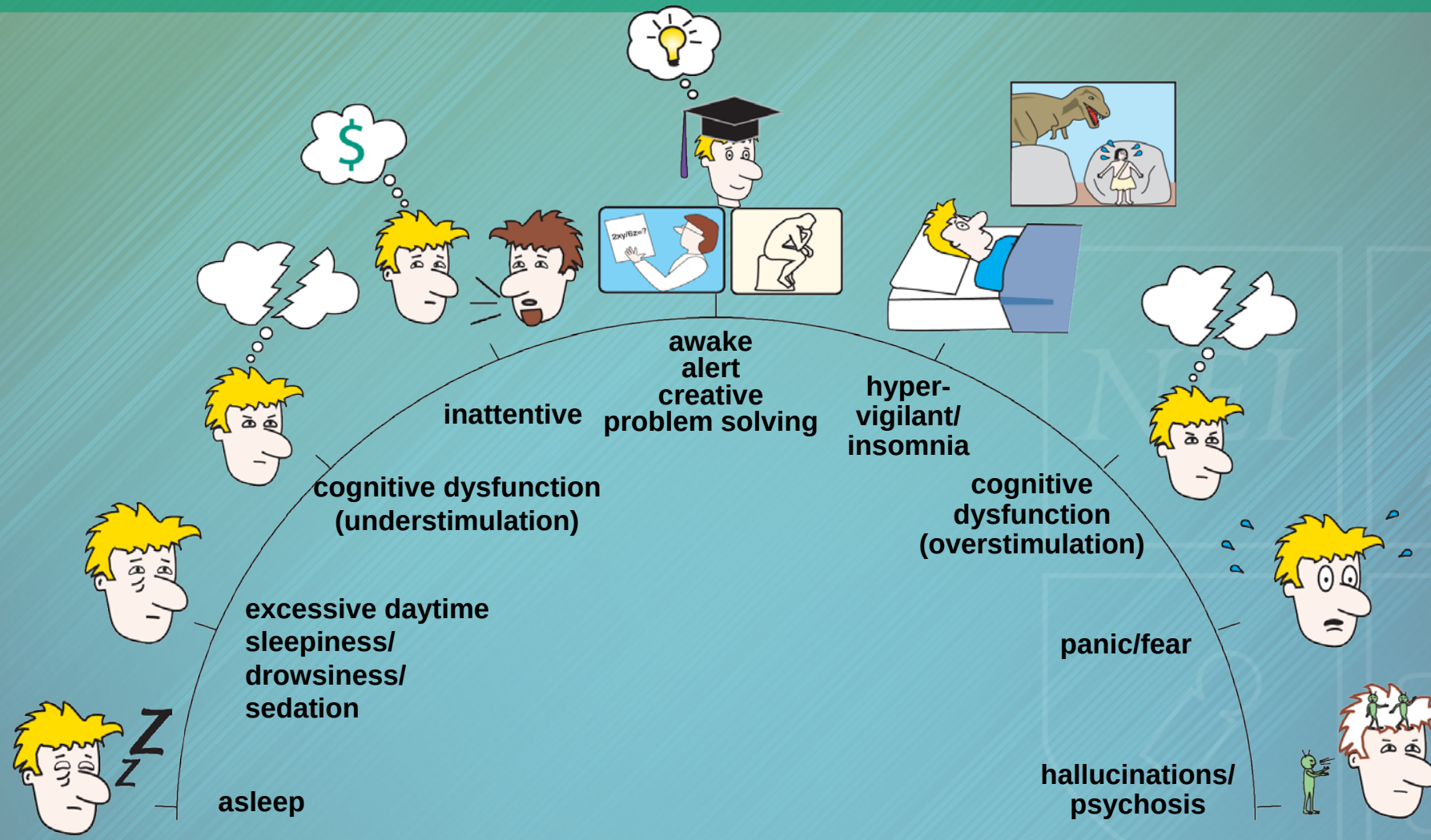
Neuroscience Education Institute

FROM OREXIN TO Z-DRUGS: A CLINICAL UPDATE ON INSOMNIA

Learning Objectives

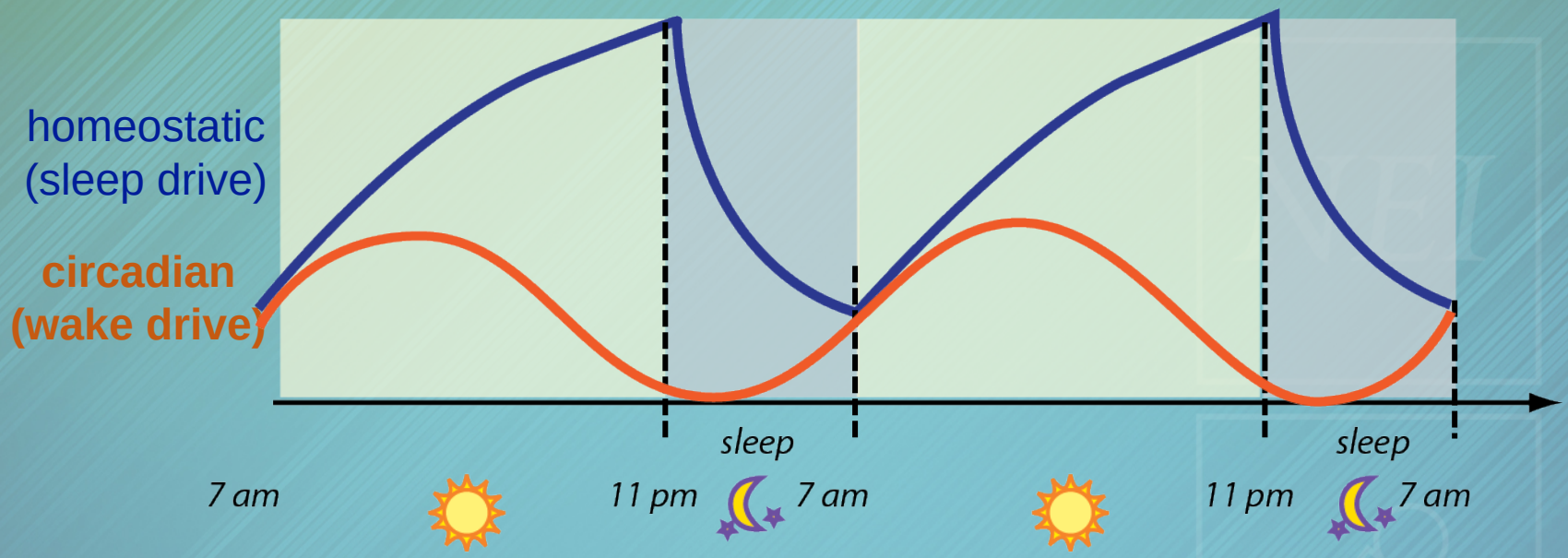
- Explain the neurobiology of sleep/wake cycles and the role of neurotransmitters in insomnia
- Differentiate the mechanistic and clinical profiles of treatments for insomnia
- Apply current best practices to the treatment of insomnia

Arousal Spectrum of Sleep and Wakefulness

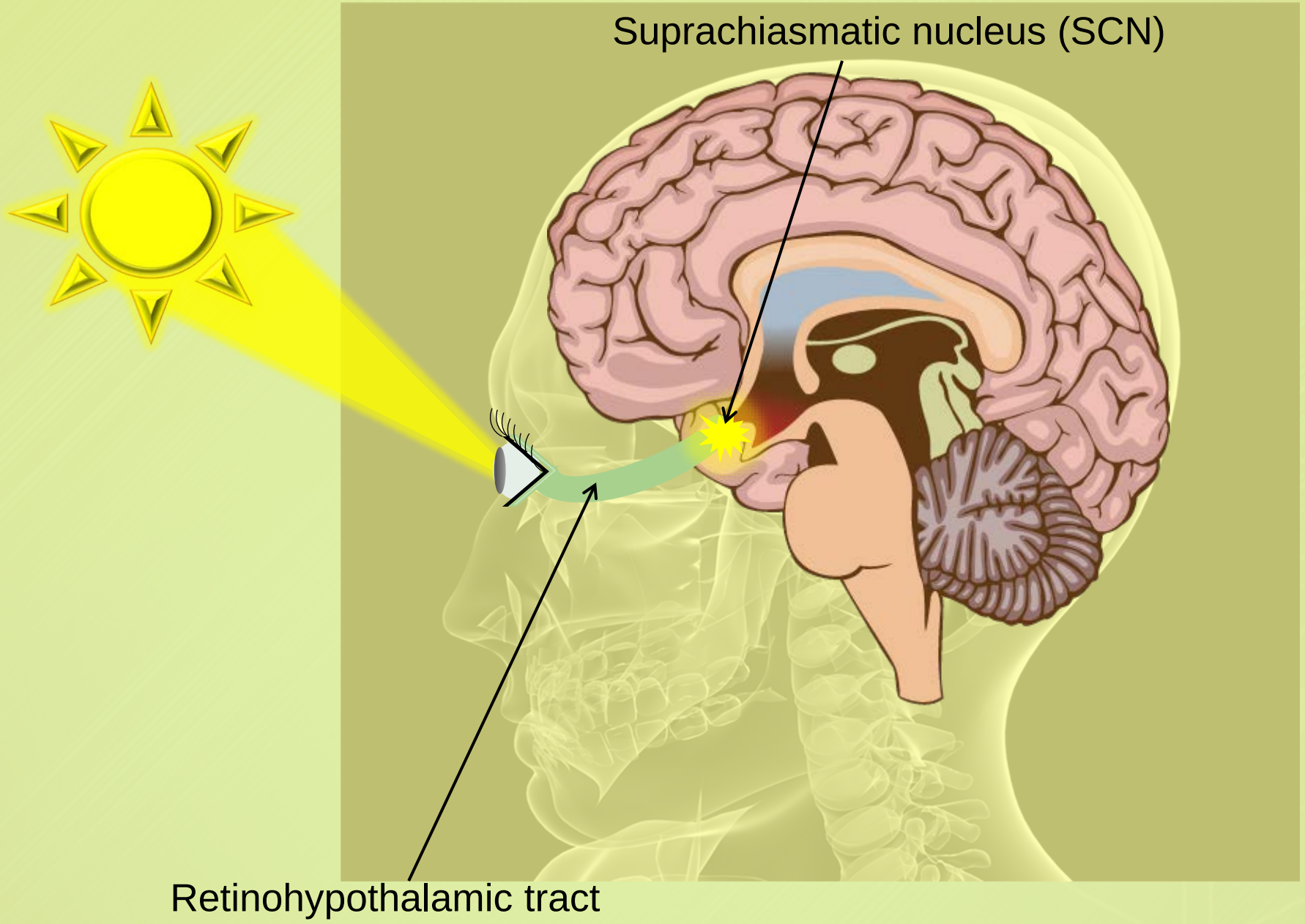


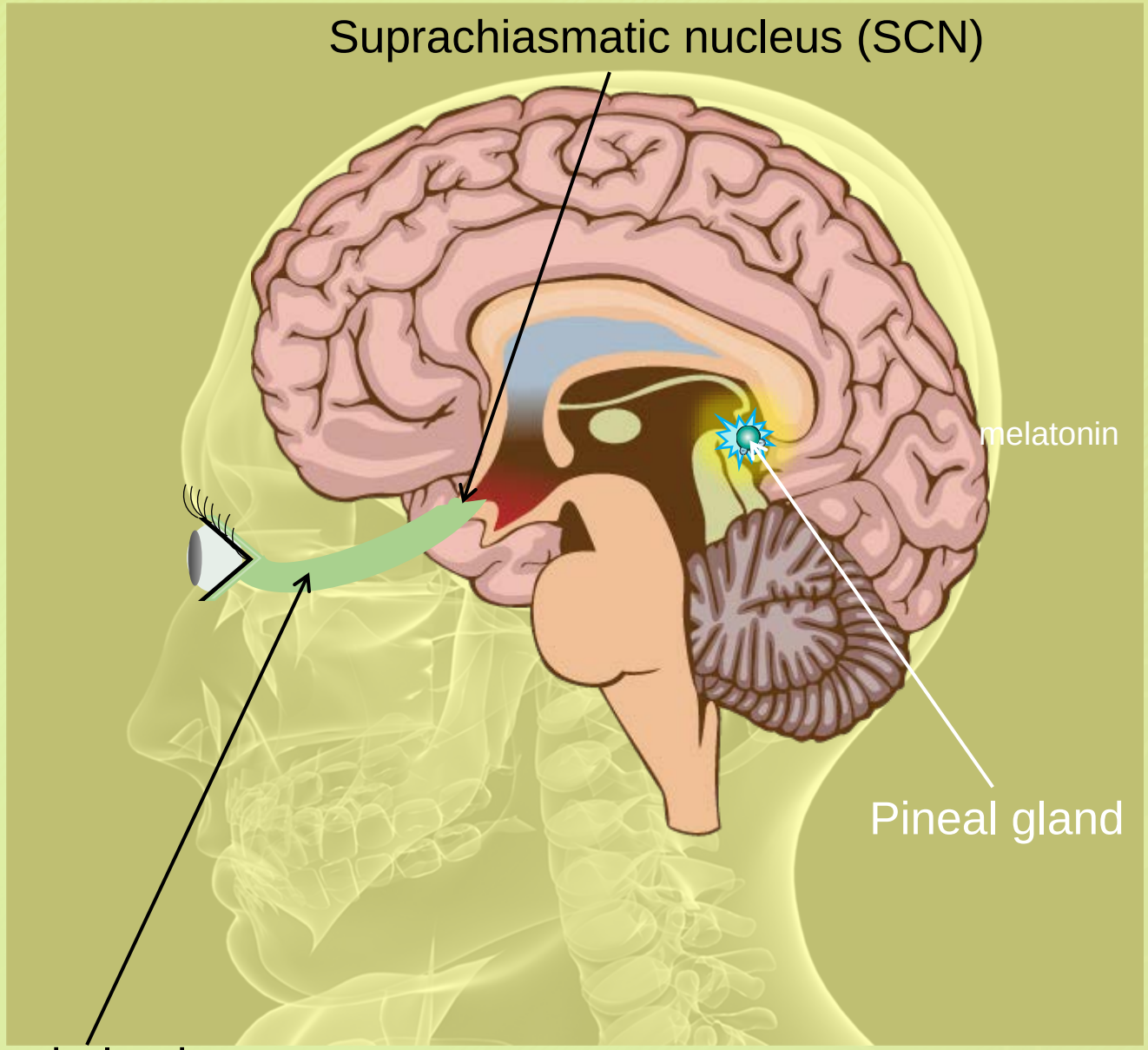
Stahl and Morrissette. Stahl's Illustrated sleep and wake disorders, 2016.

The Sleep/Wake Cycle

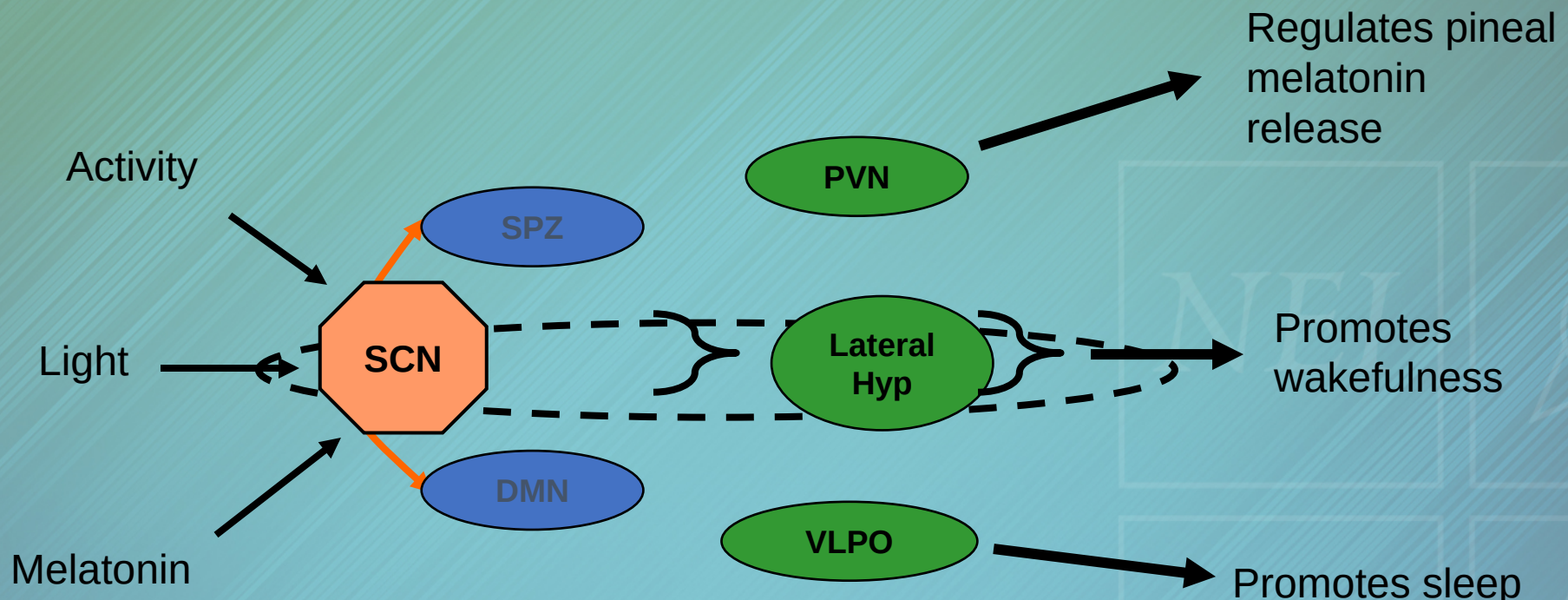


Stahl's Essential Psychopharmacology. 4th ed. 2013.


Suprachiasmatic nucleus (SCN)
Retinohypothalamic tract


Suprachiasmatic nucleus (SCN)
melatonin
Pineal gland
Retinohypothalamic tract

The Hypothalamus and Control



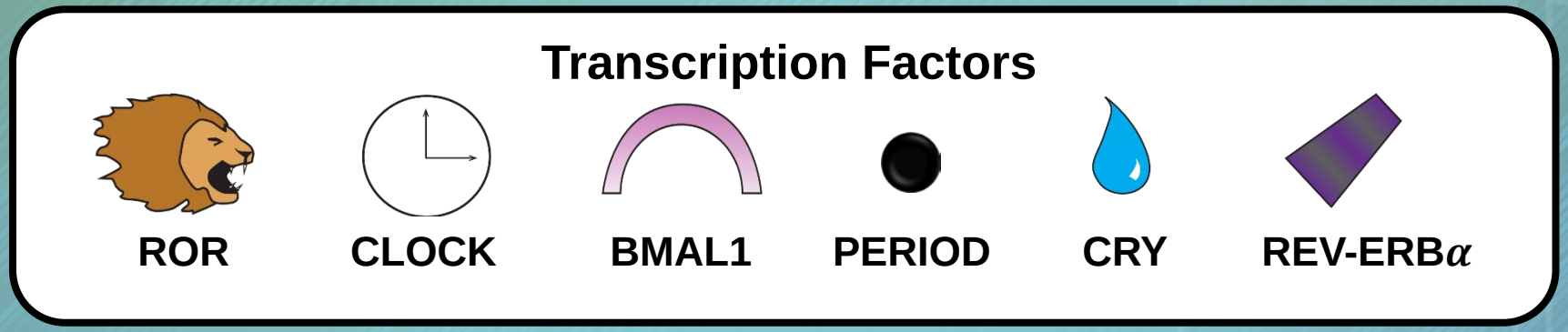
Distinct hypothalamic neurons control the sleep/wake cycle.

SCN: suprachiasmatic nucleus. **SPZ:** supraventricular zone. **DMN:** dorsomedial nucleus. **PVN:** paraventricular nucleus. **Lateral Hyp:** lateral hypothalamus. **VLPO:** ventrolateral preoptic nucleus.

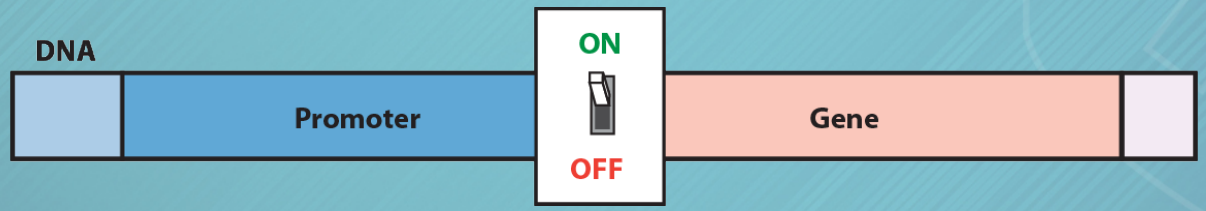
Stahl SM, Morrissette DA. Stahl's Illustrated Sleep and Wake Disorders 2016.

Circadian Rhythms Regulated at the Molecular Level

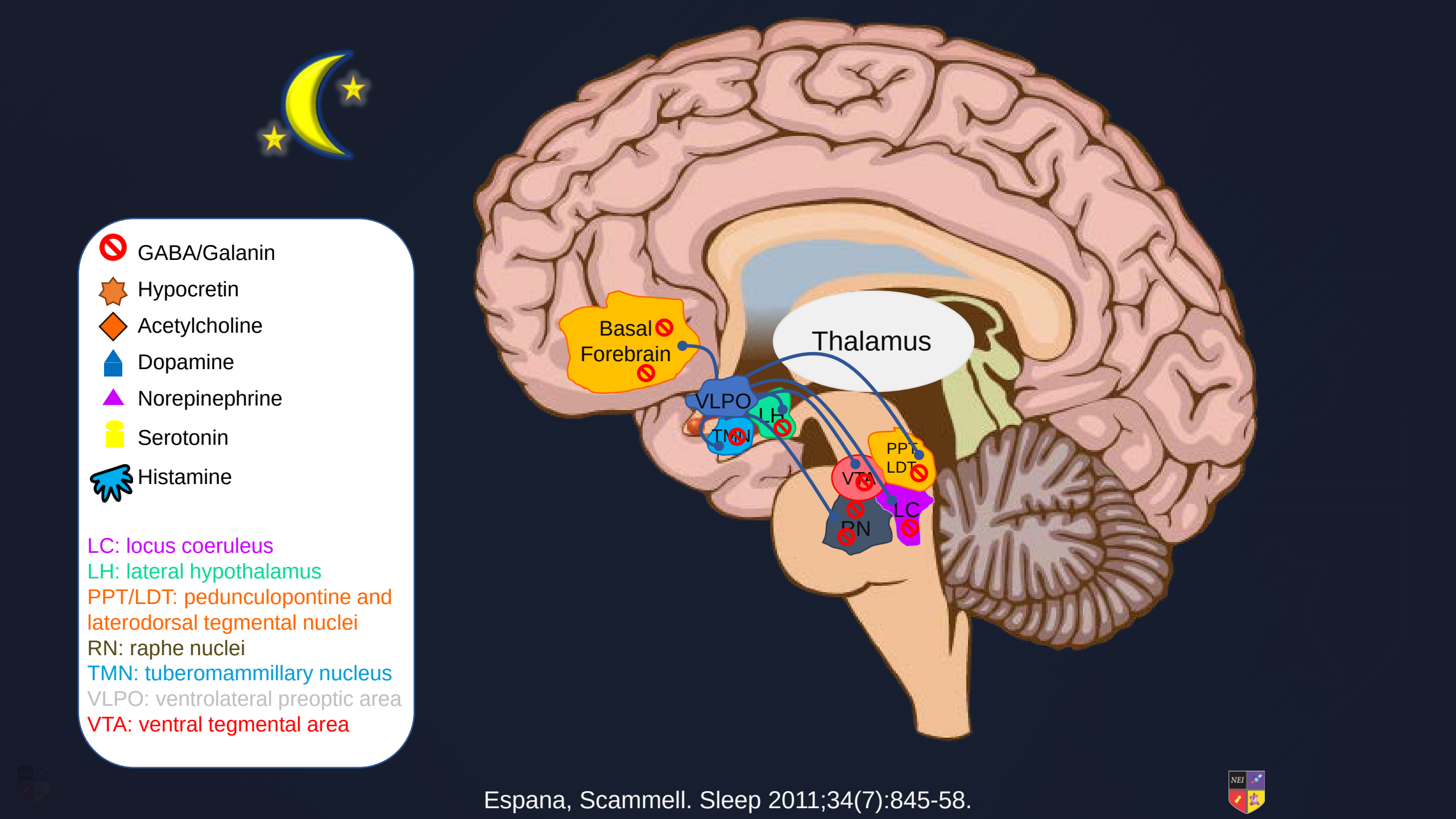
- The molecular clock consists of several transcription factors that regulate each other's expression



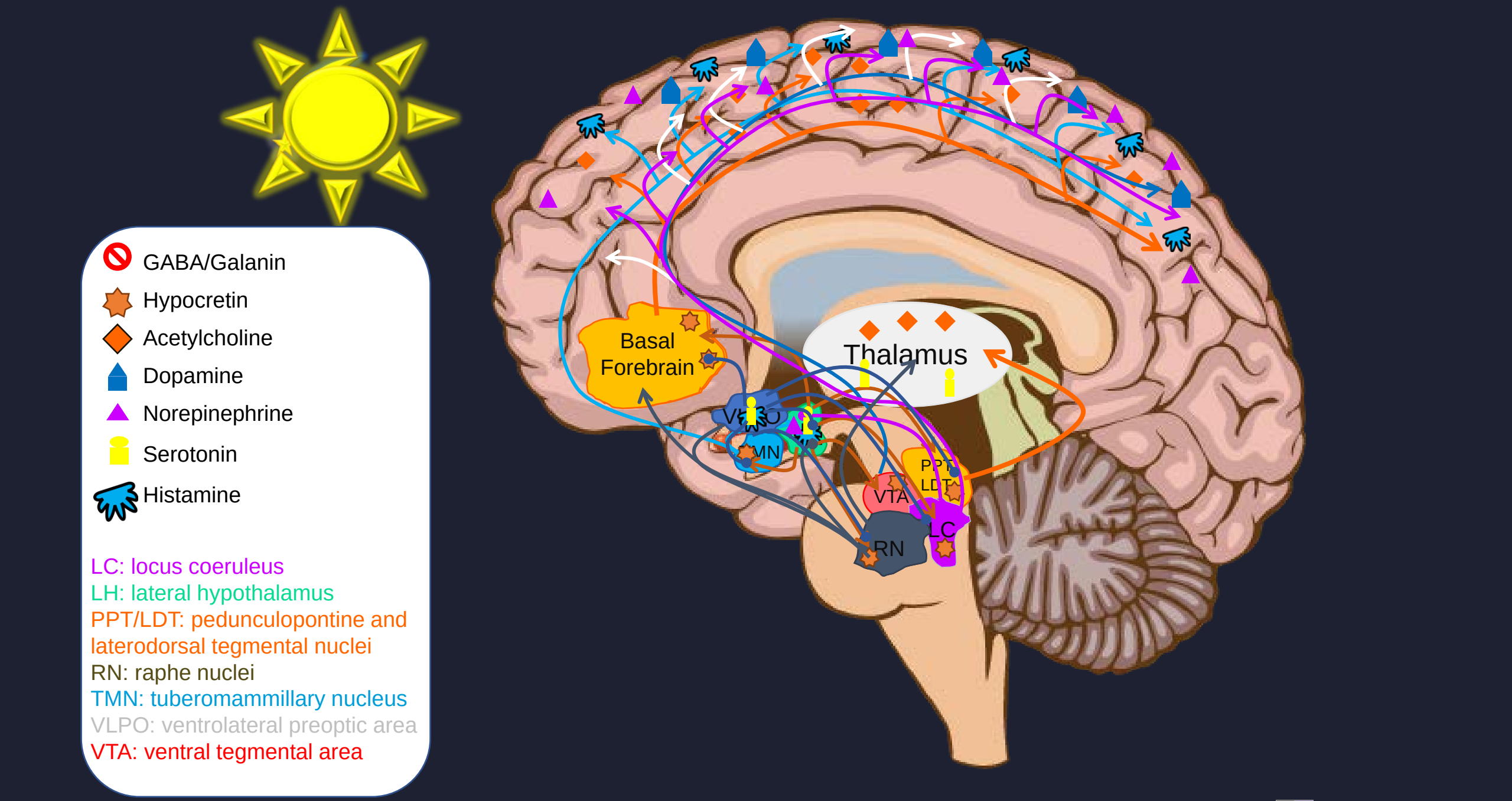
- Transcription factors bind to the promoter regions of DNA and, in doing so, turn the expression of a gene on or off



Masri S et al. Curr Opinion Oncology 2015;27:50-6;
Stahl SM, Morrissette DA. Stahl's Illustrated Sleep and Wake Disorders 2016.



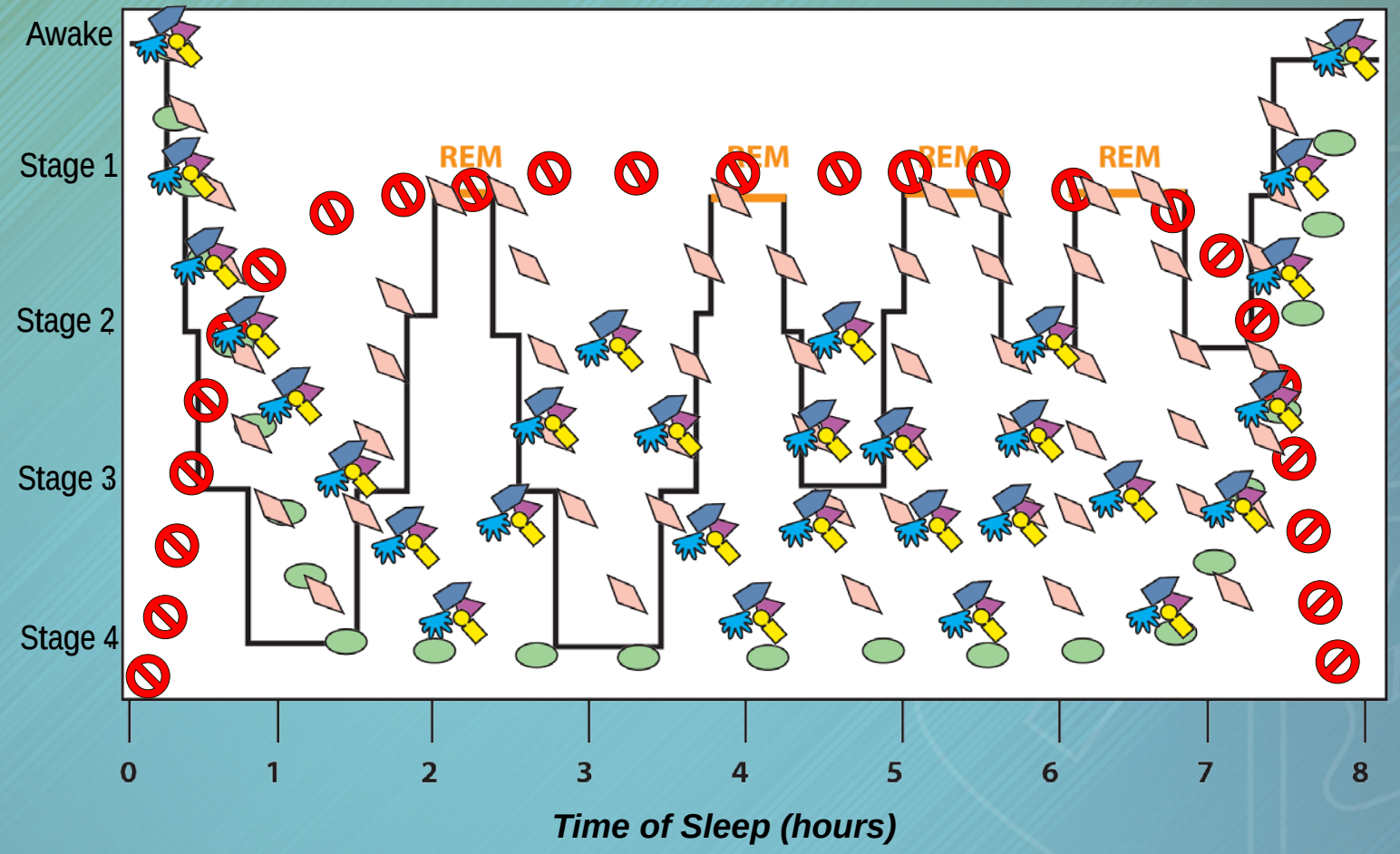
Espana, Scammell. Sleep 2011;34(7):845-58.



Espana, Scammell. Sleep 2011;34(7):845-58.

Neurotransmitter Levels Throughout the Sleep/Wake Cycle

- GABA/Galanin
- Hypocretin
- Acetylcholine
- Dopamine
- Norepinephrine
- Serotonin
- Histamine



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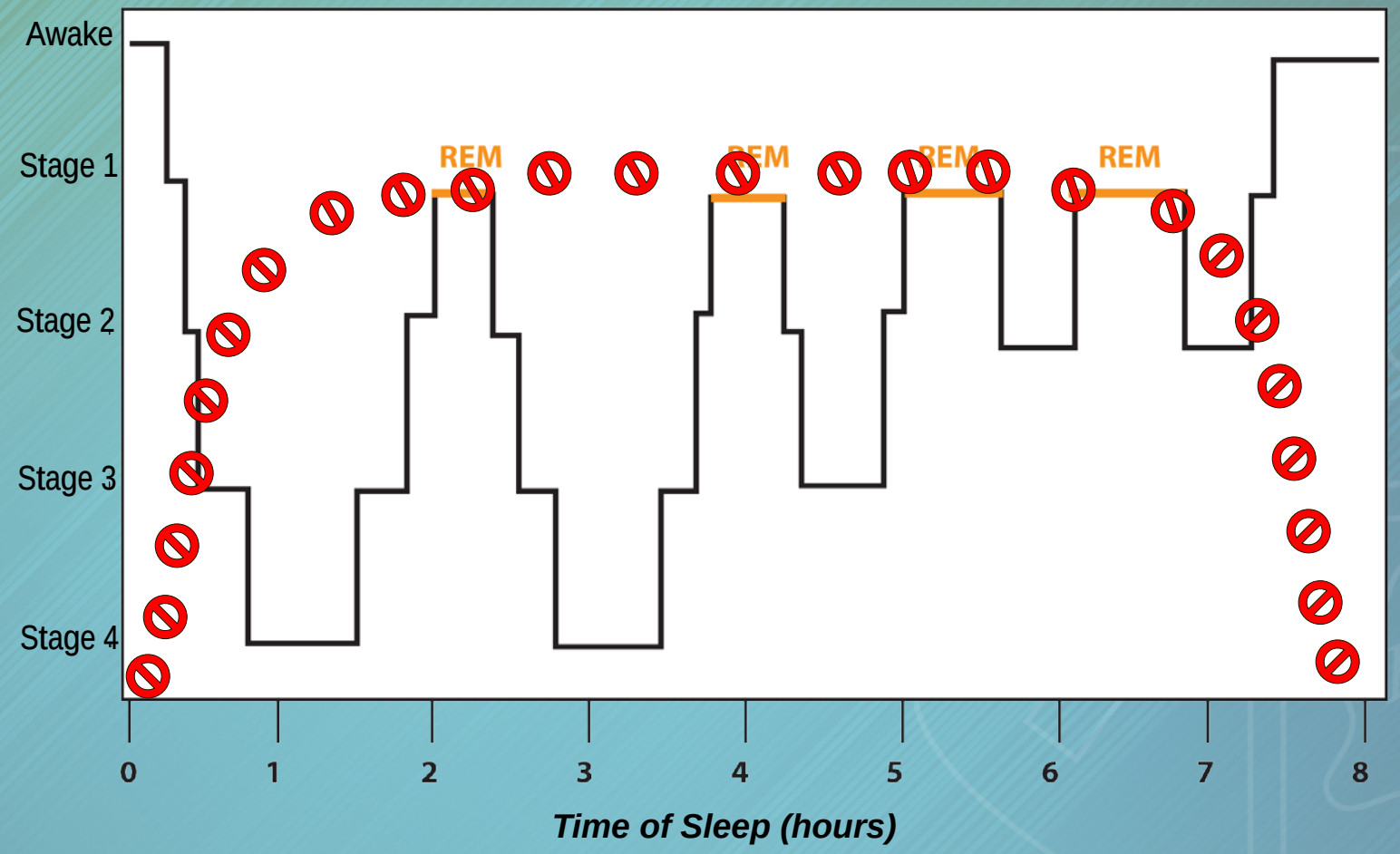

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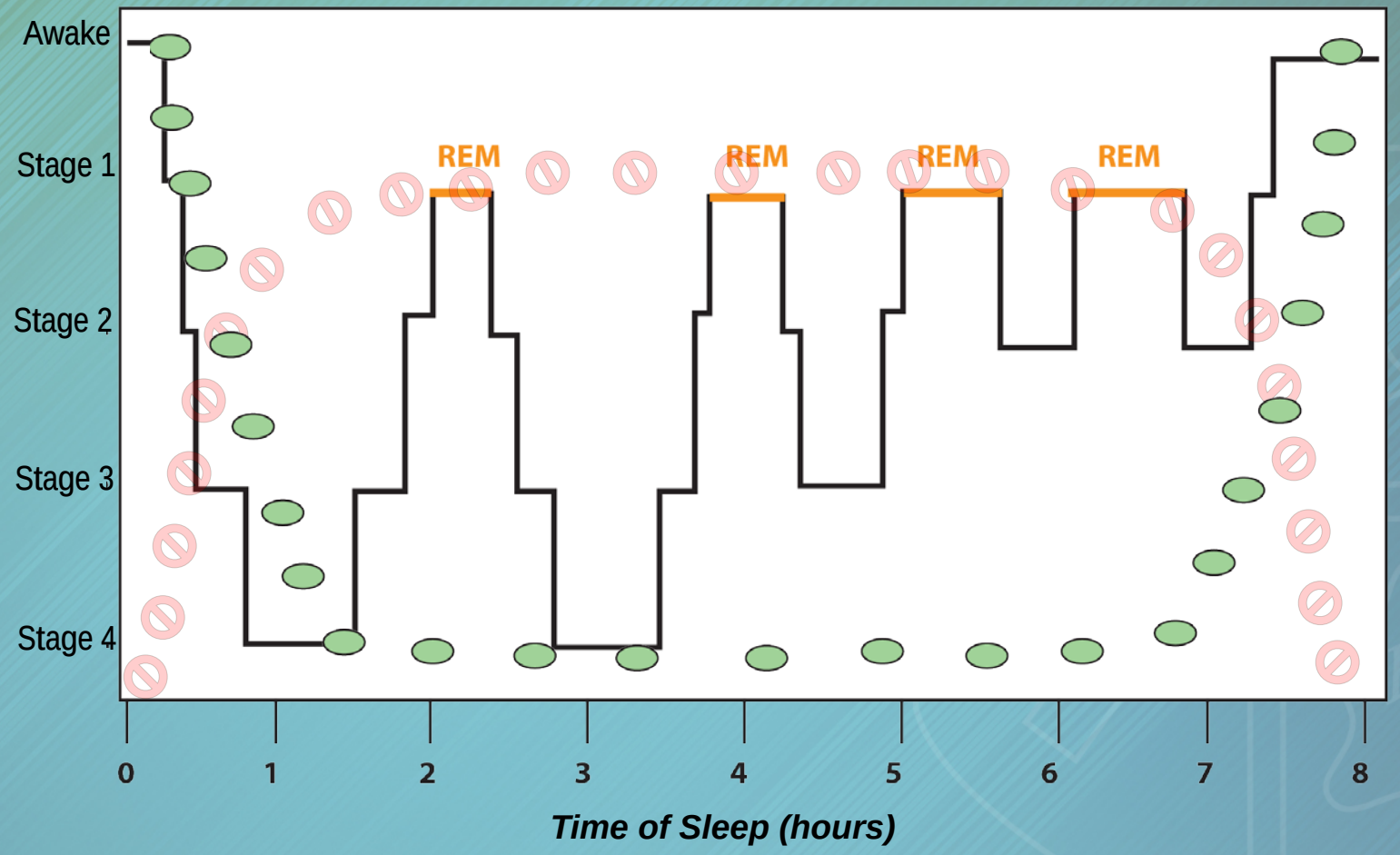
Hypocretin



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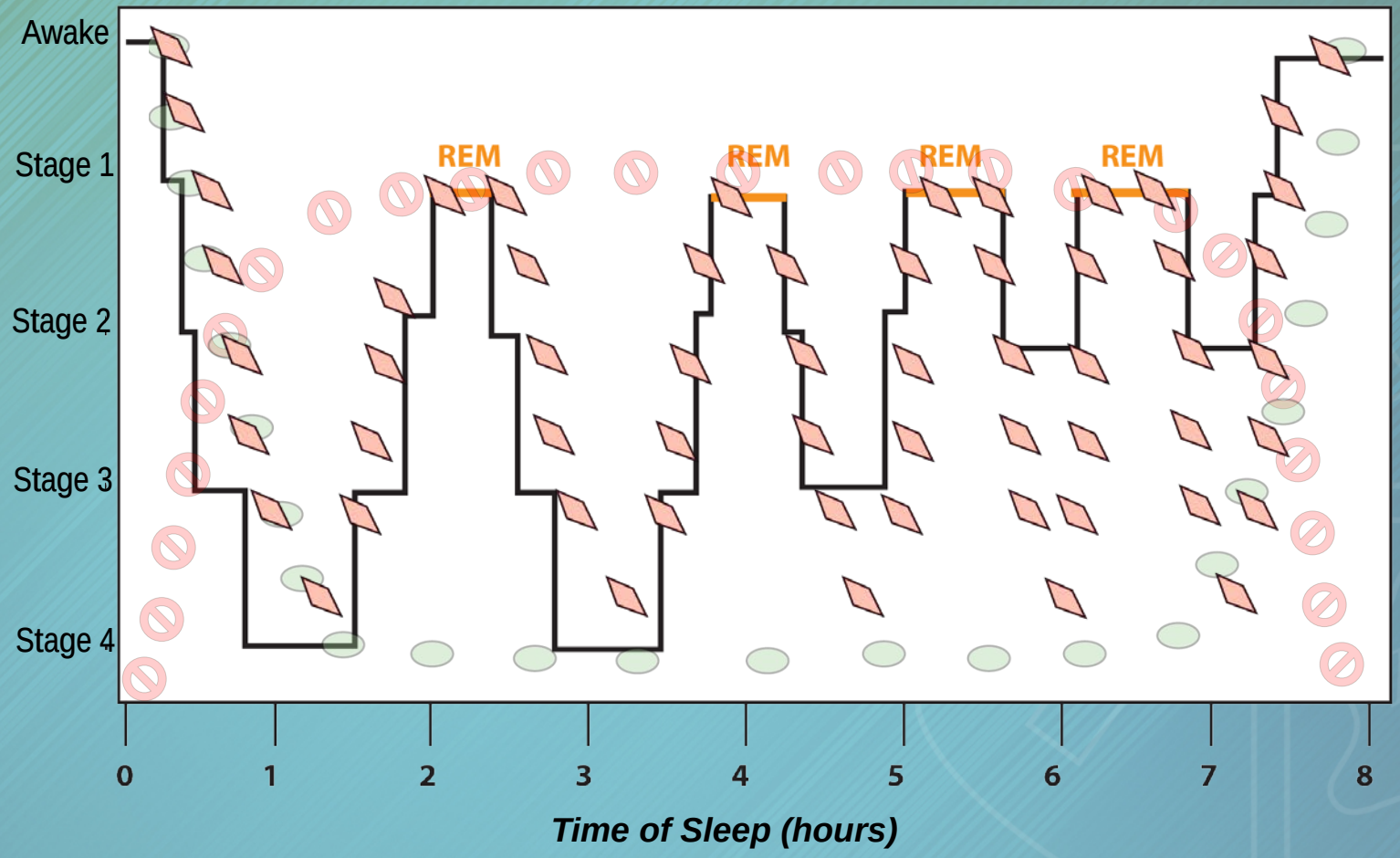

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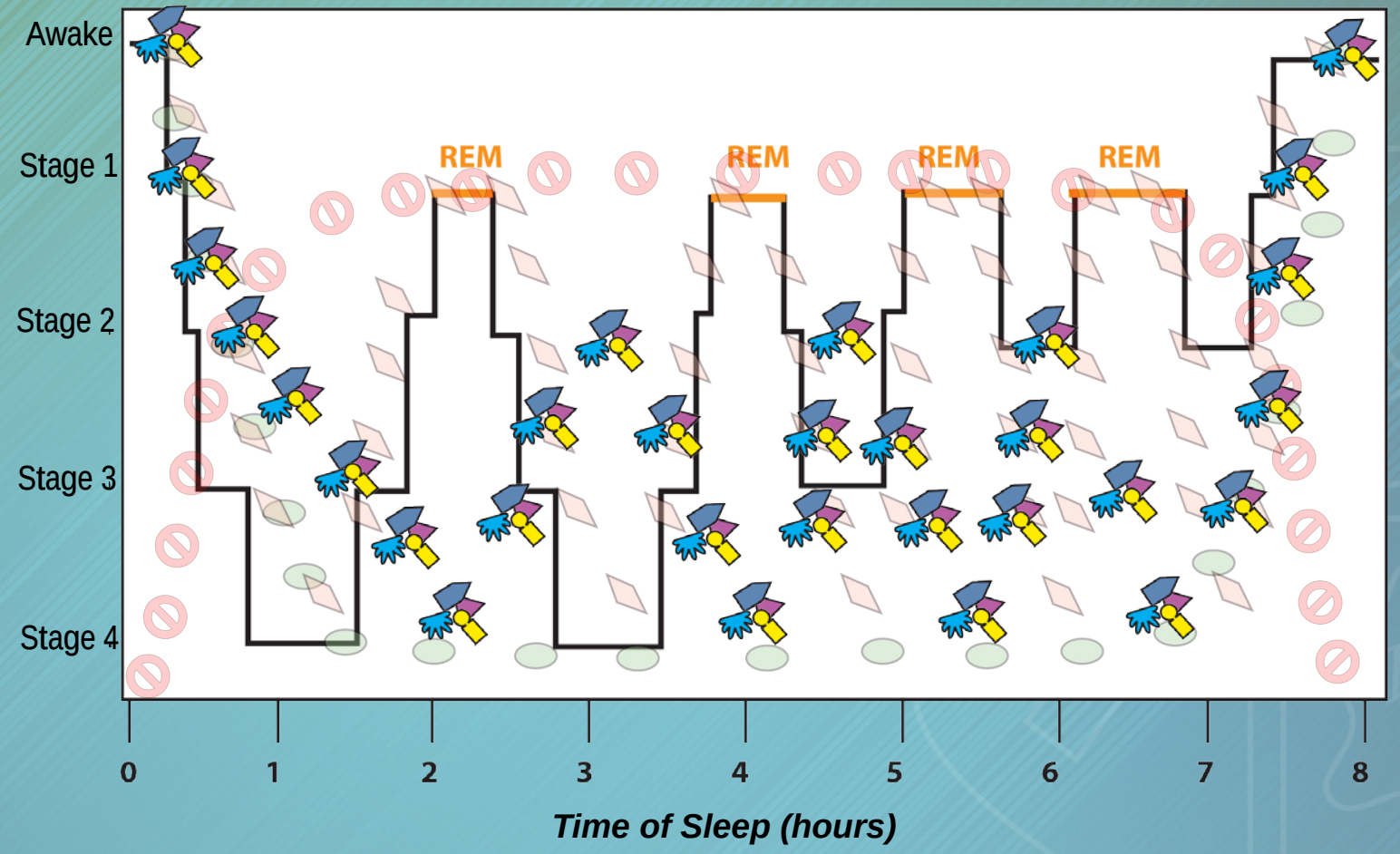
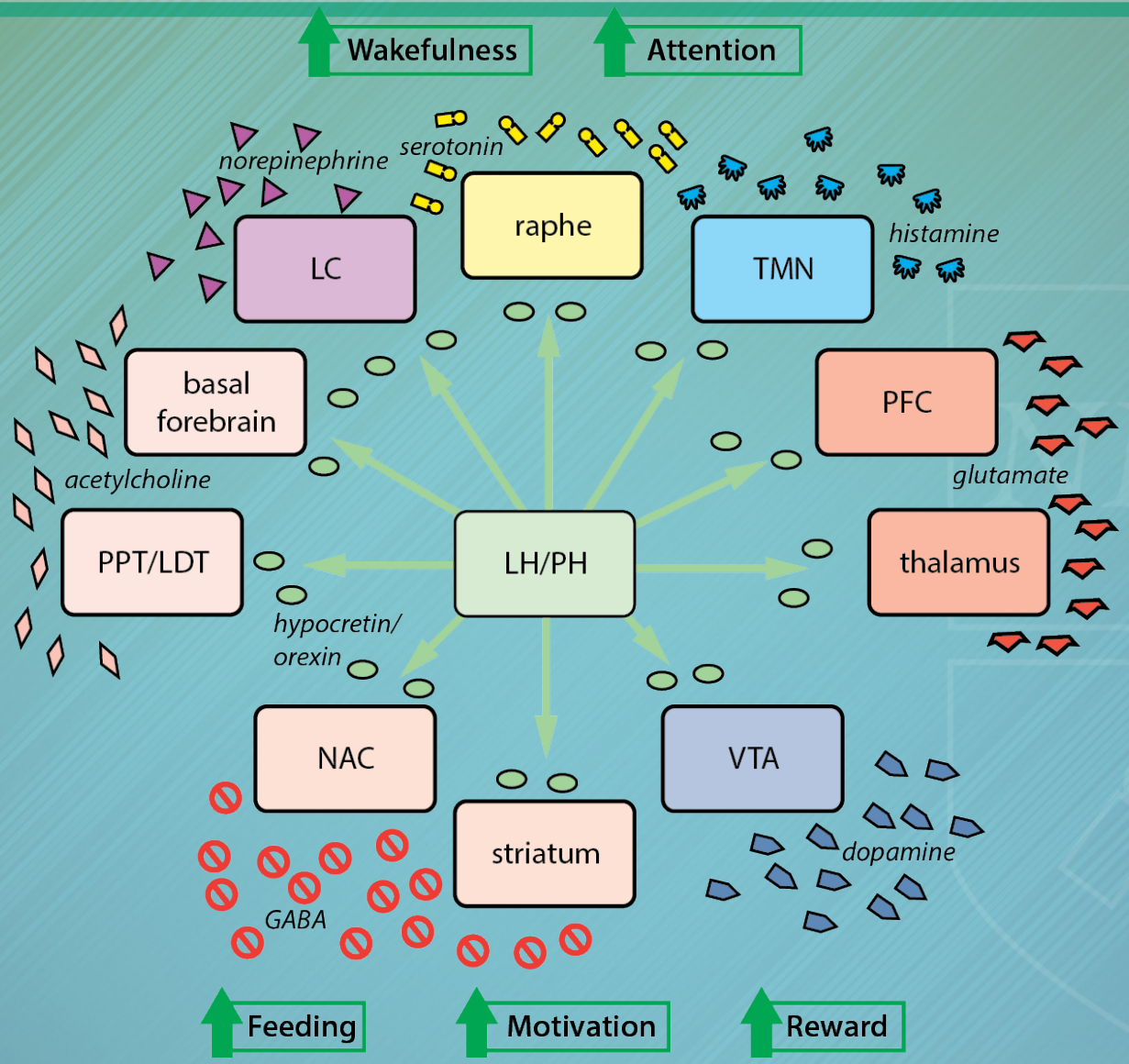


Espana, Scammell. Sleep 2011;34(7):845-58;
Stahl SM, Morrissette DA. Stahl's Illustrated Sleep and Wake Disorders 2016.

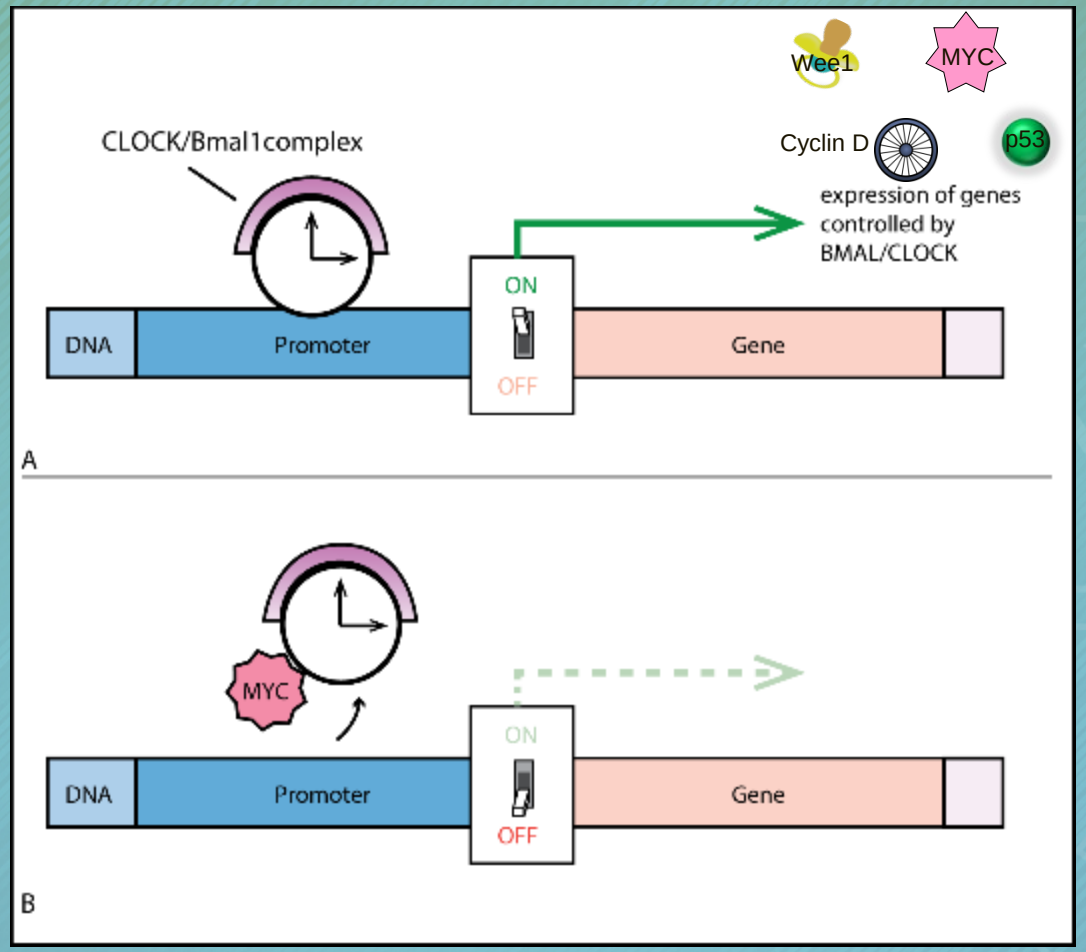
Hypocretin/Orexin Projections



LC: locus coeruleus
LH: lateral hypothalamus
PPT/LDT: pedunculopontine and laterodorsal tegmental nuclei
Raphe: raphe nuclei
TMN: tuberomammillary nucleus
VLPO: ventrolateral preoptic area
VTA: ventral tegmental area

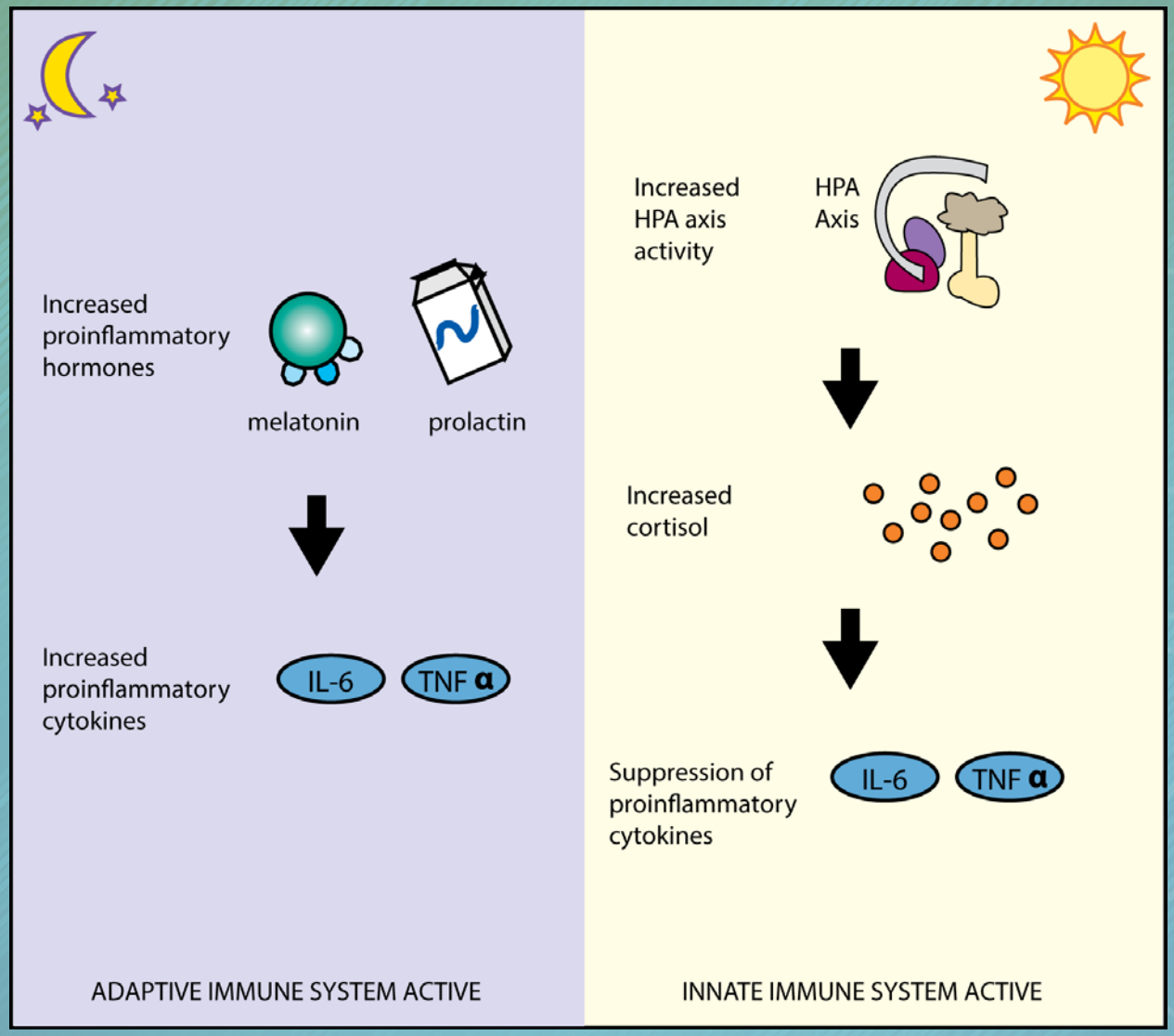
Scammel TE, Winrow CJ. Annu Rev Pharmacol Toxicol 2011;51:243-66;
Stahl SM, Morrissette DA. Stahl's Illustrated Sleep and Wake Disorders 2016.

Cancer and Circadian Rhythms



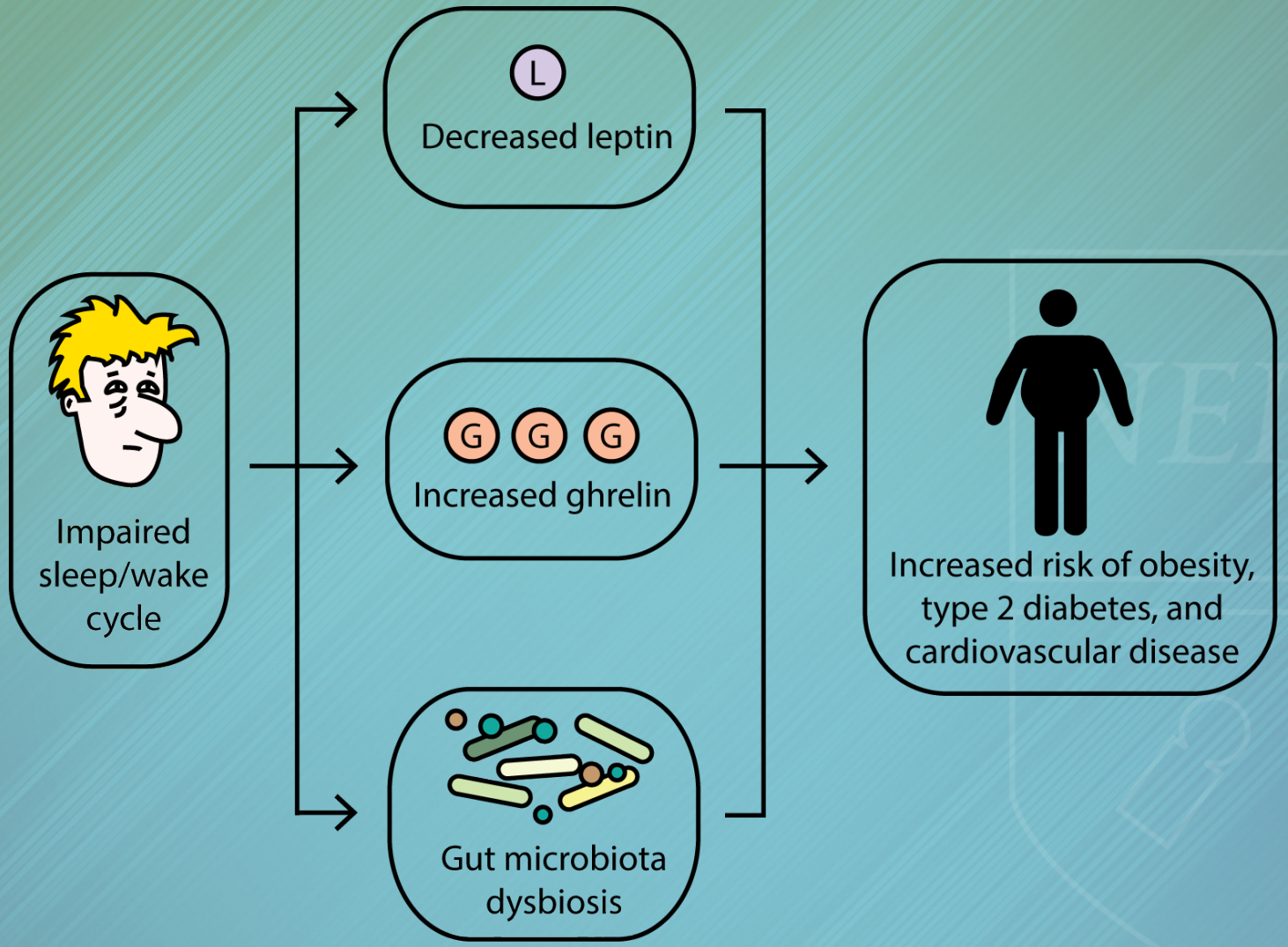
Takahashi S et al. Nat Rev Genetics 2008;9(10):764-75; Masri S et al. Curr Opinion Oncology 2015;27:50-6; Sahar S, Sassone-Corsi P. Nature 2009;9:886-96.

Sleep and Immunity



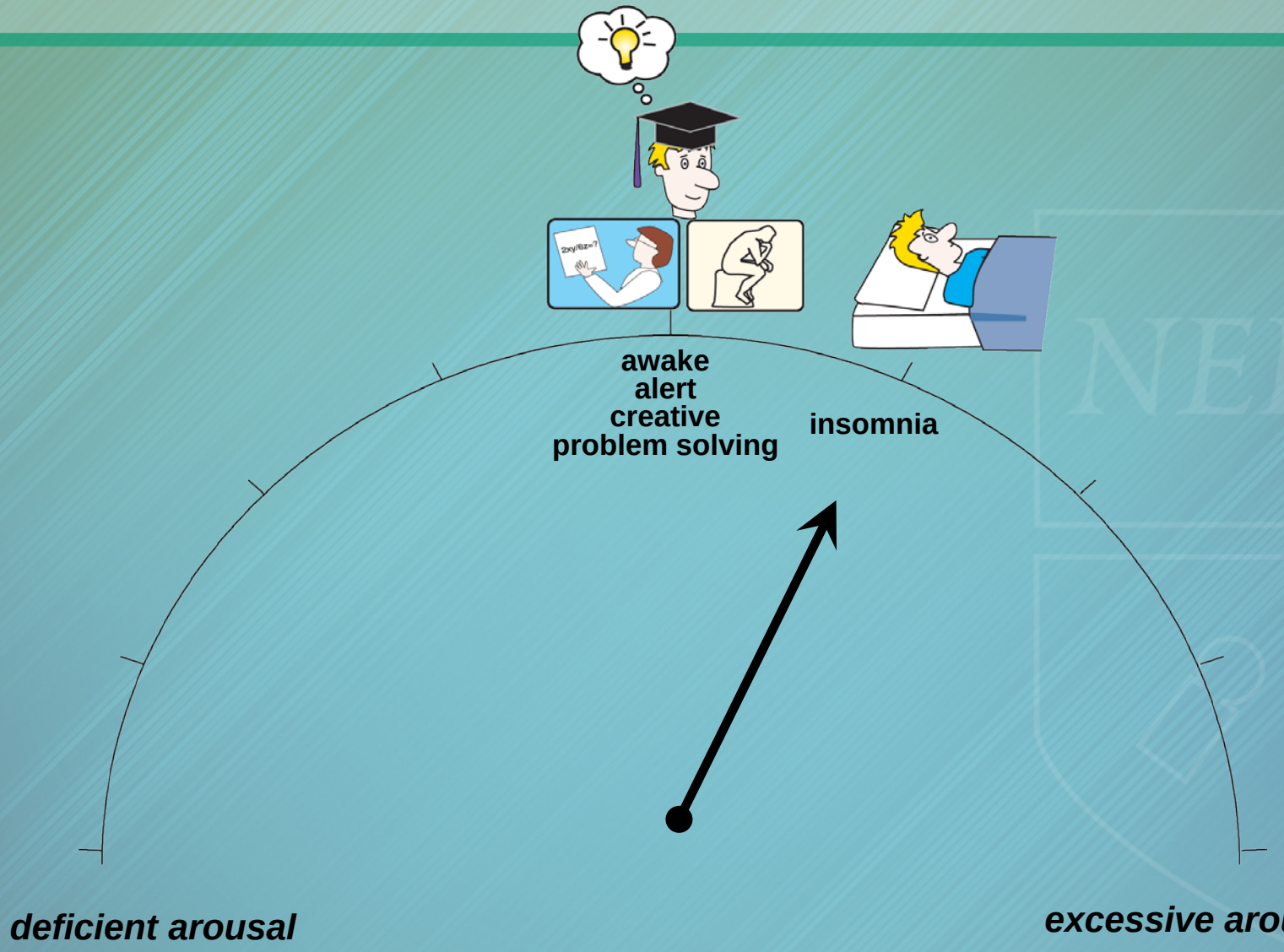
Cermakian N et al. Chronobiol Int 2013;30(7):870-88; Dresler M et al. Pharmacol Ther 2014;141:300-34; Golombek DA et al.J Physiol Paris 2013;107:310-22..

Sleep and Obesity



FroyO. Endocr Rev 2010;31(1):1-24; Orzel-Gryglewska J. Int J Occup Med Environ Health 2010;23(1):95-114; Golombek DA et al. J Physiol Paris 2013;107:310-22; Thaiss CA et al. Cell 2014;159:514-29.

Insomnia: Excessive Nighttime Arousal



Stahl's Essential Psychopharmacology. 4th ed. 2013.

Insomnia: Excessive Nighttime Arousal

- The most common sleep-wake disorder
  - Prevalence: 15% in the adult US population (40 million Americans)
- Affected individuals often complain of poor sleep quality or duration, difficulty falling asleep, nighttime awakenings, or wake times that are earlier than desired
- Importantly, the vast majority of the time, insomnia is comorbid with medical and psychiatric disorders

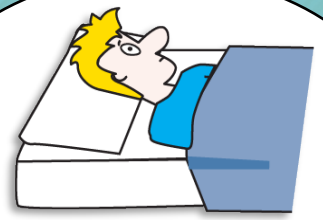
Reeve K, Bailes B. JNP 2010;6(1):53-60.

Conditions Associated With Insomnia

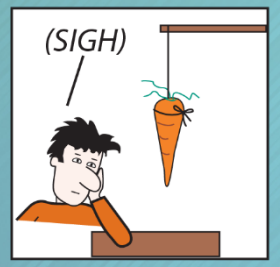
Substance Abuse

Medication Side Effects

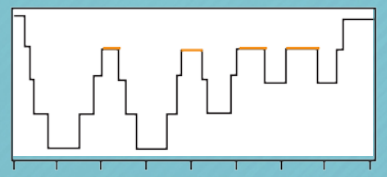
Medical Conditions



Insomnia



Behavioral/Psychological Causes



Sleep/Wake Disorders

Psychiatric Conditions

- **2x** more likely to develop **anxiety**
- **4x** more likely to develop **depression**
- **7x** more likely to develop **SUD**

Dresler M et al., Pharmacol Ther 2014;141:300-34; Espana, Scammell. Sleep 2011;34(7):845-58; Morin CM, Benca R. Chronic insomnia. Lancet 2012;379:1129-41.

Insomnia: DSM-5 Diagnostic Criteria

- Complaint of dissatisfaction with sleep quantity or quality, associated with at least one of the following symptoms:
  - Difficulty initiating sleep
  - Difficulty maintaining sleep
  - Early-morning awakening with inability to return to sleep
- Sleep disturbance causes distress or impairment in social, occupational, educational, academic, behavioral, or other important areas of functioning
- Disturbance occurs at least 3 nights per week and is present for at least 3 months
- Disturbance is not attributable to the physiologic effects of a substance or a coexisting medical or mental disorder

Association AP. Diagnostic and Statistical Manual of Mental Disorders, DSM-V 2013.

Insomnia Severity Index

Please rate the *CURRENT (i.e., LAST 2 WEEKS) SEVERITY* of your insomnia problem(s).

Insomnia problem	None	Mild	Moderate	Severe	Very Severe
1. Difficulty falling asleep	0	1	2	3	4
2. Difficulty staying asleep	0	1	2	3	4
3. Problem waking up too early	0	1	2	3	4

4. How SATISFIED/DISSATISFIED are you with your CURRENT sleep pattern?				
Very Satisfied	Satisfied	Moderately Satisfied	Dissatisfied	Very Dissatisfied
0	1	2	3	4

5. How NOTICEABLE to others do you think your sleep problem is in terms of impairing the quality of your life?				
Not at All Noticeable	A Little	Somewhat	Much	Very Much Noticeable

6. How WORRIED/DISTRESSED are you about your current sleep problem?				
Not at All Worried	A Little	Somewhat	Much	Very Much Worried
0	1	2	3	4

7. To what extent do you consider your sleep problem to INTERFERE with your daily functioning (e.g., daytime fatigue, mood, ability to function at work/daily chores, concentration, memory, mood) CURRENTLY?				
Not at All Interfering	A Little	Somewhat	Much	Very Much Interfering
0	1	2	3	4

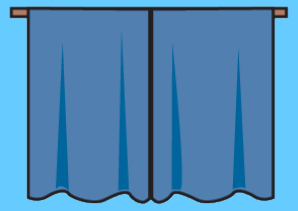
Total score categories:
0–7 = No clinically significant insomnia
8–14 = Subthreshold insomnia
15–21 = Clinical insomnia (moderate severity)
22–28 = Clinical insomnia (severe)

Bastien CH et al., Sleep Med 2001;2(4):297-307.

Sleep-Wake Hygiene

Sleep Time

No stimulants before bed



Dark room

Cool environment

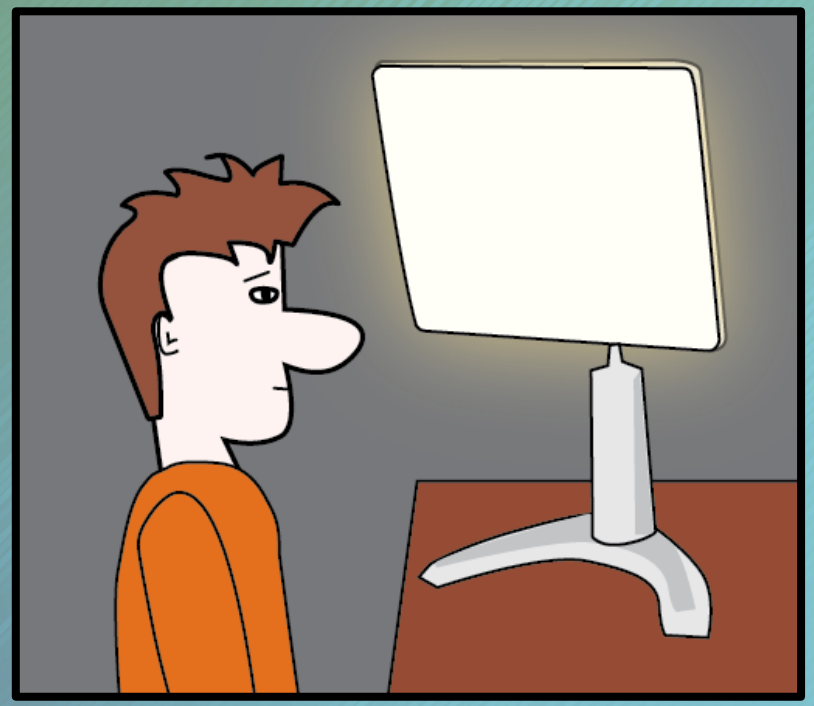
No disturbances

Wake Time

Activity

Bright Light

Resetting Circadian Rhythms



Bright Light Therapy

Suppresses melatonin release

- Treatment with 10,000 lux, bright, blue light for 30 minutes a day may be used to reset circadian rhythms
- Shown to improve performance, alertness, and mood during the night shift can be improved in shift workers

Bonacci JM et al. J Pharm Pract 2015;28(5):473-8; Crowley SJ et al. Sleep 2004;27(6):1077-87; Stahl's Essential Psychopharmacology. 4th ed. 2013.

Theoretical Pharmacological Targets

- To promote wakefulness

  - Inhibit
    - GABA
    - Galanin
  - Enhance
    - DA
    - NE
    - 5HT
    - Hcrt
    - ACh
    - HA

- To promote sleep

  - Inhibit
    - DA
    - NE
    - 5HT
    - Hcrt
    - ACh
    - HA
  - Enhance
    - GABA
    - Galanin

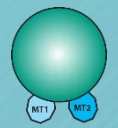
Espana RA, Scammell TE. Sleep 2011;34(7):845-58.

Resetting Circadian Rhythms

- **Melatonergic** agents promote sleep by resetting the sleep/wake cycle
- Endogenous melatonin is secreted by the pineal gland during periods of darkness
- Acts on the suprachiasmatic nucleus to regulate circadian rhythms
- Melatonin may help to adjust circadian rhythms if taken 3 hours before dim-light melatonin onset

Melatonin

- Acts at MT1 and MT2 receptors as well as at the MT3 site
- Available over the counter

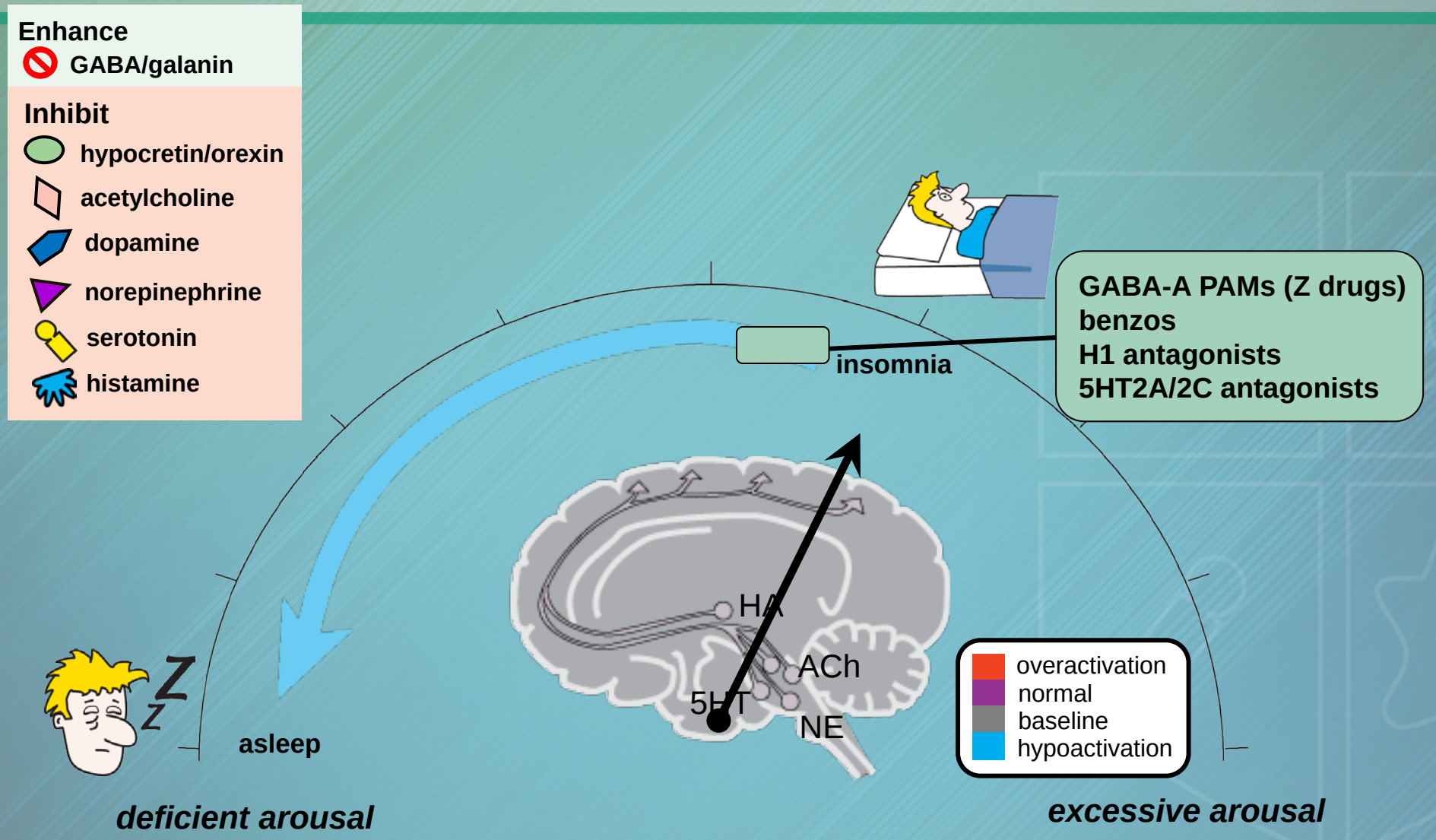


MT1 and MT2 Receptor Agonists

- Improve sleep onset
  - **ramelteon:** FDA-approved for the treatment of insomnia
  - **tasimelteon:** FDA-approved for Non-24-Hour Sleep-Wake Disorder

Bonacci JM et al. J Pharm Pract 2015;28(5):473-8; Crowley SJ et al. Sleep 2004;27(6):1077-87; Stahl's Essential Psychopharmacology. 4th ed. 2013.

Promoting Sleep



Stahl's Essential Psychopharmacology. 4th ed. 2013.

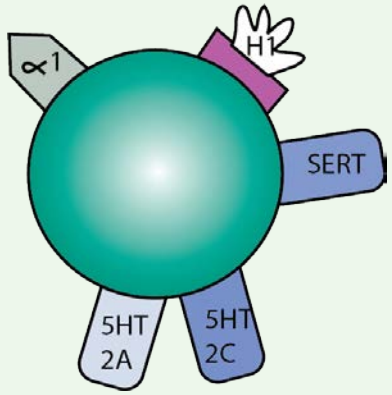
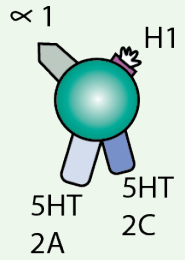
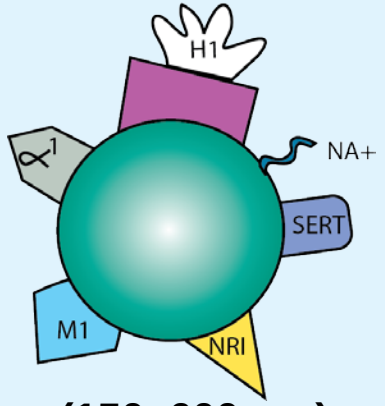
Pharmacological Treatments for Insomnia

Pharmacological Agent	FDA-Approved for Insomnia
Benzodiazepine Hypnotics	
Estazolam	✓
Flurazepam	✓
Quazepam	✓
Temazepam	✓
Triazolam	✓
Nonbenzodiazepine Hypnotics	
Eszopiclone	✓
Zaleplon	✓
Zolpidem	✓
Antidepressants	
Doxepin	✓
Trazodone	

Pharmacological Agent	FDA-Approved for Insomnia
Hypocretin/Orexin Antagonist	
Suvorexant	✓
Lemborexant	✓
Melatonin Receptor Agonists	
Melatonin	
Ramelteon	✓
Tasimelteon	
Antipsychotics	
Quetiapine	
Olanzapine	
Anticonvulsants	
Clonazepam	
Gabapentin	
Tiagabine	

Stahl SM, Morrissette DA. Stahl's Illustrated Sleep and Wake Disorders 2016.

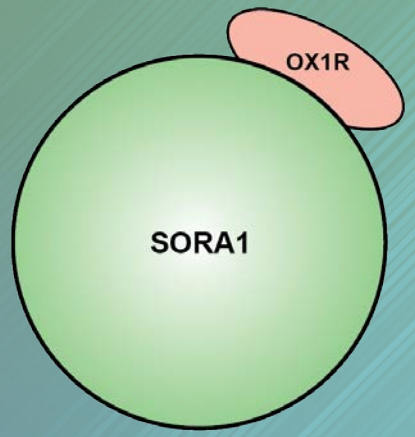
Mechanism of Trazodone and Doxepin as Hypnotics

	Antidepressant dose	Hypnotic dose
Trazodone	 **(150–600 mg)**	 **(25–150 mg)**
Doxepin	 **(150–600 mg)**	 **(1–6 mg)**

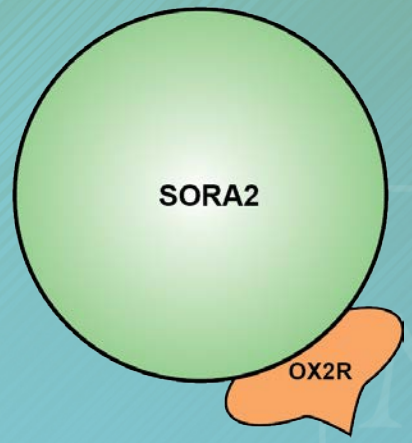
Stahl SM. Stahl's Essential Psychopharmacology. 4th ed. 2013.

Orexin Receptor Antagonist

Single Orexin Receptor Antagonist (SORAs)

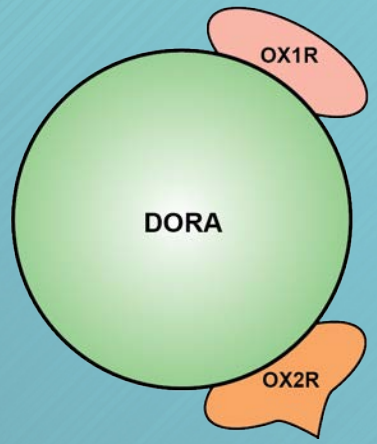


SORA1 works selectively at orexin 1 receptor



SORA2 works selectively at orexin 2 receptor

Dual Orexin Receptor Antagonist (DORA)

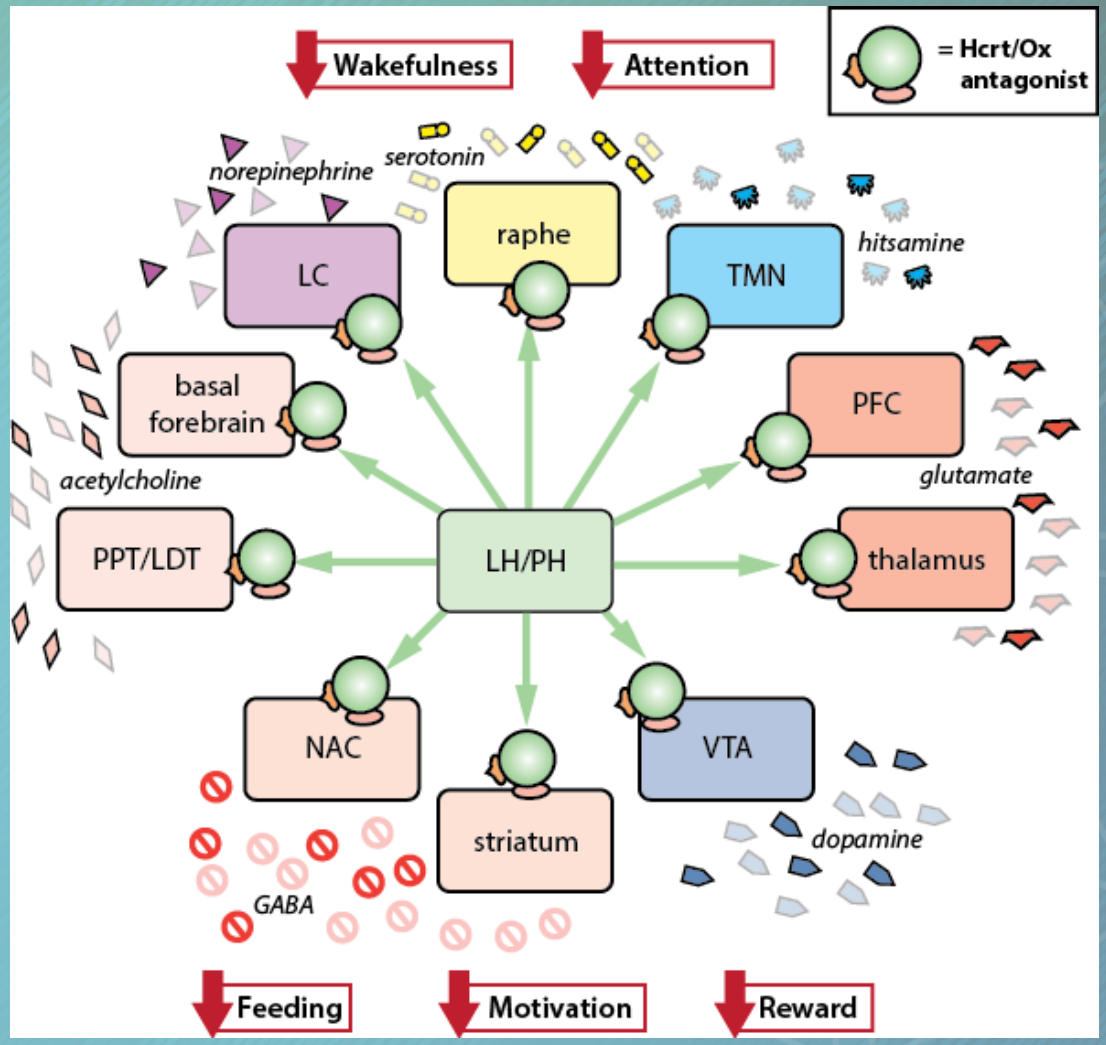


DORA bind to both orexin 1 and orexin 2 receptors

Stahl SM. Stahl's Essential Psychopharmacology. 4th ed. 2013.

Blocking Orexin Receptors With Antagonist Agents May Help to Promote Sleep

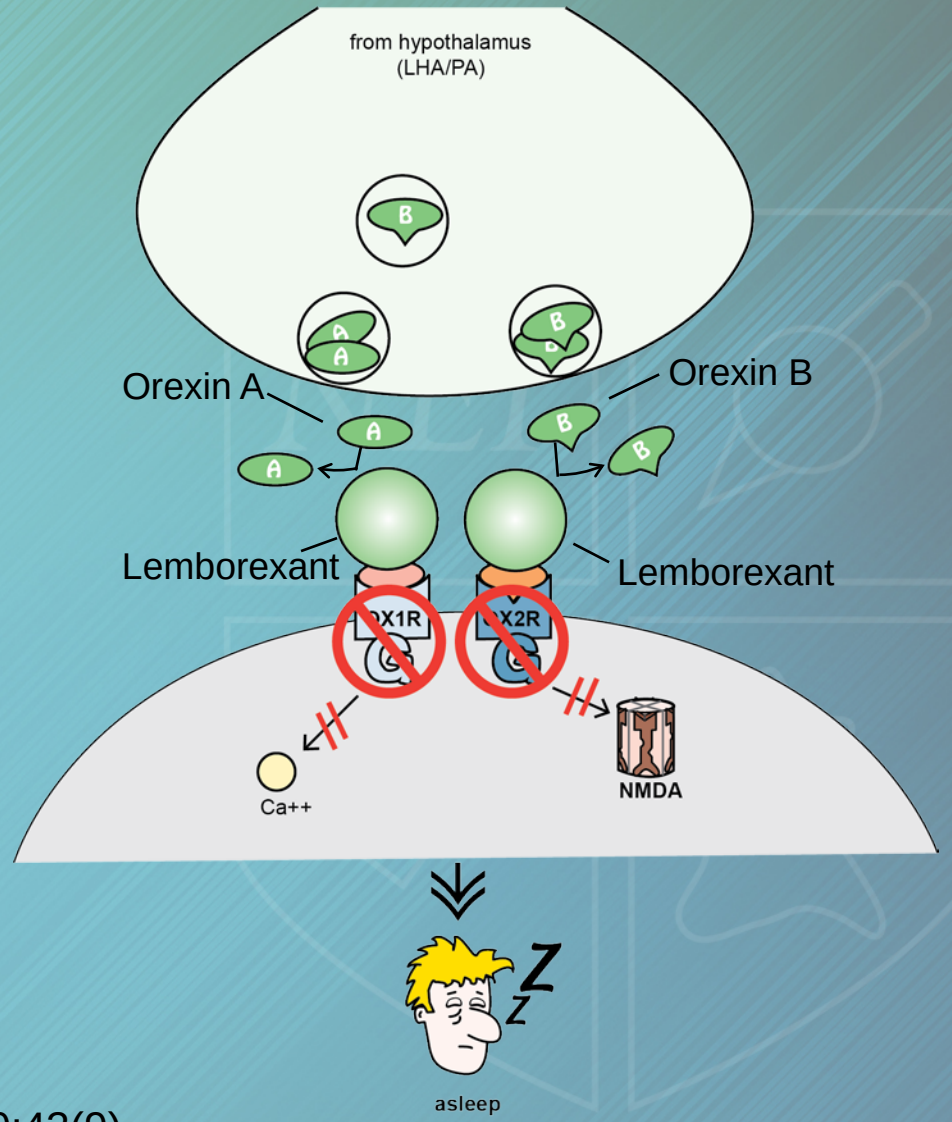
- Binding of orexin to OXR1 and OXR2 receptors promotes wakefulness; orexin antagonists promote sleep by blocking these receptors



Lemborexant

The latest FDA-approved treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance in adults

- Multicenter, randomized, double-blind, parallel-group phase III study
  - Results showed decreases from baseline in patient-reported (subjective) sleep onset latency and subjective wake after sleep onset, and increases from baseline in subjective sleep efficiency, were significantly greater with 5mg lemborexant and 10 mg lemborexant versus placebo
- FDA approved at both 5 and 10 mg doses for insomnia



Kärppä M et al. Sleep. 2020;43(9)

Nonpharmacological Treatments for Insomnia

- Relaxation training
  - Aimed to reduce somatic tension and intrusive thoughts that interfere with sleep
- Stimulus control therapy
  - Get out of bed if not sleepy; use bed only for sleeping; no napping
- Sleep restriction therapy
  - Limit time spent in bed to produce mild sleep deprivation; results in more consolidated sleep
- Intensive sleep retraining
  - 25-hour sleep deprivation period in which the patient is given 50 sleep onset trials but awoken following 3 minutes of sleep
- Cognitive behavioral therapy
  - Reduce negative attitudes and misconceptions about sleep

Summary

- The neurobiology and molecular underpinnings of sleep are complex
- The quality and quantity of sleep can greatly affect our physical and mental health
- There are numerous pharmacological and nonpharmacological treatment options available that target various components of the sleep/wake circuit to improve sleep/wake

Posttest Question

A 30-year-old patient with narcolepsy with cataplexy demonstrates profound loss of hypocretin/orexin (Hcrt/Ox) neurons in the lateral hypothalamus. Hcrt/Ox typically stimulates:

A. Acetylcholine release from the basal forebrain
B. Acetylcholine release from the pedunculopontine nucleus
C. Acetylcholine release from the laterodorsal tegmental area
D. All of the above
E. None of the above

Posttest Question

Sarah is a 19-year-old college student who is interested in using over-the-counter melatonin to help with her sleep/wake cycle while studying for final exams. Which of the following statements is true regarding endogenous melatonin?

A. Melatonin is released from the pineal gland during periods of light
B. Melatonin is released from the pineal gland during periods of darkness
C. Melatonin is released from the suprachiasmatic nucleus during periods of darkness
D. Melatonin is released from the suprachiasmatic nucleus during periods of light

Posttest Question

Peggy is a 59-year-old patient who suffers from insomnia. Among the FDA-approved treatments for insomnia are dual orexin receptors antagonists (DORA) suvorexant and lemborexant. The blockade of hypocretin/orexin receptors via hypocretin/orexin antagonists typically:

A. Increases histamine levels
B. Lowers histamine levels
C. Does not effect histamine levels

APPENDIX

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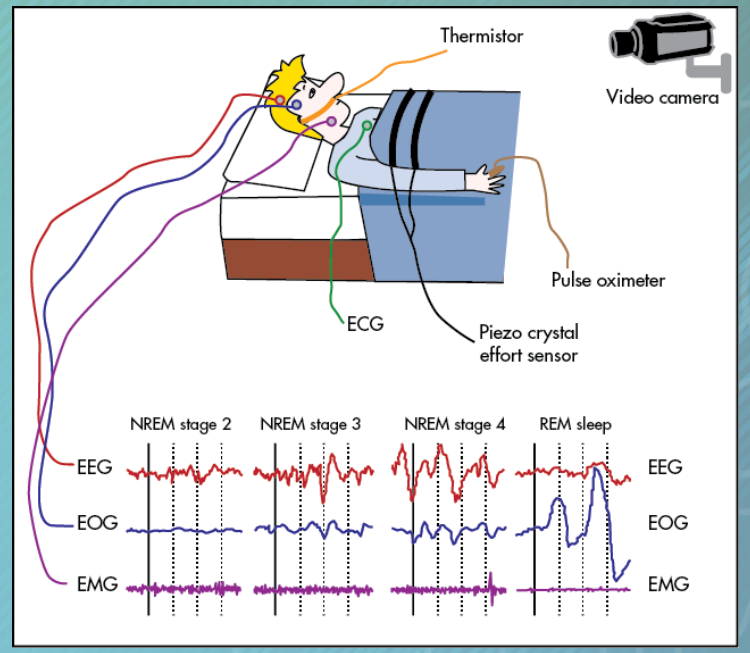
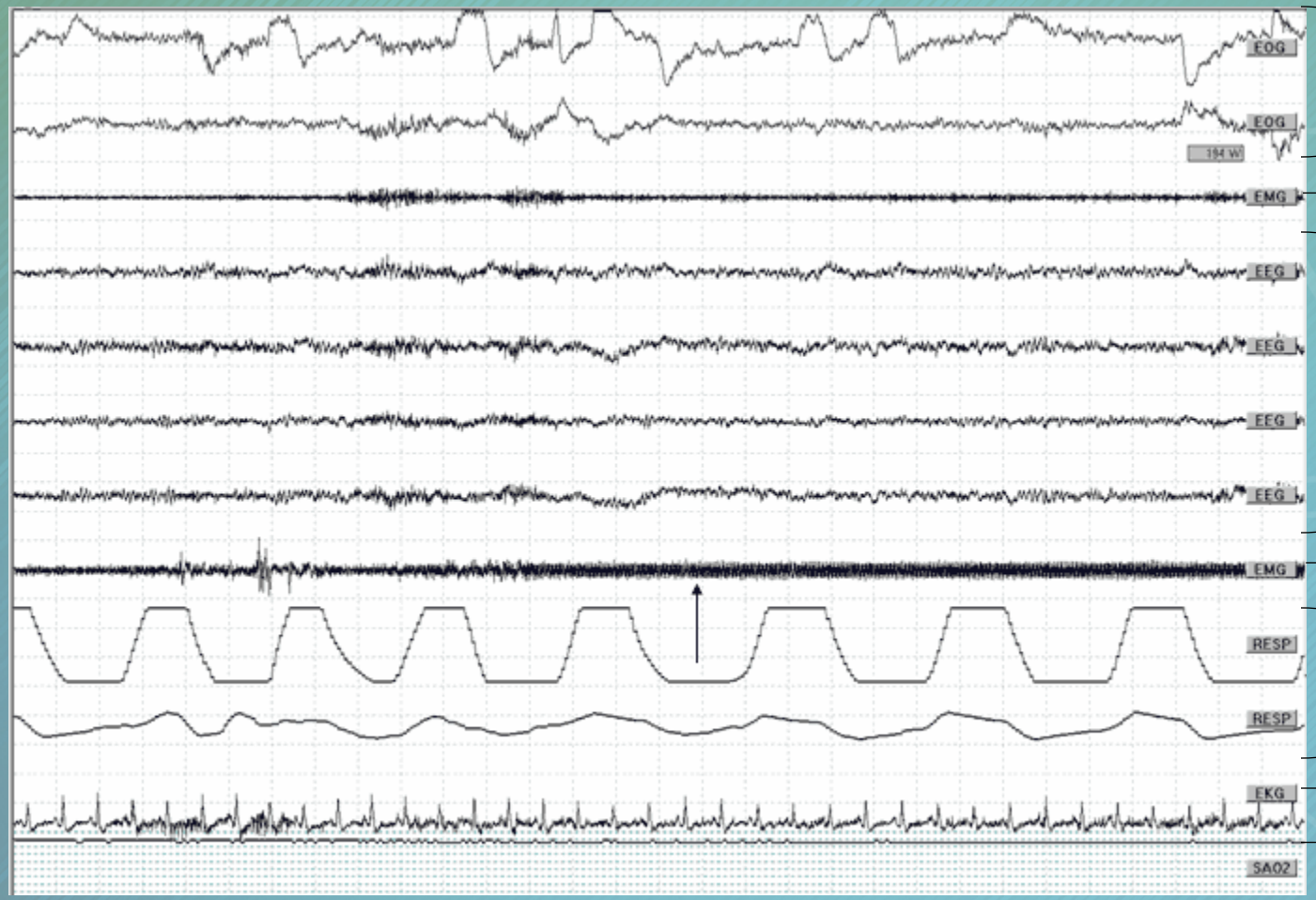
Polysomnography

- Electroencephalogram (EEG) determines sleep stages
- Electrooculogram (EOG) measures eye movement to identify rapid eye movement (REM) sleep
- Electromyogram (EMG) measures muscle activity via electrodes on the chin, jawbone, and calf muscles
- Electrocardiogram (ECG) is used to measure heart rate and rhythm
- Breathing is measured with a piezo crystal effort sensor, which utilizes 2 Velcro bands around the chest and abdomen to measure movements and effort
- Airflow is measured with a thermistor secured under the nose, and oxygen saturation can be measured by a pulse oximeter on the finger or ear lobe
- The patient may be videotaped



Polysomnography



Multiple Sleep Latency Testing

Method

Nocturnal polysomnogram

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5 daytime nap opportunities

Quiet, dark room

2-hour intervals

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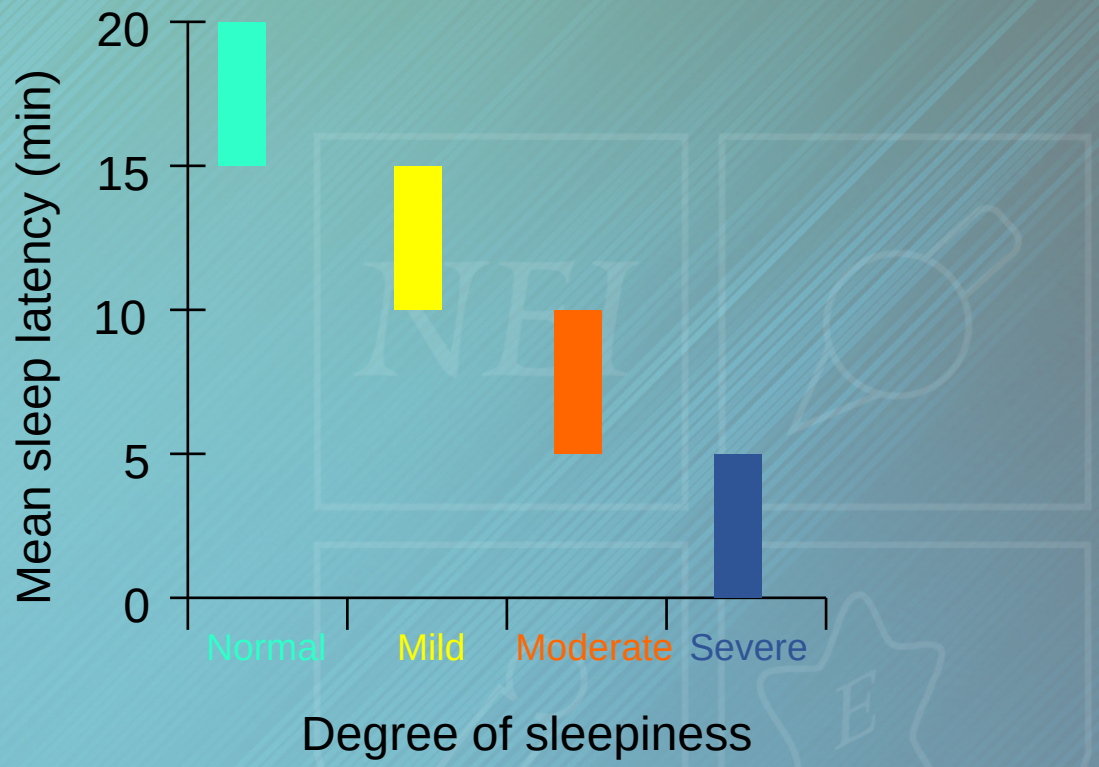
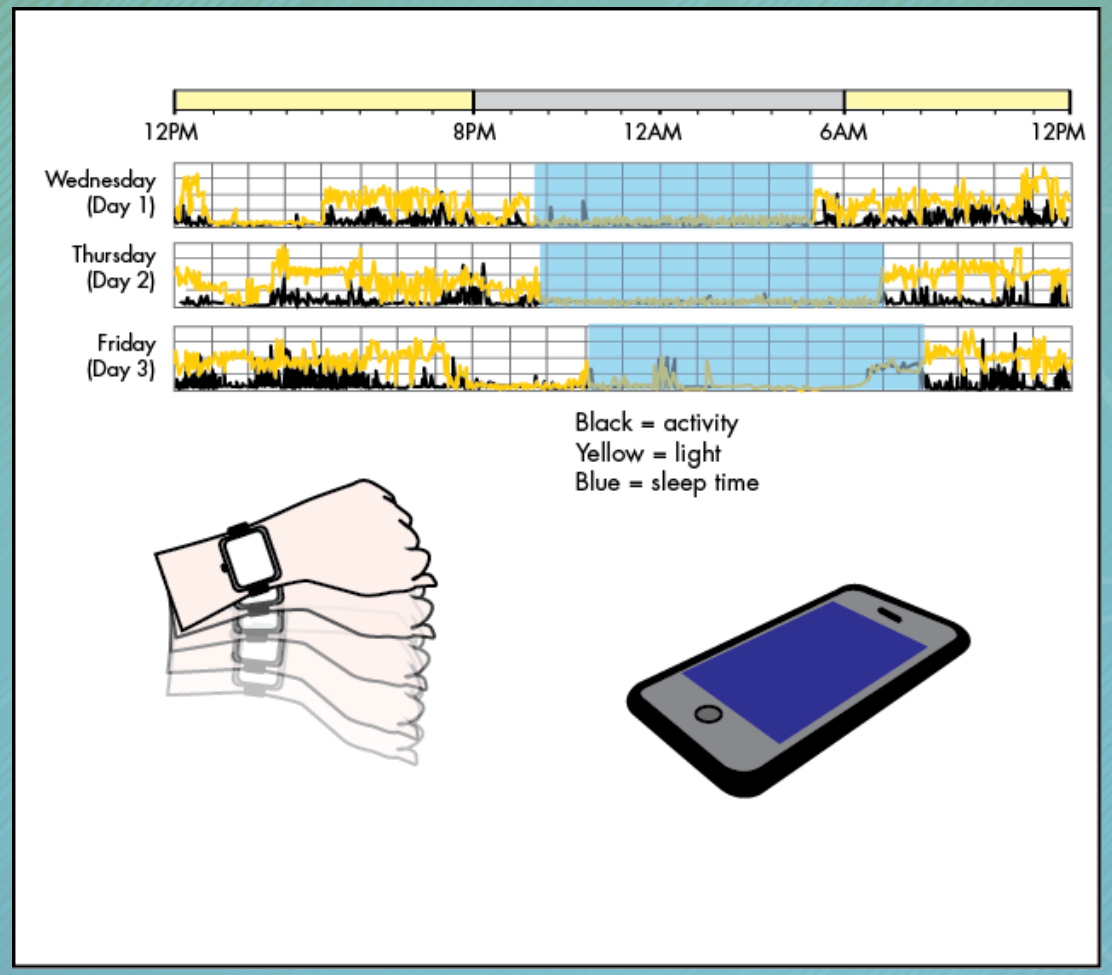
Score time to sleep onset

Max time: 20 min

Wake patient 15 min from sleep onset



Actigraphy


12PM
8PM
12AM
6AM
12PM
Wednesday
(Day 1)
Thursday
(Day 2)
Friday
(Day 3)
Black = activity
Yellow = light
Blue = sleep time

Sleep-Wake Diary

	First day	*Second day*	*Third day*	*Fourth day*
Complete in morning				
Bedtime (date/time)	10:45 p.m. (4/10)			
Rise time (date/time)	7:00 a.m. (4/11)			
Estimated time to fall asleep	30 minutes			
Estimated number of awakenings and total time awake	5 times 2 hours			
Estimated amount of sleep obtained	4 hours			
Complete at bedtime				
Naps (number, time, and duration)	1 at 3:30 p.m. 45 minutes			
Alcoholic drinks (number and time)	1 drink at 8:00 p.m. 2 drinks at 9:00 p.m.			
List stresses of the day	Flat tire Argued with son			
Rate how you felt today 1 = Very tired/sleepy 2 = Somewhat tired/sleepy 3 = Fairly alert 4 = Wide awake	2			
Irritability level 1 = None 2 = Some 3 = Moderate 4 = Fairly high 5 = High	5			
Medications				

Epworth Sleepiness Scale

Situation:	would never doze (0)	slight chance of dozing (1)	moderate chance of dozing (2)	high chance of dozing (3)
1. Sitting and reading	○	○	○	○
2. Watching TV	○	○	○	○
3. Sitting, inactive in a public place (e.g., a theatre or a meeting)	○	○	○	○
4. As a passenger in a car for an hour without a break	○	○	○	○
5. Lying down to rest in the afternoon when circumstances permit	○	○	○	○
6. Sitting and taking to someone	○	○	○	○
7. Sitting quietly after a lunch without alcohol	○	○	○	○
8. In a car, while stopped for a few minutes in traffic	○	○	○	○

Calculate Total Score

Interpretation:

Score	
0-9	Normal (a low score does not exclude significant daytime sleepiness)
10-11	Borderline
12-24	Abnormal