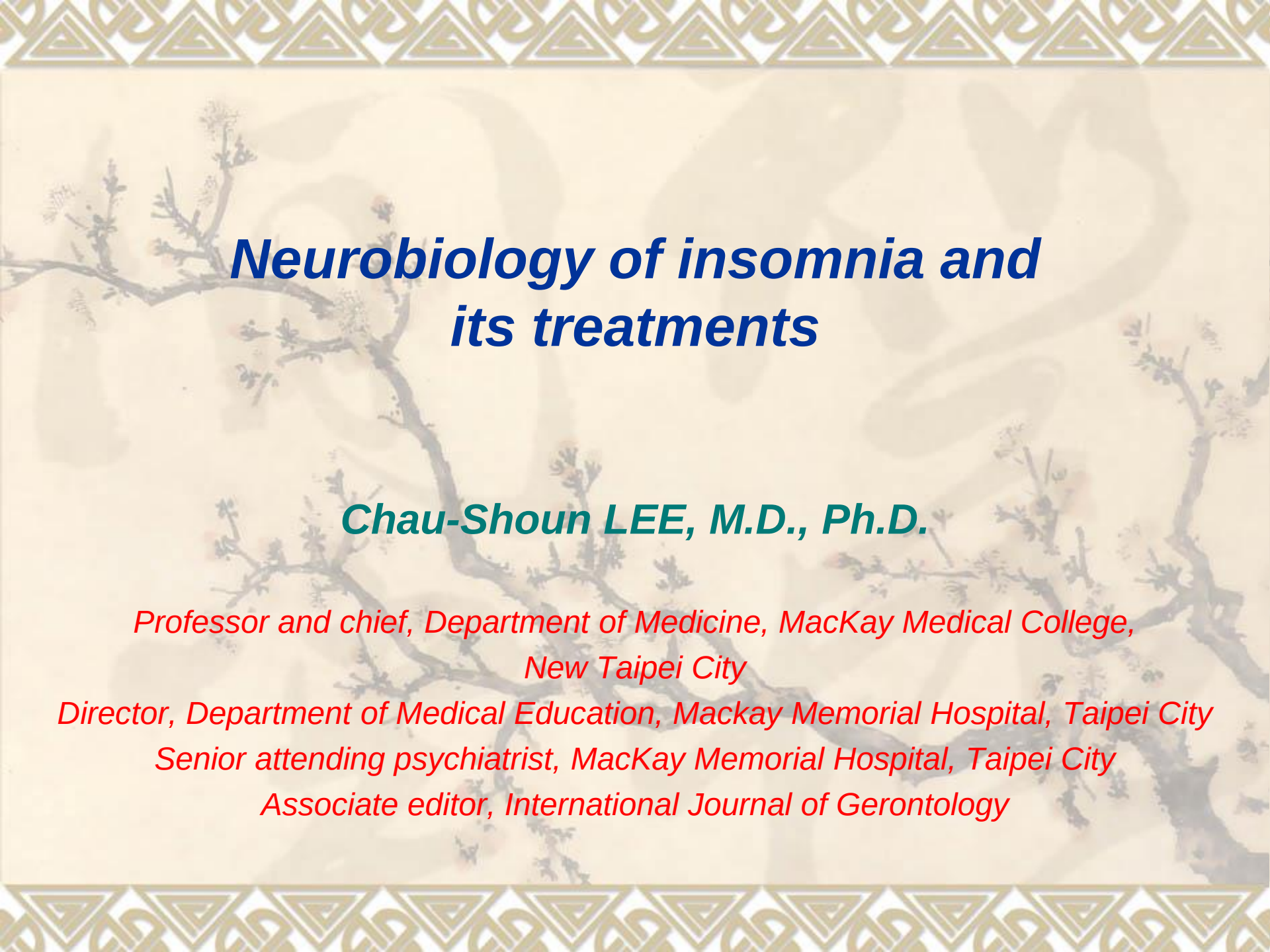




Neurobiology of insomnia and its treatments

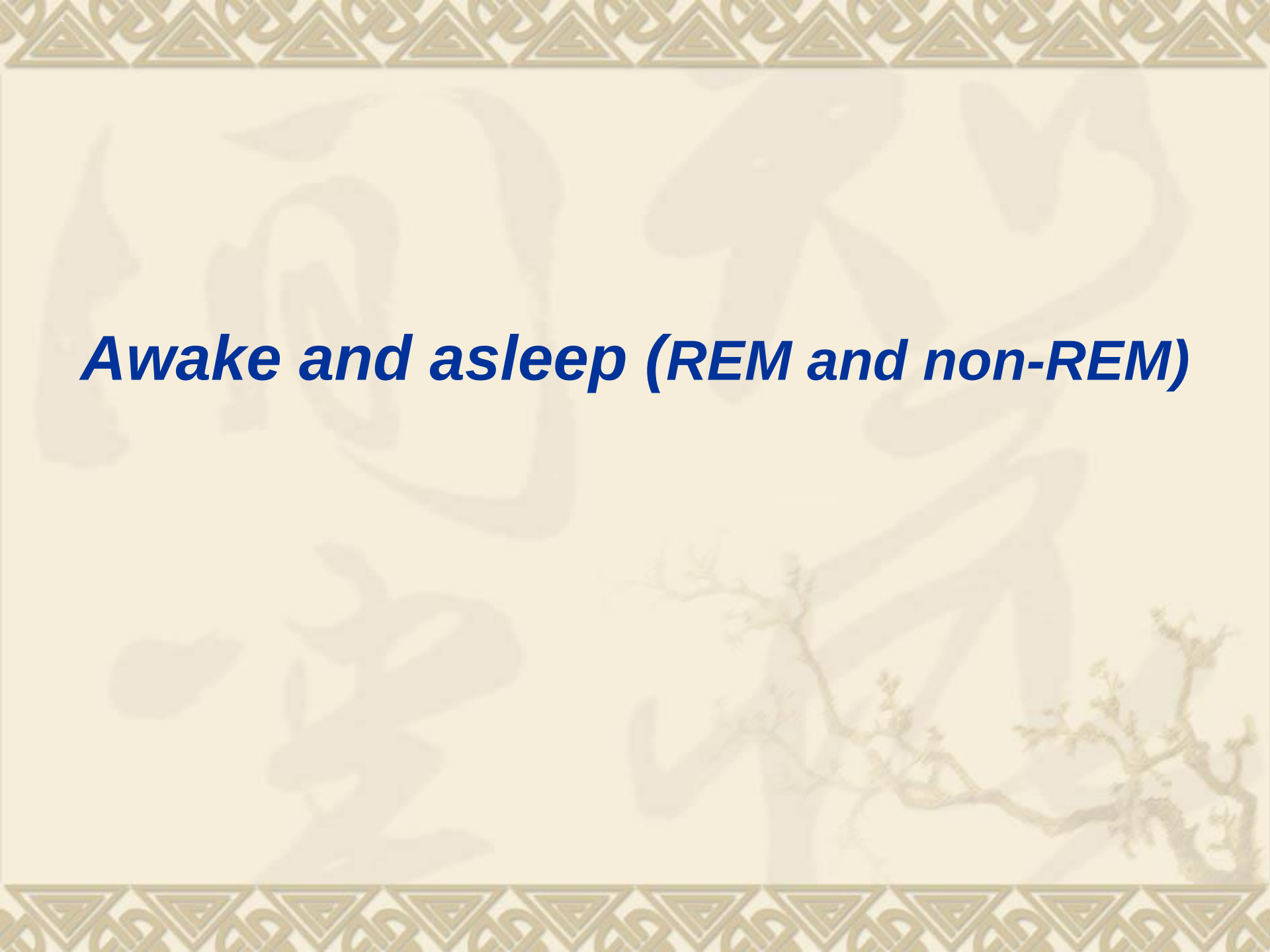
Chau-Shoun LEE, M.D., Ph.D.

*Professor and chief, Department of Medicine, MacKay Medical College,
New Taipei City*

Director, Department of Medical Education, Mackay Memorial Hospital, Taipei City

Senior attending psychiatrist, MacKay Memorial Hospital, Taipei City

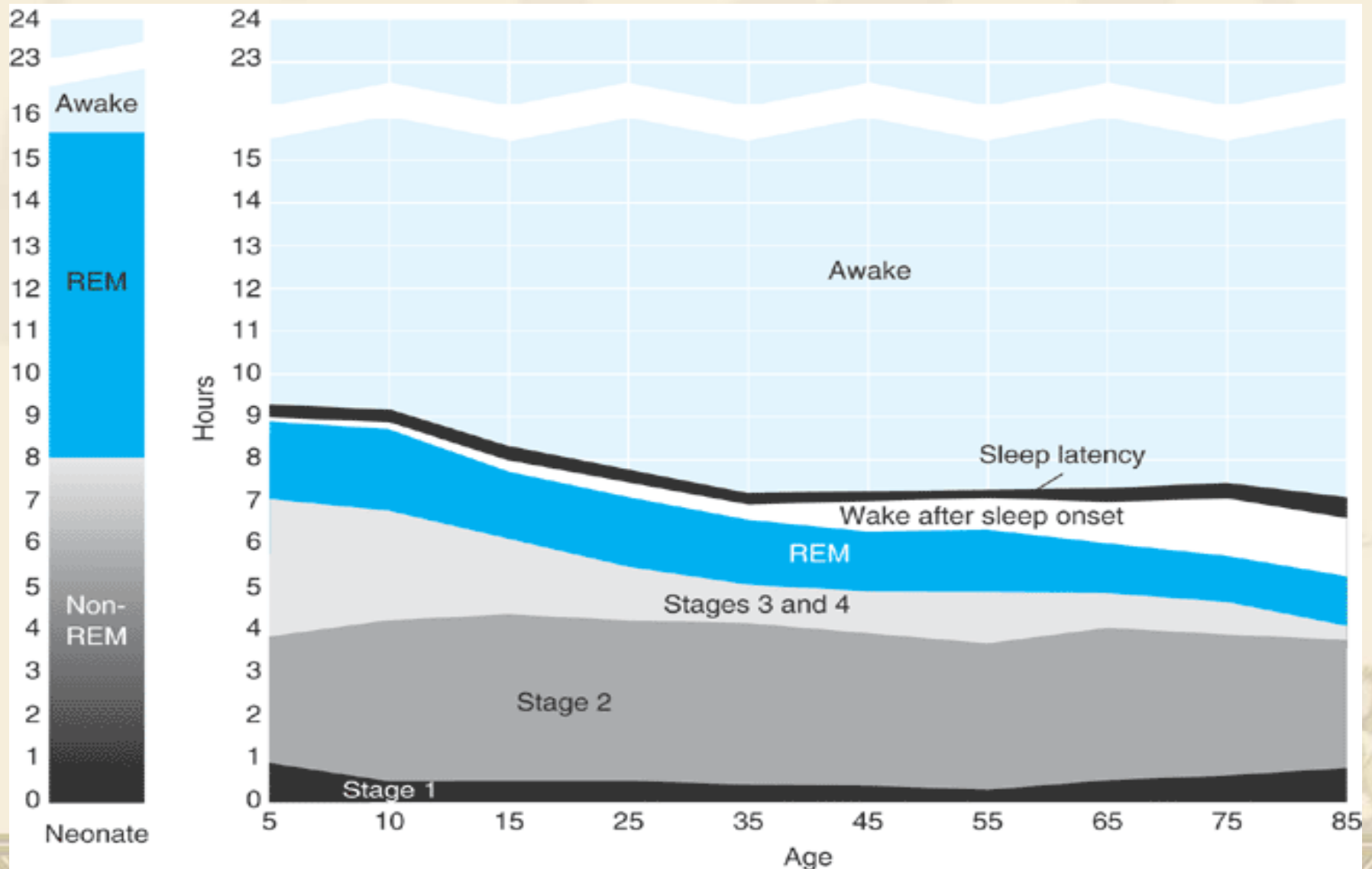
Associate editor, International Journal of Gerontology



Awake and asleep (REM and non-REM)

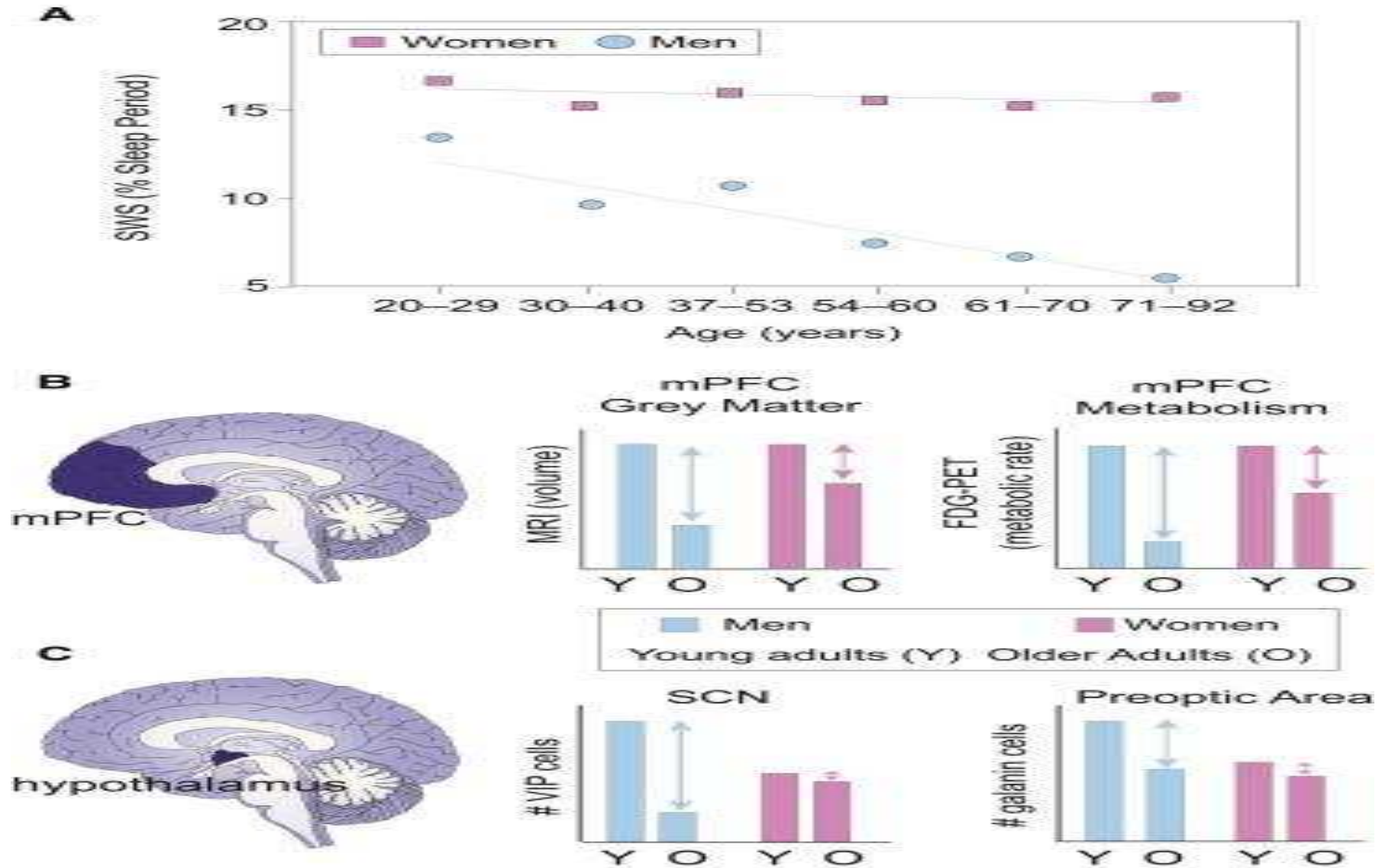


Sleep duration across lifespan--- Ohayon MM, 2004

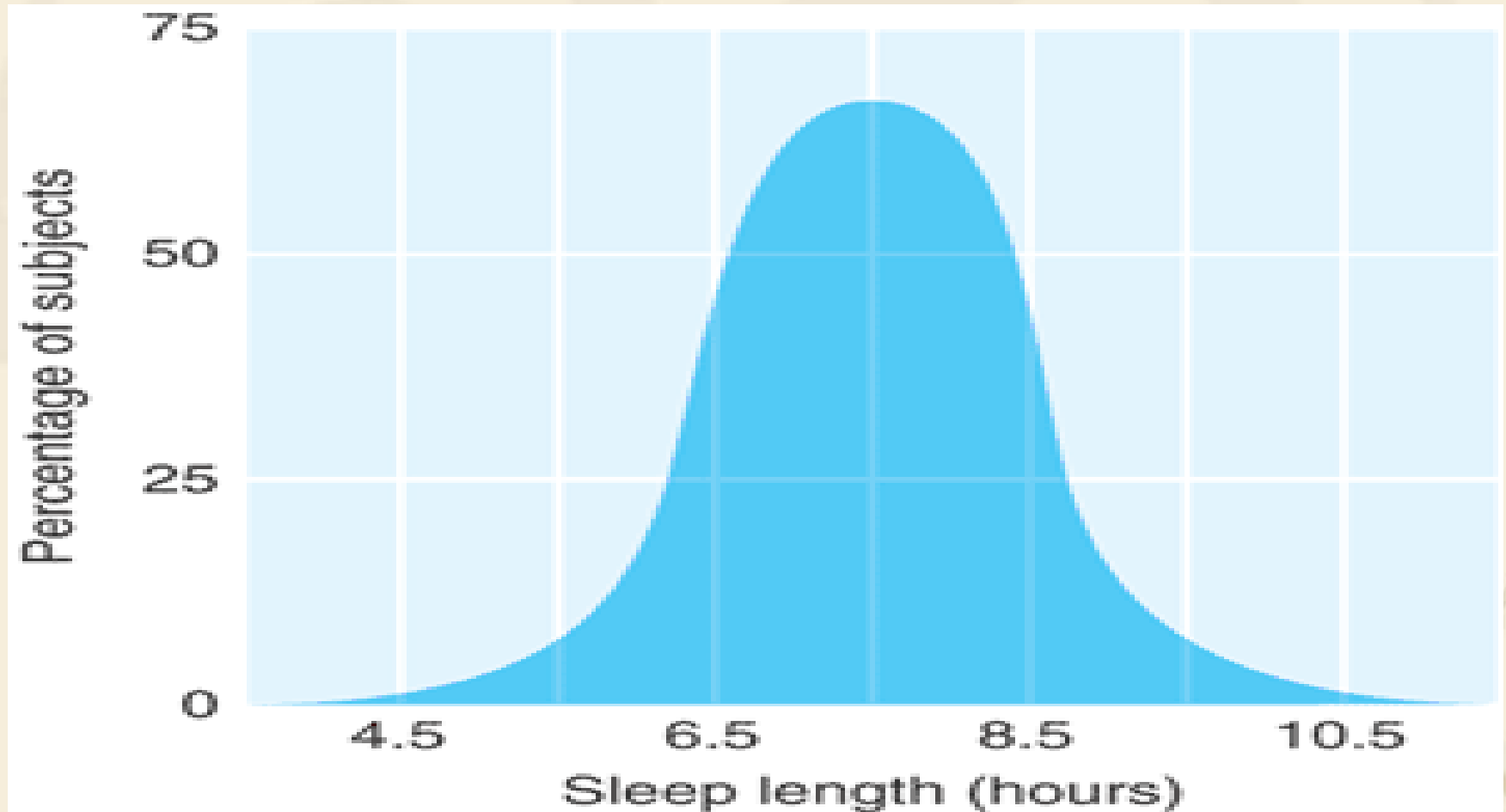


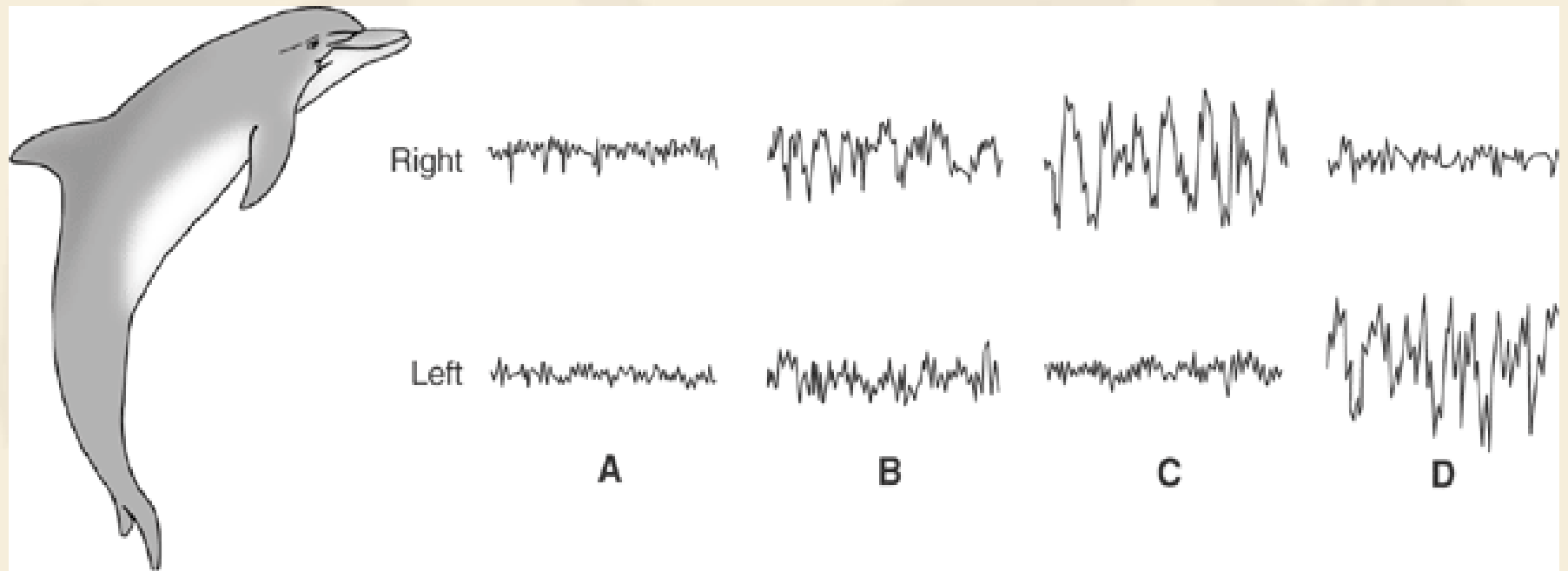
VIP, **Vasoactive intestinal peptide**, acts as a major synchronizing agent among SCN neurons and plays a role in synchronizing the SCN with light cues. **Galanin** is predominantly an inhibitory, hyperpolarizing neuropeptide

Mander BA et al, Neuron 2017



The duration of sleep for adults -- Hobson JA, 1989



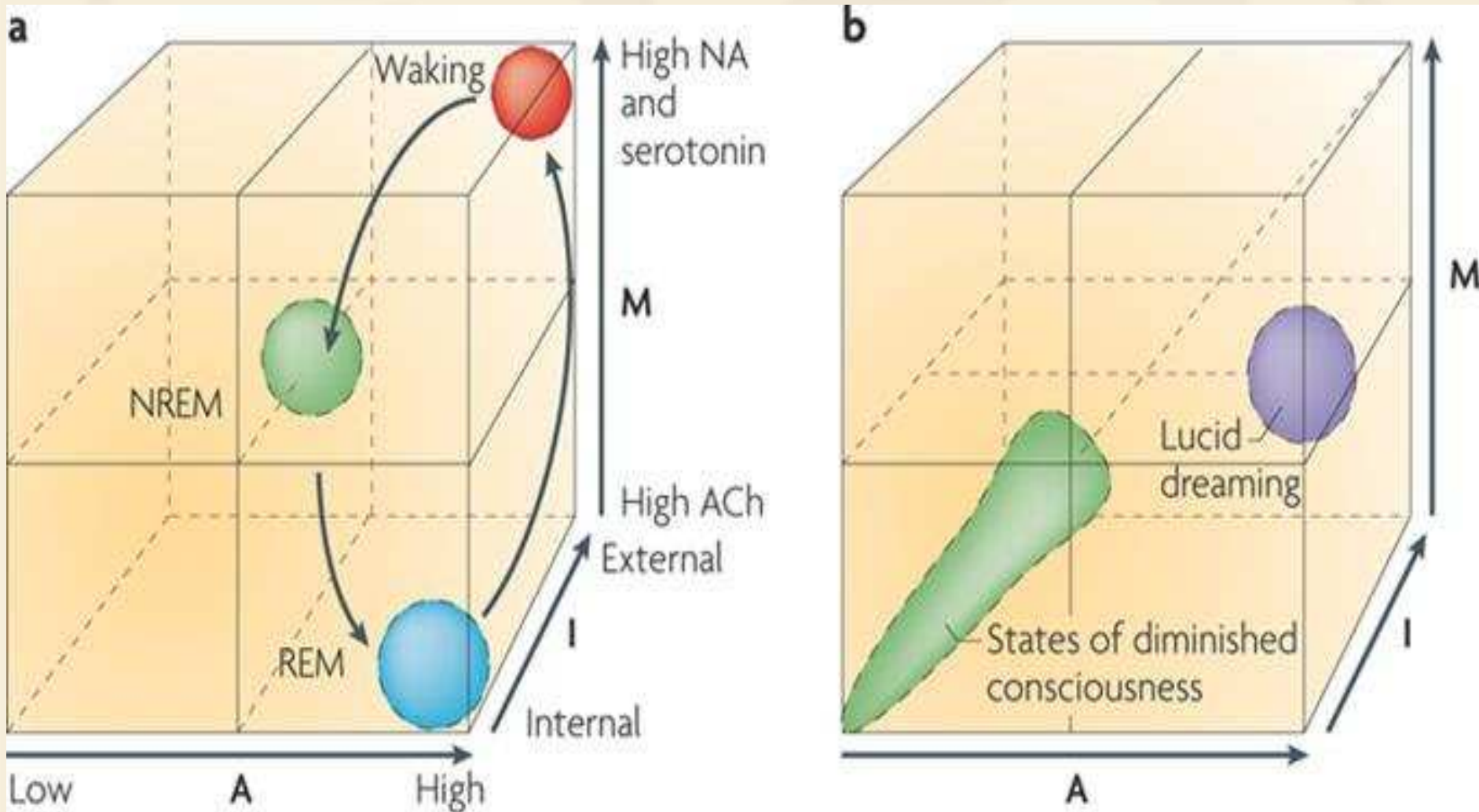


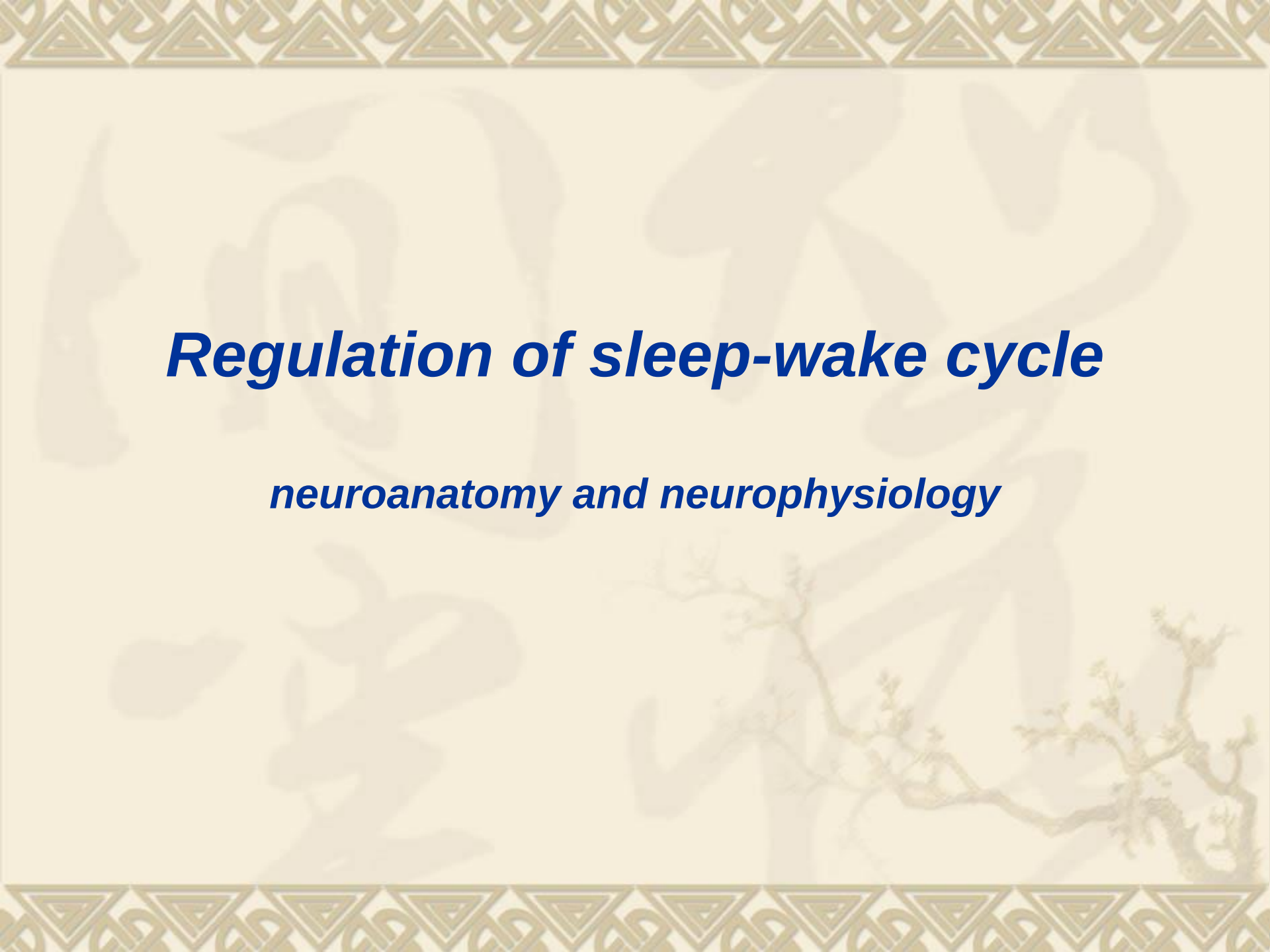
Electroencephalographic tracings from bottlenose dolphins.

(Adapted from Mujhametov LM. Sleep in marine mammals. In: Borbely AA, ed. 1984 and Purves D, Augustine GJ, Fitzpatrick D, et al. *Neuroscience*, 3rd ed. Sunderland, MA: Sinauer; 2004.)



AIM model of brain–mind state control: non-rapid eye movement (NREM); rapid eye movement (REM) sleep; The x axis represents A (for activation), the y axis M (for modulation) and the z axis I (for input–output gating); ACh, acetylcholine; NA, noradrenaline.

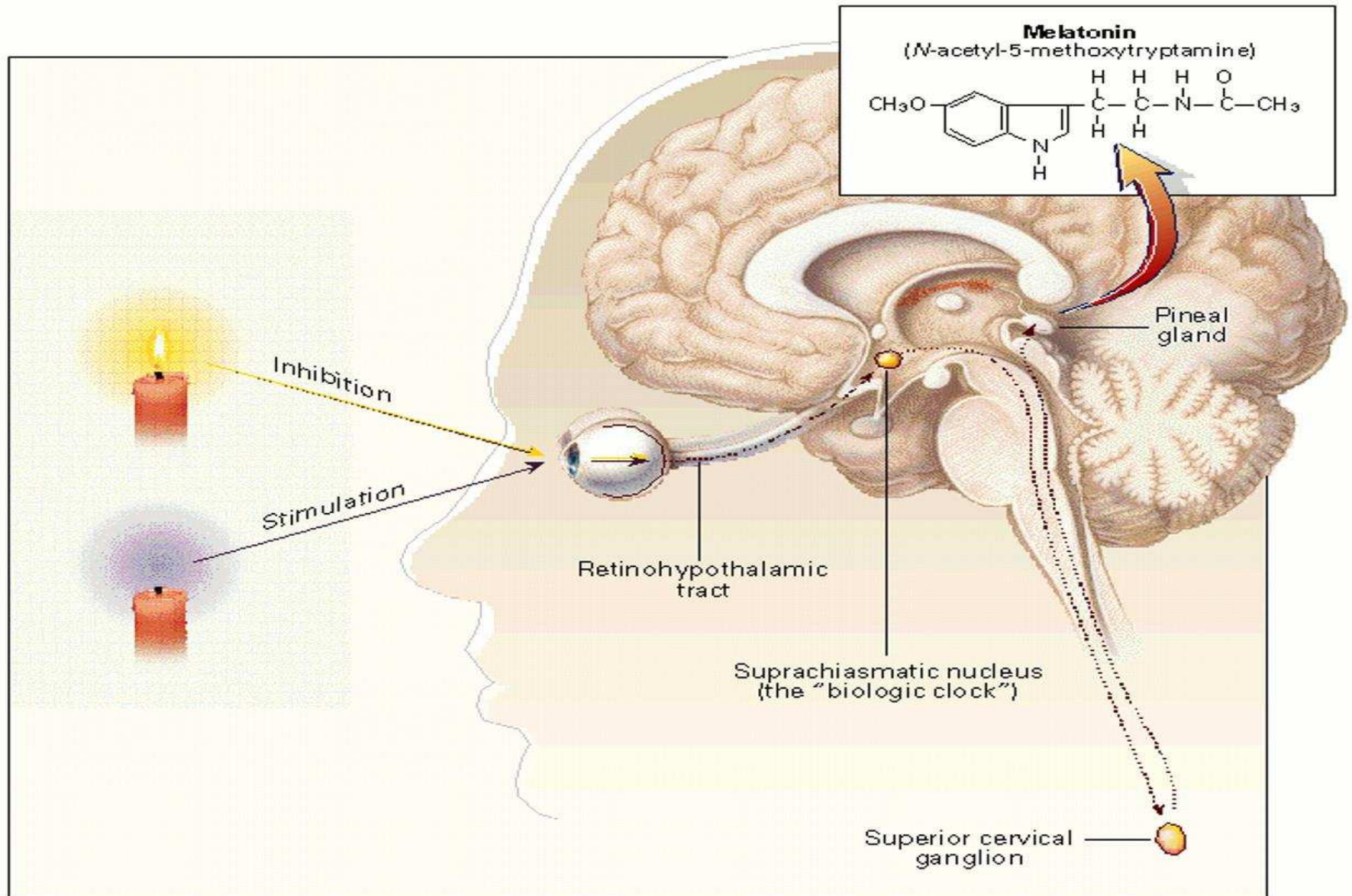




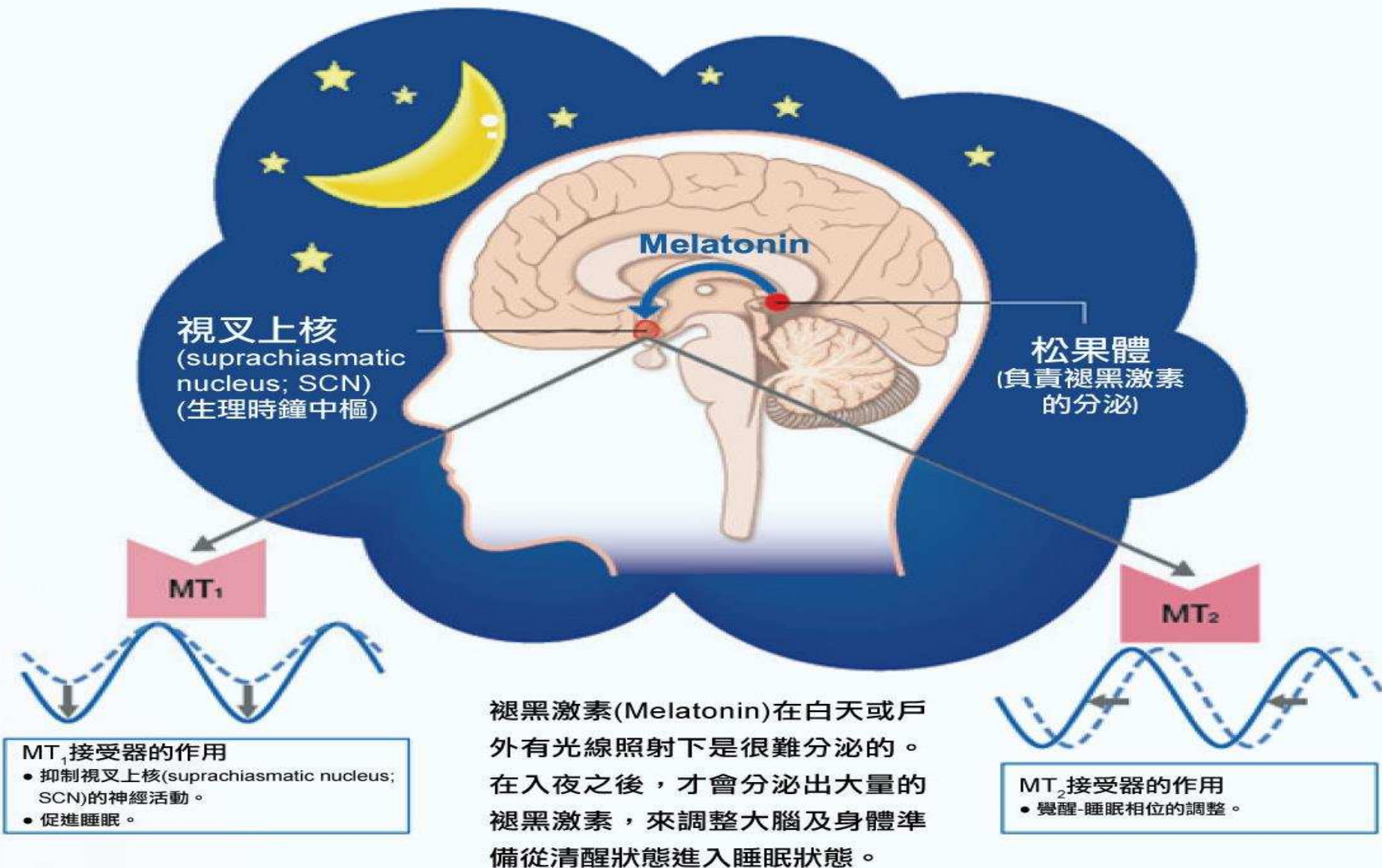
Regulation of sleep-wake cycle

neuroanatomy and neurophysiology





褪黑激素接受器



Melatonin and Age

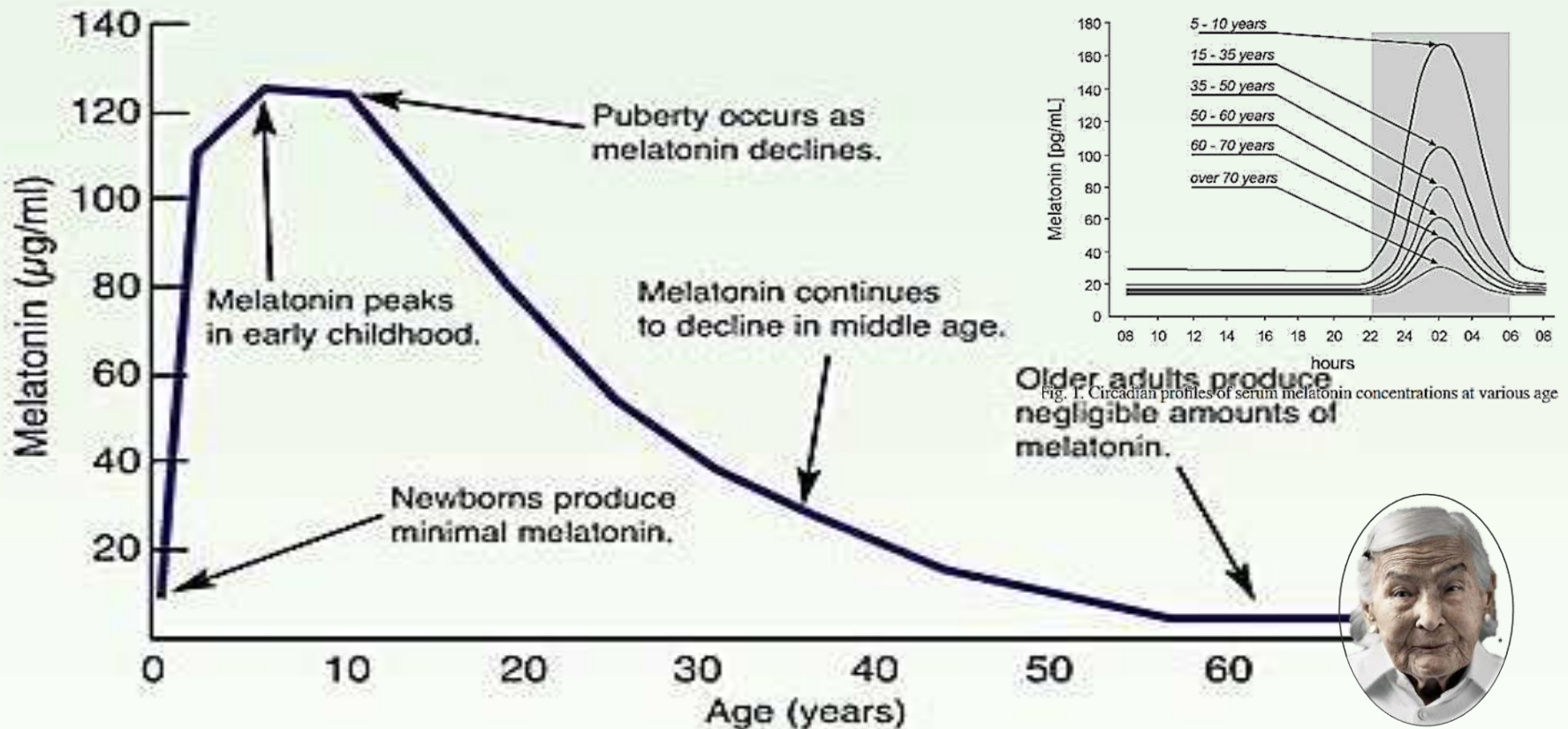
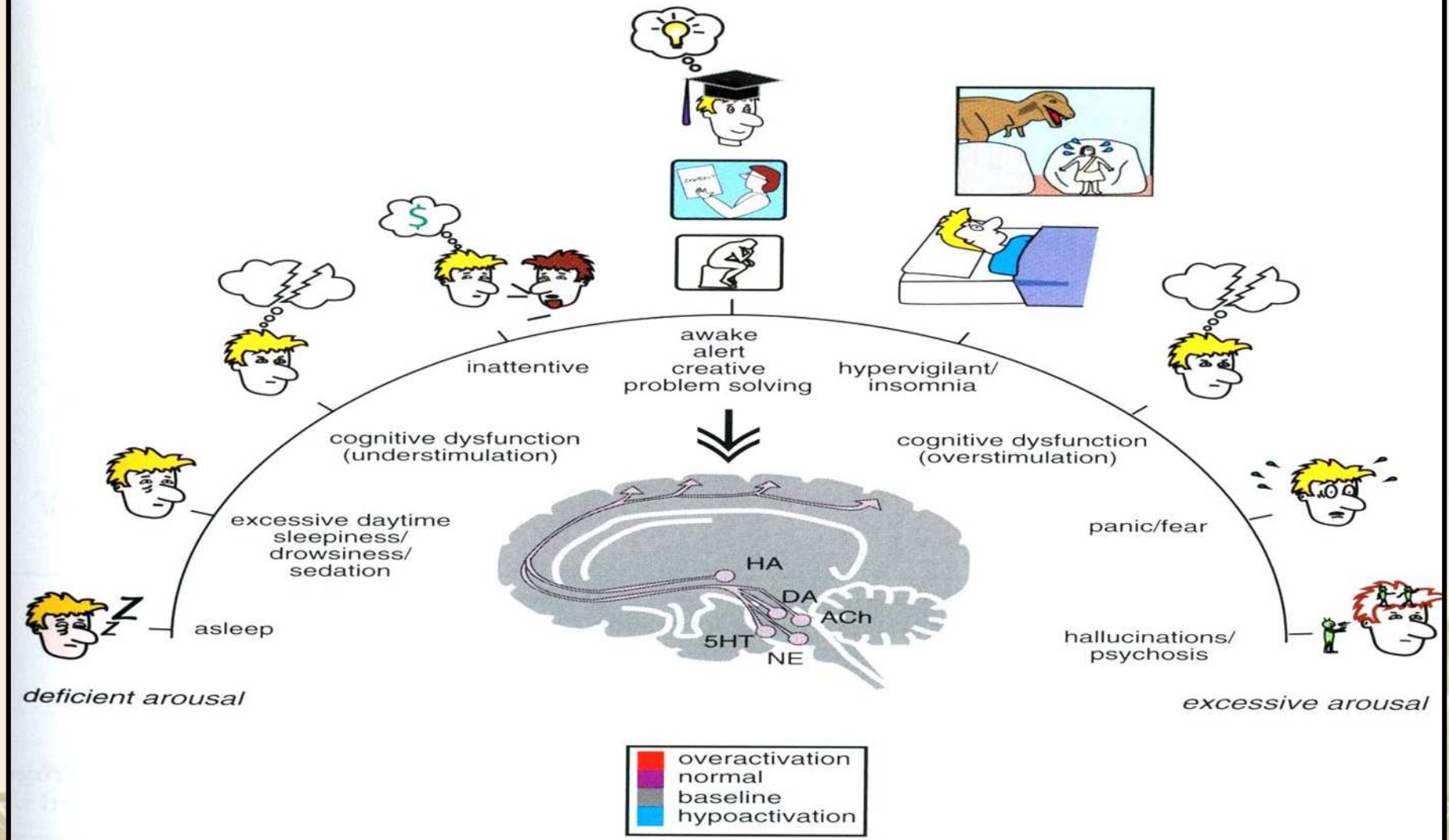


Fig. 1. Age-related decrease in hormone production in humans.

Arousal spectrum of sleep and wakefulness

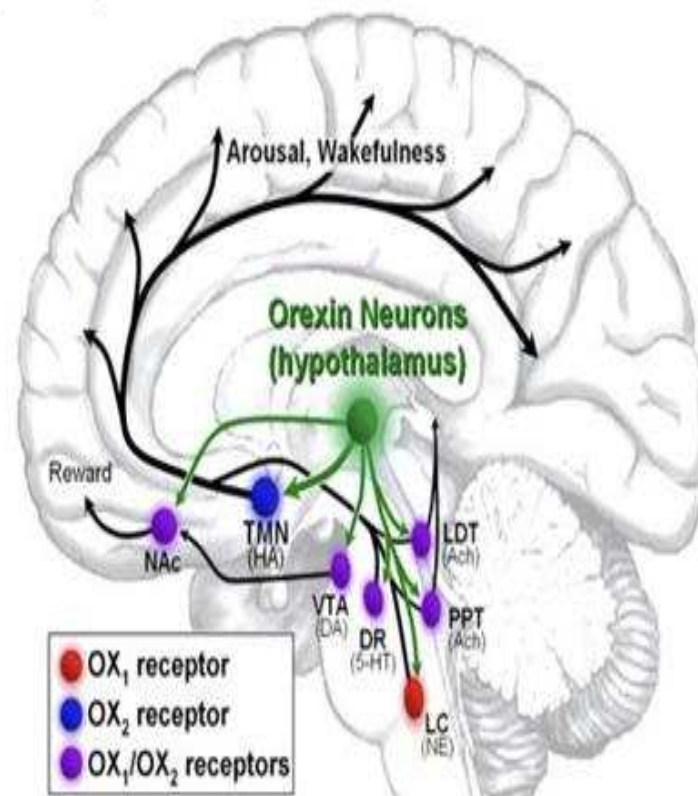
Arousal Spectrum of Sleep and Wakefulness



Major Neurotransmitter Systems Underlying Sleep, Arousal, and Sedation

- ❖ **Sedating agents may inhibit neurotransmitter systems of arousal, or augment neurotransmitter systems of sleep**
- ❖ **Neurotransmitters of arousal**
 - ❧ Histamine (via central H₁ receptors)
 - ❧ Norepinephrine (via central α_1 receptors)
 - ❧ Acetylcholine (via central M₁ receptors)
 - ❧ Serotonin (via several receptors)
 - ❧ Orexin (also known as hypocretin)
- ❖ **Neurotransmitters of sleep**
 - ❧ GABA (via central GABA_A receptors)

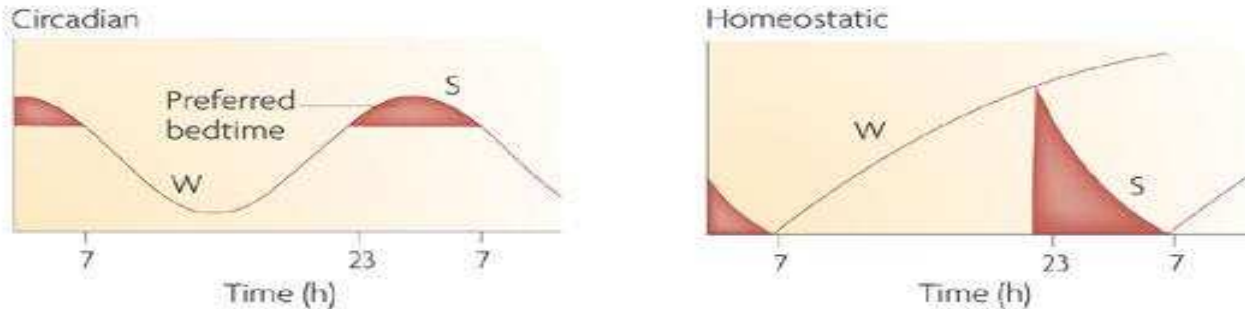
- Orexins (hypocretins) are two neuropeptides (Orexin-A & Orexin-B) secreted from orexin-containing neurons, mainly in the **lateral hypothalamus** (LH).
- Orexins orchestrate their effects by binding and activating two G-protein-coupled receptors (GPCRs), **orexin receptor type 1 (OX1R)** and **type 2 (OX2R)**.
- Orexin/receptor pathways play vital regulatory roles in many physiological processes, especially feeding behavior, sleep–wake rhythm, reward and addiction and energy balance.
- Furthermore several reports showed that orexin/receptor pathways are involved in pathological processes of neurological diseases such as narcolepsy, depression, ischemic stroke, drug addiction and Alzheimer's disease (AD).



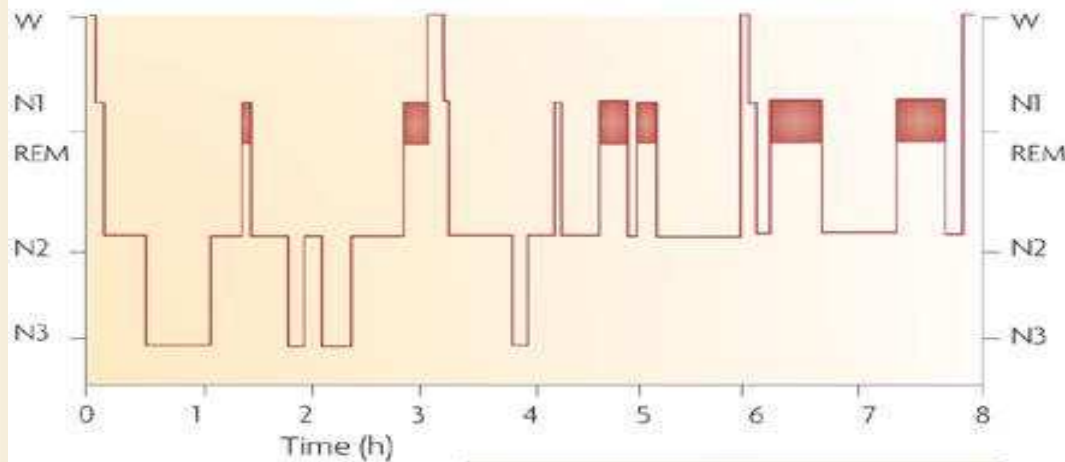
Sleep phenotypes: a Sleep regulation: S, sleep; W, waking b |Sleep quantity and qualitynon:

rapid eye movement (NREM) and rapid eye movement (REM) a transitional stage 1 (N1), followed by stage 2 (N2) when alpha activity disappears, and then N3 or slow wave sleep (SWS) electroencephalogram (EEG)----Chiara Cirelli, 2009

a Sleep regulation



b Sleep quantity and quality



Measures of sleep quantity

- Sleep duration (h per day)
- % NREM and REM sleep
- % NREM stages (N1-3)

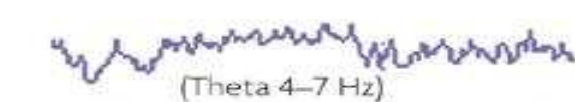
Measures of sleep quality

- Latency to sleep onset
- Latency to REM sleep onset
- Brief awakenings after sleep onset
- SWA in NREM sleep

Waking



REM sleep

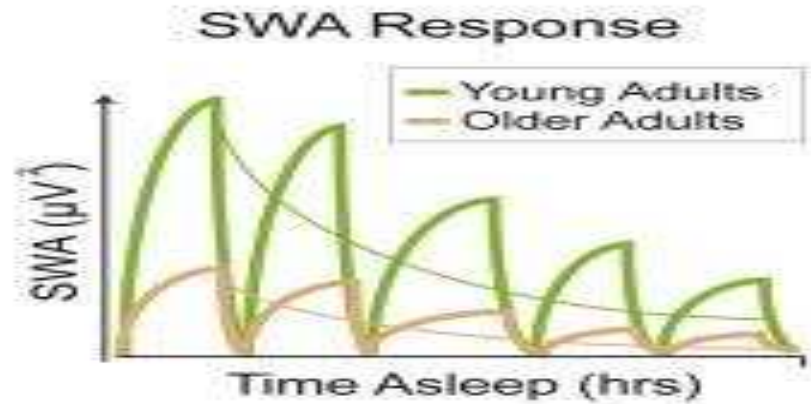
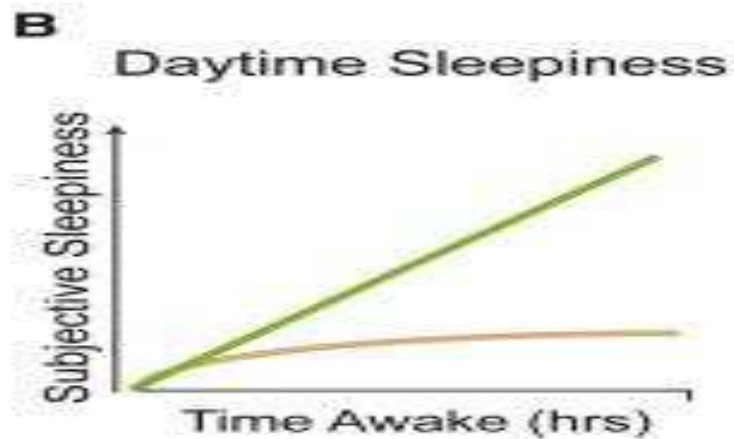


NREM sleep stage N2

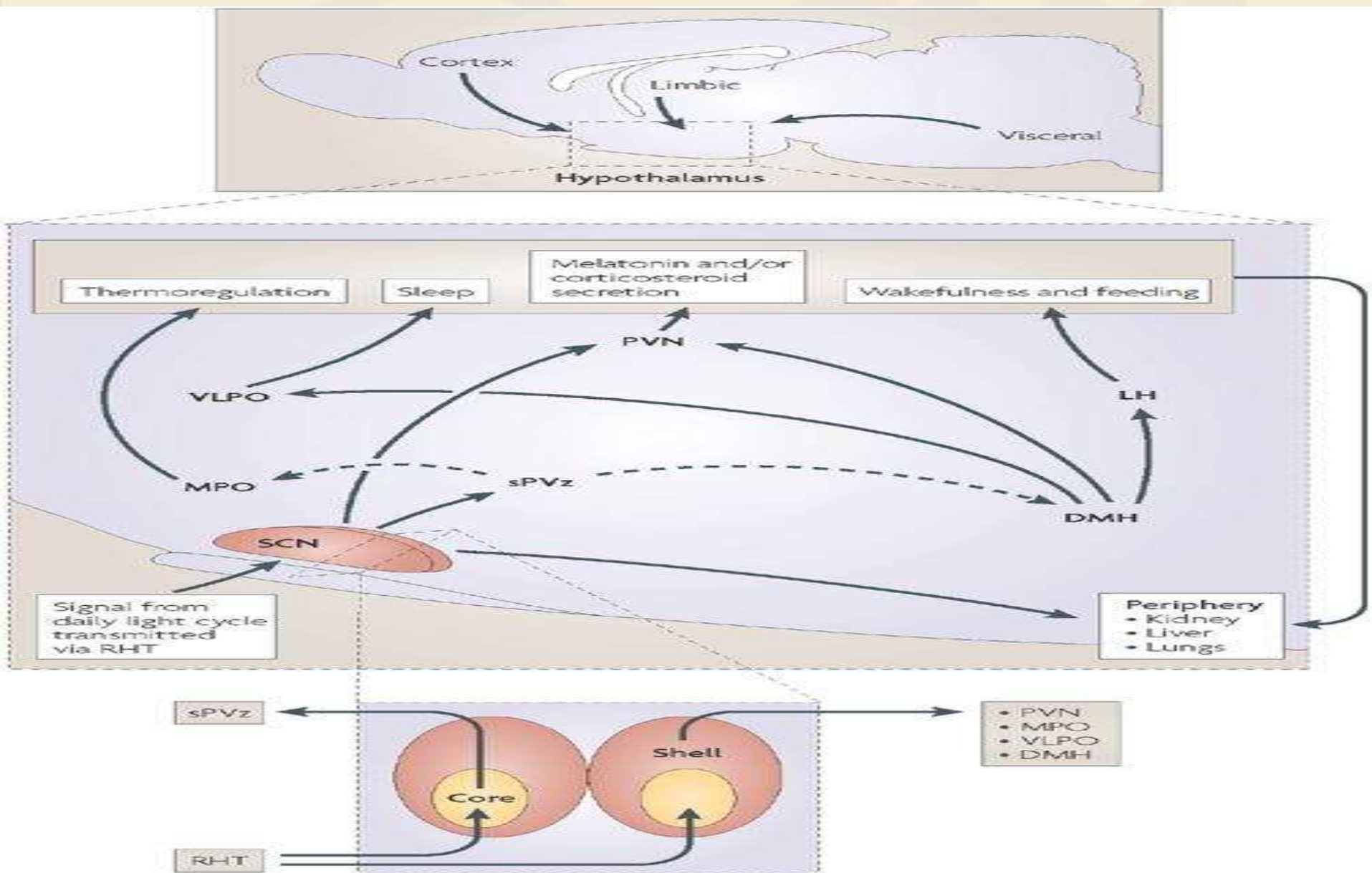


NREM sleep stage N3 (SWS)

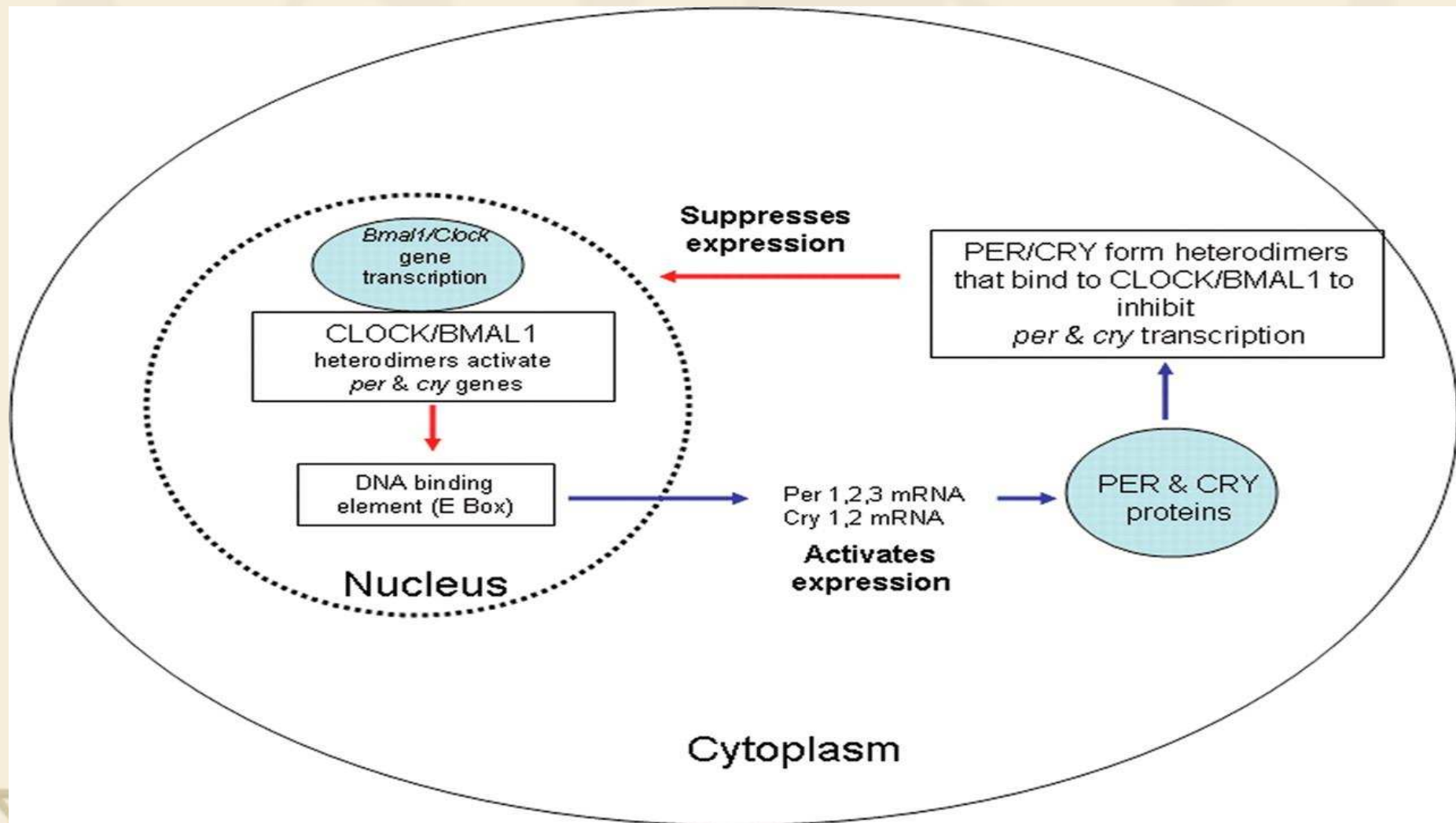


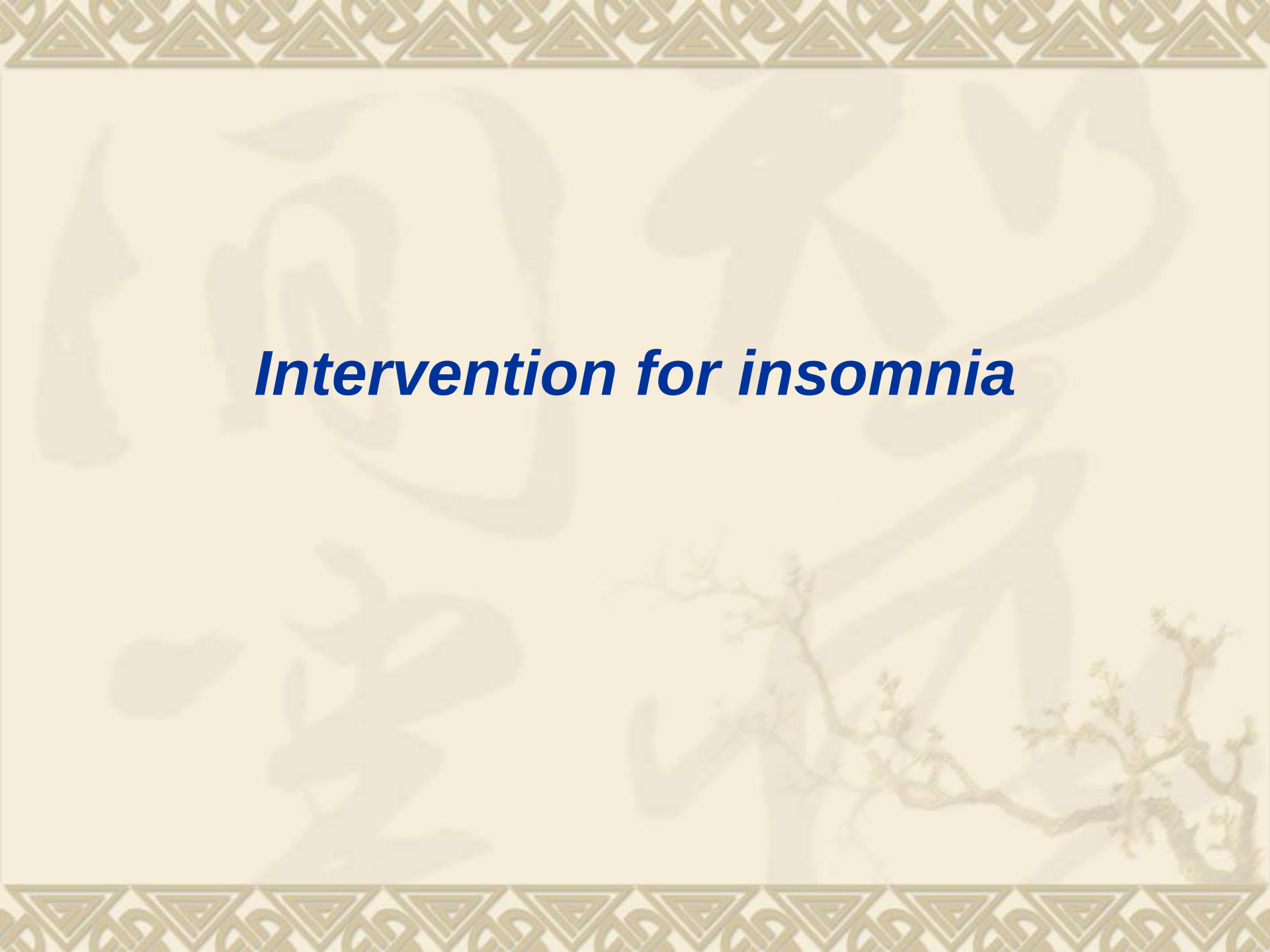


RHT: retino-hypothalamic tract, PVN: paraventricular nucleus, VLPO: ventro-lateral preoptic nucleus, LH: lateral hypothalamus, DMH: dorso-medial hypothalamus, MPO: medial preoptic nucleus, SCN: supra-chiasmatic nucleus

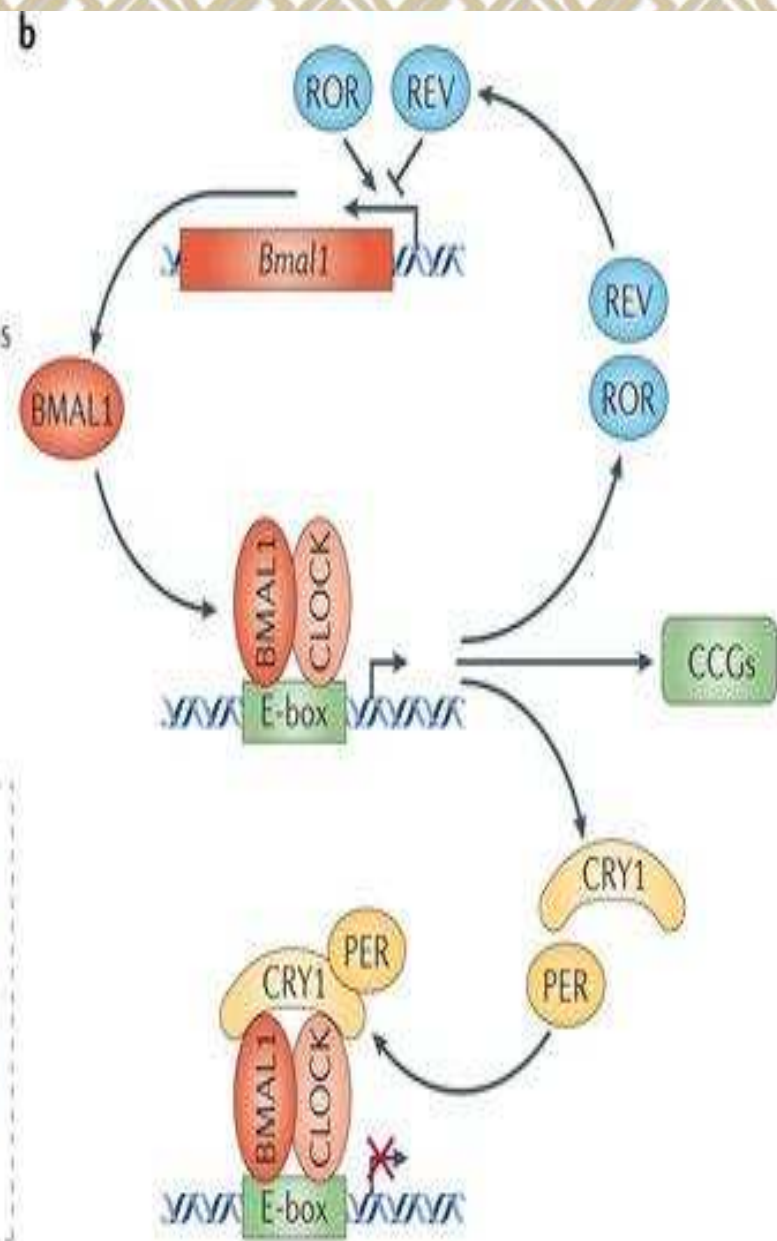
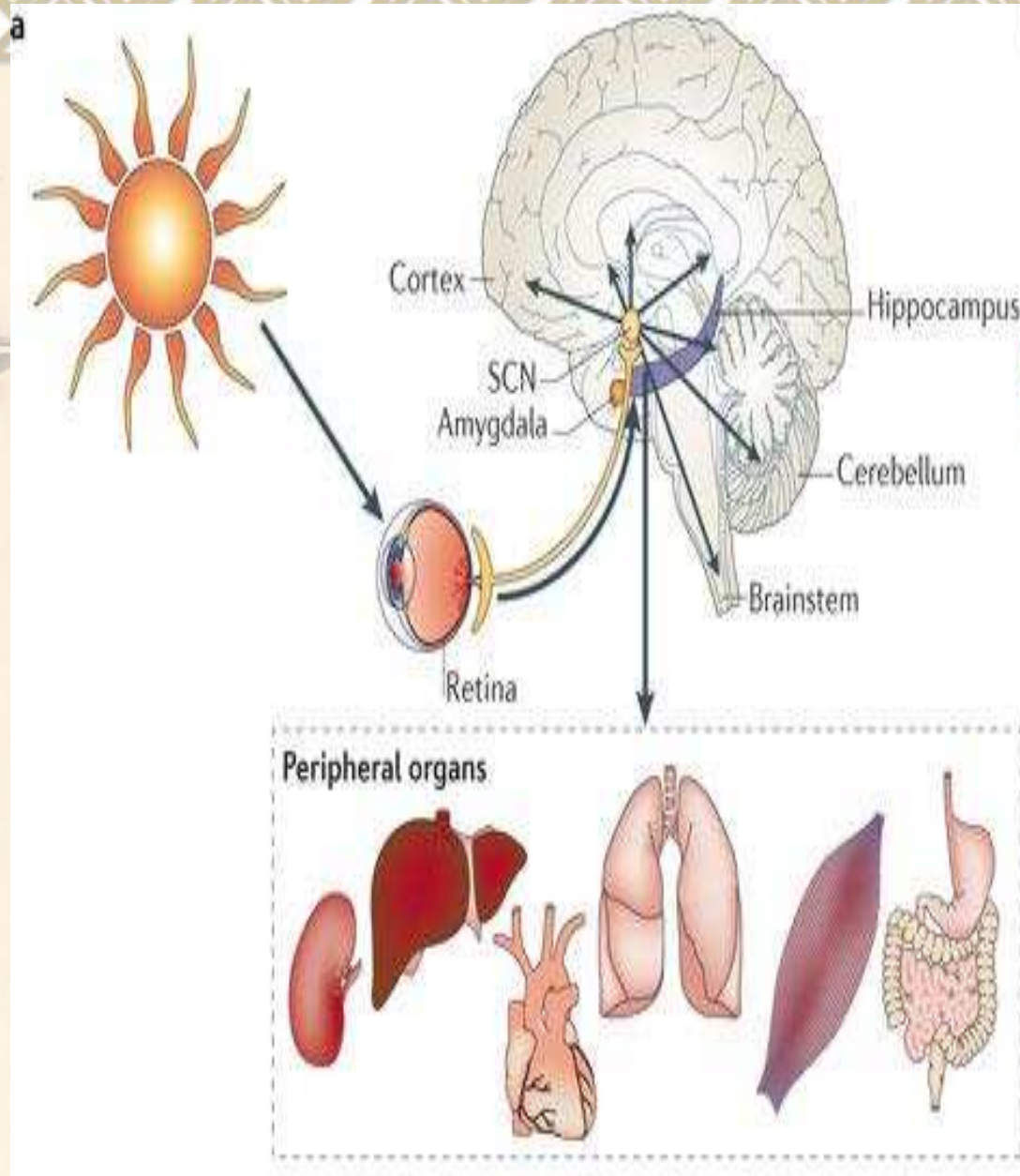


Autoregulatory feedback mechanisms in the regulation of circadian clock in the SCN-- [Bunney JN](#), [Potkin SG](#), 2008





Intervention for insomnia



Therapeutic Goals in Treating Insomnia



Sleep Onset

- Time to fall asleep

Sleep Maintenance

- Number of awakenings
- Duration of awakenings

Sleep Duration

- Total sleep time



Next-Day Functioning

- Alertness
- Functioning
- Vitality

Classification of insomnia

❖ **Primary insomnia^{1,2}**

- ❧ Sleep difficulty for ≥ 1 month
- ❧ Independent for another sleep or mental disorder
- ❧ A clinically significant impairment of functioning
- ❧ Not due to substance or general medical condition
- ❧ 25-30% of insomnia cases³

❖ **Comorbid insomnia^{1,2}**

- ❧ Insomnia associated with
- ❧ A mental disorder
- ❧ A medical condition
- ❧ Substance-induced sleep disorder, insomnia type
- ❧ Up to 75% of cases in general practice³

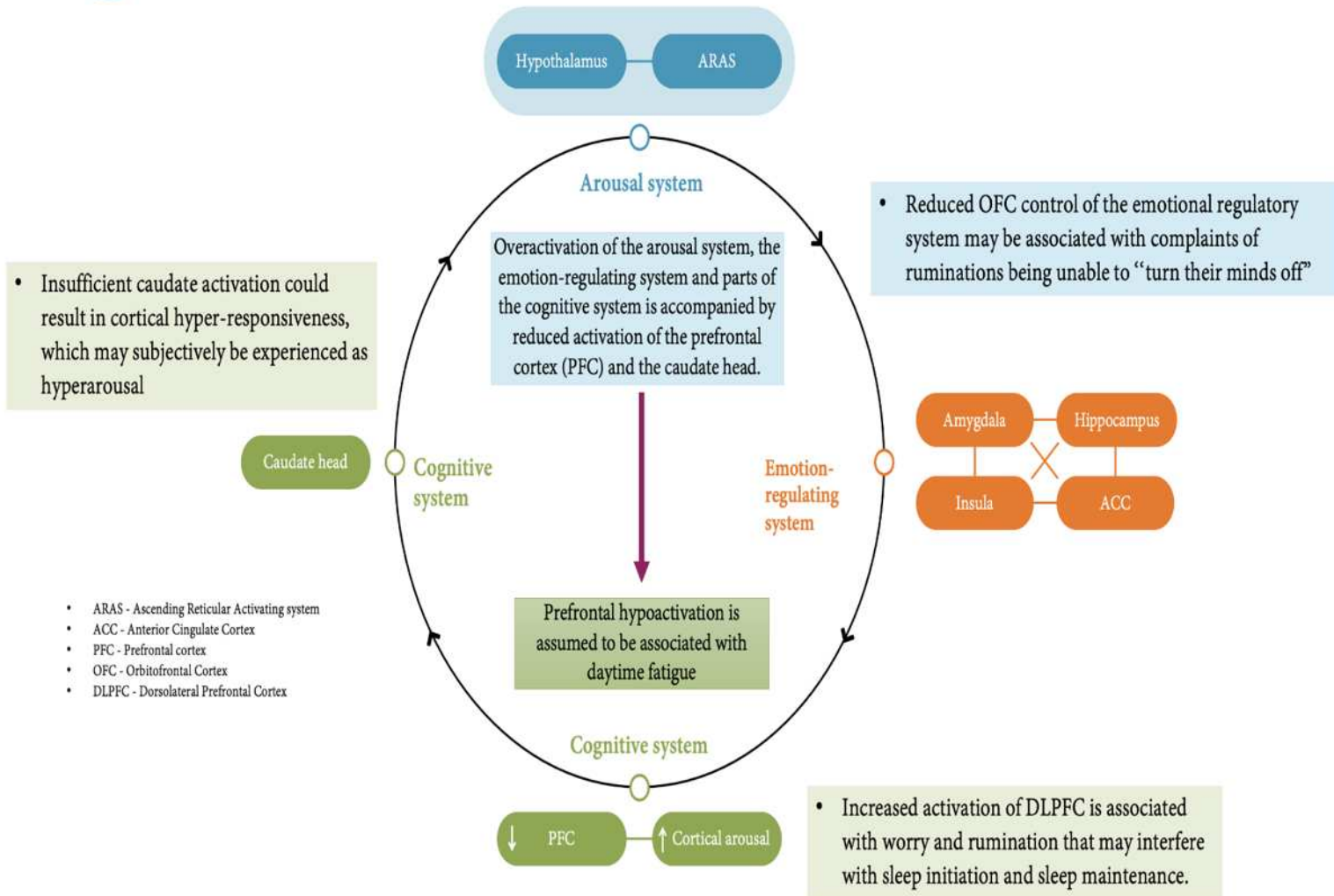
1.American Psychiatric Association. Diagnostic and statistical Manual of mental disorders 4th ed text rev(DSM-IV TR)

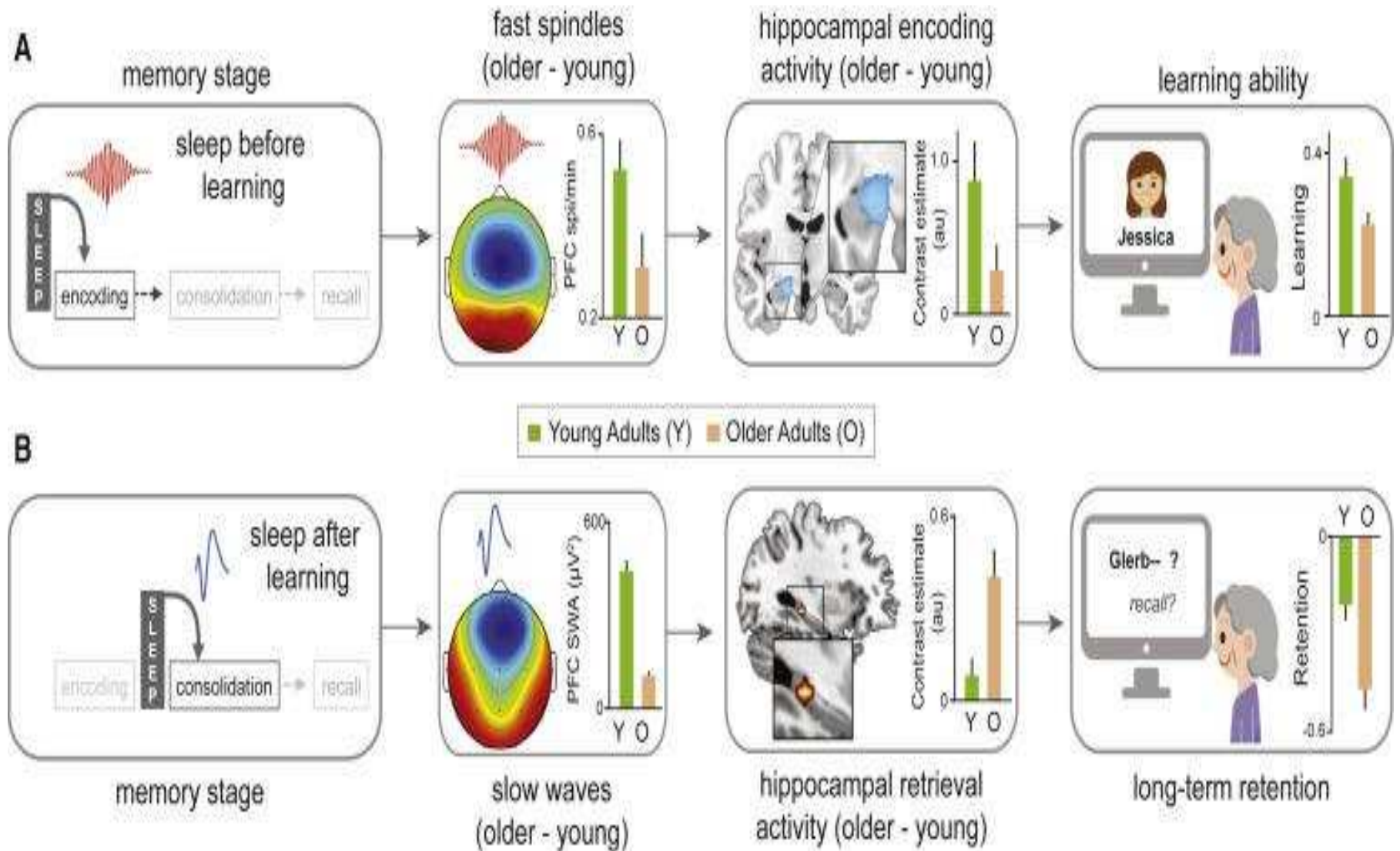
2.NIH State-of the Science Conference Statement J Clin Slep Med. 2005;1:412-421

3. Leger D, et al. *Curr Med Res & Opin* 2005;21:1785-92

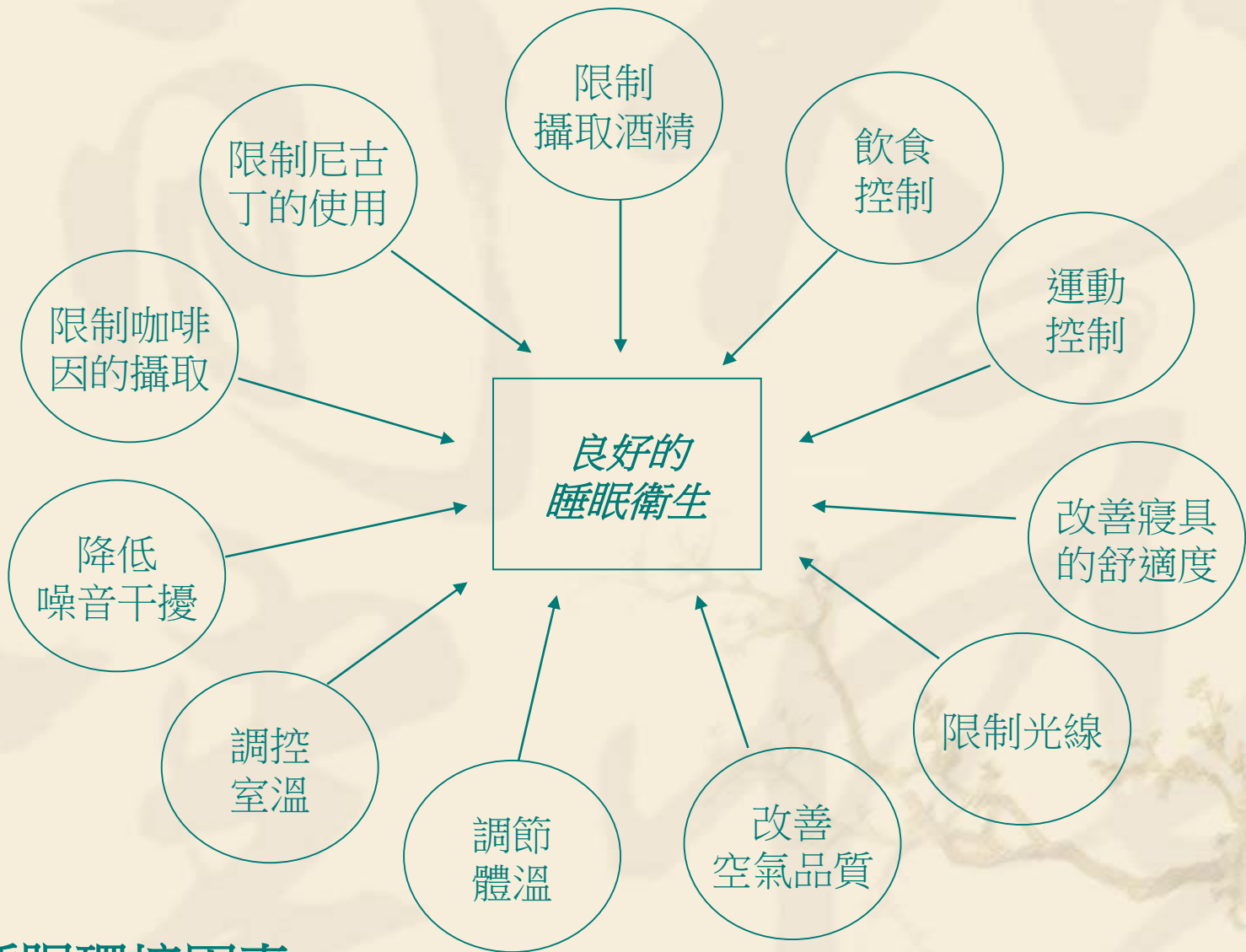
NEUROBIOLOGY OF INSOMNIA

Interactions between Cognitive, Arousal and Emotional Regulating systems

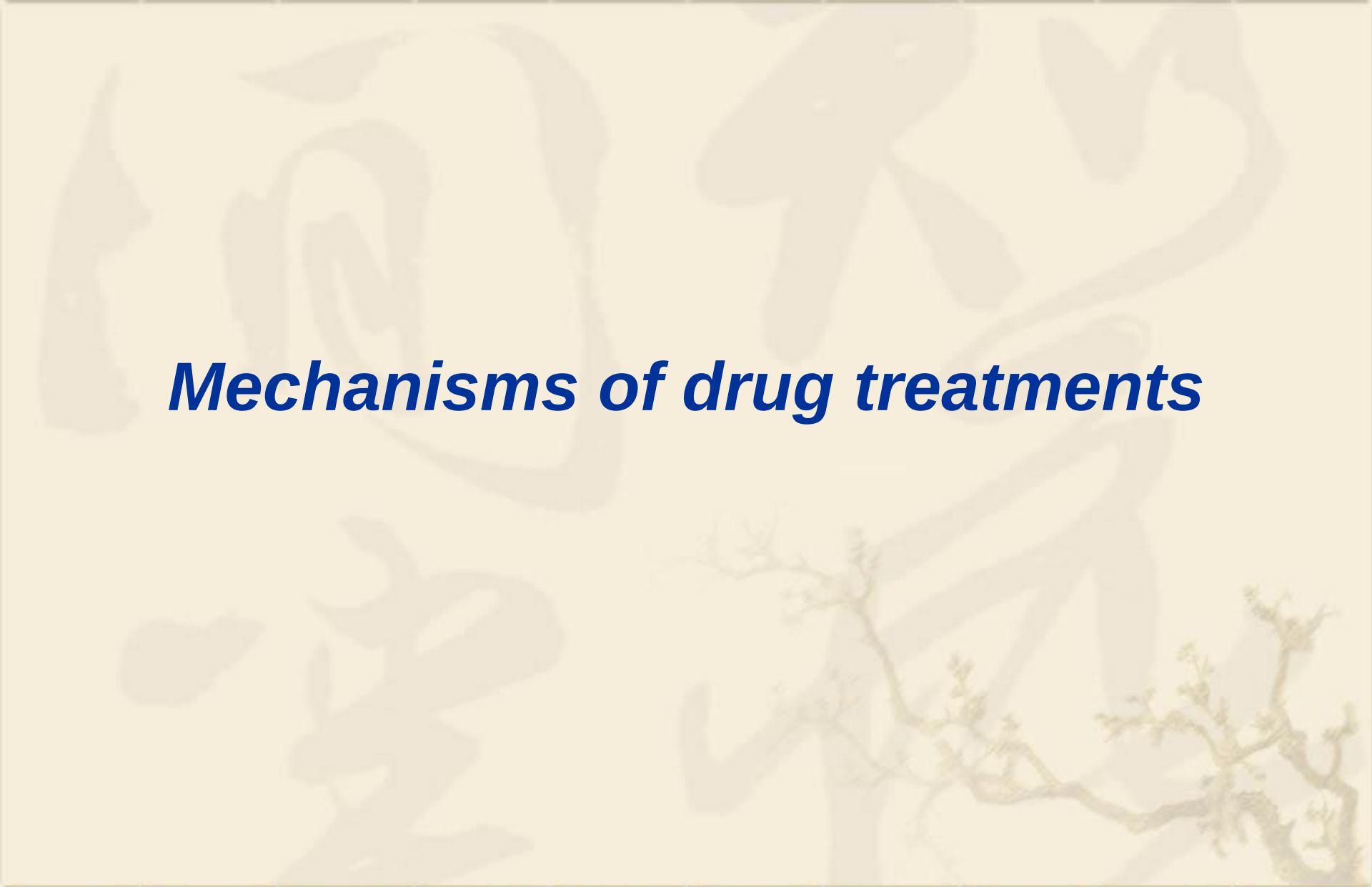




生活型態

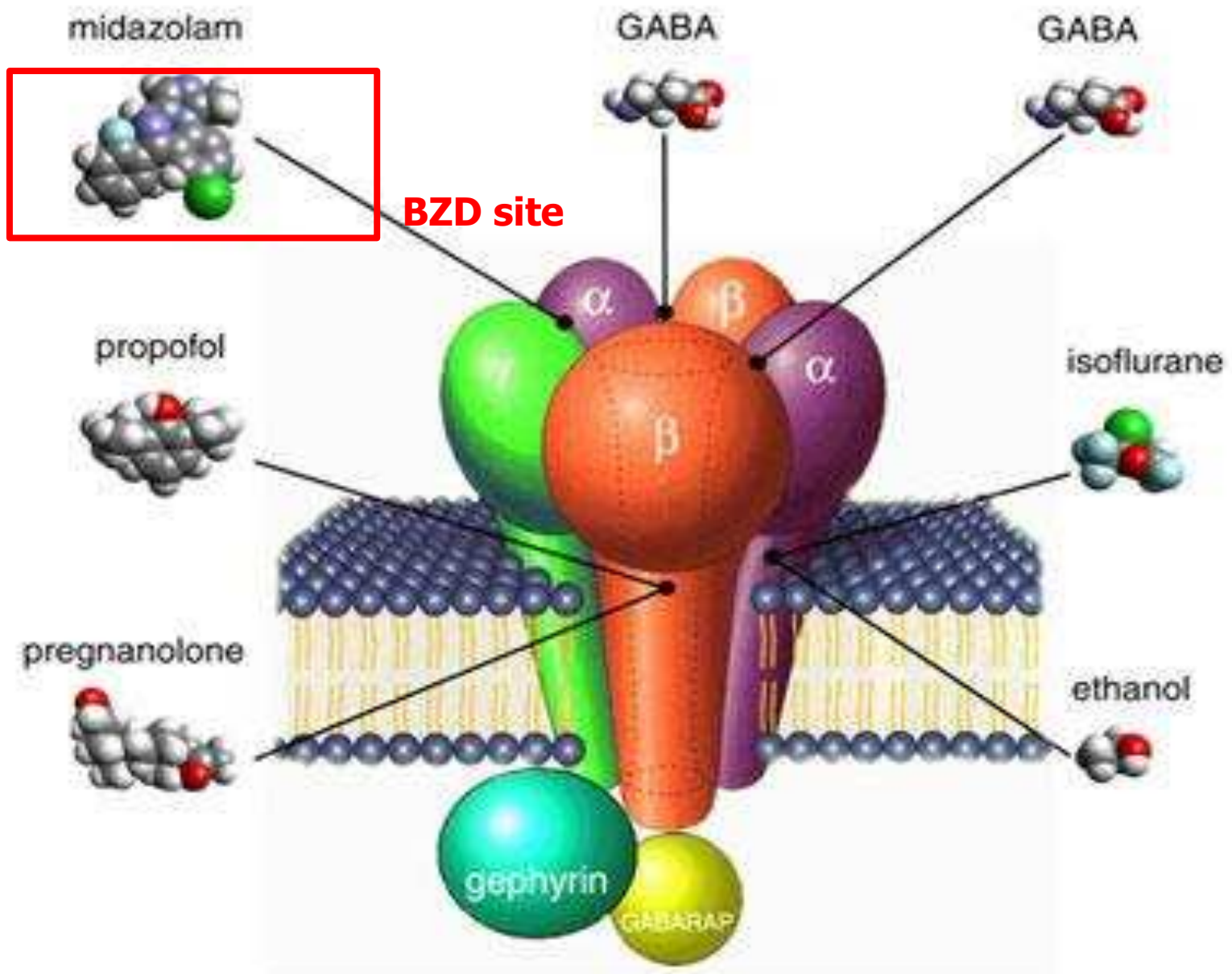


睡眠環境因素

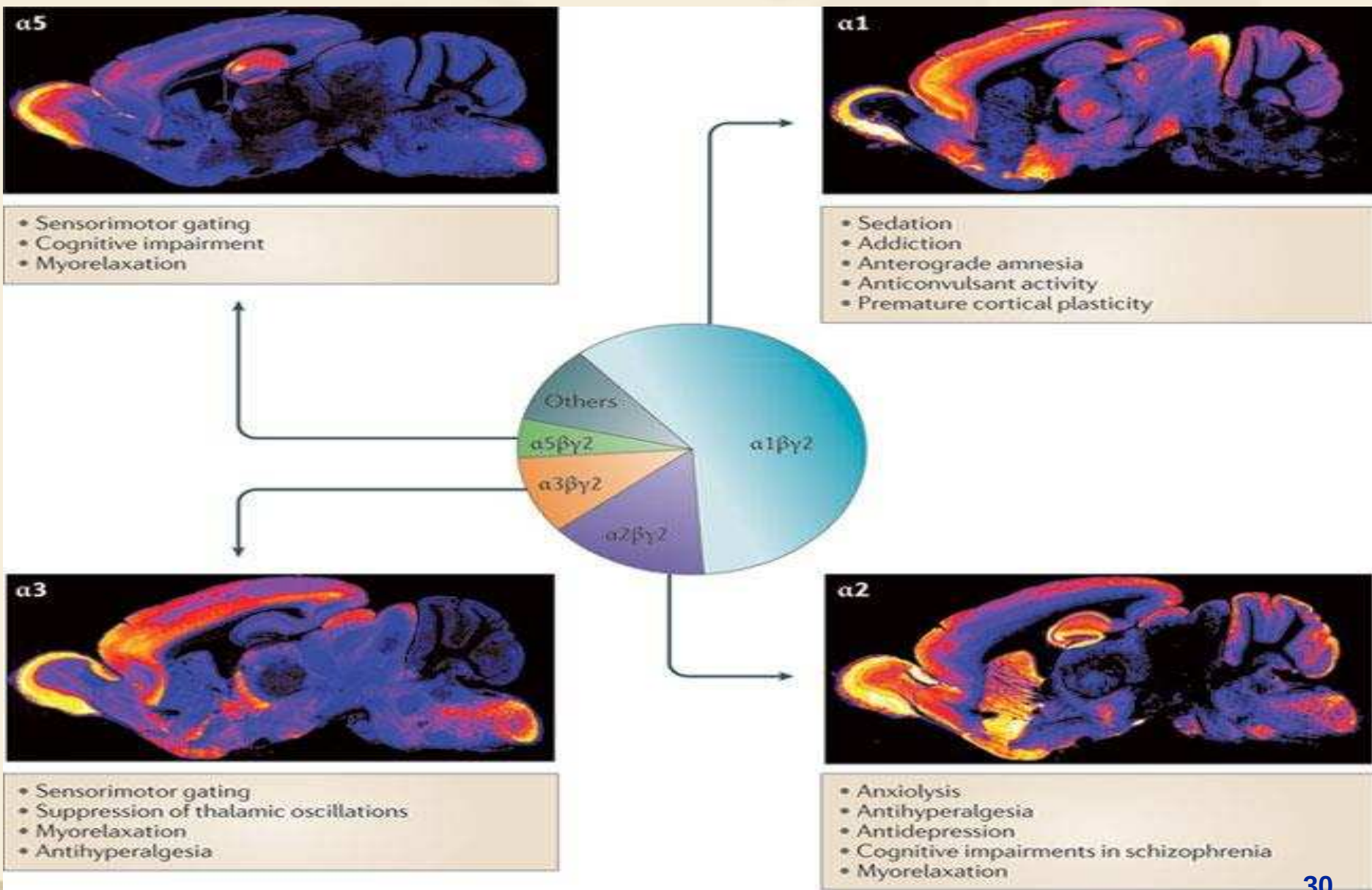


Mechanisms of drug treatments





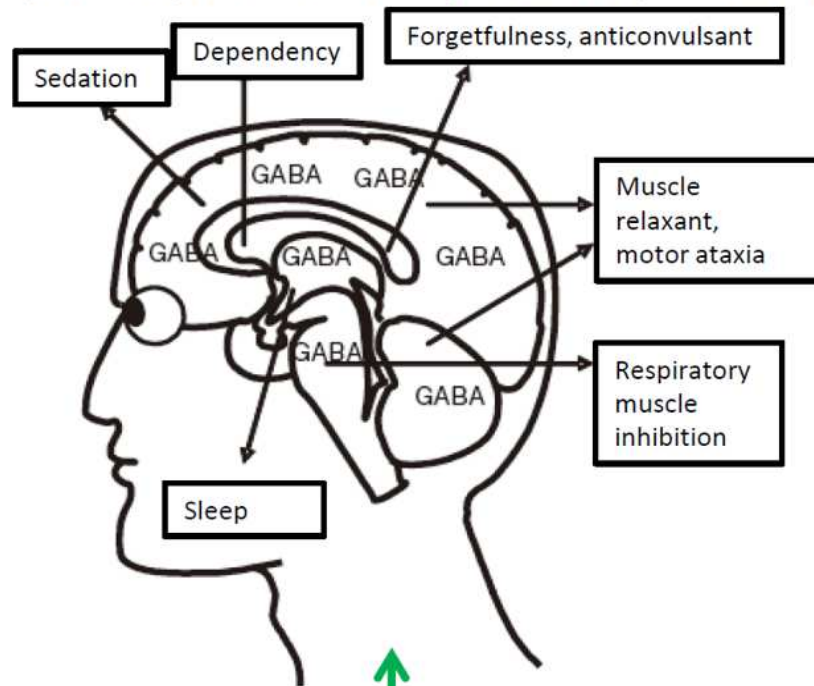
Pharmacological effects and distribution of GABAA receptor α subunits



Differences in mechanism of action between Ramelteon and drugs acting on GABAA receptors (BZPs or Z-drugs)

Drugs that act on GABAA receptors

(have multiple central nervous system effects apart from sleep)



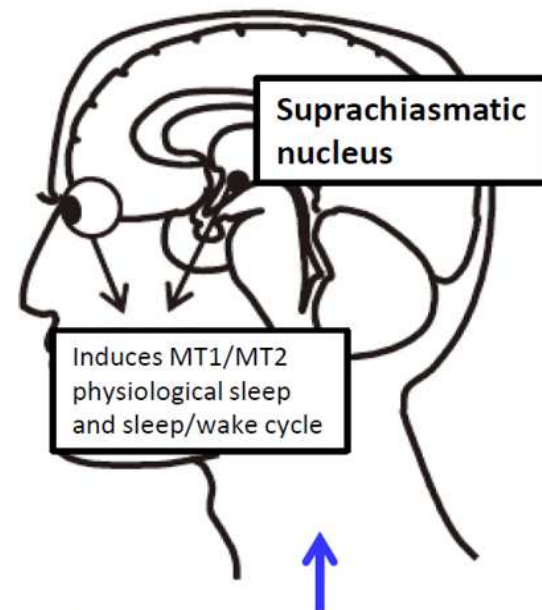
BZP (Z-drug) sleep medications affect sleep by controlling the reticular activating system

= sedating sleep

BZP: Benzodiazepine

Drugs that act on MT1 and MT2

(effects only on sleep awake control or circadian rhythm)



Ramelteon normalize sleep/awake regulation
= non-sedating sleep

Orexin receptors and sleep

OX1R, type 1 orexin receptor; OX2R, type 2 orexin receptor; DR, dorsal raphe; TMN, tuberomammillary nucleus; LDT, laterodorsal tegmental nucleus; PPT, pedunculopontine tegmental nucleus; LC, locus coeruleus.

The orexin/OXR system strongly involves in regulating the sleep-wake cycle owing to its role in promoting and sustaining wakefulness

Orexin levels have a significant correlation to the

- OA levels had significantly higher in the patients with insomnia disorder than normal sleepers.
- OA levels were detected to have a positive relationship with the course and severity of insomnia.

Because the orexin/OXR system promotes wakefulness, antagonists that block orexin receptors would promote sleep and inhibit wakefulness.

- Single orexin receptor antagonists (SORAs)
- Dual orexin receptor antagonists (DORAs)

