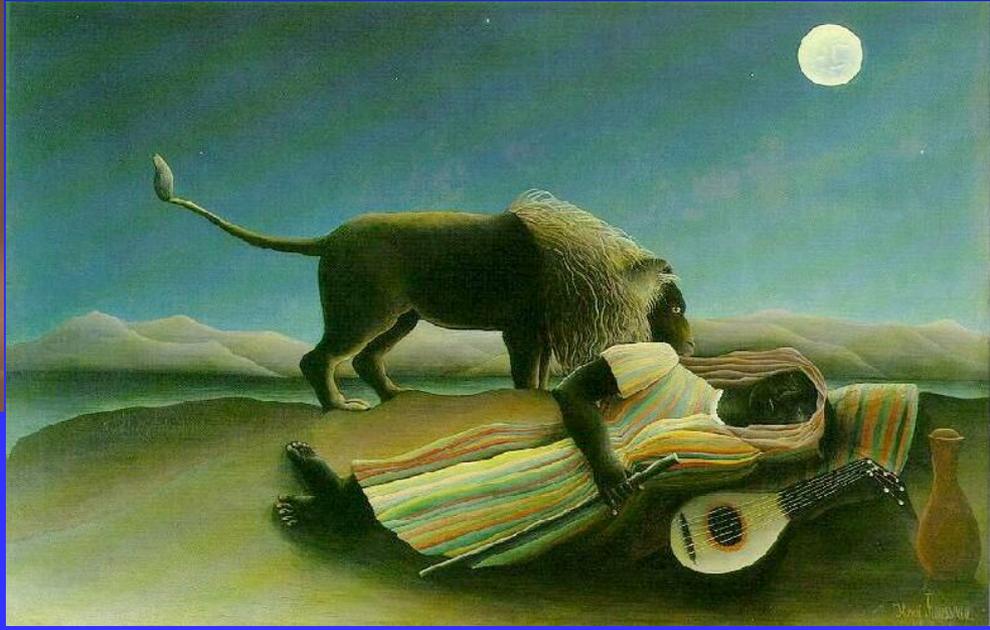




Sleep & Chronic Pain

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The material presented in this lecture has no relationship with any of these potential conflicts

Aims of the Lecture

- Provide a brief overview of the longitudinal and quantitative sensory testing literature describing the sleep-pain relationship.
- Discuss 2 promising mechanisms, associated with aging by which sleep disruption and / or sleep loss may induce hyperalgesia and increase risk for chronic pain
 - 1) Diminished Pain Inhibitory Capacity (CPM)
 - 2) Increased Inflammation
- Briefly discuss emerging literature testing whether improving sleep improves chronic pain

Public Health Impact of Chronic Pain

Years Lived with Disability (YLDs)

Original Investigation

The State of US Health, 1990-2010 Burden of Diseases, Injuries, and Risk Factors

US Burden of Disease Collaborators

JAMA. 2013;310(6):591-608. doi:10.1001/jama.2013.13805
Published online July 10, 2013.

**Low Back Pain
Alone = \$ 96 B /
annum (Mehra,
2012)**

Table 2. YLD Numbers in 1990 and 2010 for Both Sexes Combined for the 30 Leading Diseases and Injuries Contributing to YLDs in 2010 in the United States and Percentage Change From 1990 to 2010, Ranked by the Magnitude of YLDs in 2010^a

Diseases and Injuries	YLD Rank		No. of YLDs (In Thousands)		Median Change, %	
	1990	2010	1990	2010	YLDs	Age-Standardized YLD Rate
Low back pain	1 (1-3)	1 (1-3)	2538.00 (1771.4-3427.2)	3180.60 (2179.5-4318.6)	24.9 (13.8 to 38.4)	-3 (-11.6 to 7.3)
Major depressive disorder	2 (1-5)	2 (1-4)	2142.50 (1525.2-2843.7)	3048.90 (2151.3-4122.3)	42.7 (9.2 to 83.3)	13.4 (-12.9 to 46.3)
Other musculoskeletal disorders	3 (1-4)	3 (2-4)	2024.40 (1664.7-2311.9)	2602.50 (2138.0-2986.8)	28.5 (18.9 to 38.9)	-0.2 (-8.0 to 7.8)
Neck pain	4 (2-6)	4 (2-6)	1652.70 (1151.0-2296.4)	2134.40 (1482.6-2934.4)	29.1 (17.4 to 41.1)	0.2 (-9.1 to 9.5)
Anxiety disorders	5 (2-6)	5 (3-6)	1541.00 (1078.5-2172.8)	1866.10 (1310.2-2569.3)	21.3 (4.7 to 39.5)	-1.5 (-15.2 to 13.1)
Chronic obstructive pulmonary disease	6 (4-9)	6 (3-10)	1304.10 (761.3-2007.2)	1745.40 (1011.9-2601.4)	34.1 (4.6 to 70.9)	-1.5 (-23.2 to 25.0)
Drug use disorders	7 (6-10)	7 (6-10)	996.9 (722.3-1337.9)	1295.50 (921.6-1725.1)	29.8 (6.5 to 58.6)	20.1 (-1.4 to 47.1)
Diabetes	8 (7-15)	8 (6-11)	747.7 (506.1-1059.3)	1164.90 (789.1-1648.6)	56.2 (38.4 to 74.8)	11.2 (-1.4 to 24.5)
Osteoarthritis	12 (8-19)	9 (7-17)	637.6 (393.1-972.0)	994 (611.5-1471.0)	56.1 (28.3 to 88.3)	5.5 (-13.7 to 27.8)
Asthma	9 (7-19)	10 (7-19)	769.3 (418.1-1229.5)	932 (504.7-1469.3)	21.2 (11.5 to 31.6)	-0.8 (-9.4 to 8.2)

Sleep Deficiency & Chronic Pain are Highly Comorbid Health Epidemics

Restless Legs Syndrome 4-5%

(Edwards, Allen, Earley, Smith, 2011)

Circadian Rhythm d/o

Chronic Insomnia

10-15%

Chronic Pain

11.5-55.2%

50% - 88%

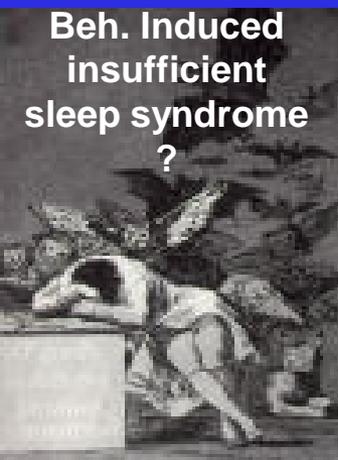
39-75%
Webster et al.
2008

Sleep Apnea

4-20%

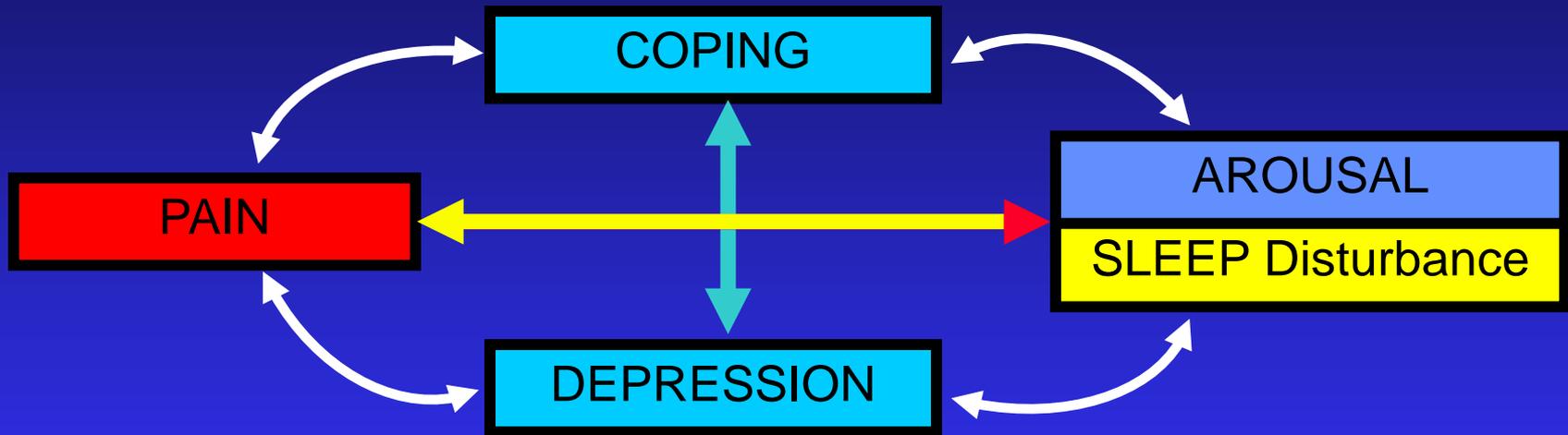
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Moldofsky's Paradigm Shift

Sleep-Pain Interactions



Classic, Uncontrolled Sleep Stage Deprivation Studies Suggest Complex Reciprocal Interaction

➤ Moldofsky (1975 & 1976); Lentz & Landis et. al (1999)

What do the longitudinal clinical data show ?

- In chronic pain: relationship is bidirectional (Sleep ↔ Pain)
e.g., (Affleck, 1996; Stone, 1997; Smith, 2010)
- Poor sleep increases odds of developing widespread pain (WP)
 - In general population [Gupta (2007)] ---3 fold increased risk over 15 Mos.
 - In those with a regional pain disorder [Mikkelsen (1999)]
- Restorative sleep linked to 3 fold remission rate from WP [Davies (2008)]
- Insomnia Increases risk of chronic pain after acute injury [Castillo (2006)]

Burn Injury

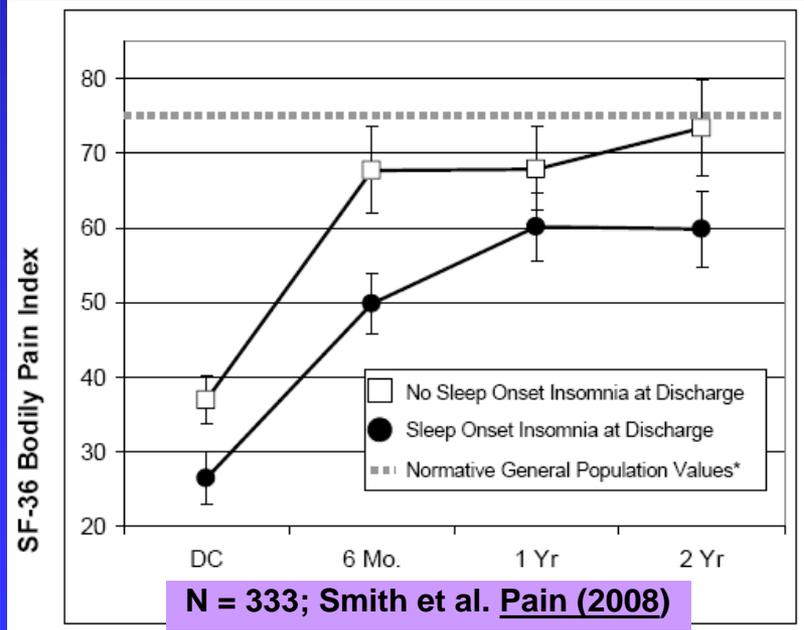
Sleep Onset Insomnia During Hospitalization Predicts

↓ Rate of Improvement in Pain

Controlling for:

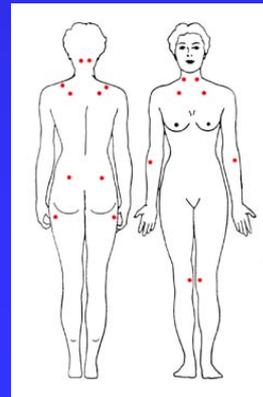
Premorbid mental health sx, general health

In hospital pain severity, total burn surface area, total graft area, mental health SX, ICU time



Experimental Sleep Disruption Induces Hyperalgesia and / or spontaneous pain in Healthy Adults

- 1) Sleep apnea phenotype (TST preserved): (e.g., Moldofsky, 1975, Lentz & Landis, 1999)
 - Selective sleep stage deprivation primarily SWS vs. REM
- 2) Insomnia phenotype [prolonged multiple forced awakenings (e.g., Smith et al., 2007; Roehrs, 2006)]
- 3) Insufficient Sleep Syndrome Phenotype (restricted sleep opportunity) (e.g., Ablin & Clauw et. al., Roehrs (2006), Haack (2005).
- 4) Medical School Phenotype (total sleep deprivation) (e.g. Roehrs, 2006), Kundermann, 2004, Onen, 2001)
 - Sleep architecture specific effects somewhat unclear, both REM and SWS disruption may induce HA
 - Effects are pain specific - no change in touch / warmth detection (Kundermann, 2004)
 - Sleep extension in sleepy subjects :
↓ **Pain Sensitivity** (Roehrs (2012))



Quantitative Sensory Testing and Aging

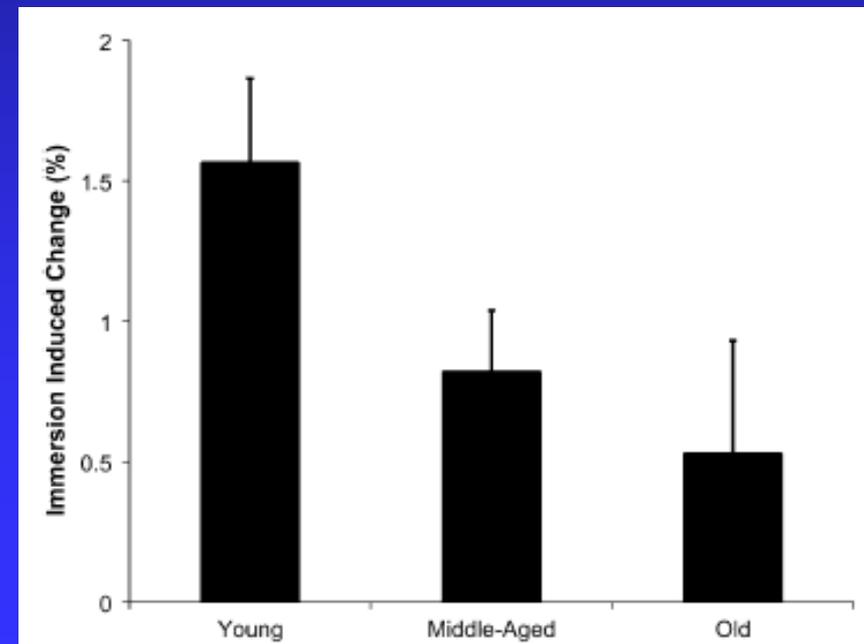
- Pain thresholds: Older adults have higher pain thresholds (less sensitive)

➤ e.g., Riley, JL et. al., JOP (2014)

- Pain modulation: adults demonstrate impaired Pain Modulation

- Reduced Pain Inhibitory Capacity
 - [Conditioned Pain Modulation (CPM)]
 - Riley, Jlet al. Pain (2012)

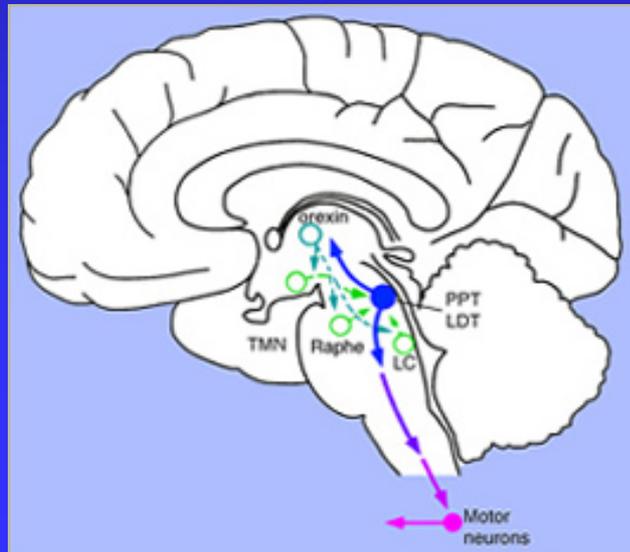
Reduced CPM by Age



What are the Mechanisms of Sleep Disturbance Induced Hyperalgesia?



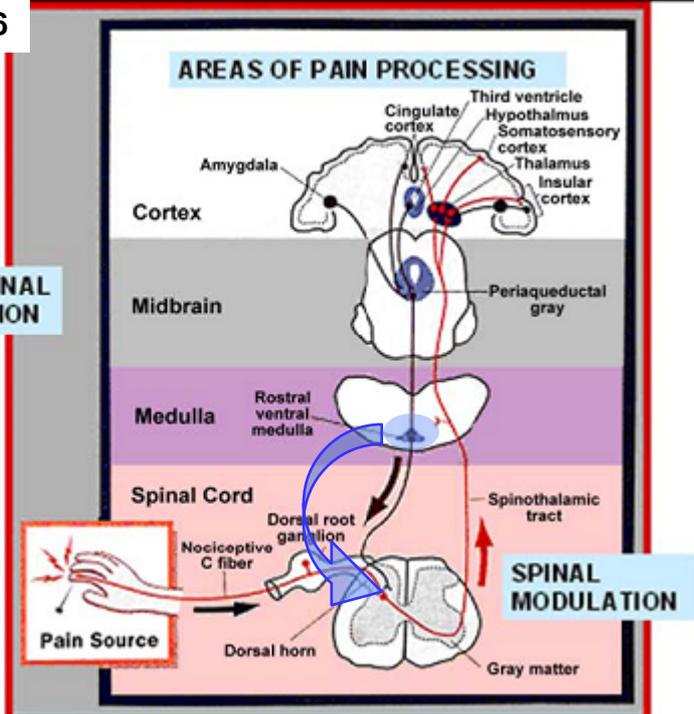
- Sleep and pain systems share many overlapping neurobiologic substrates
- Does sleep disturbance alter descending pain modulatory systems associated with central sensitization and if so... at what levels of the neuroaxis?



DeLeo, 2006

PERIPHERAL MODULATION

SUPRASPINAL MODULATION



Laboratory Measures of Pain Inhibition

Conditioned Pain Modulation (aka DNIC)

- “Pain inhibits pain”
- Simultaneous application of 2 noxious stimuli
 - Phasic (Pressure Pain Threshold—algometry)
 - Conditioning stimulus administered at distant site
 - Cold pressor task: 45 secs (contra lateral side)
- **↑ Pain threshold (↓ pain sensitivity)** during tonic painful stimulus from baseline
- Supraspinally mediated inhibition of wide dynamic range neurons in dorsal horn (LeBars, 1992)
 - Cervical transection studies
- Mediated by endogenous opioids ? (blocked by naloxone)
 - Willer, 1990; Julien N, 2006; Anderson; 2002
 - **Not simply distraction—thalamic lesion** (Broucker, 1990)



Impaired CPM Is Associated with Several Chronic Pain Disorders

- Fibromyalgia

- Luatenbacher, 1997
- Kosek & Hansson, 1997
- Staud, Pain (2003)

- Temporomandibular J / D

- Maixner, 1995
- Kashima, 1999

- Irritable Bowel Syndrome

- Wilder-Smith, 2004

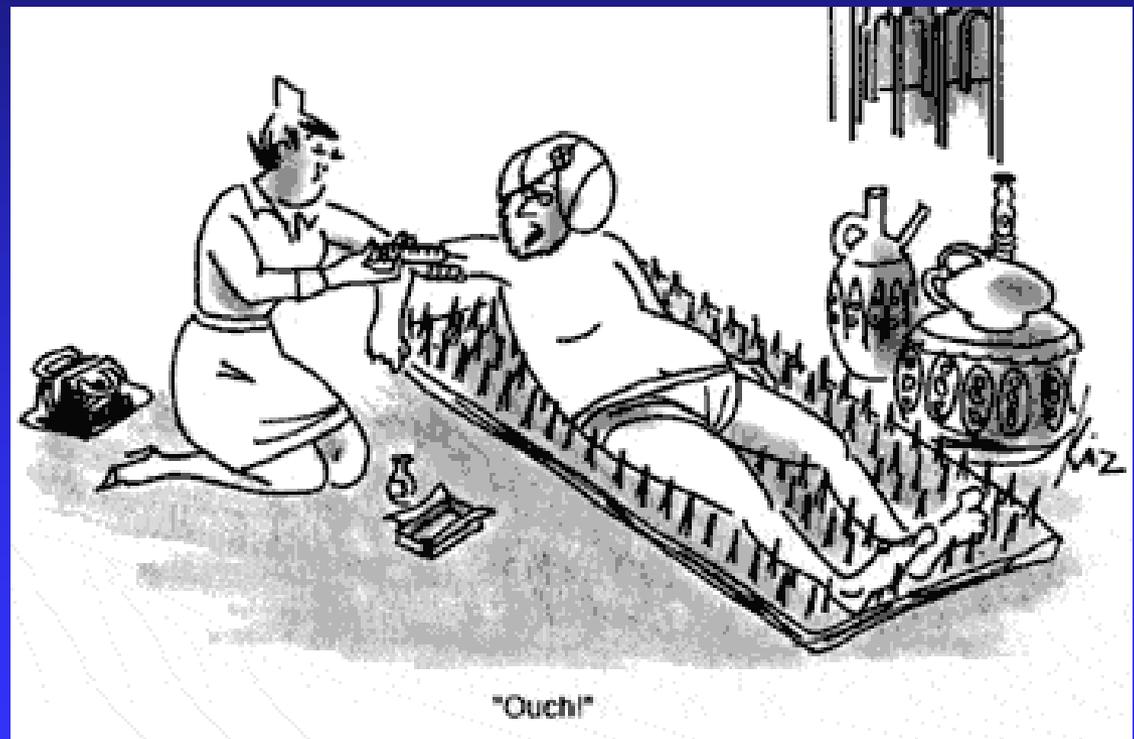
- Low Back Pain

- Peters et al., 1992

- Tension headache

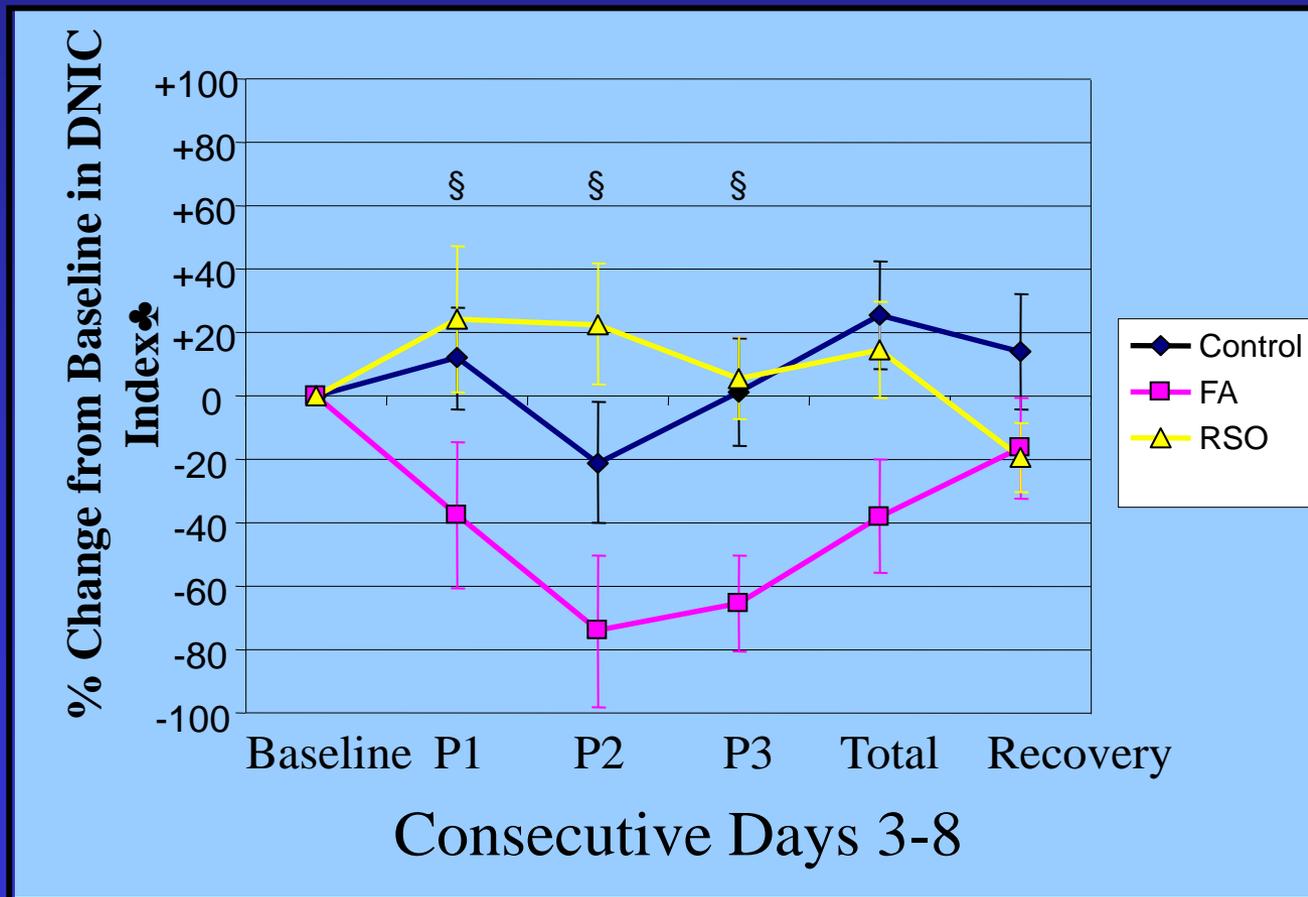
- Pielsticker, 2005

THE ABSENCE OF CPM



Experimental effects of Sleep loss on Pain Inhibitory Capacity

Sleep Disruption, But Not Sleep Restriction Impairs Conditioned Pain Modulation (CPM)



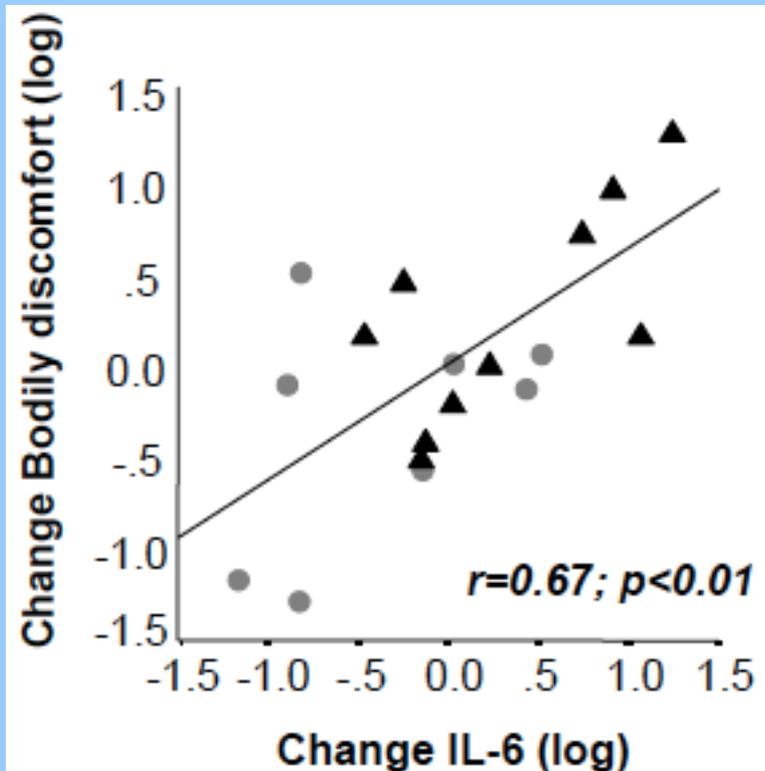
Poor Sleep Subsequently Linked to Impaired Pain Inhibitory Capacity (CPM) pain disorders and in Primary Insomnia

Name	Disorder	N	Outcomes
1. Monica Haack (2011), <u>Euro. Jo. of Pain</u>	Primary Insomnia	17	Insomnia ↓CPM compared to control
2. Edwards RR. (2009), <u>Euro. Jo. of Pain</u>	TMJ/D (chronic Jaw pain)	53	↓PSG Sleep Efficiency, ↓CPM
3. Paul-Savoi E (2012), <u>Open Rheumatology</u>	Fibromyalgia	89	↓Sleep quality , ↓CPM
4. Lee YC (2013), <u>Arthritis & Rheum.</u>	Rheumatoid Arthritis	58	↓Sleep quality , ↓CPM
5. Petrov ME. (2015), <u>Jo. of Pain</u>	Knee Osteo-Arthritis	137	↑ Insomnia sev. (ISI), ↓CPM, especially in Whites

Inflammation: A Good Candidate Mechanism of Sleep Disruption Induced Hyperalgesia

- Total and/or Partial Sleep Deprivation Enhances Inflammation:
 - Circulating IL-6 (Vgontzas, 2004),
 - Cellular level (PBMCs)
 - ❖ Transcription (nfKB)
 - ❖ Gene expression IL-6 & TNF
 - ❖ Capacity to produce IL-6 & TNF (Irwin MR, (2006 & 2008))
- Basic Science Work Demonstrates a Major Role for Inflammation in Peripheral & Central Sensitization (e.g., Milligan & Watkins, Nat Rev Neurosci (2009))
- Inflammation is linked in separate studies with Sleep, & Chronic Pain Disorders [e.g., Vgontzas (2003), RA & OA (Livshits et al. Arthrit & Rheum (2009))]

Correlation Between Spontaneous Pain & IL-6 After Chronic Partial Sleep Deprivation
[Haack Mullington, sleep (2007)]



Clinical Implications



"Last week I probably slept an average of two hours a night.
"I couldn't stop thinking. My body was exhausted, and my mind was still going."



Does Treating Insomnia and / or Other Sleep Disorders Comorbid with Chronic Pain Improve Pain Outcomes?

- Just beginning to receive systematic research attention
- Minimal Literature on effects of PAP therapy and Pain
 - Some in Headache Patients (e.g. Johnson KG, 2013)
- Handful of small studies of cognitive-behavioral RX for insomnia in CP

Clinical Trials of CBT-I in Chronic Pain

Name	Pain Type	N	Sleep Outcomes
1. Currie et al. (2000)	Mixed Pain	60	↑ Sleep Continuity: Diary & Actigraphy , 3 Mo. FU
2. Edinger et al. (2005)	Fibromyalgia	42	↑ Sleep Continuity: Diary & Actigraphy , 6 Mo. FU
3. Vitiello et al (2009)	Osteoarthritis	51	↑ Sleep Continuity: Diary, 1YR FU
4. Jungquist et al. (2010)	Neck and Back	28	↑ Sleep Continuity: Diary, FU data in preparation

- Standard, multi-component CBT-I: SRT and SCT
- Effect Sizes: Moderate to Large & comparable to CBT-I for PI
- Outcomes maintained at follow-up (3 mos -1 Year)

CAVEATS

- No PSG outcomes
- All were attentional or waitlist control, No Double –blinded studies

CBT-I in Knee Osteoarthritis

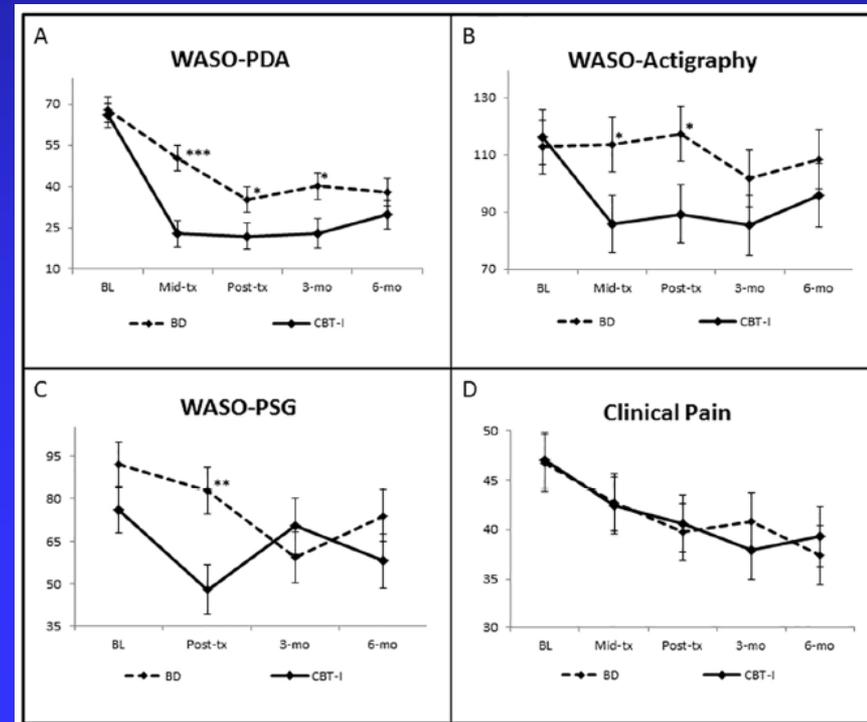
(Smith et al. (2015) Arthr. & Rheum)

A randomized, Double-blind, Active Placebo Controlled Trial

- N = 100 KOA patients confirmed via knee radiographs
- 8 weeks CBT vs. 8 weeks behavioral desensitization
- Full home ambulatory PSG measured at baseline, Post, 3, and 6 Mo
- Patients with AHI >10 ruled out

Sleep Findings

- Both groups demonstrated large improvements in sleep on most diary, actigraphy and PSG measures.
- CBT-I outperformed BD on WASO (primary outcome)
 - Diary (M= -12 mins); $P < .001$
 - Actigraphy (M= -14 mins); ($p < .05$)
 - PSG ($P = .08$)

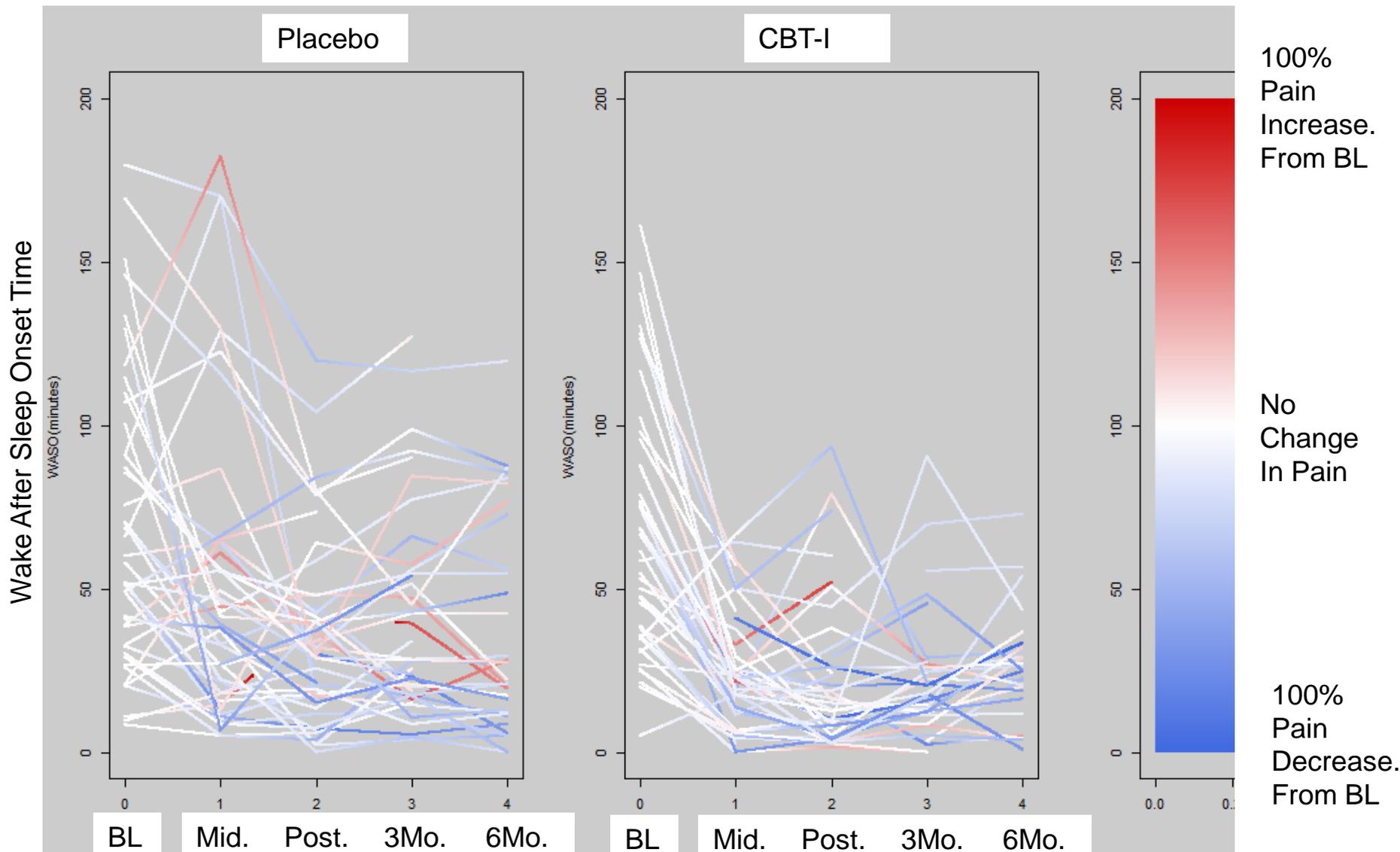


CBT-I Reduces Pain in Knee Osteoarthritis (N=100)

Smith et. al, Arthritis and Rheumatology, 2015 (NIH: R01 AR05487)

33% achieved ≥ 30 Reduction in Pain

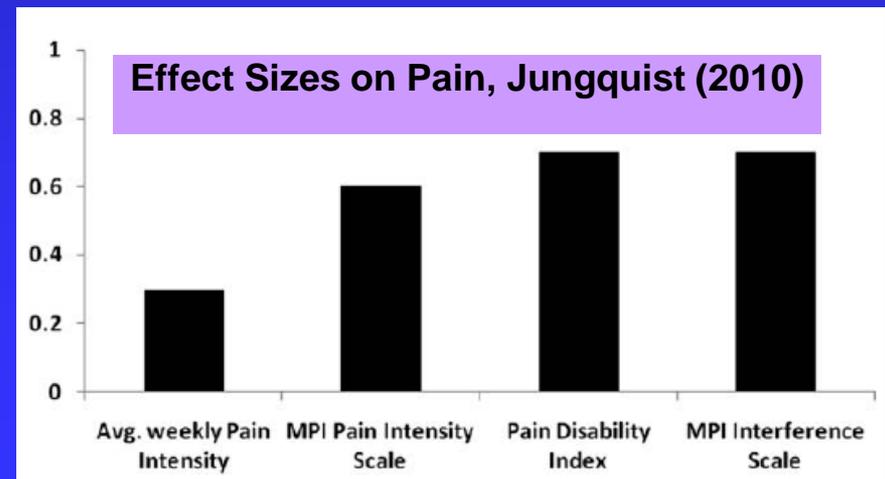
Reductions in over 6 Mos pain were mediated by pre-post reductions in WASO



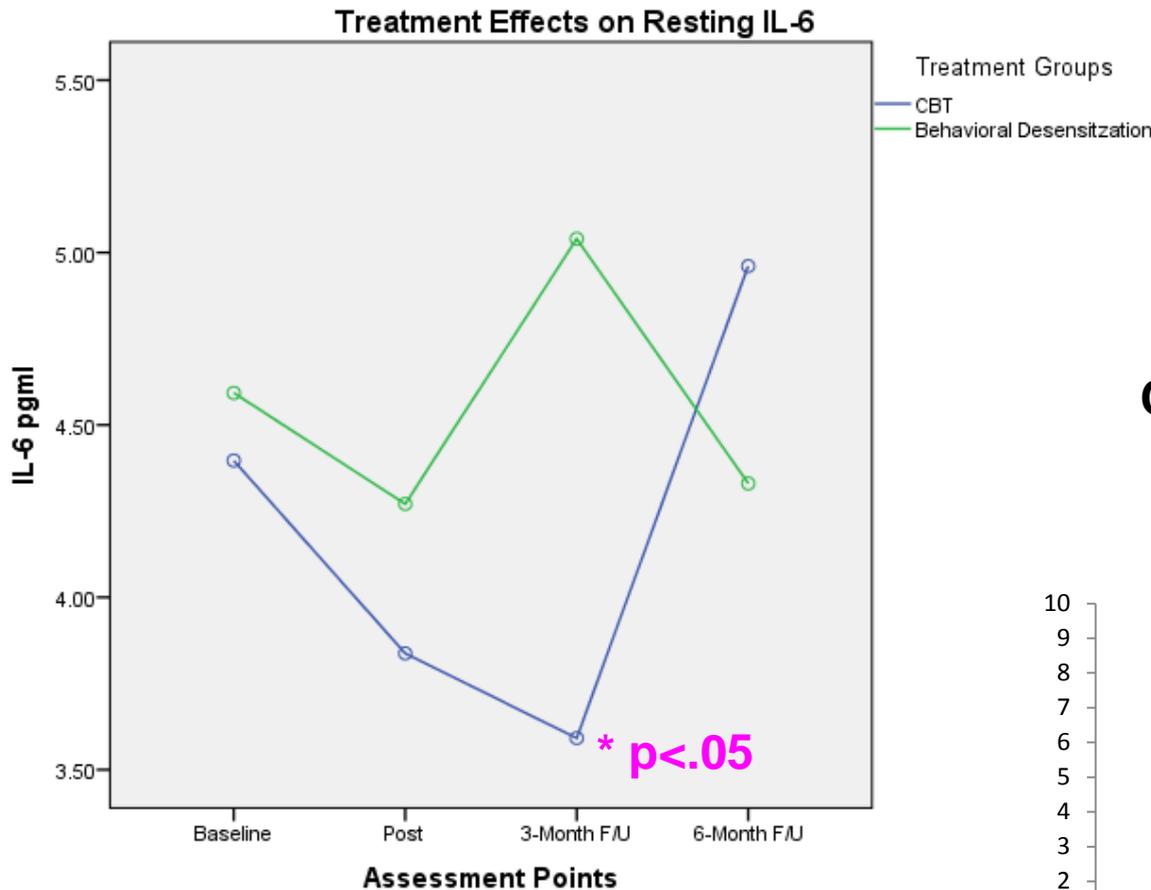
Does CBT-I Improve Pain ?

Name	Pain Type	N	Pain Outcomes
1. Currie et al. (2000)	Mixed Pain	60	No: cohen's d @ 3 mo's = <u>.41</u>
2. Edinger et al. (2005)	Fibromyalgia	42	No, but Sort of (Sleep hygiene subgroup that spontaneously adopted SRT and SCT)
3. Vitiello et al (2009)	Osteoarthritis	51	Yes (on some but not all measures)
4. Jungquist et al. (2010)	Neck and Back	28	Pain No, but Pain-related interference YES

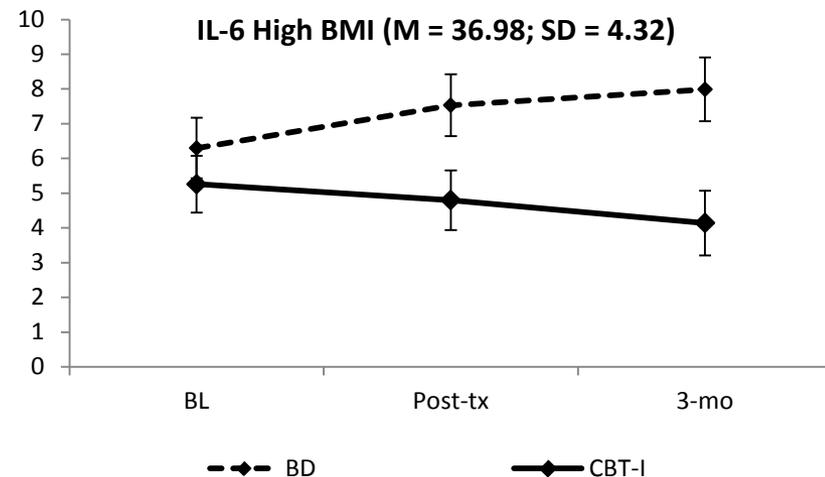
- Most of studies were not designed to answer this question
- Effect Sizes of CBT-I on Pain are promising



CBT-I Significantly Reduces Resting IL-6 Over 3 Months, but not 6-Months



CBT-I effects on Obese Subjects



Take Home Messages

- 1) Poor sleep is a risk factor for developing chronic pain
- 2) Multiple forms of sleep disruption / loss induce hyperalgesia and central sensitization of nociception
- 3) Two candidate mechanisms of sleep disruption hyperalgesia, associated with aging are:
 - A. impaired descending pain inhibitory capacity
 - B. increased systemic inflammation
- 4) Research on Mechanisms is needed
- 5) Clinical issues implications:
 - A. Aggressive treatment of underlying sleep problems is likely to improve pain control

THANK YOU!

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