Circadian Rhythms: Effects on Health

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Disclosures

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• NIH (NHLBI, NIA)
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• Harmony
• Apnimed

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Other
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American Board of Internal Medicine Sleep Medicine Examination and Policy Committee
As the world turns...there are prominent dynamic changes in our biology.
Sleep/Wake Cycle
Circadian and Homeostatic Process

Circadian Rhythms and Sleep

Daily Physiologic and Behavioral Patterns

**Midnight (24:00)**
- Bowel movements suppressed

**22:30**
- Melatonin secretion starts

**21:00**
- Highest body temperature

**19:00**
- Highest BP

**18:00**
- Greatest cardiovascular efficiency and muscle strength

**17:00**
- Fastest reaction time

**15:30**
- Best coordination

**14:30**
- Noon (12:00)

**02:00**
- Deepest sleep

**04:30**
- Lowest body temperature

**06:00**
- Sharpest rise in BP

**06:45**
- Melatonin secretion stops

**07:30**
- Prothrombotic factors

**08:30**
- Highest testosterone secretion

**09:00**
- High alertness

**10:00**
- BP, blood pressure.

Circadian Rhythms and Sleep Regulation of Physiological Cycles

- Subjective Alertness, Deviation From Mean
- Memory, Deviation From Mean
- Core Body Temperature
- Mood, Relative Change
- Melatonin, pmol/L
- Median Systolic BP, mm Hg
- Insulin, µIU/mL
- Serum Leptin, mg/L

References:
Disease symptoms with day-night rhythms

Cardiovascular system

Myocardial Infarction
(incidence peaks at ~9AM)

Pulmonary & immune system

Asthma Symptoms
(peak at ~4AM)

Central nervous system activity

Temporal lobe epilepsy
(incidence peaks at ~5PM)


Redrawn from each reference noted on slide
The Nobel Prize in Physiology/Medicine 2017 was awarded jointly to Jeffrey C. Hall, Michael Rosbash and Michael W. Young

A Remarkable Year for Clocks

Nineteenth-century philosophers proposed that God was a clockmaker who created the world and then let it run.

In 1998, a volley of rapid-fire discoveries revealed the stunning universality of the clock workings: Across the tree of life, from bacteria to humans, clocks use oscillating proteins in feedback loops to keep time.
Genetic Components of Mammalian Clock Systems

BMAL1, brain and muscle ARNT-like 1; CK1e, casein kinase 1 epsilon; CLOCK, circadian locomotor output cycles kaput; CRY, cryptochrome; E-box, consensus DNA sequence to which BMAL-CLOCK heterodimers bind and regulate transcription; PER1, period 1; PER2, period 2; PER3, period 3.

Determinants of Circadian Rhythms and Sleep/Wake Expression

Information about the light environment

Peripheral clocks

Melanopsin containing retinal ganglion cell-blue light

Social Work
Food
Activity

Temperature

Melatonin

Pancreas
Liver
Adipose
Heart
GI tract
Muscle
WBCs
Kidney
Breast

GI, gastrointestinal; PG, pineal gland; RHT, retinohypothalamic tract; SCN, suprachiasmatic nucleus; WBC, white blood cell.

Circadian Dysfunction: Implications for Health and Disease Beyond Sleep and Wake Functions

CRSD, circadian rhythm sleep disorder.
Complex Interactions of Sleep and Circadian Rhythms: Role in Health and Disease
Timing of Light Exposure, Meals, Activity and Sleep: Key for health

Malaysia to Western Australia (Jun. 2018)

Videos produced by the ISS Crew Earth Observations Facility and Earth Science & Remote Sensing Unit NASA Johnson Space Center

eol.jsc.nasa.gov/BeyondThePhotography/CrewEarthObservationsVideos/ Gateway to Astronaut Photography (eol.jsc.nasa.gov)

For replication and crediting information, please see our guidelines on our main video page.

Circadian Health and Light: A Report on the National Heart, Lung, and Blood Institute’s Workshop

Ivy C. Mason,++ Mohamed Boubekri,† Mariana G. Figueiro,‡ Brant P. Hasler,§ Samer Hattar,|| Steven M. Hill,¶ Randy J. Nelson,* Katherine M. Sharkey,∗ Kenneth P. Wright Jr.,+++ Windy A. Boyd,** Marishka K. Brown,§§ Aaron D. Laposky,§§ Michael J. Twery,§§ and Phyllis C. Zee,**
Timing of Mean Light Exposure and BMI

Every hour later of MLiT above 500 lux = 1.28 BMI

Reid, Santostasi, et al, PLOS One 2014
N=59; 31.7 ± 11.8 years; average BMI: 24.1 ± 4.2

Baron KG and Zee PC, Obesity, 2011
It’s Not Only How Much You Sleep, BUT When

MIDPOINT
### Sleep and Timing: Risk for Obesity, Diabetes

(N=13,429/16,415)

<table>
<thead>
<tr>
<th></th>
<th>BMI (kg/m²)</th>
<th>Log of Fasting Glucose</th>
<th>Log of HOMA - Insulin Resistance</th>
<th>2-hour glucose (mg/dl)</th>
<th>HbA1c</th>
</tr>
</thead>
</table>
| **Weekly Bedtime**<sup>a</sup> (per clock hour) | -0.0895 (0.046) | **Diabetes<sup>c</sup>: 0.0266 (0.009)**<sup>**</sup>  
No diabetes: 0.0010 (0.001) | 0.0128 (0.007) | -0.4410 (0.218)<sup>*</sup> | **Diabetes**: 0.0691 (0.0363)  
No diabetes: -0.0066 (0.0036) |
| **Weekly Wake time**<sup>a</sup> (per clock hour) | -0.0008 (0.046) | 0.0026 (0.001)<sup>*</sup> | 0.0133 (0.007) | -0.1250 (0.212) | 0.0032 (0.005) |
| **Weekly mid sleep point**<sup>b</sup> (per clock hour) | -0.0664 (0.041) | **Diabetes<sup>c</sup>: 0.0232 (0.009)**<sup>∗</sup>  
No diabetes: 0.0012 (0.001) | 0.0145 (0.006)<sup>∗</sup> | -0.3283 (0.235) | 0.0008 (0.005) |
| **Chronotype**<sup>b</sup> (per clock hour) | -0.0120 (0.035) | 0.0017 (0.001) | 0.0118 (0.005)<sup>∗</sup> | -0.1740 (0.186) | 0.0008 (0.004) |

<sup>a</sup> Adjusted for age, gender, ethnic subgroup, study site, income, education, household size, years in US (<10 vs ≥10 y), marital status, sleep duration, AHI category (<15 vs ≥15), diabetes, employment/shift work status.

<sup>b</sup> Adjusted for age, gender, ethnic subgroup, study site, income, education, household size, years in US (<10 vs ≥10 y), marital status, AHI category (<15 vs ≥15), diabetes, employment/shift work status.

<sup>c</sup> The effect by diabetes status based on the model with interaction term.

***: P<0.001, **: P<0.01, *: P<0.05

Knutson K et al, SLEEP, 2017
Objectively measured short sleep duration and later sleep midpoint in pregnancy are associated with a higher risk of gestational diabetes

Francesca L. Facco, MD, MSCI; William A. Grobman, MD, MBA; Kathryn J. Reid, PhD; Corette B. Parker, DrPH; Shannon M. Hunter, MS; Robert M. Silver, MD; Robert C. Basner, MD; George R. Saade, MD; Grace W. Pien, MD, MSCE; Shalini Manchanda, MD; Judette M. Louis, MD, MPH; Chia-Ling Nhan-Chang, MD; Judith H. Chung, MD, PhD; Deborah A. Wing, MD, MBA; Hyagriv N. Simhan, MD, MS; David M. Haas, MD, MS; Jay Iams, MD; Samuel Parry, MD; Phyllis C. Zee, MD, PhD

Total n=782

<table>
<thead>
<tr>
<th>Sleep characteristic</th>
<th>Hypertensive disease of pregnancy</th>
<th>Gestational diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>Crude OR (95% CI)</td>
</tr>
<tr>
<td>Sleep duration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;7 h</td>
<td>27/218 (12.4)</td>
<td>1.10 (0.68—1.78)</td>
</tr>
<tr>
<td>≥7 h</td>
<td>64/564 (11.3)</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P value = .6850</td>
</tr>
<tr>
<td>Sleep midpoint</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;5 AM</td>
<td>17/148 (11.5)</td>
<td>0.98 (0.56—1.72)</td>
</tr>
<tr>
<td>≤5 AM</td>
<td>74/634 (11.7)</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P value = .9497</td>
</tr>
</tbody>
</table>

Facco et al, AJOG, 2018
Environment, Behavior, Physiology, Genes, Molecules...Circadian Health

Misalignment of environmental/behavioral cycles relative to the endogenous circadian system

Behavior misaligned with peripheral clocks

Misalignment within the endogenous circadian system

Peripheral clocks misaligned with SCN

Desynchrony among organs

Sleep and Circadian Dysfunction
Neurodegeneration
Neurodegeneration and Altered Circadian Rhythms

Alzheimer’s
Parkinson’s
Huntington’s
Traumatic Brain Injury
Chronic Traumatic Encephalopathy

Delayed/damped rhythms
activity, sleep
temperature
melatonin, cortisol
circadian/clock genes

Neurodegeneration
Circadian/Sleep
Disease severity and Progression?

References
Schlosser Covell et al. 2012
Aziz et al. 2009
Boone et al. 2012
Mathias, Alvaro 2012

Courtesy: Allada
Circadian and Sleep Dysfunction and Risk for Cognitive Impairment and Alzheimer’s Disease

Sleep-Wake Fragmentation

Actogram:

No Dementia

7-14 days actigraphy

Ju J et al, Brain, 2017
Sleep Disturbances as Risk Factor for Dementia

- Insomnia predicts AD (not all cause dementia)
- SDB predicts AD - all dementias
- Sleep fragmentation predicts AD
- Different sleep disturbances may play distinct roles in dementia pathology


N=25,847; Mean follow up: 9.49 y
Evidence for sleep-wake and circadian dysfunction in Non-Motor Manifestations of Parkinson’s Disease

Nocturnal sleep disturbances in PD
60% of patients versus 30% of healthy controls \(^1\)

Excessive daytime somnolence (EDS)
16% of patients versus 1% of healthy controls \(^1\)

EDS has been associated with three-fold increase in the risk of developing PD \(^2\)

\(^1\)Tandberg et al. 1998; \(^2\)Abbott et al. 2005
Neurodegenerative Disorders
Parkinson’s Disease

Timed Light Therapy Improves Daytime Sleepiness Associated with Parkinson’s Disease

- Dim Red: 300 lux (n=15)
- 0900-1100; 1700-1900 (2 weeks)

<table>
<thead>
<tr>
<th>Change</th>
<th>Bright Light</th>
<th>Dim Red Light</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>EES score</td>
<td>4.75 ± 1.84</td>
<td>1.79 ± 2.89</td>
<td>0.005</td>
</tr>
</tbody>
</table>

- increase sleep quality (PSQI, PDSS)
- decreased sleep fragmentation
- decreased sleep latency
- increased daily physical activity level (actigraphy)
- improved total UPDRS score (motor and activity of daily living)

The “Brainwashing” Function of Sleep

Neurodegenerative Disease
Alzheimer’s

Neurotoxins
Beta amyloid
Tau

Disrupted Sleep

References
Schlosser Covell et al. 2012
Aziz et al. 2009
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Beta amyloid
Tau

References
Schlosser Covell et al. 2012
Aziz et al. 2009
Boone et al. 2012
Mathias, Alvaro 2012

Xie et al 2013 Science
Focus has been too much light at night…. *BUT the most prominent finding is too little light during the day!* Can increasing light during the day improve clinical outcomes?

Clinical Areas Receptive to Circadian Medicine

- Cardio-metabolic
  - Children
  - Adults
  - Pregnancy
- Cancer
- Psychiatric (bipolar)
- Pharmacotherapeutics
- Critical Care
- Neurodegenerative Disorders

- Circadian Rhythm Sleep Disorders
- Shift Workers

- Epilepsy
  - Autism
  & Cognitive Disorders

- Dravet, SUDEP

- Alzheimer's
The Future of Circadian and Sleep Medicine: Developing Clinically Practical and Relevant Biomarkers

WORKSHOP REPORT

Developing Biomarker Arrays Predicting Sleep and Circadian-Coupled Risks to Health

Janet M. Mullington, PhD; Sabra M. Abbott, MD, PhD; Judith E. Carroll, PhD; Christopher J. Davis, MS, PhD; Derk-Jan Dijk, PhD; David F. Dinges, PhD; Philip R. Gehrman, PhD; Geoffrey S. Ginsburg, MD, PhD; David Gozal, MD, MBA; Monika Haack, PhD; Diane C. Lim, MD; Madalina Macrea, MD, MPH, PhD; Allan I. Pack, MBChB, PhD, FRCP; David T. Plante, MD; Jennifer A. Teske, PhD; Phyllis C. Zee, MD, PhD

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Clinic Circadian Biomarkers

Actigraphy/Logs/ MCTQ

Sleep propensity

5 am- noon

Salivary Melatonin

Pupillometry

Clinical and Genetic Database
Chronodiagnosics: Biological Timing in Clinic and Medicine

Chronodiagnosics using Time Stamps:
Assessing Temporal Organization in a Sample to Reveal Disease Pathogenesis or Drug Toxicity

Temporal Profiling

Morning

Evening

Gene Expression

Temporal Genome Expression Signature

Computational quantitation of temporal organization from a single sample

Mechanistic understanding of disease pathogenesis or toxin/drug action from network analysis

Diagnostic/Therapeutic/Countermassure Development

Applied to any “-omics”, e.g., metabolomics, to human samples, e.g., blood
An Interdisciplinary Collaboration

• **Math** ........ Rosemary Braun * Bill Kath * Marta Iwanaszko

• **Biology** ... Ravi Allada * Ela Kula-Eversole

• **Clinical** .... Phyllis Zee * Sabra Abbott * Kathryn Reid

Universal method for robust detection of circadian state from gene expression

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Edited by Joseph S. Takahashi, Howard Hughes Medical Institute and University of Texas Southwestern Medical Center, Dallas, TX, and approved July 23, 2018 (received for review January 8, 2018)

Circadian clocks play a key role in regulating a vast array of biological processes, with significant implications for human health. and research settings (melatonin, cortisol, core body temperature, actigraphy, and even core clock gene expression) (21), they

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**Center for Circadian and Sleep Medicine**
TimeSignature Predictive Genes

Expression levels of ~40 genes is sufficient to tell time

Braun, R, Allada, Zee et al, PNAS, 2018
Accuracy vs. draw spacing

Two-draw TimeStamp accuracy vs. draw interval

Elapsed time between first and second draws (hrs)
Circadian-Time Based Targeting of Drugs

Tissue-specific Rhythmically of Expressed Human Genes

Rhythmically Expressed Drug Targets - Including for Cancer Drugs

Sleep and Circadian Disturbance: Broad Implications for Disease Expression and Treatments

Modified from Sulli G et al, TIPS, 2018
Center for Sleep and Circadian Medicine

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2P01AG011412-18 ; R01 HL140580-01;
R01 HL105549; R01 HL098297; R01 HL092140;
U10HD063036 ; UM1HL112856; U01HL111478;
*K23 HL091508 ; * K23NS072283 ; *5K12HD05588 ;
NCRR-00048 ; T32 HL07909; DARPA ; Philips