Stress/Anxiety and Chronic Pain: Interactions, Assessment, and Treatment Approaches

Plus, Outcomes from the SPIN Randomized Controlled Trial

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Research supported by NIH/NIAMS (AR055160, McCrae, PI, Robinson, Co-PI)
Registered trial NCT02001077

"Discuss the cognitive activation theory of stress (CATS) and its relationship to pain (and sleep)"

Briefly describe treatment options for chronic pain (and sleep) and relationship to CATS

Describe the impact of cognitive behavioral treatments for pain (CBT-P) and insomnia (CBT-I) on pain, sleep, mood, and neuroimaging outcomes in adults with comorbid fibromyalgia and chronic insomnia

Objectives

Stress/Anxiety & Chronic Pain

Stress/Anxiety related conditions common in chronic pain patients

Atkinson, Ancoli-Israel, Slater, Garfin, & Gillin (1988)
Morin, Gibson, & Wade (1998)
Pillowsky, Crettenden, & Townley (1985)

Central Sensitization & Arousal

Atkinson, Ancoli-Israel, Slater, Garfin, & Gillin (1988)
Morin, Gibson, & Wade (1998)
Pillowsky, Crettenden, & Townley (1985)

Women may be at particular risk

Pain
Psychological symptoms
Insomnia

Common Underlying Mechanisms

Brain structural differences

Fibromyalgia
atrophy of gray matter in amygdala, cingulate, insula, medial frontal cortex, parahippocampus, and prefrontal cortex

Insomnia

Insomnia is characterized by sleep disruption, decreased sleep efficiency, and increased daytime fatigue

Insomnia may be negatively associated with hippocampal volume

Research supported by NIH/NIAMS (AR055160, McCrae, PI, Robinson, Co-PI)
Registered trial NCT02001077
Common Underlying Mechanisms

Brain functional differences
- **Fibromyalgia**
  - several fMRI paradigms (e.g., exposure to pain or non-painful pressure, anticipation of pain) have different patterns of activation compared to healthy controls
  - Craggs, Staud, Robinson, Perlstein, & Price (2012)
  - Staud, Craggs, Perlstein, Robinson, & Price (2008)
  - Staud, Craggs, Robinson, Perlstein, & Price (2007)
  - indicating dysregulation in neural networks involved in pain processing & inhibition

- **Fibromyalgia & insomnia**
  - heightened activity and patterns of connectivity compared to healthy individuals at waking rest
  - Cifre, Sitges, Fraiman, Munoz, Balenzuela, Gonzalez-Roldan et al. (2012)
  - Altena, Van Der Werf, Sanz-Arigita, Voorn, Rombouts, Kuijer, & Van Someren (2008)
  - Huang, Liang, Jia, Zhan, Li, Ding, et al. (2012)
  - Napadow, LaCount, Park, As-Sanie, Clauw, & Harris, (2010)

Influencing CNS Mechanisms

Can brain structure and function be altered with intervention?
- At least two other studies have reported preliminary evidence that patterns of brain functioning can be altered through behavioral treatments for both fibromyalgia and insomnia
  - Altena, Van Der Werf, Sanz-Arigita, Voorn, Rombouts, Kuijer, & Van Someren (2008)
  - Johnson, Toljander, Kivela, & van Someren (2009)
  - SPIN Randomized Clinical Trial

  - *novel preliminary evidence that improving sleep may help restore or "normalize" brain function in pain and sleep processing areas and may arrest or even reverse chronic pain's negative impact on brain morphology by increasing gray matter and the thickness of the cortical ribbon.*
  - Research supported by NIH/NIAMS (AR055160 McCrae, PI)
  - Registered trial NCT02648077

Treatment Options

- **Pharmacological**
  - Often does not improve pain per se
  - Improves pain-related coping
    - Martinez, Reis & Nahm (2009)
    - Nac, Tadmor & Tadmor (2004)

- **CBT-P**
  - Preferred for chronic insomnia
  - Decreases unwanted wakefulness during night
  - Improves sleep quality ratings
    - Martinez, Ares, & Sanchez-Juncal-Pereiro et al. (2013)
    - Sanders, Hodgkins, Craske, & Reis (2009)
  - Conceptualization of insomnia in context of comorbid conditions
  - CBT-I as a ‘a’ if not ‘the’ frontline treatment for chronic insomnia
  - Why? Targets cognitive and behavioral factors maintaining chronic insomnia
    - *All data from the Science Consensus Conference on Chronic Insomnia (2015)*

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SPIN

Sleep and Pain in Fibromyalgia: Central Sensitization and Hyperalgesia

- **Goal**
  - To examine the potential mechanistic role of insomnia in chronic pain

- **Conceptual Model**
  - Cognitive Activation Theory of Stress (CATS)
    - Ziedonis, Deloite (2002)
  - Chronic pain & insomnia = disorders of arousal
  - Sustained arousal & lack of resolution (theta sleep) ➔ Central Sensitization
  - Shared neural mechanisms
Hypothesis: Improved sleep (via CBT-I) will reverse Central Sensitization Fibromyalgia
- Ideal Clinical Population: >50% meet criteria for chronic insomnia
Approach
- Patients with comorbid diagnoses—fibromyalgia & chronic insomnia
- Random assignment to CBT-I, CBT-P, or waitlist control
- 8 weeks, manualized protocols

Specific Aim 1
Sleep Psychophysical & Behavioral Outcomes
- Does CBT-I improve sleep in FM patients with insomnia compared to CBT-P and waitlist control?
Hypothesis:
- CBT-I will significantly improve sleep onset latency, wake after sleep onset, sleep efficiency, and sleep quality compared to CBT-P and WLC.

Specific Aim 2
Pain Psychophysical & Behavioral Outcomes
- Does CBT-P improve pain in FM patients with insomnia compared to CBT-I and waitlist control?
Hypothesis:
- CBT-P will significantly improve clinical pain compared to CBT-I and WLC.
Specific Aim 3
Brain Function

- Does the brain’s response to pain decrease following treatment with CBT-I or CBT-P?

Hypothesis:
- Improved sleep and pain expected to reduce the brain’s response to pain in regions associated with pain-related processing.

Sample

- 113 fibromyalgia patients with insomnia (18+ yrs)
- fibromyalgia (ACR 1990 criteria)
- ≥ 11 of 18 tender points
- insomnia (AASM, APA, & RDC criteria)
- 6+ months
- baseline sleep diaries confirm sx. frequency & severity

Exclusionary criteria:
- other sleep disorders
- severe psychiatric disorders
- significant medical or neurological disorder
- cognitive impairment
- hypnotics—none or stabilized for 6 months

Specific Aim 4
Brain Structure

- Does cortical thickness increase following treatment with CBT-I or CBT-P?

Hypothesis:
- Improved sleep and pain expected to reverse structural changes associated with FM. Expect thickening of cortex following treatment.

Study Design

- Baseline assessment (2 weeks) → Treatment/waitlist (8 weeks) → Post-treatment assessment (2 weeks) → 6 Month follow-up assessment (2 weeks)
Assessment Procedures

- Intertee
- Polysomnography
- Sleep diaries (2 weeks)
- Actigraphy (2 weeks)
- Tender point exam
- Questionnaires
- Thermal testing
- MRI + thermal testing

Thermal testing

Polysomnography

Sleep diaries (2 weeks)

Actigraphy (2 weeks)

Assessment Procedures

Interview

Thermal testing

Actigraphy

Sleep diaries (2 weeks)

MRI + thermal testing

Questionnaires

Tender point exam

Components:

- CBT-I
- CBT-P
  - Sleep education
  - Sleep hygiene
  - Stimulus control
  - Sleep restriction
  - 10-minute hybrid relaxation
  - Cognitive therapy
  - Pain education
  - Activity pacing
  - Progressive muscle relaxation
  - Visual imagery
  - Autogenic relaxation
  - Cognitive therapy

Aim 1

Sleep Outcomes

Treatment Protocols

- 8 individual sessions (~50 minutes each)
- Therapists = Predoctoral psychology trainees
- Treatment integrity strictly monitored (Lichstein, Riedel, & Grieves, 1994).
- Components:

<table>
<thead>
<tr>
<th>CBT-I</th>
<th>CBT-P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep education</td>
<td>Pain education</td>
</tr>
<tr>
<td>Sleep hygiene</td>
<td>Activity pacing</td>
</tr>
<tr>
<td>Stimulus control</td>
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<td>10-minute hybrid relaxation</td>
<td>Autogenic relaxation</td>
</tr>
<tr>
<td>Cognitive therapy</td>
<td>Cognitive therapy</td>
</tr>
</tbody>
</table>

Sleep Outcomes

- Repeated measures ANOVAs group by time interactions across all three assessment time points:

<table>
<thead>
<tr>
<th>Variable</th>
<th>F</th>
<th>p</th>
<th>$\eta^2$</th>
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</thead>
<tbody>
<tr>
<td>Napping</td>
<td>2.52</td>
<td>.05</td>
<td>.04</td>
</tr>
<tr>
<td>Sleep onset latency</td>
<td>2.07</td>
<td>.11</td>
<td>.04</td>
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<tr>
<td>Wake after sleep onset</td>
<td>5.79</td>
<td>.00</td>
<td>.10</td>
</tr>
<tr>
<td>Number of awakenings</td>
<td>3.07</td>
<td>.02</td>
<td>.05</td>
</tr>
<tr>
<td>Total sleep time</td>
<td>1.05</td>
<td>.38</td>
<td>.02</td>
</tr>
<tr>
<td>Sleep efficiency</td>
<td>6.46</td>
<td>.00</td>
<td>.11</td>
</tr>
<tr>
<td>Sleep Quality Rating</td>
<td>5.34</td>
<td>.00</td>
<td>.09</td>
</tr>
</tbody>
</table>
Wake After Sleep Onset

Sleep Efficiency

Pain Outcomes

- Repeated measures ANOVAs group by time interactions across all three assessment time points:

<table>
<thead>
<tr>
<th>Variable</th>
<th>F</th>
<th>$\rho$</th>
<th>$\eta^2_p$</th>
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<tbody>
<tr>
<td>Pain intensity</td>
<td>1.34</td>
<td>.26</td>
<td>.03</td>
</tr>
<tr>
<td>Pain unpleasantness</td>
<td>1.38</td>
<td>.25</td>
<td>.03</td>
</tr>
<tr>
<td>Temporal summation</td>
<td>3.46</td>
<td>.04</td>
<td>.07</td>
</tr>
<tr>
<td>Patient Centered Outcomes</td>
<td>1.61</td>
<td>.18</td>
<td>.05</td>
</tr>
</tbody>
</table>
Aim 3  
Brain Function

Response to painful heat stimulus  
Baseline and post-treatment  
Repeated measures ANOVAs group by time interactions  
17 significant clusters ($p < .005$), including:

<table>
<thead>
<tr>
<th>Brain Function</th>
<th>$F$</th>
<th>$p$</th>
<th>$\eta^2_p$</th>
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<tbody>
<tr>
<td><strong>Right Hemisphere</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Insula</td>
<td>13.04</td>
<td>.001</td>
<td>.12</td>
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<tr>
<td>Fusiform gyrus</td>
<td>11.64</td>
<td>.002</td>
<td>.10</td>
</tr>
<tr>
<td>Middle frontal gyrus</td>
<td>11.98</td>
<td>.002</td>
<td>.14</td>
</tr>
<tr>
<td><strong>Left Hemisphere</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inferior frontal gyrus</td>
<td>13.55</td>
<td>.001</td>
<td>.20</td>
</tr>
<tr>
<td>Middle frontal gyrus</td>
<td>16.10</td>
<td>.000</td>
<td>.22</td>
</tr>
<tr>
<td>Sub-gyral temporal lobe</td>
<td>13.44</td>
<td>.001</td>
<td>.11</td>
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</tbody>
</table>

Aim 4  
Brain Structure
Cortical Thickness Change

- Baseline and post-treatment
- Repeated measures ANOVAs group by time interactions:

<table>
<thead>
<tr>
<th>Region</th>
<th>F</th>
<th>p</th>
<th>( \eta^2 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right medial orbitofrontal</td>
<td>2.64</td>
<td>.09</td>
<td>.13</td>
</tr>
<tr>
<td>Right posterior cingulate</td>
<td>3.08</td>
<td>.06</td>
<td>.15</td>
</tr>
<tr>
<td>Left caudal middle frontal</td>
<td>2.64</td>
<td>.09</td>
<td>.14</td>
</tr>
<tr>
<td>Left lateral orbitofrontal</td>
<td>5.15</td>
<td>.01</td>
<td>.23</td>
</tr>
<tr>
<td>Left rostral middle frontal</td>
<td>3.67</td>
<td>.04</td>
<td>.18</td>
</tr>
<tr>
<td>Left transverse temporal</td>
<td>2.89</td>
<td>.07</td>
<td>.15</td>
</tr>
</tbody>
</table>

Predictors of Cortical Thickness Change

Hierarchical multiple regressions with residualized change scores

- As expected, CBT-I improved sleep
- By follow-up, CBT-P also had improved sleep

Discussion

Sleep
- As expected, CBT-I improved sleep
- By follow-up, CBT-P also had improved sleep

Pain
- Most pain outcomes did not improve significantly
Discussion

Brain Function
- CBT-I reduced activation in response to pain

Cortical Thickness

<table>
<thead>
<tr>
<th>CBT-I</th>
<th>CBT-P</th>
<th>WLC</th>
</tr>
</thead>
</table>

Improved sleep (through CBT-I)
reduced central sensitization

Limitations
- Underpowered for some analyses
- Durability unknown
- Lack of neuroimaging follow-up
- Specificity to FM vs. chronic pain more broadly

Future Directions
- Replicate with larger sample
- Extend
  - Include follow-up imaging assessment
  - Examine basal brain activity with resting state analyses
  - Clinical significance of imaging findings
  - Other chronic pain conditions

SPIN Team
Christina S. McCrae, PhD – PI – Sleep psychologist
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Jason G. Craggs, PhD – Co-I – Neuroscientist, Biostatistician (imaging)
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Lori Waxenberg, PhD – Co-I – Pain physiologist
Kortyn Vonhoazer, MS – Imaging technologist
Jennifer Mundt, MS – Polysomnographic technologist
Andrew O’Shea, MSc – Imaging Technologist
Jacob Williams, PhD – Therapist
Daniela Roditi, PhD – Therapist
Ryan Anderson, PhD – Therapist
Thank you!

Questions?

Functional MRI (fMRI)
- Methods
  - fMRI acquired at 3 Tesla using a Philips Achieva scanner
  - T2 gradient echo planar imaging protocol
  - 38 contiguous slices parallel to AC-PC plane

- Data Preparation
  - Software: Brain Voyager
  - Preprocessing
    - motion correction
    - slice scan time correction
    - 4mm FWHM smoothing
    - linear detrending
    - high pass temporal filtering
    - Normalization to standardized (Talairach) space

Structural MRI
- Methods
  - Data acquired at 3 Tesla using a Phillips Achieva scanner.
  - 8 channel head coil.
  - T1-weighted protocol (TR = 2000ms, TE = 4.13ms, FOV= 240mm, 1mm³ voxel size)

- Cortical Thickness Analyses (CTA)
  - Pre/post: CBTi vs. WLC
  - Software: FreeSurfer
  - Repeated measures ANOVA design
  - Creation of an unbiased within-subject template (Reuter et al., 2012) using FreeSurfer to improve reliability and power
  - ROI analysis using cortical parcellations from the Desikan-Killiany atlas