2017 SBCNA Annual Conference co-sponsored by AAPB
“Biofeedback and Neurofeedback: Cognitive and Physiological Processes for Behavioral and Physical Regulation

Integrative Management of Sensitized Chronic Pain using Autonomic Self-Regulation
Saturday, November 4, 2017

JP (Jack) Ginsberg, PhD

1. Define and describe the meaning of integrative medical management, centrally sensitized chronic pain, and Autonomic Self-Regulation (ASR)
2. Describe the basic science of heart rate variability (HRV) and its relationship to ASR technique
3. Summarize the nervous system pathways shared by sensitized chronic pain and ASR
4. Identify HRV parameters that are biomarkers of emotional and physical health
5. Discuss how ASR can be used for health assessment and behavioral change
6. Explain ASR in simple words with techniques
JP (Jack) Ginsberg, PhD

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Disclaimer and Disclosure

• Not expert in cardiology, pain, or medication
  • Neuropsychologist with some specialization in cognitive psychophysiology
• No conflict of interest, affiliations, or product endorsement
• Slides are original or freely available from internet with acknowledgment

"Materials that are included in this course may include interventions and modalities that are beyond the authorized practice of mental health professionals. As a licensed professional, you are responsible for reviewing the scope of practice, including activities that are defined in law as beyond the boundaries of practice in accordance with and in compliance with your professions standards."
D.A. Powell, PhD
Rollin McCraty, PhD
Paul Lehrer, PhD
Wasyl Malyj, PhD
Fred Shaffer, PhD
Carmen Russeniello, PhD
Jan B. Newman, MD
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

- 2 million
  People had prescription opioid use disorder

- 828,000
  People used heroin

- 135,000
  People used heroin for the first time

- 33,091
  People died from overdosing on opioids

- 15,281
  Deaths attributed to overdosing on commonly prescribed opioids

- 9,580
  Deaths attributed to overdosing on synthetic opioids

- 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/opioids/
PSYCHOLOGIST’S MODEL OF PAIN MEDICATION (OPIOID) ADDICTION

<table>
<thead>
<tr>
<th>Negative Punishment</th>
<th>Negative Reinforcement</th>
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<tbody>
<tr>
<td>Suspension</td>
<td>Medication</td>
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<tr>
<td>‘Time-out’</td>
<td>Self-Medication</td>
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<td>Positive Punishment</td>
<td>Positive Reinforcement</td>
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<tr>
<td>Fines</td>
<td>Honors</td>
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<tr>
<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 WITH SOMETHING ELSE
The Backfire Effect
I. Sensitized Chronic Pain (SCP) and Autonomic Self-Regulation (ASR)

- Define SCP and ASR
- Shared physiological basis of SCP and ASR
- How ASR reduces SCP

II. Research on using ASR for SCP
Sensitized Chronic 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

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

Mixed

Peripheral neuropathy
CRPS
Trigeminal neuralgia

Rollin Gallagher, MD, MPH
dhss.delaware.gov/dsamh/files/2007gallagherii.pps
Nociceptive Pain

Understanding Pain and Pain Amplification. Robert Benett, MD.
http://www.myalgia.com/Pain_amplification/Overview.htm
Nociceptive Pain

1. Peripheral tissues
2. Spinal cord

C Fiber

Sub P
NK1
NMDA
AMPA

Glut
C Fiber

1. Peripheral tissues
2. Spinal cord
3. Brain

= STRESS

Nociceptive Pain
To Whom It May Concern:

C Fiber Nociceptive Pain = STRESS

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

**SAM**
- Hypothalamus
- Stress
- CRH (corticotropin-releasing hormone)
- Corticotrope cells of anterior pituitary
- ACTH
- Adrenal cortex
- Mineralocorticoids
- Glucocorticoids

**HPA**
- Spinal cord
- Preganglionic sympathetic fibers
- Adrenal medulla
- Catecholamines (epinephrine and norepinephrine)
- Kidney

**More prolonged**
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 $\rightarrow$ negative feedback via GR of HC, PVN, P, and AC
  - $\downarrow$ CRH, AVP release
  - $\downarrow$ ACTH release
  - $\downarrow$ GC
  - $\downarrow$ IL-1$\beta$
Stress ends

**STRESS RESPONSE NEGATIVE FEEDBACK: II**

- Glucocorticoid $\rightarrow$ negative feedback via GR of HC, PVN, P, and AC
  - $\downarrow$ CRH, AVP release
  - $\downarrow$ ACTH release
  - $\downarrow$ GC
  - $\downarrow$ IL-1$\beta$
- Mineralocorticoid $\rightarrow$ negative feedback via GR in HC
  - $\uparrow$ Glu $\rightarrow$ GABA $\uparrow$
- Brainstem 5-HT/NE release
- Amy
- P
- neurokinin SP
ACUTEnociceptive 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)

• ➔ Stress response
• ➔ Descending pain modulation

PAIN 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)

- **Stress response**
- **Descending pain modulation**

**PAIN DOES NOT END**
CHRONIC STRESS AND PAIN
HPA AXIS
Neuropathic pain also becomes centrally sensitized.
Neuropathic 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”

- CNS previously thought to lack a lymphatic system
- yet CNS undergoes immune surveillance within meningeal compartments
- mechanisms governing entrance/exit of immune cells from CNS recently discovered
- T-cell gateways into and out of the meninges
- lymphatic vessels line dural sinuses.

Old and updated maps of the lymphatic system
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**
- Cancer
- Tissue resorption
- Postoperative pain
- Mechanical low back pain
- Sports/Exercise injuries

**Neuropathic pain**
- CRPS*
- Trigeminal neuralgia
- Central post-stroke pain
- Diabetic neuropathy
- Radiculopathy (sciatica)

**MIXED PAIN STATES:**
- Cancer
- Low back
- Pelvic
- Facial
- Crush injury
- Amputation

**SENSITIZATION**

*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 alldynia
- 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

Gallagher RM in Ebert & Kerns 2010.
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 (i.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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<tbody>
<tr>
<td>↑CRH/CRH mRNA</td>
<td>↑CRH/CRH mRNA</td>
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<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>
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<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>
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<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
Autonomic Self-Regulation (ASR)
Heart Rate Variability, Chronic Pain, and Rehabilitating the Autonomic Nervous System

By Raqef 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)

Average Heart Rate = 60 BPM

Sympathetic

Parasympathetic

HRV is Low (0)

HRV is High
Cardiac acceleration is mediated through the sympathetic nervous system with [nor]adrenaline (=[nor]epinephrine) onto the heart, other organs, and throughout the circulatory system.

Cardiac deceleration is mediated through the parasympathetic nervous system by the vagus nerve (‘vagal tone’) which outputs acetylcholine onto the heart and other organ systems, notably the gut.

The pacemaker control of heart is adrenertic (i.e. sympathetic); cholinergic (i.e. vagal) output is added and withdrawn very rapidly (msecs). When vagal tone is engaged – which is normal function - additional sympathetic adrenergic control is exerted on a slower time scale (seconds) but the pacemaker rate of HR is not reached unless parasympathetic influence is abolished by blockade.
The sympathetic and parasympathetic branches of the ANS are related by a complex non-linear function. A change in one branch may cause and increase, decrease, or no change in the other branch.

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

A change in one branch may cause and increase, decrease, or no change in the other branch.

“Left foot braking”
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.
Heart Rate Variability (HRV)

2.5 seconds of heart beat data

IBI = 975 + 225 * COS(t * PI)

Min BPM = 50 = Max ibi = 1200 msec

Mean = 65 BPM = 923 msec ibi

Max BPM = 80 = Min ibi = 750 msec
72 beats per minute @ 1 cycle/10 sec = 12 beats/cycle

72 BPM, Max-Min 20
1 cycle/10 secs, 12 beats/cycle
1 cycle (10 secs)
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.

1. Exhale, relax diaphragm, reduce cavity
2. Inhale, contract diaphragm, increase cavity
Bainbridge Reflex: RSA, cardio-respiratory coupling, lung-heart pump

Respiration produces cardiac acceleration and deceleration

Inhale, start cycle again

Increasing the depth of respiration promotes venous return through changes in right atrial (chest cavity) pressure. During inspiration, the chest wall expands and the diaphragm descends, causing right atrial pressure to fall which facilitates venous return. When pressure falls and venous return rises, cardiac rate accelerates. During expiration, the opposite occurs. Increasing right atrial pressure impedes venous return and slows HR. Increasing the depth of ventilation increases the range of HR during respiration.
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
Two Closed-Loops Model of Baroreflex System

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.

~5 s delay
0.1 Hz resonance

~15 s delay
0.03 Hz resonance
Nervous system pathways shared by sensitized chronic pain and ASR:
- Somatosensory cortex
- Hypothalamus (periventricular nucleus) → dorsal spinal column
- HPA → adrenal cortex
- Adrenal cortex → 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’)
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

72 BPM, Max-Min 20
1 cycle/10 sec, 12 beats/cycle
6 cycles (1 minute)
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

Lauren Bucholtz

A new frontier in treatment for mental illnesses and other chronic conditions is emerging from pharmaceutical companies, but from within, as mindfulness practices gain a foothold.

Mindfulness practices, as we know them today, derive in part from Buddhist meditation traditions and are often described as “paying attention in the present moment, non-judgmentally, to whatever arises.” (http://www.chicagotribune.com) Herbert Benson, MD, founder of the Benson-Henry Institute for Mind and Body Medicine at Massachusetts General Hospital, is often credited with bringing mindfulness into the realm of Western medicine. In his 1975 book TheRelaxation Response, he described techniques that mimic the beneficial effects of stress with relaxation methods similar to meditation.

These practices of disengagement in the 1970s as a malleable post holder, however. Several structured mindfulness programs have since been developed and are being implemented in clinical practice. One of these is mindfulness meditation (MBSR), pioneered by Jon Kabat-Zinn, PhD, MPH, founding executive director of the Center for Mindfulness in Medicine, Health Care, and Society at the University of Massachusetts Medical School (http://www.mindfulness.org).

Another is the Chinese-based cognitive therapy (MBCT), a blend of MBSR and cognitive-behavioral therapy established by Zindel Segal, PhD, a cognitive psychologist at the University of Toronto, along with colleagues Marc Williams, PhD, and John Teasdale, PhD (http://www.ucl.ac.uk). According to Gregory Libby, MD, director of the Benson-Henry Institute, “Mindfulness and other meditation techniques can provide significant benefits for health and mental health.”

But some doctors acknowledge the potential of these practices. “Many physicians also consider themselves grounded in Western science and will see mindfulness-based programs for mental health disorders as being somewhat outside of what is generally considered a sufficient basis for our patients,” said an internist.

Why the Growing Trend?

A recent study in the Journal of the American Medical Association, 314(13), 1327-1329 (October 6, 2015)
AUTONOMIC SELF-REGULATION

Mindful attention

RFB

PES
Compassion, gratitude, etc

HRV

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

Pre-Training

(a)

Post-Training

(c)

(b)

(d)
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
II. Research in Application of ASR for SCP
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.
ASR Coherence Autonomic Balance

Chronic Stress, Pain Sensitization Symptom Cluster
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
Neuropathic Pain

Nociceptive Pain

Central Sensitization

Chronic Pain

Stress Depression
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. Gleienzauf, 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.

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<th>Table 1 Demographics</th>
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<tr>
<td>Control</td>
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<tr>
<td>Total</td>
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<tr>
<td>Male</td>
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<tr>
<td>Mean (SD)</td>
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<tr>
<td>Treatment</td>
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<tr>
<td>Total</td>
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<tr>
<td>Male</td>
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<tr>
<td>Mean (SD)</td>
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<thead>
<tr>
<th>Table 2 Pre- and Post-training Measures for Both Groups, Mean (SD)</th>
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<tbody>
<tr>
<td>Variable</td>
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<tr>
<td>Coherence_Pre</td>
</tr>
<tr>
<td>Coherence_Post</td>
</tr>
<tr>
<td>Pain_Pre</td>
</tr>
<tr>
<td>Pain_Post</td>
</tr>
<tr>
<td>Stress_Pre</td>
</tr>
<tr>
<td>Stress_Post</td>
</tr>
<tr>
<td>Neg_Emotion_Pre</td>
</tr>
<tr>
<td>Neg_Emotion_Post</td>
</tr>
<tr>
<td>Activ_Red_Pre</td>
</tr>
<tr>
<td>Activ_Red_Post</td>
</tr>
</tbody>
</table>

<sup>a</sup> Independent t-test, 12 df, all variances equal except Neg_Emotion_Pre.
<sup>b</sup> 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 3: Pre-Post Changes of Measures in the Active HRVCB Treatment Group, Mean (SD)

<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>
</tr>
</thead>
<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>
<td>-1.8</td>
<td>.05</td>
<td>(-0.5, 0.0)</td>
</tr>
<tr>
<td>Pain</td>
<td>27.1 (4.9)</td>
<td>17.3 (4.6)</td>
<td>-36</td>
<td>0.52 (0.09)</td>
<td>6.0</td>
<td>&lt;.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>
<td>0.70 (0.03)</td>
<td>2.5</td>
<td>.02</td>
<td>(0.2, 7.84)</td>
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<tr>
<td>Neg_Emotion</td>
<td>35.0 (3.5)</td>
<td>19.8 (10.4)</td>
<td>-49</td>
<td>0.53 (0.08)</td>
<td>4.8</td>
<td>&lt;.001</td>
<td>(7.7, 22.8)</td>
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<tr>
<td>Activ_Rad</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;.001</td>
<td>(-16.0, -7.72)</td>
</tr>
</tbody>
</table>

*a* 1-tail.

*b* dependent t-test, df 7.

Abbreviations: Activ_Rad, 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

**Study Design:**

**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)
- 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**
- Collect saliva sample
- Baseline HRV, respiration

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

**Control Arm**
- Off Study Opportunity to complete 6 week HRV-B training procedure
- Post-assessment HRV, respiration
- Complete symptom cluster instruments
- Collect saliva sample
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>
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<td>Enrolled</td>
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<td>Dropped Out</td>
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<td>Completed</td>
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<table>
<thead>
<tr>
<th></th>
<th>Group A (N=17) HRVB</th>
<th>Group B (N=17) Wait List Control</th>
<th>two-tailed p-value</th>
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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>
<td>5 (29.4)</td>
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<td>Female</td>
<td>12 (70.6)</td>
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<td>3 (17.7)</td>
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<td>Race, count (%)</td>
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<td>14 (82.3)</td>
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<td>0 (0)</td>
<td>2 (11.8)</td>
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<tr>
<td>Education (years), mean ± stderr</td>
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<td>2 (11.8)</td>
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<tr>
<td>Income, count (%)</td>
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<td>Under $50,000</td>
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<td>$50,000-$100,000</td>
<td>4 (23.5)</td>
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<td>$100,000 or more</td>
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<td>4 (23.5)</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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*<0.05;**<0.01;*<0.005;
# Significance of Differences of Outcome Variables

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<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>Control</td>
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<td>Control</td>
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<tr>
<td>Control</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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<td>FOA Title: CSR&amp;D MERIT REVIEW AWARD FOR CLINICAL TRIALS</td>
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<td>AIDS: N</td>
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<tr>
<td>Humans: Y</td>
<td>Early Stage Investigator: N</td>
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<tr>
<td>Jay Ginsberg Ph.D</td>
<td>WJB Dom VA Medical Center</td>
<td>PD/PI</td>
</tr>
<tr>
<td>James Burch Ph.D</td>
<td>University of South Carolina</td>
<td>MPI</td>
</tr>
<tr>
<td>Alexander McLain Ph.D</td>
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<tr>
<td>Raouf Gharbo Ph.D</td>
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<tr>
<td>James Hebert ScD</td>
<td>University of South Carolina</td>
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<td>Francis Spinale M.D.</td>
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<tr>
<td>Tarek Sobeih Ph.D</td>
<td>Dorn Research Institute</td>
<td>Other Professional-Recruitment Coordinator</td>
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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
Planned enrollment: 40 in each arm

Number of veterans screened or prescreened: 220
Number of veterans enrolled: 30
Number of veterans completed: 27
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>
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<td>Stress</td>
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<td>Depression</td>
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<td>Pain Interferes</td>
<td>xxxxxxxxx</td>
<td>*</td>
<td></td>
<td>xx</td>
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</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
time for questions