Effects of sleep disruption on mood and pain: Role of inflammation

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Outline

- Sleep deficiency affecting mood/emotional well-being
- Sleep deficiency affecting pain/physical well-being
- Role of inflammation in the association between sleep deficiency and pain
Sleep deficiency affecting mood/emotional well-being

Population-based/clinical studies

Individuals with **irregular sleep-wake patterns**, such as shift workers, pilots, medical emergency staff have increased rates of depression and anxiety *(Bannai & Tamakoshi, review 2014).*

Individuals with **insomnia** have an increased risk of developing a mood disorder, such as depression or anxiety *(Weissmann et al., 1997; Neckelmann et al., 2007; Baglioni et al., 2010).*
Insomnia affecting mood/well-being

Well-being in insomnia without psychiatric comorbidities

Insomnia disorder N=17 (22.6 ±0.9 yrs, 11 women), individually matched with healthy participants.

SF36 Emotional Functioning

Control | Insomnia

SF36 Social Functioning

Control | Insomnia

PSS14 Perceived Stress

Control | Insomnia

N131 study – Sleep Research Society Foundation
Experimental studies

General experimental setting

Healthy participants, without history of mood- or pain-related disorders

Manipulation of sleep in form of
- Total sleep deprivation of up to 3 days
- Sleep restriction or fragmentation of up to 14 days
- Repeated episodes of sleep restriction and sleep recovery of up to one month

Controlled in-laboratory conditions

Assessment of:
- mood via questionnaires/rating scales
- affective response to emotion induction
Mood/emotional well-being in response to experimental sleep restriction

Protocol

- Healthy participants (21-40 years) without a history of sleep, mood or pain-related disorder
- Randomized to:
  - 4h of sleep/night for 12 days (23-03h, N=22) or
  - 8h of sleep/night for 12 days (23-07h, N=18)
- Assessment of mood and pain through computerized visual analog scales (VAS) presented every 2 hours throughout protocol
- 24h blood and urine collection at baseline and 10th day of partial sleep deprivation
Mood/emotional well-being in response to experimental sleep restriction

Study/Environmental Controls

**Food:** Calorie- and electrolyte-balanced diets; meals served at standard times.

**Fluids:** No caffeine.

**Body position:** In bed in a semi-supine position from 03:00 to 07:00h in sleep restriction condition; lights dimmed to <40 Lux.

**Motor activity:** Hourly walks, continuation of habitual gym routine.

**Social:** Research monitor with participants during all waking periods. Access to email/phone. Visits of friends/family.
Mood/emotional well-being in response to experimental sleep restriction

Optimism- Sociability

Prolonged sleep restriction progressively deteriorates positive outlook and social functioning.

Haack & Mullington, 2005
Association between pain and sleep was first mentioned in the Gilgamesh Epic (1900 BC): In Search of Immortality

"...my face was not sated with sweet sleep, I fretted myself with wakefulness; I filled my joints with aches."

Translation by E.A. Speiser, in Ancient Near East Texts (Princeton, 1950)
Clinical/Population-based studies

**Sleep deficiency** ↔ **pain**

**Pain reporting** → **Sleep deficiency**

- **Fibromyalgia** *(Affleck et al., 1996)*
- **Migraine** & other primary headache disorders *(rev. Alberti 2006)*
- **Surgery** *(Closs et al., 1992)*
- **General population** *(Edwards et al., 2008)*

**Sleep deficiency** → **Pain reporting**

- **Chronic widespread pain** *(Davies et al., 2008)*
- **Migraine** *(Rains & Penzien 1996)*
- **Surgery** *(Wright et al., 2009)*
- **Temporomandibular disorders (TMD)** *(Quartana et al., 2010)*
- **General population** *(Edwards et al., 2008)*
Individuals with insomnia disorder report pain on twice as many days as healthy controls.

Haack et al., 2012
Spontaneous pain in response to experimental sleep restriction

Prolonged insufficient sleep leads to an increase of spontaneous pain in a young, healthy population.

N54 study – NIH/NIMH MH60641
Evoked pain in response to sleep deficiency

Vol. III. No. 5. September, 1896.

The Psychological Review.

STUDIES FROM THE PSYCHOLOGICAL LABORATORY OF THE UNIVERSITY OF IOWA.

On the Effects of Loss of Sleep.¹

By Professor G. T. W. Patrick and Dr. J. Allen Gilbert.

Pain threshold to pressure decreased in the course of 90 hours of total sleep deprivation. N=1.

To date, numerous studies have shown that...

Experimental sleep deficiency, either in form of total sleep deprivation, selective sleep stage deprivation, sleep restriction, or sleep fragmentation leads to a decrease in pain thresholds.
Pain thresholds in insomnia disorder

**Heat Pain Threshold (°C)**

- Control: 46°C
- Insomnia: 44°C

**Pressure Pain Threshold (kPa)**

- Control: 240 kPa
- Insomnia: 220 kPa

*Haack et al., 2012*
Pain inhibition in experimental sleep disruption and insomnia

Capacity to inhibit pain assessed by Conditioned Pain Modulation Paradigm (CPM).

Pain inhibition is deteriorated in experimental sleep disruption over 3 nights (graphical estimation from Smith et al., 2007).

Pain inhibition is even more deteriorated in insomnia disorder (Haack et al., 2012; data expressed as % change from respective control levels).

Adapted from Millan, 2002
Repeated exposure to patterns of sleep restriction & recovery - Protocol

Study Day

Time of Day

- Participant Arrival/Discharge
- Sleep Period

Heavy recording period (blood draws, PSG, Dinamap, PVT)

N194 study – NIH/NHLBI HL105544
Habituation to pain in response to repeated patterns of sleep restriction & recovery

Habituation to cold pain
Cold pressor test (CPT), change from baseline (sec)

Habituation to stressors or other challenges is a key feature of many biological systems, but when undergoing repeated exposure to sleep restriction, the ability to habituate to cold pain is deteriorated.
Any form of sleep deficiency – total sleep deprivation, sleep restriction, sleep disruption, insomnia symptoms or disorder, appears to amplify **spontaneous pain reporting**.

Experimental sleep restriction, sleep disruption, or insomnia disorder is associated with

- decreased pain thresholds
- decreased pain inhibition
- decreased habituation to pain

**Mechanisms**
Sleep has a regulatory influence on all major physiological systems.

Without sufficient and good quality sleep, rhythms of all major physiological systems are dysregulated or displaced.
Various systems that become dysregulated by sleep disturbance do also affect pain processing.

Vice versa, pain affects various systems that are necessary for good quantity and quality sleep.
Inflammation
as a mechanistic pathway
inter-connecting sleep and pain?
Inflammatory response to repeated patterns of sleep restriction & recovery

IL-6 positive monocytes

(% Change from Control Sleep [8h/night for 25 days])

Repeated cycles of sleep restriction and recovery

Inflammatory markers increase across repeated episodes of sleep restriction, and do not return to baseline after a couple of nights with full sleep.

N194 study – NIH/NHLBI HL105544
Inflammatory and pain responses to experimental sleep restriction

Haack et al., 2007

△ 4h of sleep/night for 10 nights
● 8h of sleep/night for 10 nights

Change IL-6 (pg/ml)

△ 4h of sleep/night for 10 nights
● 8h of sleep/night for 10 nights

Change Pain (Log)

r=0.67; p<0.01

Haack et al., 2007
Prostaglandin E2 in response to total sleep deprivation (TSD over 3 days)

Change in urinary PGE2 metabolite (ng/day)

TSD: Sleep

Change PGE2 (log)

R = 0.52; p < 0.05

Haack et al., 2009
Overall Summary

Sleep deficiency, as it occurs in the experimental or natural environment, leads to facilitation or development of
- spontaneous pain.
- enhanced sensitivity to evoked pain.
- decreased capacity to inhibit pain and to habituate to pain.

Inflammatory mediators, such as IL-6 and PGE2, appear to play a mediating the effects of sleep deficiency and pain. Causation still needs to be established.

Identification of and targeting mechanisms important to reduce pain exacerbated by sleep deficiency.
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Sleep Research Society Foundation (MH)
Ratings of single pain items

- **General Body Pain**
- **Physical Discomfort**
- **Headache**
- **Back Pain**
- **Muscle Pain**
- **Joint Pain**

Number of days within 14 day period

Comparison between Control and Insomnia groups.
Potential mechanistic pathways

Inflammatory markers

Inflammatory mediators able to sensitize nociceptors:
- Prostaglandins, histamine, bradykinin
- Cytokines (IL-1, IL-6, TNF-alpha)

Adapted from Woolf 2004
Inflammatory markers and pain reporting in insomnia disorder

Inflammatory Composite
\(Z\) score IL-6, CRP, monocytes

Pain Frequency (days)

N131 study data, manuscript in preparation
PGs are involved in numerous homeostatic functions. 

**PGE2** appears to play a pivotal function in inflammation and pain.

**PGD2** has been shown to play a significant role in sleep-wake regulation.
Insufficient sleep in healthy, pain-free individuals increases the expression of COX-2 by monocytes.

N194 preliminary data
### Evoked pain in insomnia disorder: Participant Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Insomnia</th>
<th>Controls</th>
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<tbody>
<tr>
<td><strong>Female/Male Ratio</strong></td>
<td>11/6</td>
<td>11/6</td>
</tr>
<tr>
<td><strong>Age (yrs)</strong></td>
<td></td>
<td></td>
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<tr>
<td>Mean ±SEM</td>
<td>22.65 ± 3.52</td>
<td>24.35 ± 3.64</td>
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<tr>
<td><strong>BMI</strong></td>
<td></td>
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<tr>
<td>Mean ±SEM</td>
<td>23.27 ± 2.90</td>
<td>22.14 ± 3.51</td>
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<tr>
<td><strong>Actual Sleep Time (actigraphy)</strong></td>
<td></td>
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<tr>
<td>Mean±SEM</td>
<td>6.08 ± 1.11</td>
<td>6.82 ± 1.03</td>
</tr>
<tr>
<td><strong>Range</strong></td>
<td>3.50-7.37</td>
<td>4.47-8.12</td>
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### Screening criteria

- No current Axis I disorders (or history in last 6 months).
- No current or past history of pain-related disorders.
- Free of any medication for >1 month.
Pain facilitation in insomnia disorder

Test: Temporal summation of pain

Instruction: The temperature will rapidly increase and decrease. Rate the intensity of the sensation whenever I say ‘RATE’.
Unexpectedly, individuals with insomnia disorder showed less temporal summation than controls. Due to active pain-inhibitory system resulting in quicker habituation to pain stimuli?
**Pain inhibition in insomnia disorder**

**Test: Conditioned pain modulation (CPM)**

- Foot immersion into 47°C water
- Repeated heat pulses applied on forearm
- Foot removal

*Instruction:* … While your foot is immersed in the water bath, I will ask you to rate the intensity of the heat sensation on your forearm…. 
Pain Inhibition in insomnia disorder

Capability to inhibit pain in the CPM test deteriorated in insomnia disorder. Due to a constantly active pain-inhibitory system not able to respond to further challenge?
Low average, but also high variability of sleep duration in insomnia disorder.
A noxious stimulus undergoes significant modulation in the CNS, i.e., it can be inhibited or facilitated, before the sensation reaches consciousness and is perceived.

Triggers of pain inhibition:
- Painful stimuli
- Environmental dangers
- Negative high-arousal emotions
- Distraction/attention shift

Adapted from Millan, 2002