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UPCOMING SESSIONS

[VIEW ALL]

- **HERC Econometrics with Observational Data:**
  Econometrics Course: Introduction & Identification - 2/1/2017, 2:00pm EST
- **QUERI Implementation Network :**
  Theory and Evidence-Based Design of Audit and Feedback to Improve Quality of Care - 2/2/2017, 12:00pm EST

1/10/2017	11:00am	The Use of Complementary and Integrative Health in the OEF/OIF/OND Veteran Population	Spotlight on Pain Management	Herman, Patricia Lorenz, Karl Taylor, Stephanie
2/7/2017	**11:00am**	**Integrative Management of Centrally Amplified Pain using Autonomic Self-Regulation**	**Spotlight on Pain Management**	**Ginsberg, Jay "Jack"**
2/15/2017	2:00pm	The Cost-Effectiveness of Complementary and Alternative Treatments to Reduce Pain	HERC Health Economics Seminar	Herman, Patricia Lorenz, Karl Taylor, Stephanie
3/7/2017	11:00am	Non-Pharmacological Approaches to Chronic Musculoskeletal Pain Management: Recommendations from the State-Of-The-Art conference	Spotlight on Pain Management	Kerns, Robert Krebs, Erin

VHA Pain Management Program, Pain Research Working Group
Pain Research, Informatics, Multimorbidities and Education (PRIME) Center
Robert D. Kerns, Ph.D., Director and Special Advisor for Pain Research
Robin M. Masheb , Ph.D., Director of Education, PRIME Center
VA Connecticut Healthcare System and Dept of Psychiatry, Yale University SoM

JP (Jack) Ginsberg, PhD

Licensed Clinical Psychologist/Neuropsychologist
and Principal Investigator,
Dorn VA Medical Center
Basic Science Research Assistant Professor
University of South Carolina, School of Medicine,
Dept of Pharmacology, Physiology & Neuroscience
Columbia, SC
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Disclaimer and Disclosure

- Clinical Neuropsychologist
  - Interested in Cognitive Psychophysiology
  - MH clinical research and hypothesis testing of interventions for symptom reduction
    - Emotional self-regulation and cognitive appraisal
  - Not expert in cardiology, autonomics, or pain
- Slides are original or freely available from internet with acknowledgment
- Planned for 45-50 minutes and questions
- No conflicts of interest, affiliations, or product endorsements

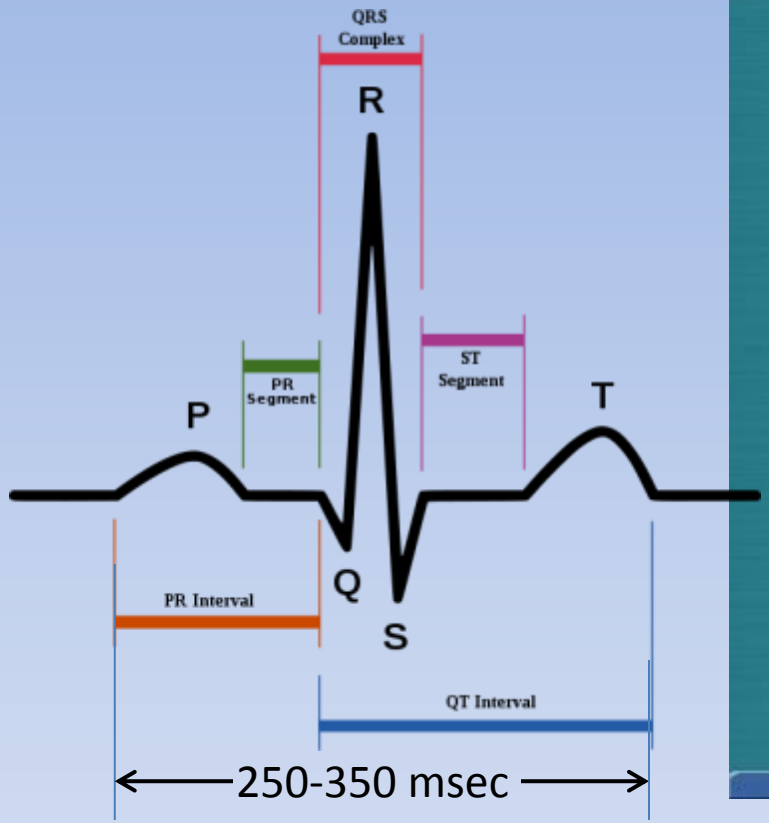
Overview

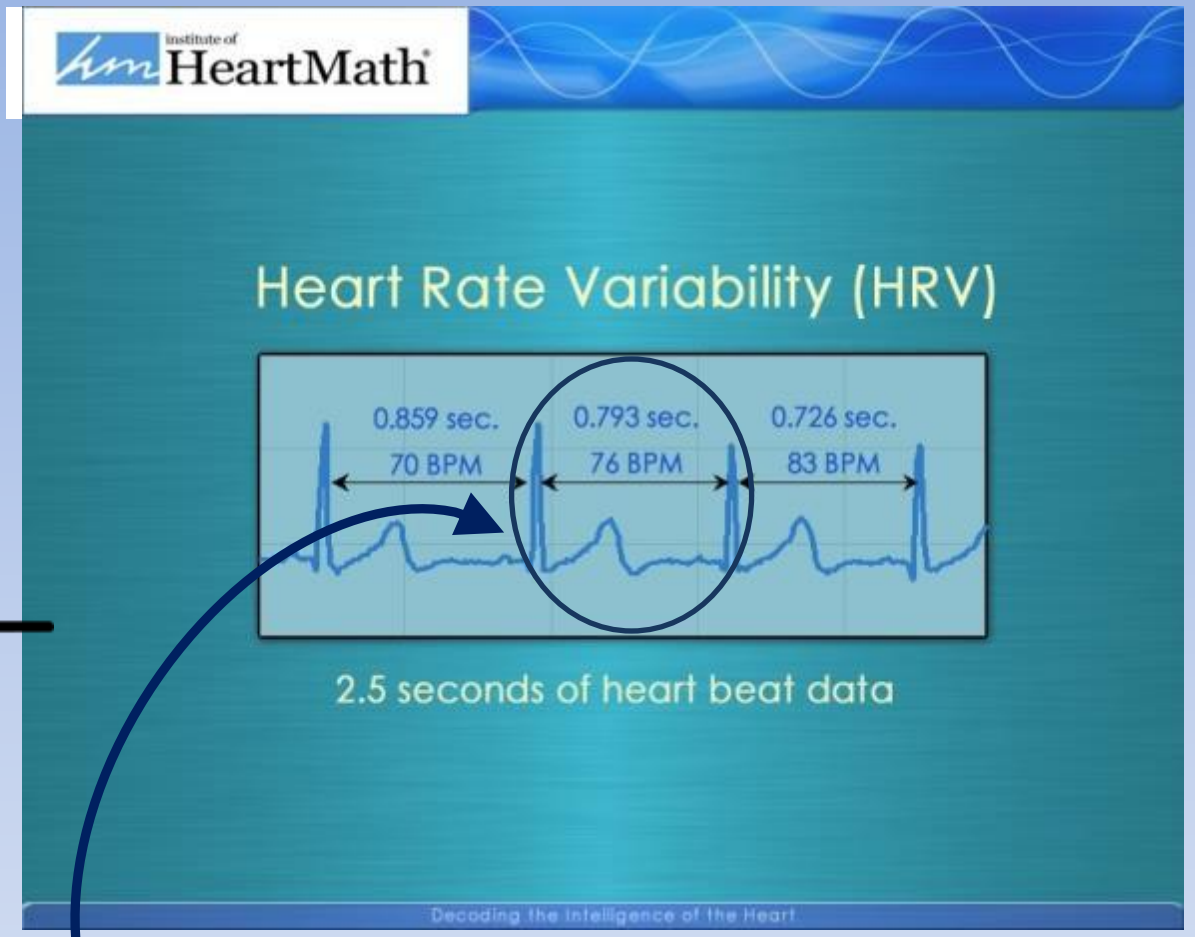
1. Autonomic Self-Regulation (ASR)
    a. Heart rate variability (HRV)
    b. HRV Biofeedback (HRVB)
        i. Coherence
        ii. Mindfulness

2. Pain and Centrally Sensitized Chronic Pain
    a. Stress and Chronic Pain as Stressor

3. Model of ASR and Centrally Sensitized Pain

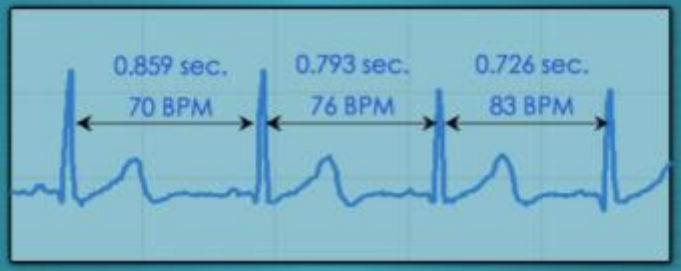
4. Research on ASR and Centrally Sensitized Chronic Pain



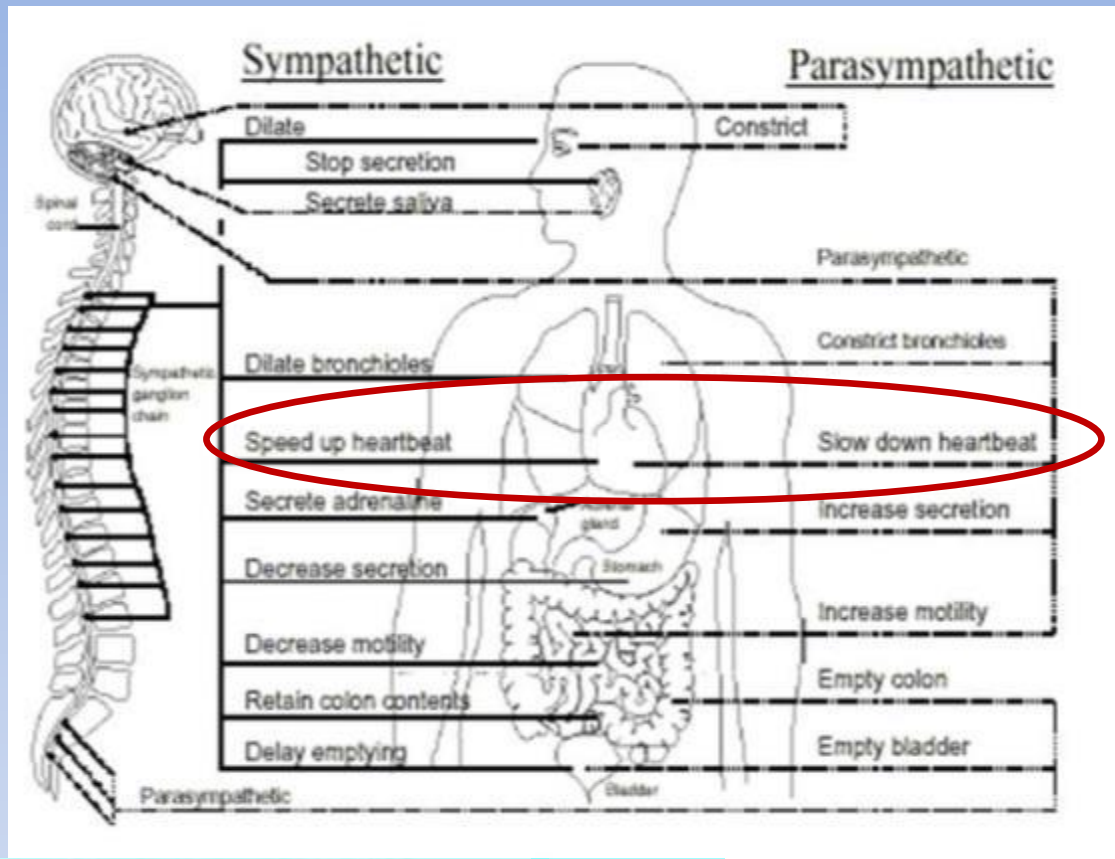


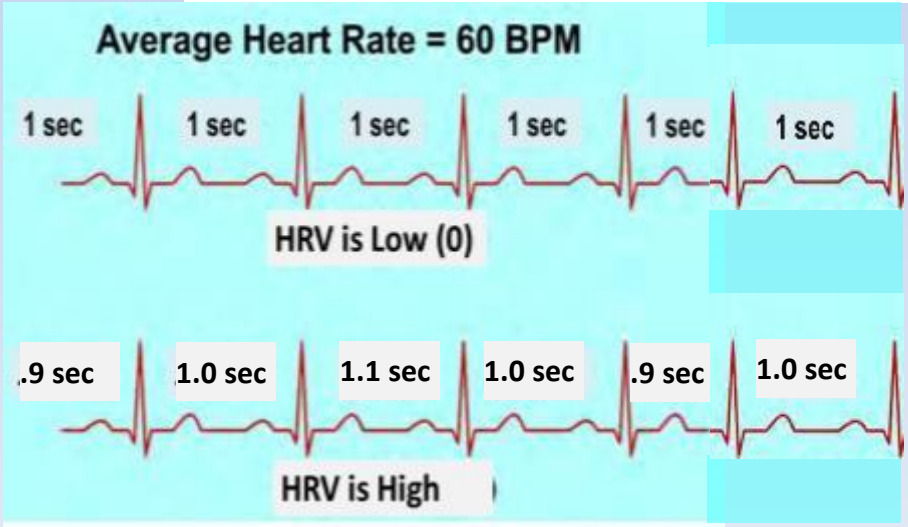
- Interbeat Interval – ‘ibi’
- instantaneous heart rate (HR)
- R-R or N-N

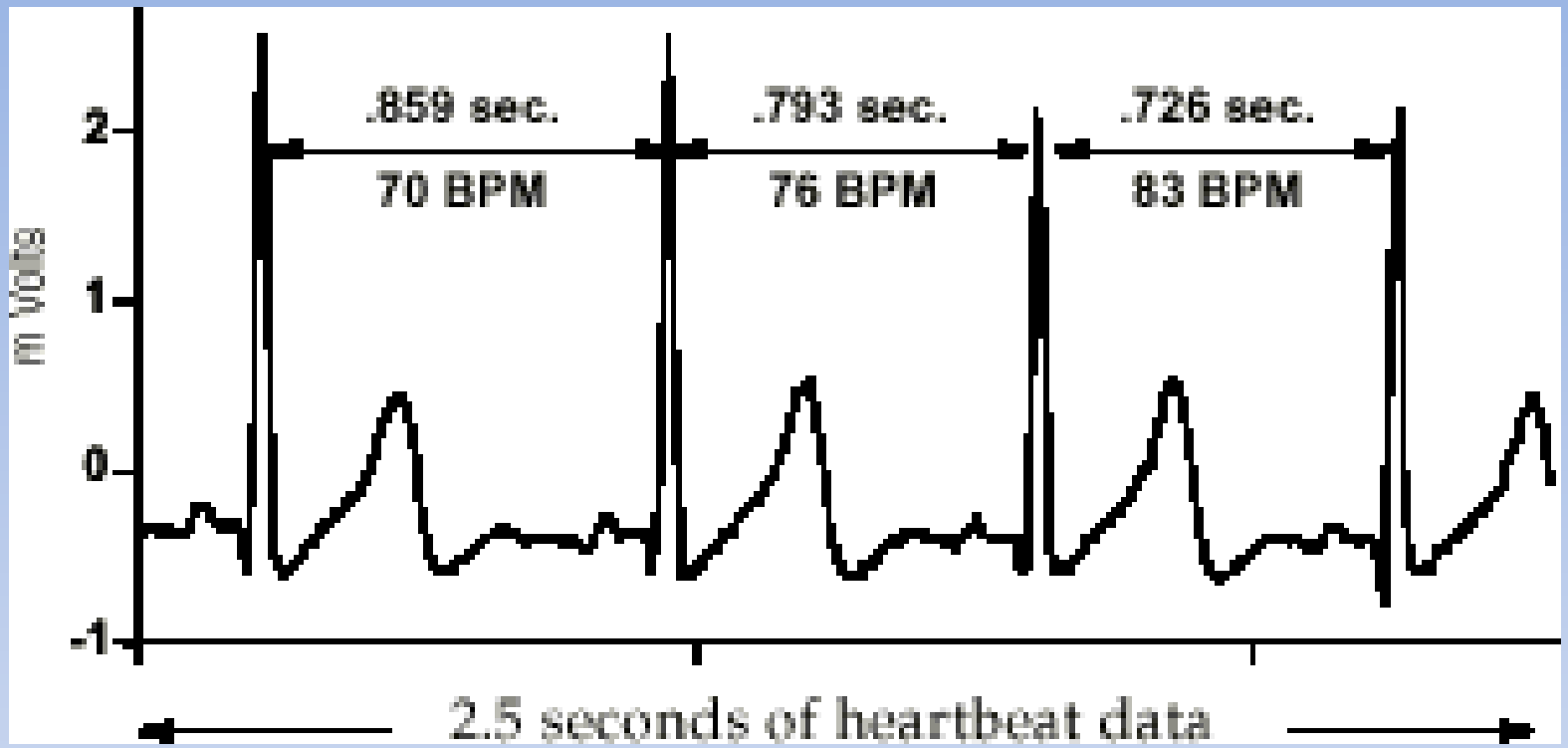
Heart Rate Variability (HRV)



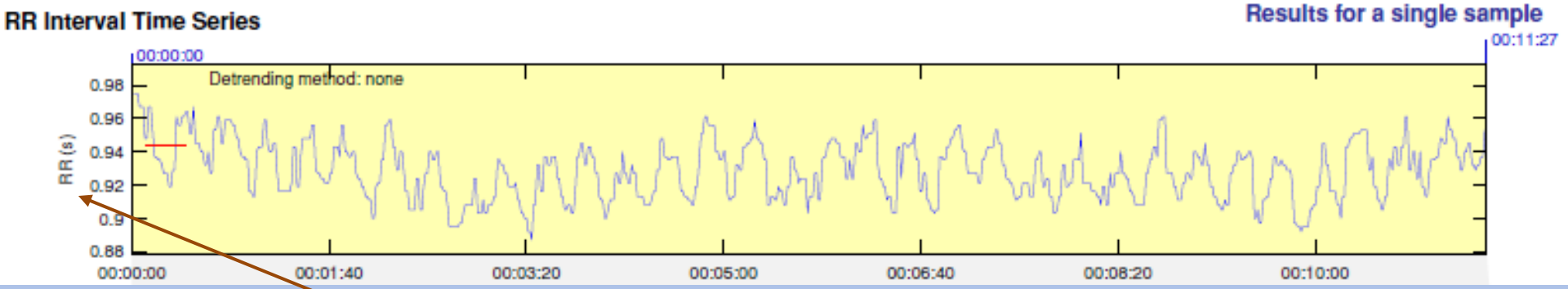
2.5 seconds of heart beat data







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



R-R Tachogram

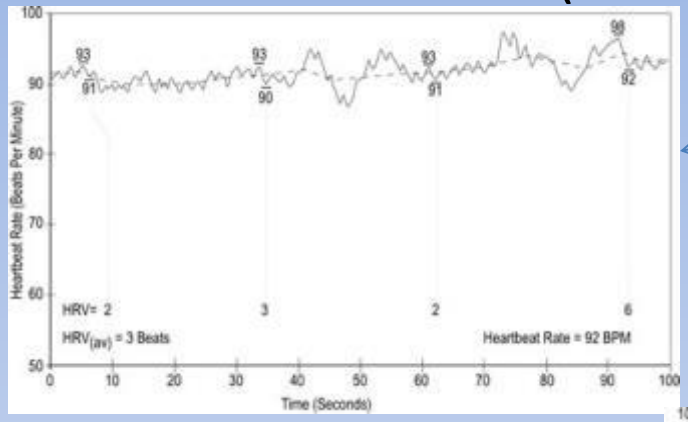
RR = interbeat interval (msec)

- ibi (msec) * BPM = 60,000
- ibi (msec) = 60,000/BPM
- BPM = 60,000/ibi (msec)

RR = ibi = msec/beat	BPM
1333	45
1200	50
1091	55
1000	**60**
857	70
833	72
800	75
750	80
667	90
600	100
500	120

Coherence of Cardiac Rhythm

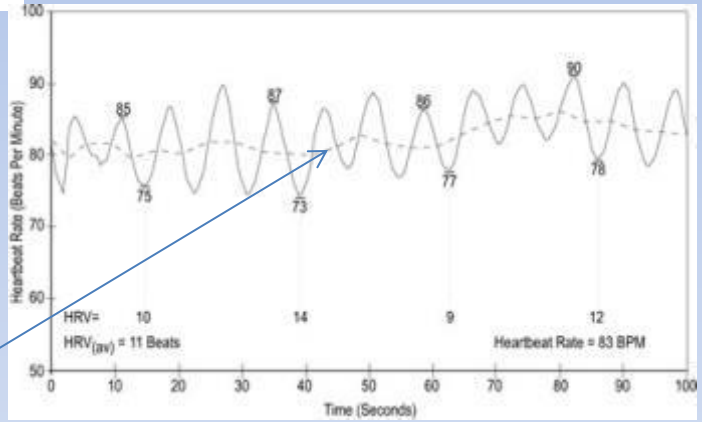
coherence.com (Richard Brown, MD and Stephen Elliot, Ph.D.)



30 BrPM (0.5 Hz) , HRV(avg) = 2

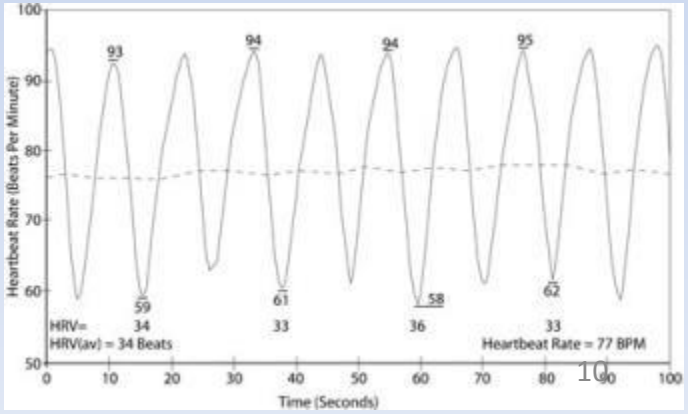
7.5 BrPM (0.125 Hz), HRV(avg) = 11

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.

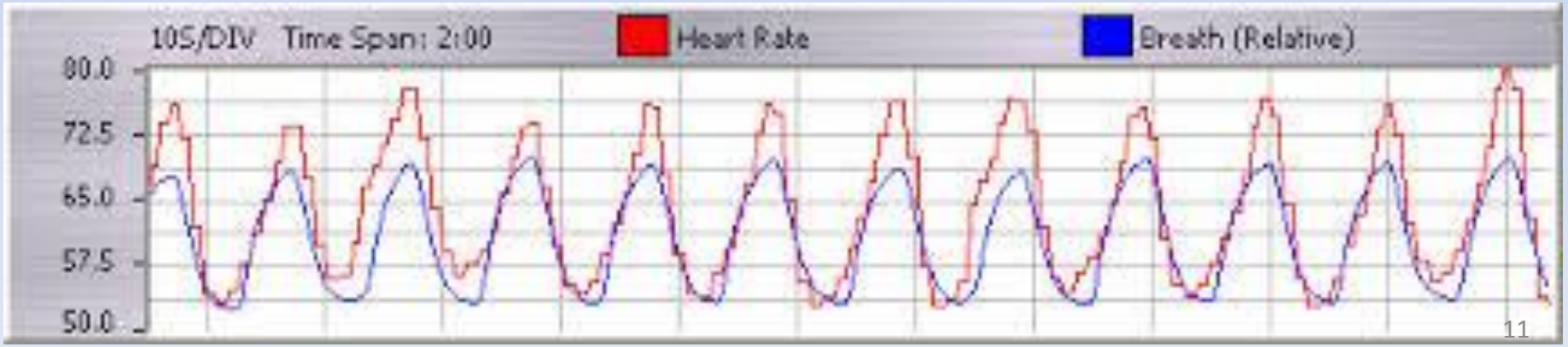
Baroreflex activates resonance ('Coherence')



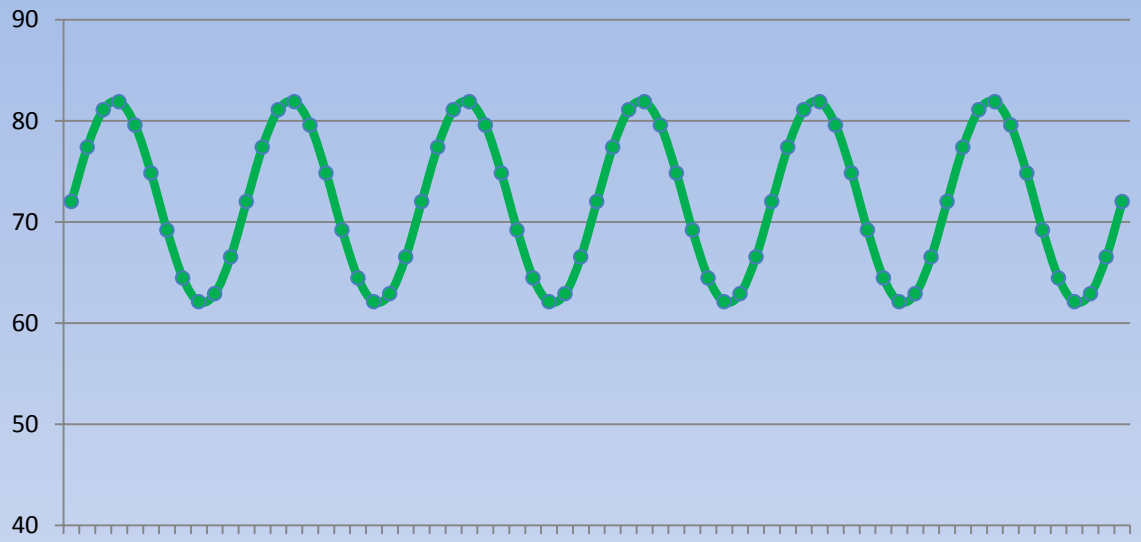
Attaining Coherence: Resonance Frequency Breathing (RFB)

- HRV is related to respiratory cycle
- At ~ 6 breaths/minute
  - HRV and respiratory cycle synchronize
  - HRV is maximized
  - Resonant Frequency Breathing
- 'Coherence'

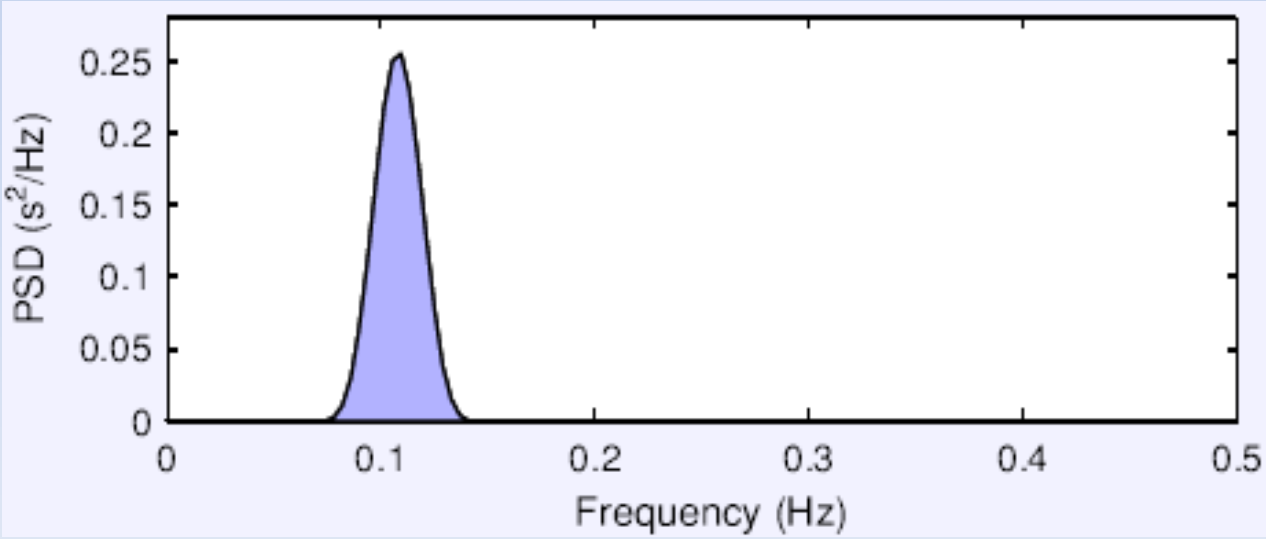
Note: 6 breaths/min=10 seconds per breath=0.1 Hz)



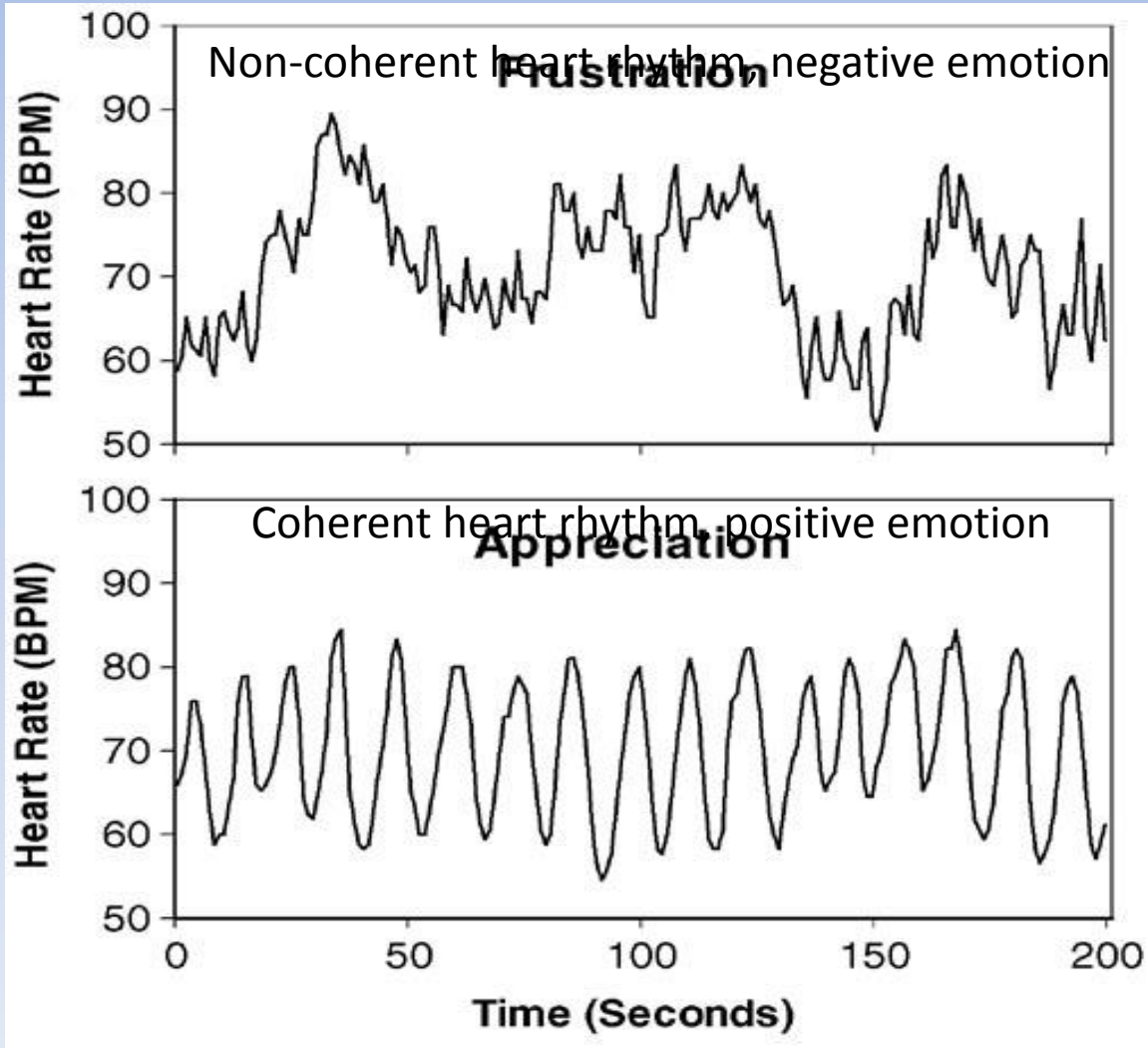
72 BPM, Max-Min 20
1 cycle/10 sec, 12 beats/cycle
6 cycles (1 minute)



Transformation of a time series to a frequency spectrum is done with the Fourier transform. A 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.



The heart rhythm pattern shown in the top graph is characterized by its erratic, irregular pattern (Non-coherence), and associated with negative emotions such as anger or frustration. The bottom graph shows a regular heart rhythm pattern (Coherence), observed when an individual is breathing properly and experiencing sustained, modulated positive emotions such as compassion or gratitude.

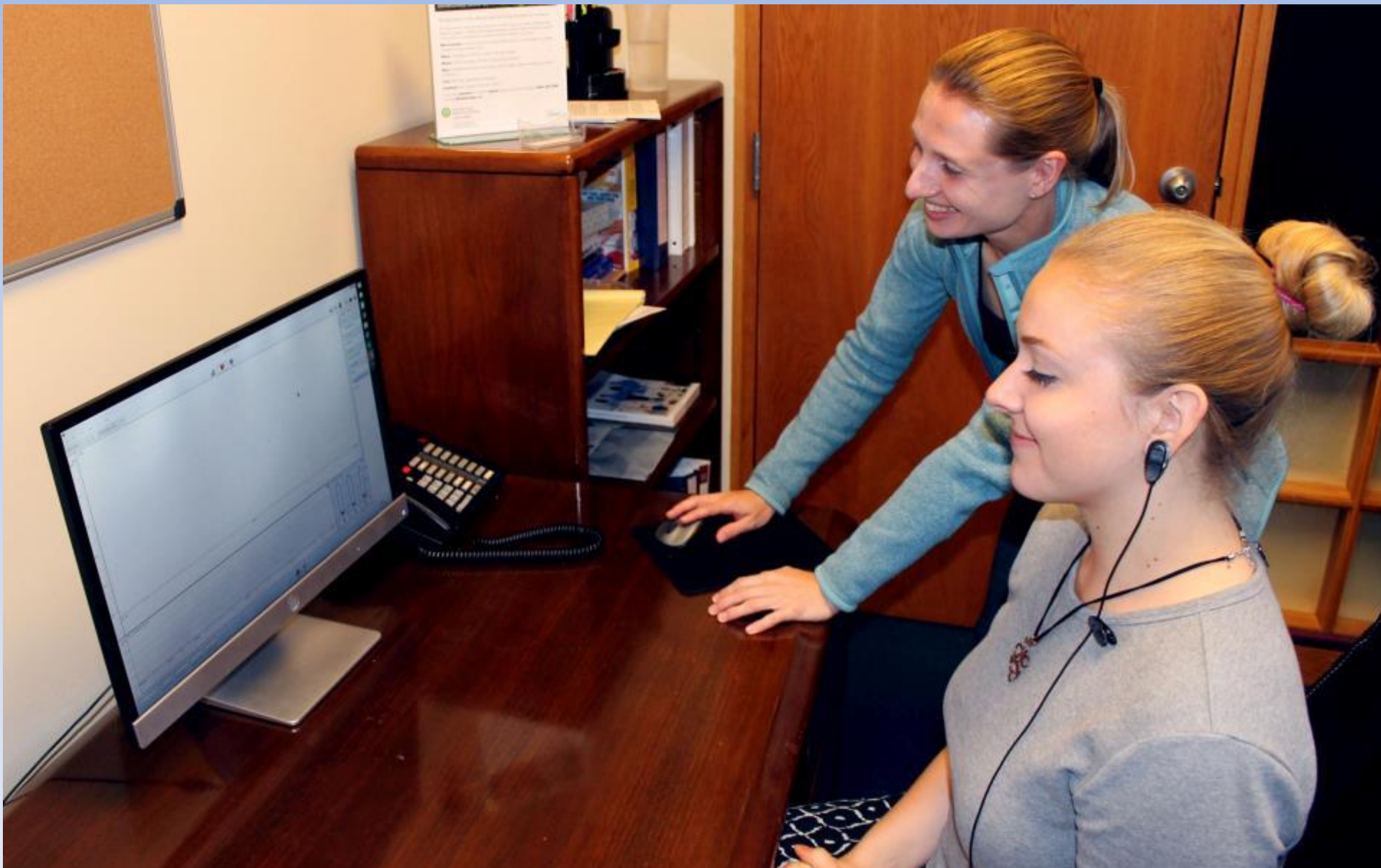


Low HRV

High HRV

HRV Biofeedback

HRV-B participant and coach

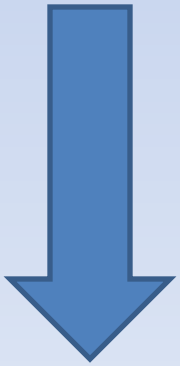


HRV-B coaching essential elements

- Paced breathing at resonant frequency.

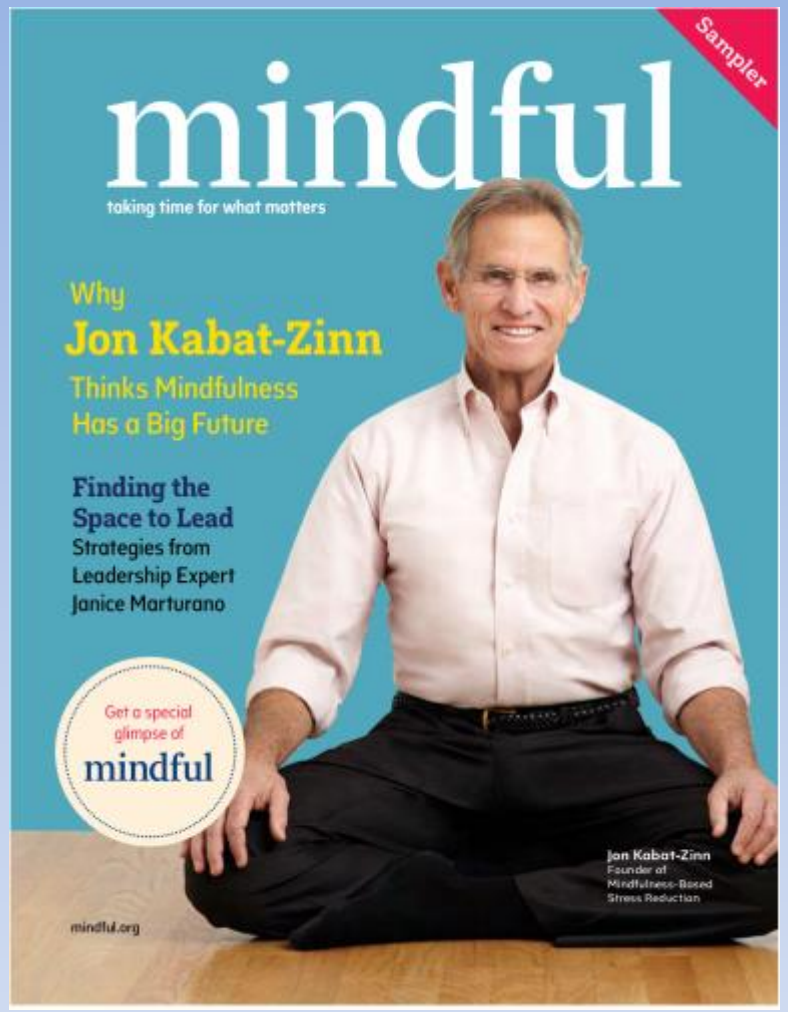
- **Mindfulness** or imagery focused on breathing and the heart. Focused attention on air entering and exiting the chest and passing thorough the heart

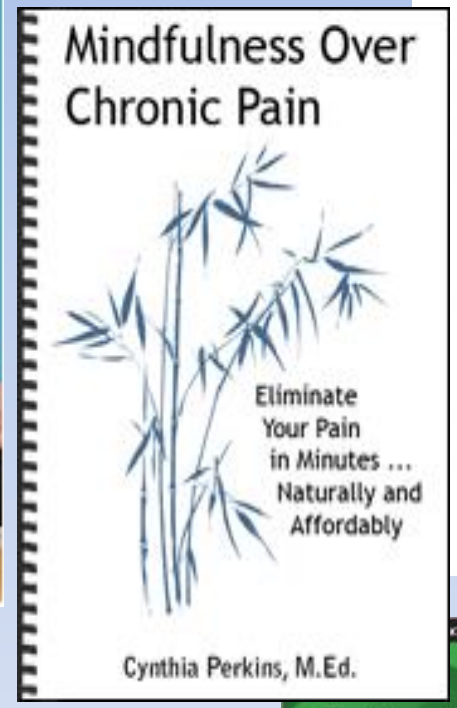
- Positive emotional state (PES). Occupy the mind during the HRVB session with thoughts of compassion, gratitude, apreciation, etc.

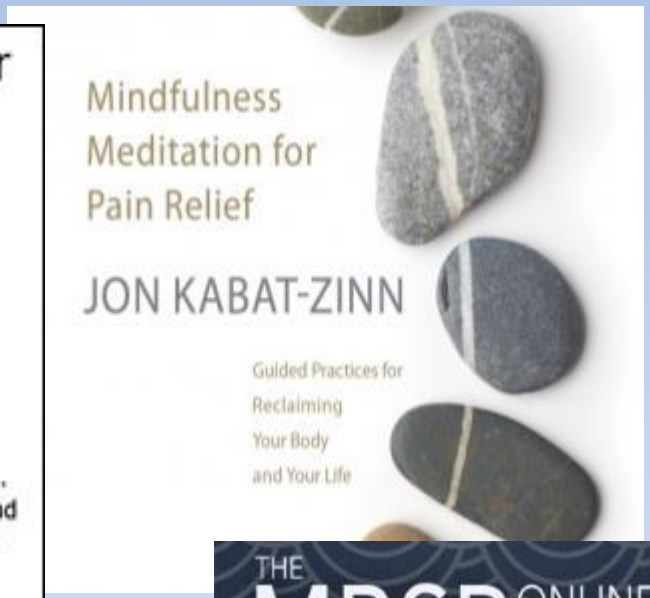


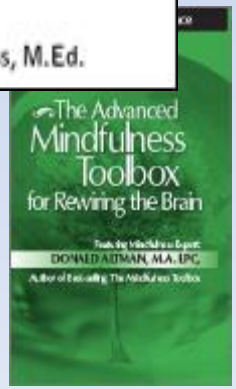
‘COHERENCE’

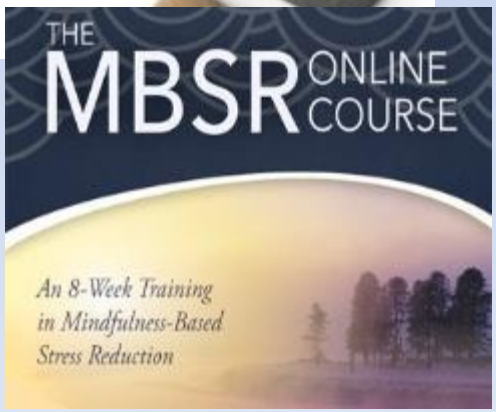
Mindfulness for Pain: books, cd's, online courses, ceu's











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

Liam Ruchlidz

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

Mindfulness practices as we know them today are rooted in 2500-year-old Buddhist meditation practices and are often described as "...paying attention to the present moment experiences with openness, curiosity, and a willingness to be with what is" (http://marc.ucla.edu/). Herbert Benson, MD, founder of the Benson-Henry Institute for Mind Body Medicine at Massachusetts General Hospital, is often credited with bringing mindfulness into the realm of Western medicine. His 1975 book The Relaxation Response outlined techniques to combat the harmful effects of stress with relaxation methods similar to meditation.

These practices did not stay lodged in the 1970s hippie macramé plant holder, however. Several structured mindfulness programs 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, PhD, MPH, founding executive director of the Center for Mindfulness in Medicine, Health Care, and Society at the University of Massachusetts Medical School (http://bit.ly/1KmRIBH).

Another is mindfulness-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 Mark Williams, PhD, and John Teasdale, PhD (http://1.usa.gov/1eOquCo).

According to Gregory Lewis Fricchione, MD, director of the Benson-Henry Institute, "...mindfulness and other meditative techniques can provide adjunctive benefits for health and that includes mental health."

Fricchione does acknowledge pockets of resistance. "Many physicians who consider themselves grounded in Western science will see mindfulness-based programs for mental health disorders as being somewhat foolish and relatively impotent in treating mental disorders, especially severe ones," he said.

That attitude may be slowly changing as researchers have begun to systematically investigate the effects of mindfulness interventions for various physical and mental health conditions, including cancer, stress, multiple sclerosis (MS), pain, anxiety, and depression (http://1.usa.gov/15JXT3R). The results of these studies may help inform physicians of the effectiveness and possible uses of mindfulness interventions in clinical practice.

Why the Growing Trend?

According to a recent work, 79% of medical schools offer some element of mindfulness training, noted co-investigator Cavin Bleck, PhD, MPH, director of the Americ

Journal of the American Medical Association, 314(13), 1327-1329 (October 6, 2015)

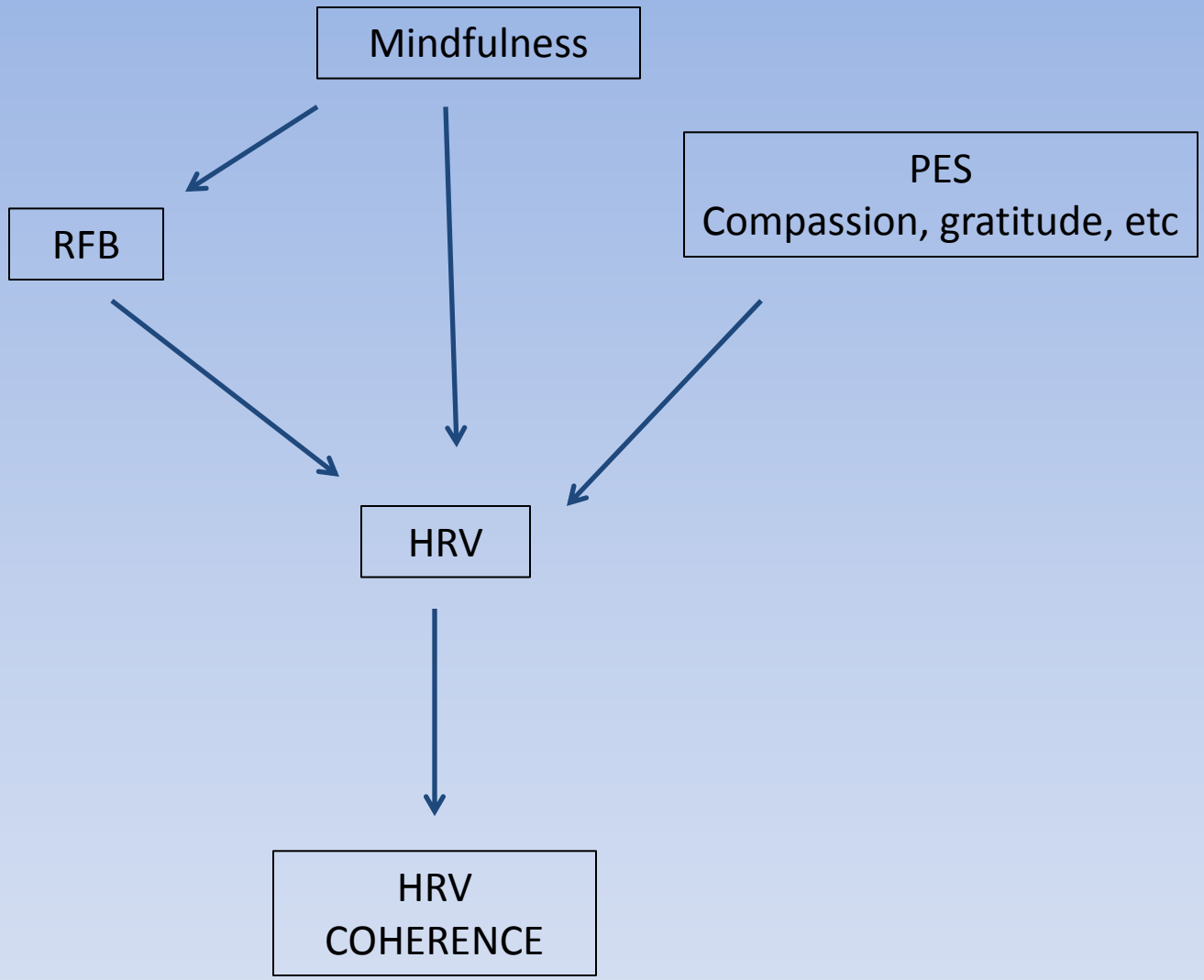
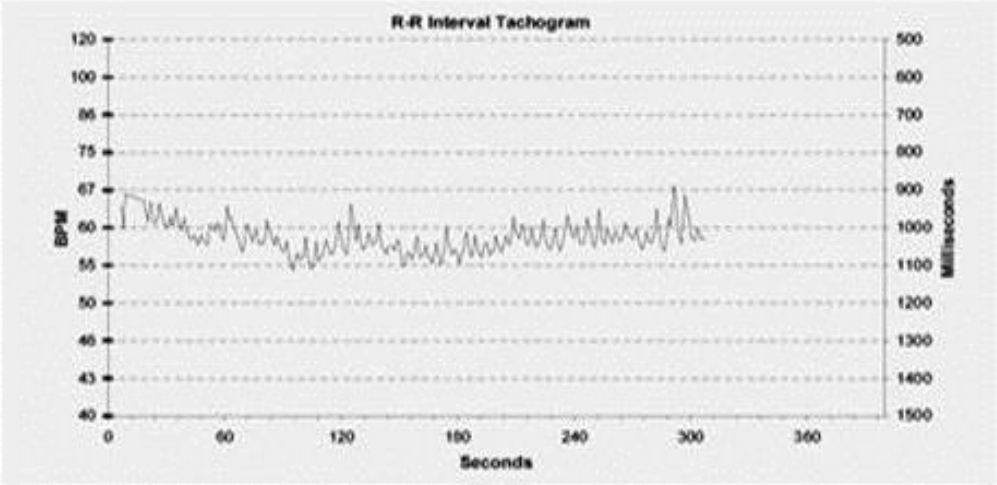

Mindfulness
RFB
PES
Compassion, gratitude, etc
HRV
HRV
COHERENCE

Figure 1 (a – d) depicts the Pre-Post HRVB Training the R-R Interval Tachogram

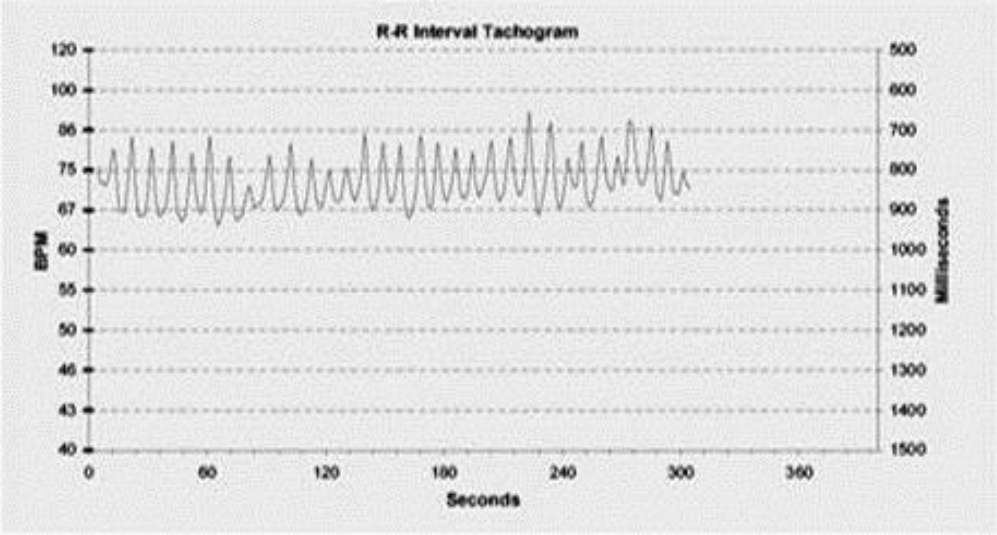
Pre-Training

(a)



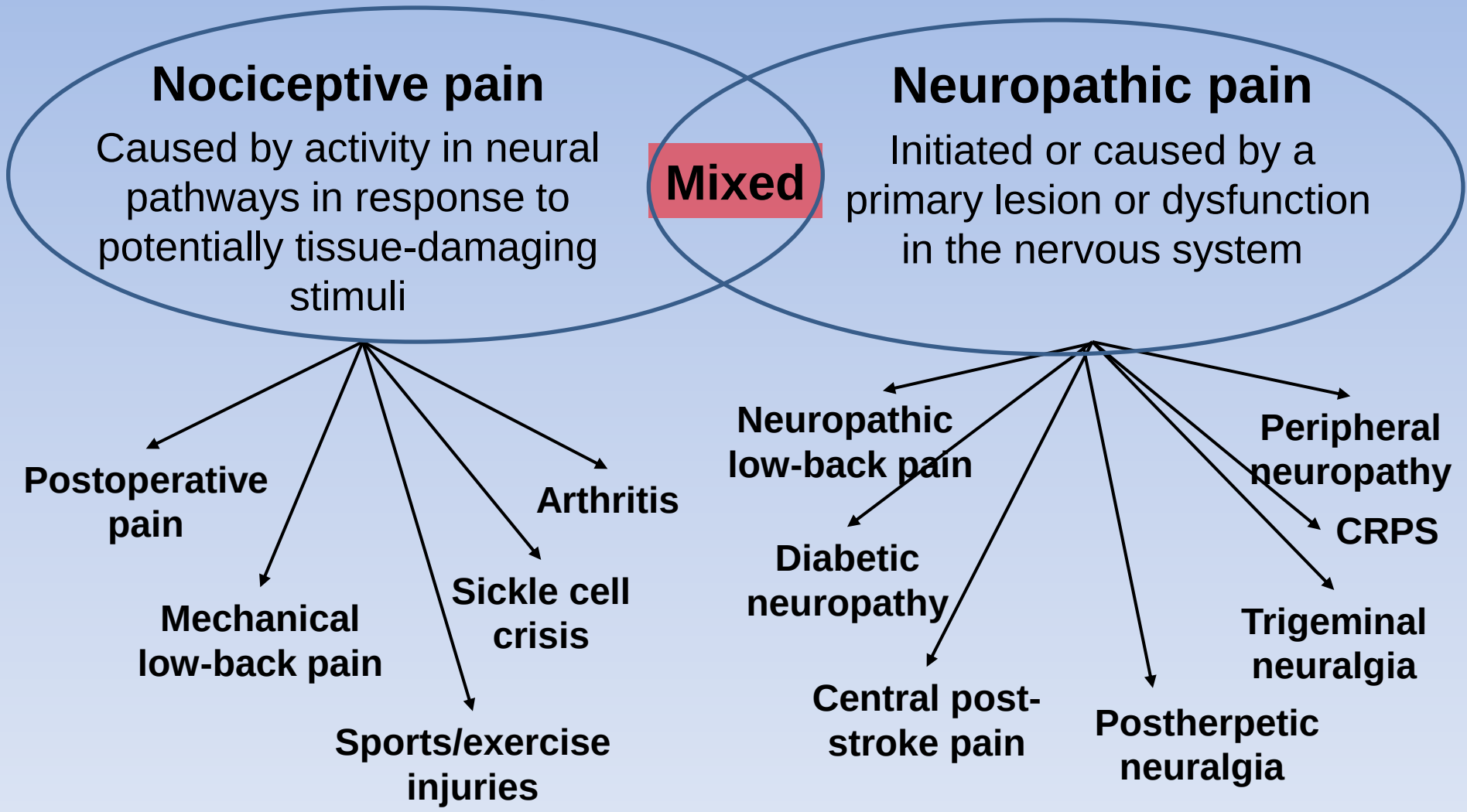
Post-Training

(c)



Pain and Centrally Sensitized Chronic Pain

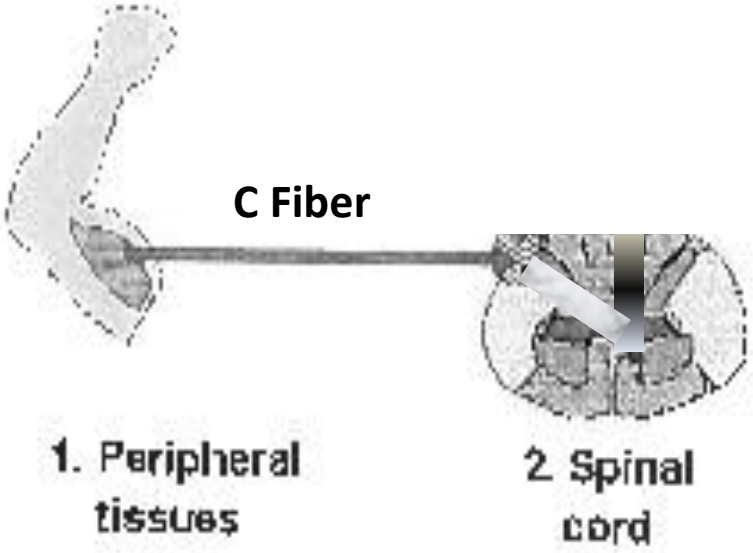
Not all pain is the same: The pathophysiology of painful diseases



Rollin Gallagher, MD, MPH

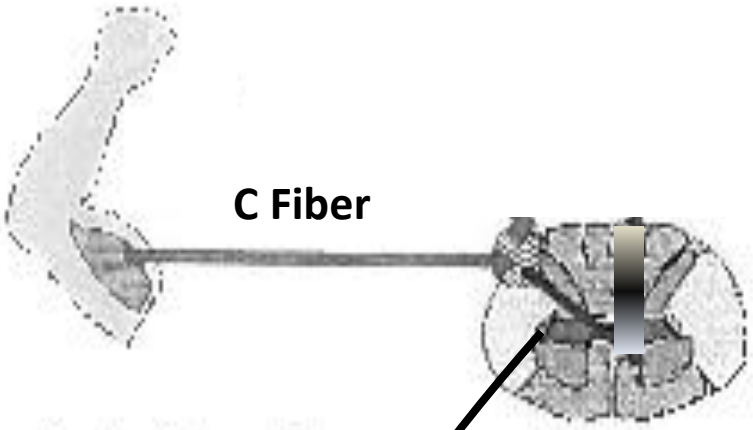
*dhss.delaware.gov/dsamh/files/2007**gallagher**ii.pps*

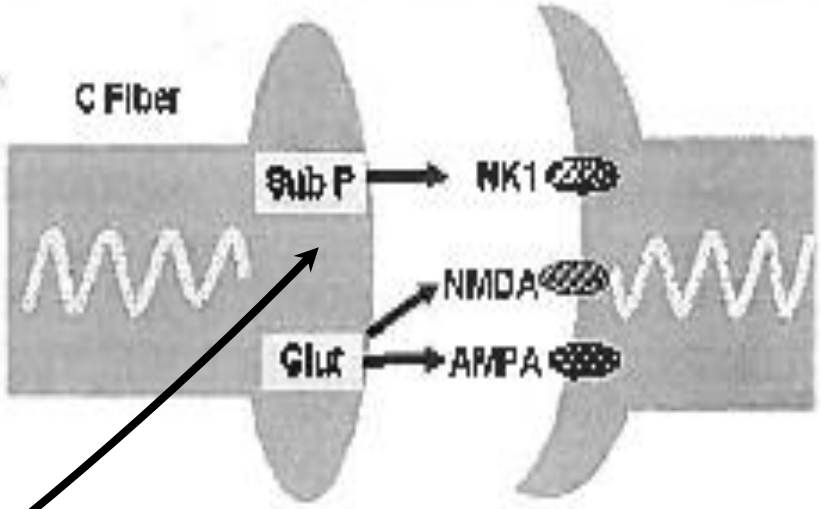
Nociceptive Pain



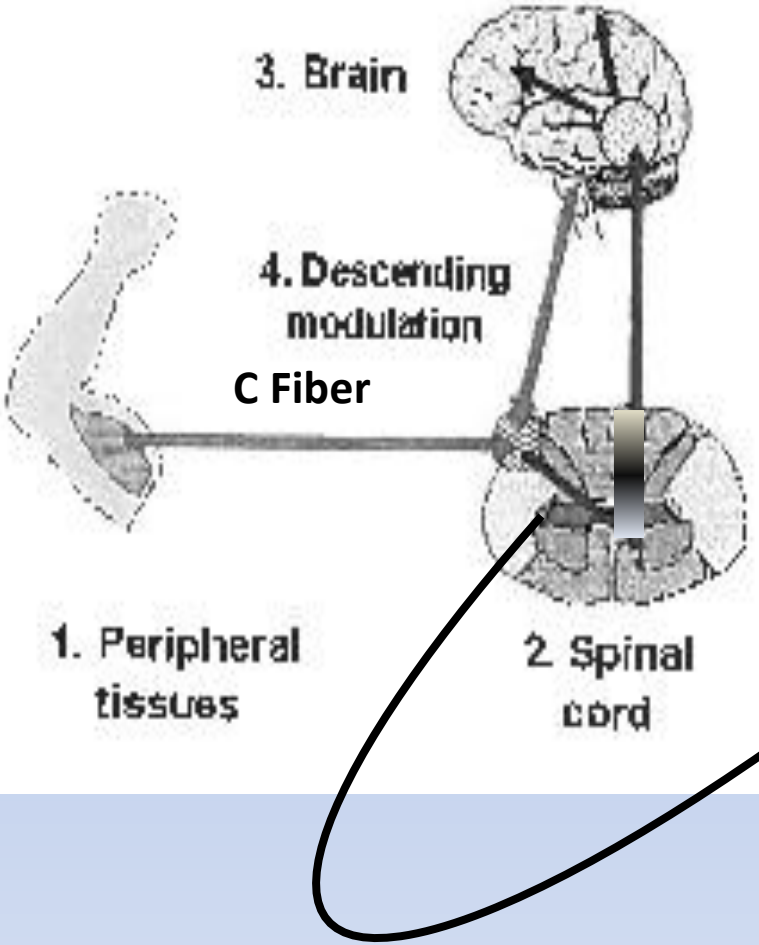
Understanding Pain and Pain Amplification. Robert Benett, MD.
http://www.myalgia.com/Pain_amplification/Overview.htm

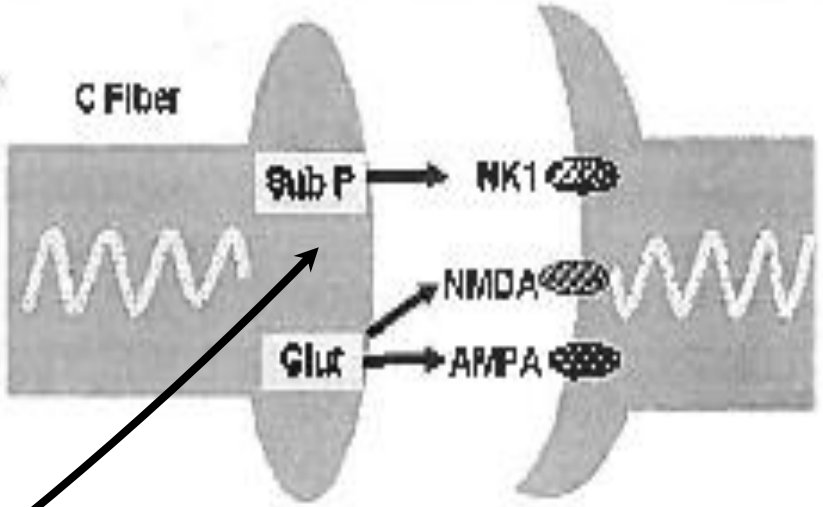
Nociceptive Pain

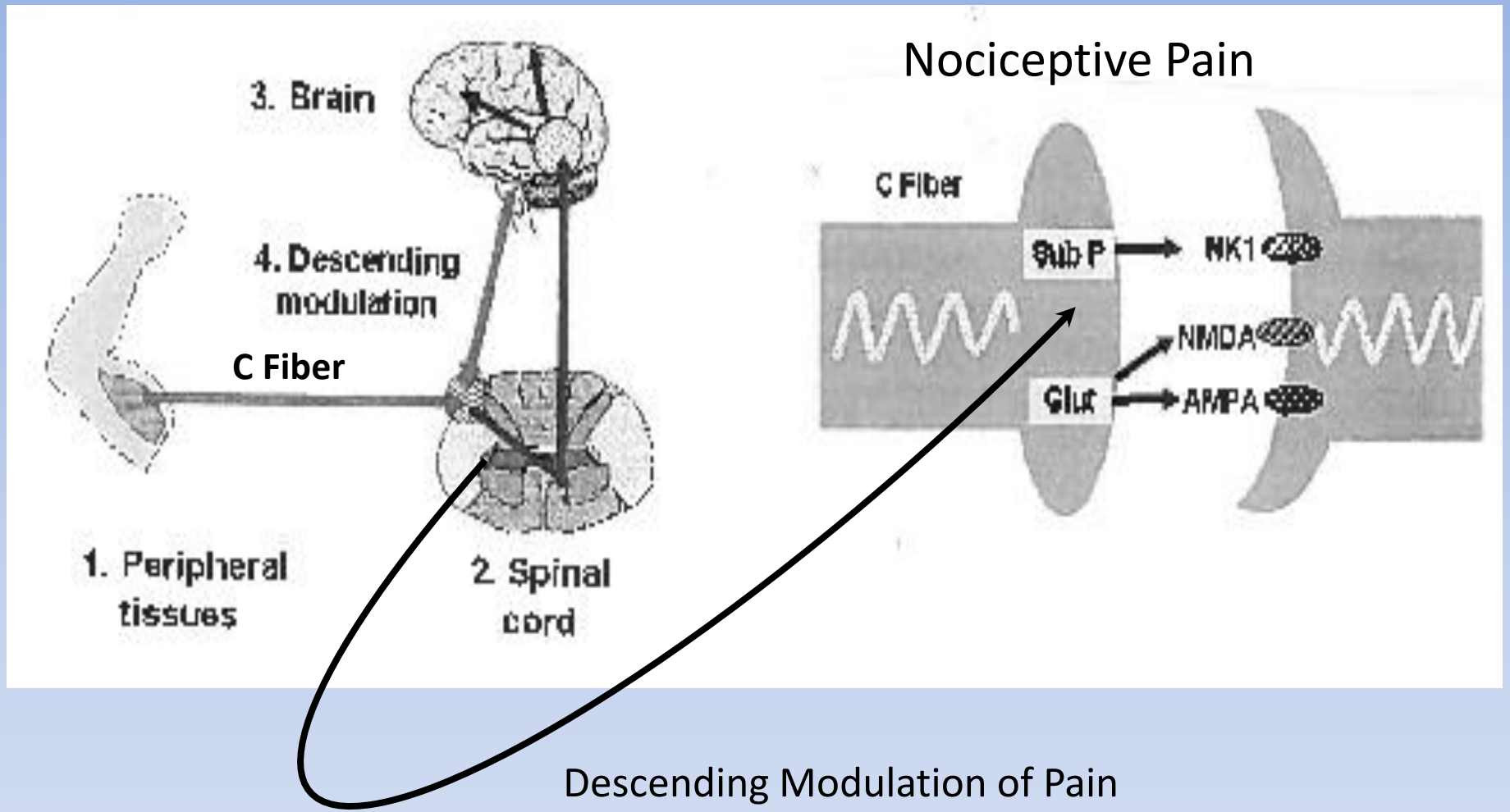




Nociceptive Pain



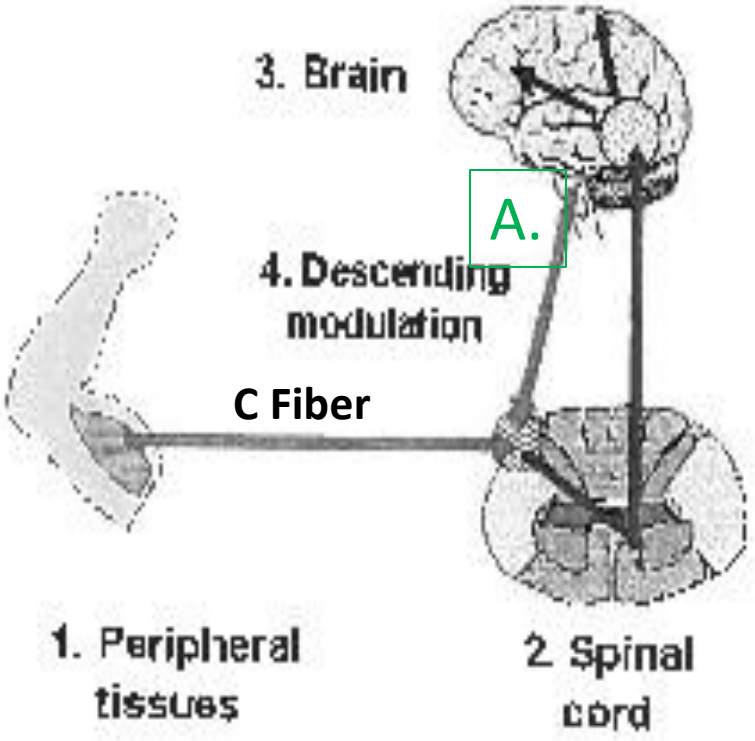




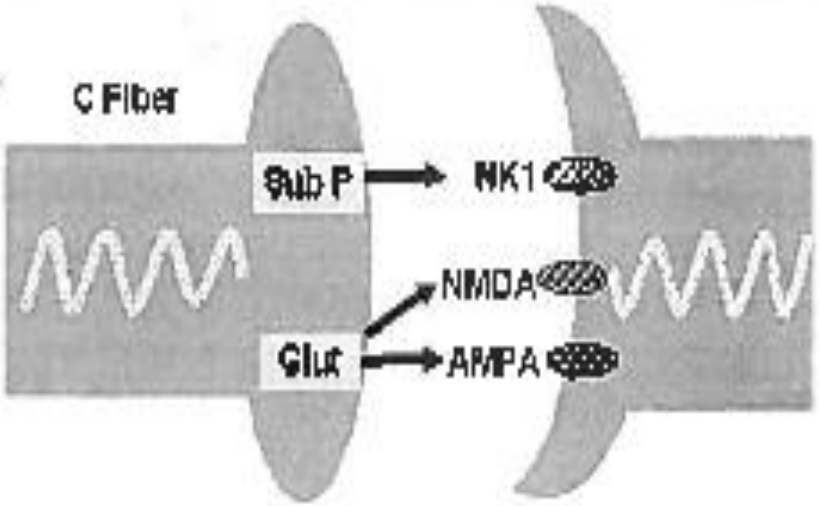
Descending Modulation of Pain

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

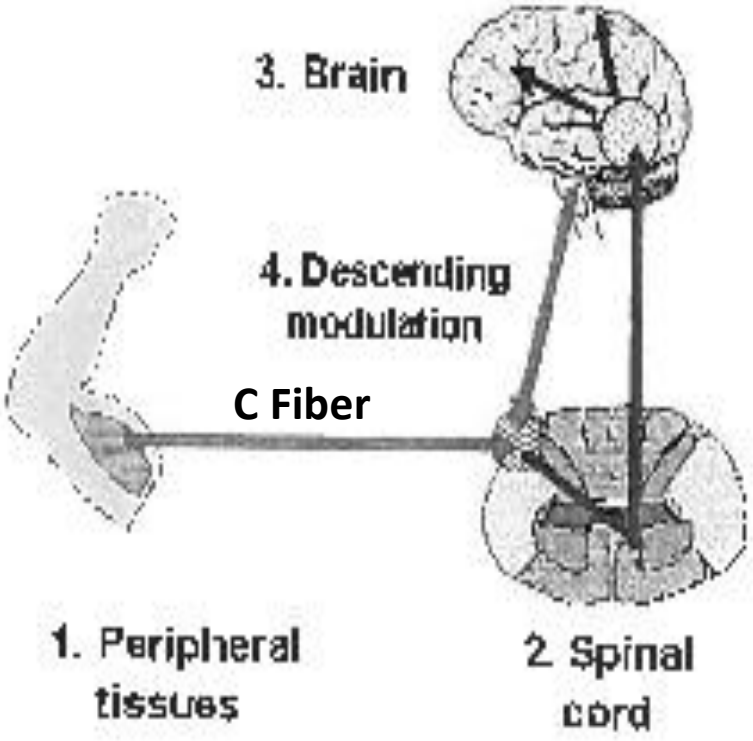
- periaqueductal gray in upper brain stem
- serotonergic from nucleus raphe magnus
- adrenergic from locus coeruleus
- dopaminergic from ventral tegmental area and hypothalamus



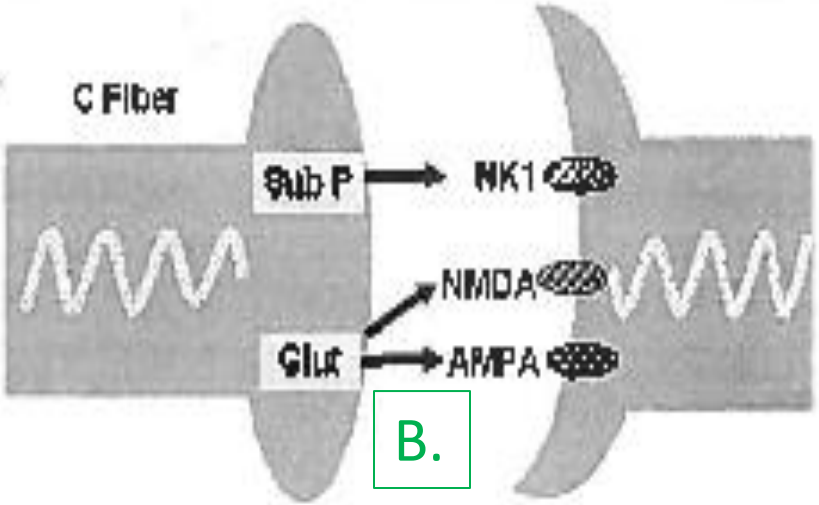
Nociceptive Pain



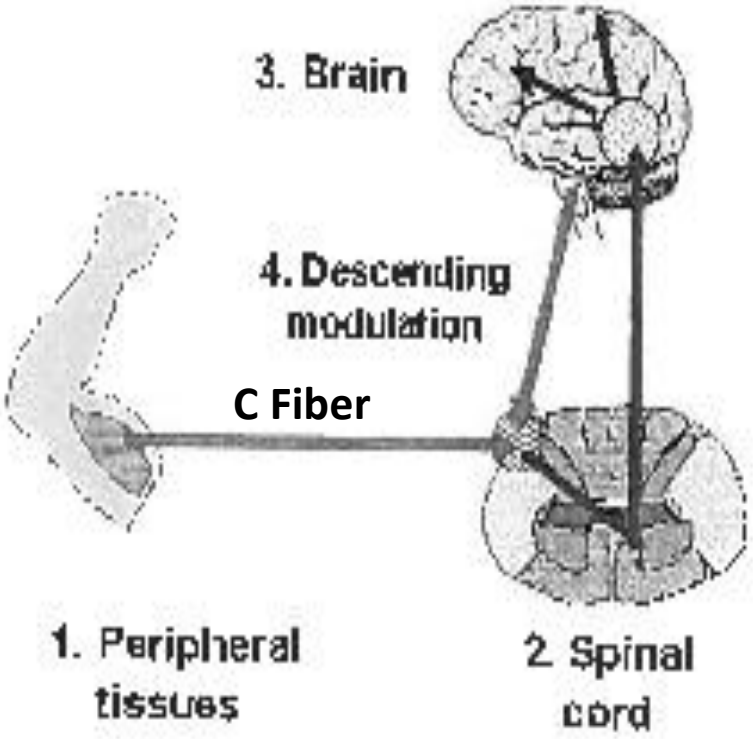
A. Antidepressants (e.g. amitriptyline, duloxetine) reduce pain by ***increasing descending pain inhibition from catecholamines***



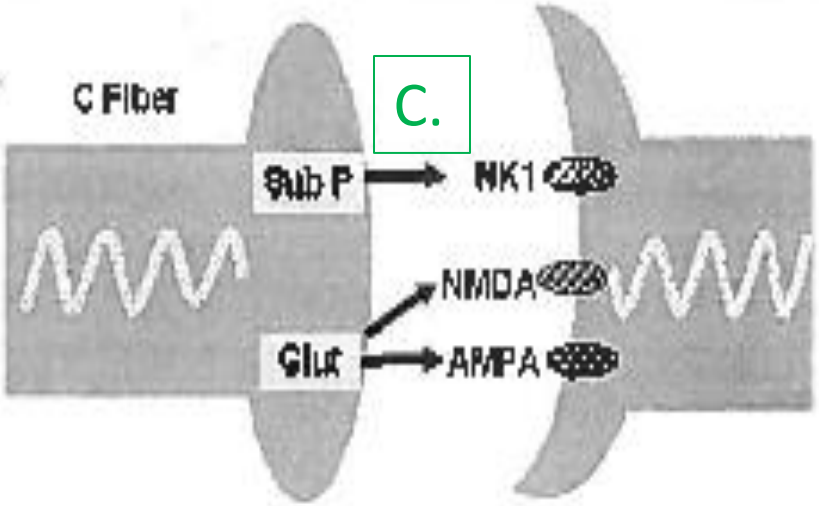
Nociceptive Pain



B. *Anti-epileptics* (e.g. gabapentin, pregabalin) reduce pain by ***limiting release of glutamate from afferent peripheral C fiber***



Nociceptive Pain

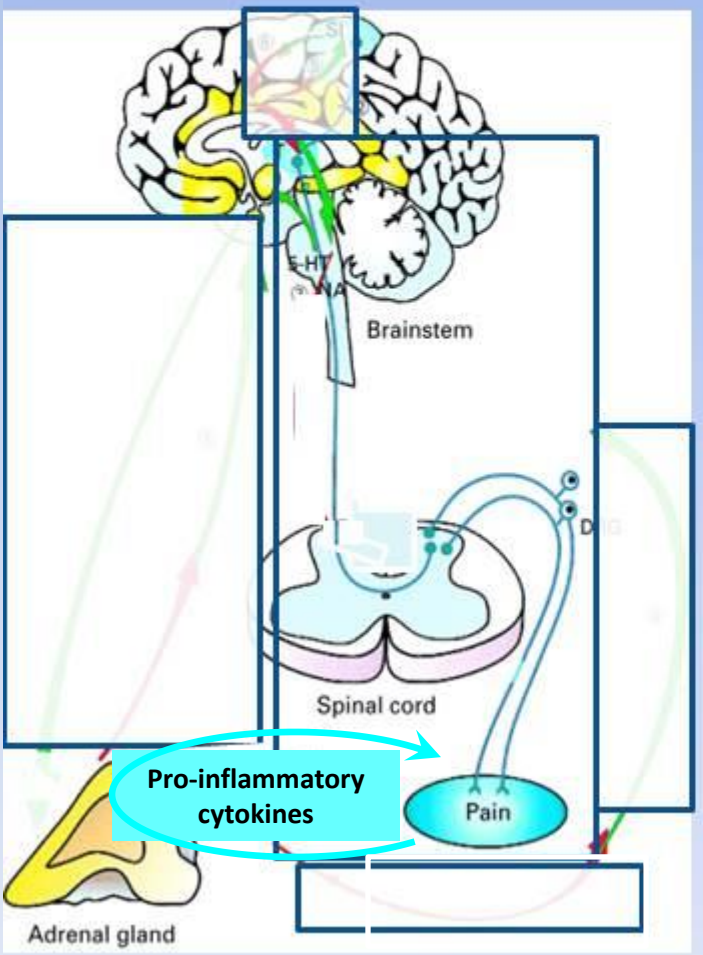


C. *Opioids (*e.g. morphine) block pain by ***activating opioid receptors and inhibiting substance P***

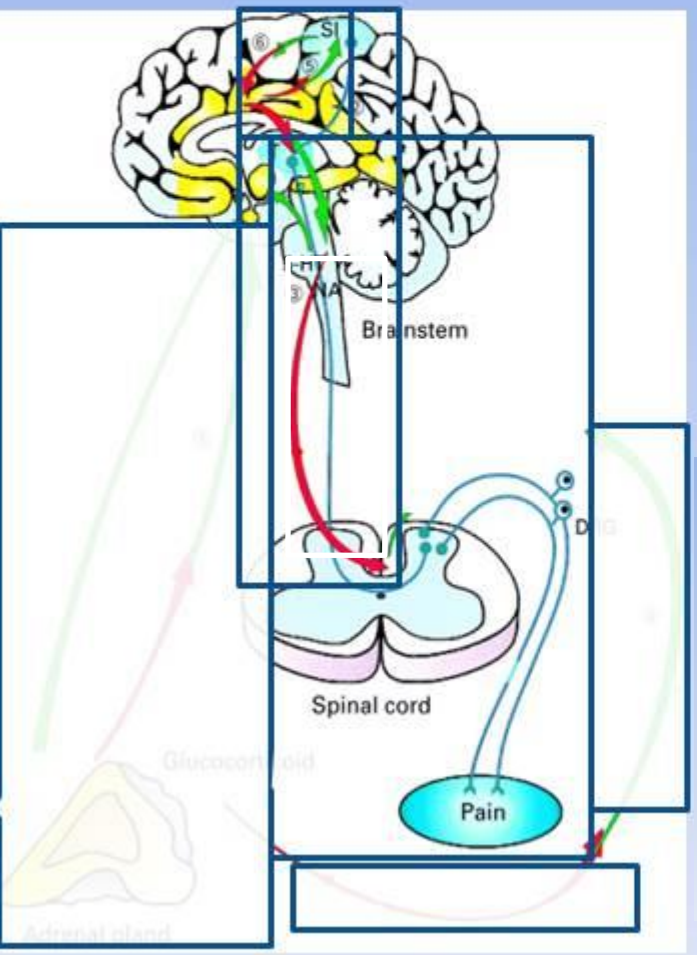
Blackburn-Munro, G. & Blackburn-Munro, R.E. (2001). Chronic Pain, Chronic Stress and Depression: Coincidence or Consequence? *Journal of Neuroendocrinology*. Volume 13 (12), 1009-1023. Springer

STRESS OF CHRONIC PAIN CAUSES CENTRAL SENSITIZATION AND DEPRESSION - I

- Inflammation / nerve injury stimulate nociceptive information to dorsal horn
- Ascends to brainstem, gated in thalamus

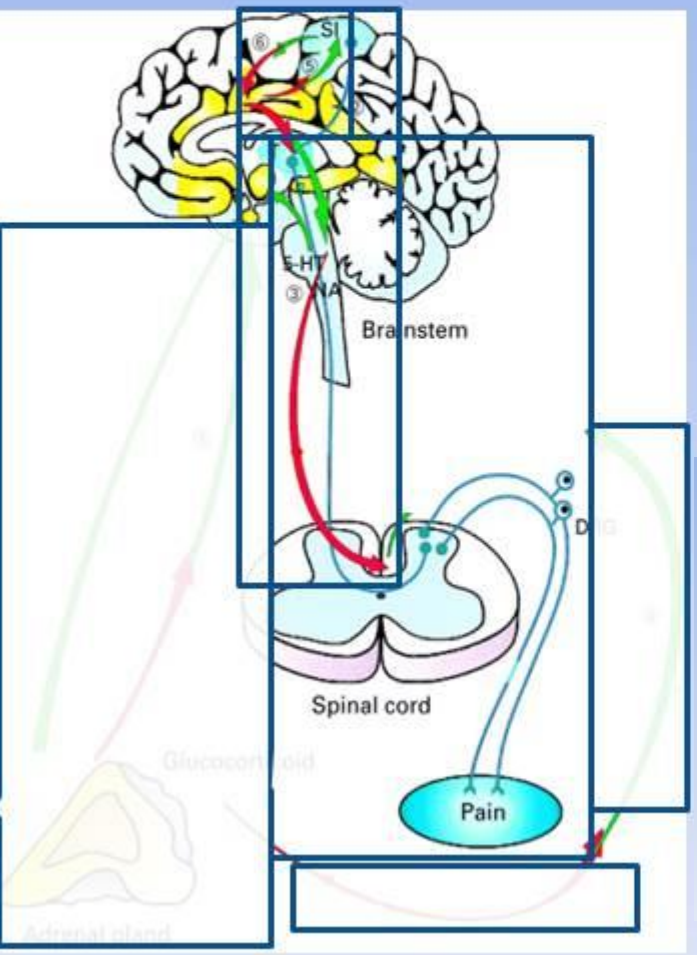


STRESS OF CHRONIC PAIN CAUSES CENTRAL SENSITIZATION AND DEPRESSION - II



- 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)
  - This is the stress pathway

STRESS OF CHRONIC PAIN CAUSES CENTRAL SENSITIZATION AND DEPRESSION - III



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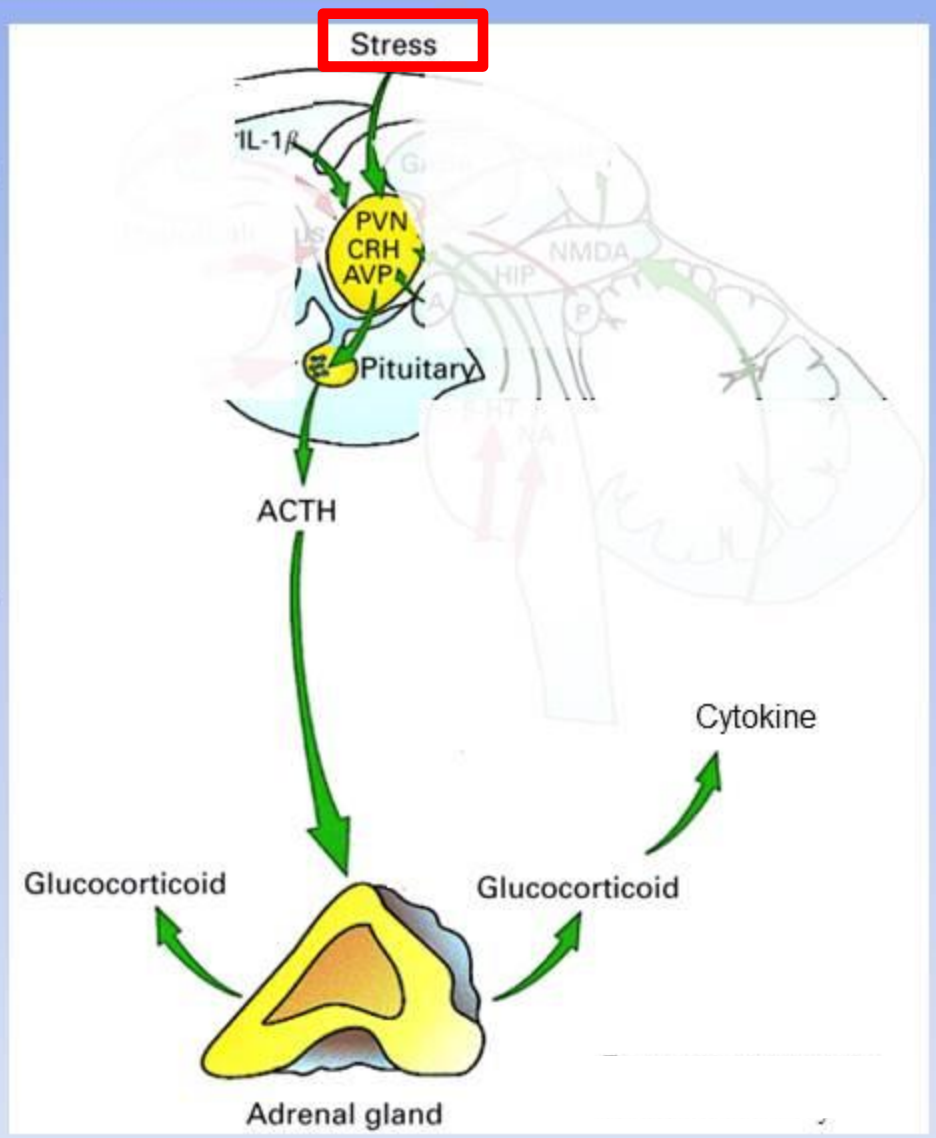
  - This is the stress pathway
- →Descending pain modulation

PAIN ENDS

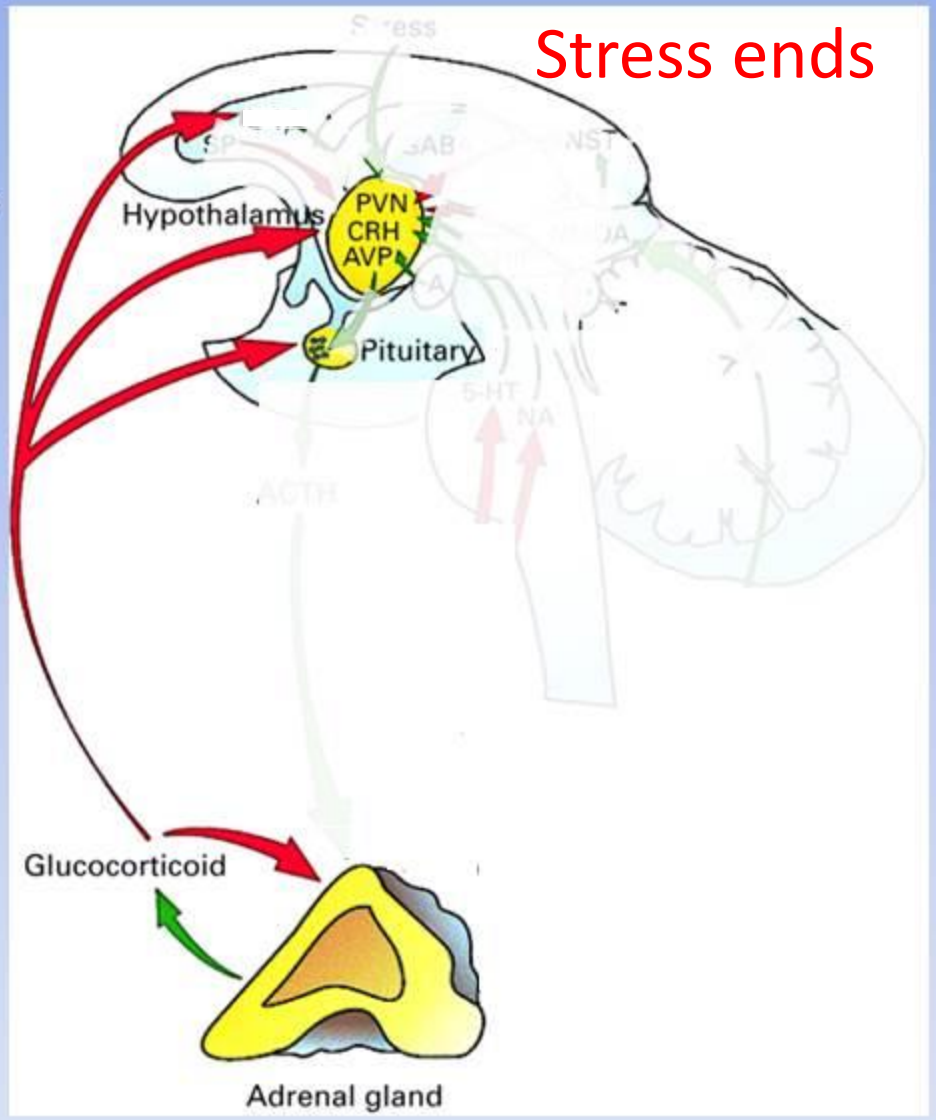
STRESS RESPONSE

- 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



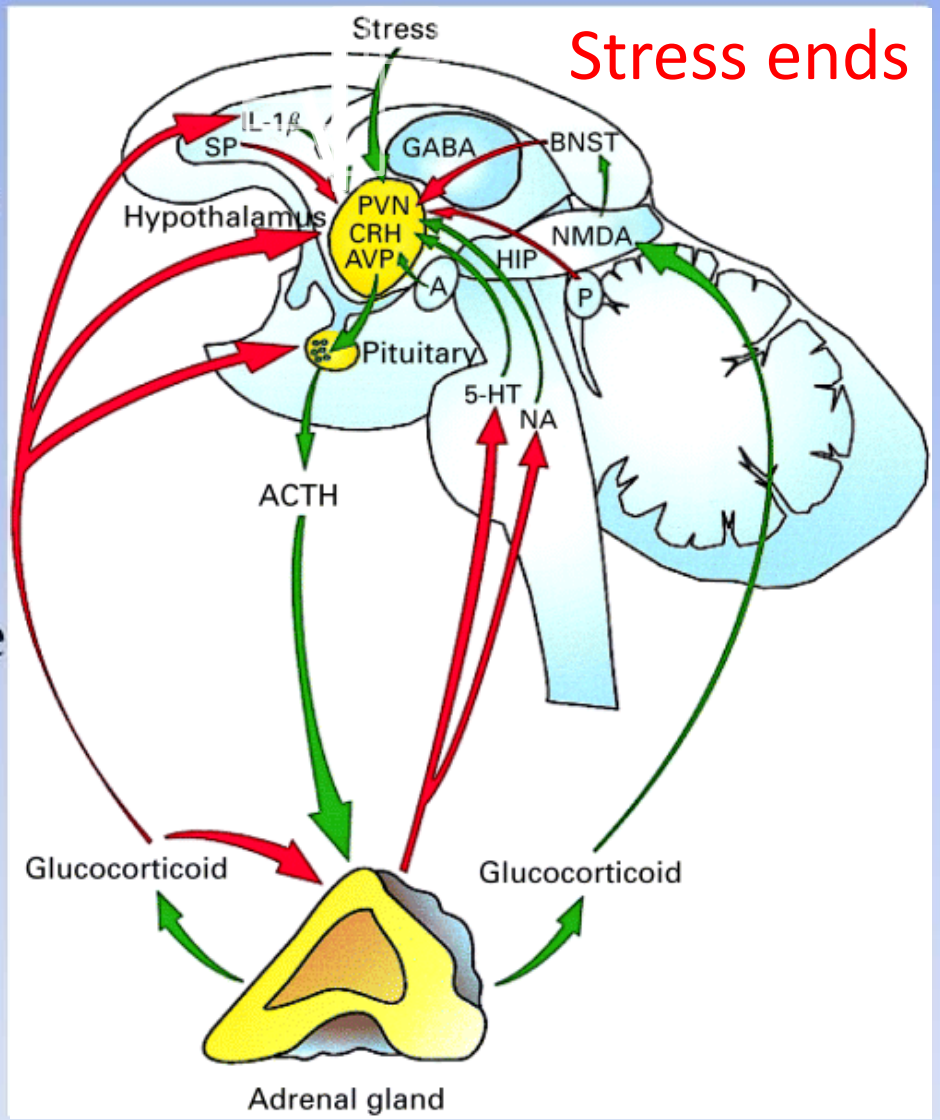
STRESS RESPONSE NEGATIVE FEEDBACK: I

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

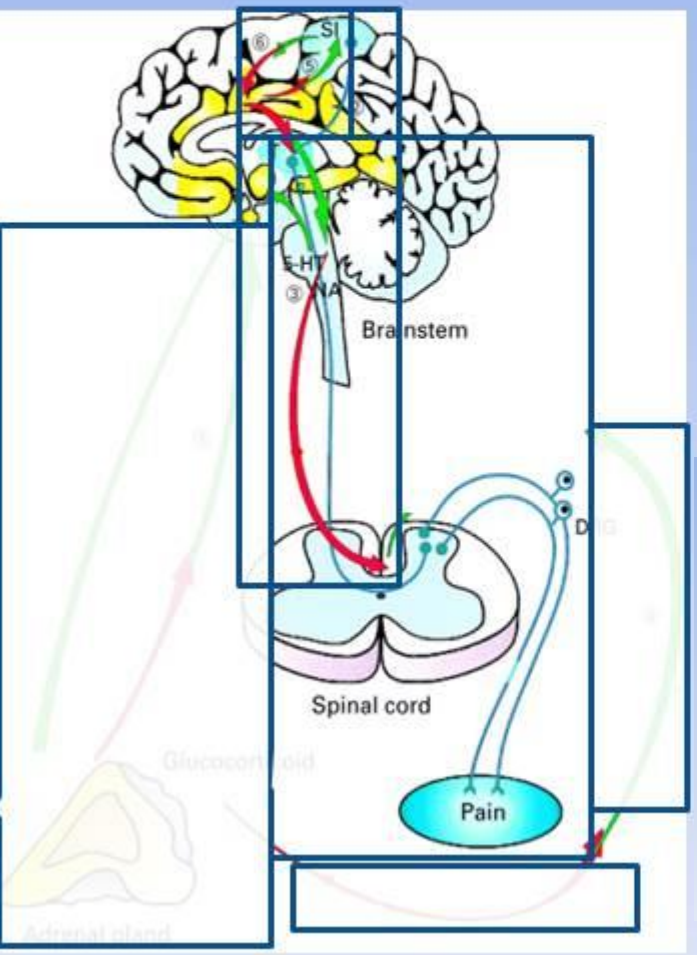


STRESS RESPONSE NEGATIVE FEEDBACK: II

- 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 OF CHRONIC PAIN CAUSES CENTRAL SENSITIZATION AND DEPRESSION - III



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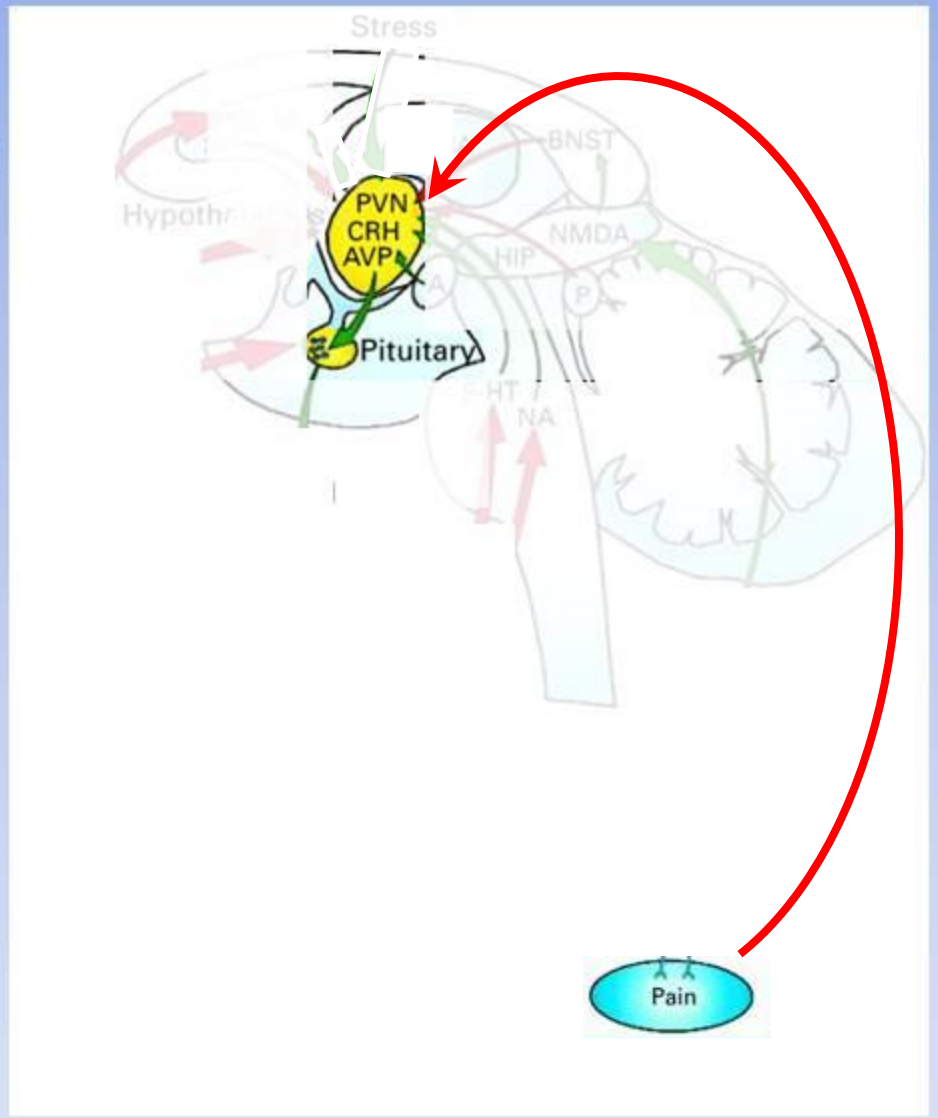
PAIN NEVER ENDS

STRESS RESPONSE

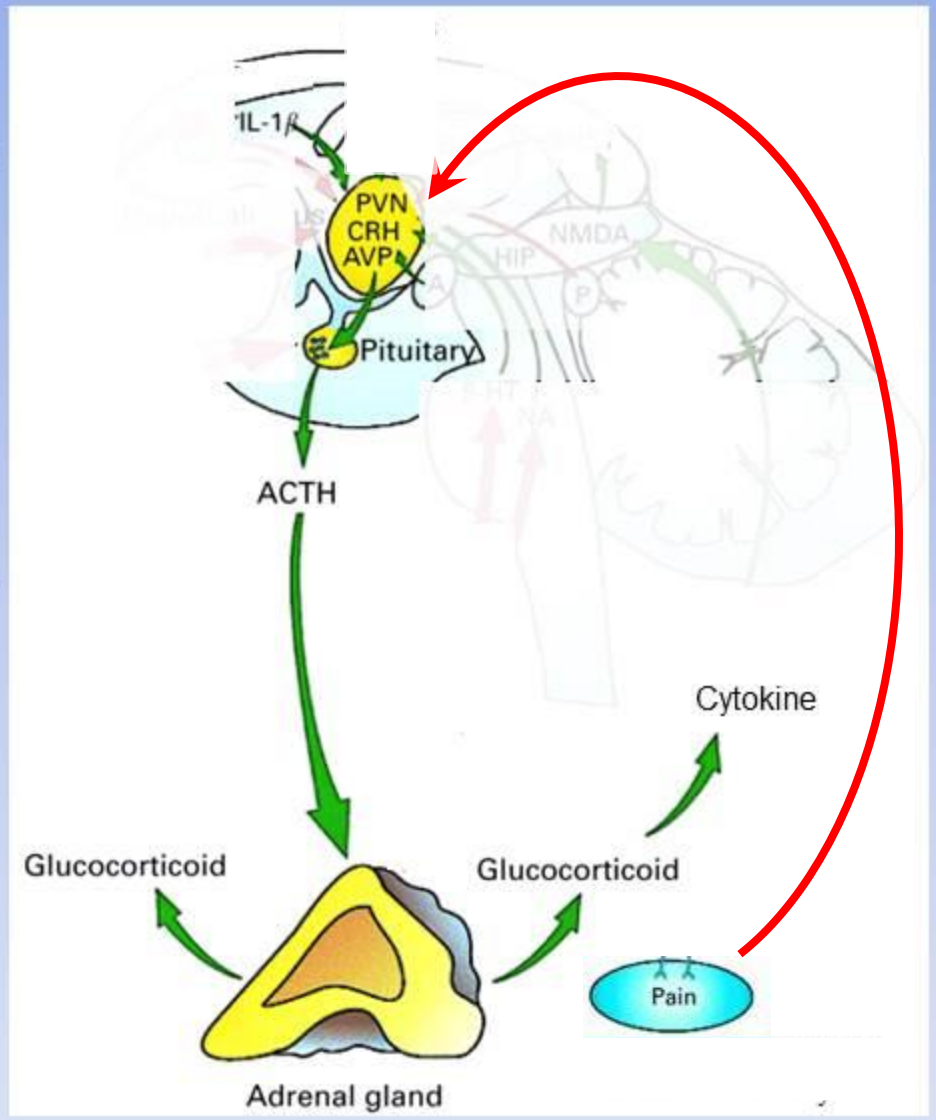
- CRH and/or AVP released
  - → anterior pituitary gland



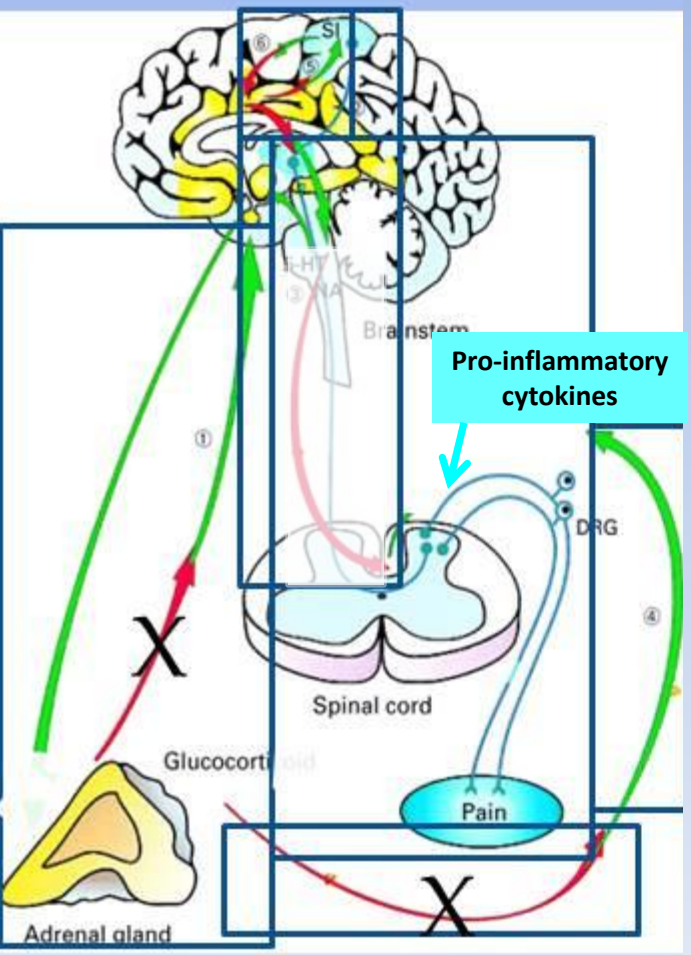
Blackburn-Munro, G. & Blackburn-Munro, R.E. (2001). Chronic Pain, Chronic Stress and Depression: Coincidence or Consequence? *Journal of Neuroendocrinology*. Volume 13 (12), 1009-1023. Springer

STRESS RESPONSE DRIVEN BY CHRONIC PAIN

- 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 OF CHRONIC PAIN CAUSES CENTRAL SENSITIZATION AND DEPRESSION



- Pain never ends (←PTSD)→
- Chronic Stress →
- '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 catecholaimes – (nor)adrenealin from locus coeruleus and dopamine from hypothalamus
- Depressed behavior and mood (fatigue, insomnia)

Depression is an expression of chronic stress

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

- Chronically stressed rodents have a profile strikingly similar to depressed people
- Depressed people are stressed
- However, not all stressed people are depressed
- The difference between stress and depression in people appears to be cortisol: when high, depression is expressed; when low, stress is the phenotype

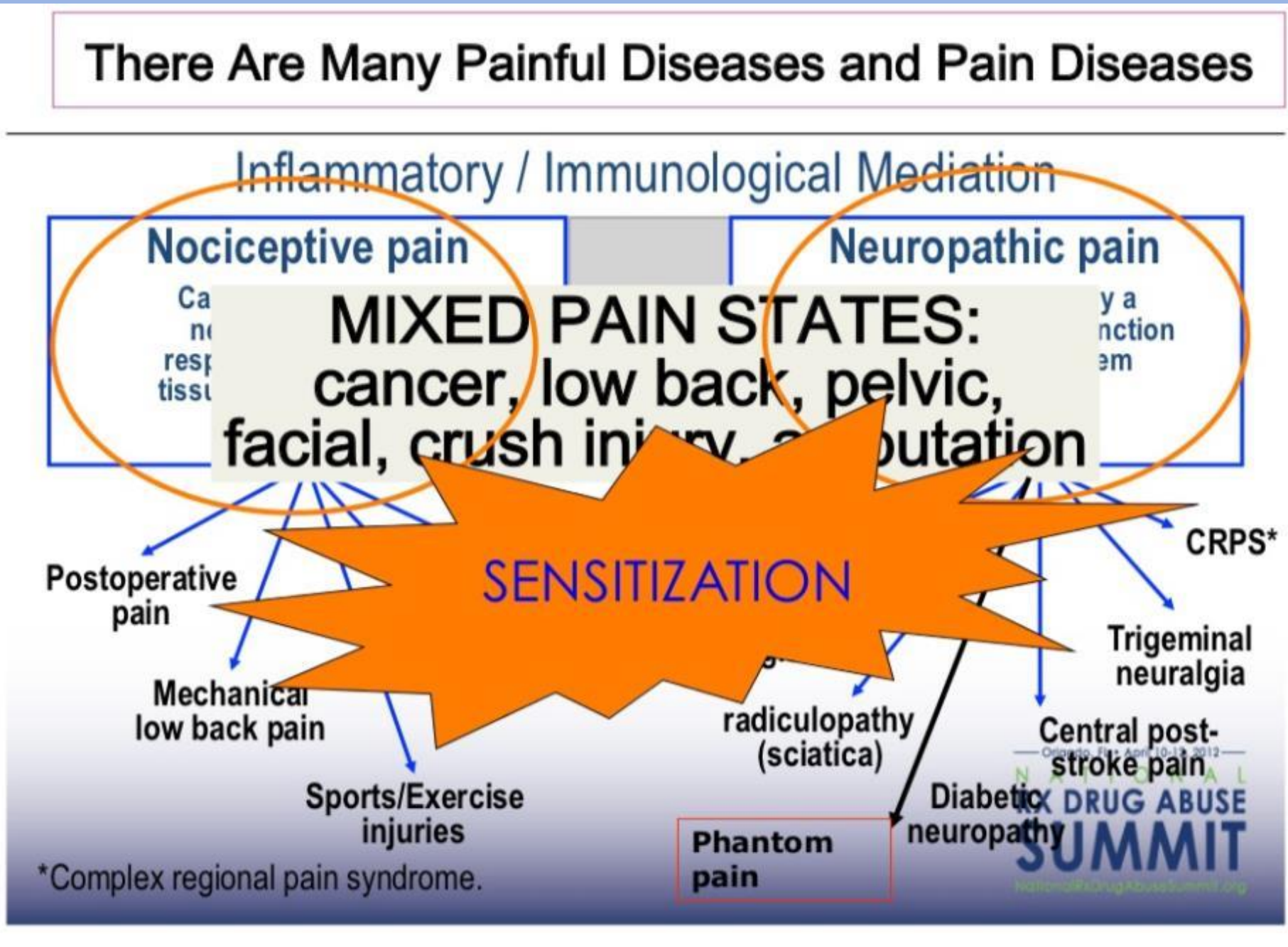
Chronic stress (rodents)	Clinical depression (humans)
↑CRH/CRH mRNA	↑CRH/CRH mRNA
↓CRH receptor affinity/number	↓CRH receptor affinity/number
↑AVP/AVP mRNA	↑AVP/AVP mRNA
↑CSF levels of CRH/AVP	↑CSF levels of CRH/AVP
↑Co-expression of CRH/AVP	↑Co-expression of CRH/AVP
↓GR/MR number/function	↓GR/MR number/function
Altered plasma ACTH concentration	Altered plasma ACTH concentration
Altered circadian rhythmicity	Altered circadian rhythmicity
Adrenal supersensitivity to ACTH	Adrenal supersensitivity to ACTH
↑Corticosterone	↑Cortisol **(*cortisol is ↓ in PTSD)**
↓Negative feedback	↓Negative feedback
Adrenal hypertrophy	Adrenal hypertrophy
Pituitary hypertrophy	Pituitary hypertrophy
Exaggerated corticosterone response	Exaggerated cortisol response
Cognitive deficit	Cognitive deficit
Behavioral disturbance	Behavioral and mood disturbance

Blackburn-Monro & Blackburn-Monro (2011).

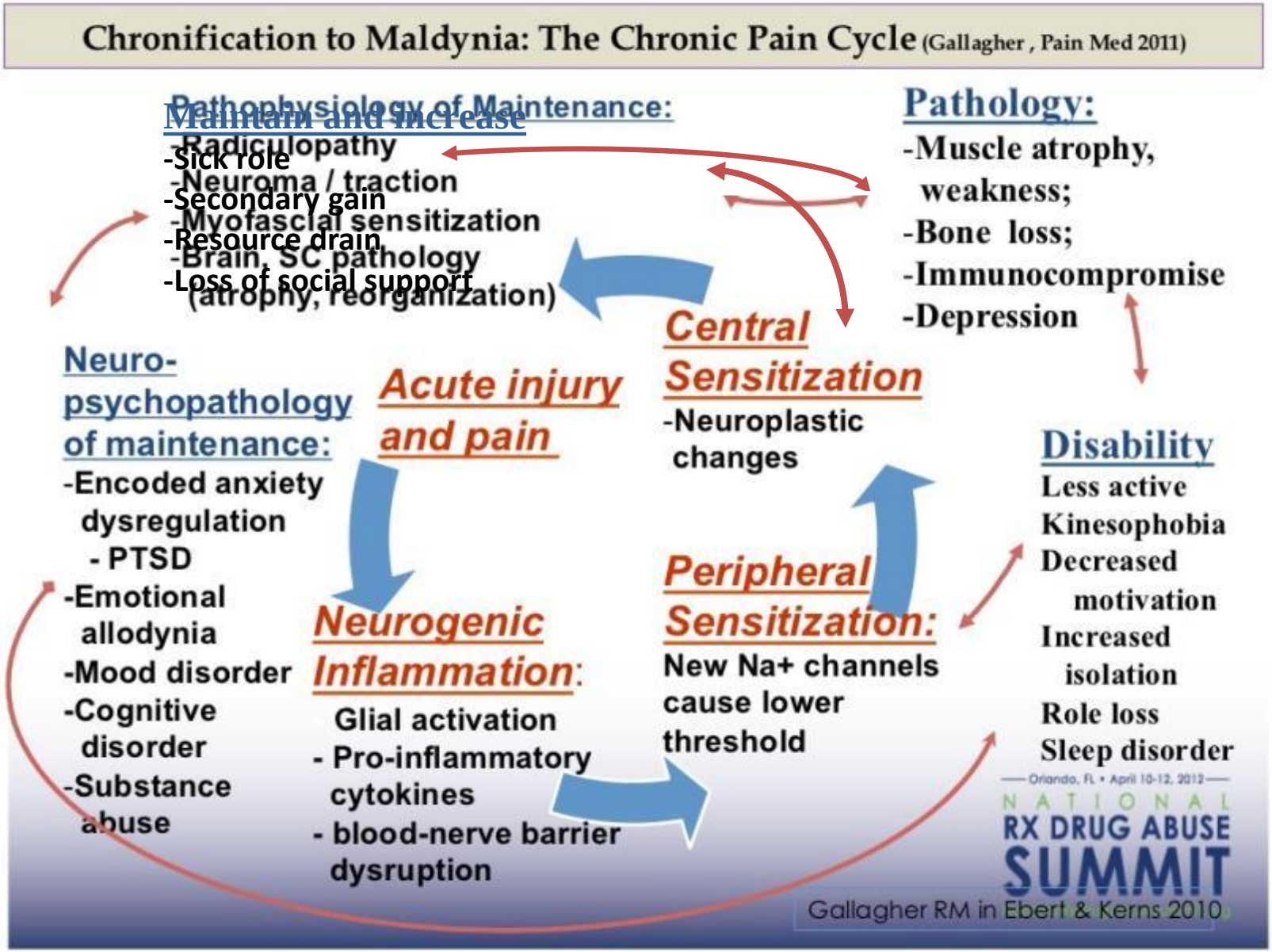
Pain and PTSD are inter-related

Moeller-Bertram, Tobias, Irina A. Strigo, Alan N. Simmons, Jan M. Schilling, Piyush Patel, and Dewleen G. Baker. "Evidence for acute central sensitization to prolonged experimental pain in posttraumatic stress disorder." *Pain Medicine* 15, no. 5 (2014): 762-771

Scioli-Salter, E. R., Forman, D. E., Otis, J. D., Gregor, K., Valovski, I., & Rasmusson, A. M. (2015). The shared neuroanatomy and neurobiology of comorbid chronic pain and PTSD: Therapeutic implications. *The Clinical journal of pain*, *31*(4), 363-374.



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


Chronification to Maldynia: The Chronic Pain Cycle (Gallagher , Pain Med 2011)
Pathophysiology of Maintenance:
-Radiculopathy
-Neuroma / traction
-Myofascial sensitization
-Brain, SC pathology
(atrophy, reorganization)
Maintain and Increase
-Sick role
-Secondary gain
-Resource drain
-Loss of social support
Pathology:
-Muscle atrophy, weakness;
-Bone loss;
-Immunocompromise
-Depression
Central Sensitization
-Neuroplastic changes
Neuro-psychopathology of maintenance:
-Encoded anxiety dysregulation - PTSD
-Emotional allodynia
-Mood disorder
-Cognitive disorder
-Substance abuse
Acute injury and pain
Neurogenic Inflammation:
Glial activation
- Pro-inflammatory cytokines
- blood-nerve barrier dysruption
Peripheral Sensitization:
New Na+ channels cause lower threshold
Disability
Less active
Kinesophobia
Decreased motivation
Increased isolation
Role loss
Sleep disorder
Orlando, FL • April 10-12, 2012
NATIONAL RX DRUG ABUSE SUMMIT
Gallagher RM in Ebert & Kerns 2010

Research on ASR and Chronic Pain

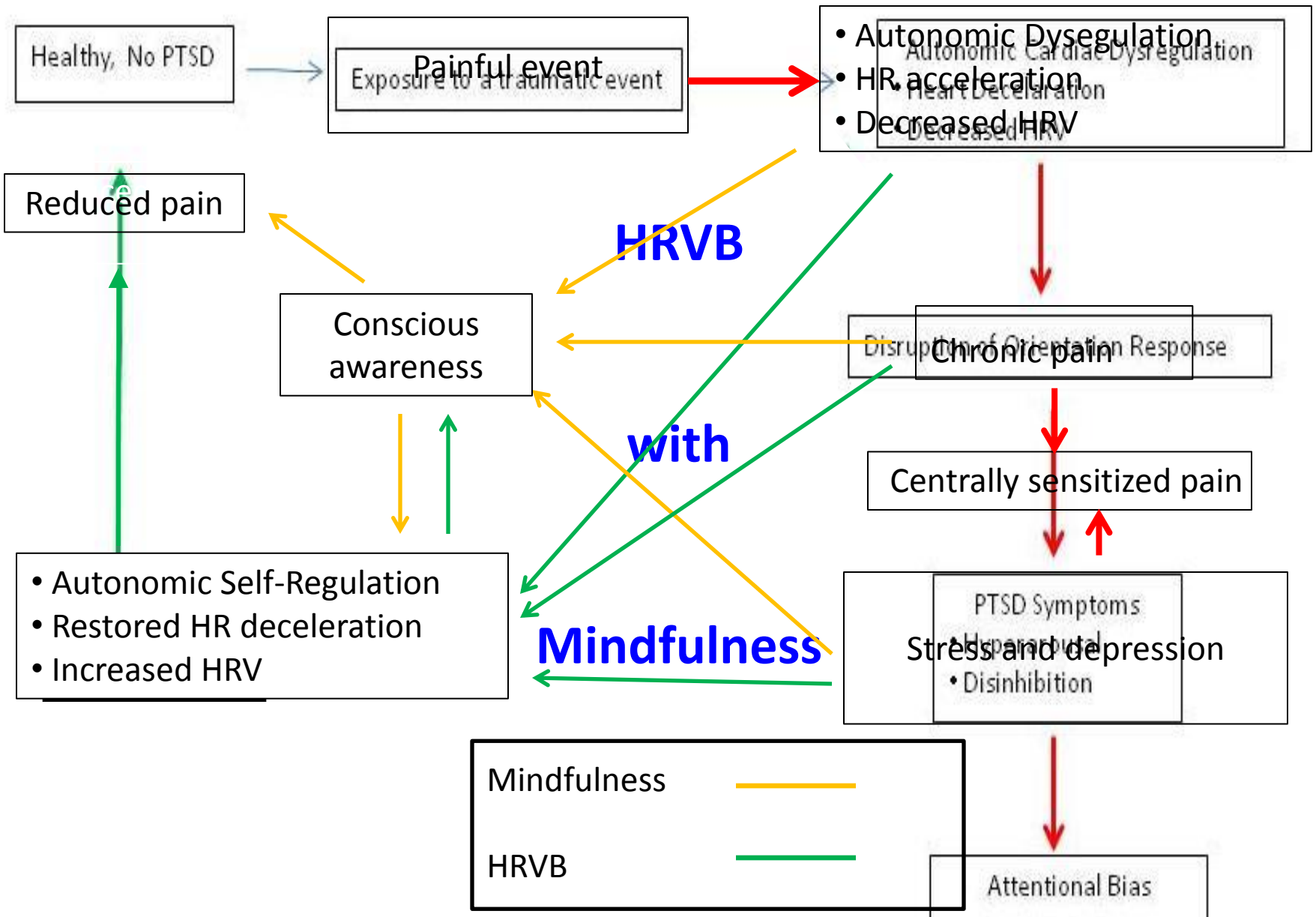
‘The Health Pathway’

Autonomic Balance

- ASR → Coherence

Central Pain Sensitization

- Stress, Depression



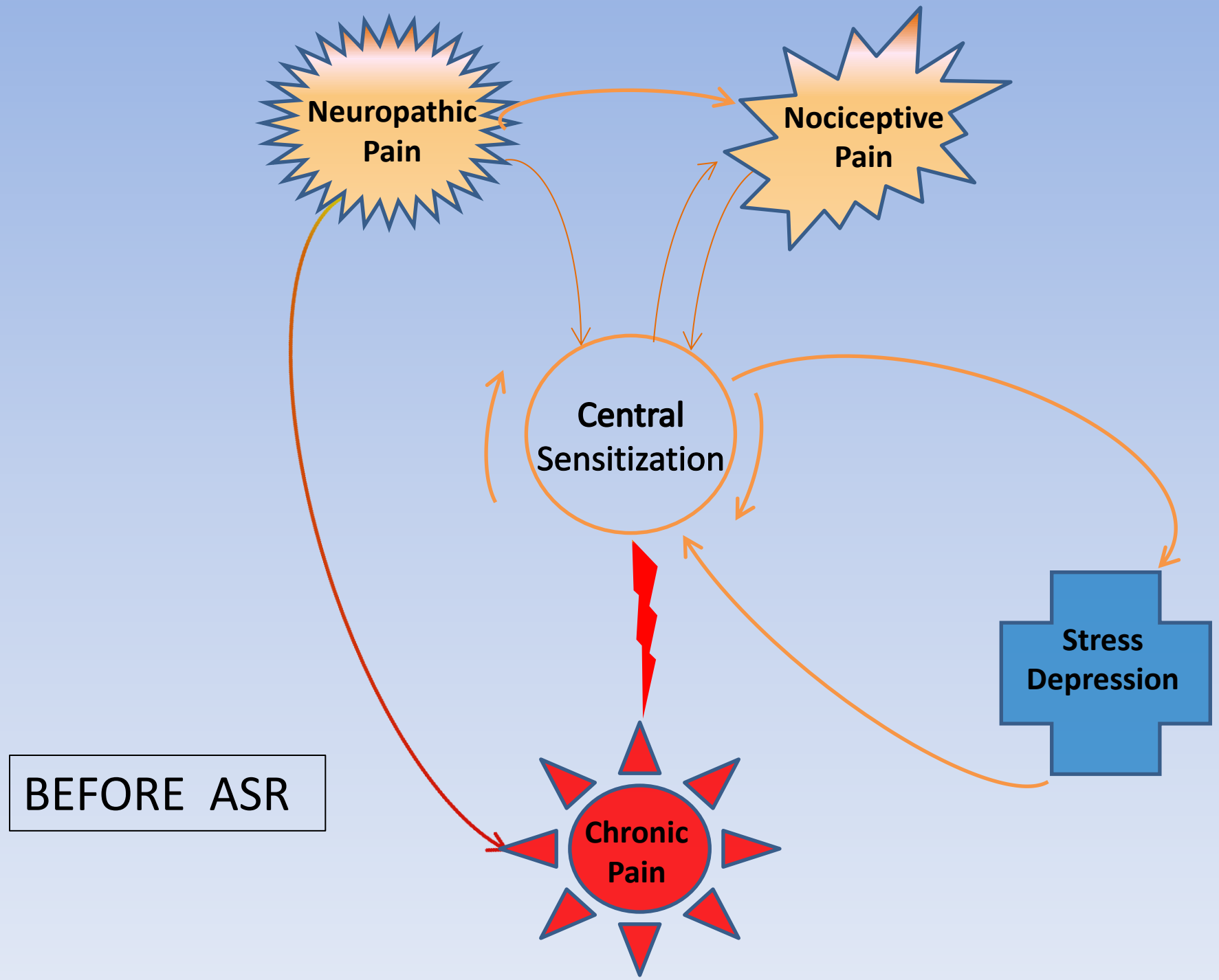
Management of Centrally Amplified Pain using Autonomic Self-Regulation

Grant, J. A., & Rainville, P. (2009). Pain sensitivity and analgesic effects of mindful states in Zen meditators: a cross-sectional study. *Psychosomatic Medicine*, *71*(1), 106-114.

McCracken, L. M., Gauntlett-Gilbert, J., & Vowles, K. E. (2007). The role of mindfulness in a contextual cognitive-behavioral analysis of chronic pain-related suffering and disability. *Pain*, *131*(1),63-69.

Zeidan, F., Gordon, N. S., Merchant, J., & Goolkasian, P. (2010). The effects of brief mindfulness meditation training on experimentally induced pain. *The Journal of Pain*, *11*(3), 199-209.

Zeidan, F., Grant, J. A., Brown, C. A., McHaffie, J. G., & Coghill, R. C. (2012). Mindfulness meditation-related pain relief: evidence for unique brain mechanisms in the regulation of pain. *Neuroscience letters*, *520*(2), 165-173.


Neuropathic Pain
Nociceptive Pain
Central Sensitization
Stress Depression
Chronic Pain
BEFORE ASR

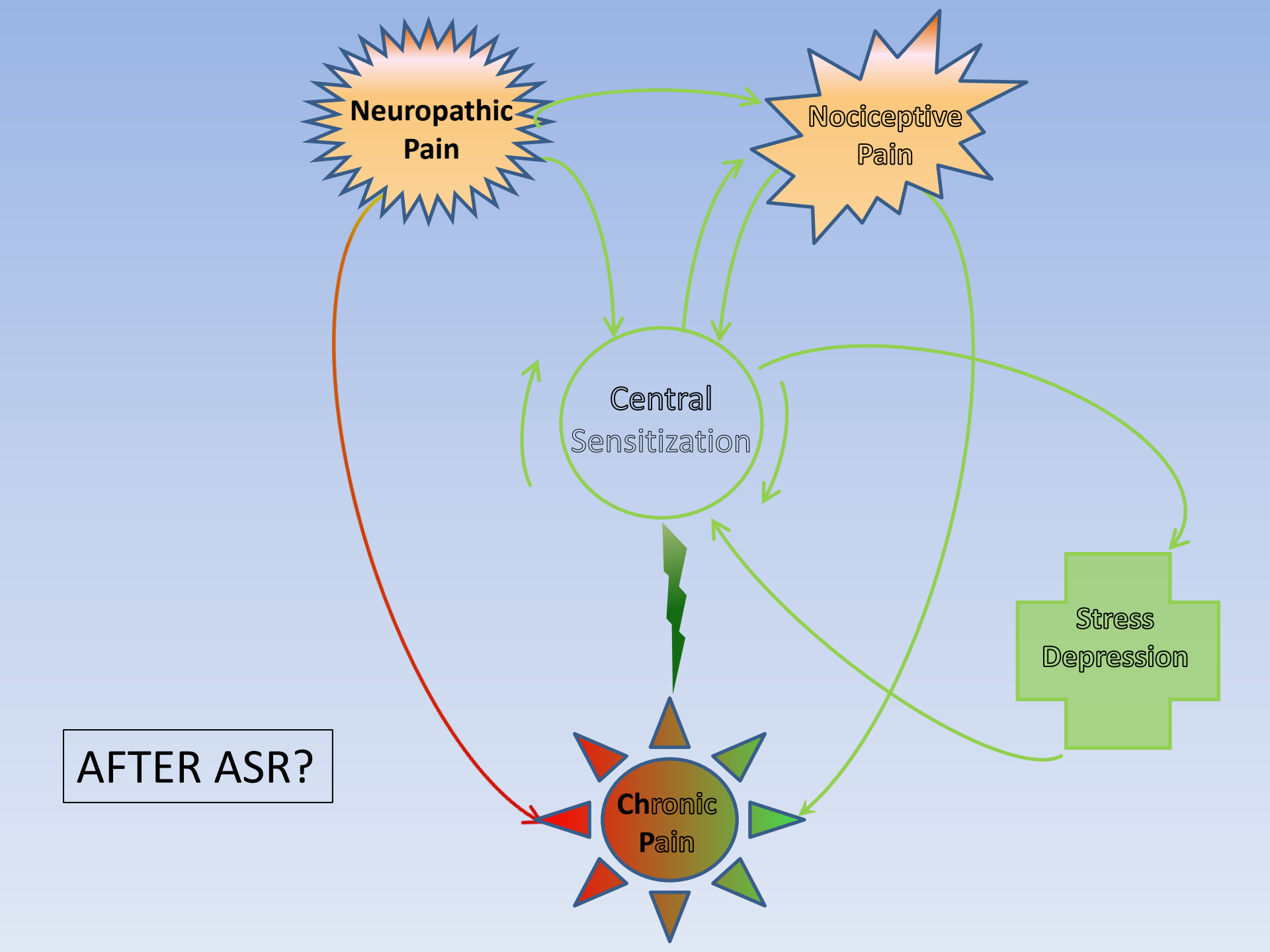
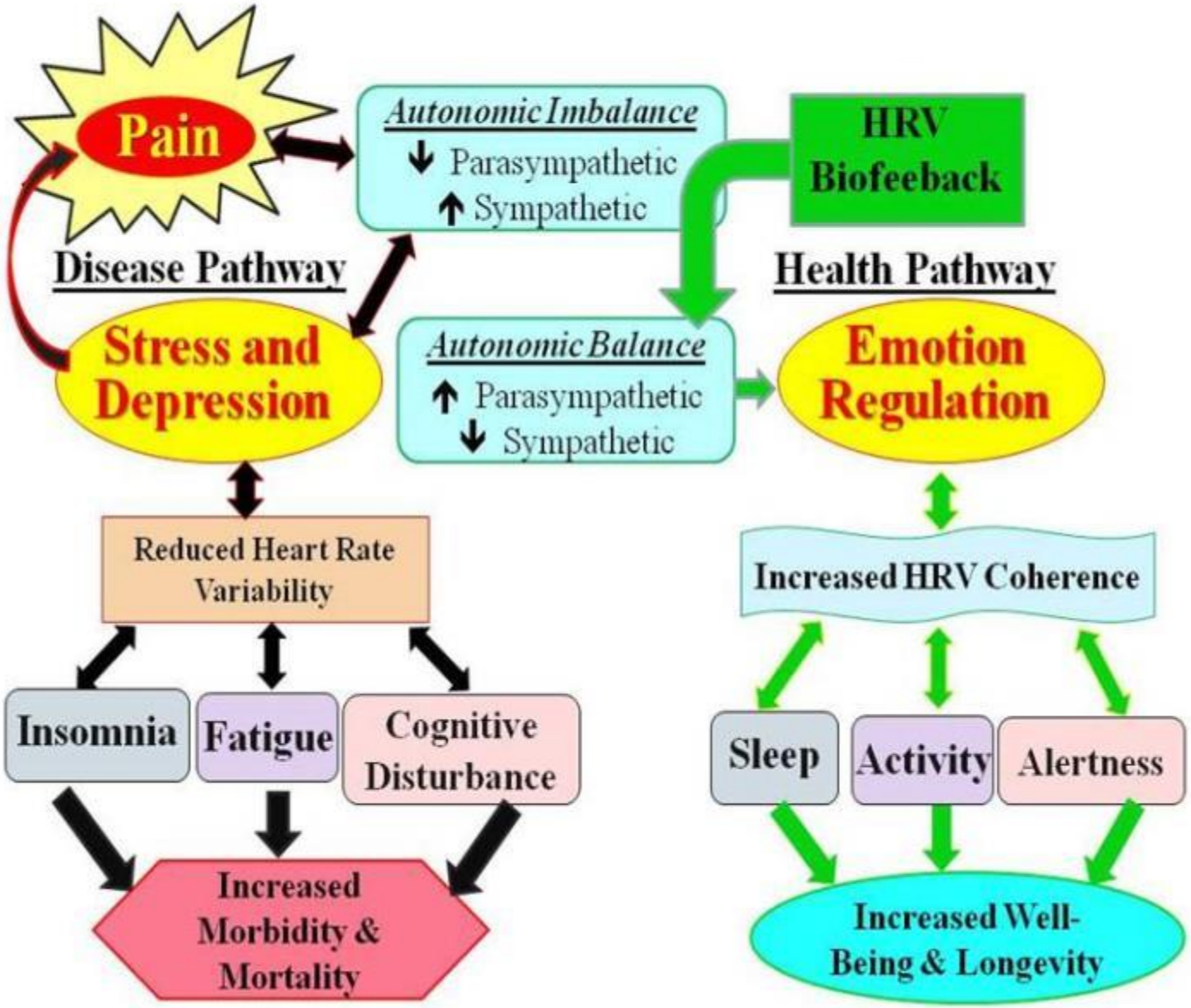

Neuropathic Pain
Nociceptive Pain
Central Sensitization
Stress Depression
Chronic Pain
AFTER ASR?

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).

PILOT STUDY

Non-pharmacological Intervention for Chronic Pain in Veterans: A Pilot Study of Heart Rate Variability Biofeedback

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Citation
Global Adv Health Med. 2014;3(2):28-33. DOI: 10.7453/gahmj.2013.075

Key Words
Coherence, heart rate variability (HRV), HRV coherence biofeedback (HRVCB); chronic pain, non-pharmacological intervention

Disclosure
The authors completed the ICMJE Form for Disclosure of Potential Conflicts of Interest and had no conflicts to disclose.

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.

Pain is Inevitable, Suffering is Optional

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

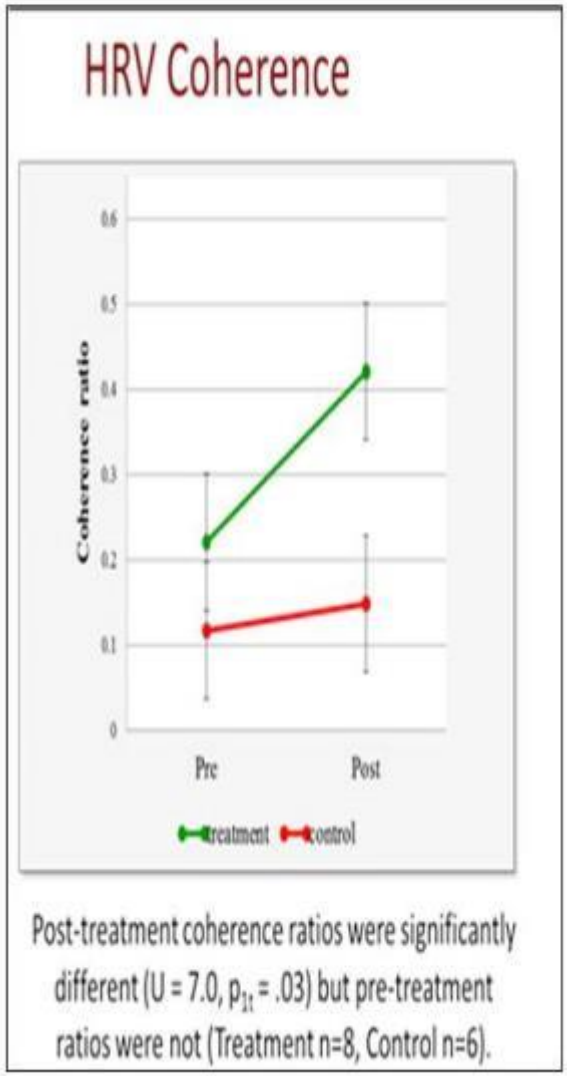
	Control	Treatment
	n (%)	n (%)
Total	6 (43)	8 (57)
Male	6 (100)	7 (88)
	Mean (SD)	Mean (SD)
Age (y)	44.8 (7.4)	44.5 (6.6)

Table 2 Pre- and Post-training Measures for Both Groups, Mean (SD)

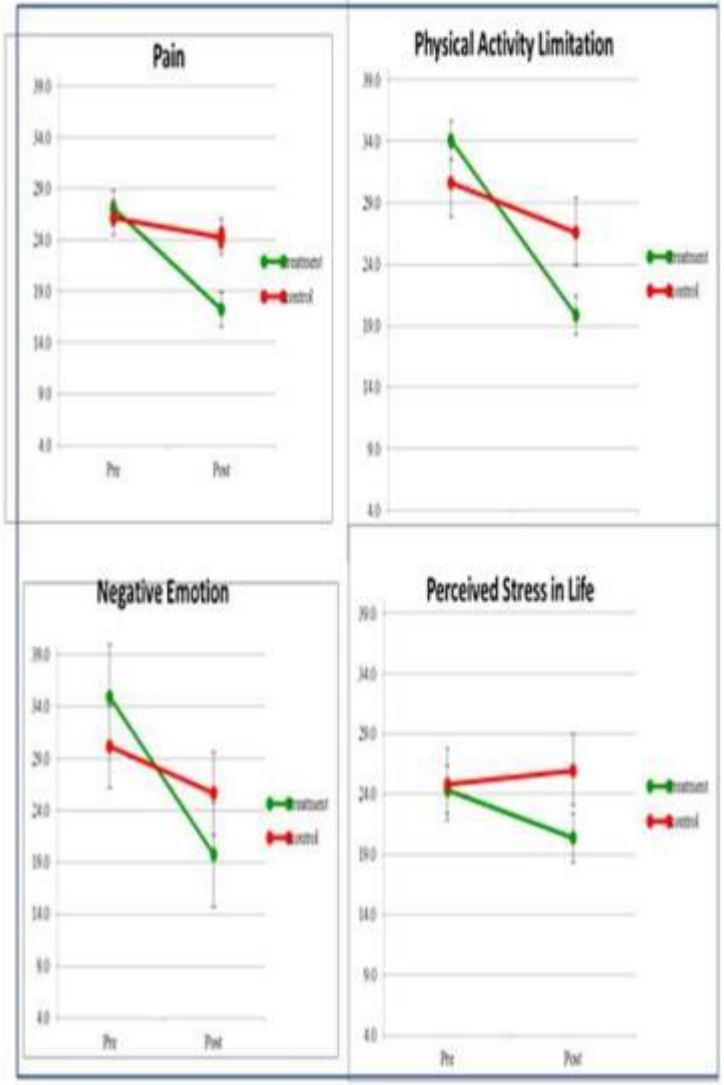
Variable	Control	Treatment	*t*-value[a]	*P*[b]	95% CI of difference
Coherence_Pre	0.12 (0.07)	0.22 (0.19)	−1.2	.24	(−0.3, 0.8)
Coherence_Post	0.15 (0.09)	0.42 (0.24)	−2.6	.02	(−0.5, −0.1)
Pain_Pre	26.2 (4.2)	27.1 (4.9)	−0.4	.70	(−6.4, 4.5)
Pain_Post	24.3 (6.9)	17.3 (4.6)	2.3	.04	(0.4, 13.8)
Stress_Pre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

[a] 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.

Figure 4. Changes in HRV Coherence and their associated effect on measures of pain, physical activity, negative emotion, and perceived stress in Veterans with chronic pain who received HRV-B + standard care (green lines) vs only standard care (red lines).



Post-treatment coherence ratios were significantly different ($U = 7.0$, $p_{11} = .03$) but pre-treatment ratios were not (Treatment n=8, Control n=6).



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)

Variable	Pre	Post	% Change	Corr_Coeff (P[a])	t-value[b]	P[a]	95% CI of difference
Coherence	0.22 (0.19)	0.42 (0.24)	191	–0.05 (0.45)	–1.8	.05	(–0.5, 0.0)
Pain	27.1 (4.9)	17.3 (4.6)	–36	0.52 (0.09)	6.0	<.001	(6.0, 13.7)
Stress	24.4 (5.8)	20.4 (6.1)	–16	0.70 (0.03)	2.5	.02	(0.2, 7.84)
Neg_Emotion	35.0 (3.5)	19.8 (10.4)	–49	0.53 (0.08)	4.8	<.001	(7.7, 22.8)
Activ_Red	34.1 (4.6)	19.9 (10.4)	–42	0.22 (0.30)	3.9	<.001	(–16.0, –7.72)

[a] 1-tail.

[b] dependent t-test, df 7.

Abbreviations: Activ_Red, activity reduction; CI, confidence interval; Corr Coeff, correlation coefficient; Neg_Emotion, negative emotion.

GREENVILLE HEALTH SYSTEM

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Cancer Institute
Center for Integrative Oncology & Survivorship

UNIVERSITY OF SOUTH CAROLINA
Arnold School of Public Health

Use of Heart Rate Variability (HRV) Biofeedback for Symptom Management among Cancer Survivors

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Center for Integrative Oncology and Survivorship
Greenville Health System Cancer Institute
Greenville, South Carolina

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Greenville Health System

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- W. Larry Gluck, M.D.
- Katie Daniels, BS

University of South Carolina

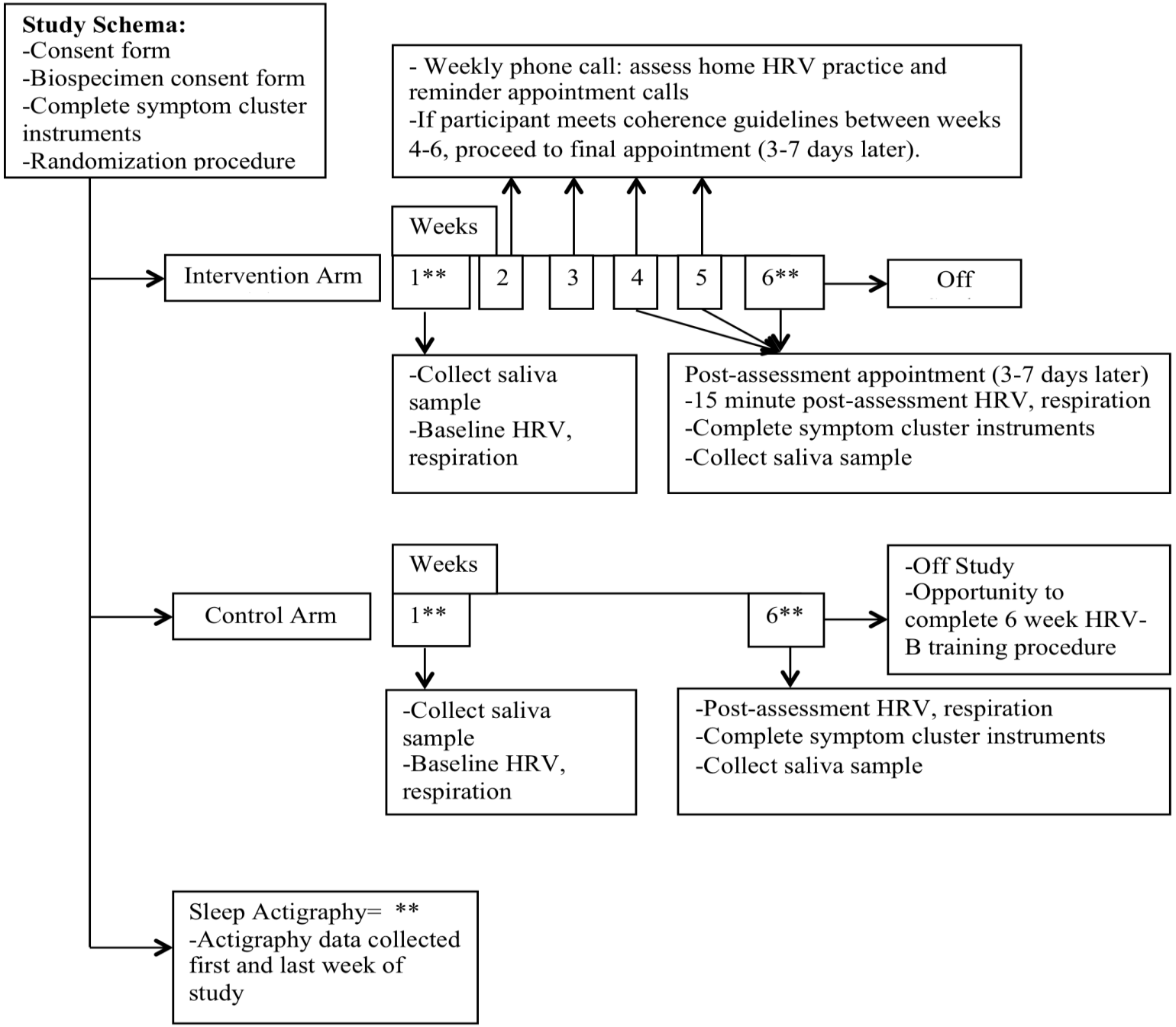
- James Burch, MS, Ph.D, co-PI
- J.P. Ginsberg, Ph.D.
- Jameson Sofge, MS
- James Hébert, MSPH, ScD

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, depression, fatigue, pain, 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)

Schema


Study Schema:
-Consent form
-Biospecimen consent form
-Complete symptom cluster instruments
-Randomization procedure
- 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
Intervention Arm
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
Weeks
Control Arm
1**
6**
-Off Study
-Opportunity to complete 6 week HRV-B training procedure
-Collect saliva sample
-Baseline HRV, respiration
-Post-assessment HRV, respiration
-Complete symptom cluster instruments
-Collect saliva sample
Sleep Actigraphy= **
-Actigraphy data collected first and last week of study

Symptom Cluster Questionnaires

- ***Socio-demographic inventory***
- ***Brief Pain Inventory (BPI)***
- ***Perceived Stress Scale (PSS)***
- ***Beck Depression Inventory–II (BDI-II0***
- **Suscro Distress Inventory**
- ***Multidimensional Fatigue Inventory (MFI, short form)***
- **Insomnia Symptom Questionnaire**
- Posttraumatic Stress Disorder Checklist – Civilian Form
- Munich Chronotype Questionnaire

Status	Total
Screened	179
Ineligible	117
Enrolled	38
Dropped Out	4
Completed	34

	Group A (N=17) HRVB	Group B (N=17) Wait List Control	two-tailed p-value
Age (years), mean ± stderr	60.0 ± 2.5	58.9 ± 2.5	0.7621
Sex, count(%)			0.0445
Male	5 (29.4)	0 (0)	
Female	12 (70.6)	17 (100)	
Ethnic Group, count (%)			0.6012
Hispanic or Latino	1 (5.9)	0 (0)	
Not Hispanic or Latino	15 (88.2)	14 (82.3)	
Refuse/Don't Know/Missing	1 (5.9)	3 (17.7)	
Race, count (%)			0.349
White	14 (82.3)	13 (76.4)	
Black or African American	1 (5.9)	2 (11.8)	
Other	2 (11.8)	0 (0)	
Refused/Don't Know/Missing	0 (0)	2 (11.8)	
Education (years), mean ± stderr			0.9279
High School	4 (23.5)	4 (23.5)	
College	7 (41.1)	6 (35.3)	
Graduate School	3 (17.7)	5 (29.4)	
Missing	3 (17.7)	2 (11.8)	
Income, count (%)			0.7665
Under $50,000	6 (35.3)	5 (29.4)	
$50,000-$100,000	4 (23.5)	5 (29.4)	
$100,000 or more	6 (35.3)	4 (23.5)	
Refuse/Don't Know/Missing	1 (5.9)	3 (17.7)	

WE ASKED ALL THE QUESTIONS OF THE PRELIMINARY DATA WE CAN, USING STRICT AND RIGOROUS STATISTICAL ANALYSIS

Means (SE) and Significance of Differences of Outcome Variables					
Variable					
	Intention to Treat			**Completers (n's and means vary from tabled values)**	
Group	**Pre-[1]**	**Post-[2]**	**LMM[3]**	**Pre-Post[4]**	**ANCOVA[5]**
COHERENCE					
HRVB	0.37(0.0)[ns]	0.84(0.3)*[u]	ns	*	*
Control	0.40(0.0)	0.33(0.0)		ns	
SDNN					
HRVB	20.5(1.7) [ns]	35.0(7.6)*[u]	*	*	*
Control	18.9(2.7)	17.6(1.4)		ns	
RMSSD					
HRVB	17.1(1.7) [ns]	25.4(4.2) *[u]	ns	*	ns
Control	15.9(2.7)	15.7(1.8)		ns	

≤.05, **≤.01,≤.005; [1]Independent t-test, 2-t, HRVB vs Control; [2]Independent t-test, 1-t, HRVB vs Control; [3]GroupxPre-Post ix; [4]Dependent t-test, 1-t; [5]Between group effect ; [u]Unequal variance; LMM=Linear Mixed Model;**

Means (SE) and Significance of Differences of Outcome Variables					
Variable					
	Intention to Treat			Completers (n's and means vary from tabled values)	
Group	Pre-[1]	Post-[2]	LMM[3]	Pre-Post[4]	ANCOVA[5]
STRESS					
HRVB	17.2(2.0)[ns]	11.4(1.7) *	**	***	*
Control	19.0(1.6)	17.2(1.6)		ns	
DEPRESSION					
HRVB	13.1(3.0) [ns]	5.5(2.5)**	***	***	*
Control	17.1(1.6)	13.6(2.2)		ns	
DISTRESS					
HRVB	14.2(3.0) [ns]	9.7(2.3)***	**	**	*
Control	20.6(1.8)	18.5(2.1)		ns	

*≤.05, **≤.01,***≤.005; [1]Independent t-test, 2-t, HRVB vs Control; [2]Independent t-test, 1-t, HRVB vs Control; [3]GroupxPre-Post ix; [4]Dependent t-test, 1-t; [5]Between group effect ; [u]Unequal variance; LMM=Linear Mixed Model;

Means (SE) and Significance of Differences of Outcome Variables					
Variable					
	Intention to Treat			Completers (n's and means vary from tabled values)	
Group	Pre-[1]	Post-[2]	LMM[3]	Pre-Post[4]	ANCOVA[5]
FATIGUE-GENERAL					
HRVB	12.4(1.0)[ns]	10.0(1.1)***	**	*	ns
Control	14.8(0.8)	14.0(0.8)		ns	
FATIGUE-MENTAL					
HRVB	11.3(1.3)[ns]	9.5(1.2)*	ns	ns	ns
Control	13.7(1.1)	13.1(1.1)		ns	
FATIGUE-REDUCED ACTIVITY					
HRVB	9.3(1.1)[ns]	6.4(0.8)*	**	*	ns
Control	10.9(1.0)	9.3(1.0)		*	

*≤.05, **≤.01,***≤.005; [1]Independent t-test, 2-t, HRVB vs Control; [2]Independent t-test, 1-t, HRVB vs Control; [3]GroupxPre-Post ix; [4]Dependent t-test, 1-t; [5]Between group effect ; [u]Unequal variance; LMM=Linear Mixed Model;

Means (SE) and Significance of Differences of Outcome Variables					
Variable					
	Intention to Treat			Completers (n's and means vary from tabled values)	
Group	Pre-[1]	Post-[2]	LMM[3]	Pre-Post[4]	ANCOVA[5]
PAIN SEVERITY					
HRVB	2.7(0.6)[ns]	1.9(0.5)[ns]	ns	ns	ns
Control	2.5(0.5)	2.7(0.6)		ns	
PAIN INTERFERENCE					
HRVB	2.4(0.8)[ns]	1.4(0.4)*[u]	ns	ns	ns
Control	3.4(0.6)	3.1(0.7)		ns	

*≤.05, **≤.01,***≤.005; [1]Independent t-test, 2-t, HRVB vs Control; [2]Independent t-test, 1-t, HRVB vs Control; [3]GroupxPre-Post ix; [4]Dependent t-test, 1-t; [5]Between group effect ; [u]Unequal variance; LMM=Linear Mixed Model;

Means (SE) and Significance of Differences of Outcome Variables					
Variable					
	Intention to Treat			Completers (n's and means vary from tabled values)	
Group	Pre-[1]	Post-[2]	LMM[3]	Pre-Post[4]	ANCOVA[5]
SLEEP SYMPTOMS					
HRVB	14.7(1.5)[ns]	8.1(1.7)***[u]	***	***	***
Control	16.5(1.3)	18.3(0.8)		ns	
SLEEP-DAYTIME IMPAIRMENT					
HRVB	10.7(1.8)[ns]	5.4(2.0)**	**	***	***
Control	12.3(1.7)	13.0(1.8)		ns	

*≤.05, **≤.01,***≤.005; [1]Independent t-test, 2-t, HRVB vs Control; [2]Independent t-test, 1-t, HRVB vs Control; [3]GroupxPre-Post ix; [4]Dependent t-test, 1-t; [5]Between group effect ; [u]Unequal variance; LMM=Linear Mixed Model;

PLANNED ANALYSES

- COVARIATE
- PRINCIPAL COMPONENTS
- HIERARCHICAL REGRESSION?

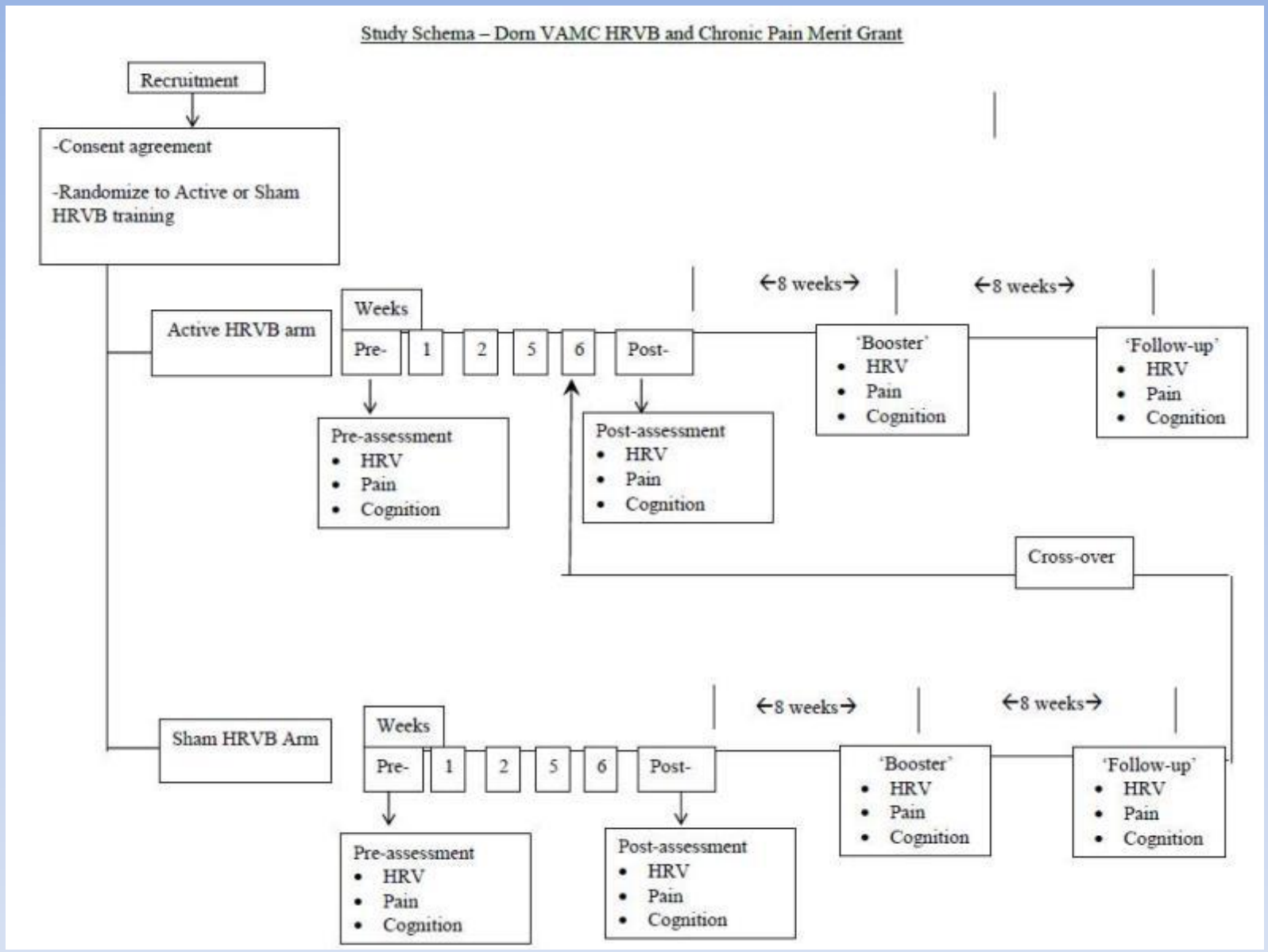
HYPOTHESIS FOR VA MERIT PROPOSAL

- 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

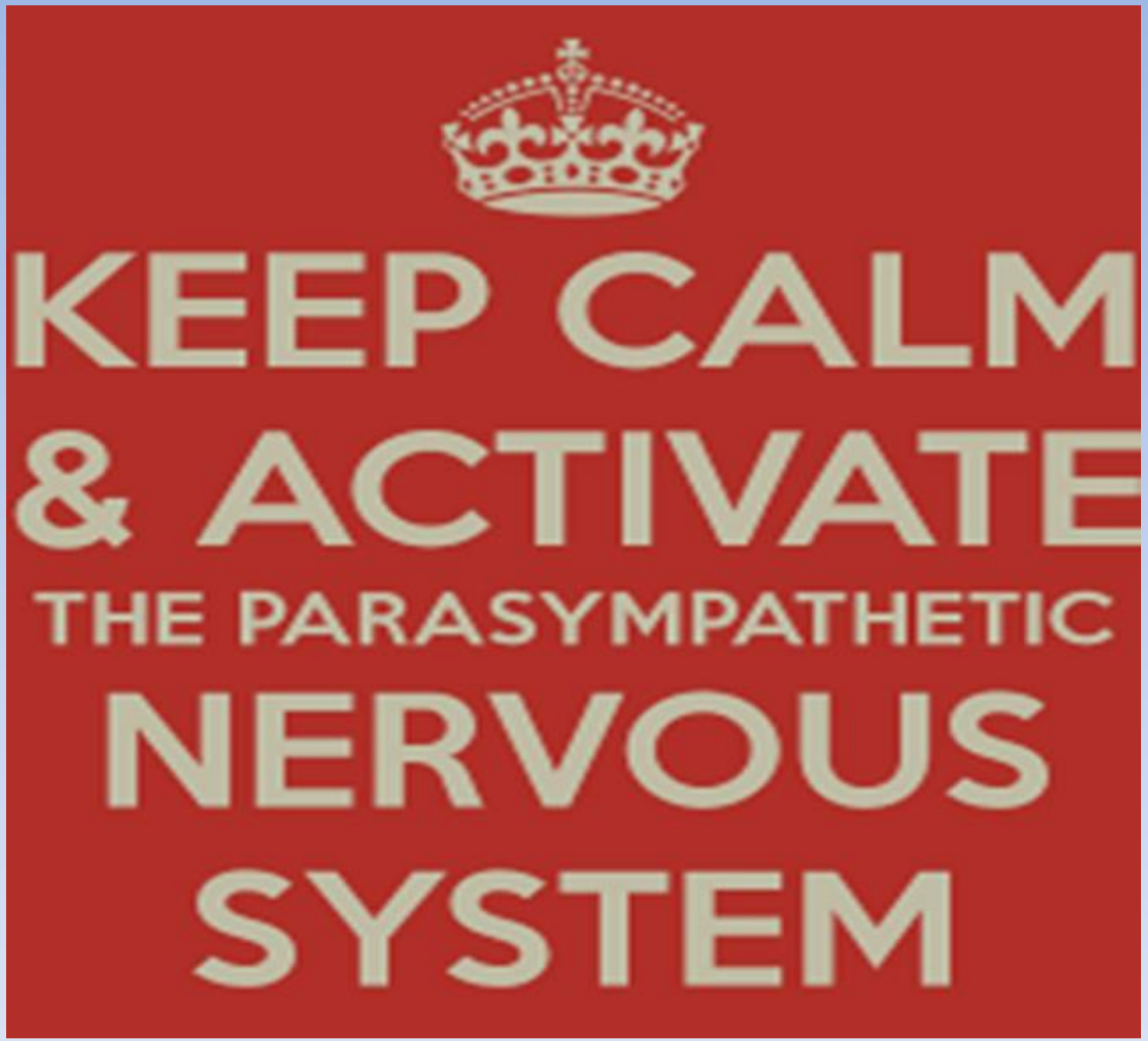
HYPOTHESIS COROLLARY

- HRVB AND COHERENCE WILL NOT IMPROVE PAIN THAT IS SOLELY FROM A NEUROPATHIC SOURCE

PI: **Ginsberg, Jay**	Title: HRV Biofeedback in Pain Patients: Pilot Intervention for Pain, Fatigue & Sleep	
Received: 09/08/2014	FOA: CX14-006	Council: 01/2015
Competition ID:	FOA Title: CSR&D MERIT REVIEW AWARD FOR CLINICAL TRIALS	
1 I01 CX001182-01A1	Dual:	Accession Number: 3732973
IPF: 10018661	Organization: VETERANS HEALTH ADMINISTRATION	
Former Number:	Department: Mental Health	
IRG/SRG: CLNA	AIDS: N	Expedited: N
Subtotal Direct Costs (excludes consortium F&A) Year 1: 198,078 Year 2: 149,913 Year 3: 149,932 Year 4: 149,935	Animals: N Humans: Y Clinical Trial: N Current HS Code: 20 HESC: N	New Investigator: N Early Stage Investigator: N
Senior/Key Personnel:	*Organization:*	*Role Category:*
Jay Ginsberg Ph.D	WJB Dorn VA Medical Center	PD/PI
James Burch Ph.D	University of South Carolina	MPI
Alexander McLain Ph.D	University of South Carolina	Co-Investigator
Raouf Gharbo Ph.D	Hampton Roads Riverside Regional Medical Center	Consultant
James Hebert ScD	University of South Carolina	Consultant
Francis Spinale M.D.	WJB Dorn VA Medical Center	Consultant
Tarek Sobeih Ph.D	Dorn Research Institute	Other Professional-Recruitment Coordinator



Number of veterans screened or prescreened: 220
Number of veterans enrolled: 10
Number of veterans completed: 9


KEEP CALM
& ACTIVATE
THE PARASYMPATHETIC
NERVOUS
SYSTEM