(Insufficient) Sleep and CNS Inflammation

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Disclosures

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"Astrocytes, Sleep and Neuroinflammation"

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"Neonatal Pain, Depression and Pain Susceptibility at Maturity in Rats"

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The presenter has no Conflicts of Interest to disclose.

Outline

1. *Significance*
2. State-of-the-Art Knowledge
3. Knowledge Gaps
4. Research Opportunities

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BMC Public Health

RESEARCH ARTICLE Open Access

Association between perceived insufficient sleep, frequent mental distress, obesity and chronic diseases among US adults, 2009 behavioral risk factor surveillance system

Yong Liu[1*†], Janet B Croft[1†], Anne G Wheaton[1], Geraldine S Perry[1], Daniel P Chapman[1], Tara W Strine[2], Lela R McKnight-Eily[1] and Letitia Presley-Cantrell[1]

- The Behavioral Risk Factor Surveillance System is a large, random-digital-dialed telephone survey conducted by the CDC.
- Sleep question added to four states in the 2006 survey, and expanded to more states for the 2008 survey.

  "During the past 30 days, for about how many days have you felt you did not get enough rest or sleep?"

- In 2009, there were 424,592 respondents and 375,653 were included in analyses.

Insufficient Sleep is Associated with Inflammatory Disease

Table 4 Odds ratios (OR) and 95% confidence intervals (CI) for the likelihoods of having chronic diseases associated with categories of insufficient sleep among adults, behavioral risk factor surveillance system (BRFSS), 2009

Number of days insufficient sleep in past 30 days	Unadjusted prevalence % (95% CI)	Model 1[1] Adjusted OR (95% CI)	Model 2[2] Adjusted OR (95% CI)	Model 3[3] Adjusted OR (95% CI)
Diabetes				
0	6.4 (6.1- 6.7)	1.00 (referent)	1.00 (referent)	1.00 (referent)
1-13	5.8 (5.5- 6.0)	0.96 (0.91-1.01)	0.95 (0.90-1.00)	0.93 (0.88-0.98)
14-29	8.0 (7.5- 8.5)	1.35 (1.26-1.45)	1.24 (1.16-1.34)[4]	1.25 (1.16-1.34)[4]
30	10.2 (9.6-10.7)	1.65 (1.54-1.76)	1.46 (1.36-1.56)[4]	1.48 (1.38-1.59)[4]
Coronary Heart Disease				
0	3.2 (2.9- 3.4)	1.00 (referent)	1.00 (referent)	1.00 (referent)
1-13	2.8 (2.6- 3.0)	0.96 (0.91-1.01)	0.95 (0.90-1.00)	0.95 (0.89-1.00)
14-29	4.5 (4.2- 4.8)	1.58 (1.47-1.70)	1.38 (1.28-1.49)[4]	1.54 (1.43-1.65)
30	6.6 (6.1- 7.1)	2.26 (2.09-2.45)	1.86 (1.71-2.02)[4]	2.18 (2.01-2.36)
Stroke				
0	1.4 (1.2- 1.5)	1.00 (referent)	1.00 (referent)	1.00 (referent)
1-13	1.2 (1.1- 1.3)	0.91 (0.84-0.98)	0.89 (0.82-0.97)	0.90 (0.83-0.98)
14-29	1.8 (1.6- 1.9)	1.31 (1.19-1.45)	1.11 (1.01-1.23)[5]	1.30 (1.18-1.44)
30	3.0 (2.7- 3.3)	2.11 (1.91-2.33)	1.68 (1.50-1.87)[4]	2.08 (1.88-2.30)
High Blood Pressure				
0	24.1(23.6-24.7)	1.00 (referent)	1.00 (referent)	1.00 (referent)
1-13	24.8 (24.3-25.3)	1.09 (1.05-1.13)	1.08 (1.04-1.12)	1.08 (1.04-1.12)
14-29	29.7 (28.9-30.5)	1.40 (1.34-1.47)	1.30 (1.23-1.36)[4]	1.31 (1.25-1.38)[4]
30	33.5 (32.5-34.5)	1.59 (1.51-1.68)	1.41 (1.34-1.49)[4]	1.46 (1.38-1.54)[4]
Asthma				
0	10.2 (9.8-10.6)	1.00 (referent)	1.00 (referent)	1.00 (referent)
1-13	12.5 (12.1-12.9)	1.24 (1.17-1.31)	1.23 (1.16-1.30)	1.23 (1.16-1.30)
14-29	17.1 (16.5-17.8)	1.76 (1.65-1.88)	1.63 (1.53-1.74)	1.70 (1.60-1.82)
30	19.7 (18.8-20.5)	2.06 (1.92-2.21)	1.82 (1.70-1.96)[4]	1.99 (1.85-2.13)
Arthritis				
0	16.4 (16.0-16.8)	1.00 (referent)	1.00 (referent)	1.00 (referent)
1-13	20.0 (19.6-20.4)	1.26 (1.22-1.30)	1.25 (1.21-1.29)	1.25 (1.20-1.29)
14-29	29.5 (28.8-30.3)	2.06 (1.97-2.15)	1.85 (1.76-1.93)	1.98 (1.90-2.08)
30	35.5 (34.5-36.5)	2.65 (2.51-2.78)	2.23 (2.12-2.35)[4]	2.52 (2.39-2.66)

[1]Model 1: adjusted odds ratios (OR) and 95% confidence interval (CI) were obtained from separate multivariate logistic models that included days of insufficient sleep and age, sex, race/ethnicity, and education as covariates.
[2]Model 2: includes the covariates in model 1 plus frequent mental distress (FMD).
[3]Model 3: includes the covariates in model 1 plus categorical body mass index (BMI).
[4]20-40% reduction in the effect due to the addition of a mediator.
[5] >60% reduction in the effect due to the addition of a mediator.

Odds Ratios (95% CI) for disease when number of days with insufficient sleep is 14-29 during the past 30 days.

Diabetes:	1.25 (1.16-1.34)
CHD:	1.54 (1.43-1.65)
Stroke:	1.30 (1.18-1.44)
HBP:	1.31 (1.25-1.38)
Asthma:	1.70 (1.60-1.82)
Arthritis:	1.98 (1.90-2.08)

OPEN ACCESS Freely available online

PLoS one

Association of Sleep Duration with Chronic Diseases in the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam Study

Anne von Ruesten[1]*, Cornelia Weikert[1], Ingo Fietze[2], Heiner Boeing[1]

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Abstract

Background: In view of the reduced number of hours devoted to sleep in modern western societies the question arises what effects might result from sleep duration on occurrence of chronic diseases.

Methods: Data from 23 620 middle-aged participants of the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam study, that were recruited between 1994–1998, were analyzed by using Cox proportional hazard regression to examine the association between self-reported sleep duration at baseline and incidence of chronic diseases, such as diabetes, myocardial infarction, stroke, and cancer.

Results: During a mean follow-up period of 7.8 years 841 incident cases of type 2 diabetes, 197 cases of myocardial infarction, 169 incident strokes, and 846 tumor cases were observed. Compared to persons sleeping 7-<8 h/day, participants with sleep duration of <6 h had a significantly increased risk of stroke (Hazard Ratio (HR) = 2.06, 95% confidence interval (CI): 1.18–3.59), cancer (HR = 1.43, 95% CI: 1.09–1.87), and overall chronic diseases (HR = 1.31, 95% CI: 1.10–1.55) in multivariable adjusted models. Self-reported daytime sleep at baseline was not associated with incident chronic diseases in the overall study sample. However, there had been an effect modification of daytime sleep by hypertension showing that daytime sleep was inversely related to chronic disease risk among non-hypertensive participants but directly related to chronic diseases among hypertensives.

Conclusion: Sleep duration of less than 6 h is a risky behavior for the development of chronic diseases, particularly stroke and cancer, and should be therefore addressed in public health campaigns.

Insufficient Sleep is Associated with Inflammatory Disease

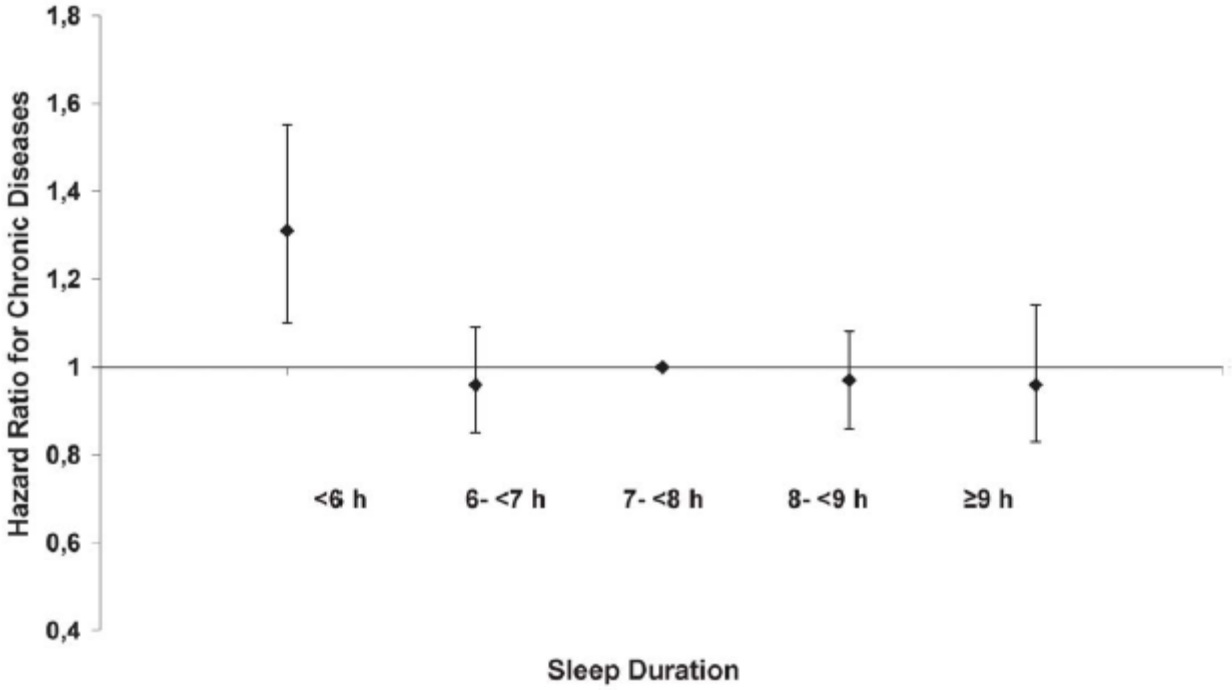


Figure 1. Association of sleep duration with overall chronic disease risk. Stratified by age and adjusted for sex, sleeping disorders, alcohol intake from beverages, smoking status, walking/cycling/sports, employment status, education, BMI, waist-to-hip ratio, prevalent hypertension at baseline, history of high blood lipid levels at baseline, consumption of caffeinated beverages, satisfaction with life, satisfaction with health, and intake of antidepressants.

Insufficient Sleep is Associated with Inflammatory Disease

Stroke (cases/person-years)	17/9 282
Crude rate per 1000 person-years	1.8
HR model 1[b]	2.32 (1.34–4.01)
HR multivariable-adjusted, model 2[c]	2.20 (1.27–3.82)
HR multivariable-adjusted, model 3[d]	2.12 (1.22–3.68)
HR multivariable-adjusted, model 4[e]	2.06 (1.18–3.59)

Myocardial infarction (cases/person-years)	18/9 282
Crude rate per 1000 person-years	1.9
HR model 1[b]	1.78 (1.07–2.97)
HR multivariable-adjusted, model 2[c]	1.54 (0.92–2.59)
HR multivariable-adjusted, model 3[d]	1.45 (0.87–2.44)
HR multivariable-adjusted, model 4[e]	1.44 (0.85–2.43)

Cancer (cases/person-years)[f]	66/9 282
Crude rate per 1000 person-years	7.1
HR model 1[b]	1.46 (1.12–1.91)
HR multivariable-adjusted, model 2[c]	1.43 (1.10–1.87)
HR multivariable-adjusted, model 3[d]	1.43 (1.09–1.87)
HR multivariable-adjusted, model 4[e]	1.43 (1.09–1.87)

Type 2 diabetes (cases/person-years)	62/9 282
Crude rate per 1000 person-years	6.7
HR model 1[b]	1.44 (1.10–1.89)
HR multivariable-adjusted, model 2[c]	1.36 (1.04–1.79)
HR multivariable-adjusted, model 3[d]	1.08 (0.82–1.42)
HR multivariable-adjusted, model 4[e]	1.06 (0.80–1.40)

Insufficient Sleep is Associated with Inflammatory Disease

Daytime Sleep, Hypertension, and Chronic Disease

Daytime Nap: Hypertensive

⇧ Overall Chronic Disease

⇧ Stroke

Daytime Nap: Non-Hypertensive

⇩ Overall Chronic Disease

⇩ Cancer

Insufficient Sleep is Associated with Inflammatory Disease

Ayas, N.T., White, D.P., Manson, J.E., Stampfer, M.J., Speizer, F.E., Malhotra, A., Hu, F.B., *2003*. **A prospective study of sleep duration and coronary heart disease in women**. Arch Intern. Med. 163**,** 205-209.

Cappuccio, F.P., Cooper, D., D'Elia, L., Strazzullo, P., Miller, M.A., *2011*. **Sleep duration predicts cardiovascular outcomes: a systematic review and meta-analysis of prospective studies**. Eur. Heart J. 32**,** 1484-1492.

Gangwisch, J.E., Heymsfield, S.B., Boden-Albala, B., Buijs, R.M., Kreier, F., Pickering, T.G., Rundle, A.G., Zammit, G.K., Malaspina, D., *2007*. **Sleep duration as a risk factor for diabetes incidence in a large U.S. sample**. Sleep 30**,** 1667-1673.

Kakizaki, M., Kuriyama, S., Sone, T., Ohmori-Matsuda, K., Hozawa, A., Nakaya, N., Fukudo, S., Tsuji, I., *2008*. **Sleep duration and the risk of breast cancer: the Ohsaki Cohort Study**. Br. J. Cancer 99**,** 1502-1505.

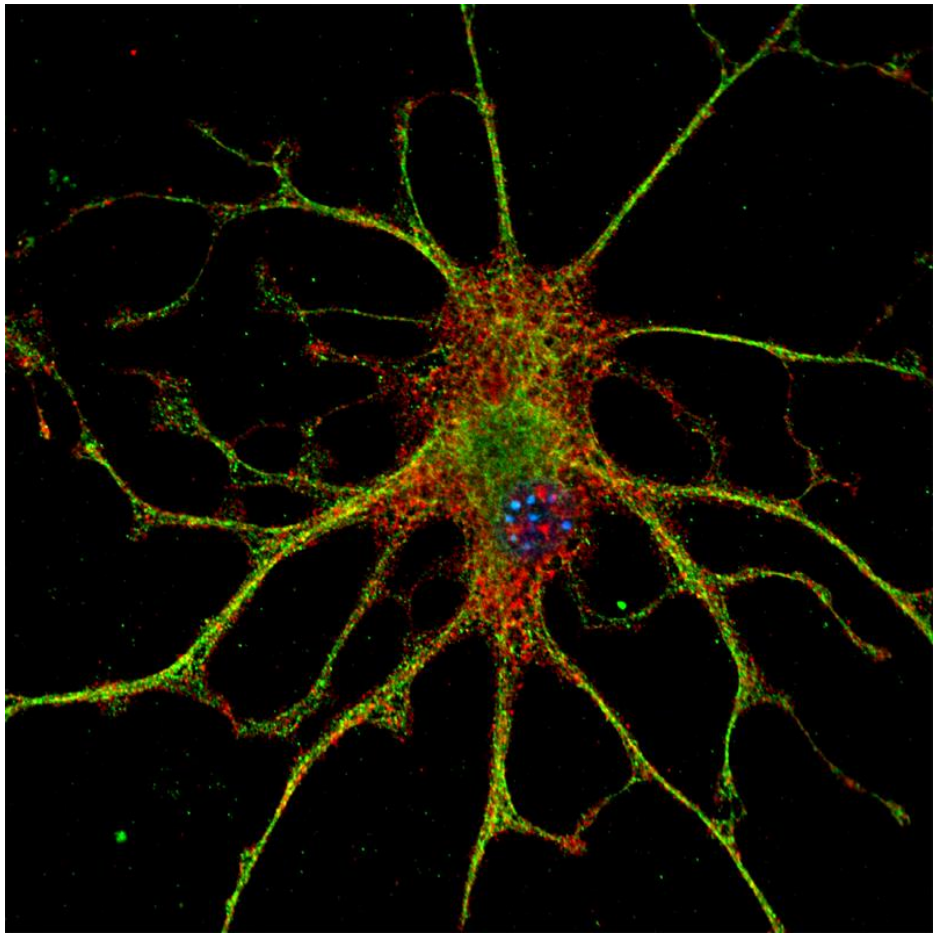
Mallon, L., Broman, J.E., Hetta, J., *2005*. **High incidence of diabetes in men with sleep complaints or short sleep duration: a 12-year follow-up study of a middle-aged population**. Diabetes Care 28**,** 2762-2767.

Meisinger, C., Heier, M., Lowel, H., Schneider, A., Doring, A., *2007*. **Sleep duration and sleep complaints and risk of myocardial infarction in middle-aged men and women from the general population: the MONICA/KORA Augsburg cohort study**. Sleep 30**,** 1121-1127.

Outline

1. *Significance*
2. *State-of-the-Art Knowledge*
3. Knowledge Gaps
4. Research Opportunities

Inflammatory “Machinery” is Present in Brain



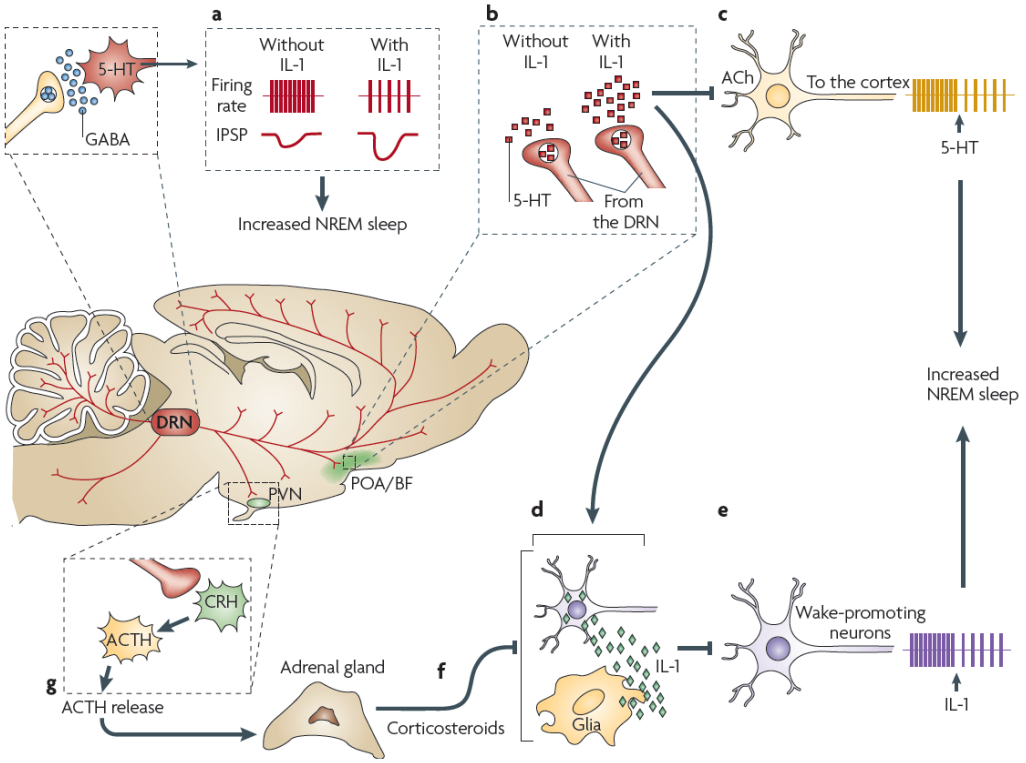
blue = DAPI (nucleoli); green = βIII tubulin (axons / filaments); red = IL-1 type 1 receptors

Some Mechanisms by which Inflammation Alters Sleep are Known

SLEEP

How (and why) the immune system makes us sleep

*Luca Imeri**‡ *and Mark R. Opp*‡§||



Nat. Rev. Neurosci. 10: 199-210, 2009.

Sleep Disruption Alters Gene Expression of Inflammatory Mediators

Neuroscience Letters 580 (2014) 27–31

Contents lists available at ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet

Chronic sleep restriction elevates brain interleukin-1 beta and tumor necrosis factor-alpha and attenuates brain-derived neurotrophic factor expression

Mark R. Zielinski[a,*], Youngsoo Kim[b], Svetlana A. Karpova[a], Robert W. McCarley[b], Robert E. Strecker[b], Dmitry Gerashchenko[a]

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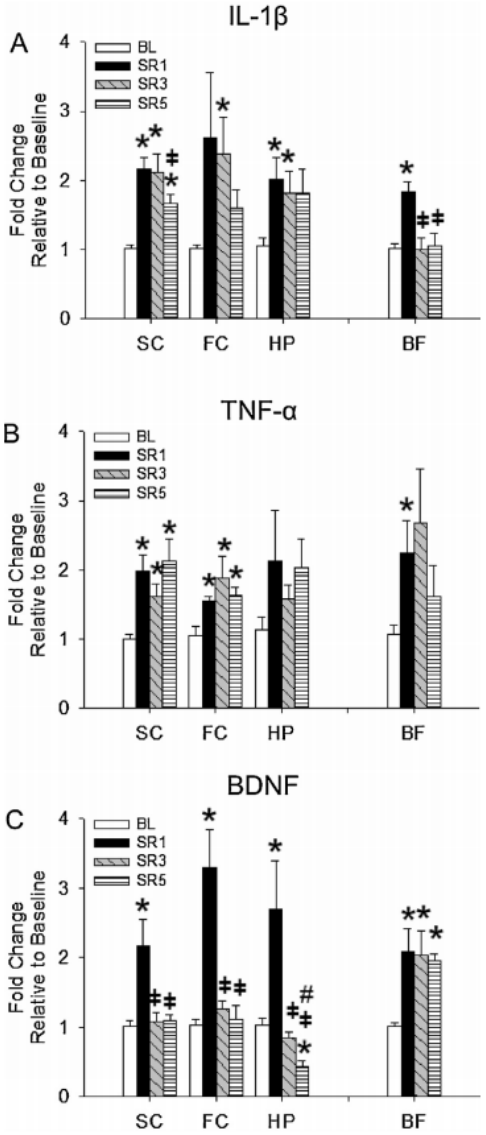
[b] Department of Psychiatry, Harvard Medical School and Veterans Affairs Boston Healthcare System, Brockton, MA 02301, USA

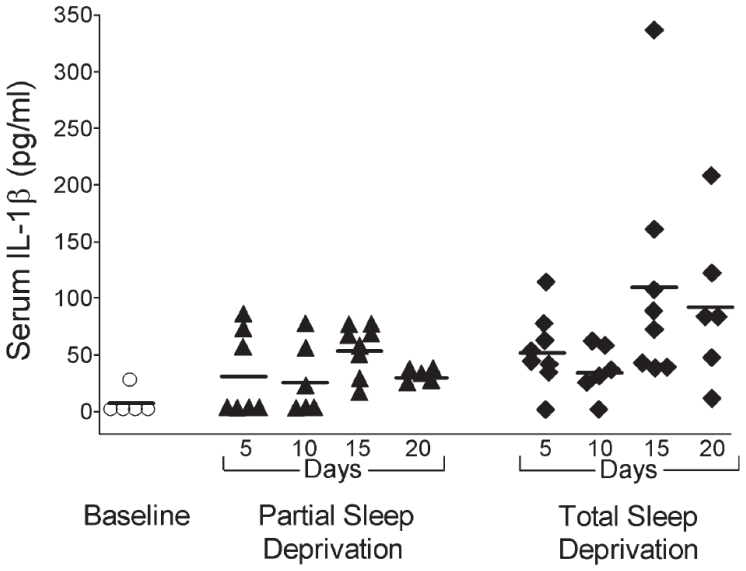


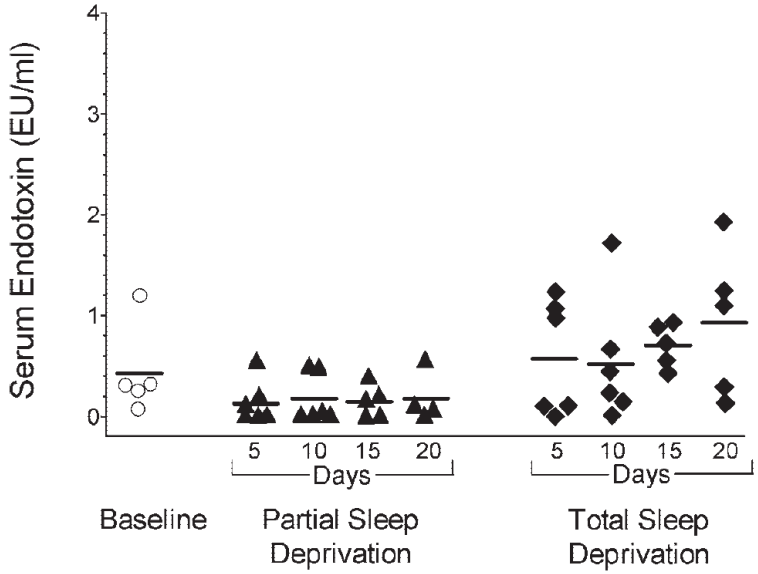
Sleep Disruption Alters Protein Expression of Inflammatory Mediators

Am J Physiol Regul Integr Comp Physiol 289: R1054–R1063, 2005.
First published June 9, 2005; doi:10.1152/ajpregu.00021.2005.

Clinical assessment of blood leukocytes, serum cytokines, and serum immunoglobulins as responses to sleep deprivation in laboratory rats

Carol A. Everson
Department of Neurology, Medical College of Wisconsin, Milwaukee, Wisconsin





Sleep Disruption Alters Protein Expression of Inflammatory Mediators

SLEEP RESTRICTION, INFLAMMATION AND PAIN

Elevated Inflammatory Markers in Response to Prolonged Sleep Restriction Are Associated With Increased Pain Experience in Healthy Volunteers

Monika Haack, PhD; Elsa Sanchez, BA; Janet M. Mullington PhD

Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, MA

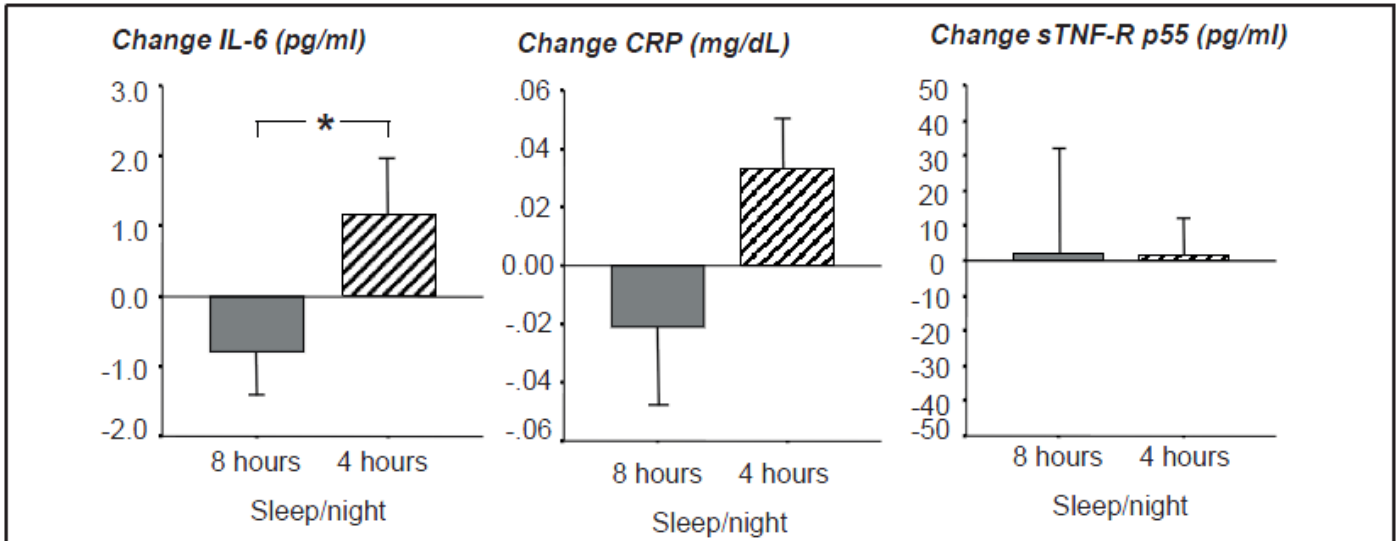


Figure 2—Change of plasma IL-6, serum CRP, and plasma sTNF-R p55 levels from baseline to the 11th day of sleeping either 8 h/night (grey bar, N=8) or 4 h/night (hatched bar, N=10 for IL-6, N=9 for sTNF-R p55). IL-6, CRP, and sTNF-R p55 were measured every 4 h and averaged across a 24-h period. Original values are presented, and statistics were based on log-transformed values. Asterisk indicates significant difference between sleep conditions.

SLEEP, Vol. 30, No. 9, 2007

ORIGINAL INVESTIGATION

Sleep Deprivation and Activation of Morning Levels of Cellular and Genomic Markers of Inflammation

Michael R. Irwin, MD; Minge Wang, MSN; Capella O. Campomayor, MS; Alicia Collado-Hidalgo, PhD; Steve Cole, PhD

Background: Inflammation is associated with increased risk of cardiovascular disorders, arthritis, diabetes mellitus, and mortality. The effects of sleep loss on the cellular and genomic mechanisms that contribute to inflammatory cytokine activity are not known.

Methods: In 30 healthy adults, monocyte intracellular proinflammatory cytokine production was repeatedly assessed during the day across 3 baseline periods and after partial sleep deprivation (awake from 11 PM to 3 AM). We analyzed the impact of sleep loss on transcription of proinflammatory cytokine genes and used DNA microarray analyses to characterize candidate transcription-control pathways that might mediate the effects of sleep loss on leukocyte gene expression.

Results: In the morning after a night of sleep loss, monocyte production of interleukin 6 and tumor necrosis factor α was significantly greater compared with morning levels following uninterrupted sleep. In addition, sleep loss induced a more than 3-fold increase in transcription of interleukin 6 messenger RNA and a 2-fold increase in tumor necrosis factor α messenger RNA. Bioinformatics analyses suggested that the inflammatory response was mediated by the nuclear factor κB inflammatory signaling system as well as through classic hormone and growth factor response pathways.

Conclusions: Sleep loss induces a functional alteration of the monocyte proinflammatory cytokine response. A modest amount of sleep loss also alters molecular processes that drive cellular immune activation and induce inflammatory cytokines; mapping the dynamics of sleep loss on molecular signaling pathways has implications for understanding the role of sleep in altering immune cell physiologic characteristics. Interventions that target sleep might constitute new strategies to constrain inflammation with effects on inflammatory disease risk.

Arch Intern Med. 2006;166:1756-1762

Sleep Deprivation and Activation of Morning Levels of Cellular and Genomic Markers of Inflammation

Michael R. Irwin, MD; Minge Wang, MSN; Capella O. Campomayor, MS; Alicia Collado-Hidalgo, PhD; Steve Cole, PhD

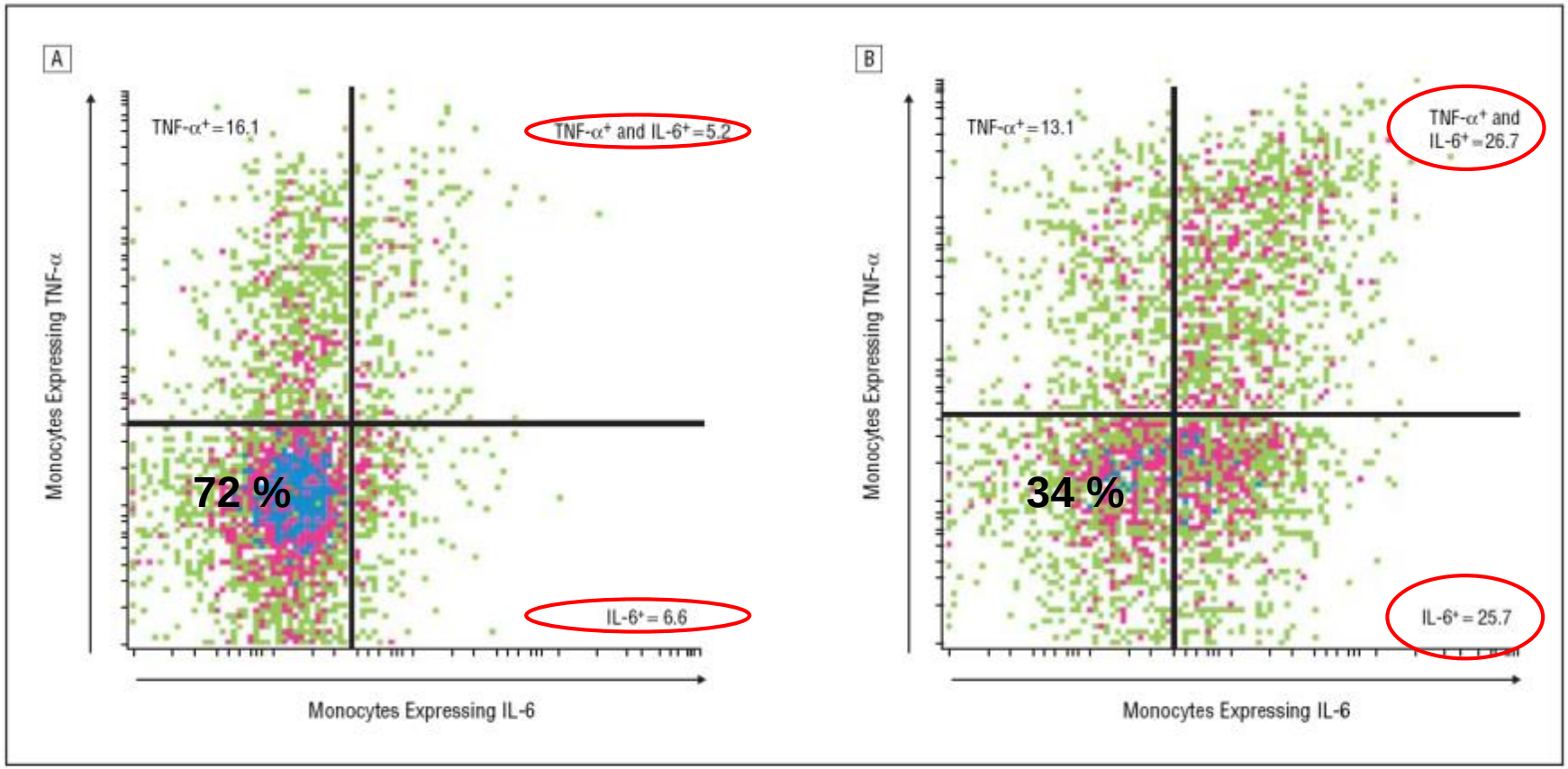
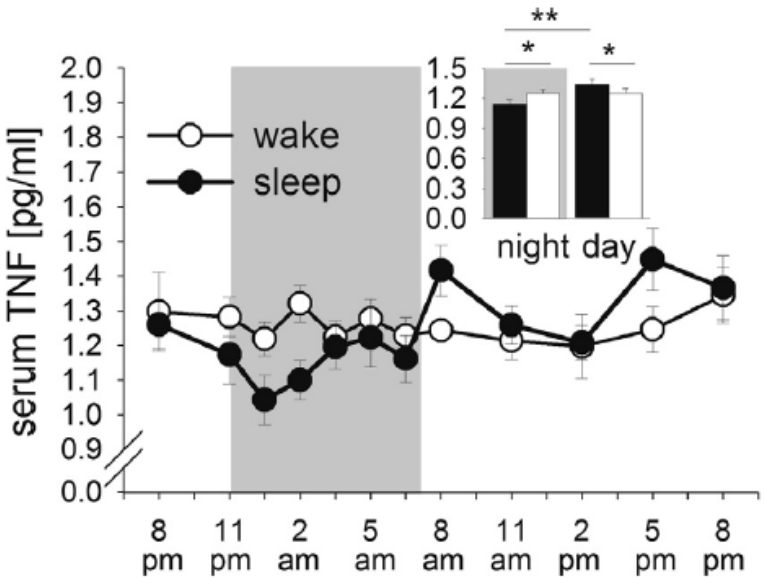


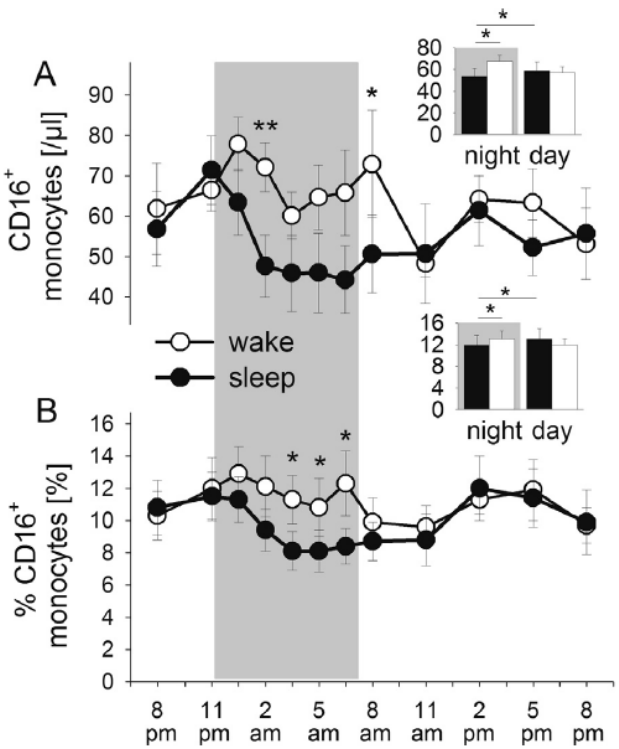
Figure 2. Representative expression of interleukin (IL) 6 and tumor necrosis factor (TNF) α in lipopolysaccharide-stimulated CD14+ cells from a participant (A) at baseline and (B) at partial sleep deprivation (PSD). Numbers indicate the percentages of the fraction of CD14+ cells that are positive for TNF-α alone (upper left), TNF-α and IL-6 (upper right), and IL-6 alone (lower right). In the baseline condition, 72.1% of the CD14+ cells are negative for both IL-6 and TNF-α whereas only 34.5% of the CD14+ cells are negative for both IL-6 and TNF-α in the PSD condition.

Sleep Disruption Alters Protein Expression of Inflammatory Mediators

Differential acute effects of sleep on spontaneous and stimulated production of tumor necrosis factor in men

Stoyan Dimitrov [a,*], Luciana Besedovsky [a], Jan Born [a,b,c,d], Tanja Lange [e,f]





Brain, Behavior, and Immunity 47 (2015) 201–210

The Journal of Clinical Endocrinology & Metabolism Vol. 82, No. 5 1313-1316

Clinical Studies

Elevation of Plasma Cytokines in Disorders of Excessive Daytime Sleepiness: Role of Sleep Disturbance and Obesity

Alexandros N. Vgontzas, Dimitris A. Papanicolaou, Edward O. Bixler, Anthony Kales, Kathy Tyson and George P. Chrousos

Sleep Research and Treatment Center, Department of Psychiatry, Pennsylvania State University (A.N.V., E.O.B., A.K., K.T.), Hershey, Pennsylvania 17033; the Developmental Endocrinology Branch, National Institute of Child Health and Human Development, National Institutes of Health (D.A.P., G.P.C.), Bethesda, Maryland 20892

- Plasma concentrations of TNF-α, IL-1β and IL-6 were determined from *narcoleptics*, *OSA patients* and *idiopathic hypersomniacs*.
- Plasma TNF-α is elevated in narcoleptics, whereas IL-6 is elevated in narcoleptic and sleep apnea patients.
- Nighttime sleep disturbance is associated with plasma TNF-α, whereas plasma IL-6 correlates with BMI.

The Journal of Clinical Endocrinology & Metabolism Vol. 89(9):4409-4413

Doi: 10.1210/jc.2003-031929

Marked Decrease in Sleepiness in Patients with Sleep Apnea by Etanercept, a Tumor Necrosis Factor-α Antagonist

A. N. Vgontzas, E. Zoumakis, H. –M. Lin, E. O. Bixler, G. Trakada, and G. P. Chrousos

Sleep Research and Treatment Center, Department of Psychiatry, (A.N.V., E.O.B., G.T.), and Health Evaluation Sciences (H. –M. L), Pennsylvania State University College of Medicine, Hershey, Pennsylvania 17033; and Pediatric and Reproductive Endocrinology Branch, National Institutes of Health (E.Z., G.P.C.), Bethesda, Maryland 20892

- The effect of antagonizing peripheral TNFα on sleep and plasma cytokines and hormones of obese male OSA patients was determined.
- Etanercept (Enbrel®) or placebo was administered to OSA patients.
- Excessive daytime sleepiness (assessed by MSLT) and apneas / hypopneas per hour are reduced by etanercept.
- Plasma IL-6 concentrations are reduced by etanercept.

Outline

1. Significance

2. State-of-the-Art Knowledge

3. Knowledge Gaps

4. Research Opportunities

Knowledge Gaps

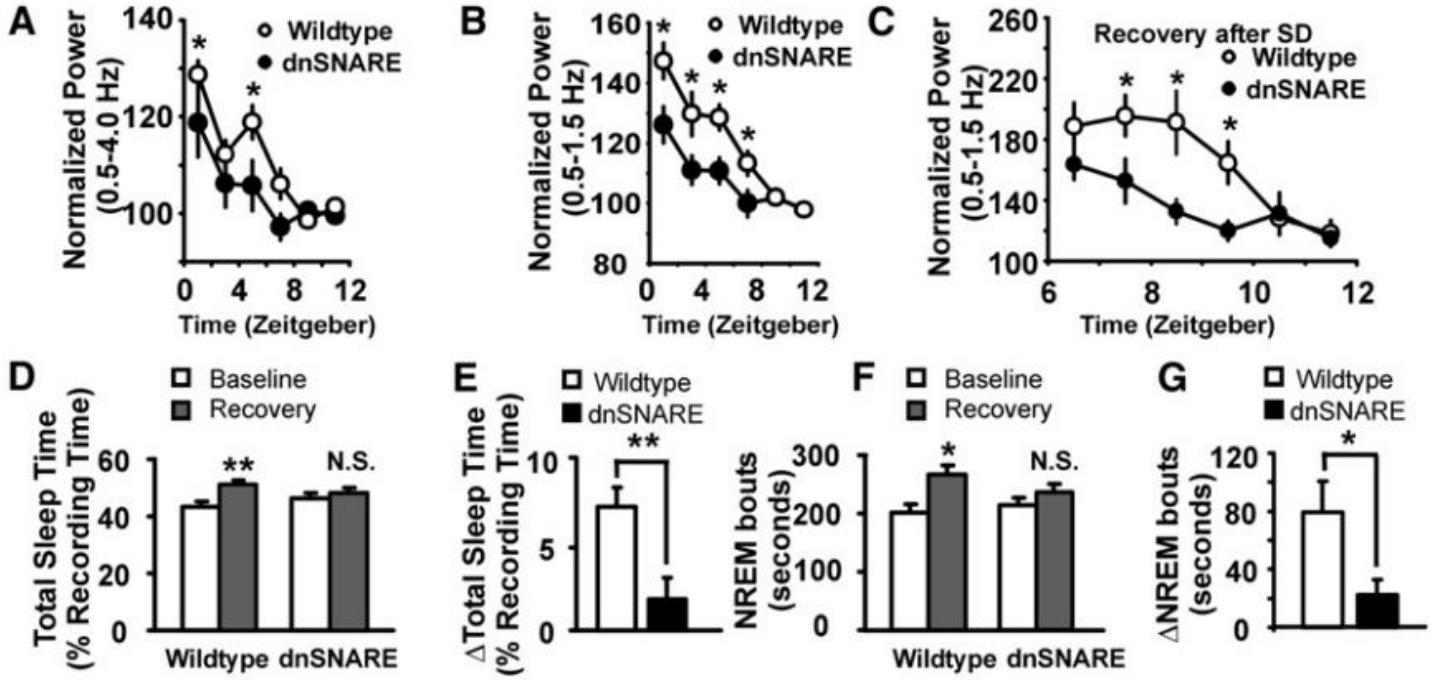
To what extent do biomarkers in "the periphery" reflect responses in the brain?

What are the contributions of non-neuronal cells to inflammatory responses to insufficient sleep?

Glia are Involved in Sleep Regulation

Astrocytic Modulation of Sleep Homeostasis and Cognitive Consequences of Sleep Loss

Michael M. Halassa,[1,3] Cedrick Florian,[2] Tommaso Fellin,[1,4] James R. Munoz,[1] So-Young Lee,[1,3] Ted Abel,[2] Philip G. Haydon,[1,3,5,*] and Marcos G. Frank[1,5]



Neuron *61*, 213–219, January 29, 2009

Outline

1. *Significance*
2. *State-of-the-Art Knowledge*
3. *Knowledge Gaps*
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Research Opportunities

FUNCTION:

What are the functional consequences of interactions among insufficient sleep, inflammation, and aging?

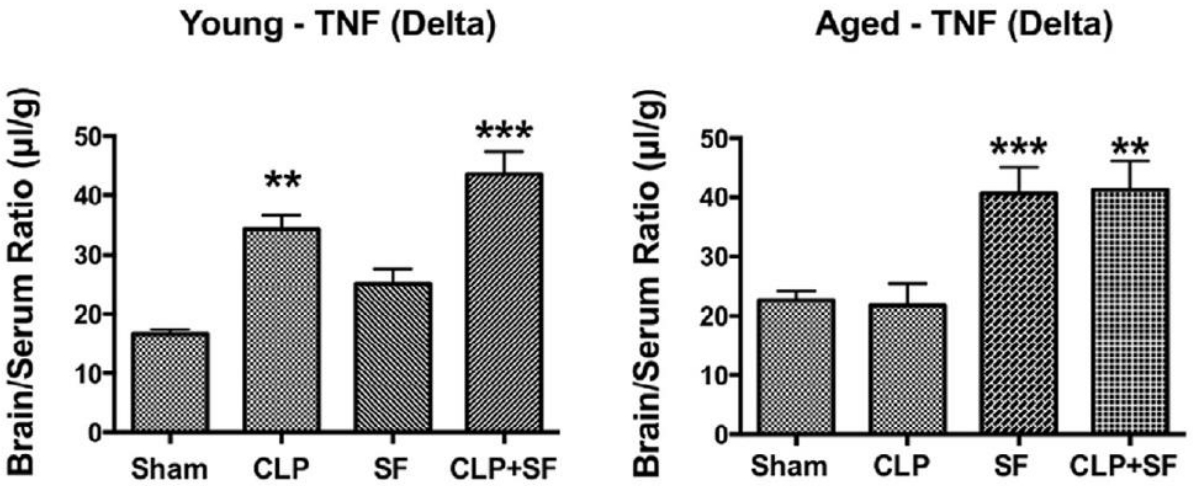
Contents lists available at ScienceDirect

Brain, Behavior, and Immunity

journal homepage: www.elsevier.com/locate/ybrbi

Sleep fragmentation and sepsis differentially impact blood–brain barrier integrity and transport of tumor necrosis factor-α in aging

Mark R. Opp [a], Amrita George [a], Kristyn M. Ringgold [a], Kim M. Hansen [b,c], Kristin M. Bullock [c], William A. Banks [b,c,*]



Research Opportunities

FUNCTION:

What are the functional consequences of interactions among insufficient sleep, inflammation, and aging?

MECHANISMS:

What cell types, and in which brain regions, transduce “sleep disruption signals” into inflammatory responses?

Research Opportunities

FUNCTION:
What are the functional consequences of interactions among insufficient sleep, inflammation, and aging?

MECHANISMS:
What cell types, and in which brain regions, transduce "sleep" signals into inflammatory responses?

What intracellular mechanisms (signaling cascades) are altered by sleep disruption to induce inflammation?

Summary

Many epidemiologic studies and meta-analyses reveal that insufficient sleep is associated with chronic inflammatory disease.

Experimental studies using human or animal subjects demonstrate that inflammatory gene and protein expression is altered by acute sleep loss or sleep disruption.

Recent studies suggest non-neuronal cell types play a critical role in the inflammatory responses to sleep loss.

Many fundamental questions concerning links between insufficient sleep and chronic inflammatory disease remain unanswered.