OSU Sleep Symposium 2019

Circadian Rhythms: Effects on Health

Phyllis C. Zee, MD, PhD

Benjamin and Virginia T. Boshes Professor in Neurology

Chief Division of Sleep Medicine

Director Center for Circadian and Sleep Medicine

Northwestern University Feinberg School of Medicine

CENTER FOR CIRCADIAN & SLEEP MEDICINE

NORTHWESTERN UNIVERSITY FEINBERG SCHOOL OF MEDICINE

Disclosures

Current research funding (Northwestern University)

- NIH (NHLBI, NIA)
- DARPA
- Jazz
- Alzheimer's Association
- Harmony
- Apnimed

Scientific Advisory Board

- Merck, Philips, Eisai, Jazz
- Weight Watchers, Equinox

NIH/NHLBI Council Member

Other

Stock ownership: Teva

American Board of Internal Medicine Sleep Medicine Examination and Policy Committee

As the world turns…there are prominent dynamic changes in our biology

WAKE-SLEEP

CIRCADIAN

RHYTHMS

WAKE

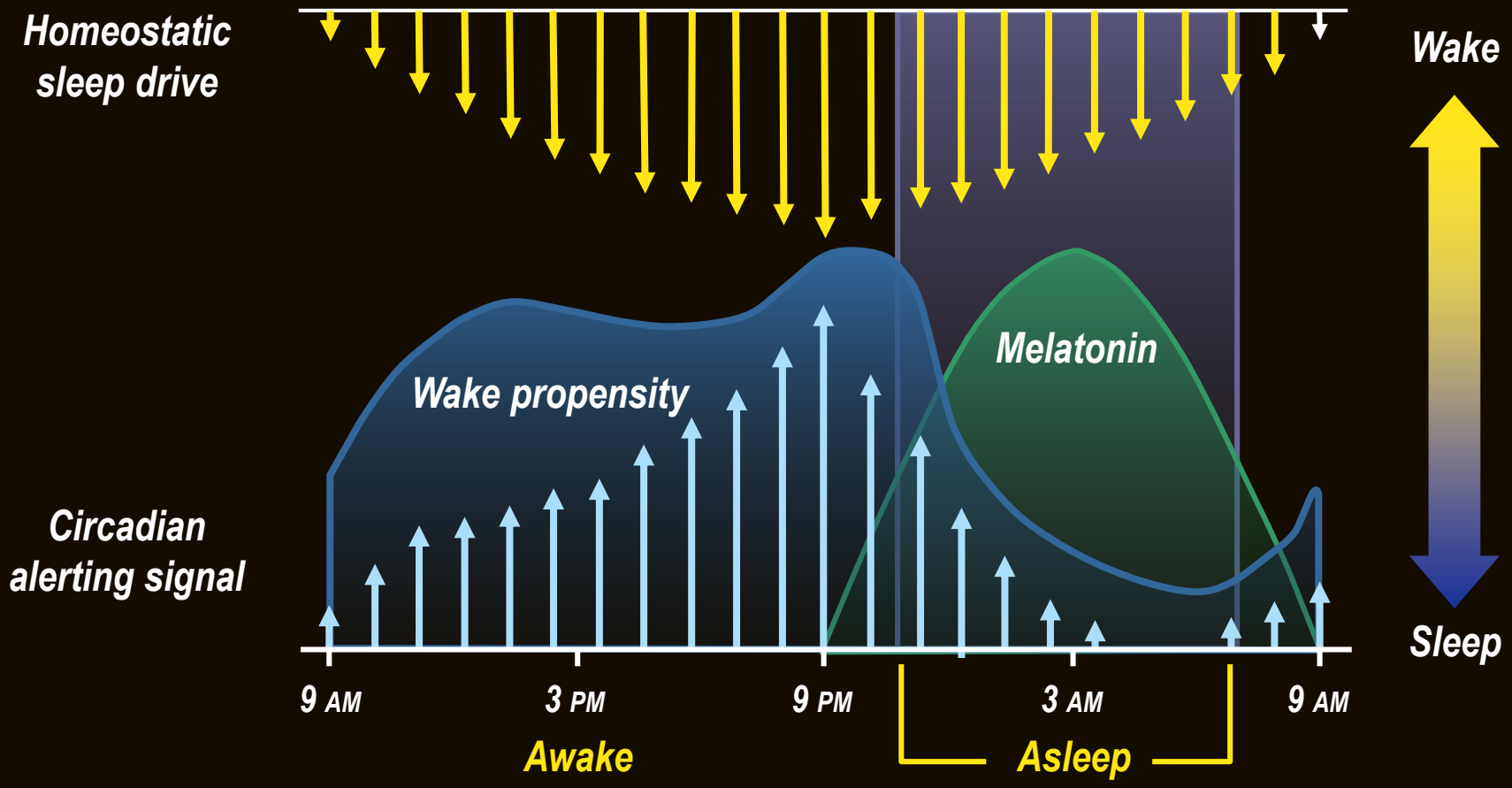
SLEEP

FUEL

METABOLISM

Sleep/Wake Cycle

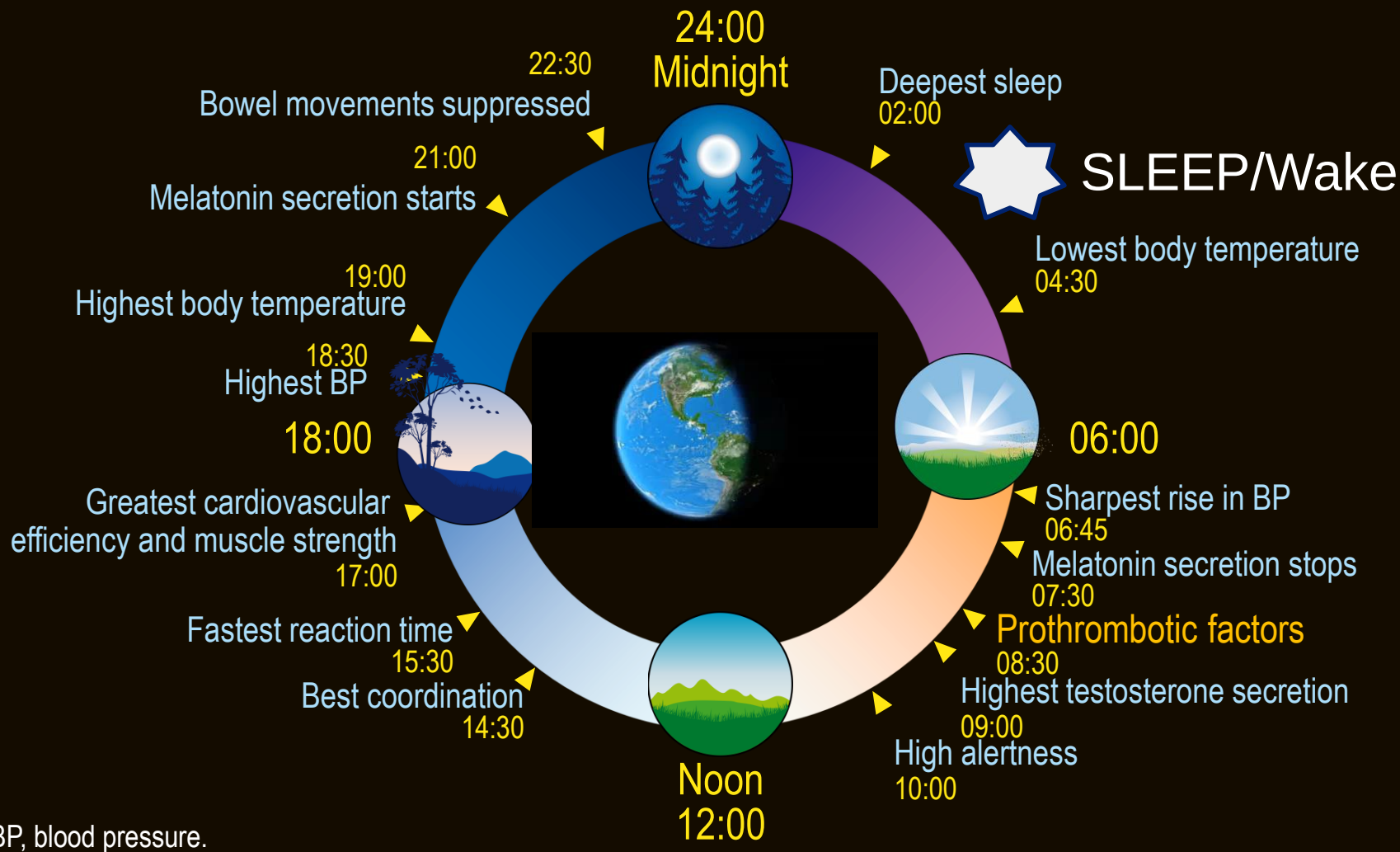
Circadian and Homeostatic Process



Dijk DJ, et al. J Physiol. 1997;505(Pt 3):851-858; Edgar DM, et al. J Neurosci. 1993;13(3):1065-1079; Kilduff TS, Kushida CA. Circadian regulation of sleep. In: Chokroverty S, ed. Sleep Disorders Medicine: Basic Science, Technical Considerations, and Clinical Aspects. 2nd ed. Boston, Mass: Butterworth-Heinemann; 1999:135-145.

Circadian Rhythms and Sleep

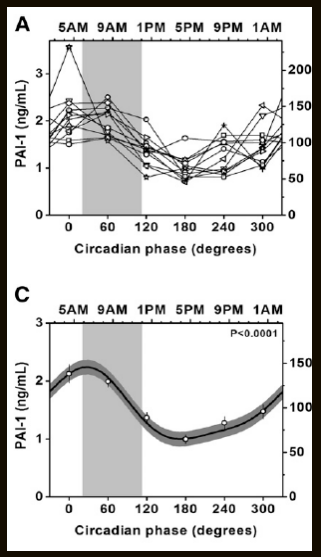
Daily Physiologic and Behavioral Patterns



BP, blood pressure.

Smolensky M, Lamberg L. The Body Clock Guide to Better Health. New York, NY: Henry Holt and Company; 2001.

Circadian Rhythms and Sleep Regulation of Physiological Cycles



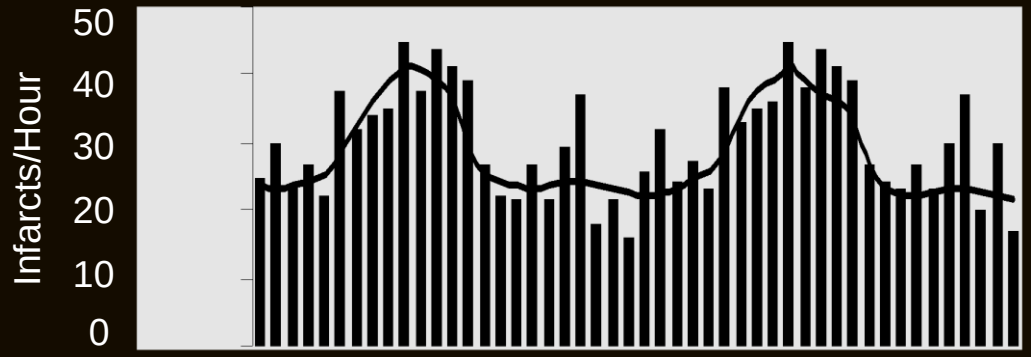
Boivin DB, et al. *Arch Gen Psychiatry*. 1997;54(2):145-152; Johnson MP, et al. *J Sleep Res*. 1992;1(1):24-29; Li L, et al. *Diabetes Res Clin Pract*. 2008;82(3):359-363; Maywood ES, et al. *Endocrinol*. 2007;148(12):5624-5634; Scheer FA, et al. *Proc Natl Acad Sci U S A*. 2009;106(11):4453-4458.; Scheer, Blood, 2014

Disease symptoms with day-night rhythms

Cardiovascular system

↓

Myocardial Infarction
(incidence peaks at ~9AM)



Pulmonary & immune system

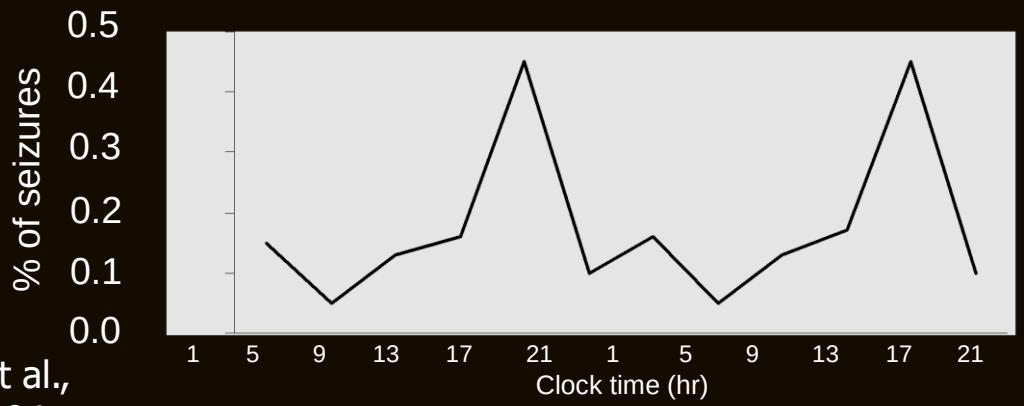
↓

Asthma Symptoms
(peak at ~4AM)

Central nervous system activity

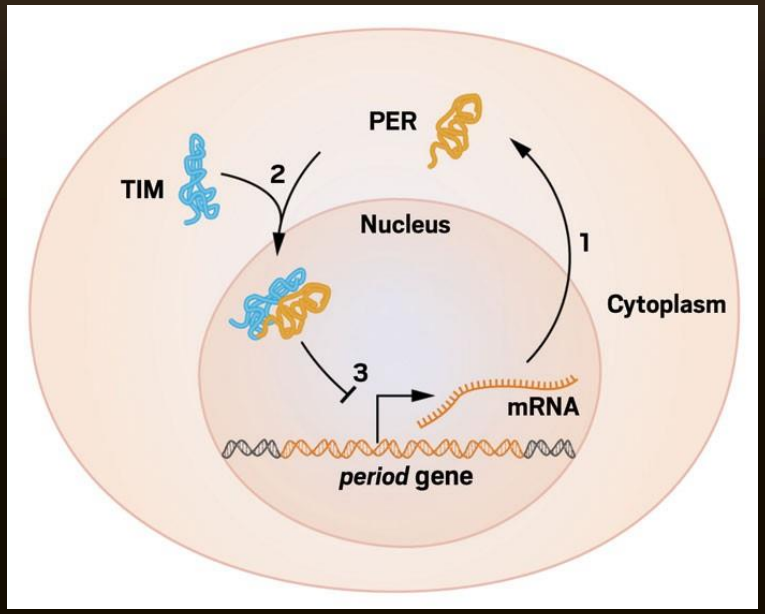
↓

Temporal lobe epilepsy
(incidence peaks at ~5PM)

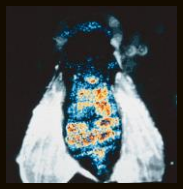


Muller J, Am J Hypertens., 1999; Dethlefsen U. et al., Klin Med, 1985; Pavlova M. et al., Epi. & Beh., 2004

Redrawn from each reference noted on slide



Discovery of molecular mechanisms controlling the circadian rhythm (1984)



The Nobel Prize in Physiology/ Medicine 2017 was awarded jointly to Jeffrey C. Hall, Michael Rosbash and Michael W. Young

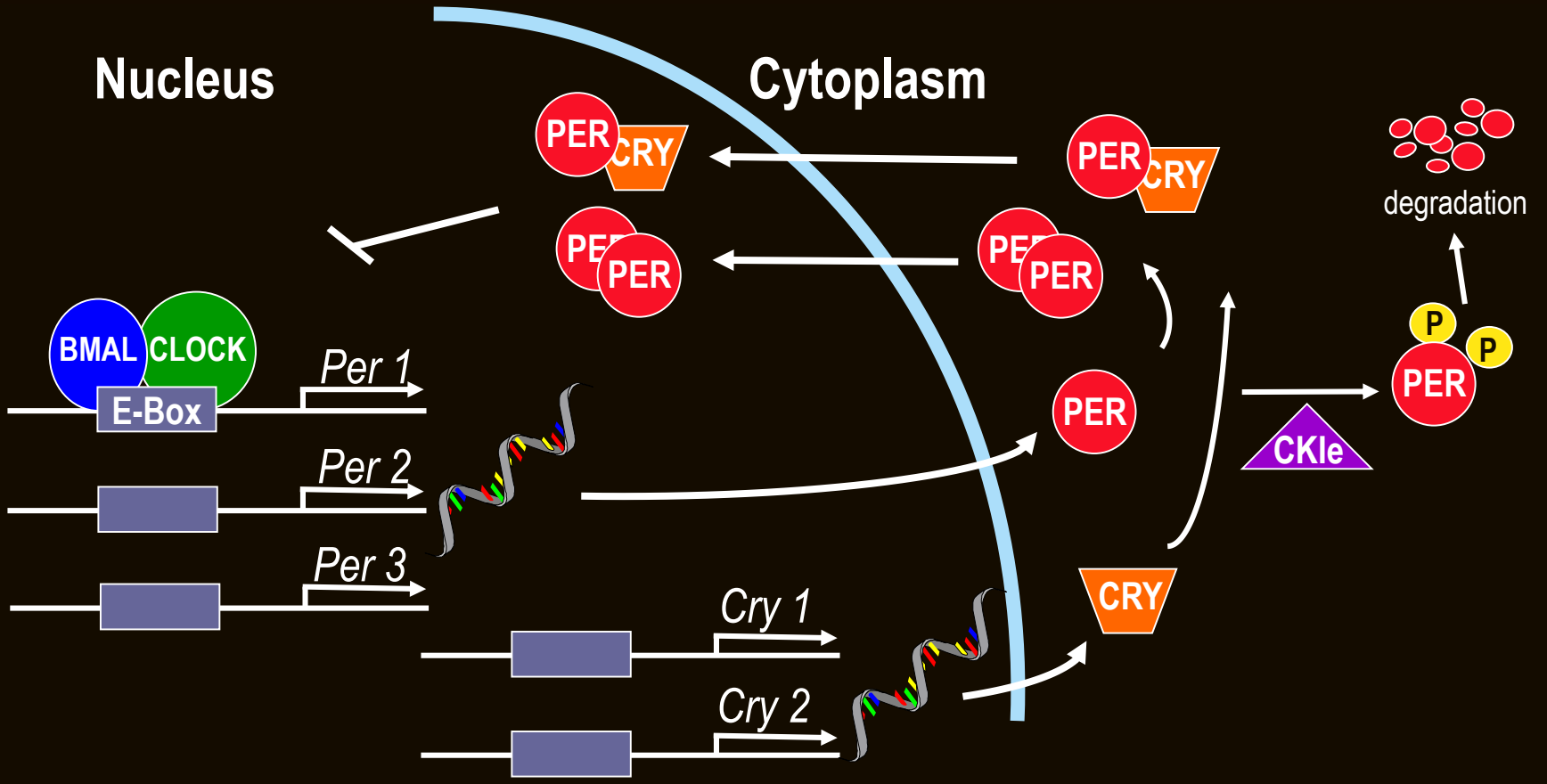
Zehring, W.A., Wheeler, D.A., Reddy, P., Konopka, R.J., Kyriacou, C.P., Rosbash, M., and Hall, J.C. (1984). Cell 39, 369–376., Bargiello, T.A., Jackson, F.R., and Young, M.W. (1984). Nature 312, 752–754.

#1 BIOMEDICAL BREAKTHROUGH OF 1998

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.

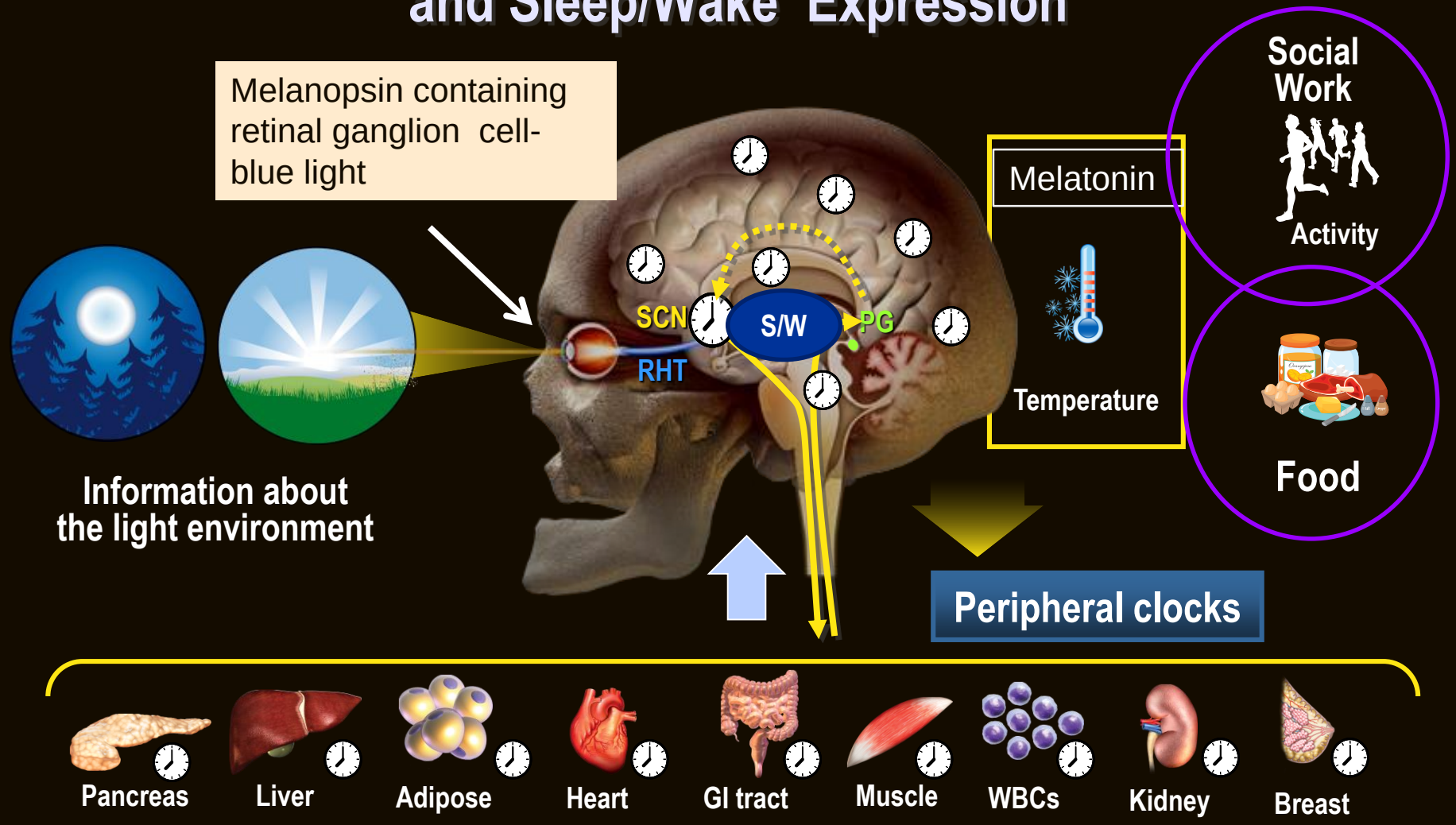
Genetic Components of Mammalian Clock Systems



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.

Ukai H, Ueda HR. *Annu Rev Physiol*. 2010;72:579-603; Yoshitane H, et al. *Mol Cell Biol*. 2009;29(13):3675-3686.

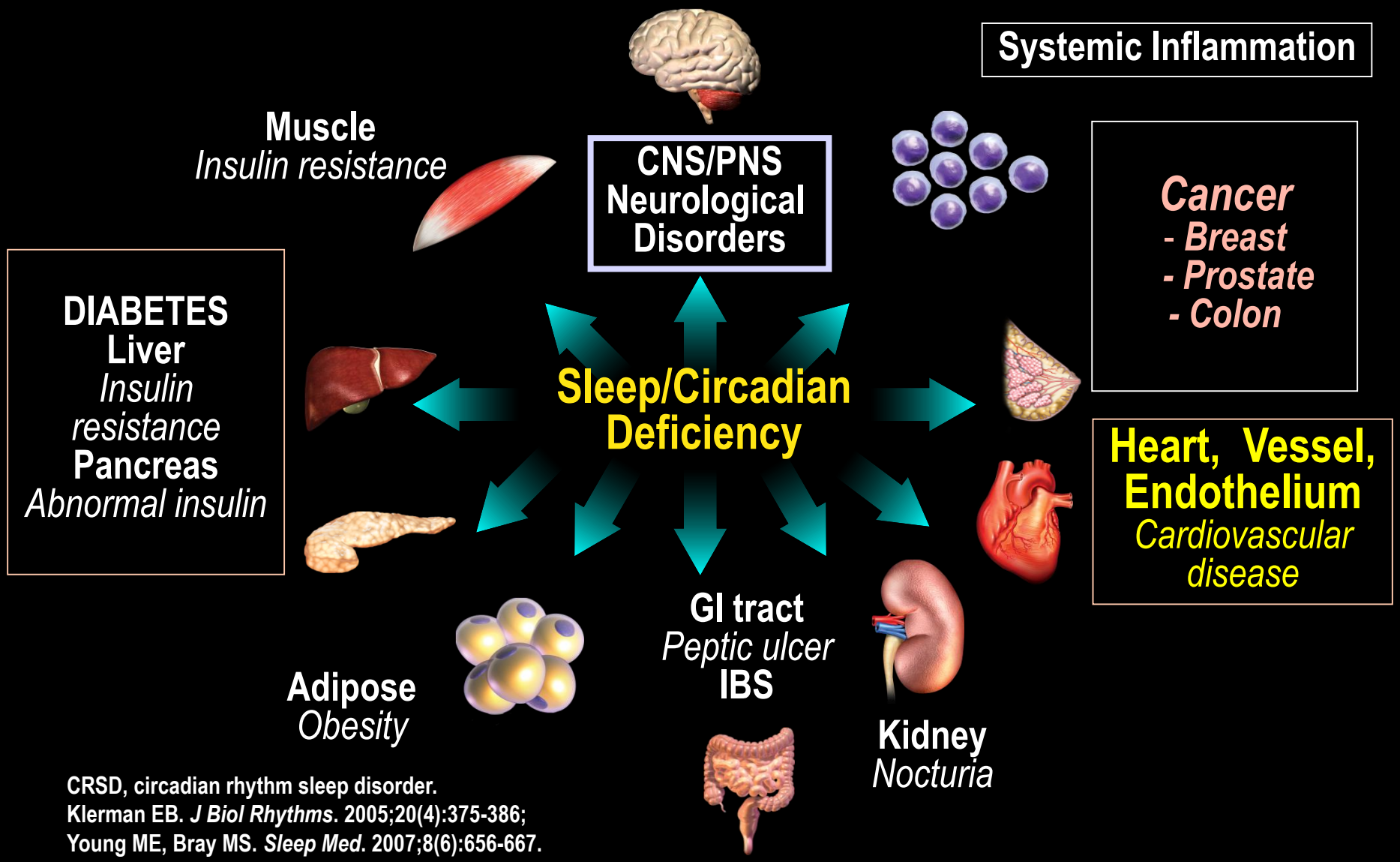
Determinants of Circadian Rhythms and Sleep/Wake Expression



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

Beckett M, Roden LC. *S Afr J Sci*. 2009;105(11-12):415-420; Dibner C, et al. *Annu Rev Physiol*. 2010;72:517-549; Young M, et al. *Sleep Med*. 2007;8(6):656-667.

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



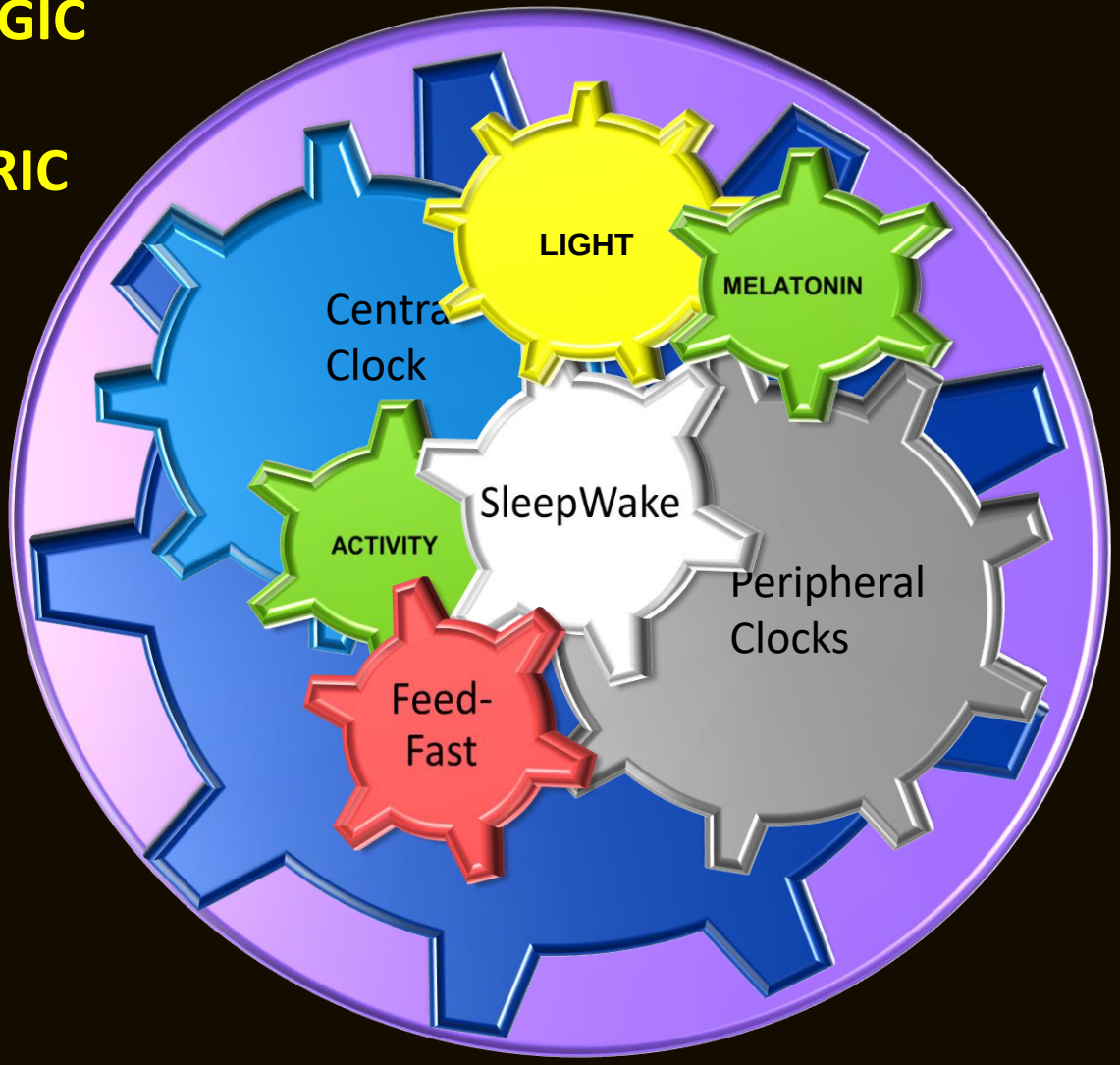
CRSD, circadian rhythm sleep disorder.

Klerman EB. *J Biol Rhythms*. 2005;20(4):375-386;
Young ME, Bray MS. *Sleep Med*. 2007;8(6):656-667.

Complex Interactions of Sleep and Circadian Rhythms: Role in Health and Disease

NEUROLOGIC

PSYCHIATRIC



DIABETES

CVD

HTN

IMMUNE

ETC…

CANCER

Cancer

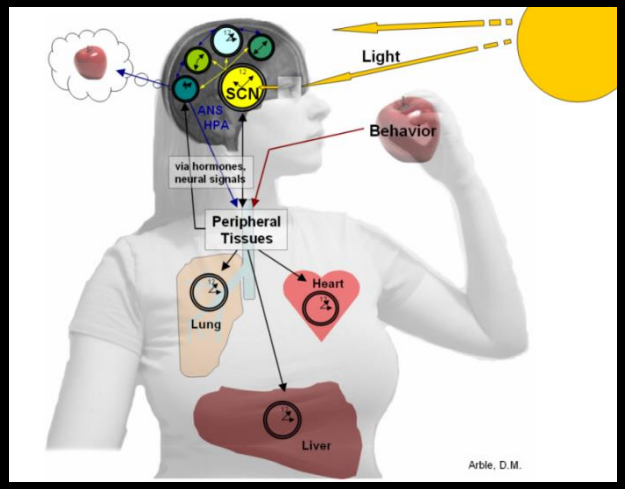
Timing of Light Exposure, Meals, Activity and Sleep: Key for health

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)

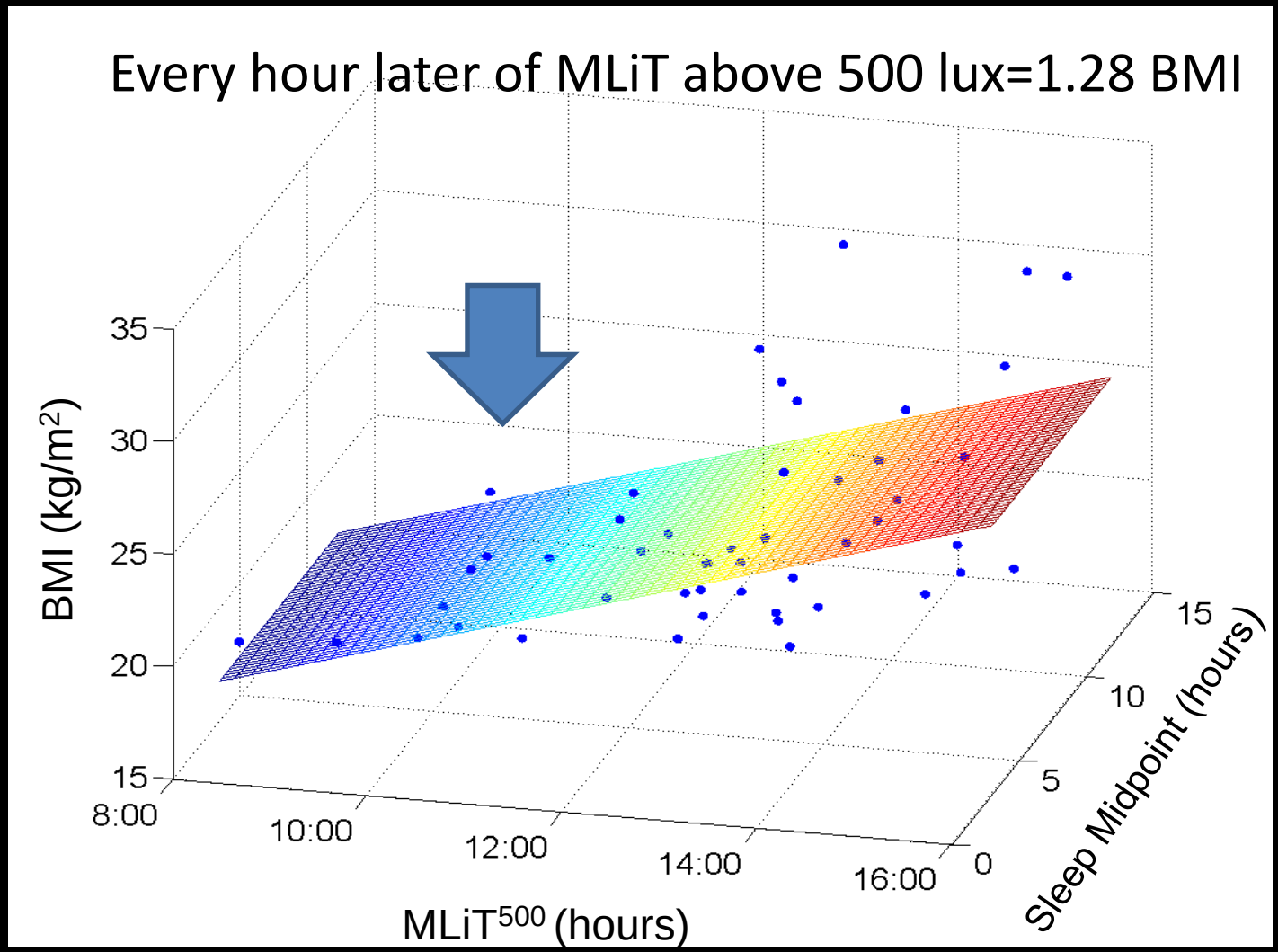
For replication and crediting information, please see our guidelines on our main video page.



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[*,1]

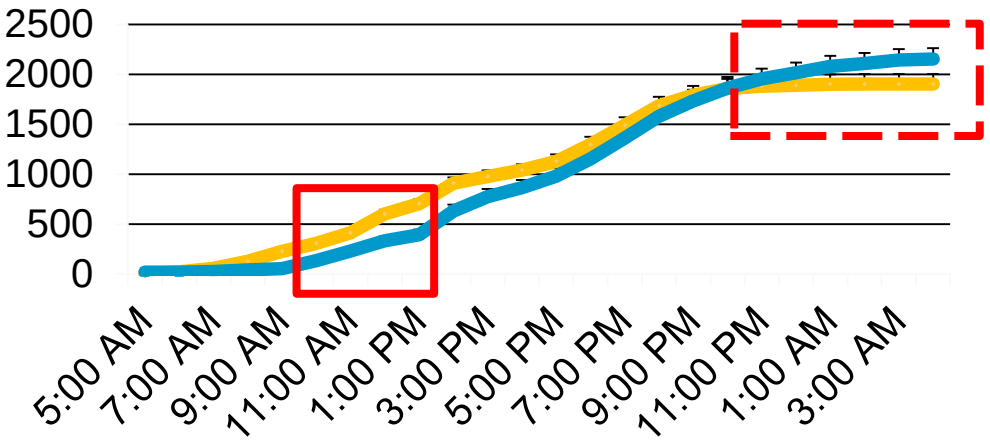
Timing of Mean Light Exposure and BMI

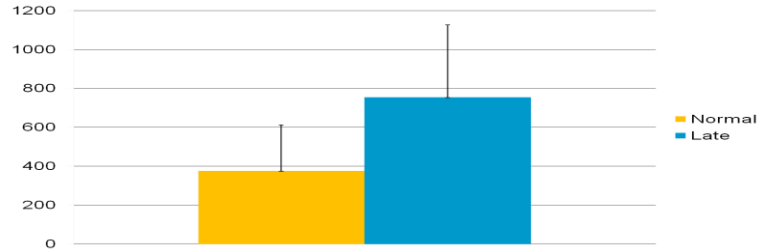


Reid, Santostasi, et al, PLOS One 2014

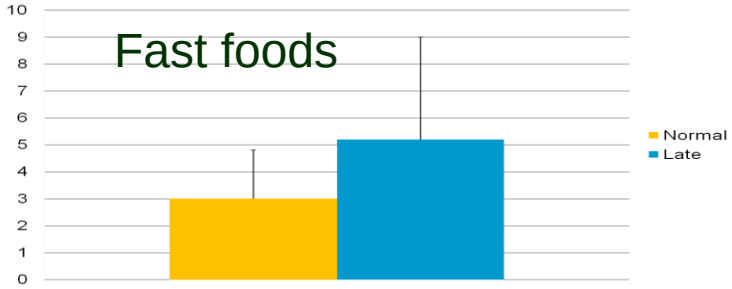
Sleep Timing, Calories, Macronutrients

N=59;
31.7 ± 11.8 years; average
BMI: 24.1 ± 4.2

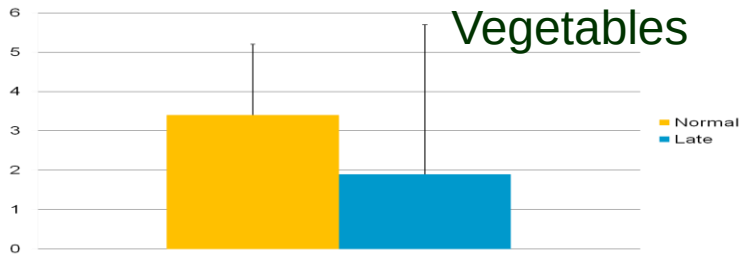




Calories after 8 pm



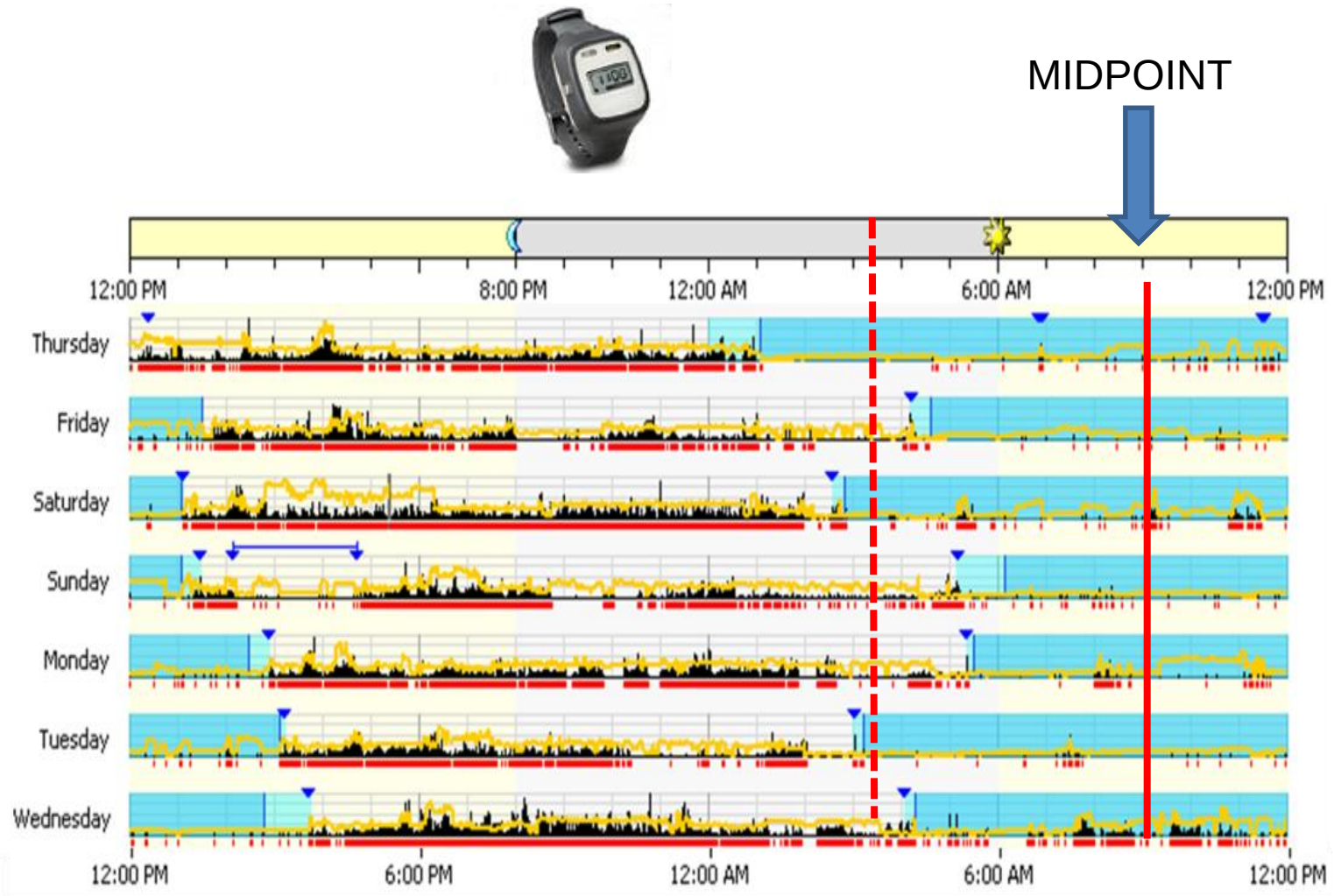
Fast foods



Vegetables

Baron KG and Zee PC, Obesity, 2011

It’s Not Only How Much You Sleep, BUT When



Sleep and Timing: Risk for Obesity, Diabetes

(N=13,429/16,415)

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

[a] 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.

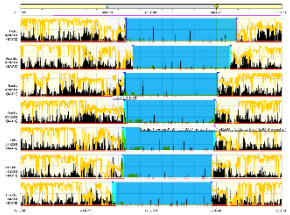
[b] Adjusted for age, gender, ethnic subgroup, study site, income, education, household size, years in US (<10 vs ≥10 y), marital status, AHI category (<15 vs ≥15), diabetes, employment/shift work status.

[c] 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



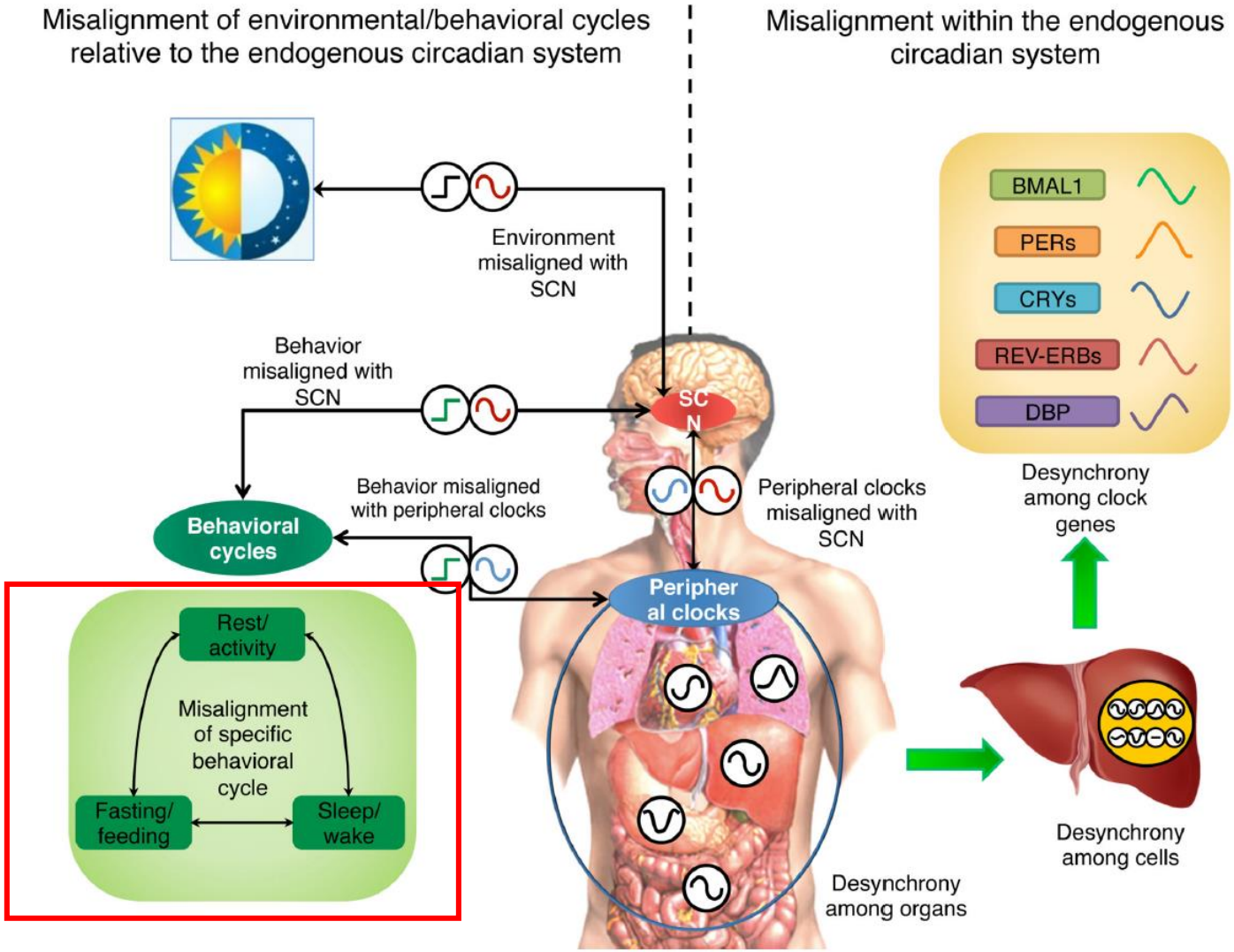
Francesca L. Facco, MD, MSCI; William A. Grobman, MD, MBA; Kathryn J. Reid, PhD; Corette B. Parker, DrPH; Shannon M. Hunter, MS; Robert M. Silver, MD; Robert C. Basner, MD; George R. Saade, MD; Grace W. Pien, MD, MSCE; Shalini Manchanda, MD; Judette M. Louis, MD, MPH; Chia-Ling Nhan-Chang, MD; Judith 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

	Hypertensive disease of pregnancy		Gestational diabetes	
Sleep characteristic	N (%)	Crude OR (95% CI)	N (%)	Crude OR (95% CI)
Sleep duration				
<7 h	27/218 (12.4)	1.10 (0.68–1.78)	15/218 (6.9)	2.24 (1.11–4.53)
≥7 h	64/564 (11.3)	1.00	18/564 (3.2)	1.00
		P value = .6850		*P* value = .0246
Sleep midpoint				
>5 AM	17/148 (11.5)	0.98 (0.56–1.72)	12/148 (8.1)	2.58 (1.24–5.36)
≤5 AM	74/634 (11.7)	1.00	21/634 (3.3)	1.00
		P value = .9497		*P* value = .0114

Facco et al, AJOG, 2018

Environment, Behavior, Physiology, Genes, Molecules…Circadian Health



Qian J and Scheer FA, Trends Endocrinol. Metab., 2016

Sleep and Circadian Dysfunction Neurodegeneration

Neurodegeneration and Altered Circadian Rhythms

Alzheimer's

Parkinson's

Huntington's

Traumatic Brain Injury

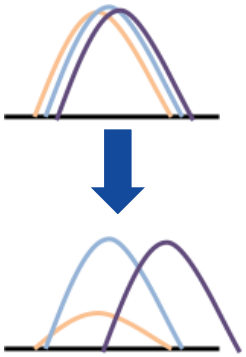
Chronic Traumatic Encephalophathy

Neurodegeneration

Circadian/Sleep

Disease severity and Progression?

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

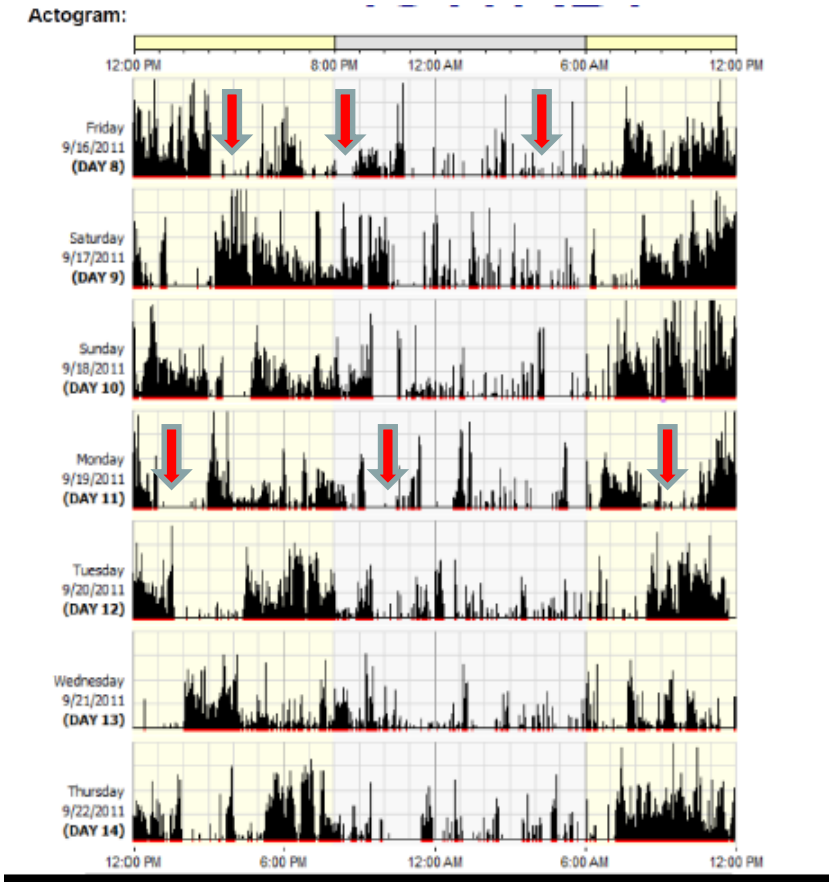


<u>References</u>
Schlosser Covell et al. 2012
Aziz et al. 2009
Morton et al. 2005, Pallier, et al. 2007
Boone et al. 2012
Mathias, Alvaro 2012

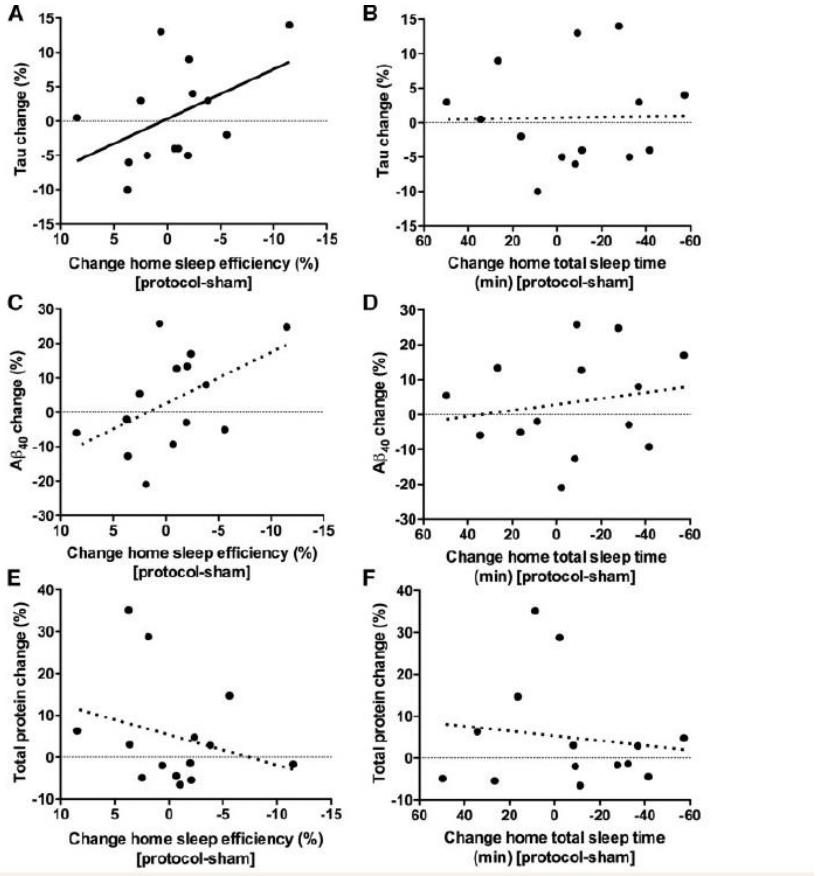
Courtesy: Allada

Circadian and Sleep Dysfunction and Risk for Cognitive Impairment and Alzheimer's Disease

Sleep-Wake Fragmentation

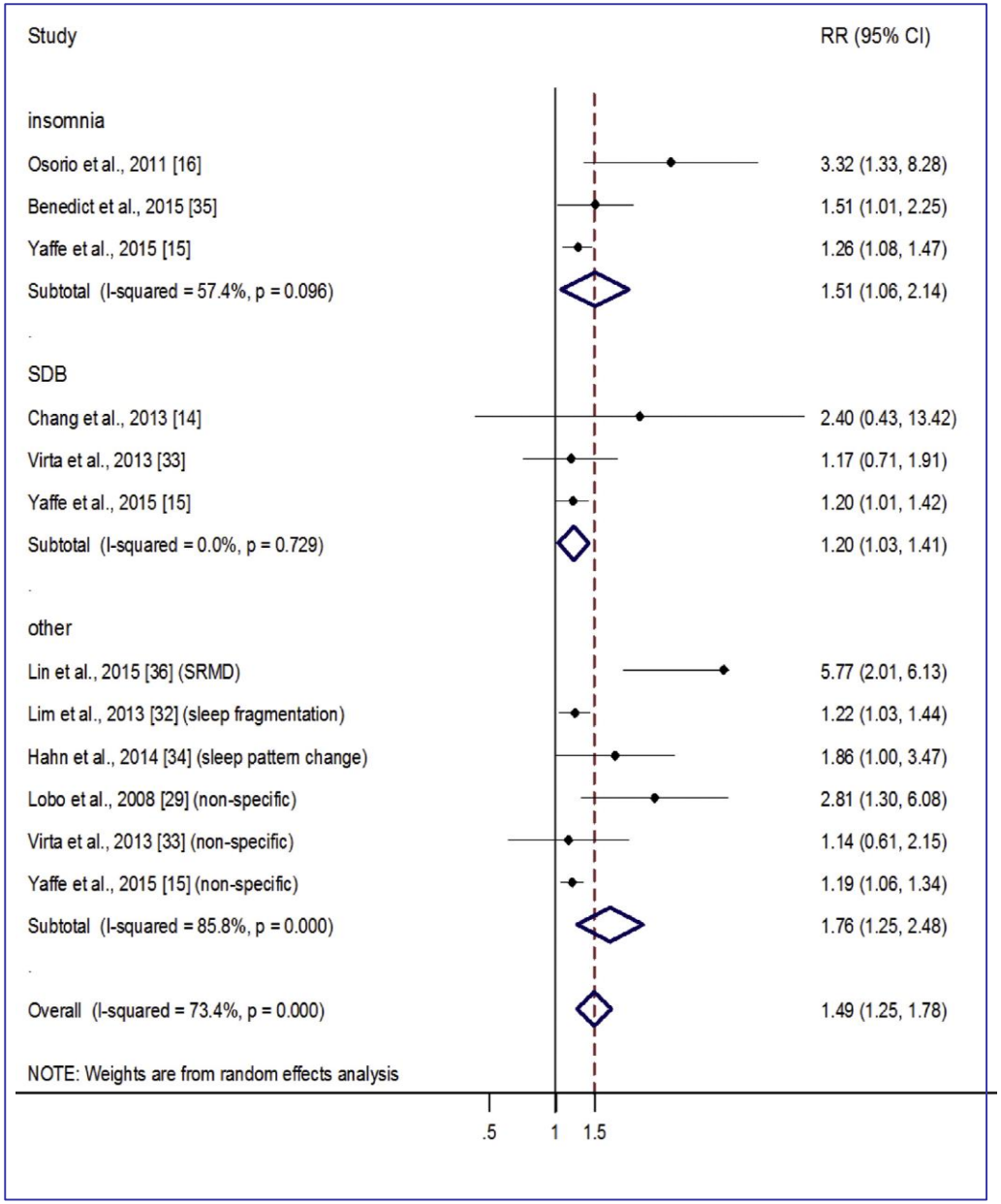


No Dementia 7-14 days actigraphy



Ju J et al, Brain, 2017

Sleep Disturbances as Risk Factor for Dementia

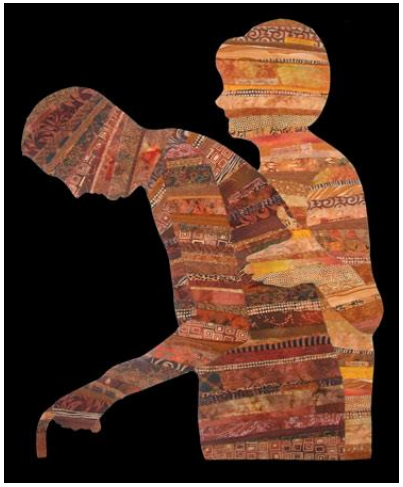


N=25,847; Mean follow up: 9.49 y

- 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

Shi L, et al, Sleep Medicine Review, In Press

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]

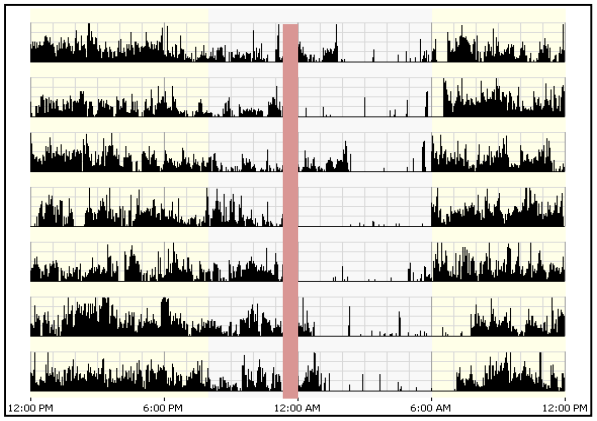
Excessive daytime somnolence (EDS)

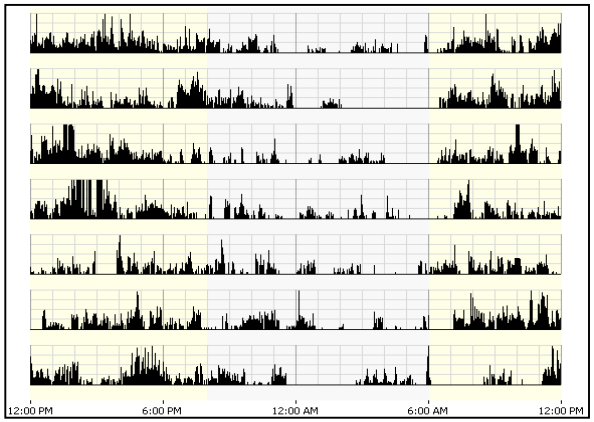
16% of patients versus 1% of healthy controls [1]

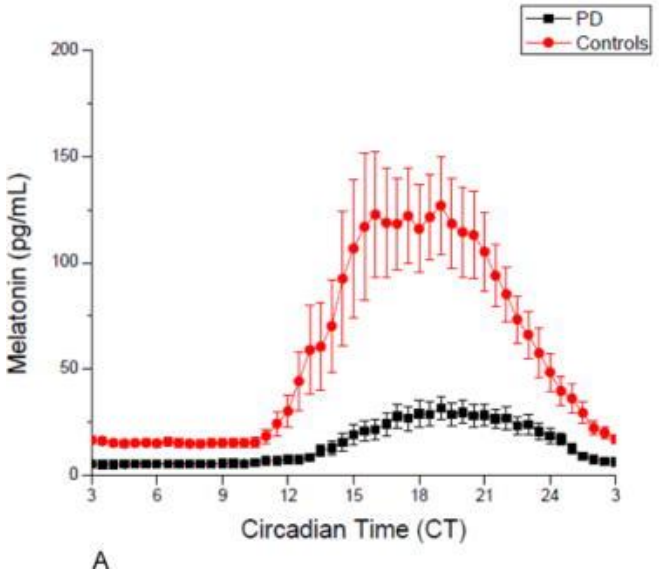
EDS has been associated with three-fold increase in the risk of developing PD [2]

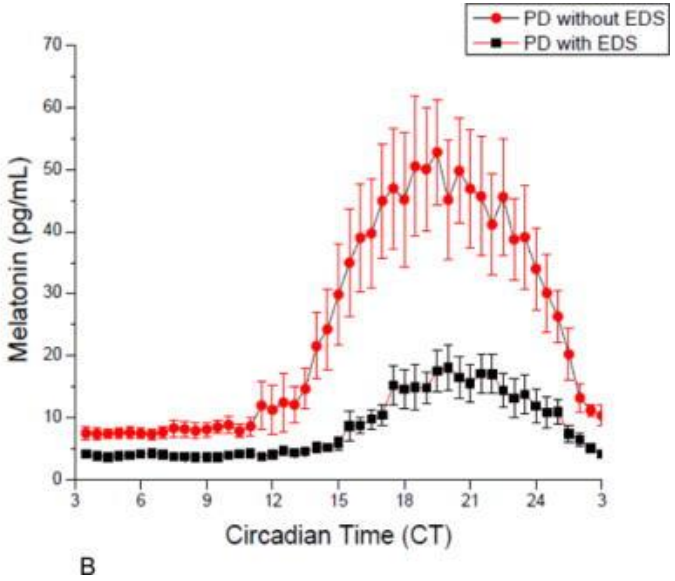
[1]Tandberg et al. 1998; [2]Abbott et al. 2005

Neurodegenerative Disorders
Parkinson's Disease









Videnovic A et al, Zee, JAMA Neurology 2014 Apr;71(4):463-9.

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

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

Change	Bright Light	Dim Red Light	*p*
EES score	4.75 ± 1.84	1.79 ± 2.89	0.005

- **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)**

Videnovic A, Klerman E, Wang W, Marconi A, Kuhta T, Zee PC. JAMA Neurology, 2017

The “Brainwashing” Function of Sleep

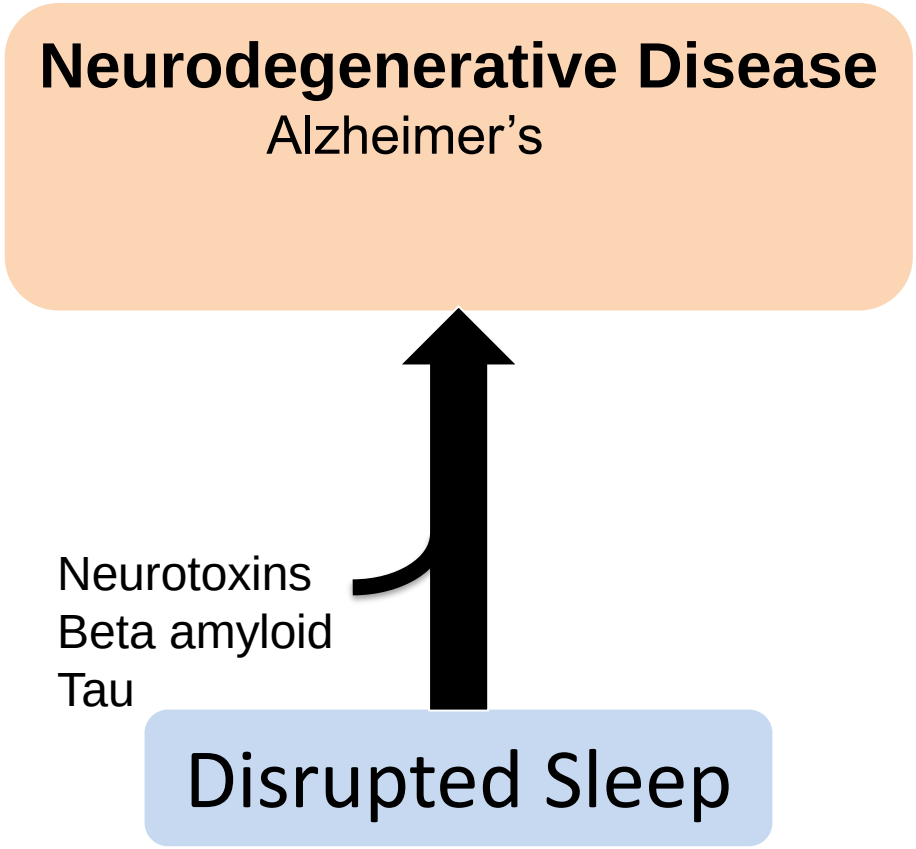
Neurodegenerative Disease
Alzheimer’s

Neurotoxins
Beta amyloid
Tau

Disrupted Sleep

References
Schlosser Covell et al. 2012
Aziz et al. 2009
Morton et al. 2005, Pallier, et al. 2007
Boone et al. 2012
Mathias, Alvaro 2012

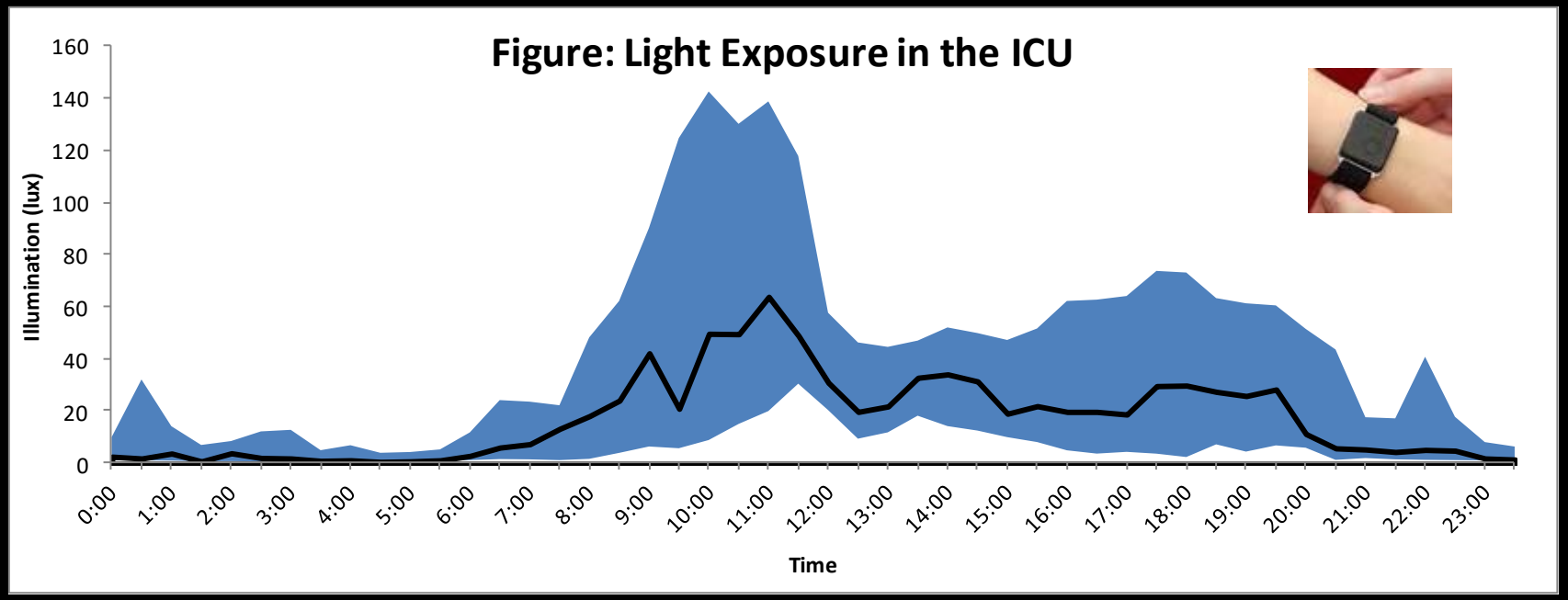
The “Brainwashing” Function of Sleep



Xie et al 2013 Science

References
Schlosser Covell et al. 2012
Aziz et al. 2009
Morton et al. 2005, Pallier, et al. 2007
Boone et al. 2012
Mathias, Alvaro 2012

Light Exposure in Neurological ICU Patients

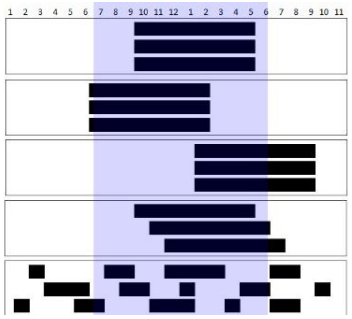


Focus has been too much light at night....
BUT the most prominent finding is too little light during the day!
Can increasing light during the day improve clinical outcomes?

Fan EP, Abbott SM, Reid KJ, **Zee PC**, Maas MB. J Crit Care. 2017

Clinical Areas Receptive to Circadian Medicine

Circadian Rhythm Sleep Disorders



Shift Workers

Cardio-metabolic

- **Children**
- **Adults**
- **Pregnancy**

Cancer

Psychiatric (bipolar)

Pharmacotherapeutics

Critical Care

Epilepsy

Dravet, SUDEP

Autism & Cognitive Disorders

Neurodegenerative Disorders

The Future of Circadian and Sleep Medicine: Developing Clinically Practical and Relevant Biomarkers

pii: sp-00097-16

http://dx.doi.org/10.5665/sleep.5616

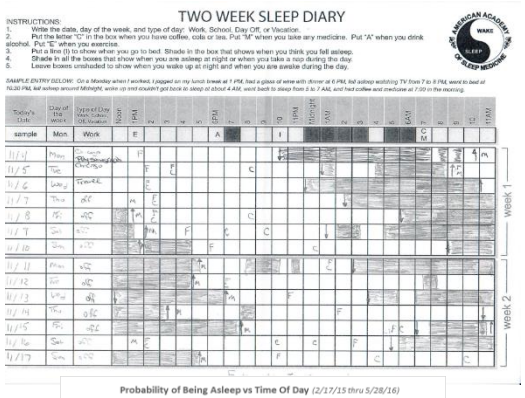
WORKSHOP REPORT

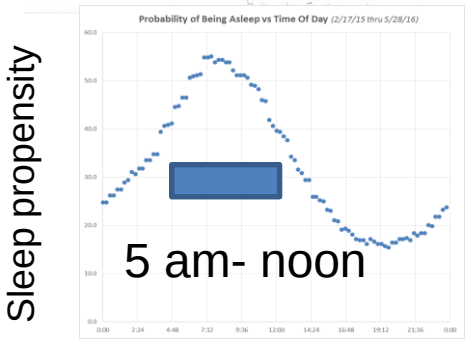
Developing Biomarker Arrays Predicting Sleep and Circadian-Coupled Risks to Health

Janet M. Mullington, PhD[1]; Sabra M. Abbott, MD, PhD[2]; Judith E. Carroll, PhD[3]; Christopher J. Davis, MS, PhD[4]; Derk-Jan Dijk, PhD[5]; David F. Dinges, PhD[6]; Philip R. Gehrman, PhD[7]; Geoffrey S. Ginsburg, MD, PhD[8]; David Gozal, MD, MBA[9]; Monika Haack, PhD[1]; Diane C. Lim, MD[10]; Madalina Macrea, MD, MPH, PhD[11,12]; Allan I. Pack, MBChB, PhD, FRCP[13]; David T. Plante, MD[14]; Jennifer A. Teske, PhD[15]; Phyllis C. Zee, MD, PhD[2]

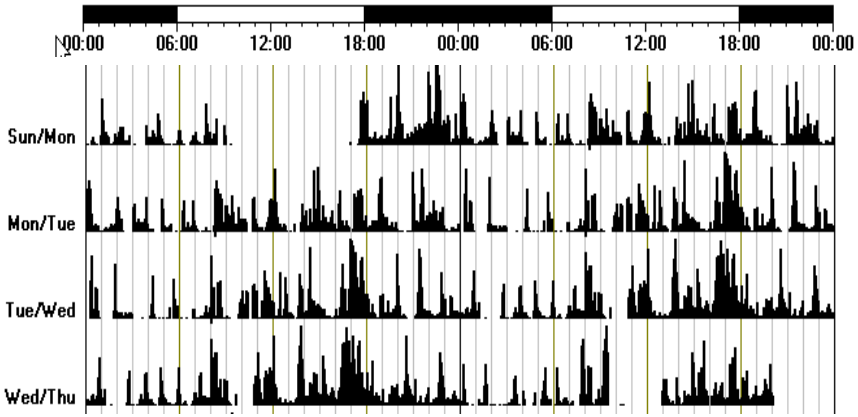
[1]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston MA; [2]Northwestern University, Chicago, IL; [3]Cousins Center for Psychoneuroimmunology, UCLA Semel Institute for Neuroscience & Human Behavior, UCLA, Los Angeles, CA; [4]Elson S. Floyd College of Medicine, Washington State University, Spokane, WA; [5]Surrey Sleep Research Centre, University of Surrey, Guildford, UK; [6]Department of Psychiatry, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; [7]Department of Psychiatry, University of Pennsylvania, Philadelphia, PA; [8]Duke Center for Applied Genomics and Precision Medicine, Duke University, Durham, NC; [9]The University of Chicago, Chicago, IL; [10]Center for Sleep and Circadian Neurobiology, University of Pennsylvania, Philadelphia, PA; [11]Salem VAMC, Salem, VA; [12]University of Virginia, Charlottesville, VA; [13]Department of Medicine, Center for Sleep and Circadian Neurobiology Translational Research Laboratories, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; [14]Wisconsin Sleep, Madison, WI; [15]Nutritional Sciences, University of Arizona, Tucson, AZ

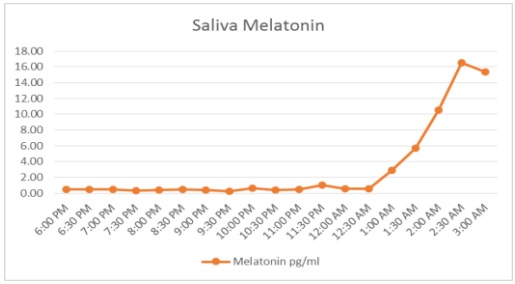
Clinic Circadian Biomarkers





Actigraphy/Logs/ MCTQ





Salivary Melatonin

Pupillometry

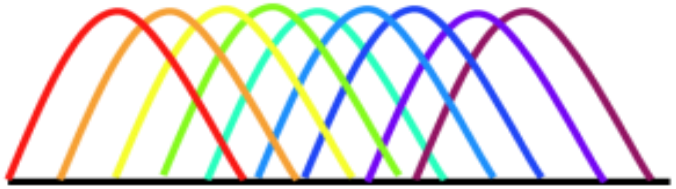
nugene

Clinical and Genetic Database

Chronodiagnostics: Biological Timing in Clinic and Medicine

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

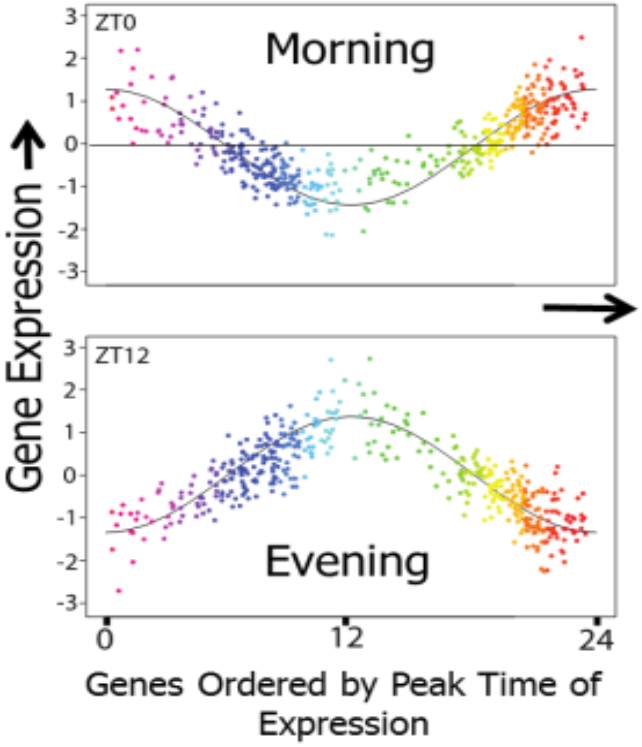
Rosemary Braun



Temporal Profiling

Sabra Abbott

Ravi Allada

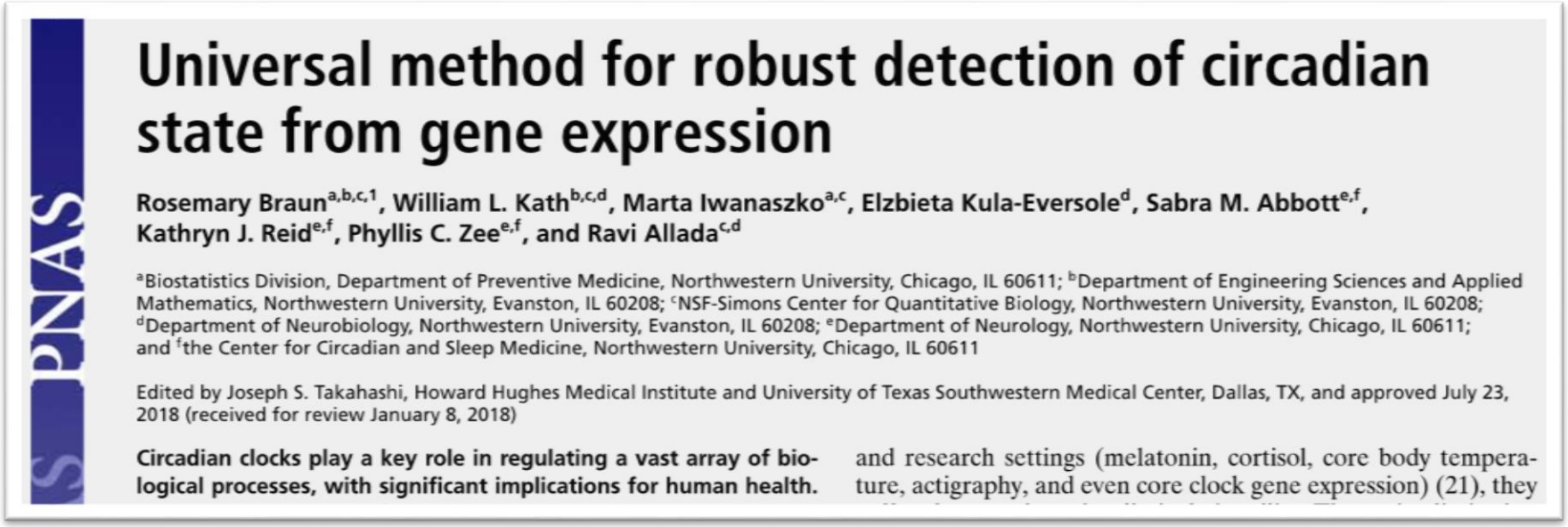


Temporal Genome Expression Signature → Computational quantitation of temporal organization from a single sample → Mechanistic understanding of disease pathogenesis or toxin/drug action from network analysis → Diagnostic/Therapeutic/Countermeasure Development

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



PNAS

Universal method for robust detection of circadian state from gene expression

Rosemary Braun[a,b,c,1], William L. Kath[b,c,d], Marta Iwanaszko[a,c], Elzbieta Kula-Eversole[d], Sabra M. Abbott[e,f], Kathryn J. Reid[e,f], Phyllis C. Zee[e,f], and Ravi Allada[c,d]

[a]Biostatistics Division, Department of Preventive Medicine, Northwestern University, Chicago, IL 60611; [b]Department of Engineering Sciences and Applied Mathematics, Northwestern University, Evanston, IL 60208; [c]NSF-Simons Center for Quantitative Biology, Northwestern University, Evanston, IL 60208; [d]Department of Neurobiology, Northwestern University, Evanston, IL 60208; [e]Department of Neurology, Northwestern University, Chicago, IL 60611; and [f]the Center for Circadian and Sleep Medicine, Northwestern University, Chicago, IL 60611

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

DARPA

James S. McDonnell Foundation

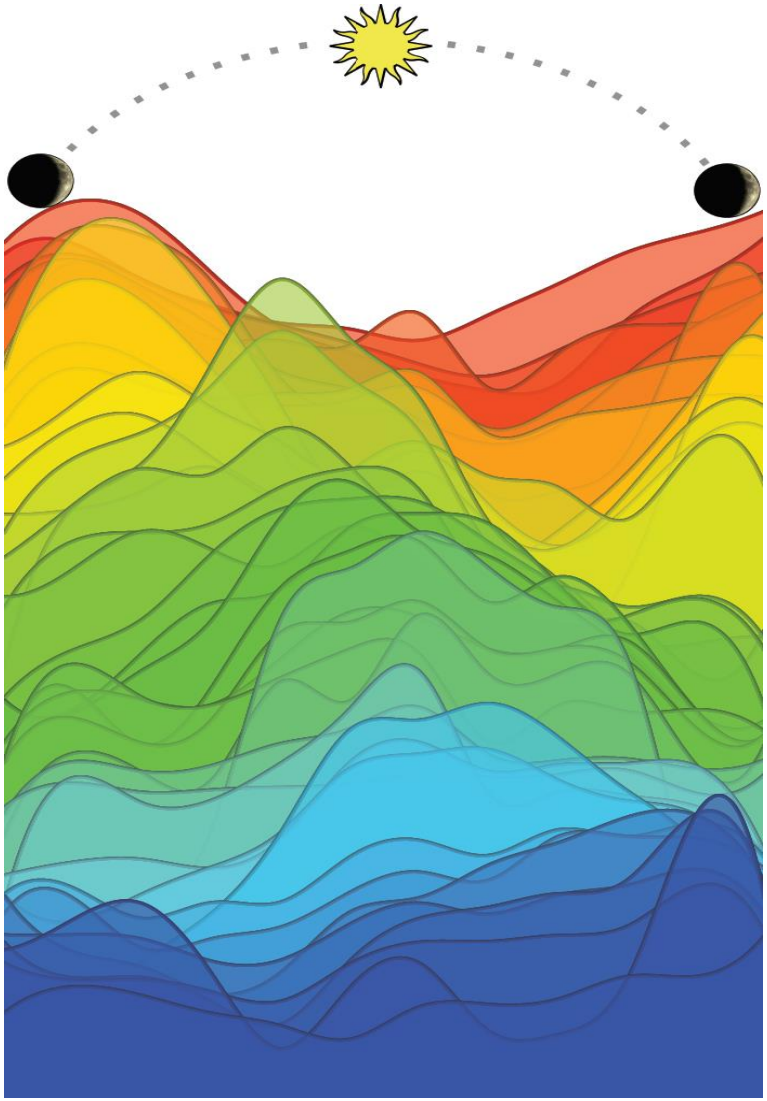
NSF

SF

Northwestern Medicine
Feinberg School of Medicine

Center for Circadian and Sleep Medicine

TimeSignature Predictive Genes



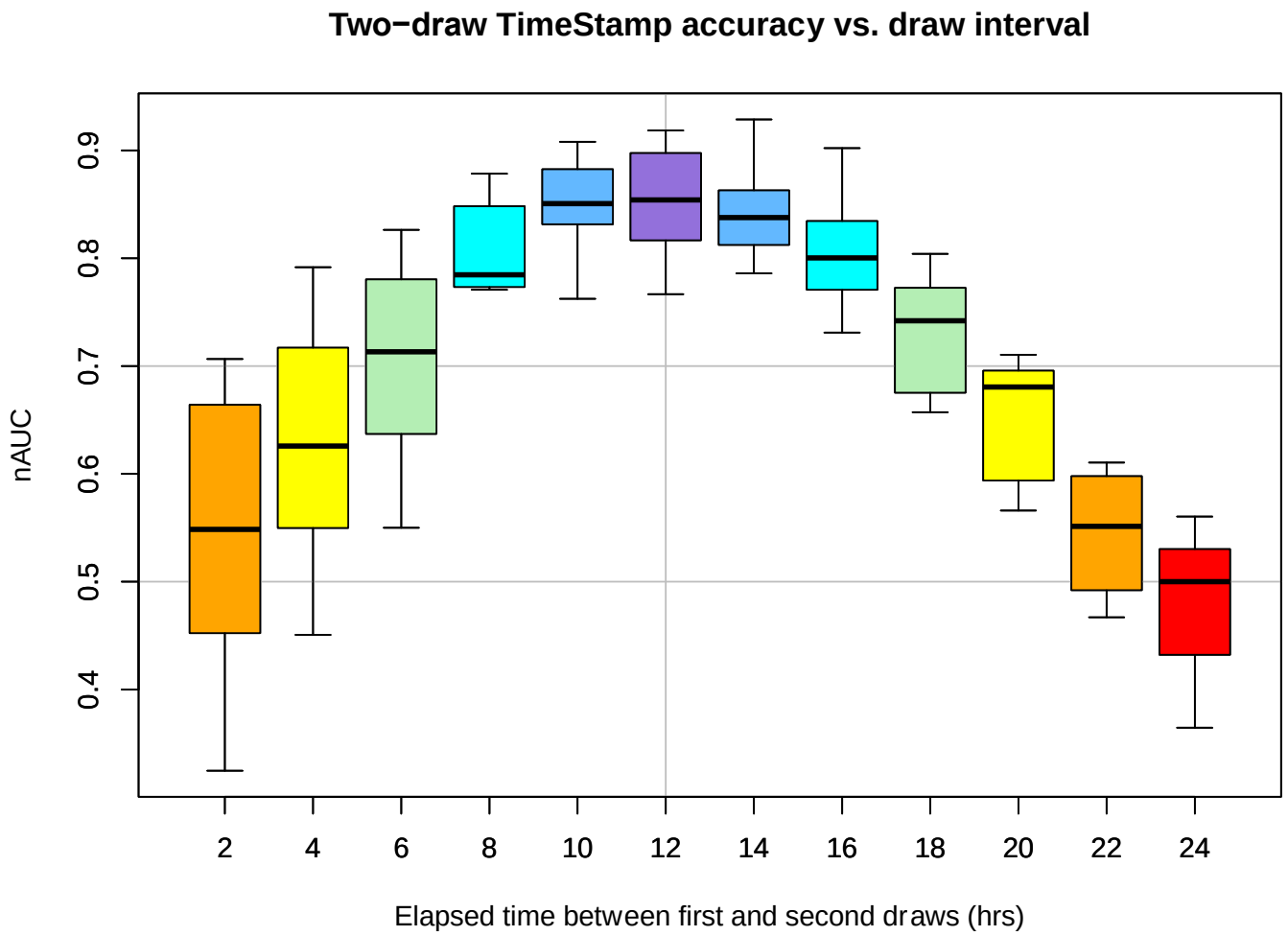
Expression levels of ~40 genes is sufficient to tell time

Table 1. TimeStamp Predictive Genes

Gene	freq.	Gene	freq.	Gene	freq.
DDIT4	1.00	GZMB	0.58	CAMKK1	0.17
GHRL	1.00	CLEC10A	0.50	DTYMK	0.17
PER1	1.00	PDK1	0.50	NPEPL1	0.08
EPHX2	0.92	GPCPD1	0.50	MS4A3	0.08
GNG2	0.83	MUM1	0.33	IL13RA1	0.08
IL1B	0.83	STIP1	0.33	ID3	0.08
DHRS13	0.83	CHSY1	0.25	MEGF6	0.08
NR1D1	0.75	AK5	0.25	TCN1	0.08
ZNF438	0.75	CYB561	0.25	NSUN3	0.08
NR1D2	0.75	SLPI	0.25	POLH	0.08
CD38	0.75	PARP2	0.25	SYT11	0.08
TIAM2	0.75	PGPEP1	0.17	SH2D1B	0.08
CD1C	0.75	C12orf75	0.17	REM2	0.08
LLGL2	0.58	FKBP4	0.17		

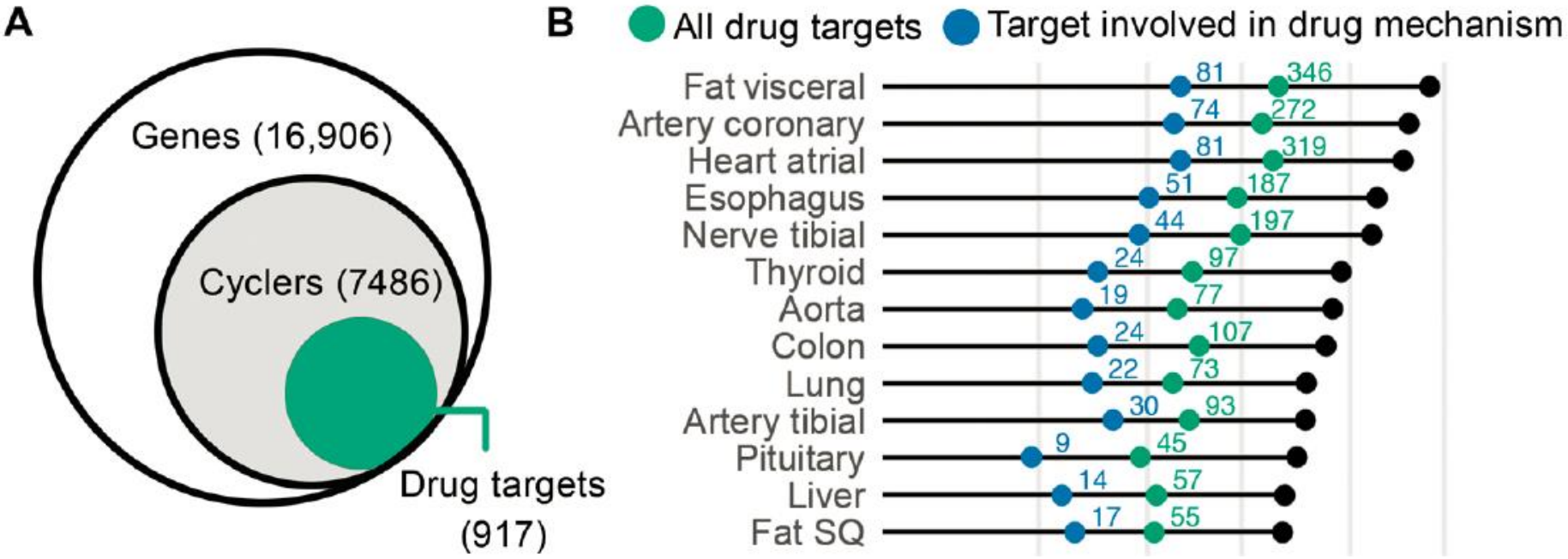
Braun, R, Allada, Zee et al, PNAS, 2018

Accuracy vs. draw spacing

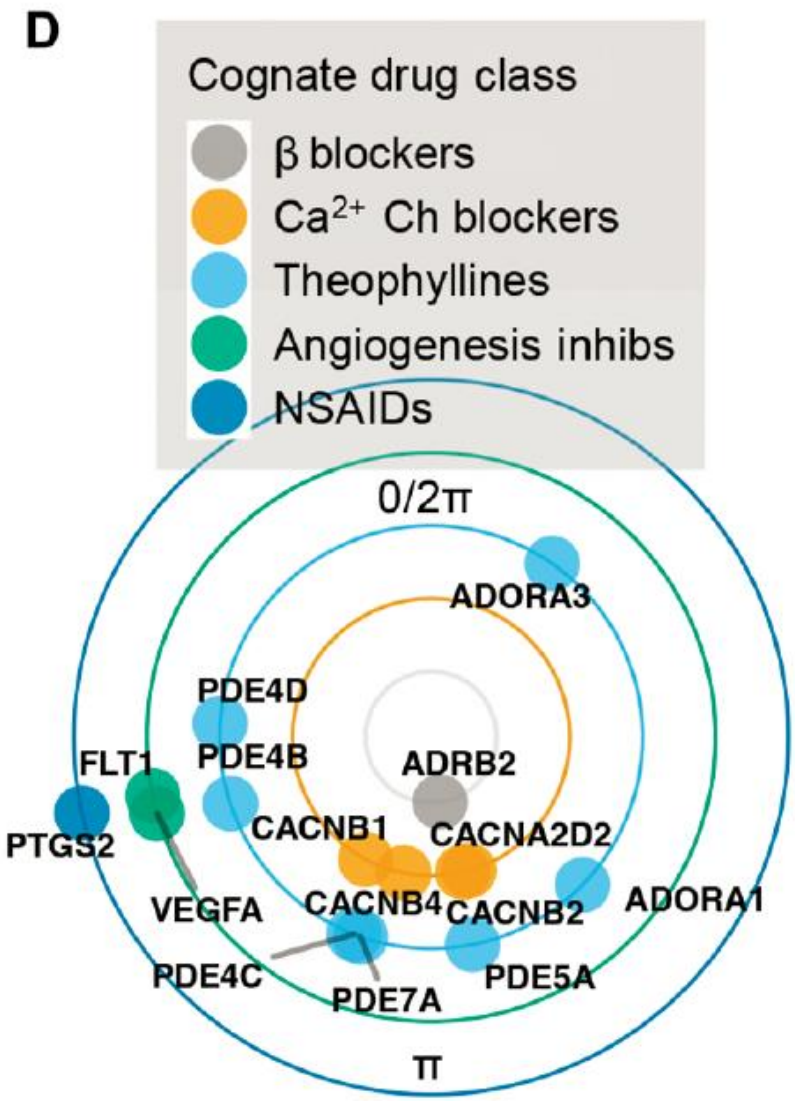


Circadian-Time Based Targeting of Drugs

Tissue-specific Rhythmically of Expressed Human Genes

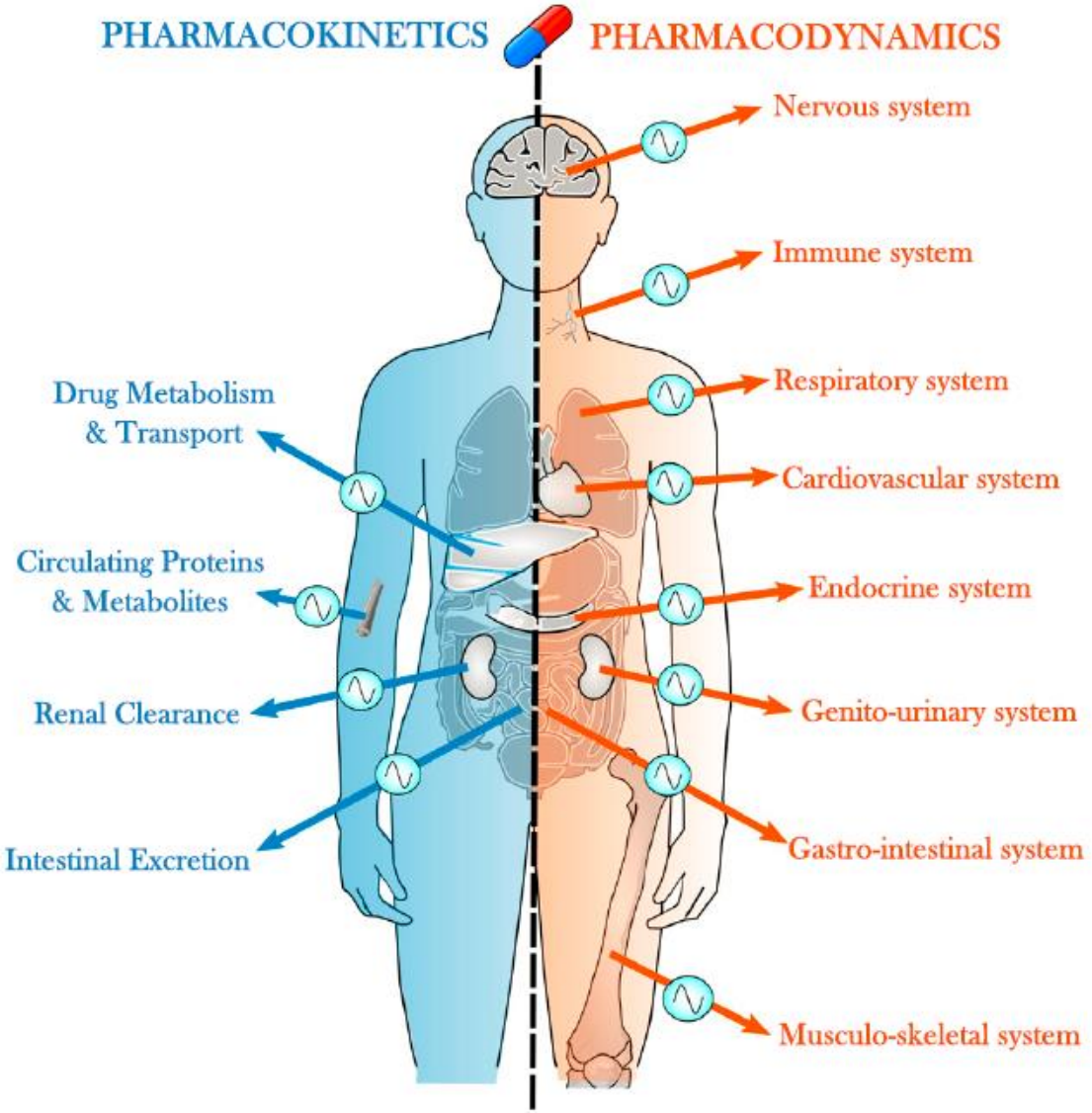


Ruben *et al*., (2018) *Sci. Transl. Med.* **10**, eaat8806 12 September 2018



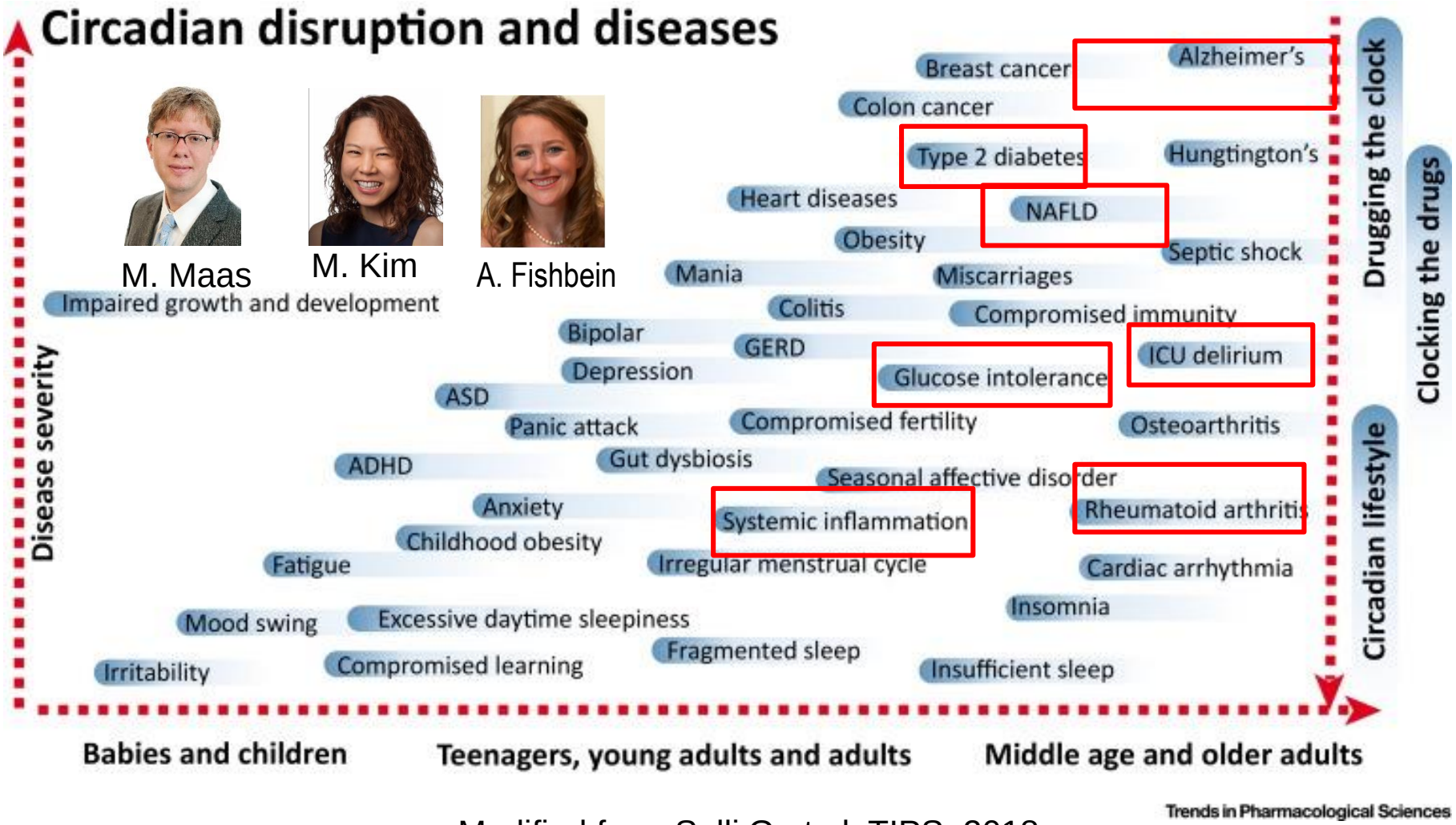
Rhythmically Expressed Drug Targets - Including for Cancer Drugs

Ruben *et al*., (2018) *Sci. Transl. Med.* **10**, eaat8806 12 September 2018



Ballesta et al., (2017) Pharmacol Rev 69:161–199.

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



Modified from Sulli G et al, TIPS, 2018

NORTHWESTERN UNIVERSITY
FEINBERG SCHOOL OF MEDICINE

Center for Sleep and Circadian Medicine

Sabra Abbott, MD, PhD
Hryar Attarian, MD
Roneil Malkani, MD
Brandon Lu, MD*
Aleks Videnovic, MD*
Kelly Glaser-Baron, PhD*
Matthew Maas, MD
Rodolfo Soca, MD
Seong J Kim, MD
Euyeon Joo, MD
Francesca Facco, MD
Ivy Cheung, PhD
Giovanni Santostasi, PhD
Nelly Papalombros

Kathryn Reid, PhD
Fred W. Turek, PhD
Joseph Bass, MD
Ravi Allada, MD, PhD
Eve Van Cauter, PhD
Kristen Knutsom, PhD
Ken Paller, PhD
Marsel Mesulam, MD
Sandra Weintraub, MD
Tanya Simuni, MD
Frank Penedo, PhD
William Gobman, MD
Jason Ong, PhD






2P01AG011412-18 ; R01 HL140580-01;

R01 HL105549; R01 HL098297; R01 HL092140;

U10HD063036 ; UM1HL112856; U01HL111478;

*K23 HL091508 ; * K23NS072283 ; *5K12HD05588 ;

NCRR-00048 ; T32 HL07909; DARPA ; Philips