Health Effects of Fatigue

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1. Fatigue and Sleepiness
2. Current Model of Sleep
3. Chronic Sleep Restriction and Performance
4. Sleep Extension Effects
5. Implications for Sleep Model
6. Sleep and Physiology / Health
Fatigue—An Inconsistently Defined Concept

-- “Fatigue is “deterioration in human performance, arising as a consequence of several potential factors, including sleepiness.” (Maher & McPhee, 1994)

-- “Fatigue…is the decline in performance that occurs in any prolonged or repeated task…. However, it is also a subjective sensation experienced by patients…” (Fischler, 1999)

-- “The term fatigue has yet to be defined in a concrete fashion” (Batelle APA Technical Report, 1998)

-- Fatigue has often been confused with sleepiness and has received little study as an independent symptom of sleep disturbance.” (Lichstein et al., 1997)
**Sleep/Performance Prediction Model**

- **Performance Decrement Algorithm**
  \[ P_t = P_{t-1} - kw(P_{t-1}', W_t, M_p) \]

- **Performance Increment Algorithm**
  \[ P_t = P_{t-1} + ks(P_{t-1}', S_t, M_p) \]

- **Circadian Rhythm Algorithm**
  \[ C_t = a \cos \left( \pi (t - c)/720 \right) + b \cos \left( \pi (t - d)/360 \right) \]

**Initialized:**
- Time, Date
- Time Zone

- **Sleep @ time t?**
  - Yes
  - No

**Symbols:**
- \( P_t \): performance potential at time \( t \)
- \( kw \): rate of decline during wake
- \( ks \): rate of recuperation during sleep
- \( M_p \): specific measure of performance
- \( C_t \): circadian influence at time \( t \)
- \( a \) and \( b \): transient time zone shift factors
- \( c \) and \( d \): acrophase of 24- and 12-hour rhythms
Cumulative Effects of CSR on Performance

Very frequent lapses of attention in all subjects equivalent to being awake 40-60 h

Frequent lapses of attention in most subjects equivalent to being awake 24-40 h


Sleep and Self-Reported Mission-Impacting Mistakes in Operation Iraqi Freedom (OIF)

![Graph showing the relationship between average hours of sleep per day and the percentage of soldiers who reported having an accident or mistake that affected the mission.](chart.png)

Source: MHAT V data
Sleep and Self-Reported Ethical Misconduct in Operation Iraqi Freedom

Source: MHAT V data
Chronic sleep restriction impairs performance

Does chronic sleep extension have the opposite effect?
Rupp et al. (2009) Study Design

1. 14-day AT-HOME “sleep schedule assessment”
   a. Reported usual TIB ~7 hrs.
   b. Used to determine “Habitual” sleep schedule

2. In-laboratory Overnights
   Sleep Extension/ Habitual
   (7 nights)

   10 (h) OR Habitual (h) TIB

3. Full-time In-laboratory
   Baseline
   (1 night)
   Sleep Restriction
   (7 nights)
   Recovery
   (5 nights)

   3 (h) TIB

   8 (h) TIB

   PVT, SSS: every hr, 0800-1800, 11 test bouts daily,
   MWT: every 2 hrs, 0800-1800, 6 test bouts daily
   Actigraphy + PSG
Recovery of PVT Lapses

Estimated means, controlling for age.

*Restrict x Group, $p = .01$
+Recov x Group, $p = .03$
Recovery of PVT Speed

*Trans x Group, p = .02

Estimated means, controlling for age.
Recovery of Subjective Alertness

Estimated means, controlling for age.
Summary of findings from Rupp et al. (2009)

1. Sleep can be “banked.” Extending nightly sleep time (to 10 hours) for one week prior to sleep restriction (7 consecutive nights with ‘time in bed’ limited to 3 hours) results in improved behavioral resilience as evidenced by:

   a. A slower rate of performance decline across days of sleep restriction

   b. A faster rate of performance recovery when nightly ‘time in bed’ is restored to 8 hours
Implications of Sleep Banking: The Pilsner Beer Glass Analogy
**Performance Prediction Model**

**Performance Decrement Algorithm**
\[ P_t = P_{t-1} - kw(P_{t-1}', W_t, M_p) \]

**Performance Increment Algorithm**
\[ P_t = P_{t-1} + ks(P_{t-1}', S_t, M_p) \]

**Circadian Rhythm Algorithm**
\[ C_t = a \cos \left( \frac{\pi (t - c)}{720} \right) + b \cos \left( \frac{\pi (t - d)}{360} \right) \]

- \( P_t \) = performance potential at time \( t \)
- \( kw \) = rate of decline during wake
- \( ks \) = rate of recuperation during sleep
- \( M_p \) = specific measure of performance
- \( C_t \) = circadian influence at time \( t \)
- \( a \) and \( b \) = transient time zone shift factors
- \( c \) and \( d \) = acrophase of 24- and 12-hour rhythms

**Initialized:**
- Time, Date, Time Zone

**Flowchart:**
- Sleep @ time \( t \) ?
  - Yes: Performance Increment Algorithm
  - No: Performance Decrement Algorithm

**Performance Capacity Reservoir**
Performance Prediction Model

- **Performance Decrement Algorithm**
  \[ Pt = P_{t-1} - kw(P_{t-1}', W_t, M_p) \]

- **Performance Increment Algorithm**
  \[ Pt = P_{t-1} + ks(P_{t-1}', S_t, M_p) \]

- **Circadian Rhythm Algorithm**
  \[ Ct = a \cos \left( \pi \left( t - \frac{c}{720} \right) \right) + b \cos \left( \pi \left( t - \frac{d}{360} \right) \right) \]

*Initialized: Time, Date, Time Zone*

- **Sleep @ time t?**
  - **No**
    - **Performance Decrement Algorithm**
    - **Performance Increment Algorithm**
  - **Yes**
    - **Circadian Rhythm Algorithm**

\[ Pt = \text{performance potential at time } t \]
\[ kw = \text{rate of decline during wake} \]
\[ ks = \text{rate of recuperation during sleep} \]
\[ M_p = \text{specific measure of performance} \]
Performance Capacity

7 hrs
9 hrs
Performance Capacity

7 hrs

9 hrs
Chronic sleep habits mediate behavioral resilience (at least during subsequent sleep restriction)
Aside: Operational Implications

1. “Extra” sleep is like “money in the bank”: Although the benefits of obtaining increased sleep may not be apparent on a typical work day, such benefits quickly become manifest when an individual faced with a “rainy day” - the challenge of extended wakefulness (i.e., during an emergency situation requiring mandatory overtime).

2. Cognitive performance capacity is not only a function of recent sleep history (i.e., how much sleep was obtained on the prior night) – it is also a function of how much sleep is obtained on a regular basis.

TAKE HOME LESSON: Workers subject to emergency calls need to regularly obtain more sleep than those with predictable work schedules. Such workers who obtain only enough sleep for nominally adequate performance during a typical work day (e.g., 6 hours of sleep per weeknight) will be ill-prepared when emergencies necessitating extended wakefulness/work hours arise – circumstances made worse by the fact that such workers will be relatively unaware of the extent of their own sleep-loss-induced impairment.
Chronic sleep habits mediate behavioral resilience (at least during subsequent sleep restriction)

Do chronic sleep habits similarly mediate physiology / pathology?
Recent findings (largely from epidemiological studies over the past decade) suggest that in addition to deficits in alertness/performance, chronic sleep restriction is associated with a variety of negative outcomes including:

- heart disease/hypertension
- metabolic syndrome/weight gain/obesity
- diabetes
- mood disorders
- mortality

From Magee et al, 2010
Chronic jet lag produces cognitive deficits.

Cho K, Ennaceur A, Cole JC, Suh CK.

Source
Department of Psychology, University of Durham, Durham, DH1 3LE, United Kingdom. Kei.Cho@bris.ac.uk

Abstract
Traveling across time zones causes disruption to the normal circadian rhythms and social schedules because of travelers' shift in time. As the endogenous circadian timing system adapts slowly to new time cues, the phase relationship between biological rhythms and external time cues are out of synchronization for a period of time. This disturbance of circadian rhythms has been shown to impair physical and psychological health (Winget et al., 1984). To test the effects of repeated jet lag on mental abilities, airline cabin crew were compared with ground crew. Salivary cortisol was used as a physiological marker for circadian disruption. The cabin crew group, who had a history of repeated jet lag, had significantly higher salivary cortisol levels in an average working day. In addition, this elevated level of cortisol was only seen in the same subjects when the cabin crew were on transmeridian flights but not domestic flights. Cabin crew also exhibited cognitive deficits, possibly in working memory, that became apparent after several years of chronic disruption of circadian rhythms.
Sleep Disturbance Impairs Stroke Recovery in the Rat

Cristina Zunzunegui, MD*1; Bo Gao, MD*1,2; Ertugrul Cam, DVM1,2; Aleksandra Hodor, MSc2; Claudio L. Bassetti, MD1,2

Study Objectives: There is a lack of experimental evidence to support the hypothesis that sleep may modulate stroke outcome as suggested by clinical observations. We have previously shown that sleep disturbance (SDIs) over 3 days aggravates brain damage in a rat model of focal cerebral ischemia. The aim of this study is to further investigate effects of SDIs on long-term stroke recovery and neuroplasticity as assessed by axonal sprouting, neurogenesis, and angiogenesis.

Design: Focal cerebral ischemia was induced by permanent occlusion of the distal branches of middle cerebral artery. Twelve hours after initiation of ischemia, SDIs was performed over 3 consecutive days (deprivation of 80% sleep during the 12-h light phase). Weekly assessments on sensorimotor function by the single pellet reaching test (SPR) were performed for 5 weeks after surgery. Axonal sprouting was evaluated by anterograde tracing with biotinylated dextran amine (BDA) and neurogenesis/angiogenesis by bromodeoxyuridine (BrdU) labelling along with cell-type markers. Control groups included ischemia without SDIs, sham with SDIs, and sham without SDIs.

Setting: Basic sleep research laboratory.

Measurements and Results: Rats subjected to SDIs after ischemia showed significantly less recovery of forearm motor skills during the poststroke period of 5 weeks. This effect was accompanied by a substantial reduction in axonal sprouting, expression of synaptophysin, and the ischemia-stimulated neural and vascular cell proliferation.

Conclusion: SD is has detrimental effects on functional and morphological/structural outcomes after stroke, suggesting a role of sleep in the modulation of recovery processes and neuroplasticity.

Keywords: Stroke, sleep, sleep deprivation, neuroplasticity, neurogenesis, axonal sprouting, brain repair

Citation: Zunzunegui C; Gao B; Cam E; Hodor A; Bassetti CL. Sleep disturbance impairs stroke recovery in the rat. SLEEP 2011;34(9):1261-1269.
Chronic Sleep Restriction and Alzheimer’s Disease?

Amyloid-β Dynamics are Regulated by Orexin and the Sleep-Wake Cycle
Jae-Eun Kang,1 Miranda M. Lim,1 Randall J. Bateman,1,2,3 James J. Lee,1 Liam P. Smyth,1 John R. Cirrito,1,2 Nobuhiro Fujiki,5 Seiji Nishino,5 and David M. Holtzman1,2,3,4*

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4 Department of Developmental Biology, Washington University, St. Louis, Missouri, 63110, USA
5 Sleep and Circadian Neurobiology Laboratory, Department of Psychiatry and Behavioral Sciences, Stanford University, Palo Alto, California, 94304, USA

Abstract
Amyloid-β (Aβ) accumulation in the brain extracellular space is a hallmark of Alzheimer’s disease. The factors regulating this process are only partly understood. Aβ aggregation is a concentration-dependent process that is likely responsive to changes in brain interstitial fluid (ISF) levels of Aβ. Using in vivo microdialysis in mice, we found that the amount of ISF Aβ correlated with wakefulness. The amount of ISF Aβ also significantly increased during acute sleep deprivation and during orexin infusion, but decreased with infusion of a dual orexin receptor antagonist. Chronic sleep restriction significantly increased, and a dual orexin receptor antagonist decreased, Aβ plaque formation in amyloid precursor protein transgenic mice. Thus, the sleep-wake cycle and orexin may play a role in the pathogenesis of Alzheimer’s disease.
Insomnia in young men and subsequent depression. The Johns Hopkins Precursors Study.
Chang PP, Ford DE, Mead LA, Cooper-Patrick L, Klag MJ.

Source
Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA.

Abstract
The Johns Hopkins Precursors Study, a long-term prospective study, was used to study the relation between self-reported sleep disturbances and subsequent clinical depression and psychiatric distress. A total of 1,053 men provided information on sleep habits during medical school at The Johns Hopkins University (classes of 1948-1964) and have been followed since graduation. During a median follow-up period of 34 years (range 1-45), 101 men developed clinical depression (cumulative incidence at 40 years, 12.2%), including 13 suicides. In Cox proportional hazards analysis adjusted for age at graduation, class year, parental history of clinical depression, coffee drinking, and measures of temperament, the relative risk of clinical depression was greater in those who reported insomnia in medical school (relative risk (RR) 2.0, 95% confidence interval (CI) 1.2-3.3) compared with those who did not and greater in those with difficulty sleeping under stress in medical school (RR 1.8, 95% CI 1.2-2.7) compared with those who did not report difficulty. There were weaker associations for those who reported poor quality of sleep (RR 1.6, 95% CI 0.9-2.9) and sleep duration of 7 hours or less (RR 1.5, 95% CI 0.9-2.3) with development of clinical depression. Similar associations were observed between reports of sleep disturbances in medical school and psychiatric distress assessed in 1988 by the General Health Questionnaire. These findings suggest that insomnia in young men is indicative of a greater risk for subsequent clinical depression and psychiatric distress that persists for at least 30 years.
Do sleep complaints contribute to age-related cognitive decline?

Altena E, Ramautar JR, Van Der Werf YD, Van Someren EJ.

Source
Department Sleep and Cognition, Netherlands Institute for Neuroscience (NIN), an Institute of the Royal Netherlands Academy of Arts and Sciences, Amsterdam, The Netherlands.

Abstract
The cognitive changes that occur with ageing are usually referred to as 'age-related cognitive decline'. The most pronounced changes may be found in the executive functions that require integrity of the prefrontal cortical circuitry. With age, sleep also changes profoundly, with more sleep fragmentation, earlier awakenings and less slow wave sleep as its main features. Interestingly, experimental sleep deprivation studies in healthy young adults showed a particularly consistent effect on executive functions, suggesting that sleep problems might contribute to the cognitive changes accompanying older age. We here investigate this possibility by reviewing reports on age-related and insomnia-related changes in cognition and brain function and structure, as found in studies investigating subjective complaints, objective functioning in everyday life, neuropsychological assessment, psychometry, structural and functional magnetic resonance imaging, electroencephalography, positron emission tomography and transcranial magnetic stimulation. The chapter focuses on the 'normal' age-related sleep changes that are experienced as insomnia - that is, fragmentation of sleep, more superficial sleep, more wake after sleep onset and earlier awakenings - rather than on specific sleep disturbances as sleep-disordered breathing, restless legs or periodic limb movements during sleep, for all of which the risk increases with age. It turned out that relatively few studies directly addressed the question whether elderly with different degrees of sleep complaints are differentially affected by 'age-related cognitive decline'. Still, several similarities between age-related and insomnia-related cognitive and brain changes are apparent, notably with respect to performance requiring integrity of the prefrontal cortical system. We suggest that at least part of what we regard as age-related changes may, in fact, be due to poor sleep, which is in some cases a treatable condition. Further research directly comparing aged good sleepers versus aged insomniacs will need to elucidate how sleep disturbances are involved in the cognitive, structural and functional changes observed with increasing age. The findings suggest that discrimination of subtypes of poor sleep at high age will aid in understanding the mechanisms by which it affects cognition and brain function.

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Conclusions: Sleep and Health

Recent findings suggest an association between chronic sleep restriction (CSR) and deficits in health, mood, alertness and performance.

It is reasonable to hypothesize that increased nightly sleep improves physical, psychological, and behavioral resilience.
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Back-Up Slides
Adenosine Hypothesis: The physiological basis of differences between acute total sleep deprivation vs. chronic sleep loss?
Normal Sleep/Wake Schedule

Adenosine (AD) induces sleepiness, A1 receptor antagonists (e.g., caffeine) enhance wakefulness.

Extracellular adenosine (AD) accumulates in the cholinergic basal forebrain during wakefulness (Porkka-Heiskanen et al., 1997) as sleep debt increases.

Process is reversed across sleep, when extracellular adenosine concentrations are reduced. This facilitates next-day alertness (Porkka-Heiskanen, 1999).
Initially, sleep loss results in the accumulation of extracellular adenosine to higher-than-normal levels – resulting in increased binding at A1 receptors and increased sleepiness.
However, across several days of sleep restriction AD levels begin to normalize – i.e., return to baseline levels that characterize normal amounts of wake and sleep.

It is as if the basal forebrain’s ability to pump out adenosine is beginning to fatigue. But this does not result in a reduced pressure to sleep because...
As the level of extracellular adenosine is reduced with extended sleep loss, the number of A1 receptors proliferates (A1 receptor upregulation). The increasing density of A1 receptors in the face of decreasing extracellular adenosine serves to "keep the pressure on" - essentially ensuring that an elevated drive to sleep is maintained.

Several Days of Sleep Restriction
Strecker et al., (2006) suggest that it is essentially the ratio of ‘extracellular adenosine level’ to ‘A1 receptor density’ that determines the pressure to sleep (“sleep debt”).
Why a Relatively Extended Recovery in the Habitual Sleep Group?

ONE POSSIBILITY: Recovery sleep rapidly restores the ability of the basal forebrain to “pump out” extracellular adenosine – more rapidly, in fact, than A1 receptors can be downregulated to their “normal density”.

This combination – normal (restored) level of extracellular adenosine and upregulated A1 receptors – results in an “extension” of elevated sleepiness (i.e., until A1 receptors are also downregulated to their normal density level).
How Might Sleep Extension Improve Resilience?

**Hypothesis:** Sleep extension has the opposite effect of sleep restriction – downregulation of A1 receptors. And a relatively lower density of A1 receptors at the beginning of the sleep restriction period partially offsets the A1 upregulating effect of sleep restriction – meaning that there are less A1 receptors to inhibit alertness and performance during both the sleep restriction and recovery sleep phases.
Background, Aims, and Hypotheses

- Subjects differ substantially in their responses to acute, total sleep deprivation and chronic sleep restriction.

- Within subjects, responses to 2 separate bouts of acute, total sleep deprivation are stable (Van Dongen et al., 2004), suggesting TRAIT.

- UNKNOWN: whether response is stable between different sleep loss scenarios (acute, total sleep deprivation v. chronic, restricted sleep).

**Aim:** Determine extent to which response to acute, total sleep deprivation v. chronic, restricted sleep is TRAIT-LIKE.

**Hypothesis:** Subjects displaying greater relative vulnerability to acute, total sleep deprivation will also show greater relative vulnerability to chronic, restricted sleep.

- **N = 19 (11 men, 8 women)**
- **Mean age [SD] = 28.1 [4.7] years**

<table>
<thead>
<tr>
<th>PHASE</th>
<th>STUDY DAY</th>
<th>DURATION (days)</th>
<th>TIME IN BED (Hrs)</th>
<th>MEASURES</th>
</tr>
</thead>
<tbody>
<tr>
<td>OVERNIGHTS</td>
<td>O1-O6</td>
<td>6</td>
<td>10</td>
<td>Actigraphy</td>
</tr>
<tr>
<td>BASELINE</td>
<td>BL</td>
<td>1</td>
<td>10</td>
<td>PVT, Math, N-Back</td>
</tr>
<tr>
<td>TOTAL SLEEP DEPRIVATION</td>
<td>SD1-SD2</td>
<td>2</td>
<td>0</td>
<td>PVT, Math, N-Back</td>
</tr>
<tr>
<td>SLEEP RESTRICTION</td>
<td>SR1-SR7</td>
<td>7</td>
<td>3</td>
<td>PVT, Math, N-Back</td>
</tr>
<tr>
<td>RECOVERY</td>
<td>R1-R3</td>
<td>3</td>
<td>8</td>
<td>PVT, Math, N-Back</td>
</tr>
</tbody>
</table>
**Metrics**

**PVT-192**

Lapses = # RT ≥ 500 msecs

Speed = 1/RT * 1000

**ANAM**

Mathematical Processing

8 - 2 + 3 =

N-back (Running Memory)

Throughput

(Correct responses/ minute )
Statistical Analyses - Stability of Response

1. **Response calculated by averaging outcomes over:**
   - **TSD:** last 12 hours of challenge (0800 - 2000)
   - **CSR:** last 12 hours of restriction Day 7 (0800 - 2000)

2. **Separated between-subjects variance** $s^2_{bs}$ **from within-subjects variance** $s^2_{ws}$ - linear mixed-model analysis of variance, restricted maximum likelihood method, fixed-effects order (TSD or CSR first)

3. **Intraclass correlation coefficient (ICC) calculated** - ratio of $s^2_{bs}$ to $s^2_{TOT}$

4. **Wald Z test** - significance of ICC values

Results: Stability of Response, sleep loss

- **PVT Lapses**
  - ICC = 0.86
  - Wald Z-test: $F = 2.70$, $p < 0.05$
  - Order effect: $F = 1.30$, ns

- **PVT Speed**
  - ICC = 0.79
  - Wald Z-test: $F = 2.57$, $p < 0.05$
  - Order effect: $F = 1.19$, ns
Results: Stability of Response to Sleep Loss

**Math Processing**

- TOTAL SLEEP DEPRIVATION
- CHRONIC SLEEP RESTRICTION

*ICC = 0.51*

Wald Z-test: $F = 1.87$, $p = 0.06$

Order effect: $F = 0.42$, ns

**N - Back**

*ICC = 0.67*

Wald Z-test: $F = 2.29$, $p < 0.05$

Order effect: $F = 0.81$, ns
Summary and Future Directions

- **Responsivity to different types of sleep loss is trait-like:** subjects who displayed greater vulnerability to TSD also displayed greater vulnerability to CSR

- **Trait-like aspects of responsivity to sleep loss extend to chronic sleep restriction**

- **An acute TSD challenge can be used to predict an individual’s vulnerability to CSR**

- **FUTURE DIRECTIONS:** Determine role of genetic polymorphisms and AD receptor density changes in responsivity to TSD/CSR

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**Poster ID # 240.** ADORA2A Polymorphism Regulates Neurobehavioral Performance Response to Chronic Sleep Restriction.

**Poster ID # 241.** PER3 Polymorphisms Impact Neurobehavioral Performance During Chronic Sleep Restriction.

**Poster ID # 242.** PER3 4-repeat Allele Is Associated With Faster Recovery of Neurobehavioral Performance Following Chronic Sleep Restriction.
**Mean (SE) number of Lapses**

**Genotype**

<table>
<thead>
<tr>
<th>Genotype</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>4/4</td>
<td>7</td>
</tr>
<tr>
<td>4/5</td>
<td>10</td>
</tr>
<tr>
<td>5/5</td>
<td>2*</td>
</tr>
</tbody>
</table>

*Not included in analyses*
Estimated means, controlling for age.
Estimated means, controlling for age.

*Trans x Group, p = .02
*Restrict x Group*, < .01

Group, p < .01

Estimated means, controlling for age.
Estimated means, controlling for age.
1. **AT-HOME HABITUAL SLEEP**  
   *(Actigraphy)*

2. **IN-LABORATORY OVERNIGHTS**  
   *(Actigraphy)*

3. **FULL-TIME IN-LABORATORY** *(PSG)*

**Sleep Period**

**Mean Hours (+SD)**

- **Extended**
- **Habitual**

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**Total Sleep Time**

**Mean Hours (+SD)**

- **Baseline**
- **Restriction**
- **Recovery**

* main effect group, p < .05