

Fatigue in the Setting of Disease

# Sleep Disruption

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Phyllis C. Zee, MD, PhD

Northwestern University  
Feinberg School of Medicine



# Disclaimer and Disclosures

## **Disclaimer**

This certifies that the views expressed in this presentation are those of the author and do not reflect the official policy of the NIH.

## **Disclosure**

This certifies that I, Phyllis C. Zee, have no financial relationship that is relevant to the subject matter of this presentation.

Consultant and advisory board for companies with products related to sleep therapeutics: Eisai, Jazz, Harmony, Takeda.

***CIRCADIAN RHYTHMS***

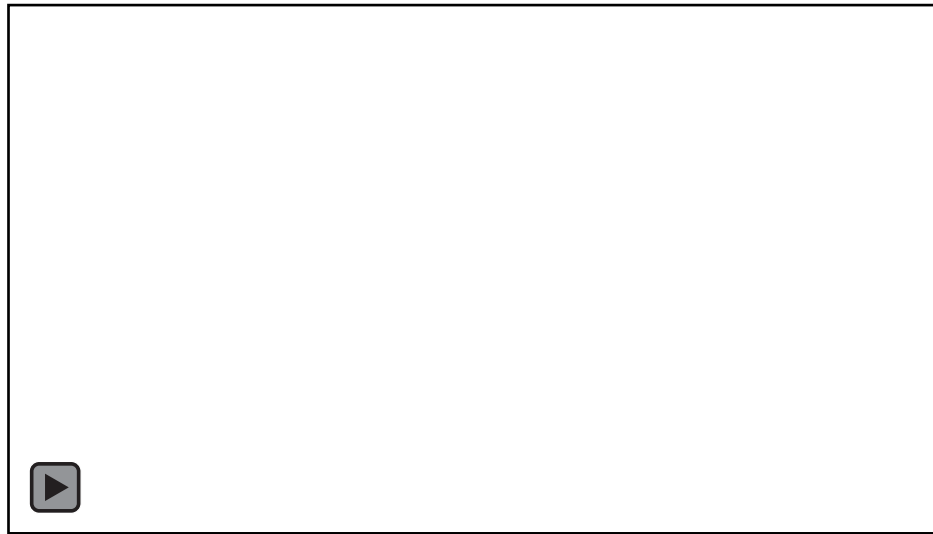
***REST (SLEEP)***

***ACTIVITY (WAKE)***

***FUEL***

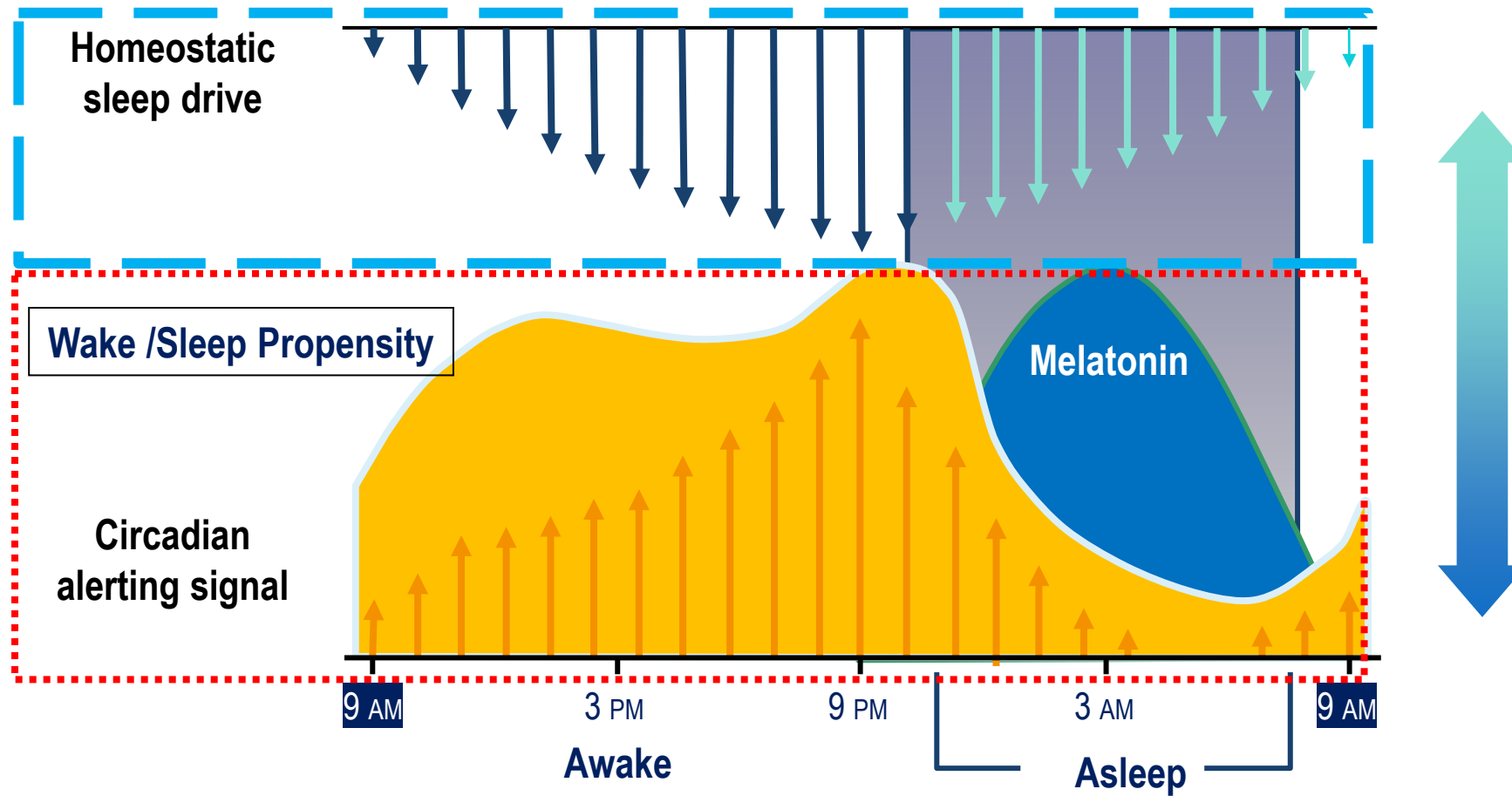
***METABOLISM***

# From the Beginning



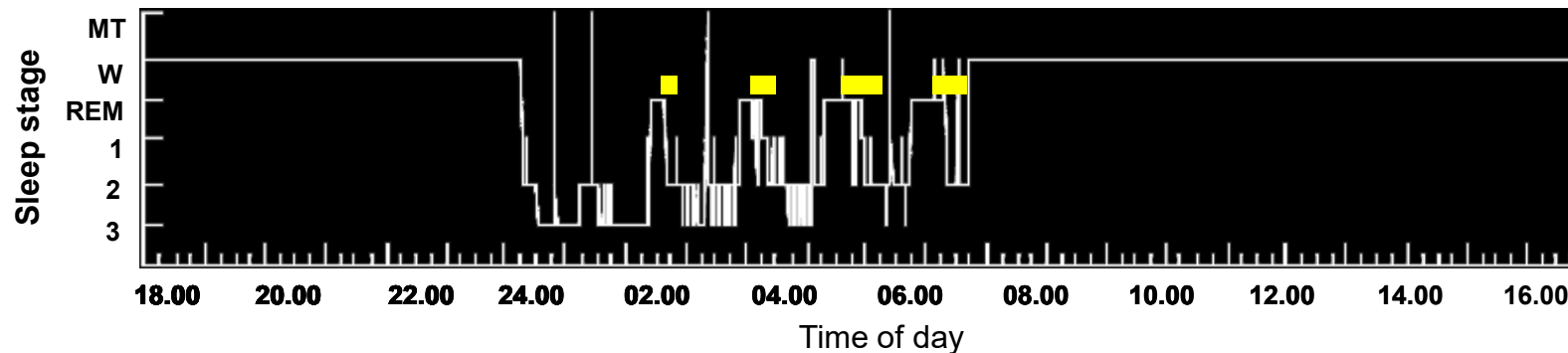
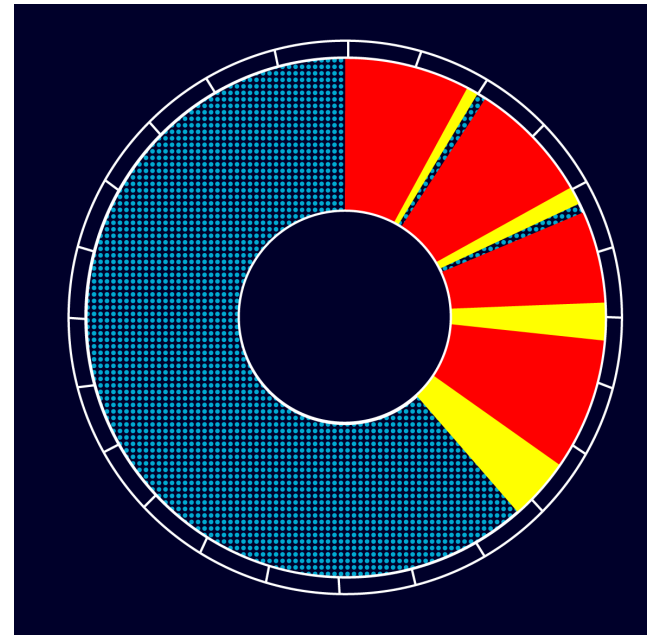
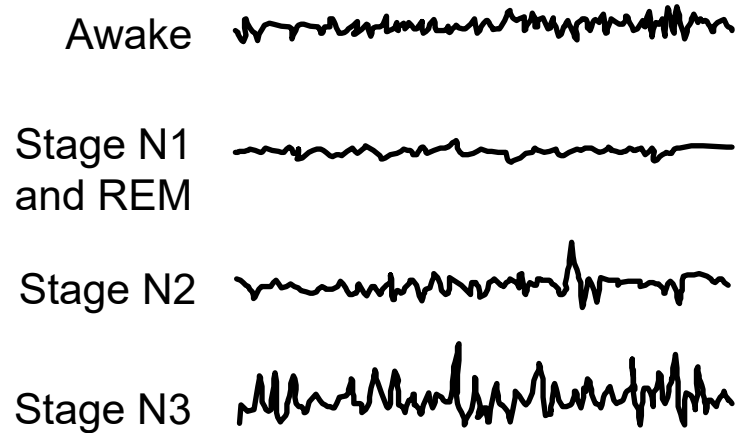
# Physiological Determinants of Sleep/Wake Regulation

## *Circadian and Sleep Homeostatic Processes*



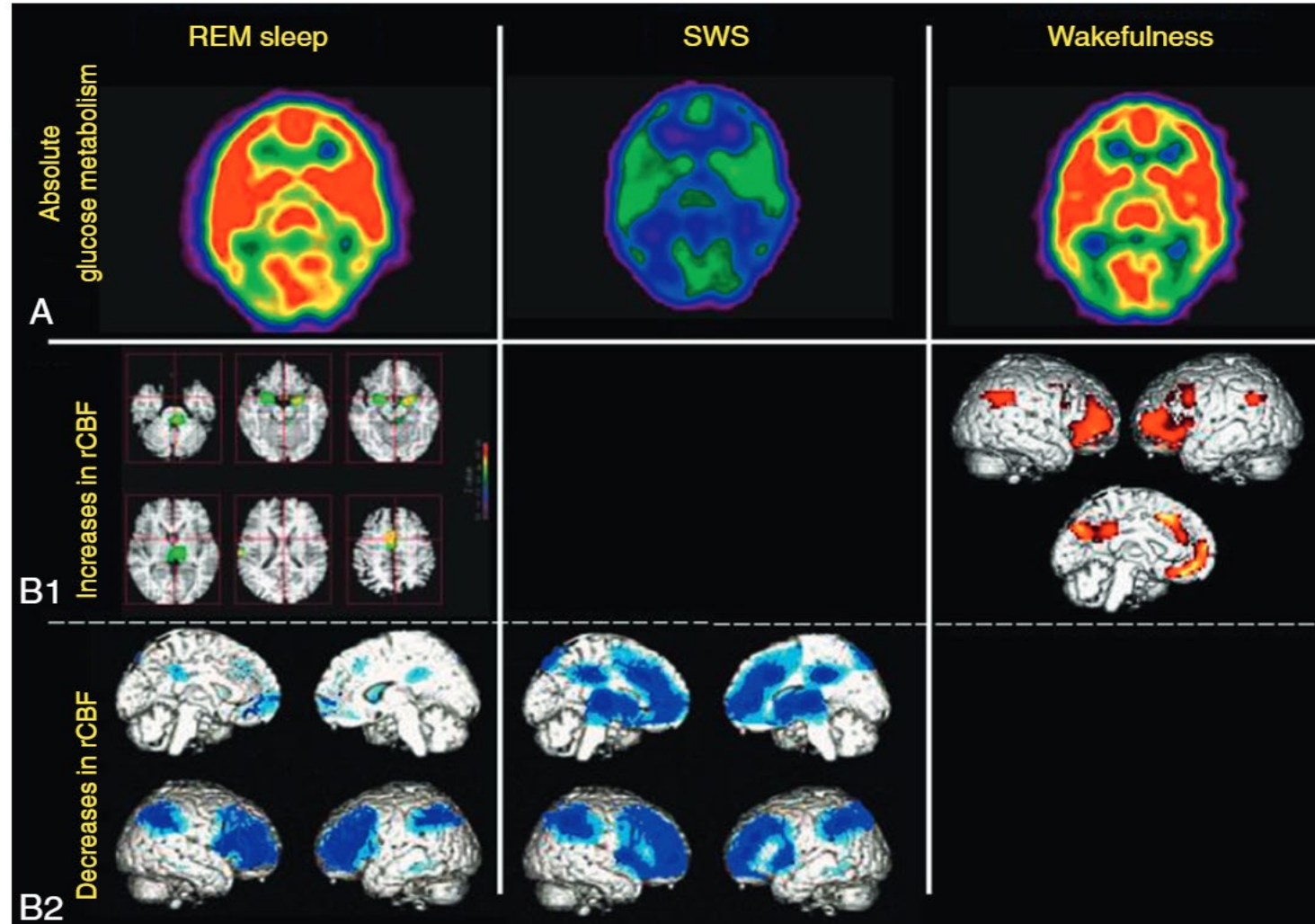
Dijk DJ, et al. *J Physiol.* 1997;505(Pt 3):851-858; Edgar DM, et al. *J Neurosci.* 1993;13(3):1065-1079; Kilduff TS, Kushida CA. Circadian regulation of sleep. In: Chokroverty S, ed. *Sleep Disorders Medicine: Basic Science, Technical Considerations, and Clinical Aspects.* 2nd ed. Boston, Mass: Butterworth-Heinemann;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

# Recurring Dynamic Cycles of Wake and Sleep



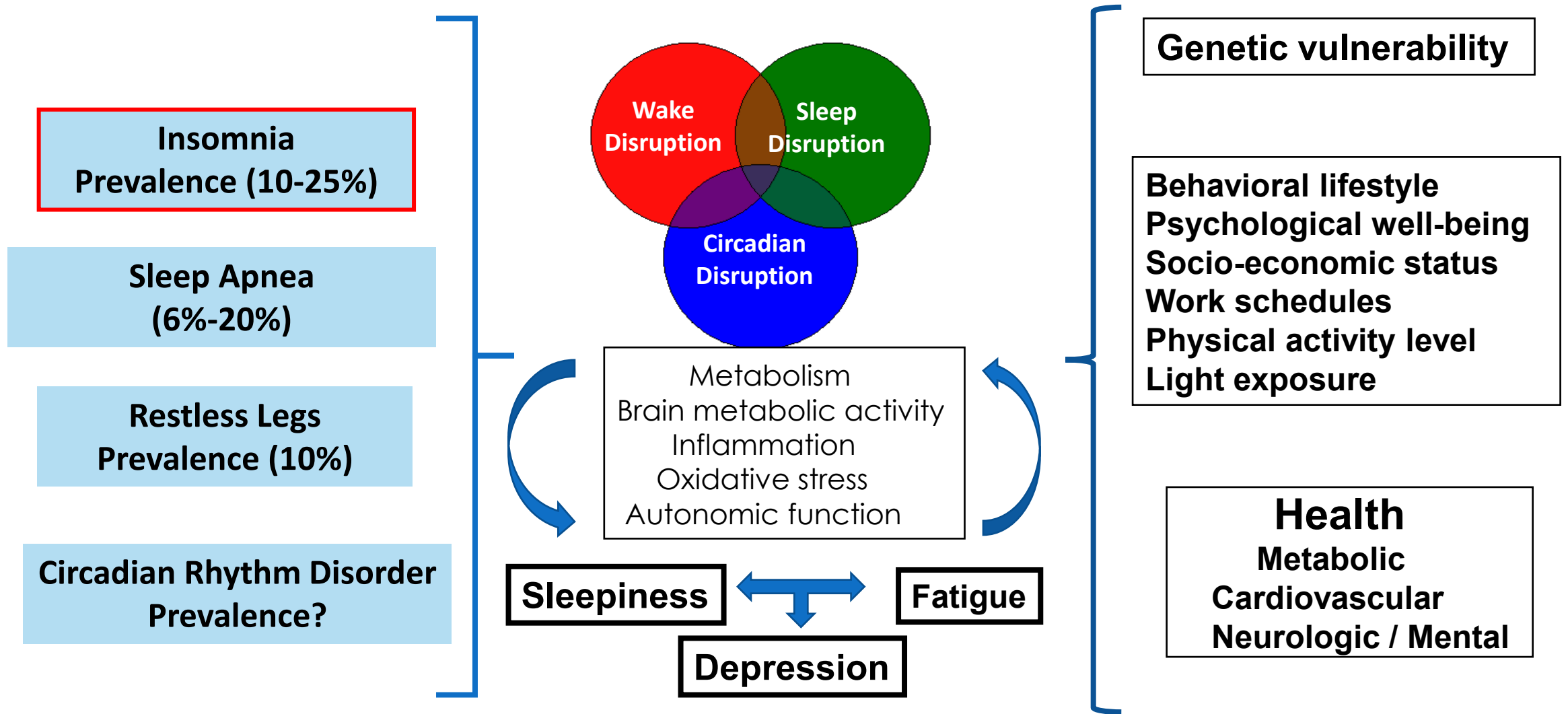
Courtesy of R. Ristanovic, MD.

# Brain Metabolic Activity in Wake and Sleep



Braun AR et al, Brain, 1997; Desseilles M, Dang-Vu, Maquet, P, Hand Clin Neurol 2011

# Sleep/Wake Disruption and Fatigue



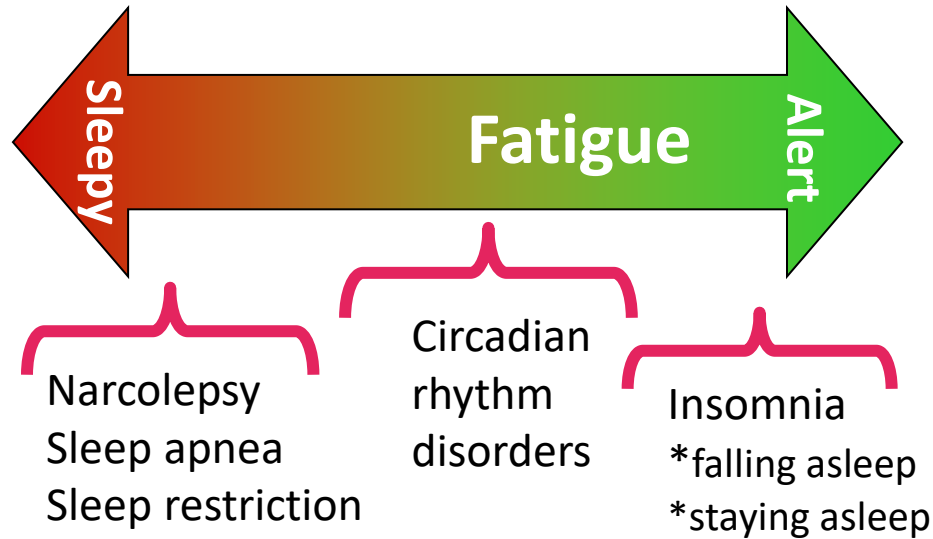
Zee and Turek, Arch Int Med, 2006; Young T, et al. Am J Respir Crit Care 2002; Hornyak M, et al. J Clin Psychiatry 2005; Ohayon MM, Roth T. J Psychosom Res 2002;53:547-554.



# The Alertness-Sleepiness-Fatigue Spectrum

**Sleepiness** - the need for sleep, or propensity to fall asleep

**Fatigue** - the sensation of weariness, tiredness, exhaustion, loss of energy; the desire to rest, lack of motivation...



\*Edenshaw YW, JAGS 2016

## Measures of Sleep Quality and Sleepiness

### Subjective

- Pittsburgh Sleep Quality Index (PSQI)
- PROMIS Sleep Quality/Disturbance
- Epworth Sleepiness Scale (ESS)
- Karolinska Sleepiness Scale (KSS)
- Stanford Sleepiness Scale (SSS)

### Objective

- Polysomnography
- Actigraphy
- Multiple Sleep Latency Test (MSLT)
- Maintenance of wakefulness test
- Wake EEG
- Pupillometry

Carskadon MA et al, Sleep 1986; Shahid A et al, J Psychosomatic Res, 2010; Johns MW. J sleep Res, 2000;



## Sleep Disorders and Fatigue

Group studied	Fatigue Severity Scale
Sleep disorders	4.8 (1.4)
Multiple sclerosis	4.8 (1.3)
Systemic lupus	4.6 (1.5)
Chronic fatigue syndrome	6.1 (0.8)

Lichstein K et al, Behav Res Ther, 1997

## Relationship between sleepiness and fatigue

Table 3. The Pearson correlation between Fatigue Severity Scale (FSS) scores and plausible predictors

Predictor	<i>r</i>
<i>Demographic and anthropometric variables</i>	
BMI	0.19**
Age	0.00
Gender <sup>1</sup>	0.29**
Smoking history <sup>2</sup>	0.20**
<i>Sleep and sleepiness</i>	
Sleep efficiency percent	-0.16*
MSLT	-0.08
<i>Psychological and sleep pathology</i>	
MMPI-depression	0.44**
MMPI-average	0.45**
Myoclonus arousal index	0.06
Respiratory disturbance index	-0.04
Oxygen desaturation	-0.16*
MSLT REM	0.00

\* $P < 0.05$ , \*\* $P < 0.01$ .

<sup>1</sup>The coding scheme we used indicates that a positive correlation is associated with being female.

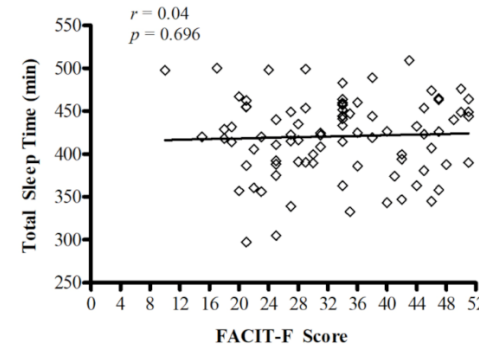
<sup>2</sup>The coding scheme we used indicates that a positive correlation is associated with smoking more.

# Actigraphy Derived Measures of Sleep and Fatigue in Cancer

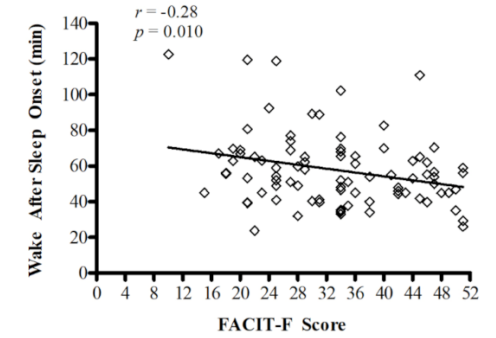


- All types of invasive cancer N=87 (fatigued 51; non fatigued 36)
- Actigraphy (14 days)
- Sleep Diary (14 days)
- Cancer related fatigue (FACIT-F)
- Insomnia Severity Index (ISI)

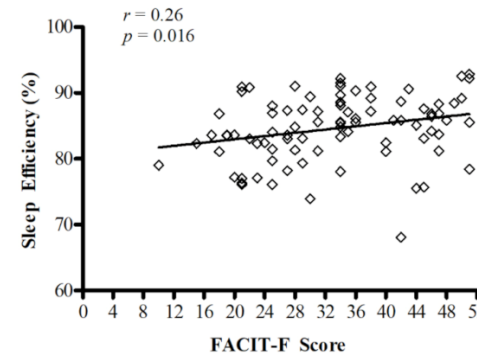
Martin, T et al, Curr Oncol, 2021



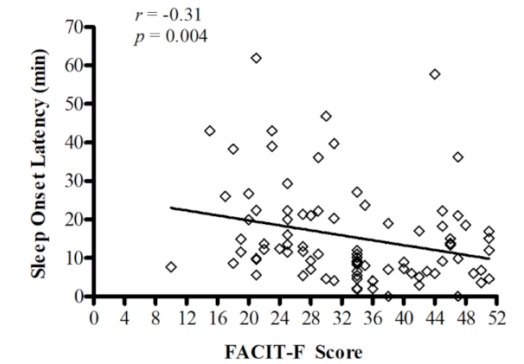
(A)



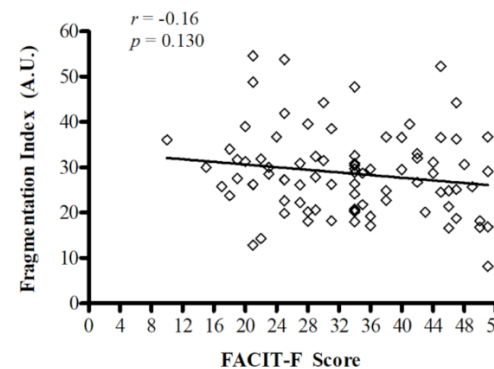
(B)



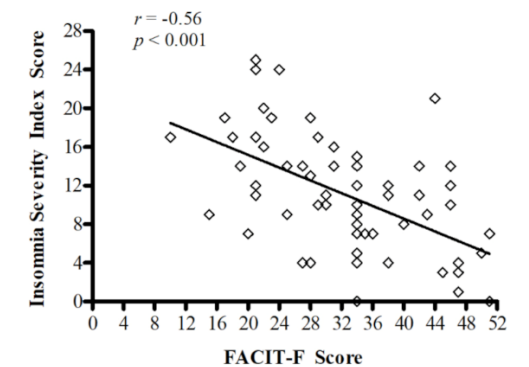
(C)



(D)



(E)



(F)

# Subjective sleepiness and Fatigue: Independent/interrelated consequence of sleep disorders?

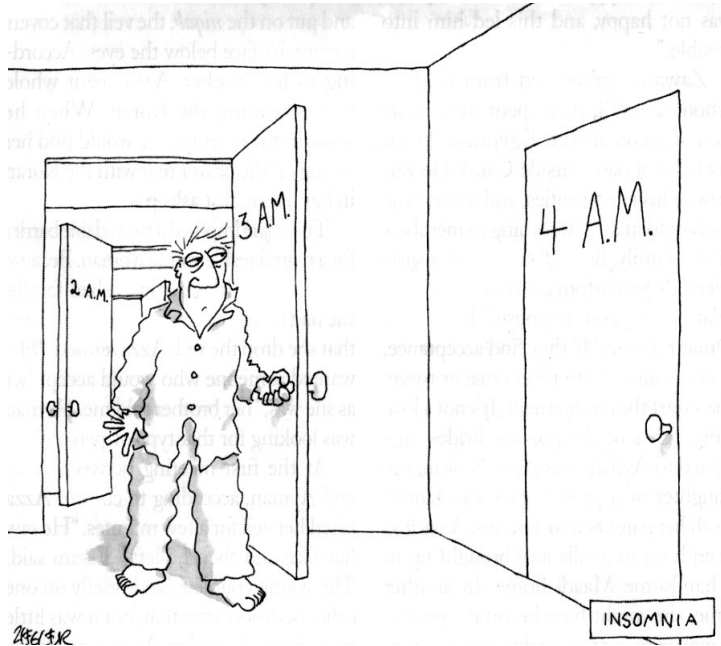
	<i>High fatigue/ low sleepiness</i>	<i>High fatigue/ high sleepiness</i>	<i>Low fatigue/ low sleepiness</i>	<i>Low fatigue/ high sleepiness</i>	<i>Significance</i>
Age	45.0 ± 15.0	43.0 ± 14.0	48.2 ± 16.8	50.2 ± 13.6	NS
BMI	28.1 ± 6.7	31.5 ± 11.7	27.6 ± 7.6	30.7 ± 6.7	$F(3,279) = 3.0, P < 0.03$
ESS Score	6.9 ± 3.8	17.2 ± 2.7	5.4 ± 2.8	14.5 ± 2.9	$F(3,279) = 138.5, P < 0.0001$
FSS Score	5.1 ± 0.9	5.4 ± 1.0	2.1 ± 0.7	1.9 ± 0.6	$F(3,279) = 143.0, P < 0.0001$
CES-D Score	21.7 ± 11.0	23.0 ± 11.9	13.2 ± 10.6	19.4 ± 11.2	$F(3,279) = 6.86, P < 0.001^*$
THAT Score	26.3 ± 8.0	23.12 ± 6.8	32.7 ± 9.5	25.0 ± 12.0	$F(3,279) = 10.35, P < 0.001^*$
IIRS Score	42.1 ± 16.6	49.9 ± 17.3	23.9 ± 10.5	30.4 ± 15.0	$F(3,279) = 21.0, P < 0.0001^*$

	<i>FSS Score</i>	<i>ESS Score</i>	<i>THAT Score</i>	<i>CES-D Score</i>	<i>IIRS Score</i>
Obstructive sleep apnea ( $n = 93$ )	4.4 ± 1.6	9.8 ± 5.6	28.6 ± 8.8	18.9 ± 12.5	39.2 ± 20.8
Periodic leg movements ( $n = 33$ )	4.6 ± 1.4	8.7 ± 5.5	27.0 ± 7.8	20.6 ± 12.5	39.9 ± 15.1
Restless legs syndrome ( $n = 12$ )	5.1 ± 1.0	11.9 ± 7.3	24.3 ± 6.3	18.4 ± 11.7	39.1 ± 17.3
Insomnia ( $n = 33$ )	4.4 ± 1.5	7.6 ± 5.2	28.0 ± 9.1	16.8 ± 8.5	39.4 ± 16.8
Depression ( $n = 58$ )	4.9 ± 1.4	7.7 ± 4.6	24.0 ± 8.5	27.0 ± 10.5	43.9 ± 17.4
Narcolepsy ( $n = 9$ )	4.8 ± 1.2	16.2 ± 3.5	21.5 ± 6.2	15.8 ± 7.3	39.4 ± 14.6
Parasomnia ( $n = 11$ )	5.2 ± 1.2	9.3 ± 6.2	21.5 ± 7.1	29.4 ± 5.6	44.3 ± 18.2
Delayed sleep phase syndrome( $n = 15$ )	4.6 ± 1.6	7.0 ± 5.6	25.4 ± 7.8	19.0 ± 9.9	35.3 ± 16.9

Hossain JL et al, Journal Sleep Res, 2005

# Sleep-Wake Disturbances: How Do Patients Present?

## Insomnia

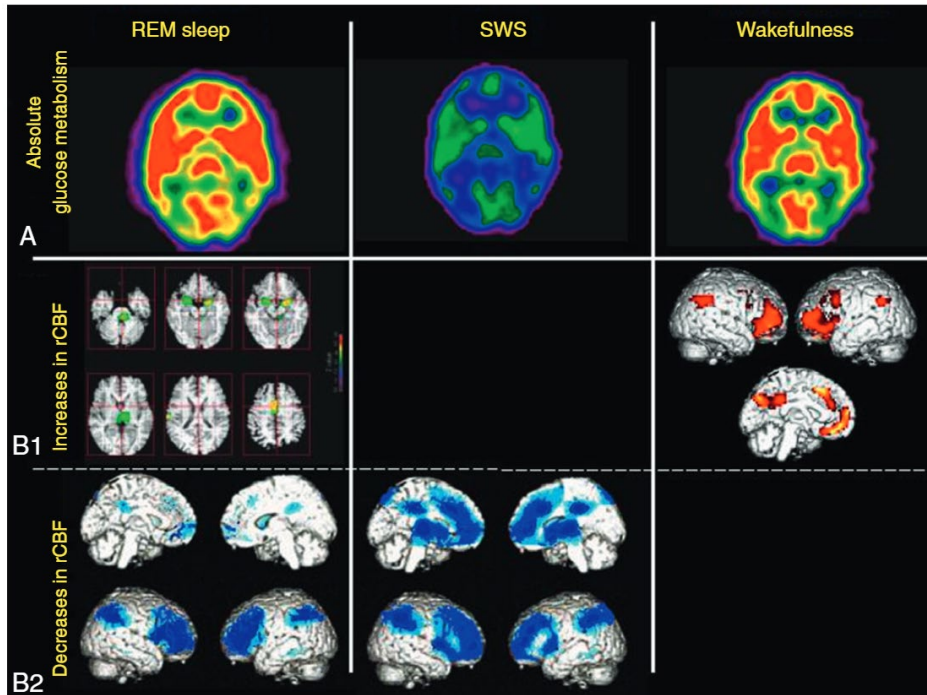


Courtesy: D Buysse

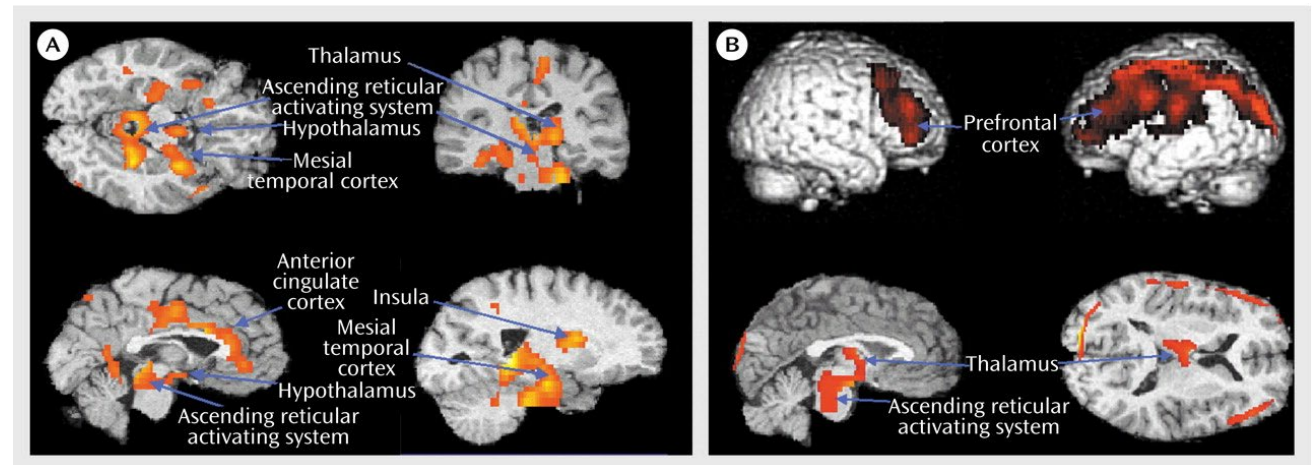
“My creativity diminishes, my irritability increases, my disposition suffers, my outlook is gloomier, my muscles feel weaker, my energy is kaput some days. Some days I'm too tired to accomplish anything but still unable to nap or sleep. It's an odd sensation. I feel as if I've been deprived of sleep and am exhausted but at the same time, as if I had drunk 5 cups of coffee and were overstimulated.”

# Brain Metabolic Activity in Wake and Sleep

## Healthy Sleep



## Insomnia



Structures that did not show decreased metabolic rate from waking to sleep

Relative metabolism while awake was higher in healthy subjects compared to insomnia

Braun AR et al, Brain, 1997; Deseilles M, Dang-Vu, Maquet, P, Hand Clin Neurol 2011

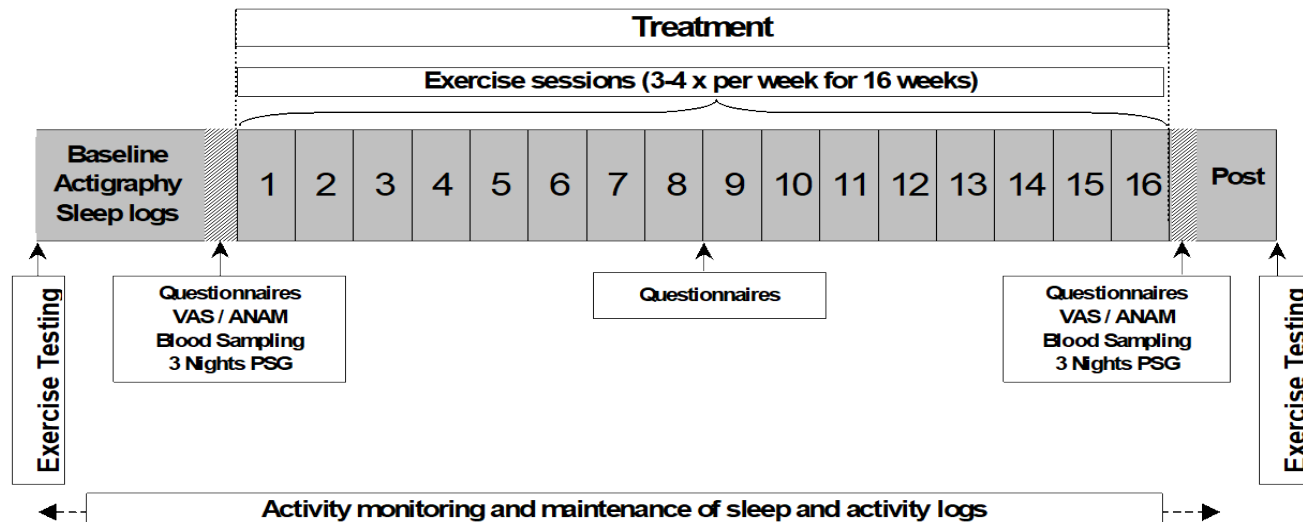
Nofzinger EA et al, Am J Psychiatry, 2004

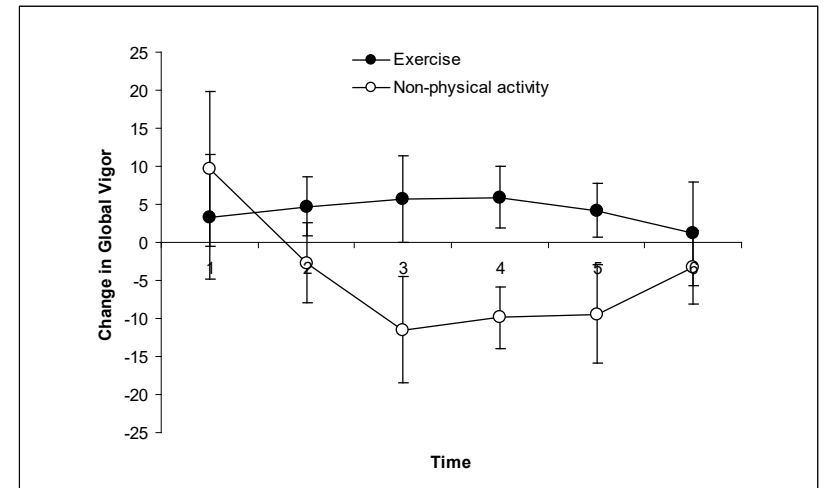
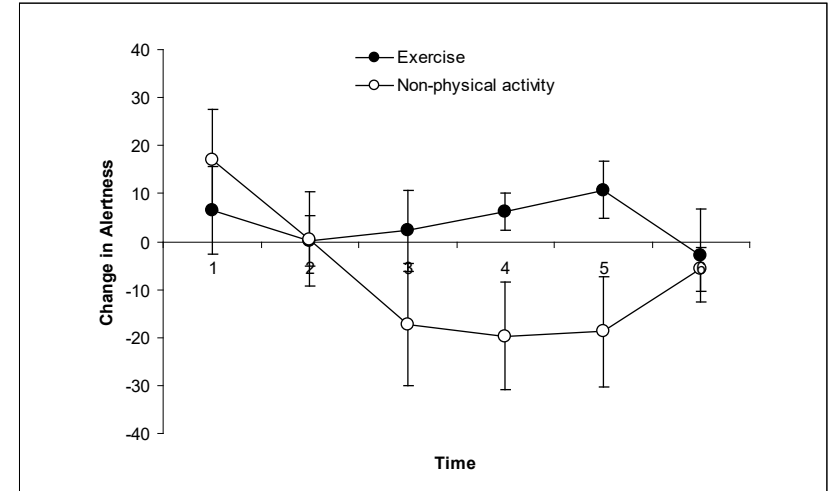
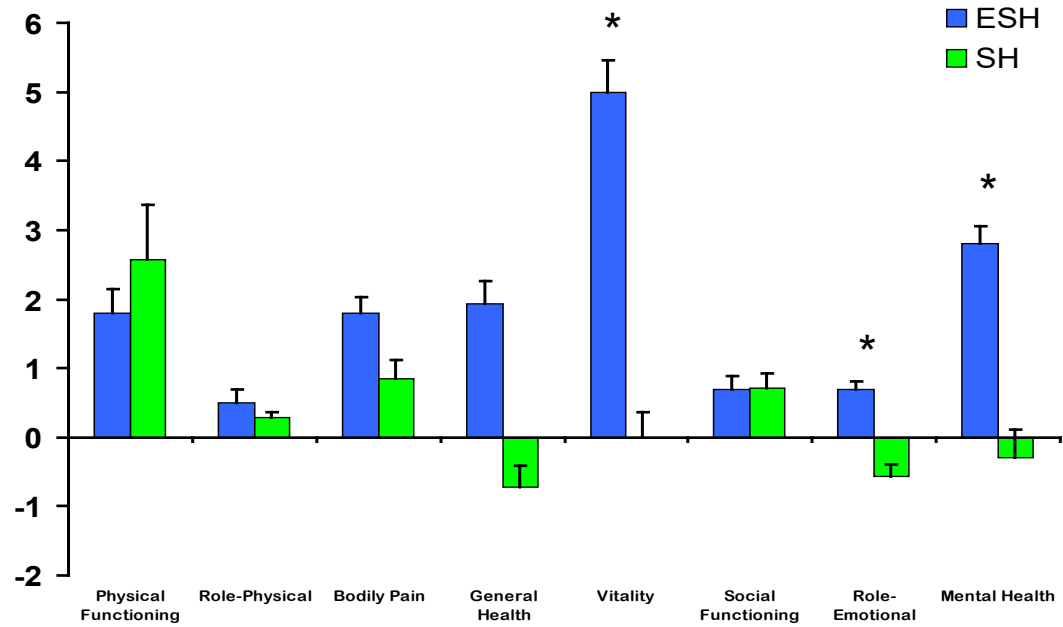
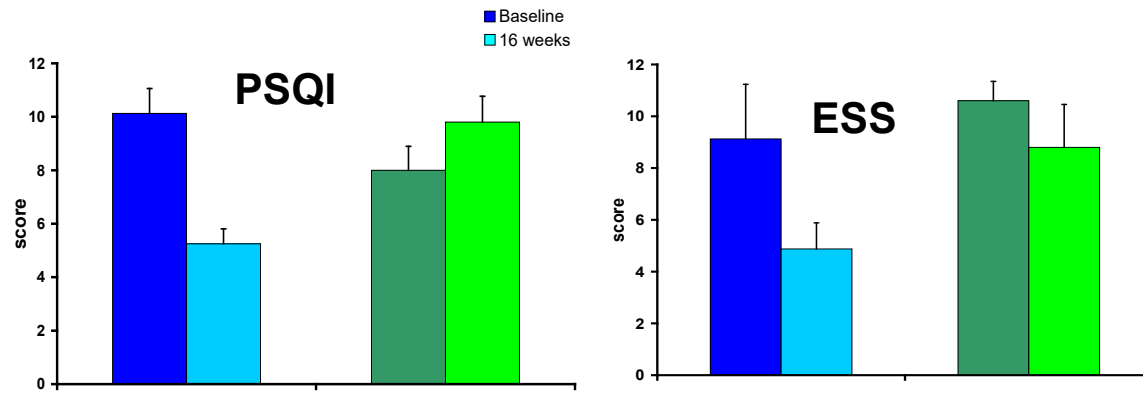


# Interventions for Chronic Insomnia in Older Adults



- Age 55 and older with diagnosis of insomnia
- No primary sleep pathology other than insomnia
- No cognitive impairment (MMSE < 25)

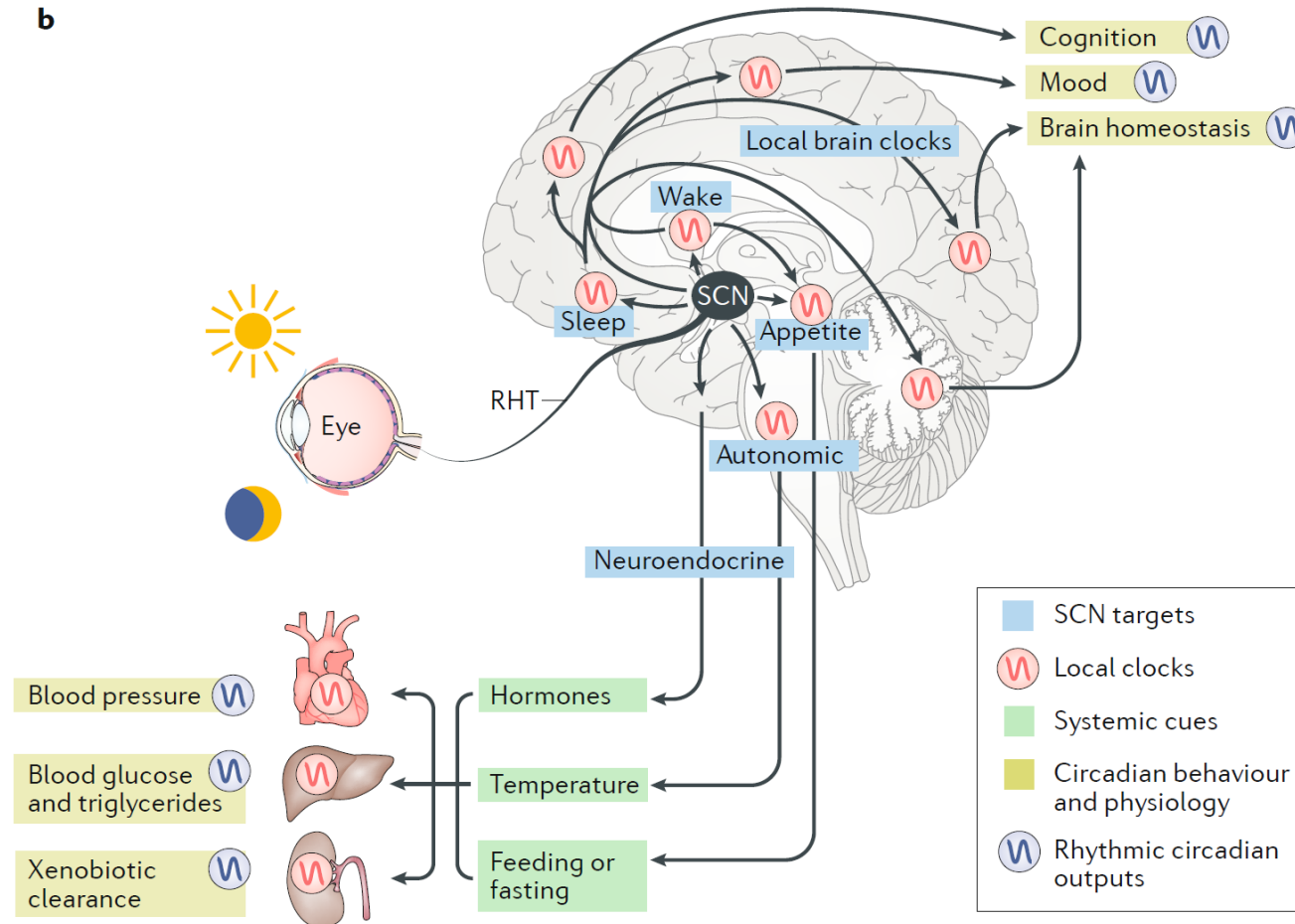




Reid, KR et al, Sleep Med 2010; baron K et al, JCSM, 2013

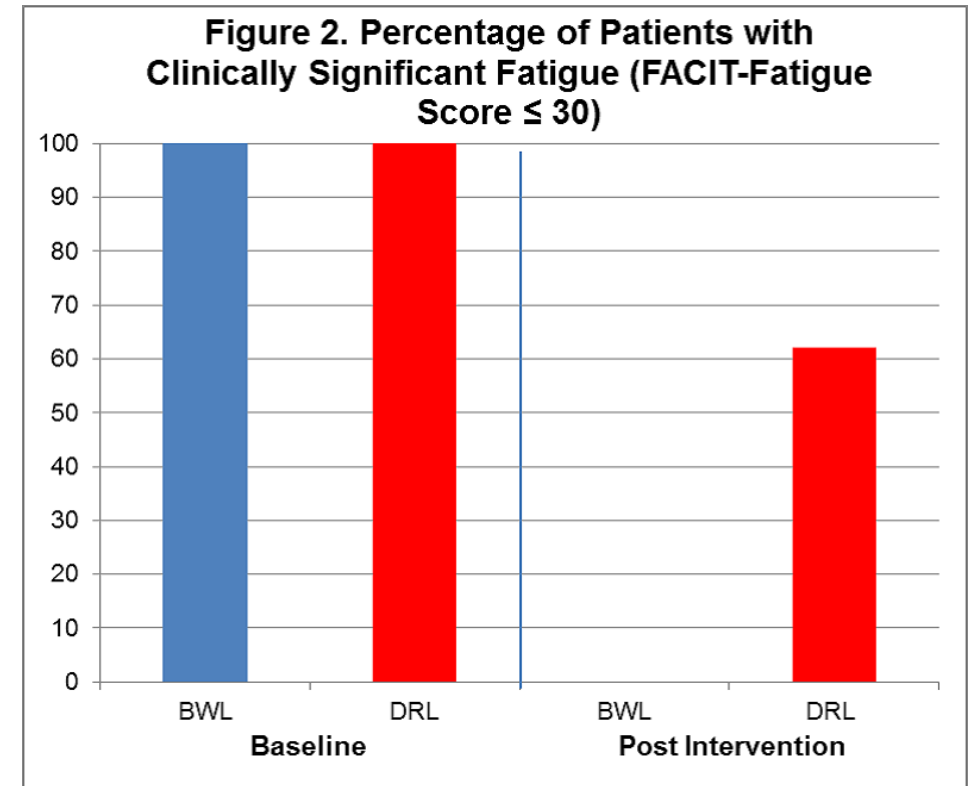
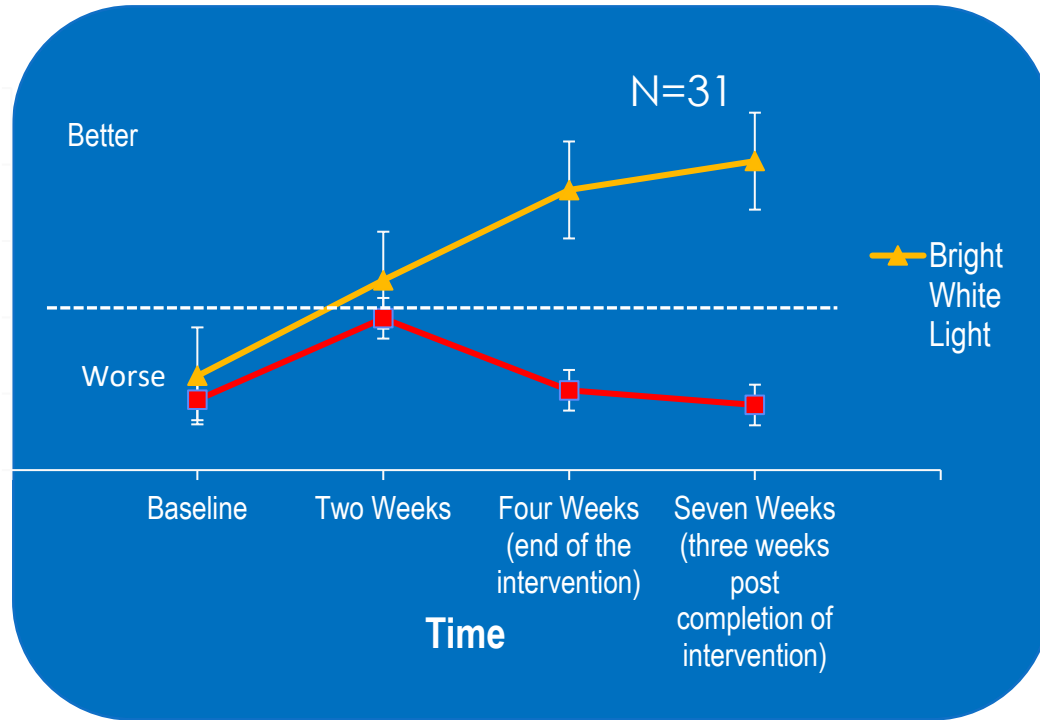


# Light Therapy, Sleep Disturbance and Fatigue



Hastings MH, Maywood ES, Brancaccio M, Nat Rev, 2018

# Light Therapy and Fatigue in Cancer Survivors with Sleep Disturbance



# Fatigue and sleep disruption-disorder

- Majority of research on fatigue and sleep disturbance are in the context of other medical, neurological and psychiatric disorders in which both are common
- Sleep medicine: If not excessive sleepiness-then fatigue
- Limited objective clinical and research measures/biomarkers
- Differentiating sleepiness and fatigue objectively makes a difference in management approaches

