Sleep & Headache

Pongsakorn Tanayapong, MD

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Vibhavadi Hospital

Sleep and Headache

- Headache disorders are modulated by sleep, and sleep can be disrupted by headache, potentially creating a vicious circle of reinforcement.
- Headache and sleep disorders share bidirectional relationship.
  - Neuroanatomical pathways
  - Neurotransmitters
- Understanding this relationship may suggest effectively therapeutic approaches for both sleep and headache disorders.

Outline

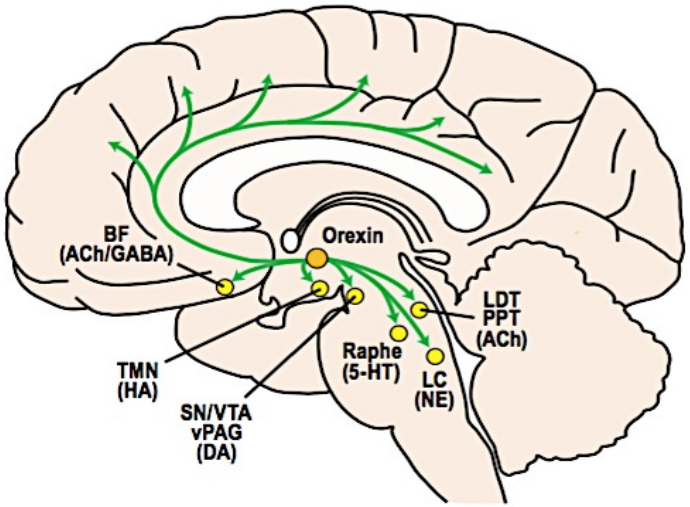
- Sleep-related Headaches
- Pathophysiology
- Headache Disorders and Sleep
- Treatment

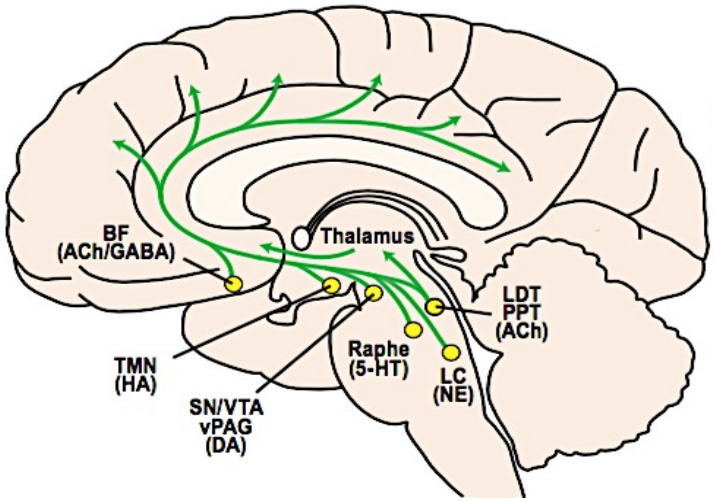
Sleep-related Headaches

- A group of unilateral or bilateral cephalalgias of varying severity and duration that
  - occur during sleep or
  - upon awakening from sleep
- Prevalence is 17% of all headache patients.
- Primary headaches
  - Occur during daytime and sleep: migraine, cluster, other TACs
  - Occur solely with sleep: hypnic headache
- Secondary headaches

ICSD-3 AASM, 2014

Neuroanatomy of Sleep



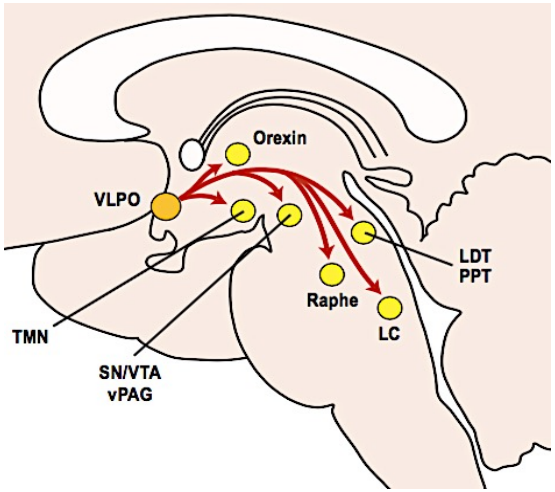


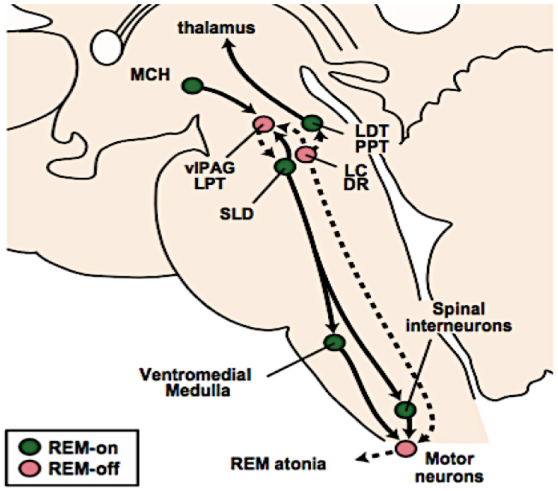
Wakefulness

Neurotransmitter	Wakefulness	NREM sleep	REM sleep
Acetylcholine	↑↑	—	↑↑
Monoamines	↑↑	↑	—
Orexin/Hypocretin	↑↑	—	—
MCH	—	—	↑↑
VLPO/MNPO	—	↑↑	↑↑

Neuronal activity: ↑↑, rapid firing rate; ↑, slower firing rate; —, little or no firing.

NREM

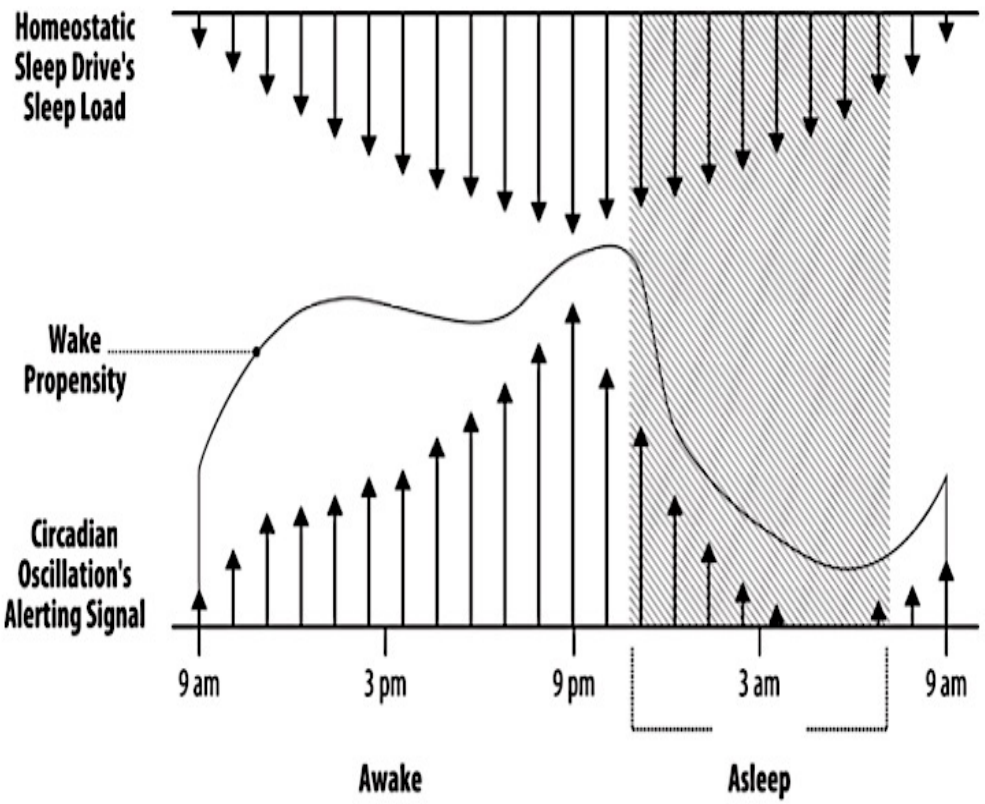


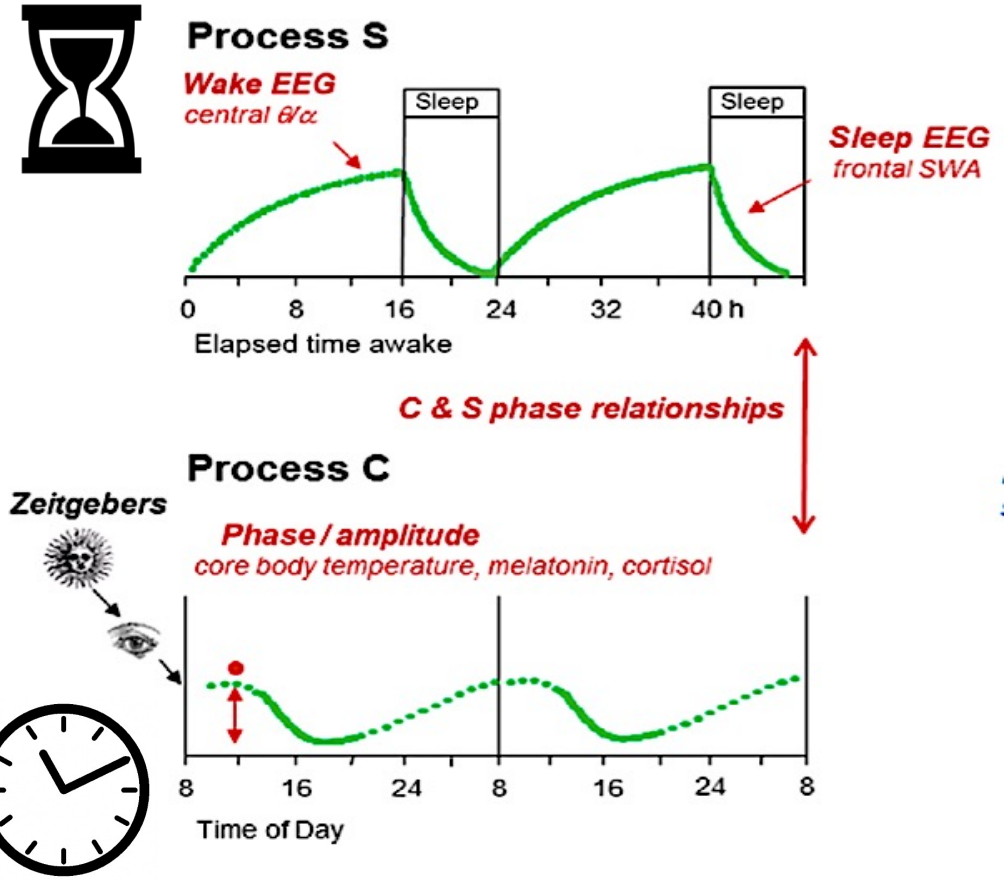


REM **Sleep**

España RA, et al. SLEEP 2011;34(7):845-58

Sleep Propensity

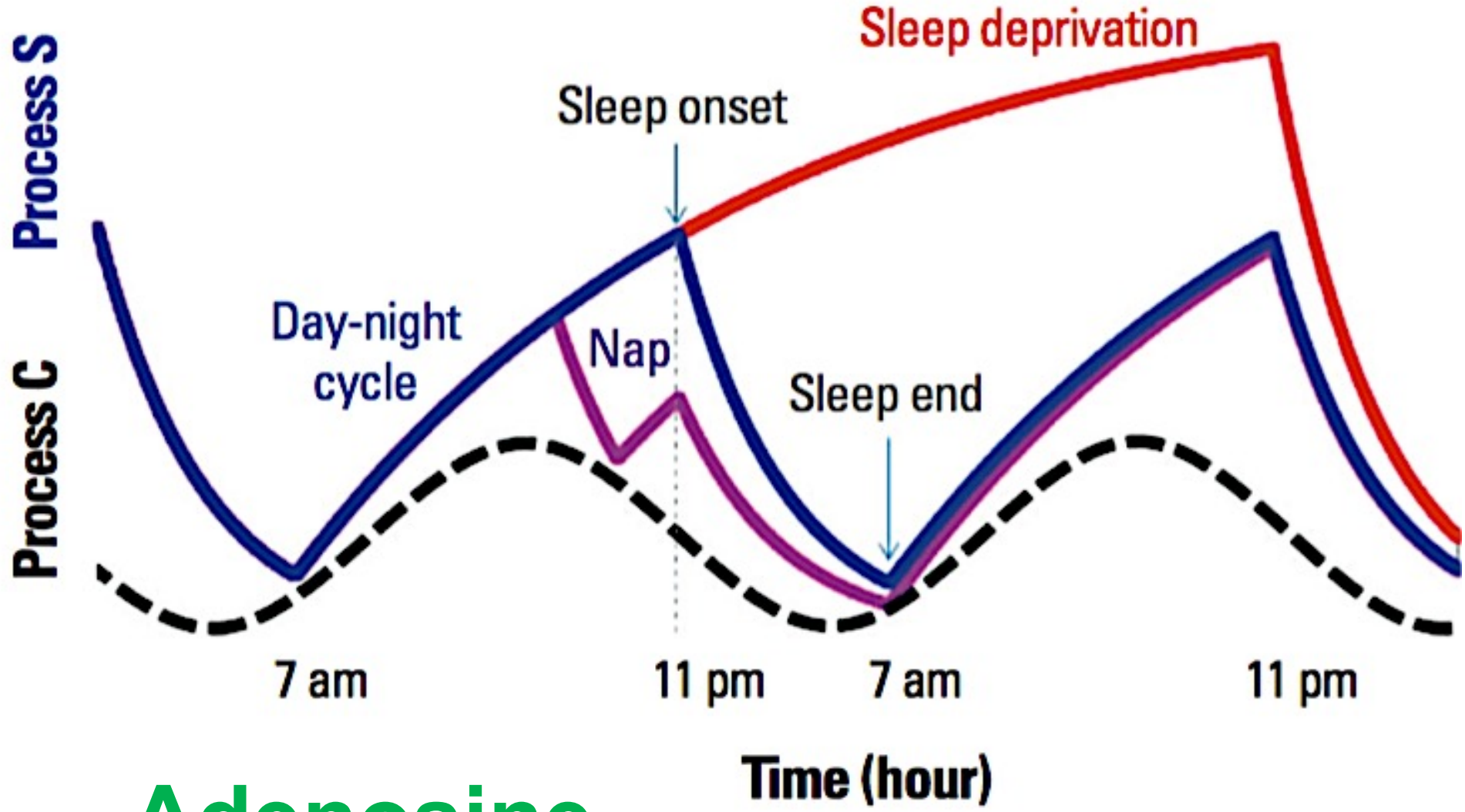




Homeostatic process (process S) accumulates during wakefulness and declines during sleep.
Circadian process (process C) helps regulate the timing of wakefulness and sleep.

Borbely AA, et al. J Sleep Resp 2016; 25: 131-43

Sleep Homeostasis (Process S)



Adenosine

and other somnogens

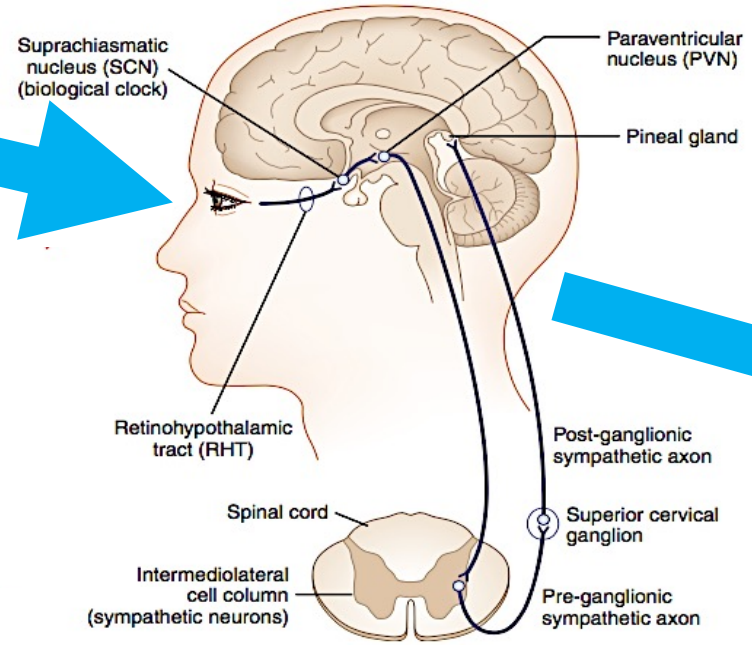
Koo DL, et al. Hanyang Med Rev 2013;33:190-196

Circadian Control (Process C)

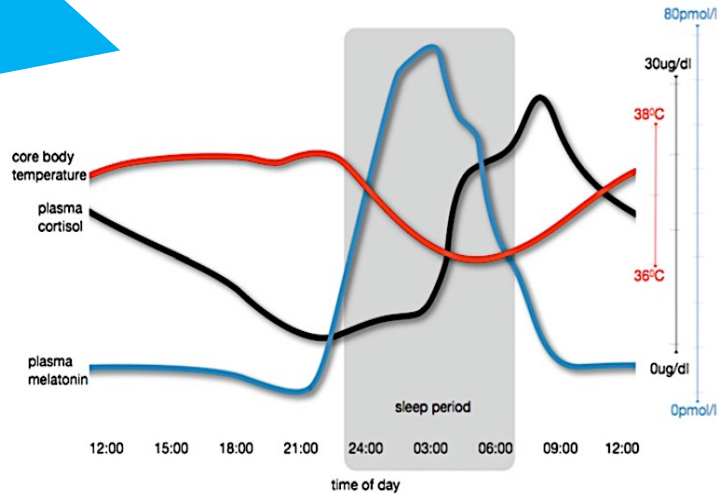
Input
("Zeitgeber" or Time giver)

Pacemaker (Oscillator)

Suprachiasmatic Nucleus (SCN)

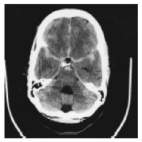


Output

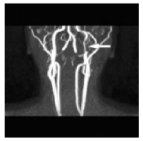


Neuroanatomy of Headache

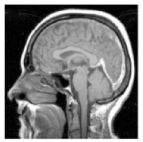
Pain can originate from multiple structures in the head and neck



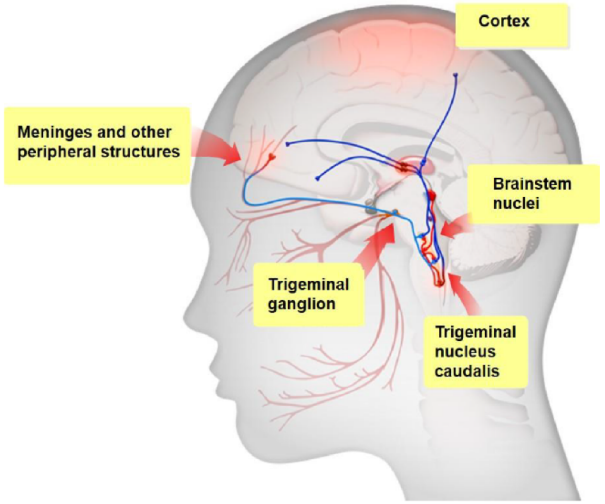
Meninges



Vessels

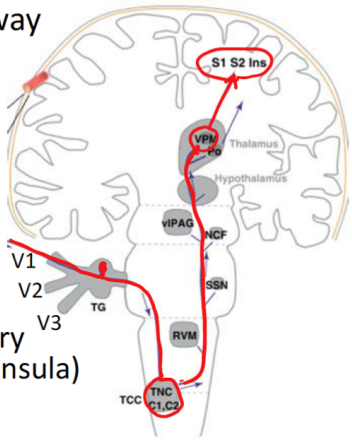


Other structures



Pain Signals: Ascending Pathway

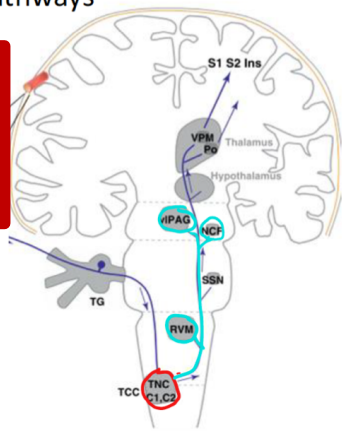
- Trigeminal nerve
- Trigeminal ganglion
- Spinal trigeminal tract
- Trigeminal nucleus caudalis
- Trigeminothalamic tract
- Thalamus (VPM)
- Cortex (primary and secondary somatosensory cortices and insula)



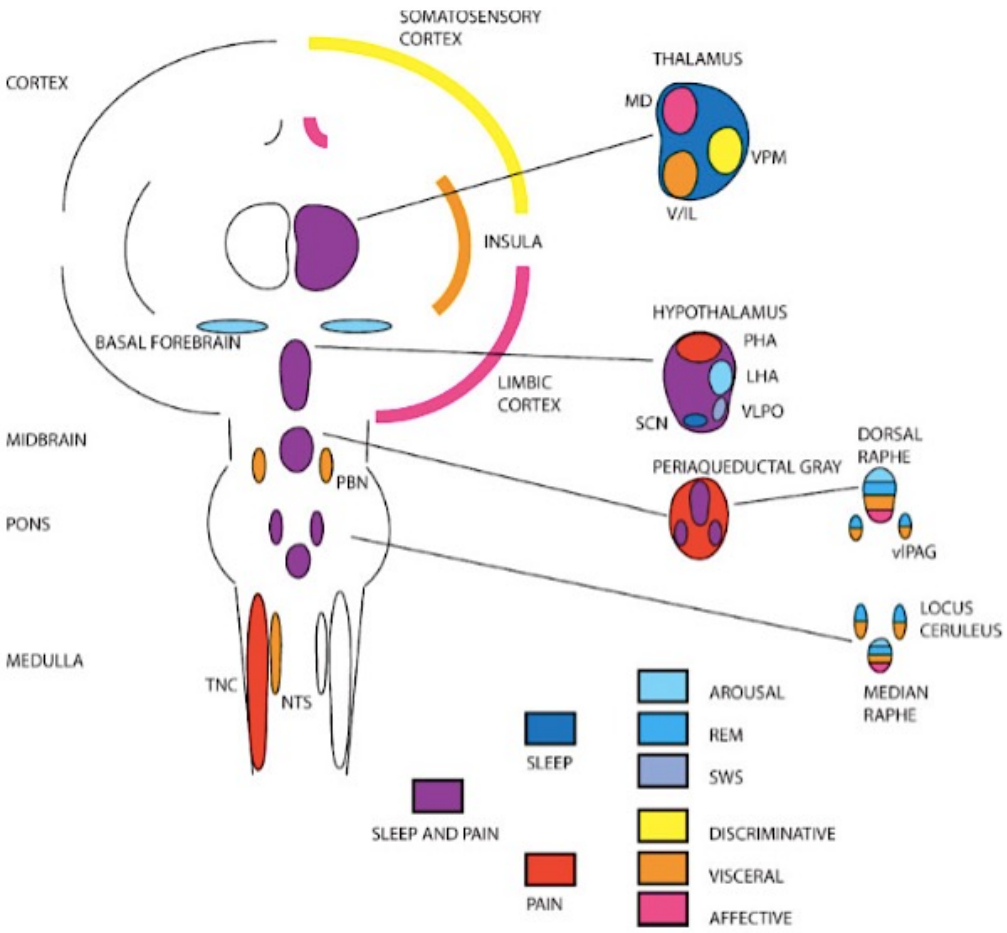
Pain Modulation: Descending Pathways

Multiple brainstem sites mediate **antinociception** (Periaqueductal Gray, locus coeruleus, nucleus cuneiformis, nucleus raphe magnus, rostroventral medulla)

- Rostroventral medulla and other areas **facilitate pain** through different descending pathways



Shared Anatomy of Headache and Sleep



- The most prominent shared structures involved in nociception and sleep
  - Hypothalamus (PHA, LHA)
  - Periaqueductal Gray (vlPAG)

Brennan KC, et al. Semin Neurol 2009; 29:406-17

Ventrolateral Periaqueductal Gray (vlPAG)

- Stimulation of PAG has affected
  - Antinociception

Veloso F, et al. Headache 1998;38(7):507–515

- Animal models: REM sleep deprivation → greater pain sensitivity in rats

Onen SH, et al. Brain Res 2001;900 (2): 261-7

- REM-off cells
  - Associated with arousal from REM sleep and/or derangements in REM, found in these headache disorders
    - Cluster headache
    - Migraine
    - Paroxysmal hemicrania
    - Hypnic headache

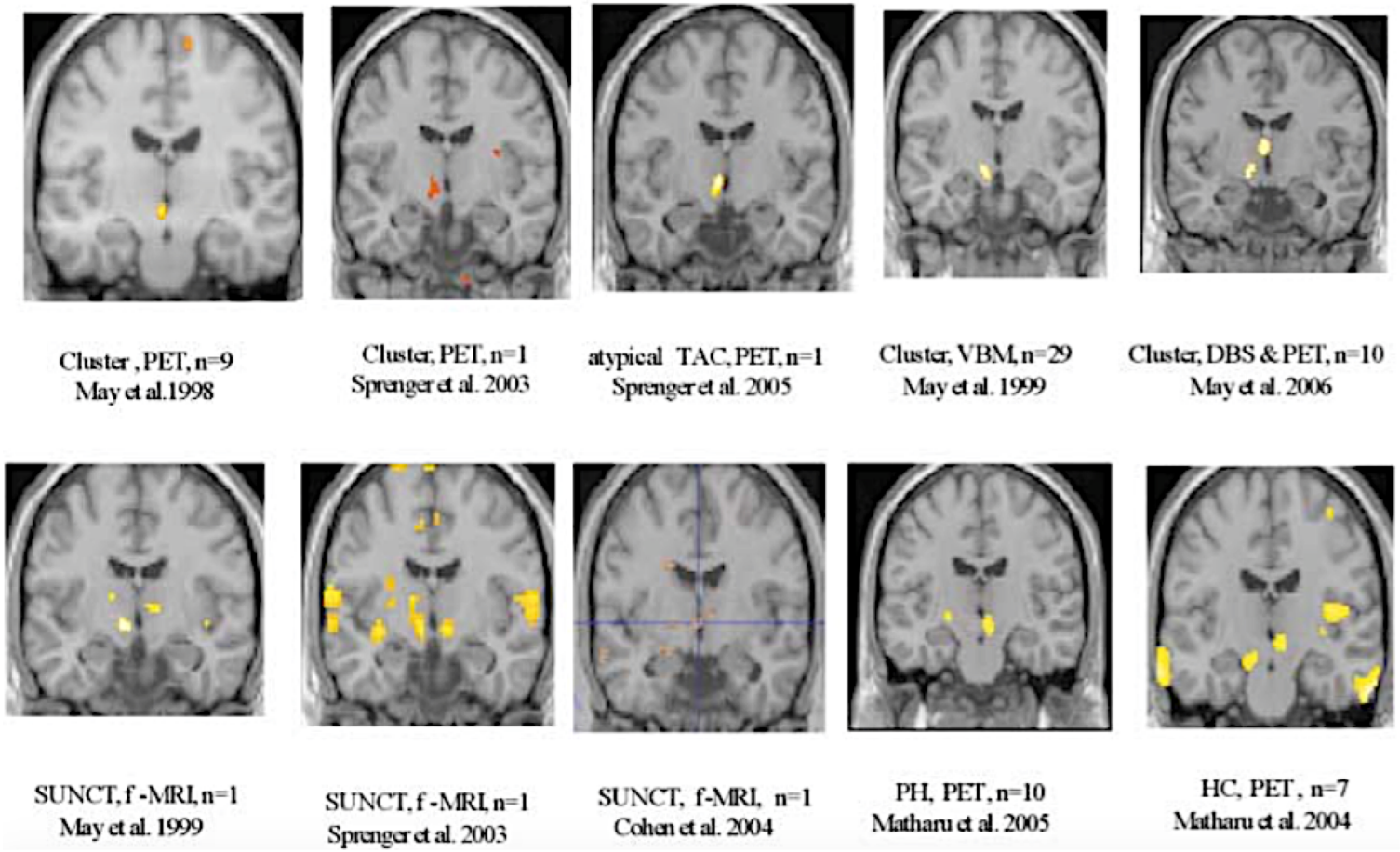
Fuller PM, et al. J Biol Rhythms 2006;21(6):482–93

Hypothalamus

- Hypothalamus (posterior regions) → activated during trigeminal autonomic cephalalgia (TAC) attacks
- Brainstem (dorsal pontine) → activated during migraine attacks
- Hypothalamus and interconnected brainstem → responsible for the **Chronobiological Features** of these headaches

Montagna P. Neurol Sci 2006 May;27 Suppl 2:S138-43

Hypothalamic Activation in TACs



- Multiple imaging studies in different types of primary headaches have identified activation in regions consistent with posterior hypothalamus during the headache phase. This pattern has been particularly prominent in TACs.

May A. J Headache Pain 2006; 7:174–84

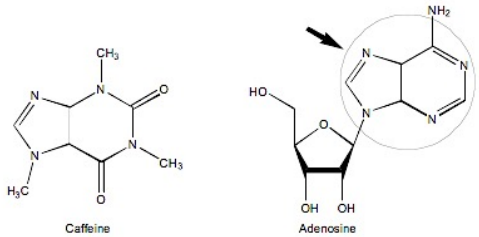
Neurotransmitter (Neurochemical) Perspective

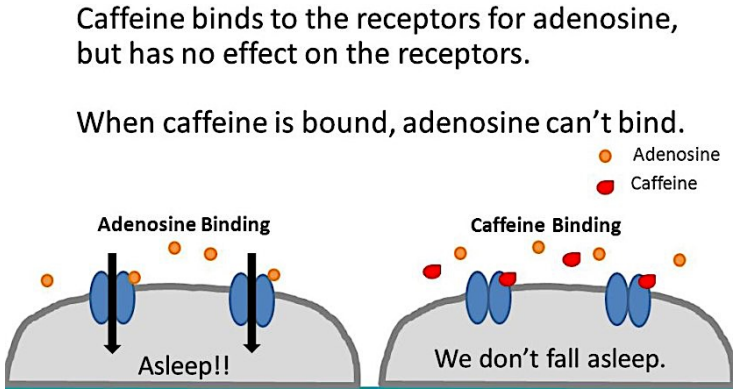
- Many neurotransmitters involve in both the regulation of sleep and the evolution of headaches.
  - e.g., Adenosine, Melatonin, Orexin
  - Adenosine
    - Adenosine receptor
      - Subtypes: A1, A2A, A2B, and A3
      - Distributed in different anatomic locations, sometimes with opposite functions
    - Adenosine concentrations increase with prolonged wakefulness, and decrease with sleep.
      - Increased activity of VLPO
      - Decreased activity of Basal Forebrain Cholinergic neuron

Brennan KC, et al. Semin Neurol 2009; 29:406-17

Examples of Adenosine and Headache

- Selective A1 agonists inhibit trigeminal nociception; A2A receptors can induce pain and vasodilatation.
  - Caffeine
    - an adenosine A1 and A2A antagonist
    - an analgesic that is commonly used for all types of headache (excedrin contains 65 mg of caffeine, equivalent to a cup of coffee)
  - Dipyridamole
    - a phosphodiesterase inhibitor
    - adenosine re-uptake inhibitor, that has headache as its major side effect, and induces migraine-like headache in migraine patients

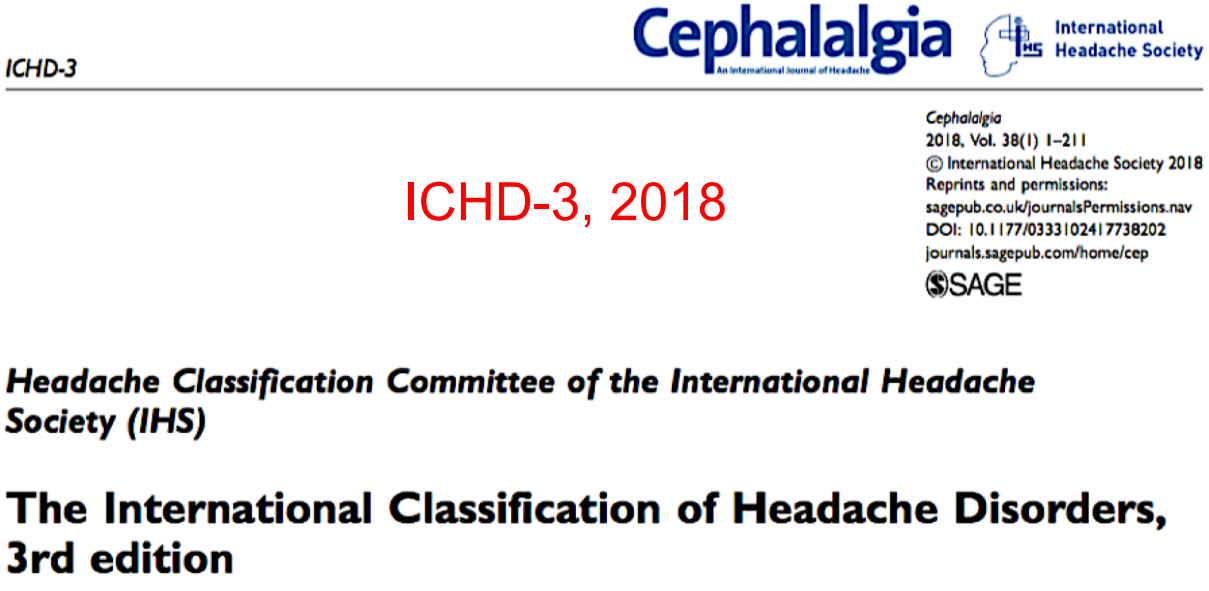


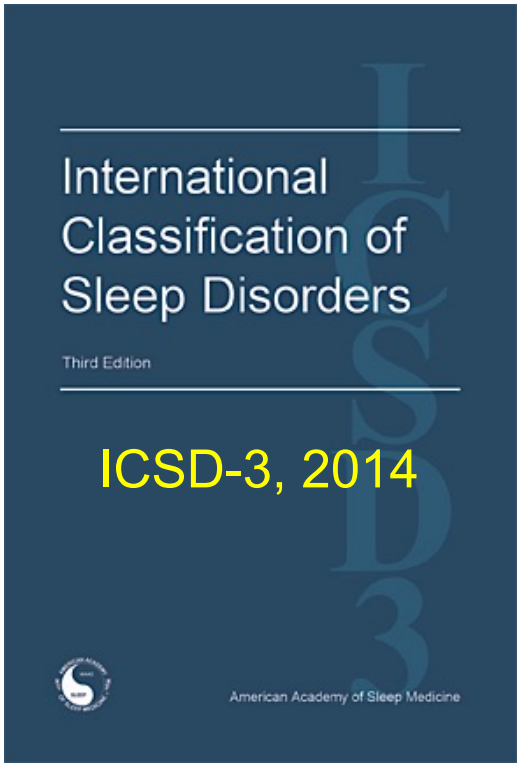


Brennan KC, et al. Semin Neurol 2009; 29:406-17

The Sleep and Headache Disorders

- Migraine
- Cluster headache
- Hypnic headache
- Sleep apnea headache





Migraine

Diagnostic criteria:

A. At least five attacks[1] fulfilling criteria B-D

B. Headache attacks lasting 4-72 hr (untreated or unsuccessfully treated)[2;3]

C. Headache has at least two of the following four characteristics:
   1. unilateral location
   2. pulsating quality
   3. moderate or severe pain intensity
   4. aggravation by or causing avoidance of routine physical activity (eg, walking or climbing stairs)

D. During headache at least one of the following:
   1. nausea and/or vomiting
   2. photophobia and phonophobia

E. Not better accounted for by another ICHD-3 diagnosis.

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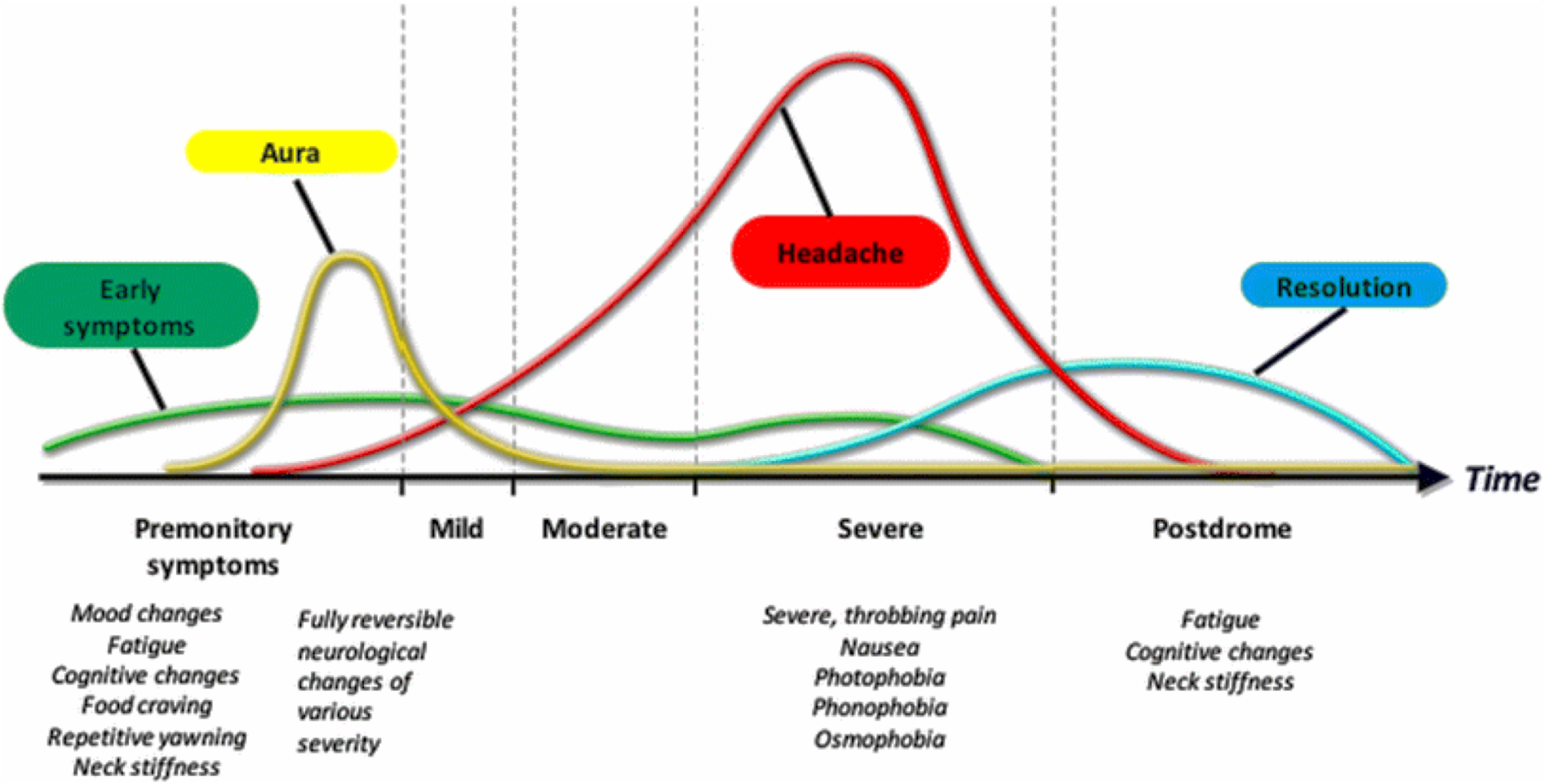
Migraine: A Continuum of Symptoms



Linde M. Cephalalgia 2006, 26; 712-21

Relationship between Migraine and Sleep

- Migraine includes a constellation of symptoms
  - Cerebral cortex (Typical Aura)
    - visual symptom: scintillation, scotoma
    - cortical sensory symptom
    - language dysfunction
  - Brainstem or diencephalic structures:
    - Prodromal symptoms: hunger and thirst, polyuria, and yawning
    - Ictal symptoms: vomiting, flushing and pallor
    - Brainstem aura: vertigo, tinnitus, dysarthria, diplopia, ataxia, and impaired consciousness
  - Still others not clearly localizable: light and sound sensitivity, fatigue, and mood changes

Linde M. Cephalalgia 2006, 26; 712-21

Relationship between Migraine and Sleep

- Migraine has chronobiologic features → indicate mechanisms controlled by the hypothalamus
  - Menstrual cycle in females
  - Circadian phenotype
    - Approximately 50% of migraine attacks occur in the morning hours (4am-9am).
- The end of the sleep cycle - early morning hours → **An increased fraction of REM sleep** relative to NREM

Migraine and Sleep disorders

- Sleep often terminates headache; changes in sleep patterns can trigger migraine attacks.
  - e.g., decreased sleep, increased sleep, or changing time zones

- Sleep was the second most commonly reported migraine trigger by a recent meta-analysis.

Pellegrino ABW, et al.Cephalalgia 2018; 38(6): 1188-98

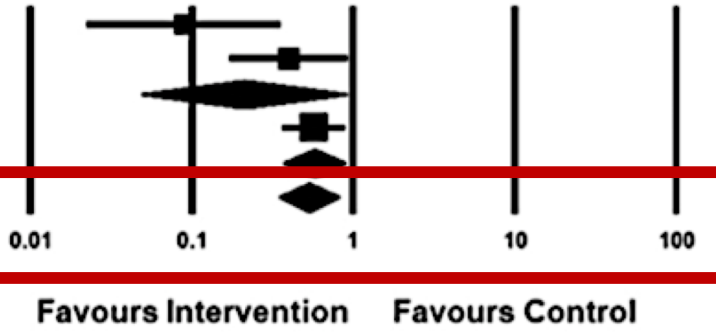
- Migraine is related to many sleep disorders.
  - Insomnia
  - Parasomnias (sleepwalking, night terrors)
  - RLS

Sleep Sci. 2012;5(1):28-32

Migraine and Sleep disorders

Meta-Analysis (Random Effects) of Psychological Sleep Interventions for Headache Frequency (Adults)

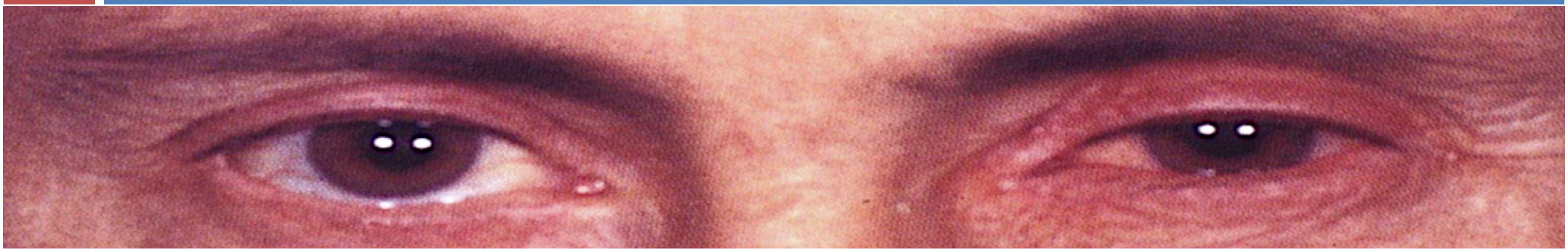
Group by Intervention Type	Study name	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value
Psychological/Behavioural	Calhoun & Ford, 2007	0.089	0.022	0.353	-3.437	0.001
Psychological/Behavioural	Smitherman et al., 2016	0.400	0.173	0.925	-2.141	0.032
Psychological/Behavioural		0.209	0.048	0.902	-2.098	0.036
Psychological/Behavioural & Drug	Ruff et al., 2009	0.571	0.366	0.890	-2.475	0.013
Psychological/Behavioural & Drug		0.571	0.366	0.890	-2.475	0.013
Overall		0.525	0.343	0.802	-2.977	0.003



- Behavioral modification of sleep (sleep restriction, stimulus control and sleep hygiene) was beneficial in
  - reducing the frequency of headache
  - changing characteristics of headache from chronic to episodic migraine

Sullivan DP, et al. Sci Rep 2019;9: 6411

Cluster Headache



Diagnostic criteria:

A. At least five attacks fulfilling criteria B-D

B. Severe or very severe unilateral orbital, supraorbital and/or temporal pain lasting 15-180 minutes (when untreated)[1]

C. Either or both of the following:

1. at least one of the following symptoms or signs, ipsilateral to the headache:
   - conjunctival injection and/or lacrimation
   - nasal congestion and/or rhinorrhoea
   - eyelid oedema
   - forehead and facial sweating
   - miosis and/or ptosis
2. a sense of restlessness or agitation

D. Occurring with a frequency between one every other day and 8 per day[2]

E. Not better accounted for by another ICHD-3 diagnosis.

Trigeminal distribution of Pain
Trigeminovascular system

Cranial autonomic symptoms
Trigeminoautonomic reflex

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Relationship between CH and Sleep

- CH is a disorder intricately associated with sleep, often with the strongest **chronobiological pattern**.
  - awakens the patient at the same time each night (82%)
    → **Circadian rhythmicity**
  - tends to occur in clusters in the same season each year (56%)
    → **Circannual periodicity**

Hypothalamic involvement
(suprachiasmatic nucleus; SCN)

Zurak N. Cephalalgia. 1997;17(7):723-8.

Relationship between CH and Sleep

- A majority of CH occur from sleep.
  - 75% occur between 9 PM-10 AM.
- The attack occurs 90 minutes after falling asleep → coincident with the first episode of REM sleep
- A strong predilection for attacks → **strongly related to REM sleep**

CH and Sleep disorders

- Cluster headache patients have a high risk for OSA.
- OSA prevalence of up to 80% has been reported in a CH population.
- Mechanism:
  - possibly secondary to hypoxia; suggested by the therapeutic effect of oxygen administration in the abortion of a cluster headache attack
- PSG is necessary in patients with CH resistant to usual treatment.

Graff-Radford SB, et al. Headache. 2004;44(6):607-10

Hypnic Headache

Diagnostic criteria:

A. Recurrent headache attacks fulfilling criteria B-E

B. Developing only during sleep, and causing wakening

C. Occurring on ≥10 days/month for >3 months

D. Lasting from 15 minutes up to 4 hours after waking

E. No cranial autonomic symptoms or restlessness

F. Not better accounted for by another ICHD-3 diagnosis[1;2].

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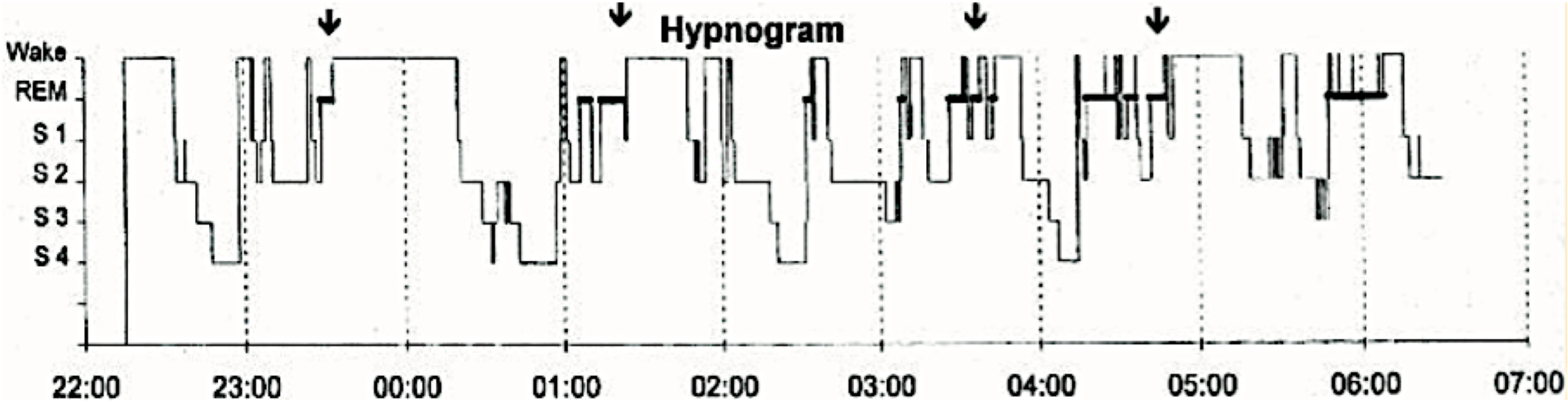
Relationship between HH and Sleep

- HH is a rare, primary headache disorder that is described exclusively during sleep.
- Diffuse headache, most often mild to moderate intensity that wakes the patient (often an elderly female) from sleep, generally around 1-3 AM
- Need to exclude SDB, nocturnal HT, hypoglycemia as cause
- Brain MRI warranted to rule out intracranial, parasellar lesion.
- Distinguish from CH by lack of cranial autonomic symptoms

Relationship between HH and Sleep

- The specificity of headache timing can be remarkable; its colloquial name is “alarm clock headache.”

- Tends to occur **during REM sleep**.
  (but can begin from NREM)



Evers S, et al. Pract Neurol 2005; 5:144-9

Relationship between HH and Sleep

- Begin after 50 → associated with age-related sleep physiology:
  - Decreased SWS
  - Increased fragmented sleep

- Mechanisms:
  - Hypothalamic dysfunction; because of
    - apparent cyclicity
    - response to lithium suggest a pathophysiologic connection with cluster headache
    - reduced gray matter volume in the posterior hypothalamus by a voxel based morphometric MRI study; increased gray matter volume in cluster
  - May be related to reduced melatonin

Holle D, et al.Ann Neurol. 2011;69(3):533

- Hypothesis:
  - HH may represent an age-related phenotypic change of another sleep-related primary headache: cluster.

Brennan KC, et al. Semin Neurol 2009; 29:406-17

HH and Sleep disorders

- There are reports of association between HH and OSA or REM-related oxygen desaturation, owing to an increased AHI in this group.

- Presumably, OSA prevalence is related to the age of the population rather than to the disease itself.

Holle D, et al. Cephalalgia. 2011;31(3):286–90.

Sleep Apnea Headache

10. Headache attributed to disorder of homoeostasis

10.1 Headache attributed to hypoxia and/or hypercapnia
- 10.1.1 High-altitude headache
- 10.1.2 Headache attributed to aeroplane travel
- 10.1.3 Diving headache
- 10.1.4 Sleep apnoea headache

10.2 Dialysis headache
10.3 Headache attributed to arterial hypertension
- 10.3.1 Headache attributed to phaeochromocytoma
- 10.3.2 Headache attributed to hypertensive crisis without hypertensive encephalopathy
- 10.3.3 Headache attributed to hypertensive encephalopathy
- 10.3.4 Headache attributed to pre-eclampsia or eclampsia
- 10.3.5 Headache attributed to autonomic dysreflexia

10.4 Headache attributed to hypothyroidism
10.5 Headache attributed to fasting
10.6 Cardiac cephalalgia
10.7 Headache attributed to other disorder of homoeostasis

- A headache due to a disorder of homeostasis
  - specifically as a result of hypoxemia or hypercapnia

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Sleep Apnea Headache

Diagnostic criteria:

A. Headache present on awakening after sleep and fulfilling criterion C

B. Sleep apnoea with apnoea-hypopnoea index ≥5 has been diagnosed[1]

C. Evidence of causation demonstrated by at least two of the following:
   1. headache has developed in temporal relation to the onset of sleep apnoea
   2. either or both of the following:
      a) headache has worsened in parallel with worsening of sleep apnoea
      b) headache has significantly improved or remitted in parallel with improvement in or resolution of sleep apnoea
   3. headache has at least one of the following three characteristics:
      a) recurring on ≥15 days/month
      b) all of the following:
         – bilateral location
         – pressing quality
         – not accompanied by nausea, photophobia or phonophobia
      c) resolving within 4 hours

D. Not better accounted for by another ICHD-3 diagnosis[2].

Notes:

1. The apnoea-hypopnoea index is calculated by dividing the number of apnoeic events by the number of hours of sleep (5-15/hr = mild; 15-30/hr = moderate; >30/hr = severe).
2. A definitive diagnosis requires overnight polysomnography.

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Sleep Apnea Headache

- Diffuse pressing mild to moderate intensity head pain, typically resolving within 30min-4hrs after awakening (60% in less than 30min; 81% by 4 hrs)
- Often associated with OSA, but can be seen in any type of SDB
- OSA pts with headache compared with those without headache
  - more time in overnight PSG with SpO2 less than 90%
  - lower nadir SpO2
- Improvement in headache with PAP use (more so if PAP-adherent)

Sleep Apnea Headache

- Mechanisms:
  - **Hypoxemia and hypercapnia** cause generalized intra- and extracranial vasodilatation.
  - **The reduced pH** caused by hypercapnia can also activate nociceptive neurons and cause vasodilatation.
  - Sudden and large increases in cerebral blood flow and volume can **increase intracranial pressure**, which puts traction on the pain-sensitive dura and dural sinuses.

Increased Intracranial Pressure

5. Headache attributed to trauma or injury to the head and/or neck
6. Headache attributed to cranial and/or cervical vascular disorder
7. Headache attributed to non-vascular intracranial disorder
8. Headache attributed to a substance or its withdrawal
9. Headache attributed to infection
10. Headache attributed to disorder of homoeostasis
11. Headache or facial pain attributed to disorder of the cranium, neck, eyes, ears, nose, sinuses, teeth, mouth or other facial or cervical structure
12. Headache attributed to psychiatric disorder

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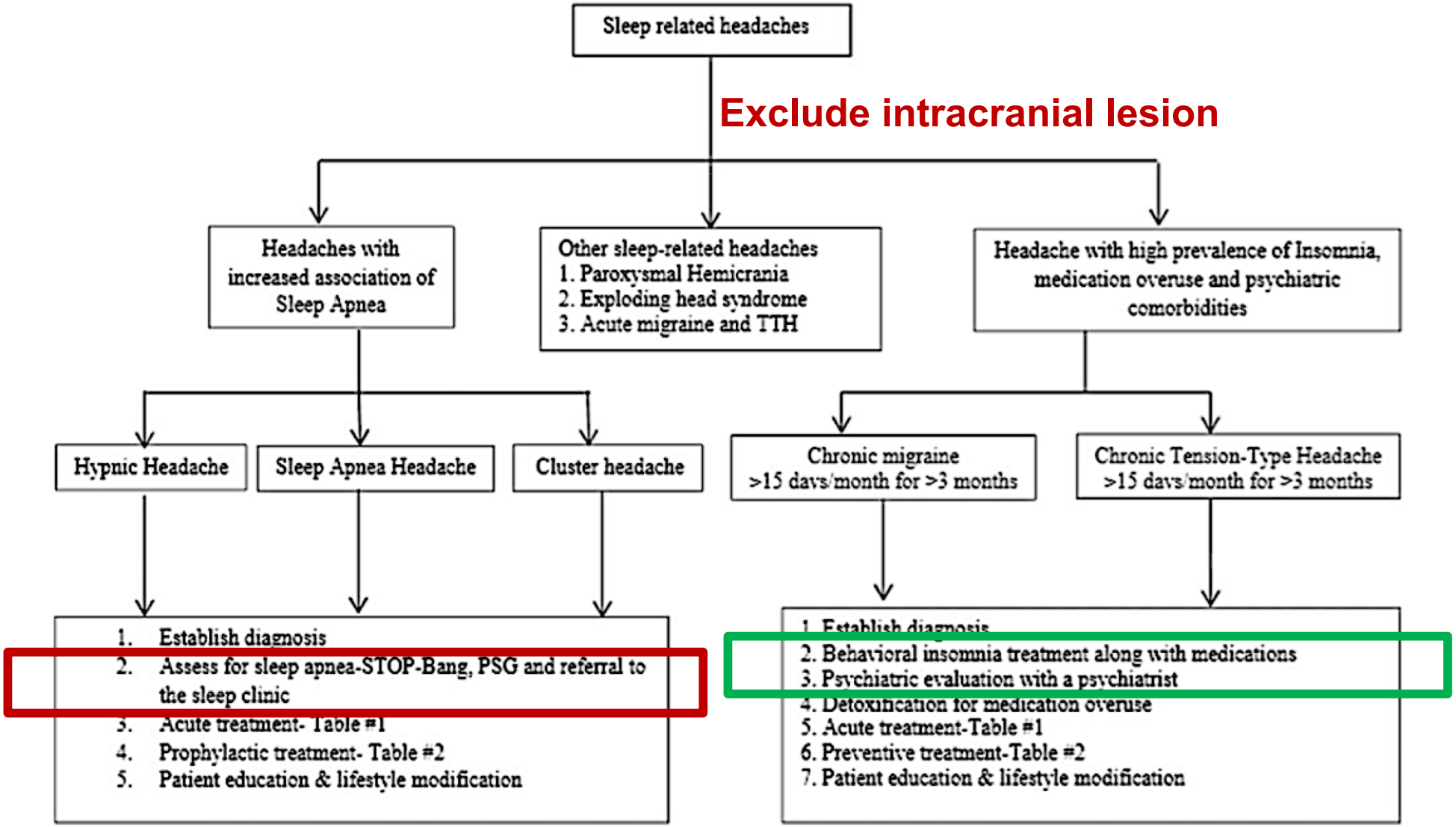
Increased Intracranial Pressure

- Patients with increased ICP may complain of
  - Headache in the morning or headache that starts after recumbence
  - Improving after the patient is up for 30 to 60 minutes
- Associated symptoms:
  - N/V, signs of focal neurological deficits, and papilledema
- Examples:
  - Space-occupying lesion, CVST, Pseudotumor cerebri
- Tend to improve with treatment of the primary lesion and a decrease in ICP

Treatment



Singh NN, et al. Curr Treat Options Neurol 2013; 15: 704-22

Pharmacologic Treatment

- Migraine
  - Acute: NSAIDS, ergot, triptan
  - Preventive: antiepileptic, BB, CCB, antidepressant
- Cluster
  - Acute: O2, triptan
  - Preventive: verapamil, lithium, melatonin, steroid (transitional prophylaxis)
- HH (based on case reports)
  - Caffeine 40-60mg at bedtime, melatonin, indomethacin, lithium, topiramate, flunarizine

Nonpharmacologic Treatment

- Biorhythm
  - Regular sleep schedule/sleep hygiene, regular meal, regular exercise
- Trigger management
  - Migraine: food (tyramine, MSG, nitrate, alc), stress, **sleep habit change**, weather change, bright sunlight, strong odor
  - Cluster: alcohol, vasodilating substance, high altitude, **sleep apnea**
- Screening of **insomnia** and **other sleep-related disorders**
- Screening of psychiatric comorbidities esp. in chronic headache, MOH

Conclusions

- Sleep triggers headaches, and headaches can lead to poor sleep.
- Sleep problems and headache possibly co-occur as a result of the dysregulation of shared brain substrates.
  - Anatomic
    - Hypothalamus → Chronobiological features
      - Cluster → circadian and circannual rhythmicity
      - Hypnic → alarm clock pattern
    - PAG → Preferential occurrence during REM: migraine, cluster, hypnic, TACs
      - Silencing of anti-nociceptive network of PAG
  - Neurotransmitters
- Treatment
  - Exclusion of secondary headache: intracranial lesion
  - Screening for sleep disorders with proper tests: Sleep diary, Sleep questionnaire, PSG
  - Nonpharmacology and Pharmacology
- Treatment of headache cannot be optimized without attention to sleep hygiene and sleep disorders.