, duloxetine) reduce pain by increasing descending pain inhibition from catecholamines.
B. Anti-epileptics (e.g. gabapentin, pregabalin) reduce pain by limiting release of glutamate from afferent peripheral C fiber.
C. Opioids (e.g. morphine) block pain by activating opioid receptors and inhibiting substance P.
ACUTE NOCICEPTIVE PAIN – I

- Inflammation / nerve injury stimulate nociceptive information to dorsal horn
- Ascends to brainstem, gated in thalamus
ACUTE NOCICEPTIVE PAIN – II

- Inflammation / nerve injury stimulate nociceptive information to dorsal horn
- Ascends to brainstem, gated in thalamus
- Cognitive appraisal in SI cortex
- Acute pain increases arousal via sympathetic and GC routes (excitatory reciprocal link between somatosensory and limbic cortices)
ACUTE NOCICEPTIVE PAIN – II

- Inflammation / nerve injury stimulate nociceptive information to dorsal horn
- Ascends to brainstem, gated in thalamus
- Cognitive appraisal in SI cortex
- Acute pain increases arousal via sympathetic and GC routes (excitatory reciprocal link between somatosensory and limbic cortices)
- ➡️ Stress response
The Stress Response:
Sympathomedullary Pathway (SAM)
The Hypothalamic Pituitary-Adrenal (HPA) System
ADRENAL GLANDS

- Adrenal Cortex
- Adrenal Medulla
Short-term stress response:
1. Increased heart rate
2. Increased blood pressure
3. Liver converts glycogen to glucose and releases glucose to blood
4. Dilation of bronchioles
5. Changes in blood flow patterns leading to increased alertness, decreased digestive system activity, and reduced urine output
6. Increased metabolic rate

Long-term stress response:
1. Retention of sodium and water by kidneys
2. Increased blood volume and blood pressure
3. Proteins and fats converted to glucose or broken down for energy
4. Increased blood sugar
5. Suppression of immune system

Diagram:
- SAM (Spinal cord to Adrenal medulla to Kidney)
- HPA (Hypothalamus to CRH to Corticotrope cells of anterior pituitary to ACTH to Adrenal cortex)
- Catecholamines (epinephrine and norepinephrine)
- Mineralocorticoids and Glucocorticoids
HPA STRESS RESPONSE

- CRH and/or AVP released
  - → anterior pituitary gland
- Stimulates ACTH release
  - → adrenal cortex
  - → triggers release of glucocorticoid and pro-inflammatory cytokines (e.g. IL-1β) release
STRESS RESPONSE NEGATIVE FEEDBACK: I

- Glucocorticoid → negative feedback via GR of HC, PVN, P, and AC
  - ↓ CRH, AVP release
  - ↓ ACTH release
  - ↓ GC
  - ↓ IL-1β
Stress ends

STRESS RESPONSE NEGATIVE FEEDBACK: II

- Glucocorticoid → negative feedback via GR of HC, PVN, P, and AC
  - ↓ CRH, AVP release
  - ↓ ACTH release
  - ↓ GC
  - ↓ IL-1β
- Mineralocorticoid → negative feedback via GR in HC
  - ↑ Glu → GABA ↑
- Brainstem 5-HT/NE release
- Amy
- P
- neurokinin SP

Stress ends
ACUTE NOCICEPTIVE PAIN – III

- Inflammation / nerve injury stimulate nociceptive information to dorsal horn
- Ascends to brainstem, gated in thalamus
- Cognitive appraisal in SI cortex
- Acute pain increases arousal via sympathetic and GC routes (excitatory reciprocal link between somatosensory and limbic cortices)

- \(\rightarrow\) Stress response
- \(\rightarrow\) Descending pain modulation

PAIN ENDS
• Inflammation / nerve injury stimulate nociceptive information to dorsal horn
• Ascends to brainstem, gated in thalamus
• Cognitive appraisal in SI cortex
• Acute pain increases arousal via sympathetic and GC routes (excitatory reciprocal link between somatosensory and limbic cortices)

⇒ Stress response
⇒ Descending pain modulation

PAIN DOES NOT END
CHRONIC STRESS AND PAIN
HPA AXIS
Neuropathic Pain
Neuropathic Pain

Mineralocorticoid

Glucocorticoid

Adrenal gland

Cytokine

Pituitary

PVN CRH AVP

IL-1β

Stress

ACTH

Pain

CHRONIC STRESS AND PAIN
HPA AXIS
CHRONIC STRESS AND PAIN CAUSES
CENTRAL SENSITIZATION AND DEPRESSION

- Pain does not end →
- Stress does not end →
- ‘HPA overdrive’ →
- Loss of GC inhibition of pro-inflammatory cytokines
- Proliferation of peripheral inflammation
- Heightened pain
- Disinhibition of descending cortical pain modulation (‘nociceptive braking’) →
- Depletion of catecholamines – (nor)adrenaline from locus coeruleus and dopamine from hypothalamus
- Depressed behavior and mood
- “THE IMMUNE RUNAWAY TRAIN”
In sensitized chronic nociceptive pain, descending top-down modulation of pain is lost.
There Are Many Painful Diseases and Pain Diseases

Inflammatory / Immunological Mediation

Nociceptive pain

Neuropathic pain

MIXED PAIN STATES:
cancer, low back, pelvic, facial, crush injury, amputation

SENSITIZATION

Postoperative pain

Mechanical low back pain

Sports/Exercise injuries

Central post-stroke pain

Trigeminal neuralgia

CRPS*

Radiculopathy (sciatica)

Diabetic neuropathy

Phantom pain

*Complex regional pain syndrome.
Maintain and increase
- Sick role
- Secondary gain
- Resource drain
- Loss of social support

Pathology:
- Muscle atrophy, weakness;
- Bone loss;
- Immunocompromise
- Depression

Neuro-psychopathology of maintenance:
- Encoded anxiety dysregulation
  - PTSD
- Emotional allodynia
- Mood disorder
- Cognitive disorder
- Substance abuse

Acute injury and pain

Central Sensitization
- Neuroplastic changes

Disability
- Less active
- Kinesophobia
- Decreased motivation
- Increased isolation
- Role loss
- Sleep disorder

Peripheral Sensitization:
New Na+ channels cause lower threshold

Neurogenic Inflammation:
- Glial activation
- Pro-inflammatory cytokines
- Blood-nerve barrier disruption
Depression is an expression of chronic stress in humans

Rodents show stress in their behavior; humans show stress in their behavior and mood

- Chronically stressed rodents have a neuromodulator profile strikingly similar to depressed people
  - Animals cannot report mood!
- Depressed people are stressed and report depressed mood
- However, not all stressed people are depressed (.e. not all stressed people report depressed mood)
- The difference between stress and depression in people appears to be cortisol: when high, depression is expressed; when low, stress is the phenotype
<table>
<thead>
<tr>
<th>Chronic stress (rodents)</th>
<th>Clinical depression (humans)</th>
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</thead>
<tbody>
<tr>
<td>↑CRH/CRH mRNA</td>
<td>↑CRH/CRH mRNA</td>
</tr>
<tr>
<td>↓CRH receptor affinity/number</td>
<td>↓CRH receptor affinity/number</td>
</tr>
<tr>
<td>↑AVP/AVP mRNA</td>
<td>↑AVP/AVP mRNA</td>
</tr>
<tr>
<td>↑CSF levels of CRH/AVP</td>
<td>↑CSF levels of CRH/AVP</td>
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<tr>
<td>↑Co-expression of CRH/AVP</td>
<td>↑Co-expression of CRH/AVP</td>
</tr>
<tr>
<td>↓GR/MR number/function</td>
<td>↓GR/MR number/function</td>
</tr>
<tr>
<td>Altered plasma ACTH concentration</td>
<td>Altered plasma ACTH concentration</td>
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<tr>
<td>Altered circadian rhythmicity</td>
<td>Altered circadian rhythmicity</td>
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<tr>
<td>Adrenal supersensitivity to ACTH</td>
<td>Adrenal supersensitivity to ACTH</td>
</tr>
<tr>
<td>↑Corticosterone</td>
<td>↑Cortisol (*cortisol is ↓ in PTSD)</td>
</tr>
<tr>
<td>↓Negative feedback</td>
<td>↓Negative feedback</td>
</tr>
<tr>
<td>Adrenal hypertrophy</td>
<td>Adrenal hypertrophy</td>
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<tr>
<td>Pituitary hypertrophy</td>
<td>Pituitary hypertrophy</td>
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<tr>
<td>Exaggerated corticosterone response</td>
<td>Exaggerated cortisol response</td>
</tr>
<tr>
<td>Cognitive deficit</td>
<td>Cognitive deficit</td>
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<tr>
<td>Behavioral disturbance</td>
<td>Behavioral and mood disturbance</td>
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Selection of Diagnoses and Symptoms that Suggest Central Sensitization

• Chronic abdominal pain
• Chronic fatigue
• Chronic joint pain
• Chronic low-back pain
• Chronic non-specific pain
• Chronic tension headaches
• **Fibromyalgia**
• **Irritable bowel syndrome**
• Multiple drug or food allergies or intolerances (self-diagnosed)
• Chronic pelvic pain
• Postural orthostatic tachycardia syndrome (POTS)
• **Temporomandibular, myofascial pain disorders**
• Whiplash-associated pain disorders
• Widespread non-specific pain
FIBROMYALGIA

- Etiology not yet validated
- One widespread hypothesis is central sensitization
  - People with fibromyalgia have a lower threshold for pain due to increased reactivity in the nociceptive pain processing pathway from periphery through spinal cord and brain
  - Neuropathic pain and major depressive disorder often co-occur with fibromyalgia
- May be due to genetic or epigenetic factors
  - Polymorphisms of genes involved in serotoninergic, dopaminergic, catecholaminergic, monoaminergic, glutamatergic, neurotrophic, opioid and/or proinflammatory cytokine signaling.
  - These polymorphisms are not specific for fibromyalgia
- Known to be associated with allied disorders
  - chronic fatigue syndrome
  - irritable bowel syndrome
  - Depression
- Individuals with the 5-HT2A receptor 102T/C polymorphism at increased risk of fibromyalgia.
- In these vulnerable individuals, psychological stress or illness can cause abnormalities in inflammatory and stress pathways
  - Dysregulate pain sensitivity and mood
  - The ‘volume’ of the neurons are abnormally high
  - Hyper-excitability is accompanied by
    - Under-activity of CNS inhibitory pain pathways
    - Neurochemical dysregulation results in problems in mood, sleep, and energy,
Individuals with FM (red) given a low-intensity stimulus produced moderate pain (red). The same or higher intensity stimulus in controls given caused the same amount of pain (green). However, controls given nearly twice as much pressure caused comparable amounts of pain as lower intensity stimuli in FM individuals (blue).

Healing irritable bowel syndrome with diaphragmatic breathing

Posted: June 23, 2017
Erik Peper, Lauren Mason and Cindy Huey

• Slow diaphragmatic abdominal breathing to establish health
  • “Digestion and regeneration occurs when the person feels safe.”

• Erect versus collapsed posture note that there is less space for the abdomen to expand in the protective collapsed position

• Observe how you inhale

• Observe and change your breathing during the day

• Learn diaphragmatic breathing and the correct way to breathe

• Take a deep breath. If you feel you are moving upward and becoming a little bit taller, your breathing is wrong

“A breath of fresh air-Improve health with breathing”
Temporomandibular joint dysfunction
Also called: TMJ, TMJ syndrome
Pain and compromised movement of the jaw joint and the surrounding muscles.

‘Adrenaline (norepinephrine) aggravation theory of pain’: effects via sympathetic innervation of human muscle spindle

“... sympathetic innervation is not restricted to the blood vessels supplying spindles. Knowledge about direct sympathetic innervation of the muscle spindle might expand our understanding of motor and proprioceptive dysfunction under stress conditions, for example, chronic muscle pain syndromes. ‘
Autonomic Self-Regulation (ASR)
Recommendation that six non-pharmacologic treatments be made available to every current and former service member with chronic pain ... These treatments replace some portion of opioid therapy, minimizing both exposure that could lead to an opioid use disorder and excessive prescribing that leaves behind unused opioids for misuse, abuse, or diversion.
Heart Rate Variability, Chronic Pain, and Rehabilitating the Autonomic Nervous System

By Raouf Gharbo, DO, and J.P. Ginsberg, PhD

Integrative Management of Sensitized Chronic Pain with Ambulatory Autonomic Self-Regulation

By J.P. Ginsberg, PhD
The three components of Autonomic Self-Regulation are:

1. HRV Biofeedback = resonant frequency breathing
2. Mindful attention
3. Positive emotional state
ASR coaching essential elements

• Paced breathing at resonant frequency and the production of HRV Coherence through HRV Biofeedback

• Mindfulness or imagery focused on breathing and the heart. Focused attention on air entering and exiting the chest and passing thorough the heart

• Positive emotional state (PES). Occupy the mind during the HRVB session with thoughts of compassion, gratitude, appreciation, etc.

‘COHERENCE’
HRV, HRV Coherence, and HRV Biofeedback (HRVB)

• Interbeat Interval – ‘ibi’
• instantaneous heart rate (HR)
• R-R or N-N

Heart Rate Variability (HRV)

250-350 msec

Average Heart Rate = 60 BPM

HRV is Low (0)

HRV is High
The sympathetic and parasympathetic branches of the ANS are related by a complex non-liner function. A change in one branch may cause and increase, decrease, or no change in the other branch. “Left foot braking”

The sympathetic and parasympathetic branches of the ANS are related by a complex non-linear function.

A change in one branch may cause an increase, decrease, or no change in the other branch.
‘Sympatho-vagal (or autonomic system) function’ is better – and a complex function at that

Function: the relation between a set of inputs and a set of permissible outputs
HRV is an indicator of autonomic function. Variability is equal to variance, which is maximized when beat-to-beat intervals increase and decrease in a smooth rhythm, one that approximates a sine wave. A smooth sinusoidal rhythm of ibi’s is characteristic of a healthy heart under resting conditions; the amount of variability is directly related to respiration rate, and many inter-individual factors such as age, gender, height, and fitness level.
IBI = 975 + 225 * COS(t * PI)

Mean = 65 BPM = 923 msec

Min BPM = 50 = Max IBI = 1200 msec

Max BPM = 80 = Min IBI = 750 msec

2.5 seconds of heart beat data
72 beats per minute @ 1 cycle/10 sec = 12 beats/cycle
HRV is directly related to respiratory cycle
In Diaphragmatic Breathing, inhalation increases thoracic cavity volume (draws air in) due to active contraction of diaphragm; exhalation decreases cavity volume (expels air) and is passive.
Respiratory Pump alone will produce cardiac acceleration and deceleration “RSA” or cardio-respiratory coupling

Increasing the depth of respiration promotes venous return through changes in right atrial (chest cavity) pressure. Right atrial pressure falls during inspiration which facilitates venous return. During inspiration, the chest wall expands and the diaphragm descends. This expansion causes the right atrial pressure to fall. When pressure falls, cardiac rate accelerates. During expiration, the opposite occurs. Increasing right atrial pressure impedes venous return. The net effect of respiration is that increasing the depth of ventilation facilitates venous return.
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Attaining Coherence: Resonance Frequency Breathing (RFB)

• HRV is related to respiratory cycle
• At ~ 6 breaths/minute
  • HRV and respiratory cycle synchronize
  • HRV is maximized
  • Resonant Frequency Breathing
• ‘Coherence’

Note: 6 breaths/min=10 seconds per breath=0.1 Hz)
Resonance is the tendency of a system to oscillate with greater amplitude at some frequencies than at others. Relative maximum frequency of oscillation is the system's resonance frequency. At these resonance frequency, even small periodic driving forces can produce large amplitude oscillations.

Pushing a person in a swing is an example of resonance. Pushing a swing in time with its resonant frequency will make the swing go higher and higher (maximum amplitude), while attempts to push it at a faster or slower tempo results in smaller arcs.
Baroreceptor Reflex Connections
Initiated by respiration, the baroreflex links HR and VT via CNS using feedback from blood pressure. Oscillations in each system reach maximum amplitude at resonance frequency.
Nervous system pathways shared by sensitized chronic pain and ASR:

- Somatosensory cortex
- Hypothalamus (periventricular nucleus) \(\rightarrow\) dorsal spinal column
- HPA \(\rightarrow\) adrenal cortex
- Adrenal cortex \(\rightarrow\) glucocorticoids
- Peripheral pro-inflammatory cytokines
Coherence of Cardiac Rhythm

coherence.com (Richard Brown, MD and Stephen Elliot, Ph.D.)

30 BrPM (0.5 Hz), HRV(avg) = 2
7.5 BrPM (0.125 Hz), HRV(avg) = 11
5.5 BrPM (0.092 Hz), HRV(avg) = 34

The difference between the highest and lowest BPM is shown along the center; averaging across consecutive maxima yields HRV(avg), one of the many measures of HRV.

Baroreflex activates resonance (‘Coherence’)

RFB ➔
When HRV Coherence is attained, the spectral peak occurs at a frequency around 0.1 Hz
Transformation of a time series to a frequency spectrum is done with the Fourier transform. The transformed frequency spectrum is analyzed in terms of ‘power’ or area under the curve, across a range of frequencies. Power is directly related to variance of the untransformed time series.

- 0.1 Hz = 1 cycle/10 sec
- 10 sec/cycle = 6 cycles/minute
- HRV peak @ 0.1 Hz indicates Coherence
Mindfulness books, cd’s, online courses, ceu’s
Mindfulness Defined
“Moment-to-moment non-judgmental awareness”

Mindfulness in Practice
• Body Scanning
  • Lying on back
  • Quiet
  • Focus attention on organs
• Mindfulness (meditation)
  • Secular
• Yoga postures

Effects of Mindfulness
• Improves quality of life
• No evidence that Mindfulness prevents or cures disease
  • Not recommended to lower blood pressure
Exploring the Promise of Mindfulness as Medicine

Laura Buehholz

A new frontier in treatment for mental illnesses and other chronic conditions may not come from pharmaceutical companies, but from within, as mindfulness becomes gain action.

Mindfulness practices, as we know them today, were rooted in 5000-year-old Buddhist meditation techniques and are often described as "paying attention to the present moment experiences with openness, curiosity, and willingness to be with what is" (Kabat-Zinn, H.). Herbert Benson, M.D., founder of the Benson-Henry Institute for Mind Body Medicine at Massachusetts General Hospital, often credited with bringing mindfulness into the realm of Western medicine. His 1975 book The Relaxation Response outlined techniques to describe the beneficial effects of stress with relaxation methods similar to meditation.

Three professionals co-led the efforts in the 1970s: a Harvard researcher, however, several medical institutions have since been developed and are being implemented in clinical practice. One of these is Mindfulness-Based Stress Reduction (MBSR), pioneered by Jon Kabat-Zinn, Ph.D., MPH, founding director of the Stress Reduction Clinic at Massachusetts General Hospital.

Another is "Mindfulness-Based Cognitive Therapy (MBCT), a blend of MBSR and cognitive-behavioral therapy established by Zindel Segal, Ph.D., a cognitive psychologist at the University of Toronto, along with colleagues Marc Williams, Ph.D., and Jon Kabat-Zinn. According to Gregory J. Grossman, M.D., director of the Benson-Henry Institute, "Mindfulness and other meditative techniques can provide adjunctive benefits for health and mental health." The core component of mindfulness practice is a sense of presence: "Many people ask me what it feels like to be in the present moment," he said.

At the time, many researchers are now beginning to systematically investigate the effects of mindfulness interventions for various physical and mental health conditions, including cancer, stress, and multiple sclerosis (MS), pain, anxiety, and depression. The results of these studies may help inform physicians about the effectiveness and possible use of mindfulness interventions in clinical practice.

Why the Growing Trend?

According to a recent study, 79% of medical schools offer some element of mindfulness training, versus 7" treatment of the American...
Yoga was as effective as standard physical therapy for treating moderate to severe chronic low back pain in people in underserved communities.

Biofeedback Equipment

HRV monitoring and biofeedback devices are a combination of physiological recording equipment and audio and visual teaching display systems. These instruments rapidly and accurately "feed back" information about HR and HRV to the user.

The presentation of this information — often in conjunction with changes in thinking, emotions, and behavior — supports desired physiological changes. Over time, these changes can endure without continued use of an instrument.

More to say on this in the Research presentation later.
Issues remain that need to be resolved before ASR is a fully fledged integrative medical practice:

• Not all HRV monitoring and HRVB training devices have bridged from research quality to FDA approval

• Questions of privacy, confidentiality, and HIPAA rules for HRV data

• Biofeedback CPT codes are very poorly reimbursed by third-party payors, or not reimbursed at all
  
  • The fact that a third party payor does not reimburse does not mean that the intervention lacks effectiveness.
KEEP CALM & ACTIVATE THE PARASYMPATHETIC NERVOUS SYSTEM
time for questions
II. Research in Application of ASR for SCP
(45 minutes)
Lorimer Moseley, a globally known Australian pain researcher, tells this story about himself:

He was hiking in the Australian Outback with friends when he felt something scratch his left ankle. It was painful enough to make him pull his leg away, but he just kept walking, figuring he’d scraped his ankle on a stick. He woke up two days later in a hospital where doctors told him he’d been bitten by the deadly poisonous eastern brown snake, and was lucky to be alive.

Being resilient, he was out hiking again six months later when he was stopped dead in his tracks by a searing pain in his left ankle. He fell to the ground and screamed for help. His friends called an ambulance but and when they examined him they found a twig stuck in his sock. Yet, his ankle continued to hurt, he had groin pain for a week (just as he had after the snake bite), and he could not talk himself out of it.
Chronic Stress, Pain Sensitization Symptom Cluster

ASR Coherence Autonomic Balance
Fig. 1. HRV Biofeedback reduces effects of chronic pain

Chronic pain causes central sensitization and loss of negative feedback regulation of the stress response, leading to autonomic imbalance, allostatic stress, and depressed mood (Disease Pathway). When autonomic balance is restored, stress is reduced and emotional regulation is recovered (Health Pathway).
Management of Centrally Amplified Pain using Autonomic Self-Regulation

- Painful event
  - Autonomic Dysegulation
  - HR acceleration
  - Decreased HRV

- Conscious awareness
  - Autonomic Self-Regulation
  - Restored HR deceleration
  - Increased HRV

- Reduced pain

- Centrally sensitized pain

- Chronic pain

- Stress and depression

- Mindfulness
  - With
  - RFB
  - And
  - PES

- Mindfulness

- HRVB
Neuropathic Pain

Nociceptive Pain

Central Sensitization

Chronic Pain

Stress Depression
Figure 1 (a – d) depicts the Pre-Post HRVB Training the R-R Interval Tachogram and Power Spectra Density of one PTSD+ subject.

Pre-Training

(a) R-R Interval Tachogram

(b) Power Spectrum

Post-Training

(c) R-R Interval Tachogram

(d) Power Spectrum
HRV Power Spectrum

Peak Power at 0.095 Hz = 53.5 ms/Hz; Total LF power = 3695.9 ms²/Hz

Coherence ratio = 0.02
HRV Power Spectrum

Peak Power at 0.099 Hz = 960.4 ms²; Total LF Power = 2344.4 ms²/Hz

Coherence ratio = 0.26
Equipment for HRV monitoring and HRVB

**Android G1 Smart Phone**

**Armband sensors:** Alcohol (WristAS), Temp., GSR, Accelerometer

**Chestband sensors:** ECG, Respiration, GSR, Ambient & Skin Temp., Accelerometer
Past
- Static ‘snapshot’
- Sensors cabled to a desktop or laptop computer

Present
- Ambulatory, real-time, dynamic
- Naturalistic and battlefield
- Development of platforms
  - Small business, entrepreneurs, DoD and NSF grants, university research
- Reliable measurement of IBI
  - Wearable systems
    - Fitness watches
      - Continuously track HR, transfer data to software dashboard, compute HRV.
  - Small chest patches with electrodes
    - Highly miniaturized fully-featured circuits for ECG detection.
  - Vests
    - HR electrode sensors
      - Additional sensors - 3-axis accelerometers, respiration, skin conductance and skin and ambient temperatures, ‘pulse-transit-time’, EMG.
    - NASA, NFL
- Ambulatory HRV monitoring and health informatics goes along with ‘big data’ movement.
  - Wireless transmission of HR data
  - Processing algorithms in the cloud or separate servers.
  - Data mining protocols,
  - HR data analyzed for comparability with norms and with known physical and mental clinical populations.
    - Matched clinical records from other, similar cases.
  - Classify patterns and fast matching of patient data
    - Provides predictive warning of acute health crises,
    - Real time evaluation of diagnostic & treatment options for complex patient needs,
  - Precision medical care
  - Fills gaps in patient-doctor communication
Future
• Remote real-time detection of pulse
• as much accuracy as ECG:
  • radar embedded in a smartphone camera programmed to display pulses as micromovements invisible to the eye
  • video processing algorithm magnifying subtle changes in color reflecting pulse pressure skin, redness
  • microwave Doppler radar
• ... The science-fictional Star Trek medical tricorder for whole body scanning examination is no longer fictional.

Pick the optimal device for your planned needs:

• There are an extended number of devices available
• AAPB surveys the major manufacturers of biofeedback equipment every few years
• They provide descriptive information about each of their devices
• Manufacturers update the information
Study 1 – “Non-pharmacological intervention for chronic pain in Veterans: A pilot study of Heart Rate Variability”

Study 2 – “Use of Heart Rate Variability (HRV) Biofeedback for Symptom Management among Cancer Survivors”

Study 3 – “HRV Biofeedback in pain patients: Pilot intervention for pain, fatigue, & sleep”
Study 1 – “Non-pharmacological intervention for chronic pain in Veterans: A pilot study of Heart Rate Variability”
Non-pharmacological Intervention for Chronic Pain in Veterans: A Pilot Study of Heart Rate Variability Biofeedback

Melanie E. Berry, MS, United States; Iva T. Chapple, MD, United States; Jay P. Ginsberg, PhD, United States; Kurt J. Gleihauf, PhD, United States; Jeff A. Meyer, PhD, United States; Madan L. Nagpal, PhD, United States

ABSTRACT

Objective: Chronic pain is an emotionally and physically debilitating form of pain that activates the body's stress response and over time can result in lowered heart rate variability (HRV) power, which is associated with reduced resiliency and lower self-regulatory capacity. This pilot project was intended to determine the effectiveness of HRV coherence biofeedback (HRVCB) as a pain and stress management intervention for veterans with chronic pain and to estimate the effect sizes. It was hypothesized that HRVCB will increase parasympathetic activity resulting in higher HRV coherence measured as power and decrease self-reported pain symptoms in chronic pain patients.

Study Design: Fourteen veterans receiving treatment for chronic pain were enrolled in the pre-post intervention study. They were randomly assigned, with 8 subjects enrolled in the treatment group and 6 in the control group. The treatment group received biofeedback intervention plus standard care, and the other group received standard care only. The treatment group received four HRVCB training sessions as the intervention.

Measures: Pre-post measurements of HRV amplitude, HRV power spectrum variables, cardiac coherence, and self-ratings of perceived pain, stress, negative emotions, and physical activity limitation were made for both treatment and control groups.

Results: The mean pain severity for all subjects at baseline, using the self-scored Brief Pain Inventory (BPI), was 26.71 (SD=4.46; range=21-35) indicating a moderate to severe perceived pain level across the study subjects. There was no significant difference between the treatment and control groups at baseline on any of the measures. Post-HRVCB, the treatment group was significantly higher on coherence (P<.01) and lower (P=.02) on pain ratings than the control group. The treatment group showed marked and statistically significant (1-tailed) increases over the baseline in coherence ratio (191%, P=.04) and marked, significant (1-tailed) reduction in pain ratings (36%, P<.001), stress perception (16%, P=.02), negative emotions (49%, P<.001), and physical activity limitation (42%, P<.001). Significant between-group effects on all measures were found when pre-training values were used as covariates.

Conclusions: HRVCB intervention was effective in increasing HRV coherence measured as power in the upper range of the LF band and reduced perceived pain, stress, negative emotions, and physical activity limitation in veterans suffering from chronic pain. HRVCB shows promise as an effective non-pharmacological intervention to support standard treatments for chronic pain.
The pre-treatment values for control and treatment groups were not statistically different for self-ratings of pain, negative emotion, physical activity limitation, or stress.

Table 1 Demographics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>Treatment</th>
<th>t-value</th>
<th>P</th>
<th>95% CI of difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coherence_Pre</td>
<td>0.12 (0.07)</td>
<td>0.22 (0.19)</td>
<td>-1.2</td>
<td>.24</td>
<td>(-0.3, 0.8)</td>
</tr>
<tr>
<td>Coherence_Post</td>
<td>0.15 (0.09)</td>
<td>0.42 (0.24)</td>
<td>-2.6</td>
<td>.02</td>
<td>(-0.5, -0.1)</td>
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<tr>
<td>Pain_Pre</td>
<td>26.2 (4.2)</td>
<td>27.1 (4.9)</td>
<td>-0.4</td>
<td>.70</td>
<td>(-6.4, 4.5)</td>
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<tr>
<td>Pain_Post</td>
<td>24.3 (6.9)</td>
<td>17.3 (4.6)</td>
<td>2.3</td>
<td>.04</td>
<td>(0.4, 13.8)</td>
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<tr>
<td>Stress_Pre</td>
<td>24.8 (6.8)</td>
<td>24.4 (5.8)</td>
<td>0.1</td>
<td>.90</td>
<td>(-6.8, 7.8)</td>
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<tr>
<td>Stress_Post</td>
<td>26.0 (6.9)</td>
<td>20.4 (6.1)</td>
<td>1.6</td>
<td>.14</td>
<td>(-1.9, 13.2)</td>
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<tr>
<td>Neg_Emotion_Pre</td>
<td>30.2 (9.7)</td>
<td>35.0 (3.5)</td>
<td>-1.2</td>
<td>.28</td>
<td>(-15.0, 5.3)</td>
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<tr>
<td>Neg_Emotion_Post</td>
<td>25.7 (12.7)</td>
<td>19.8 (10.4)</td>
<td>1.0</td>
<td>.36</td>
<td>(-7.5, 19.4)</td>
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<tr>
<td>Activ_Red_Pre</td>
<td>30.7 (7.1)</td>
<td>34.1 (4.6)</td>
<td>-1.1</td>
<td>.30</td>
<td>(-10.2, 3.3)</td>
</tr>
<tr>
<td>Activ_Red_Post</td>
<td>26.7 (11.6)</td>
<td>19.9 (10.4)</td>
<td>1.2</td>
<td>.26</td>
<td>(-6.1, 19.7)</td>
</tr>
</tbody>
</table>

*Independent t-test, 12 df, all variances equal except Neg_Emotion_Pre.
*b 2-tail.
Abbreviations: Activ_Red, activity reduction; CI, confidence interval; Neg_Emotion, negative emotion.
Treatment effects were analyzed with ANCOVA of post scores by group, using pre scores as the covariate.
Post-HRVB training, the treatment group was significantly lower than the control group on all outcome measures (all p’s <0.05).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pre</th>
<th>Post</th>
<th>% Change</th>
<th>Corr_Coeff (P)</th>
<th>t-value</th>
<th>p</th>
<th>95% CI of difference</th>
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<tbody>
<tr>
<td>Coherence</td>
<td>0.22 (0.19)</td>
<td>0.42 (0.24)</td>
<td>191</td>
<td>-0.05 (0.45)</td>
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<td>.05</td>
<td>(-0.5, 0.0)</td>
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<td>Pain</td>
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<td>17.3 (4.6)</td>
<td>-36</td>
<td>0.52 (0.09)</td>
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<td>&lt;0.001</td>
<td>(6.0, 13.7)</td>
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<tr>
<td>Stress</td>
<td>24.4 (5.8)</td>
<td>20.4 (6.1)</td>
<td>-16</td>
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<td>&lt;0.001</td>
<td>(7.7, 22.8)</td>
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<tr>
<td>Activ.Emotion</td>
<td>34.1 (4.6)</td>
<td>19.9 (10.4)</td>
<td>-42</td>
<td>0.22 (0.30)</td>
<td>3.9</td>
<td>&lt;0.001</td>
<td>(-16.0, -7.72)</td>
</tr>
</tbody>
</table>

a 1-tail.

b dependent t-test, df 7.

Abbreviations: Activ.Emotion, activity reduction; CI, confidence interval; Corr_Coeff, correlation coefficient; Neg.Emotion, negative emotion.
Study 2 – “Use of Heart Rate Variability (HRV) Biofeedback for Symptom Management among Cancer Survivors”
Use of Heart Rate Variability (HRV) Biofeedback for Symptom Management among Cancer Survivors

Mark A. O’Rourke, MD, Medical Director
Center for Integrative Oncology and Survivorship
Greenville Health System Cancer Institute
Greenville, South Carolina
Investigators and Staff

Greenville Health System

• Mark A. O’Rourke, MD, co-PI
• Regina Franco, MSN, ANP-C
• Kerri Susko, MSW, LISW-CP
• William M. Hendry, DOM, L.Ac.
• Elizabeth Crowley, Ph.D, RN, LMSW
  • Sherry A. Stokes, M.S.
  • W. Larry Gluck, M.D.
  • Katie Daniels, BS

University of South Carolina

• James Burch, MS, Ph.D, co-PI
  • J.P. Ginsberg, Ph.D.
  • Jameson Sofge, MS
• James Hébert, MSPH, ScD
Background:
Cancer survivors have lower HRV coherence than normal controls and HRVB training improves HRV coherence, restores autonomic health

Research Question:
Will HRVB reduce late effects of cancer and its treatment, including stress, pain, depression, fatigue, and insomnia?

Method:
Randomized, waitlist controlled, clinical trial. Participants in the intervention arm receive weekly HRV-B training up to six weeks; a wait-list control group was matched to the intervention arm. Outcome measures were assessed at baseline (pre) and after week six (post)
**Study Schema:**
- Consent form
- Biospecimen consent form
- Complete symptom cluster instruments
- Randomization procedure

Intervention Arm:
- Weekly phone call: assess home HRV practice and reminder appointment calls
- If participant meets coherence guidelines between weeks 4-6, proceed to final appointment (3-7 days later).

Weeks:
1**  2  3  4  5  6**  Off

- Collect saliva sample
- Baseline HRV, respiration

Post-assessment appointment (3-7 days later)
- 15 minute post-assessment HRV, respiration
- Complete symptom cluster instruments
- Collect saliva sample

Control Arm:
- Off Study
- Opportunity to complete 6 week HRV-B training procedure

Weeks:
1**  6**

- Collect saliva sample
- Baseline HRV, respiration

Sleep Actigraphy: **
- Actigraphy data collected first and last week of study
Symptom Cluster Assessment

- **STRESS**
  - Perceived Stress Scale (PSS)
- **DEPRESSION**
  - Beck Depression Inventory–II (BDI-II)
- **FATIGUE**
  - Multidimensional Fatigue Inventory (MFI)
- **PAIN**
  - Brief Pain Inventory (BPI)
- **SLEEP**
  - Insomnia Symptom Questionnaire
- **PTSD**
  - Posttraumatic Stress Disorder Checklist
- **Chronotype**
  - Munich Chronotype Questionnaire
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<th>Status</th>
<th>Total</th>
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<td>Screened</td>
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<tr>
<td>Ineligible</td>
<td>117</td>
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<tr>
<td>Enrolled</td>
<td>38</td>
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<tr>
<td>Dropped Out</td>
<td>4</td>
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<tr>
<td>Completed</td>
<td>34</td>
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<table>
<thead>
<tr>
<th></th>
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<th>Group B (N=17) Wait List Control</th>
<th>two-tailed p-value</th>
</tr>
</thead>
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<tr>
<td>Age (years), mean ± stderr</td>
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<td>58.9 ± 2.5</td>
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<td>Sex, count(%)</td>
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<td>Male</td>
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<td>Female</td>
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<tr>
<td>Race, count (%)</td>
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<tr>
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<td>13 (76.4)</td>
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<tr>
<td>Black or African American</td>
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<td>Other</td>
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<tr>
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<td>2 (11.8)</td>
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<tr>
<td>Education (years), mean ± stderr</td>
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<td>High School</td>
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<td>4 (23.5)</td>
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<tr>
<td>College</td>
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<td>6 (35.3)</td>
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<tr>
<td>Graduate School</td>
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<td>5 (29.4)</td>
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<td>Missing</td>
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<td>2 (11.8)</td>
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<tr>
<td>Income, count (%)</td>
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<tr>
<td>Under $50,000</td>
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<td>$50,000-$100,000</td>
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<td>$100,000 or more</td>
<td>6 (35.3)</td>
<td>4 (23.5)</td>
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<tr>
<td>Refuse/Don't Know/Missing</td>
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<td>3 (17.7)</td>
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<tr>
<td></td>
<td>Depression</td>
<td>Fatigue</td>
<td>Pain Interferes</td>
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<tr>
<td>Pain Interferes</td>
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*<0.05; **<0.01; *<0.005;
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<tr>
<th>Group</th>
<th>Pre-HRVB v Control</th>
<th>Post-HRVB v Control</th>
<th>Mixed Model HRVB x Control</th>
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<tr>
<td>DEPRESSION</td>
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<td>Control</td>
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<tr>
<td>FATIGUE</td>
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<td>PAIN INTERFERENCE</td>
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<td>ns</td>
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<tr>
<td>Control</td>
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<tr>
<td>SLEEP</td>
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<tr>
<td>HRVB</td>
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#<.1, *<.05, **<.01, ***<.005
Study 3 – “HRV Biofeedback in pain patients: Pilot intervention for pain, fatigue, & sleep”
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<th>PI: Ginsberg, Jay</th>
<th>Title: HRV Biofeedback in Pain Patients: Pilot Intervention for Pain, Fatigue &amp; Sleep</th>
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<tr>
<td>AIDS: N</td>
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<tr>
<td>Animals: N</td>
<td>New Investigator: N</td>
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<td>Humans: Y</td>
<td>Early Stage Investigator: N</td>
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<td>Subtotal Direct Costs (excludes consortium F&amp;A)</td>
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<tr>
<td>Jay Ginsberg Ph.D</td>
<td>WJB Dorn VA Medical Center</td>
</tr>
<tr>
<td>James Burch Ph.D</td>
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<tr>
<td>Alexander McLain Ph.D</td>
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<tr>
<td>Raouf Gharbo Ph.D</td>
<td>Hampton Roads Riverside Regional Medical Center</td>
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<td>James Hebert ScD</td>
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<td>Francis Spinale M.D.</td>
<td>WJB Dorn VA Medical Center</td>
</tr>
<tr>
<td>Tarek Sobeih Ph.D</td>
<td>Dorn Research Institute</td>
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</tbody>
</table>
Number of veterans screened or prescreened: 220
Number of veterans enrolled: 30
Number of veterans completed: 27
HYPOTHESIS FOR VA MERIT PROPOSAL

• COHERENCE REDUCES CENTRAL SENSITIZATION OF PAIN, STRESS, AND DEPRESSION

• HRV BIOFEEDBACK PRODUCES COHERENCE

• HRV BIOFEEDBACK WILL REDUCE CENTRALLY SENSITIZED PAIN, STRESS, AND DEPRESSION

• HRVB AND COHERENCE WILL REDUCE CENTRALLY SENSITIZED PAIN AND ASSOCIATED STRESS AND DEPRESSION BECAUSE THE SAME NEURAL STRUCTURES AND CIRCUITS ARE INVOLVED IN BOTH

HYPOTHESIS COROLLARY

• HRVB AND COHERENCE WILL NOT IMPROVE PAIN THAT IS SOLELY FROM A NEUROPATHIC SOURCE
Symptom Cluster Assessment

- **STRESS**
  - Perceived Stress Scale (PSS)
- **DEPRESSION**
  - Beck Depression Inventory–II (BDI-II)
- **FATIGUE**
  - Multidimensional Fatigue Inventory (MFI)
- **PAIN**
  - Brief Pain Inventory (BPI)
- **SLEEP**
  - Insomnia Symptom Questionnaire
- **CATASTROPHIZING**
  - Pain Catastrophizing Scale (PCS)
The Pain Catastrophizing Scale
- 13-item self-report
- Thoughts/feelings about pain experience
  - “When I’m in pain ..
    - “.. I worry all the time.”
    - “.. I can’t stand it anymore.”
- 5-point scale
  - 0 (not at all) to 4 (all the time)
- Total score with three subscales
  - magnification, rumination and helplessness.

".. general psychological acceptance is a strong predictor of pain-related catastrophizing, independent of gender, age and pain intensity. Mindfulness did not predict levels of pain-related catastrophizing."

<table>
<thead>
<tr>
<th></th>
<th>Depression</th>
<th>Catastrophize</th>
<th>Fatigue</th>
<th>Pain Interferes</th>
<th>Sleep</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stress</td>
<td>***</td>
<td>***</td>
<td>***</td>
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</tr>
<tr>
<td>Depression</td>
<td>xxxxxxxxx</td>
<td>***</td>
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<td>***</td>
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<tr>
<td>Catastrophize</td>
<td>xxxxxxxxx</td>
<td>***</td>
<td>***</td>
<td>***</td>
<td>***</td>
</tr>
<tr>
<td>Fatigue</td>
<td>xxxxxxxxx</td>
<td>xxxxxxxxx</td>
<td>*</td>
<td>***</td>
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</tr>
<tr>
<td>Pain Interferes</td>
<td>xxxxxxxxx</td>
<td>xxxxxxxxx</td>
<td>*</td>
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</tr>
</tbody>
</table>

*<0.05; **<0.01; ***<0.005;
Planned research

(1) NIH RO1, Phase 2, single site, Veteran cancer survivors; psychoeducational self-management control; 4 timepoints; primary, secondary, exploratory endpoints

(2) NCI NCORP, Phase 2, multi-site, cancer survivors; pre-post; primary, secondary, exploratory endpoints.
KEEP CALM & ACTIVATE THE PARASYMPATHETIC NERVOUS SYSTEM