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Laboratory of Comparative Somnology and Neuroendocrinology, Institute of Evolutionary Physiology and Biochemistry, Russian Academy of Sciences

Circadian Rhythms: Implications for Metabolic and Brain Health

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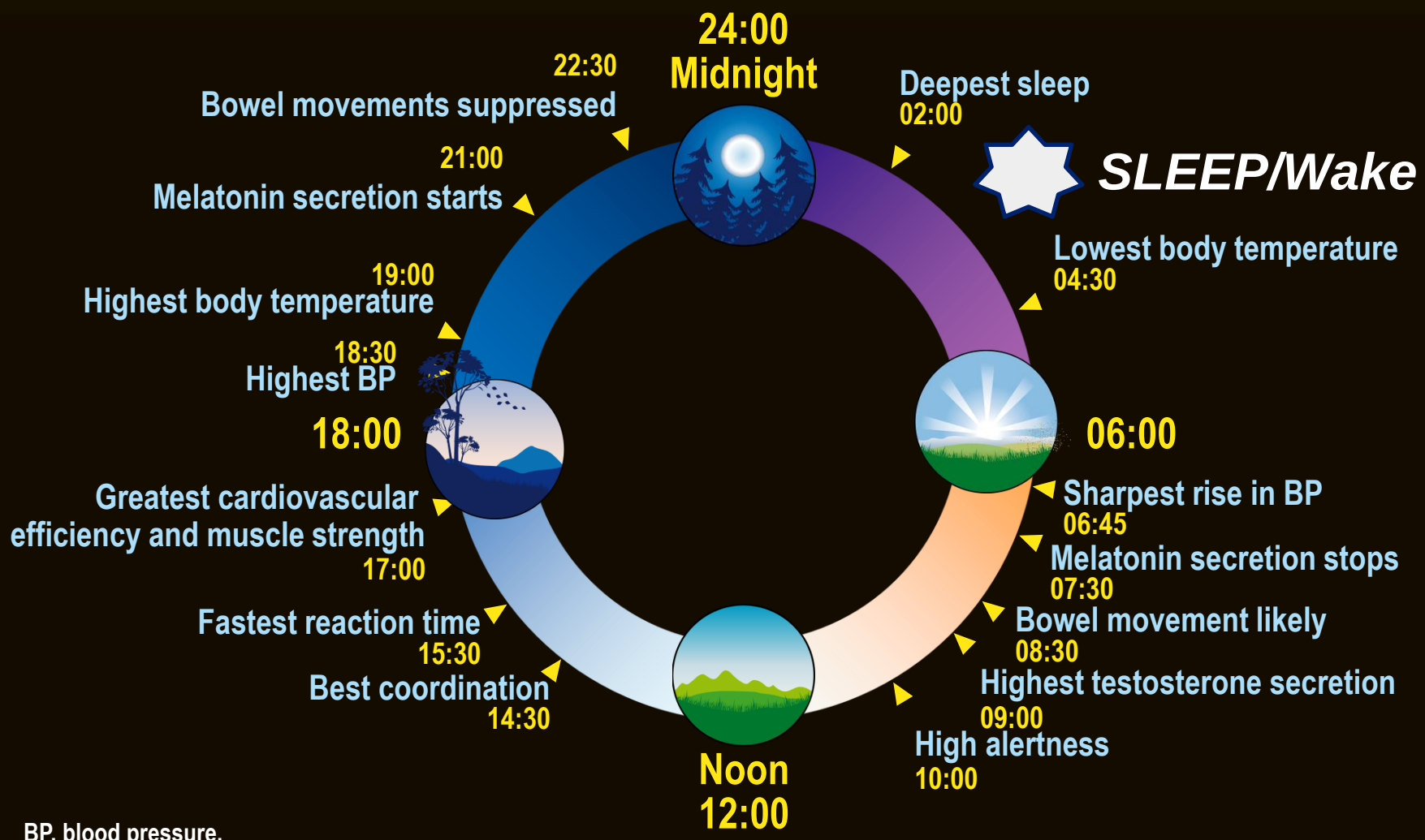
P01 AG11412 R01 HL105549 R01 HL098297
R01 HL092140 U10HD063036 UM1HL112856
U01HL111478 *K23 HL091508 * K23NS072283
*5K12HD05588 NCRR-00048 T32 HL07909

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

Circadian Rhythms

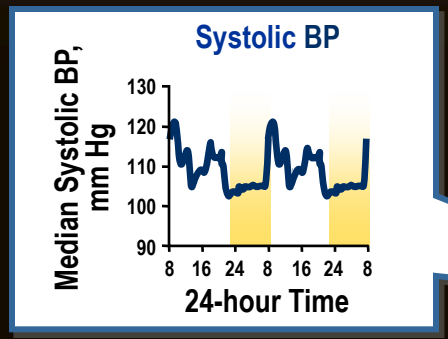
Daily Physiologic and Behavioral Patterns

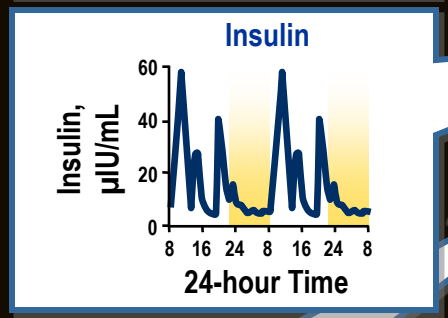


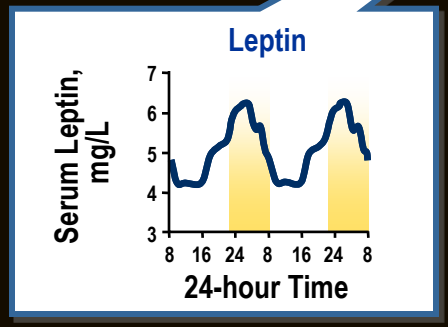
BP, blood pressure.

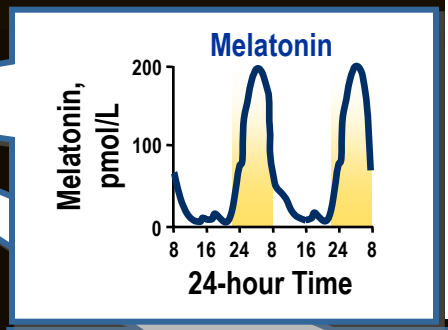
Smolensky M, Lamberg L. *The Body Clock Guide to Better Health*. New York, NY: Henry Holt and Company; 2001.

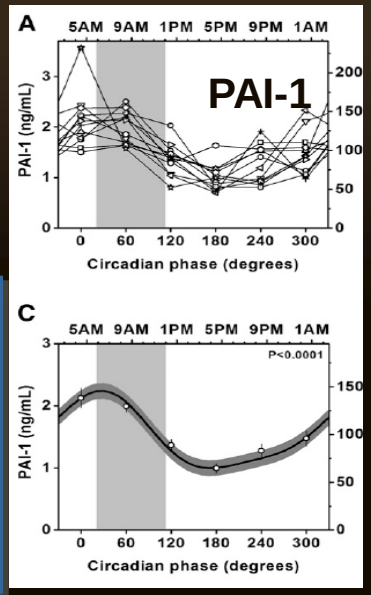
Human Circadian Rhythms
Physiological Cycles

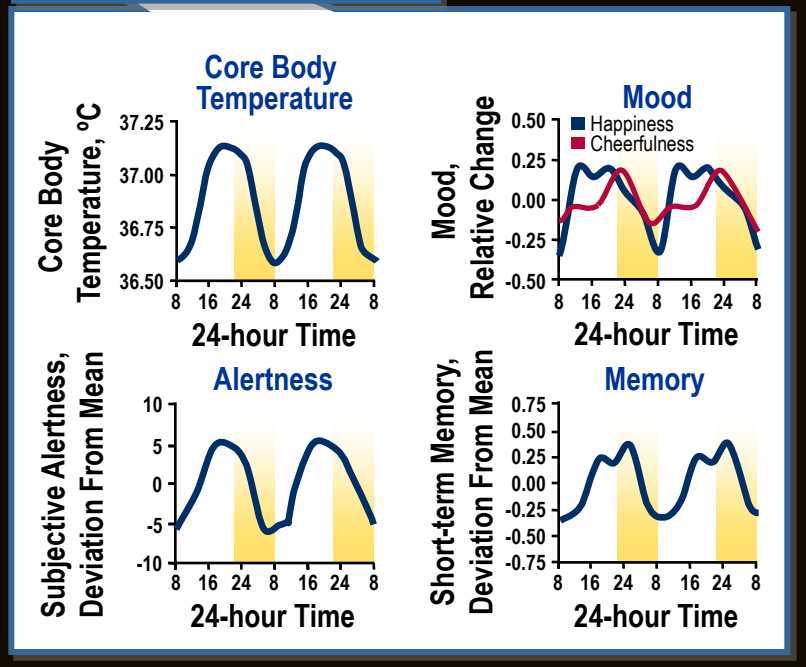






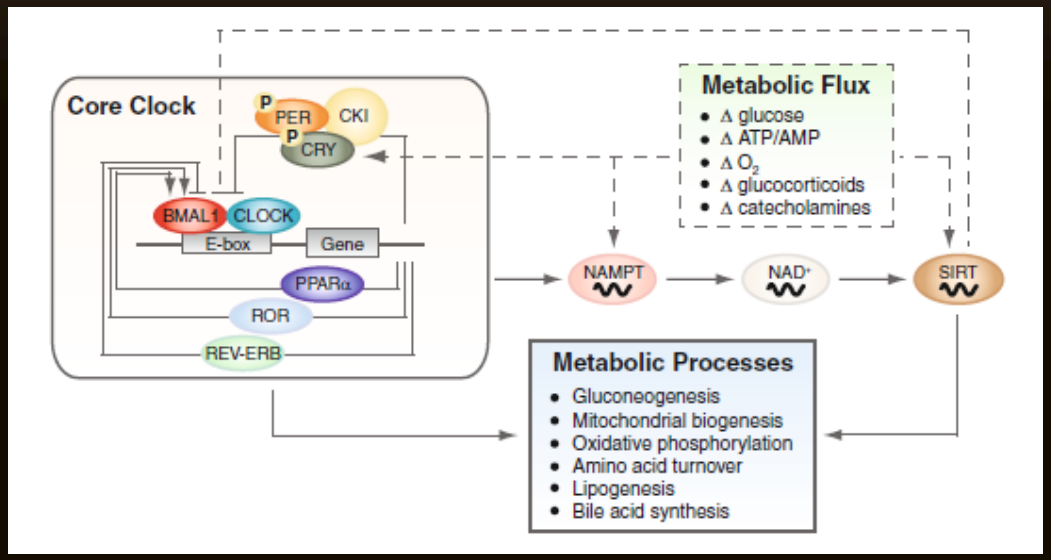


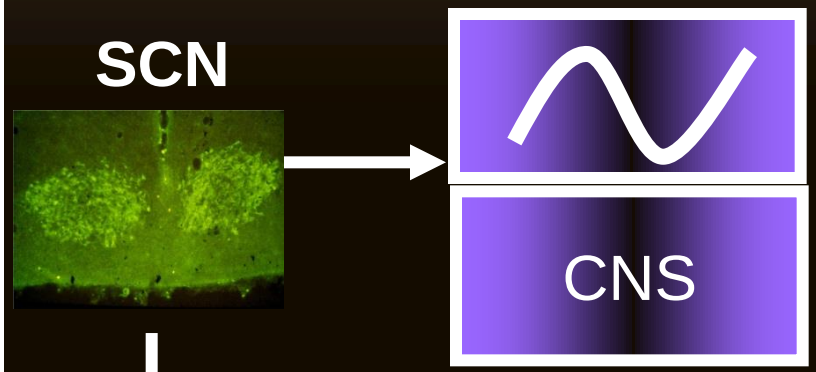




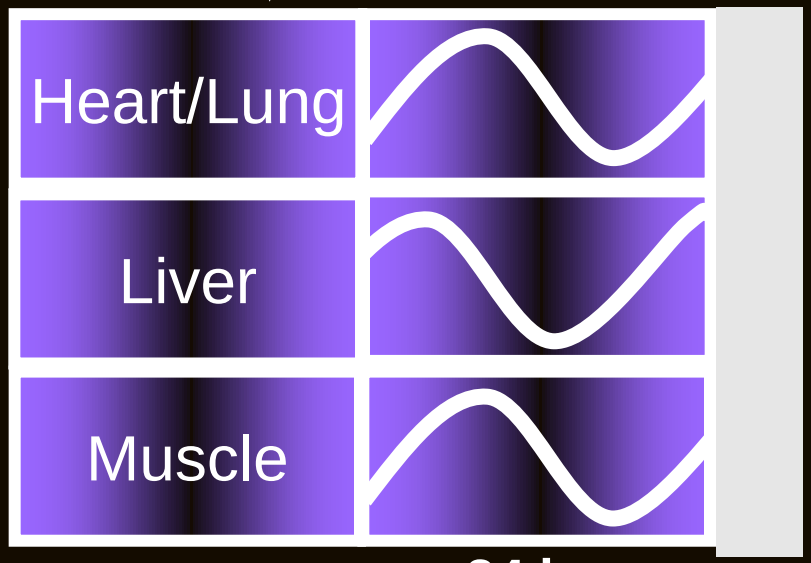
Boivin DB, et al. *Arch Gen Psychiatry*. 1997;54(2):145-152; Johnson MP, et al. *J Sleep Res*. 1992;1(1):24-29;
Li L, et al. *Diabetes Res Clin Pract*. 2008;82(3):359-363; Maywood ES, et al. *Endocrinol*. 2007;148(12):5624-5634;
Scheer FA, et al. *Proc Natl Acad Sci U S A*. 2009;106(11):4453-4458.; Scheer,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

Clock Influence is Everywhere!





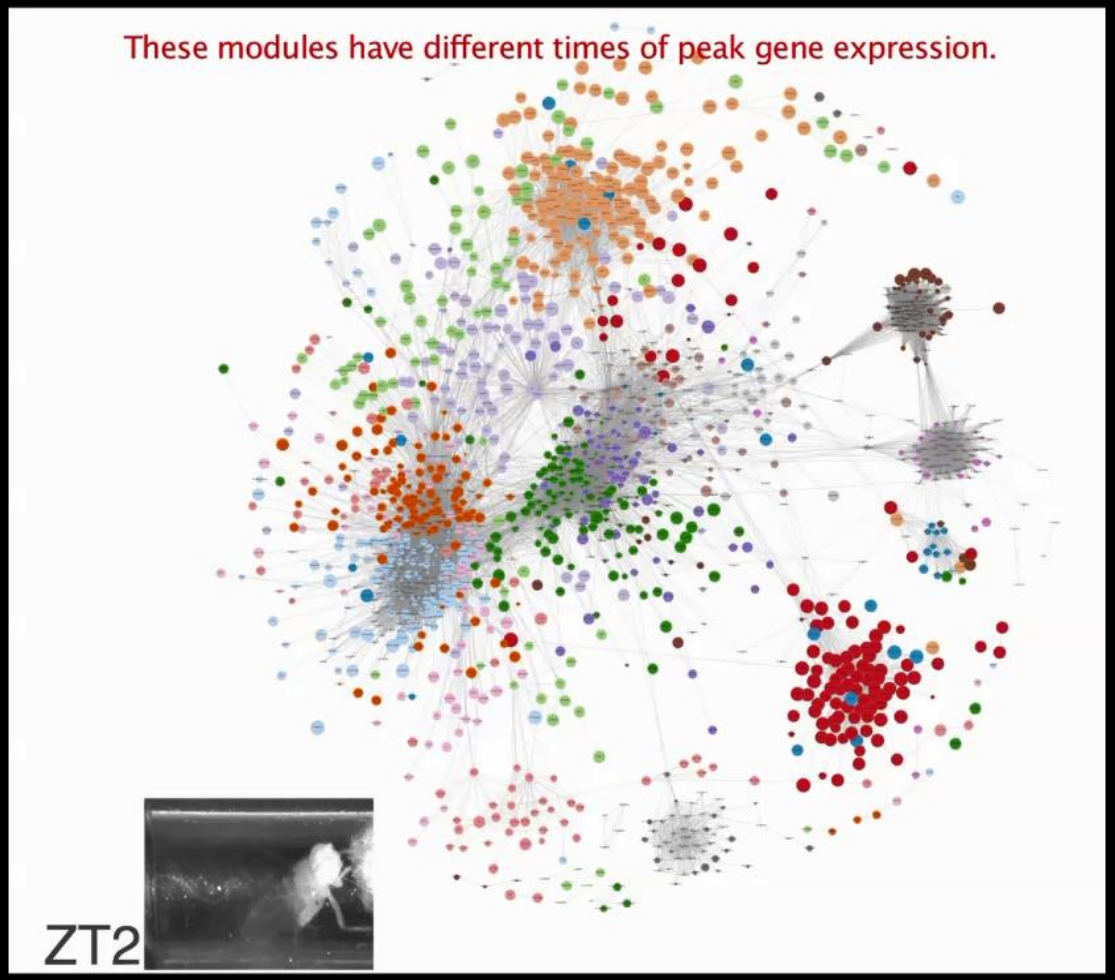
Appropriately aligned rhythms



Rhythmic expression of clock genes has been found in many tissues and (10%-20%) of all genes are rhythmic)

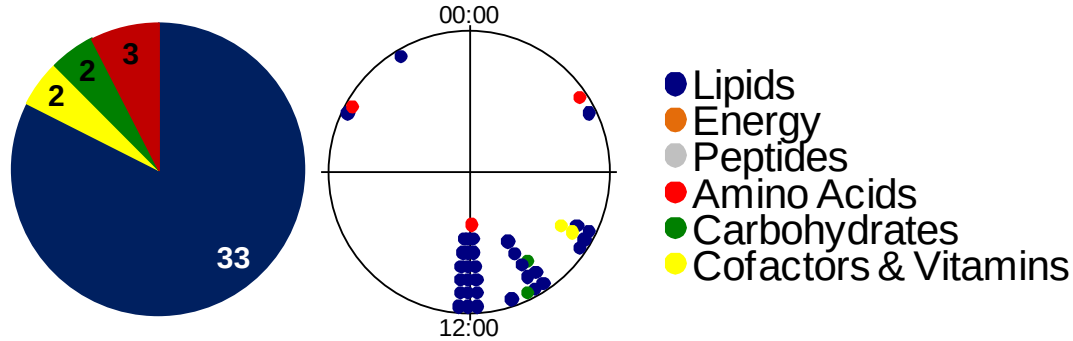
Marcheva et al, 2013

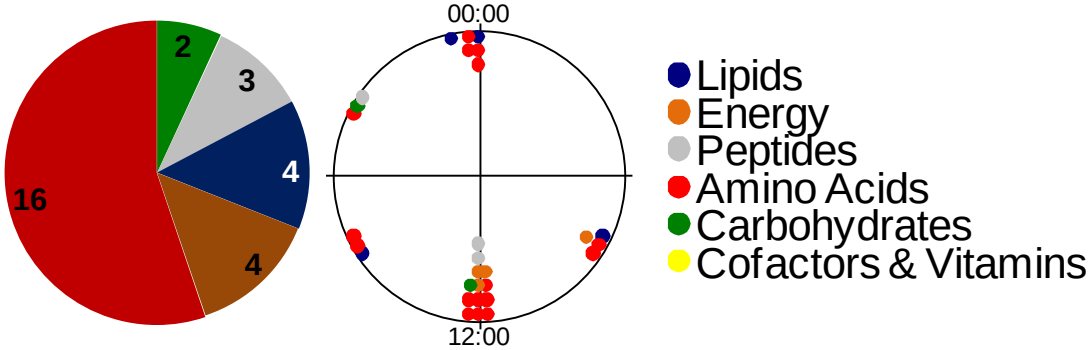
Gene expression changes across time of day

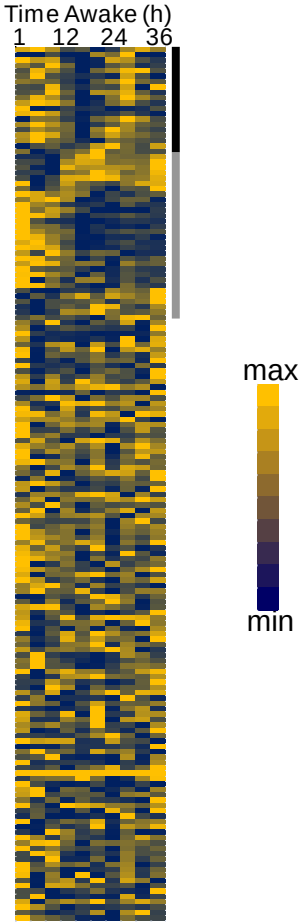


Courtesy: Ravi Allada, A. Hutchinson

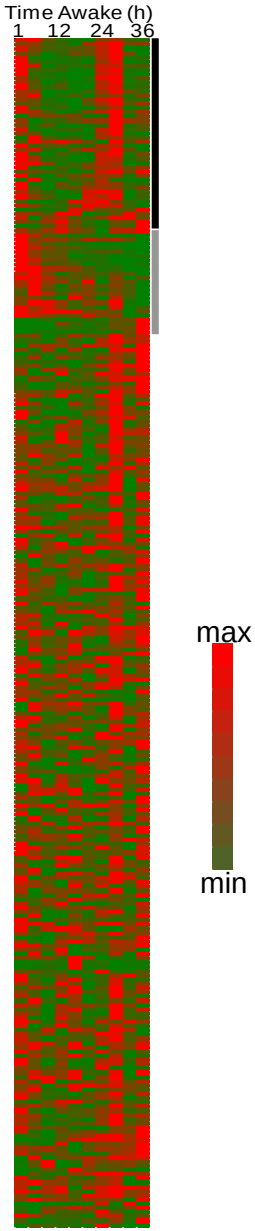
15% of Genes and Metabolites are Rhythmic







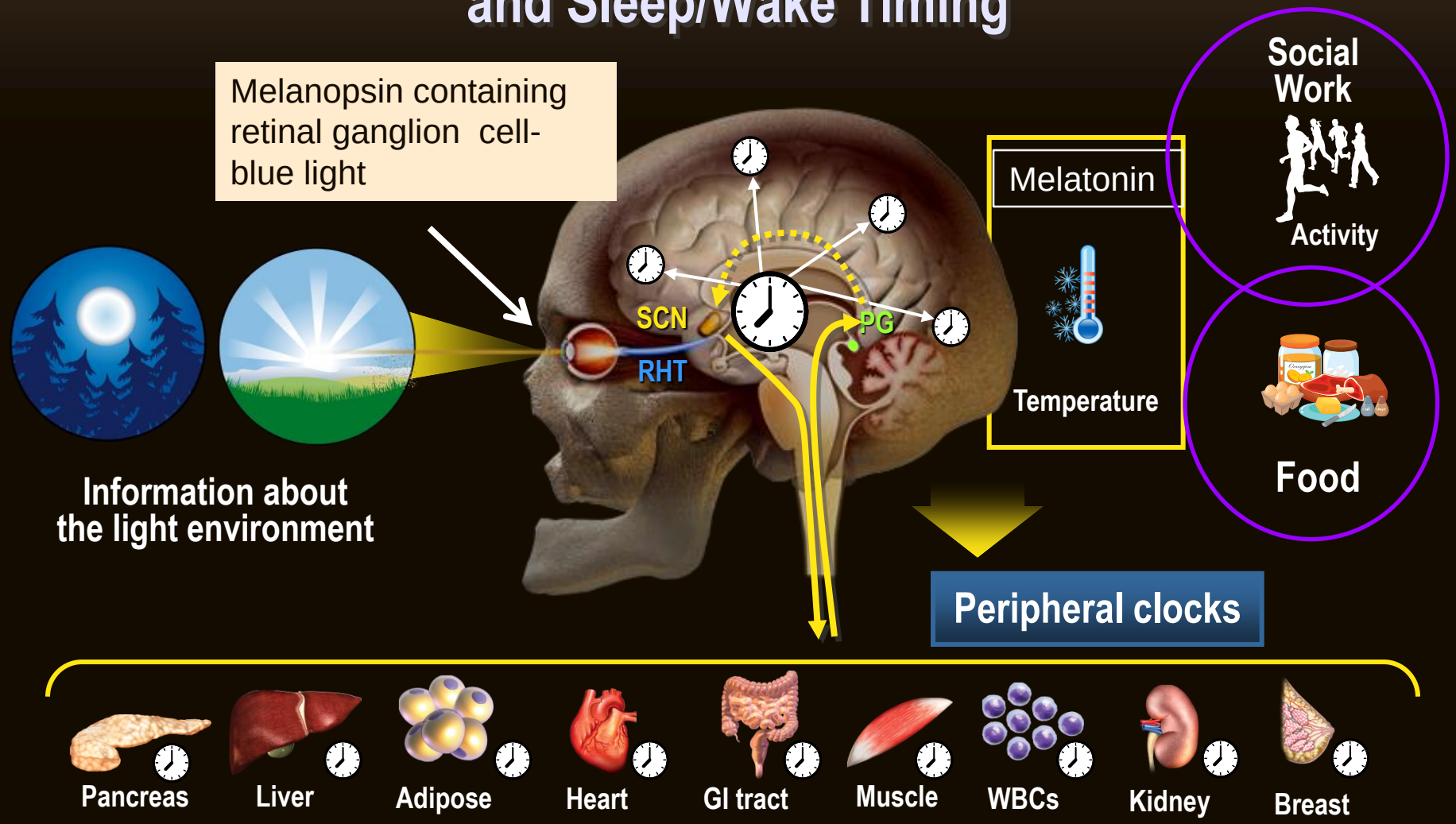
Saliva



Blood

(Dallmann, PNAS 2012)

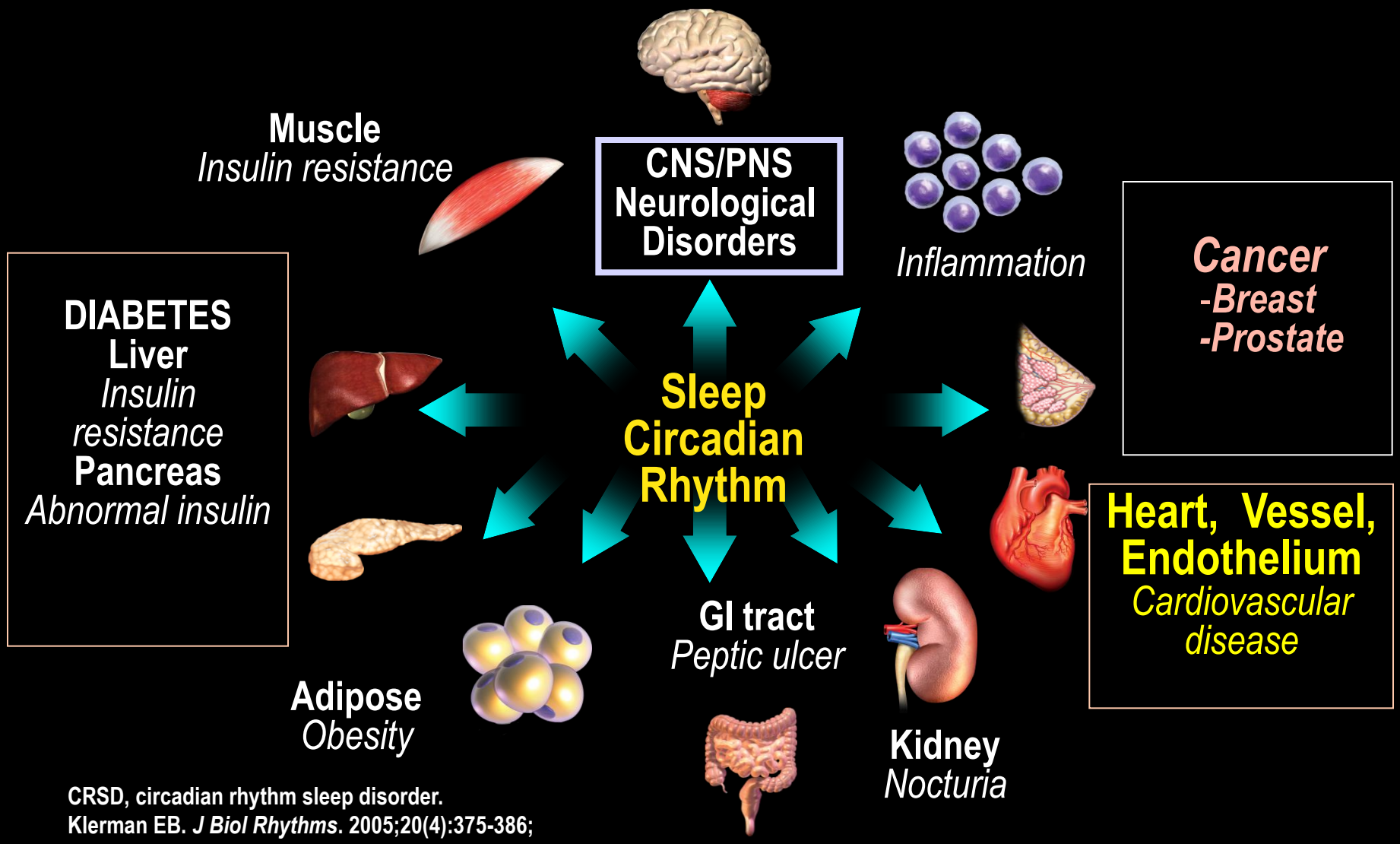
Determinants of Circadian Rhythms and Sleep/Wake Timing



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.

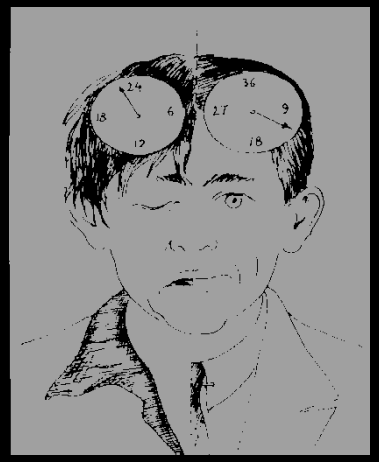
Circadian and Sleep Health
Implications for Health and Disease



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.

From Clocks to Disease: Rapid Evolution of Circadian Clock Field

2008*Nature* 458, 142-144



National Institute of Mental Health (2008)

National Institutes of Neurological Disorders and Stroke

National Heart, Lung and Blood Institute

National Institute of Diabetes and Digestive and Kidney Diseases

National Institute on Aging

National Institute on Alcohol Abuse and Alcoholism

National Institute of Arthritis and Musculoskeletal and Skin Diseases

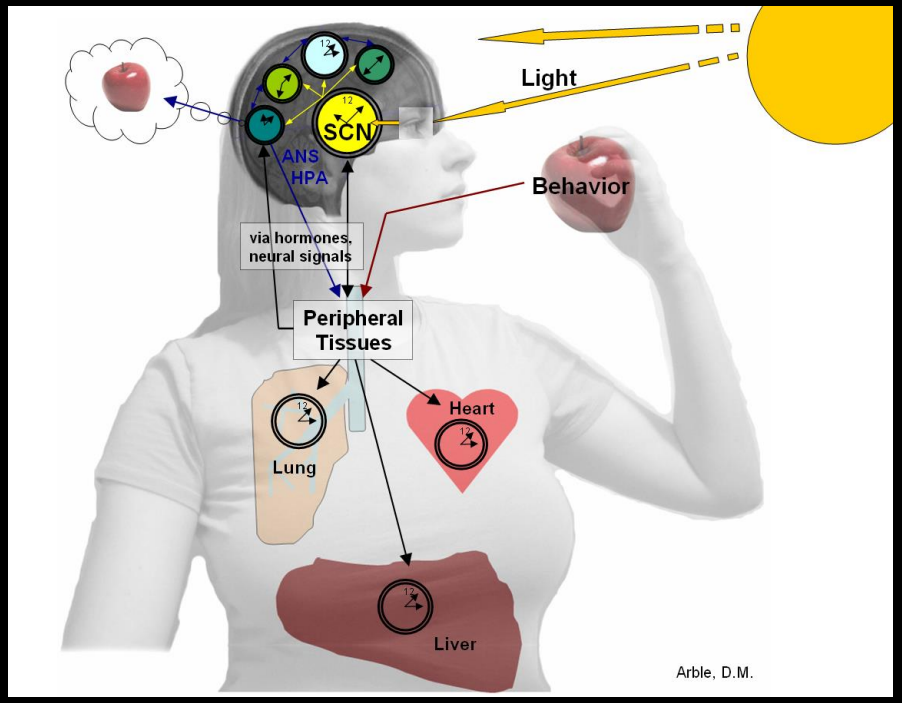
National Cancer Institute

Eunice Shriver National Institutes of Child and Health Development

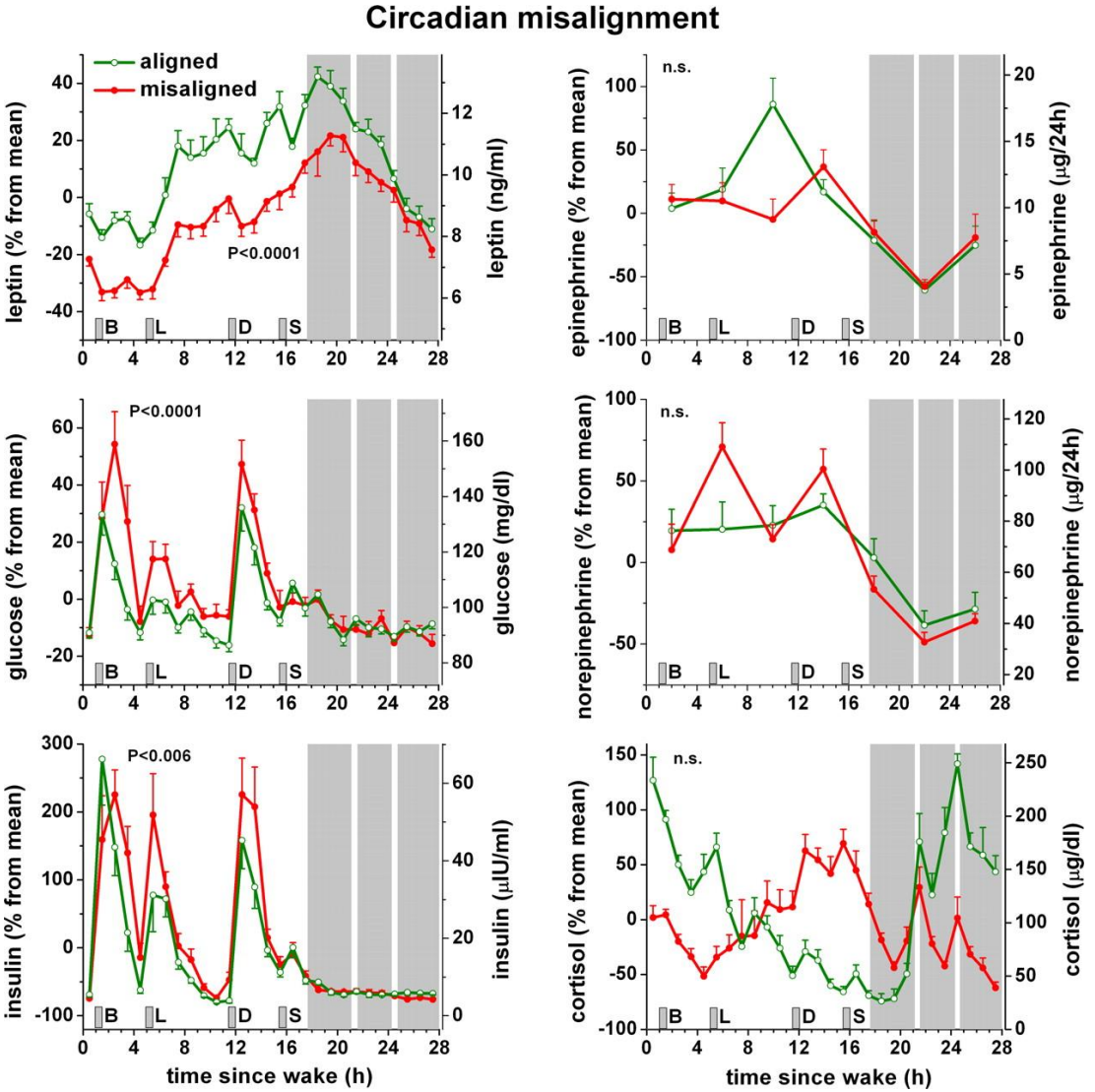
More…….

Circadian Timing, Metabolism, Cardiovascular Function and Risk for Obesity in Humans

Circadian misalignment is associated with adverse effects on appetite, glucose metabolism, cardiovascular function



Consequences of circadian misalignment on metabolic, autonomic, and endocrine function



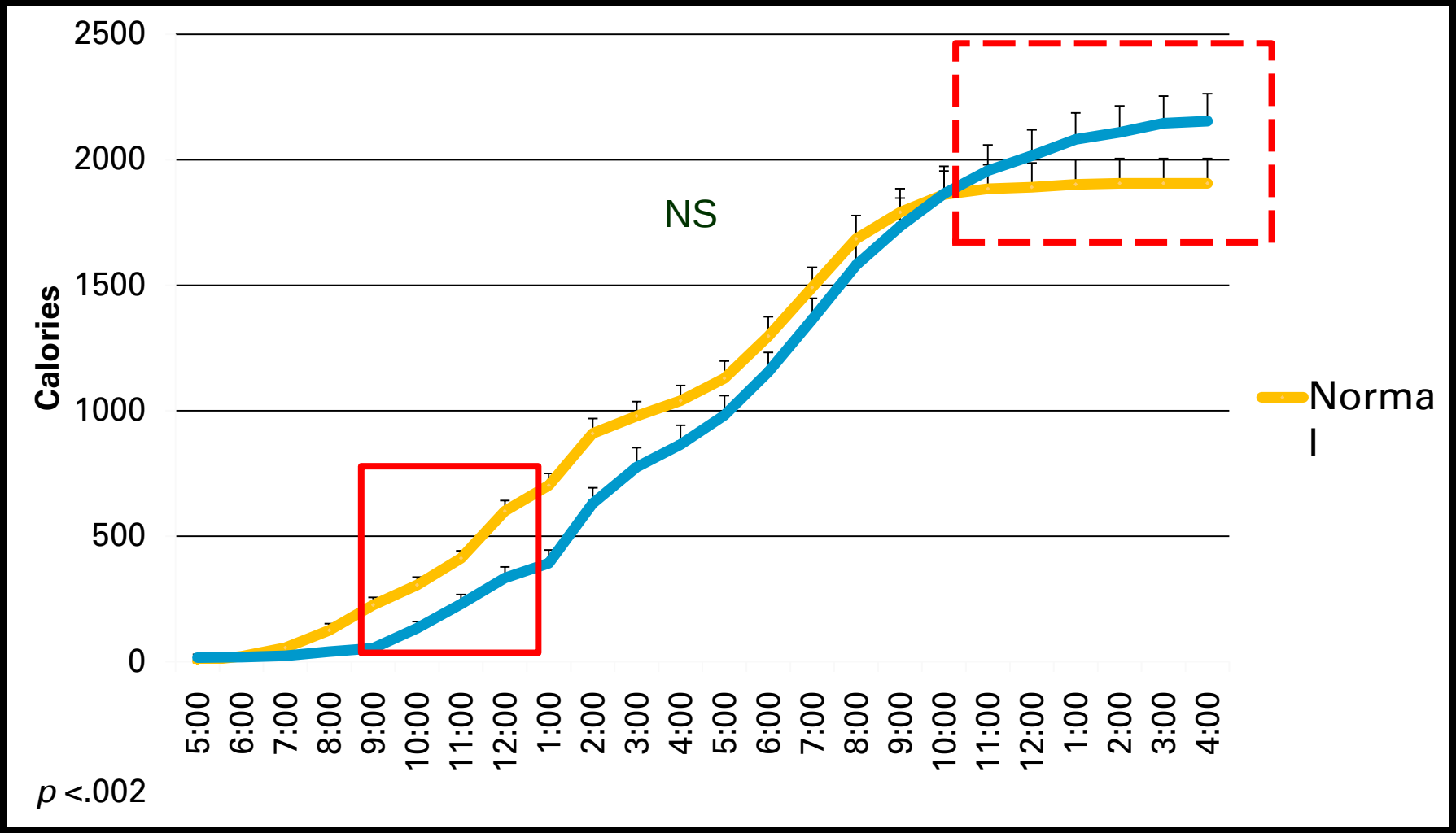
Scheer F. A. J. L. et.al. PNAS 2009;106:4453-4458

PNAS

Role of Sleep Timing, Food Timing and Light Exposure on Weight and Metabolism

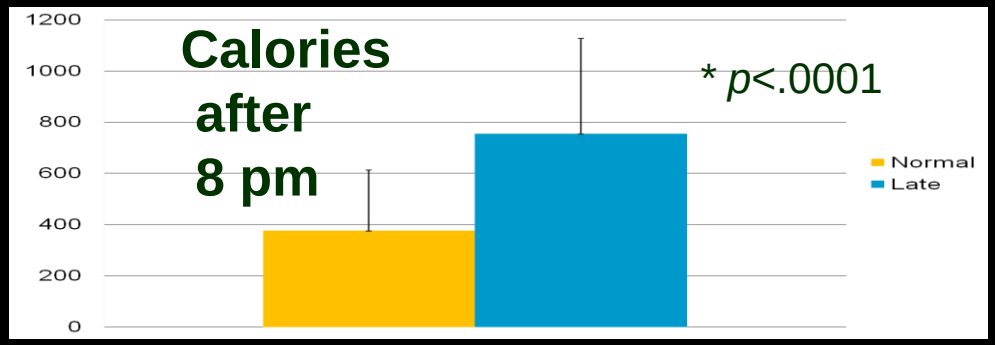
Kathryn Reid, PhD, Kelly Glaser-Baron, PhD, Ivy Cheung

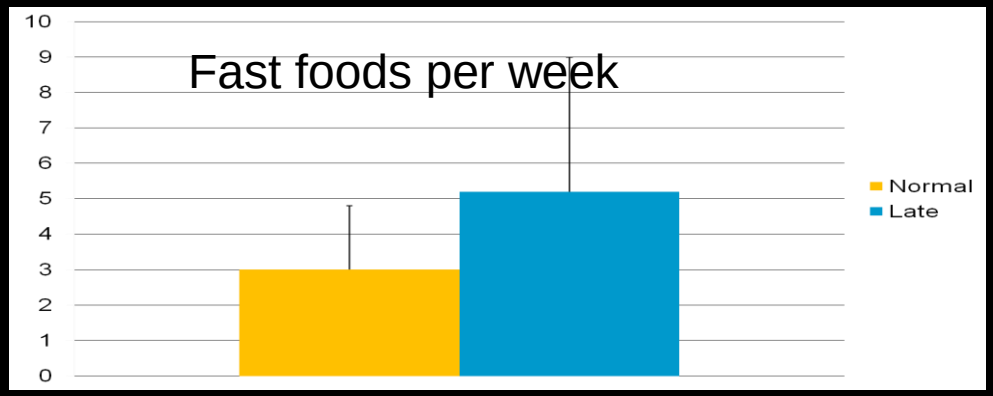
Cumulative Calorie Intake: Late Sleepers (midpoint after 5 AM)

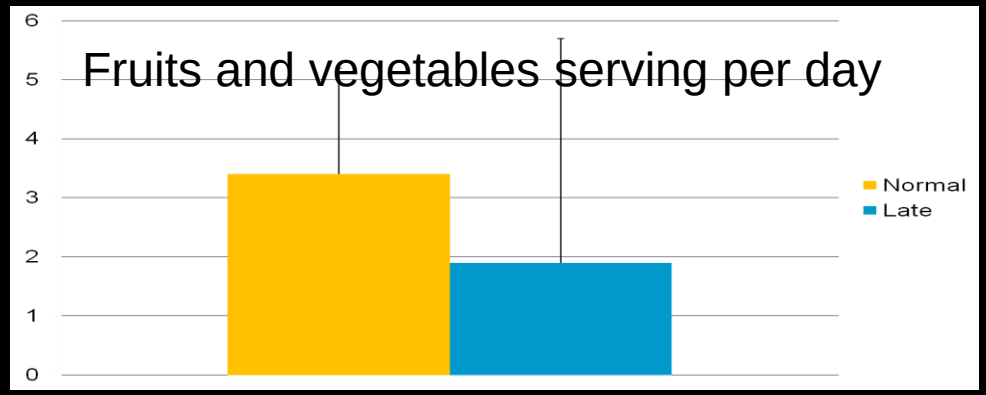


Baron KG et al, Obesity, 2011

Food Intake and Sleep Timing







The New York Times
Well
Tara Parker-Pope on Health

SEPTEMBER 3, 2009, 1:24 PM

Late Night Eating Linked to Weight Gain

By Sudeep Chand
Health reporter, BBC News

Late-night snackers are more likely to gain weight, research suggests.

A team from Northwestern University, Illinois, found that when you eat, not just how you eat, could make a big difference.

Scientists found that when mice ate at unusual hours, they put on twice as much weight, despite exercising and eating as much as others.

The study, in the journal Obesity, is said to be the first to show directly that there is a "wrong" time to eat.

Recent studies have suggested that circadian rhythms, the body's internal clock, have a role in how our bodies use up energy. However, this had been difficult to definitively pin down.

Deanna Arble, lead author of the study, said: "One of our research interests is shift workers, who tend

Eating in the middle of the night has been linked to obesity

"How or why a person gains weight is very complicated - but it is clearly not just calories in and calories out"
Fred Turek
Center for Sleep and Circadian Biology

LE FIGARO·fr

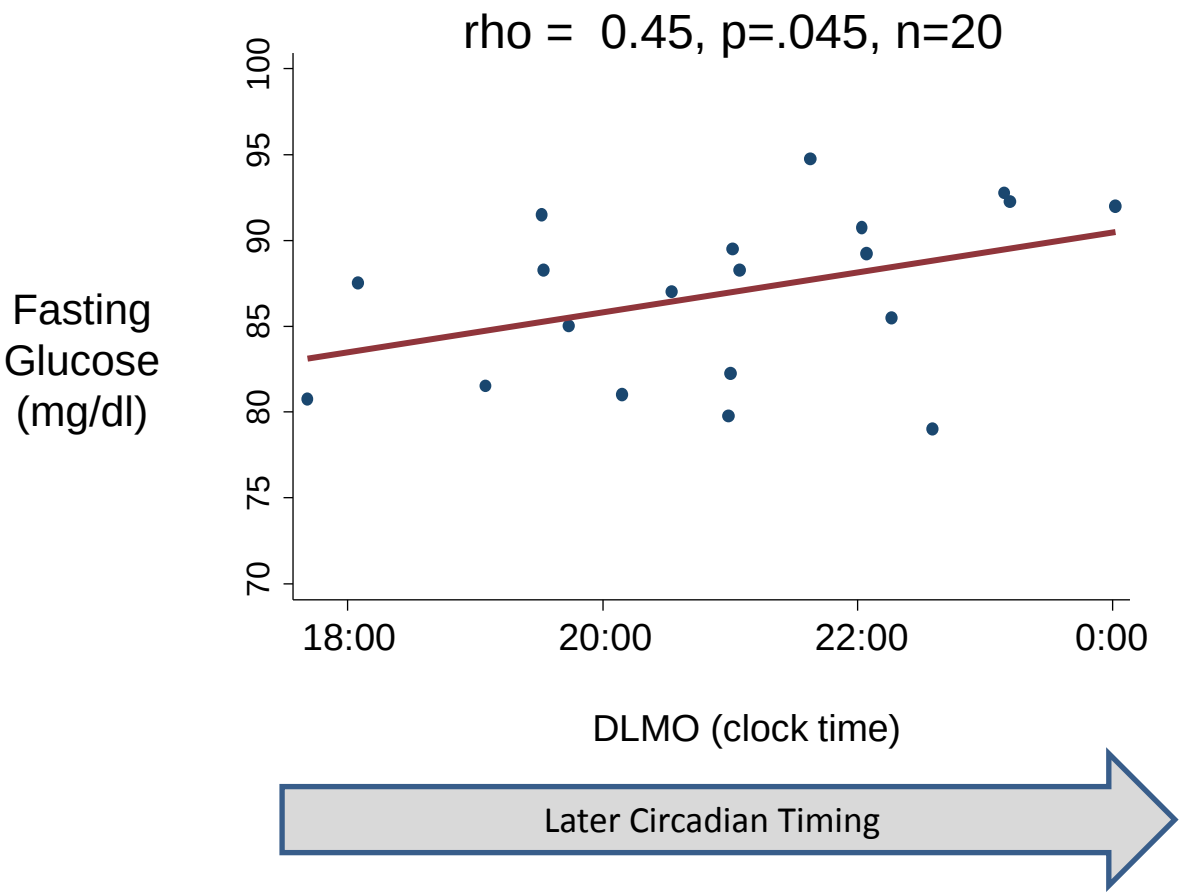
Lutter contre l'obésité en mangeant à la bonne heure

Sandrine Cabut
04/09/2009 | Mise à jour : 12:10 | Commentaires 1 | Ajouter à ma sélection

Eating at irregular hours might pack on the pounds

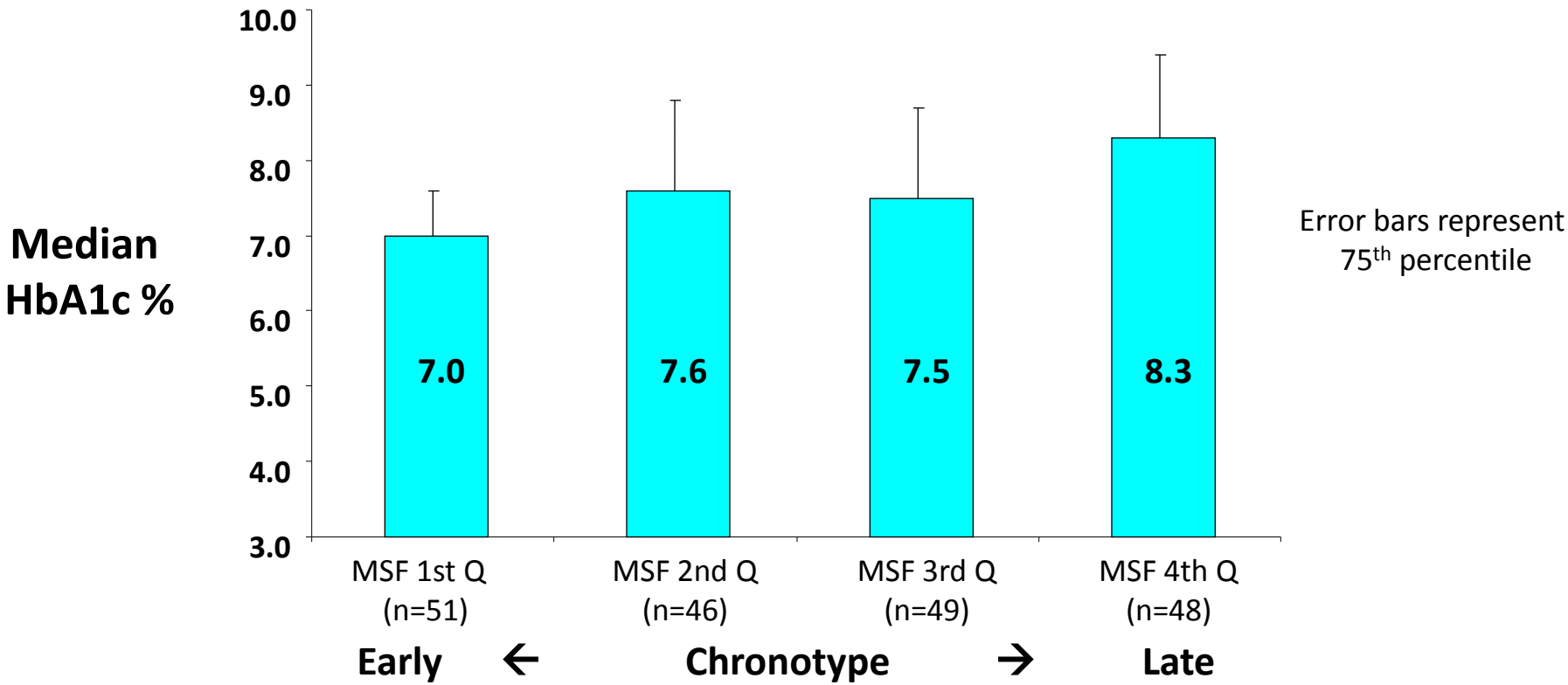
CHICAGO SUN-TIMES

Circadian Timing and Fasting Glucose



NIDDK R01 (PI Knutson):Preliminary Data

Chronotype & Glycemic Control in Type 2 Diabetes



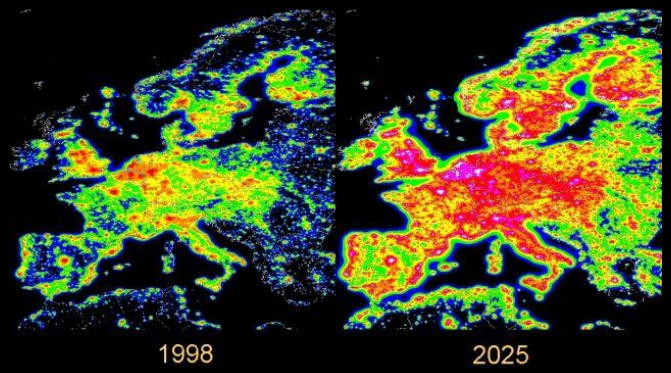
P=.001 after adjusting for age, sex, race, BMI, insulin use, depressed mood, diabetes complications, and perceived sleep debt.

Reutrakul *et al*, Diabetes Care 2013

Too much, too little at the wrong time.. Light Exposure Contribution to Obesity?

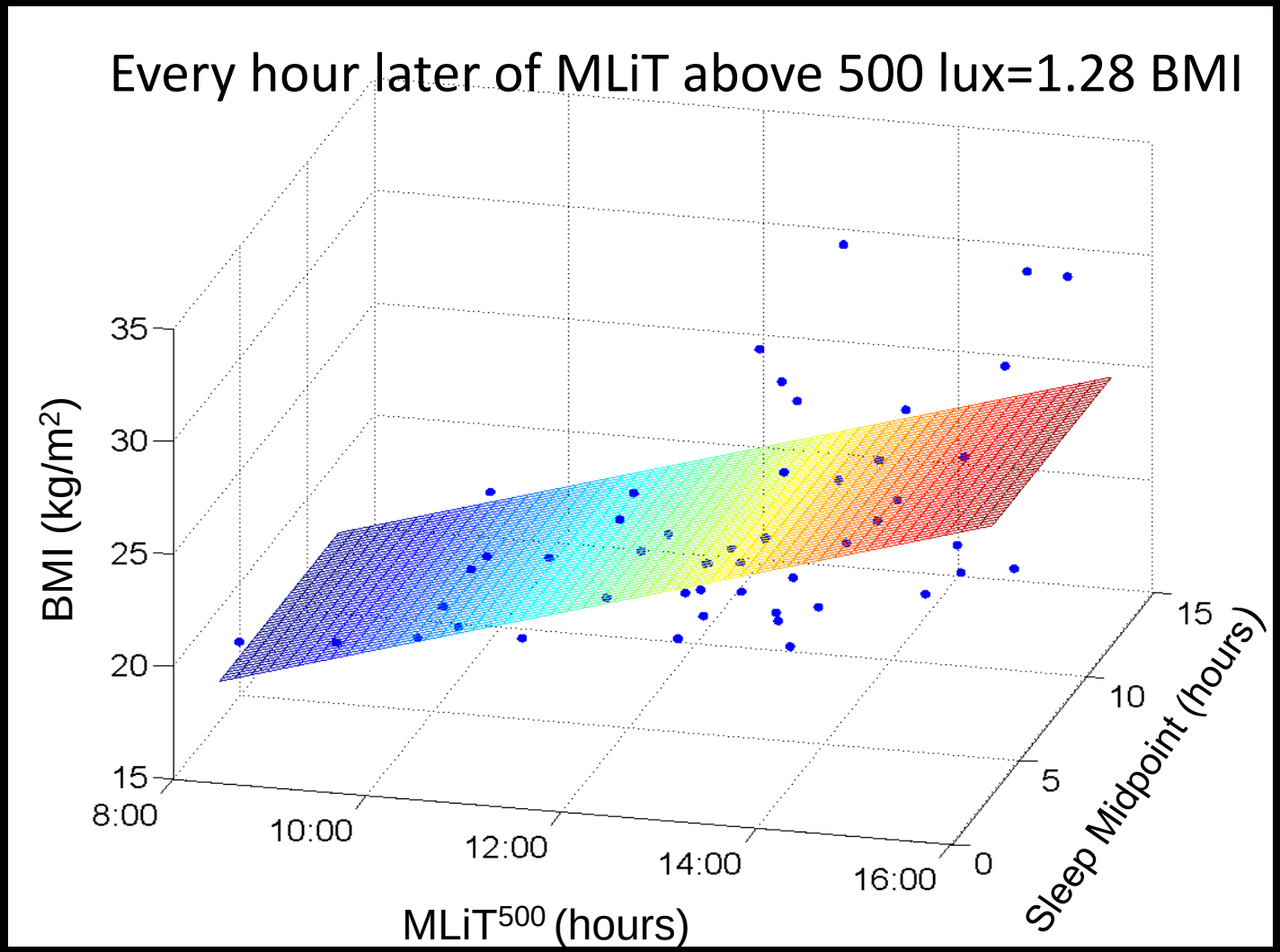
250,000 years: Fire
5,000 years: Candles
250 years: Gas lighting
120 years: Electric lighting

LIGHT POLLUTION



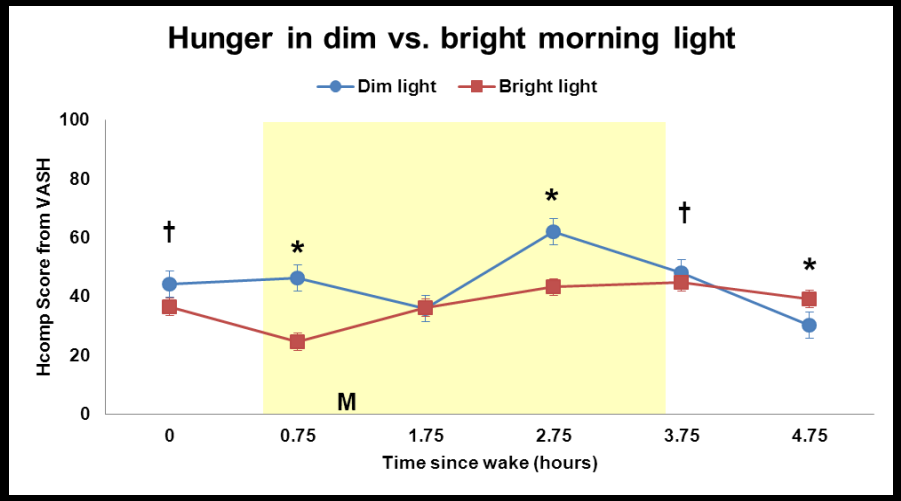
Cinzano, Falchi, Elvidge, United Nations Special Environmental Symposium, Vienna (12-16 Luglio1999)

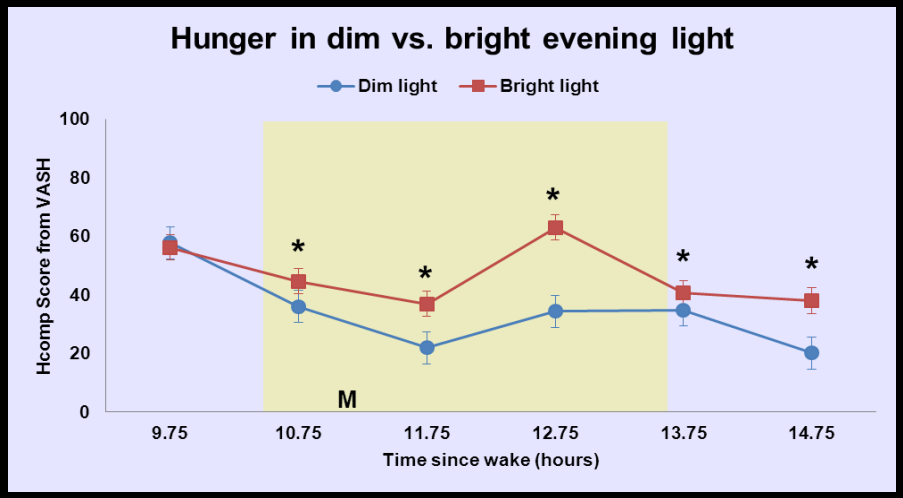
Timing of Mean Light Exposure and BMI

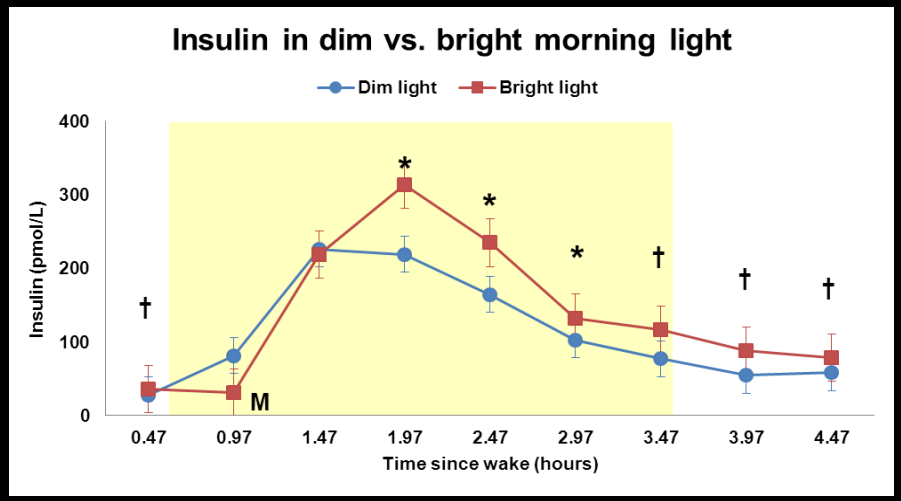


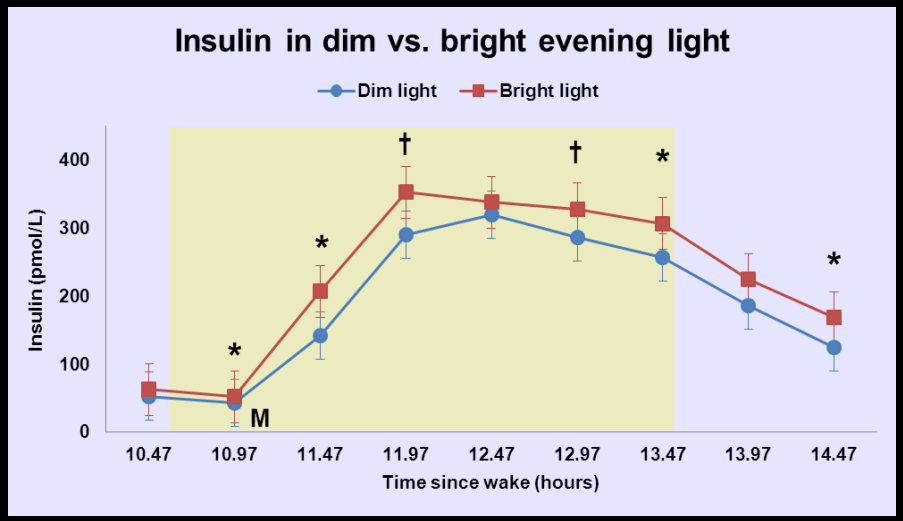
Reid, Santostasi, et al, PLOS One 2014

Effect of Light on Hunger and Metabolism





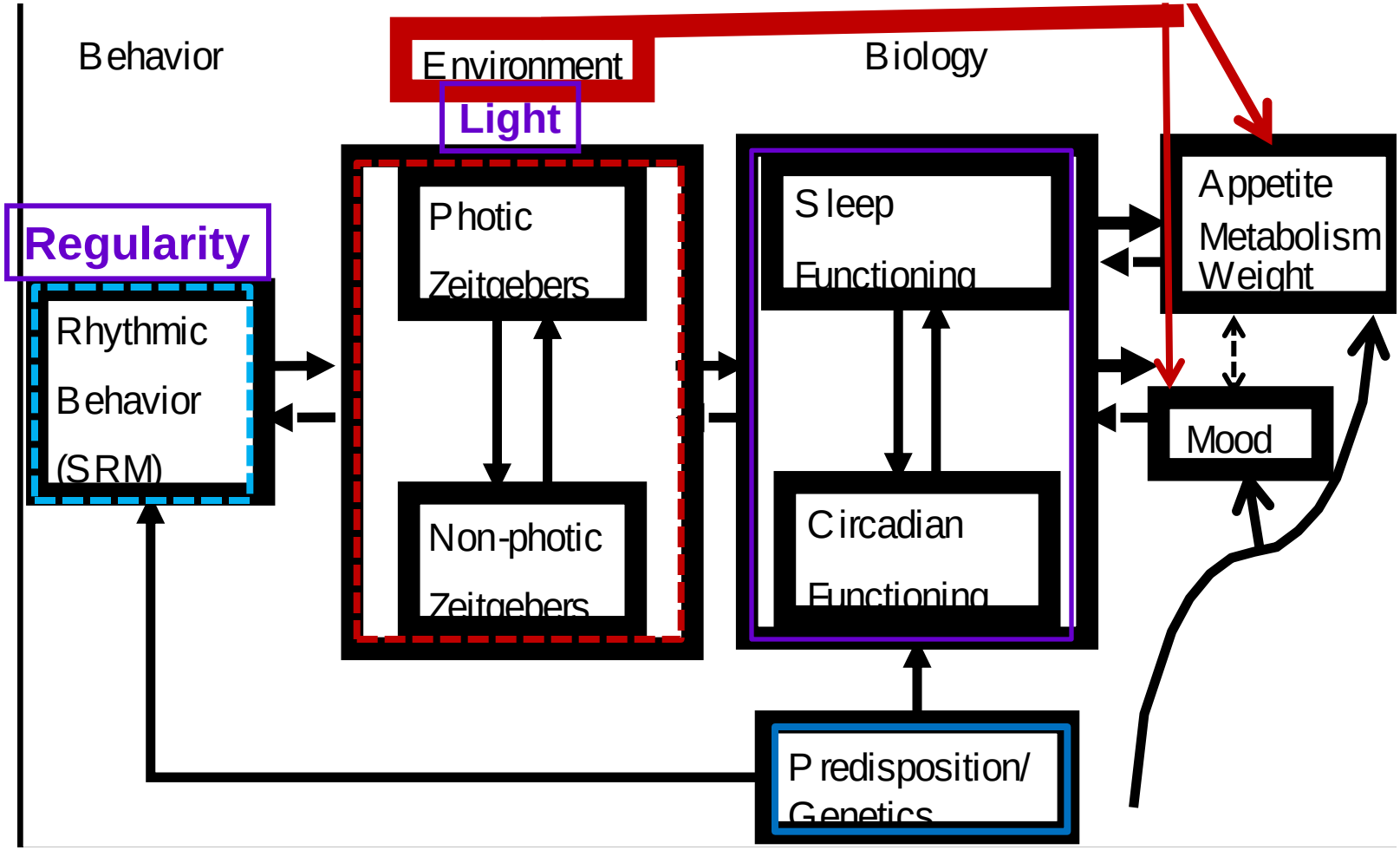




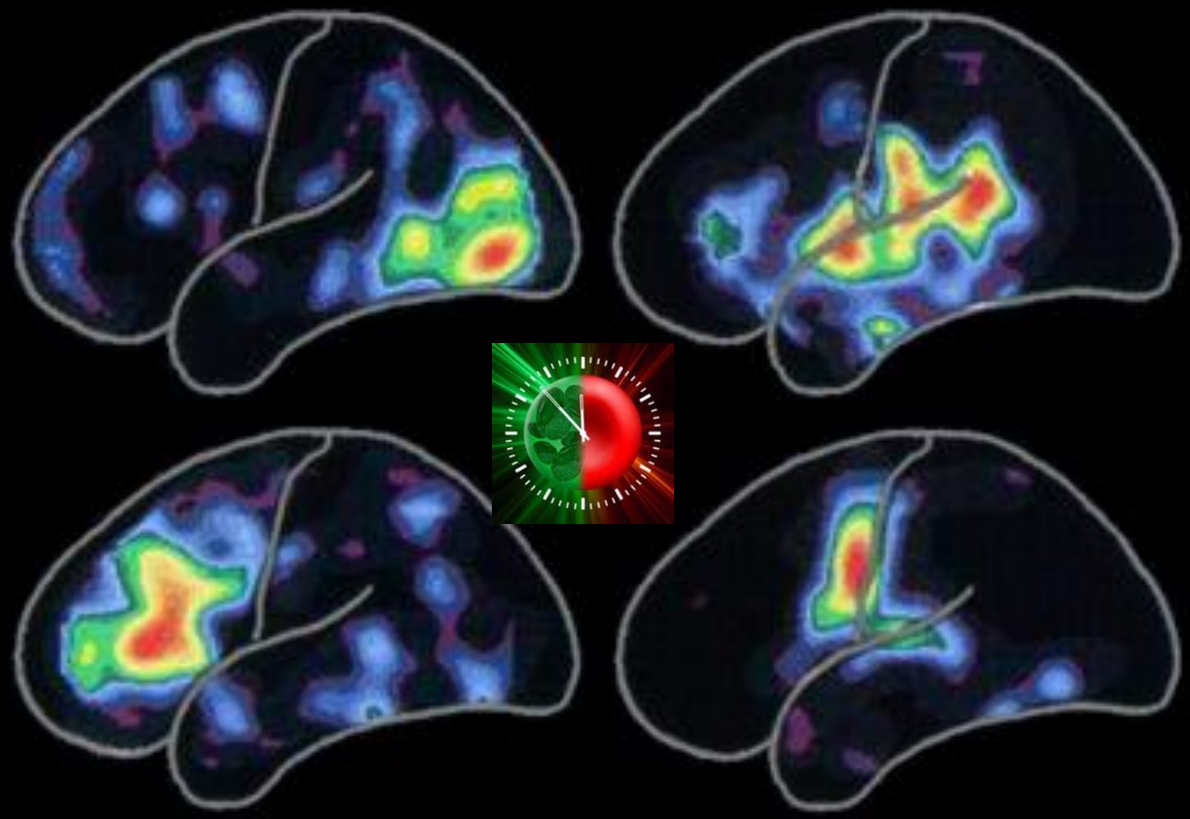
Yellow shading indicates light exposure; M denotes meal; * $p<.05$, † $p\leq0.10$

N=14 per group

Regulating light exposure, timing of food intake: Novel approaches to weight Regulation in humans?



Circadian Clocks, Sleep and Neurodegeneration



Classical View

Circadian rhythm and sleep-wake cycle disturbances are consequence of neurodegeneration.

Circadian and sleep/wake disruption exacerbate symptoms of neurodegeneration.

Improving circadian rhythms and sleep are primarily symptomatic treatments

Neurodegeneration and Altered Daily Rhythms

Alzheimer's

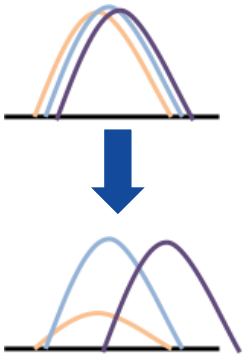
Parkinson's

Huntington's

Traumatic Brain Injury

Chronic Traumatic Encephalophathy

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



Neurodegeneration

↓

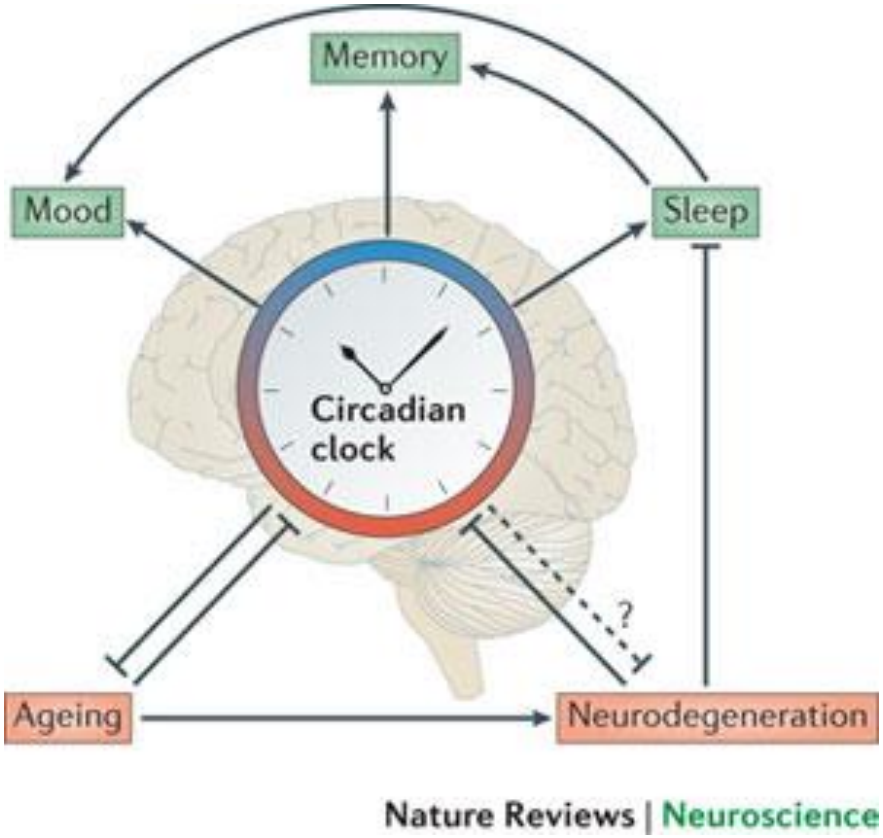
Circadian/Sleep

↓

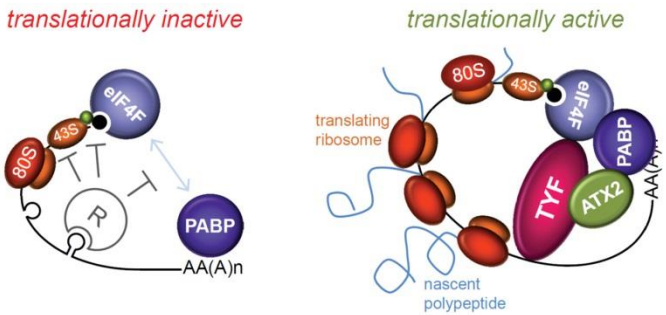
Cognition

<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

Emerging Evidence



Lim and Allada, Science 2013

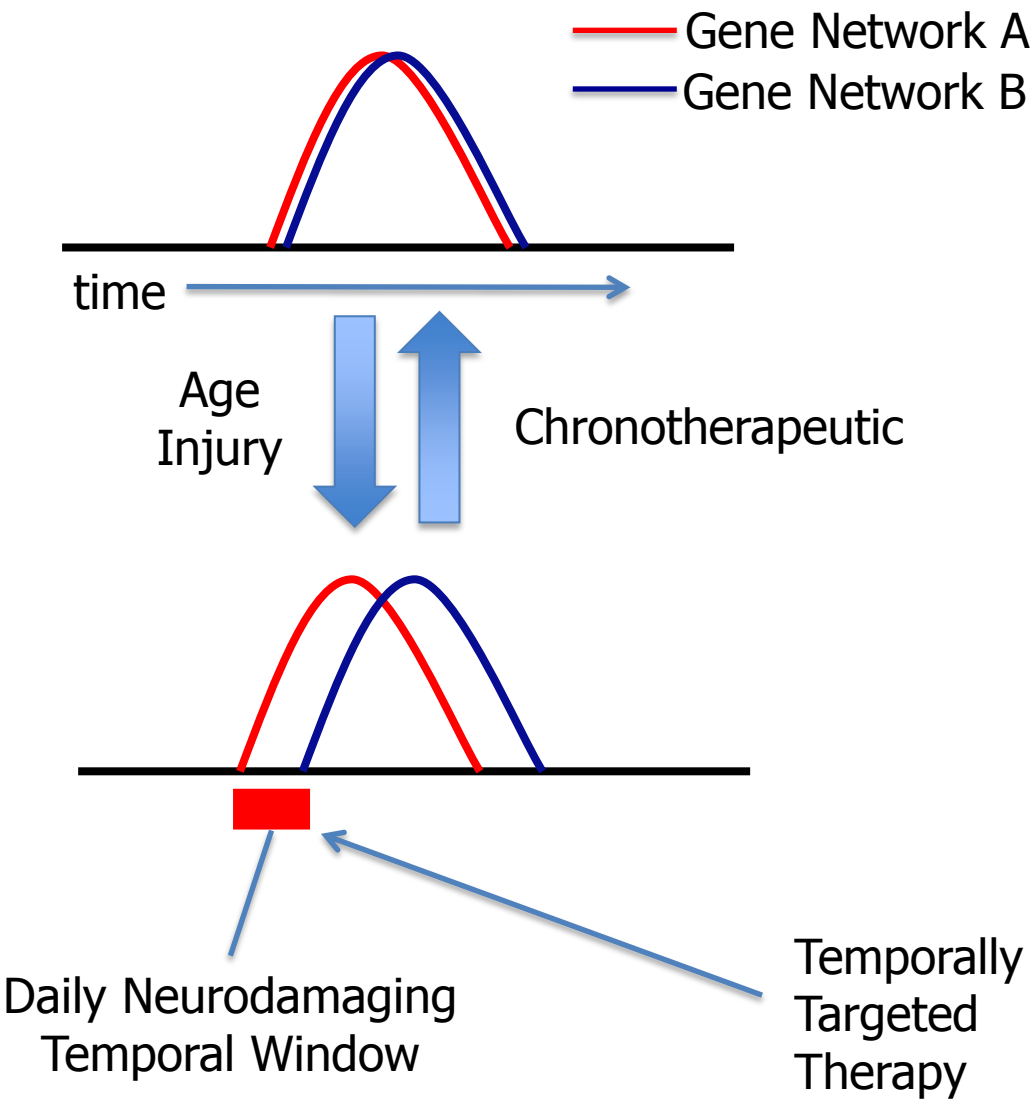


Ataxin 2 (SCA and ALS) activates translation of PER and alters sleep/wake rhythm

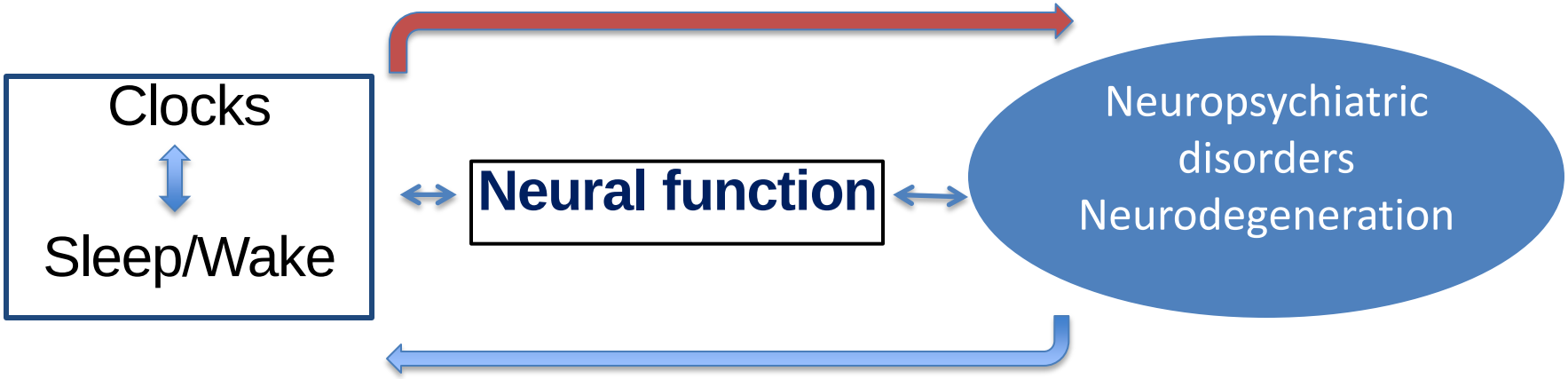
Changes in Cycling Gene Networks as a Basis for Neurodegenerative Diseases

Network A produces damage

Network B protects against damage



Updated View



Circadian and sleep function essential for neural function, connectivity and plasticity

Circadian and sleep disruption contribute to brain disorders (psychiatric, neurodegenerative, neurodevelopmental)

Improving circadian rhythms and sleep as targets for prevention and disease modification.

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

Disturbed sleep - wake cycle in PD
- Pathophysiology -

- Motor symptoms of PD
- Complex medication regimens
- Co-existent sleep disorders (sleep apnea, RLS)
- **Primary neurodegeneration of PD**
  - Central sleep regulation centers
    - Locus coeruleus
    - Raphe nucleus
    - PPT nucleus
    - Hypothalamus (hypocretin 1)
    - **Circadian system?**

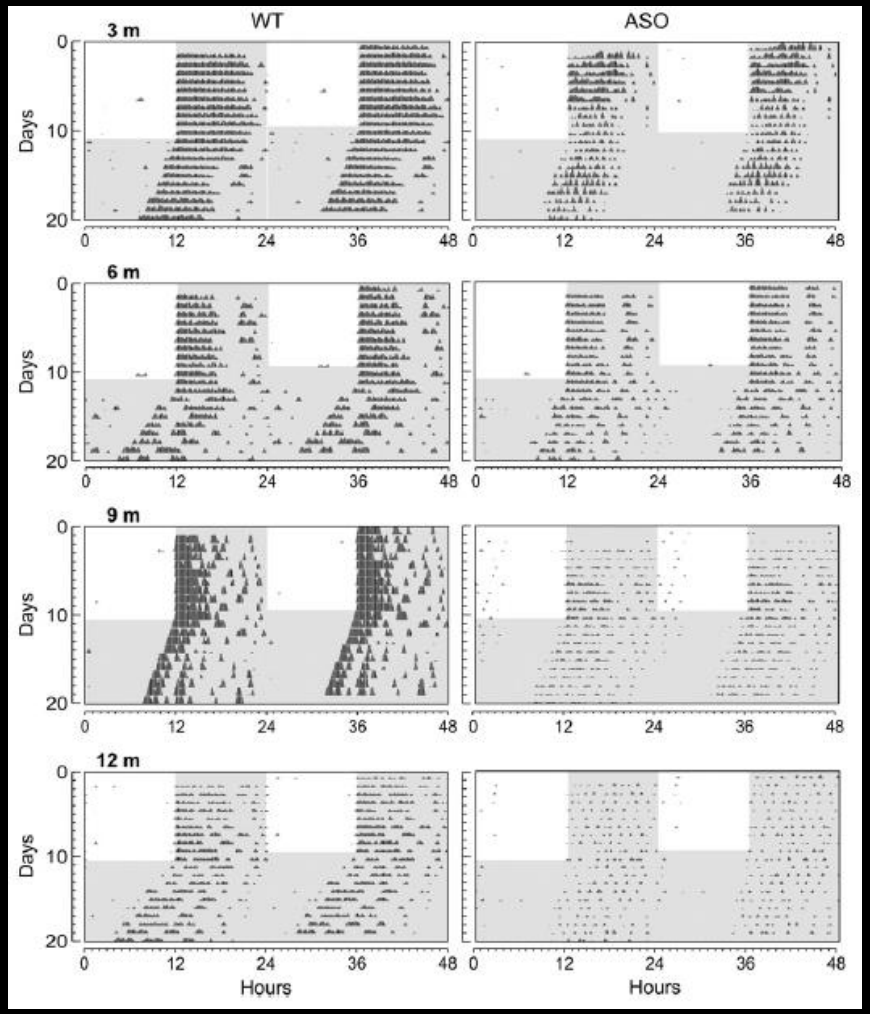
Circadian dysfunction in a mouse model of Parkinson's disease

Takashi Kudo, Dawn H. Loh, Danny Truong, Yingfei Wu, Christopher S. Colwell *

Department of Psychiatry & Biobehavioral Sciences, University of California-Los Angeles, Los Angeles, CA 90024, USA

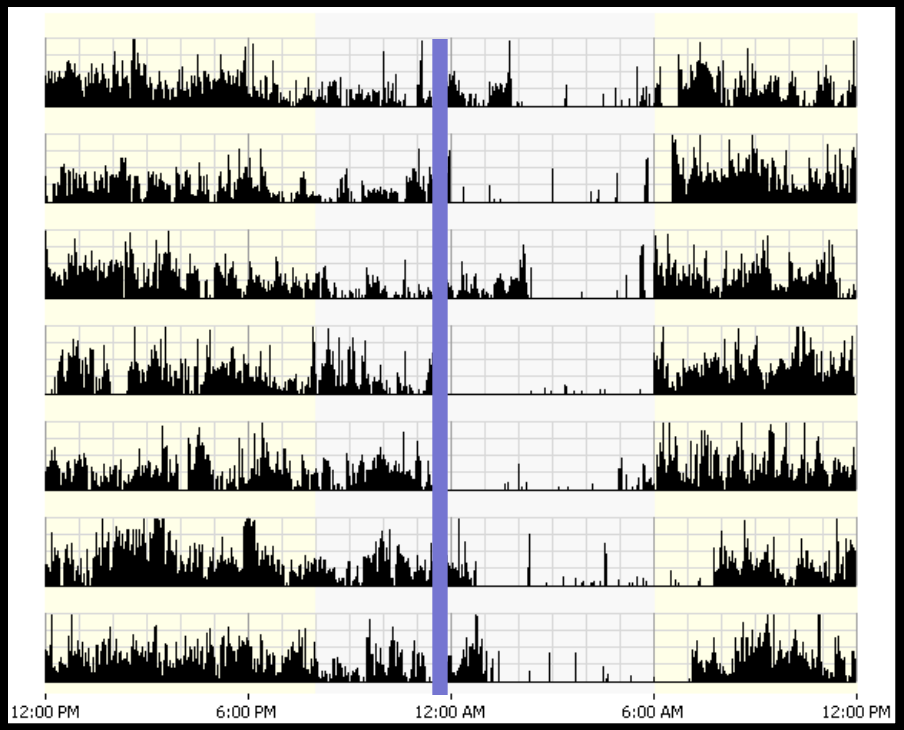
Alpha sinuclein overexpression Model of Parkinson's Disease

Dampened circadian rhythm of Rest-activity of sleep/wake cycle

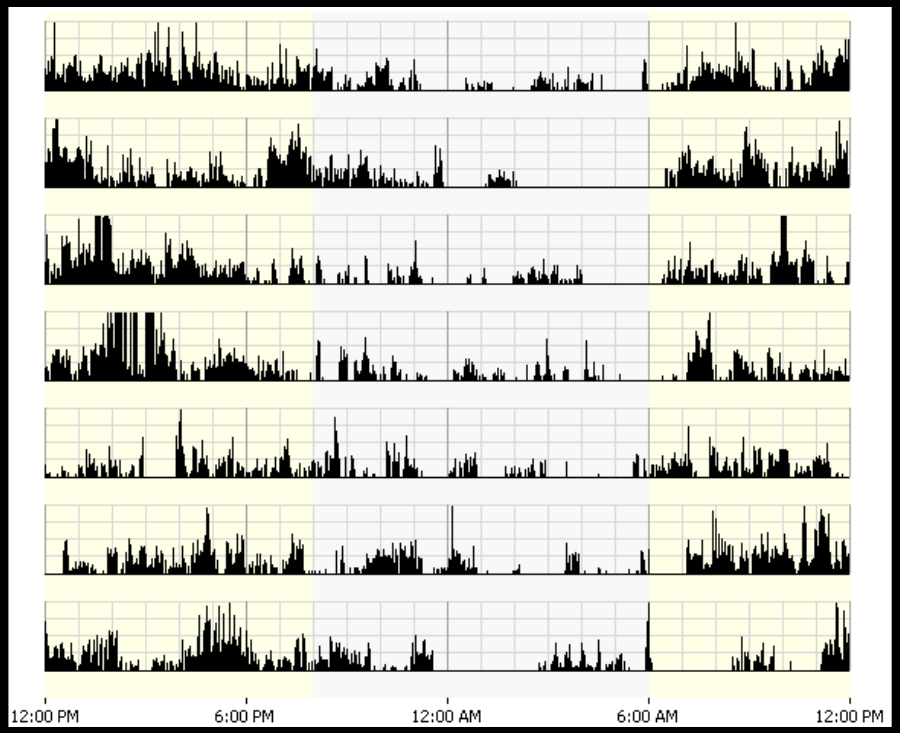


Rest-Activity Rhythm Characteristics Parkinson's Disease

Delayed



Irregular/fragmented



JAMA Neurology, 2014

Circadian Rhythm in PD

Aleks Videnovich K-23 Awardee (NINDS)

PD=20; control 20

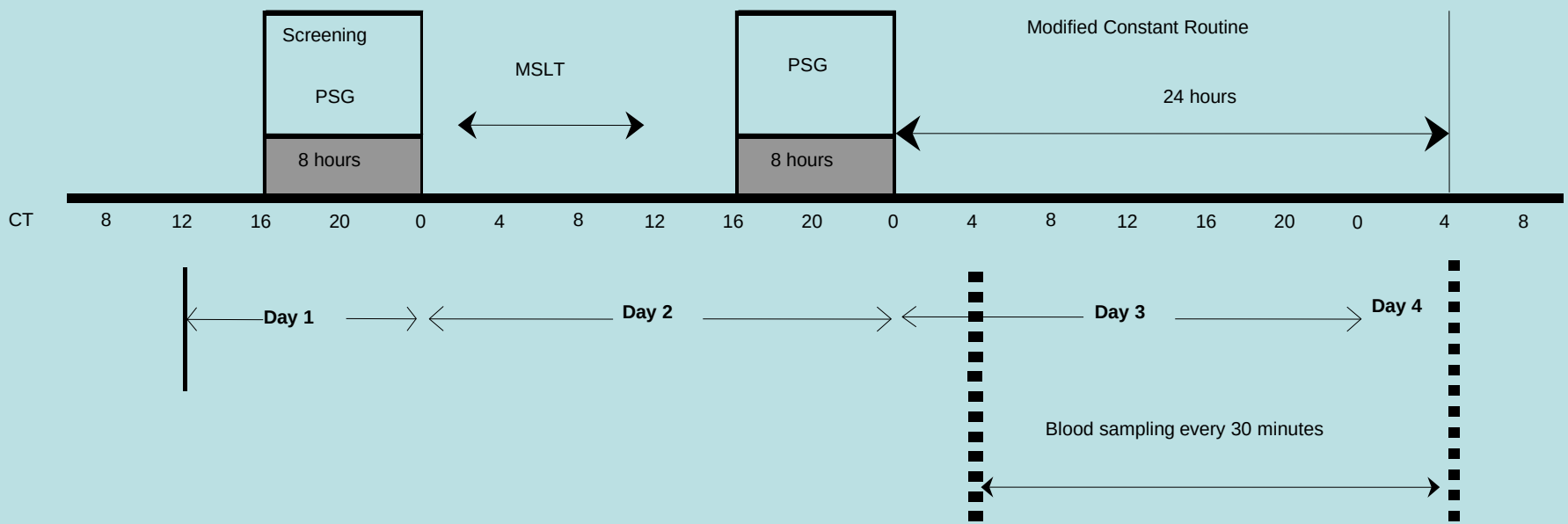
Baseline period – 14 days

- Actigraphy
- Sleep diaries

Duration: 10.3 ± 8.7
UPDRS: 34.3 ± 10.1

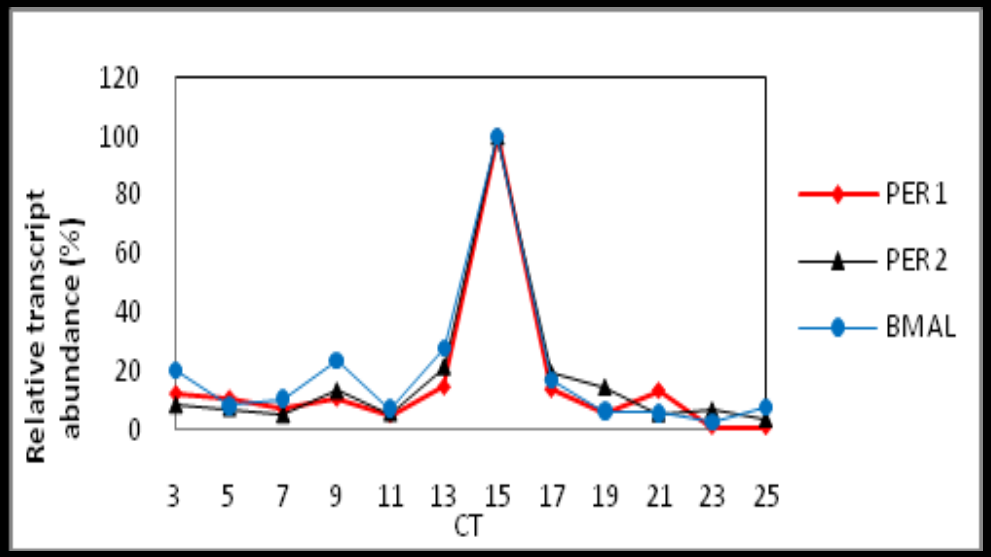
Modified Constant Routine Protocol

- Clinical Research Unit (3 days/nights)

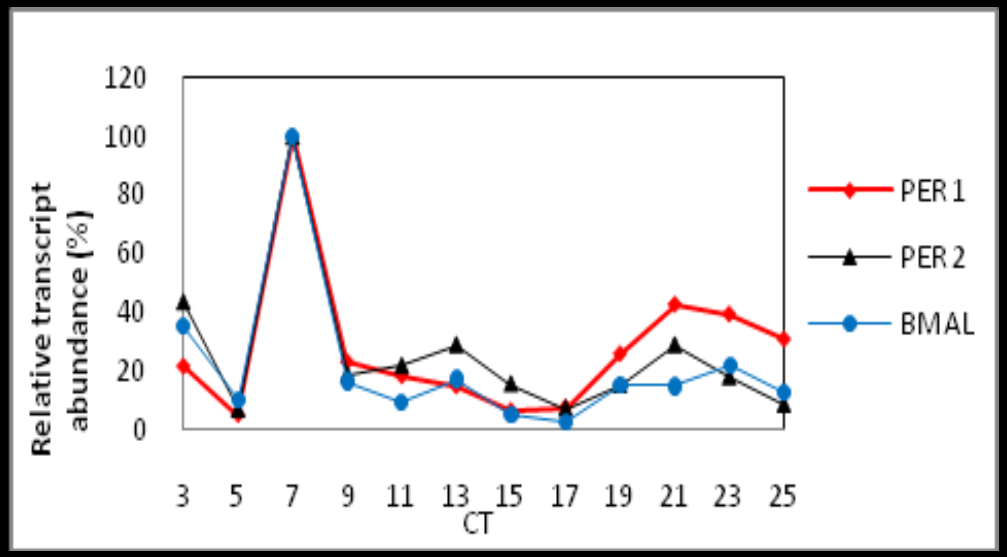


Circadian Clock Gene Expression in PMBC

control

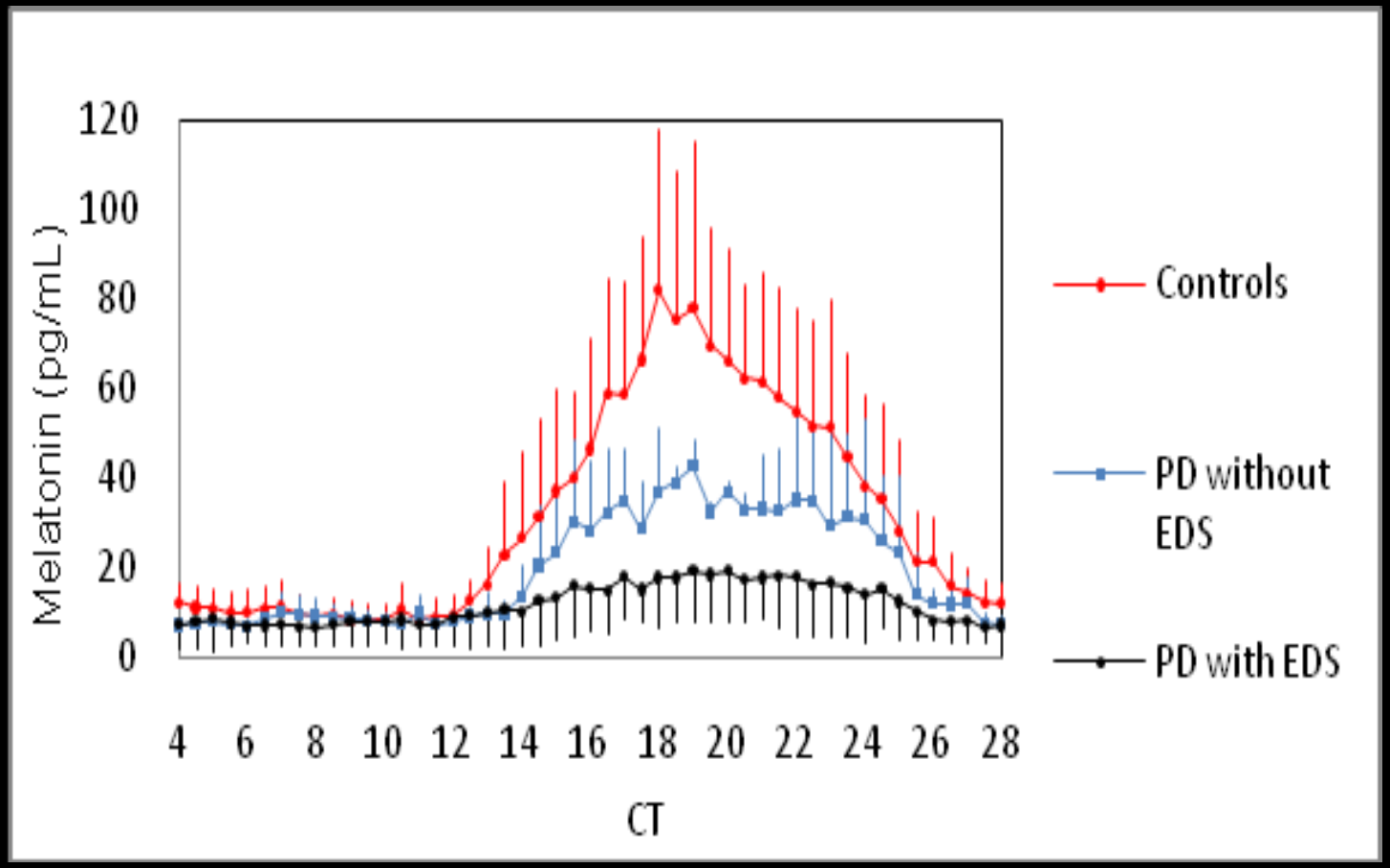


PD



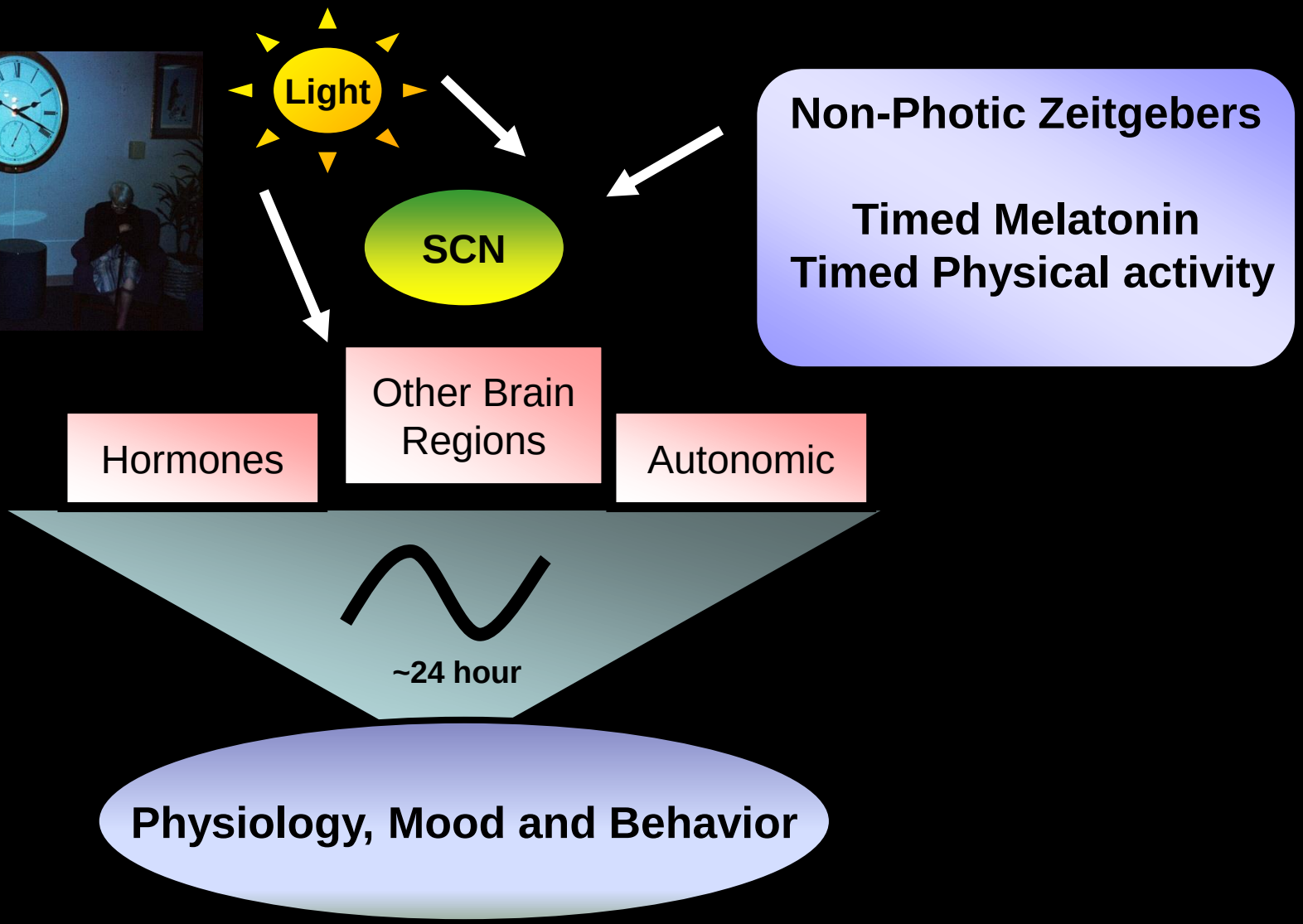
Preliminary
Unpublished

Circadian Rhythm of Melatonin in PD

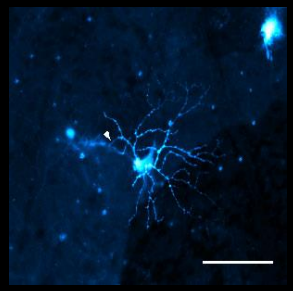


Videnovich A et al, JAMA Neurology, 2014

Circadian Based Treatments for Sleep Wake Cycle Disorder in Neuropsychiatric Disorders



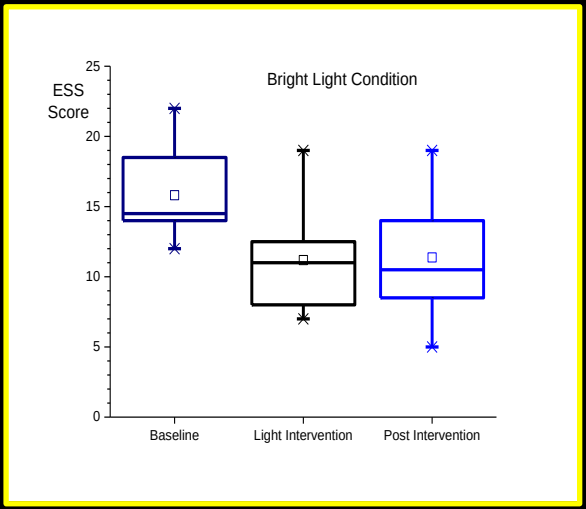
Light exposure and PD

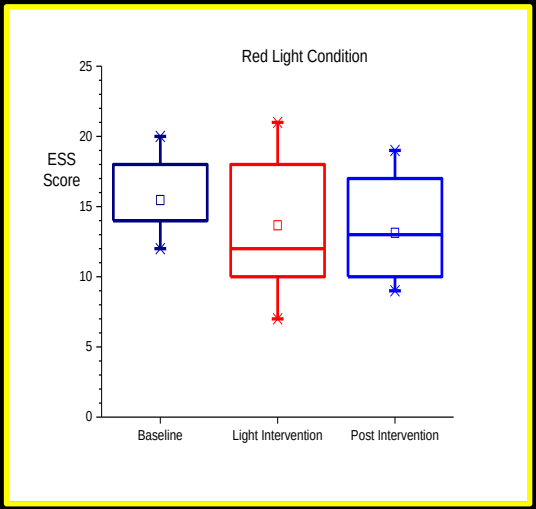


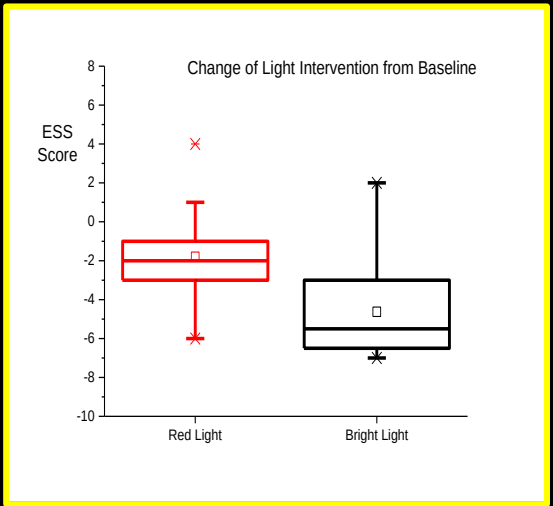
- Connections between the visual system and DA systems can increase activity on exposure to bright light. [1,2,3]
- Improvements in motor performance observed in experimental animals by housing them in a constant ambient light. [4]
- Administration of bright light to patients with PD improves bradykinesia, rigidity and depression scores.
- [5,6,7]
- Most effective frequencies of light are most likely in the blue/green spectrum (500 nm), the frequencies affected in the visual deficits in the PD population. [8]

[1] Iversen 1978
[2] Isaac 1971
[3] Seegal 1971
[4] Willis 1999
[5] Artemenko 1996
[6] Willis 2007
[7] Paus 2007
[8] Adachi-Usami 1990

Bright white Light Exposure Improves Wakefulness in Parkinson's Disease







	Bright Light	Dim Red Light	*p*
Δ EES score	4.75 ± 1.84	1.79 ± 2.89	0.002

- Bright: 3000 lux (N=15)
- Dim Red: 300 lux (N=15)
- 0900-1100; 1700-1900 for 4 weeks

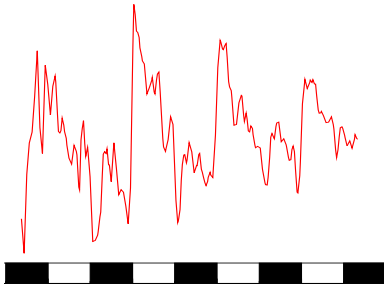
Light as Novel Therapy for Excessive Sleepiness in PD

- Supplemental exposure to bright light is well tolerated in the PD population.
- Supplemental exposure to bright light is associated with improvements in excessive daytime sleepiness associated with PD.
- Further studies are needed to optimize the wavelength, duration and exposure parameters of light therapy in the PD population.

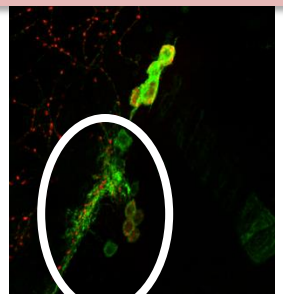
Northwestern Biochronicity Program

Manipulation of Timing

Cycling gene and Physiology Network Modules



Cardio-metabolic Neuropsychiatric



Therapeutic Targets

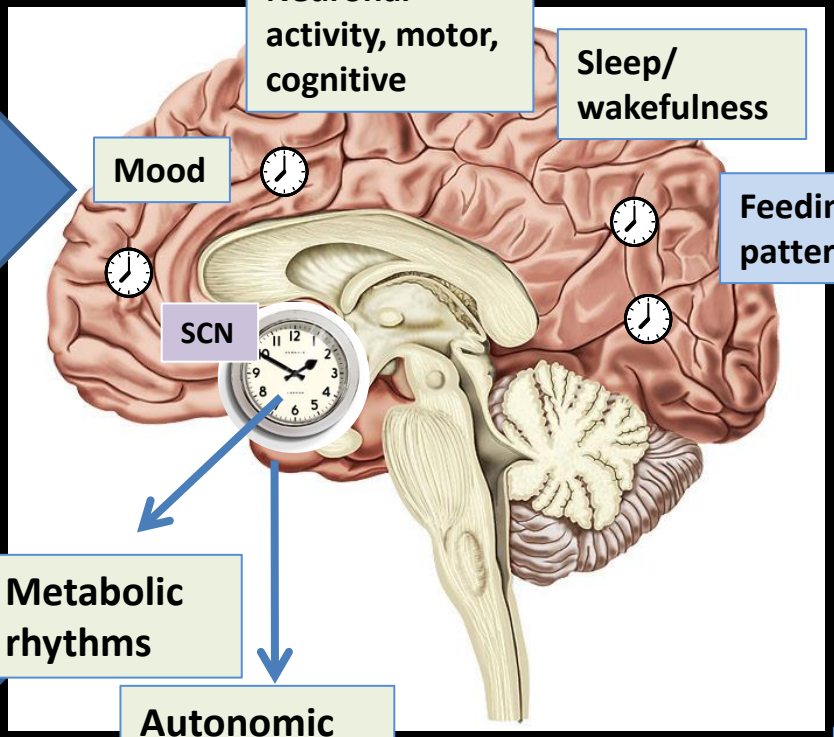
(Allada, Turek and Zee)

Integrating the Time Domain into Population Health and Personalized Medicine

- Sleep/wake
- Light/Dark
- Social
- Work

Meal Timing

Exercise timing

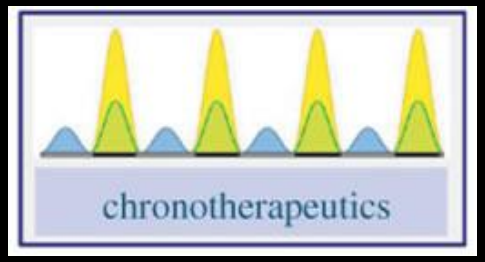


Metabolic rhythms

Autonomic system

Circadian /rhythmic Biomarkers

Clinics



Peripheral organs
And tissues

- Cell cycle, apoptosis and DNA repair
- Oxidative stress
- Metabolism
- Toxin removal
- Angiogenesis

Meeting in the Laboratory of Comparative Somnology and Neuroendocrinology, Institute of Evolutionary Physiology and Biochemistry, Russian Academy of Sciences

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