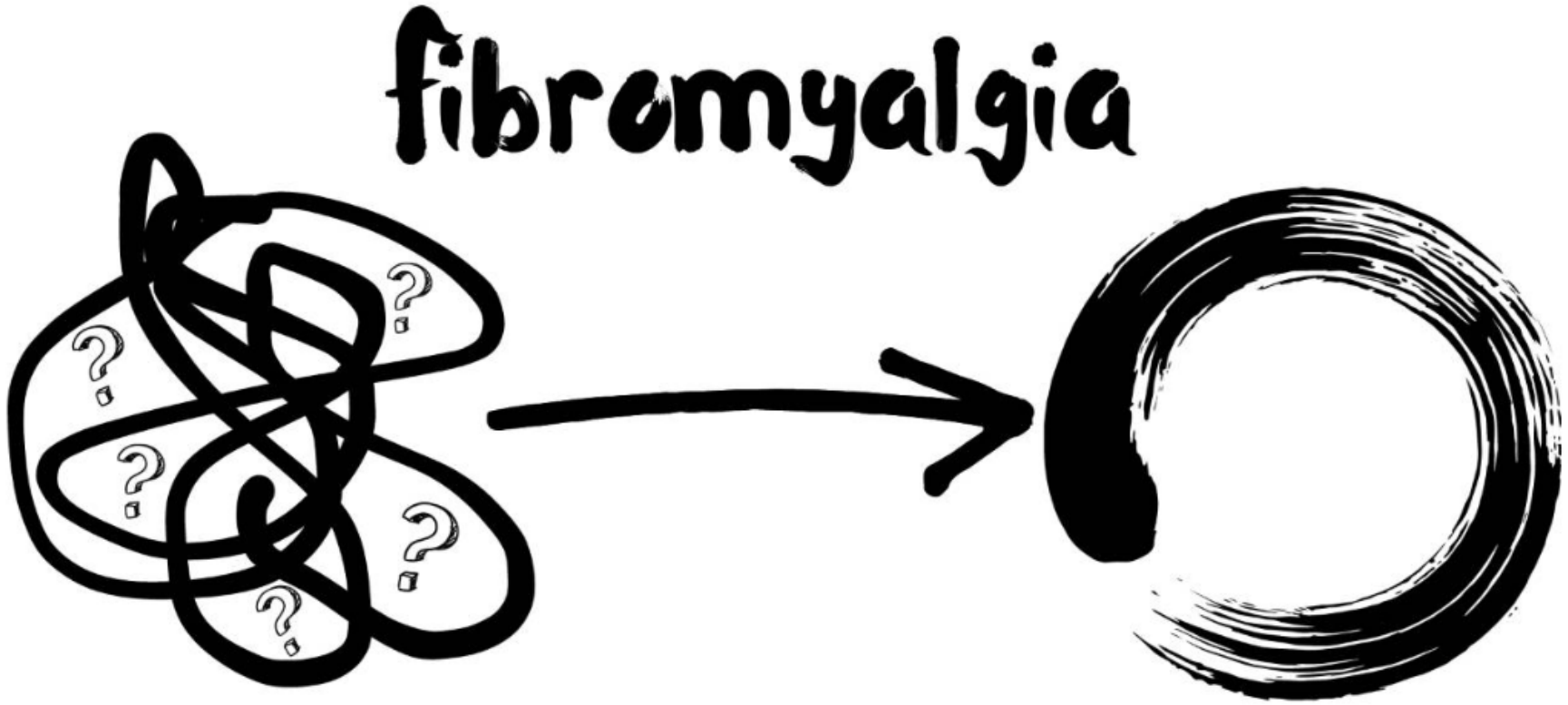
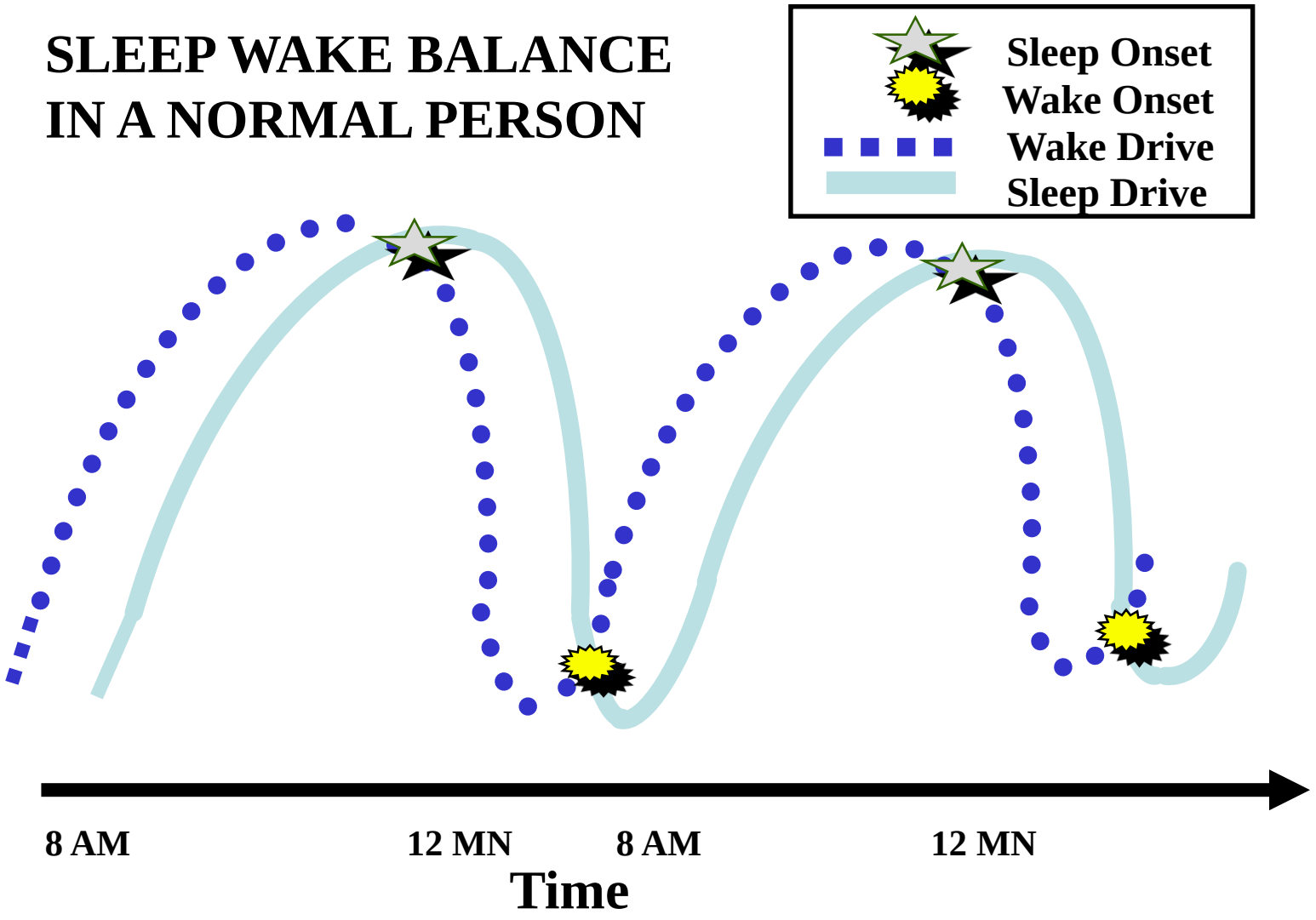


Jerald H. Simmons, M.D.

Director, Comprehensive Sleep Medicine Associates
Director, Sleep Education Consortium
www.CSMA.clinic

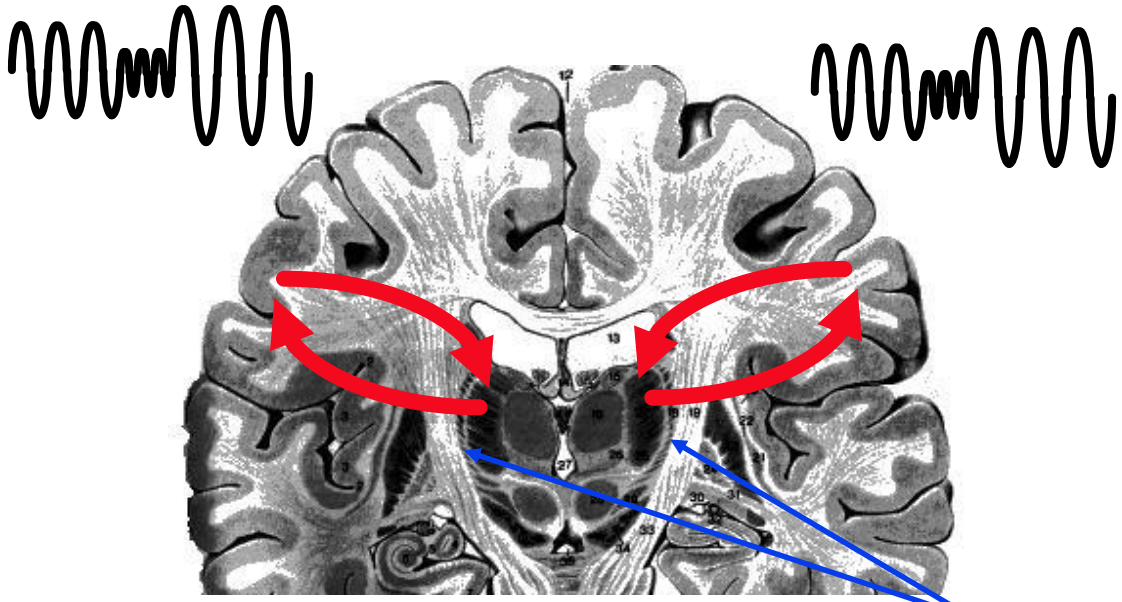
Sleep-pain connection and long term sleep solutions. Identifying sleep disorders through brainwave patterns and uncovering lasting solutions to achieve quality sleep & pain relief.

SLEEP WAKE BALANCE IN A NORMAL PERSON



Non-REM Sleep

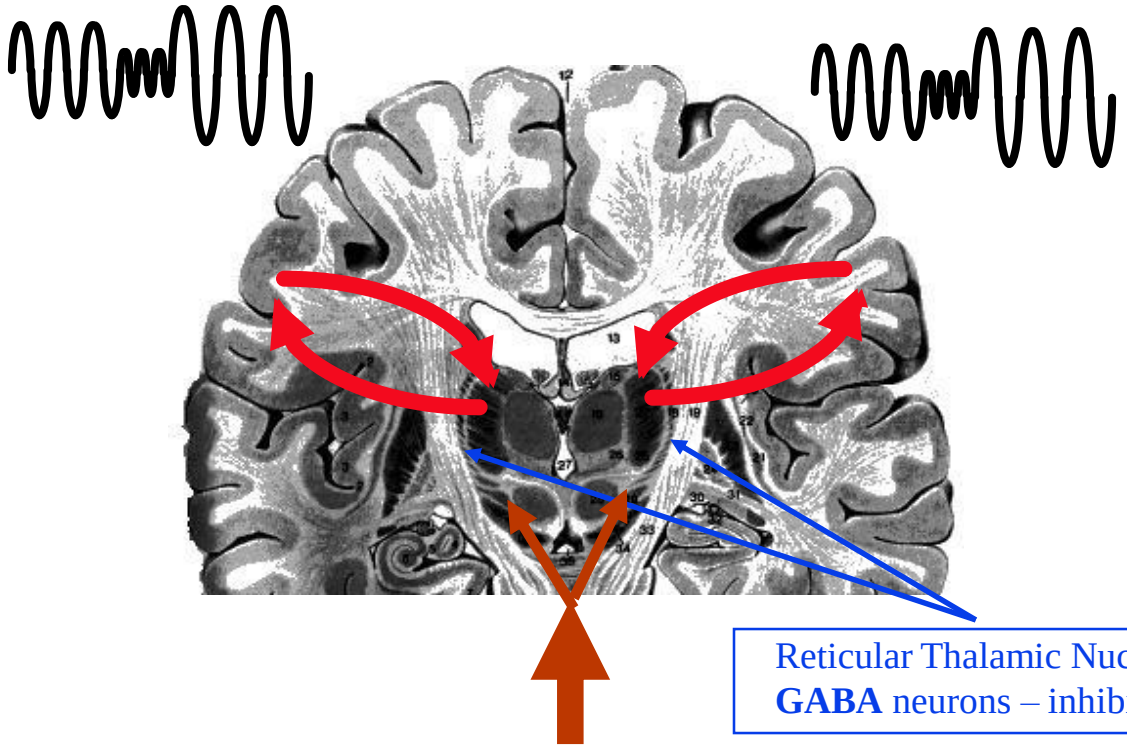
The Reticular Thalamic Nucleus inhibits sensory input from the Thalamus along the Thalamocortical pathways which produces synchronous EEG activity during Non-REM sleep



Reticular Thalamic Nucleus
GABA neurons – inhibitory, induce sleep

Wakefulness

The Ascending Reticular Activating System inhibits the Reticular Thalamic Nucleus allowing the cortex to be active during wakefulness

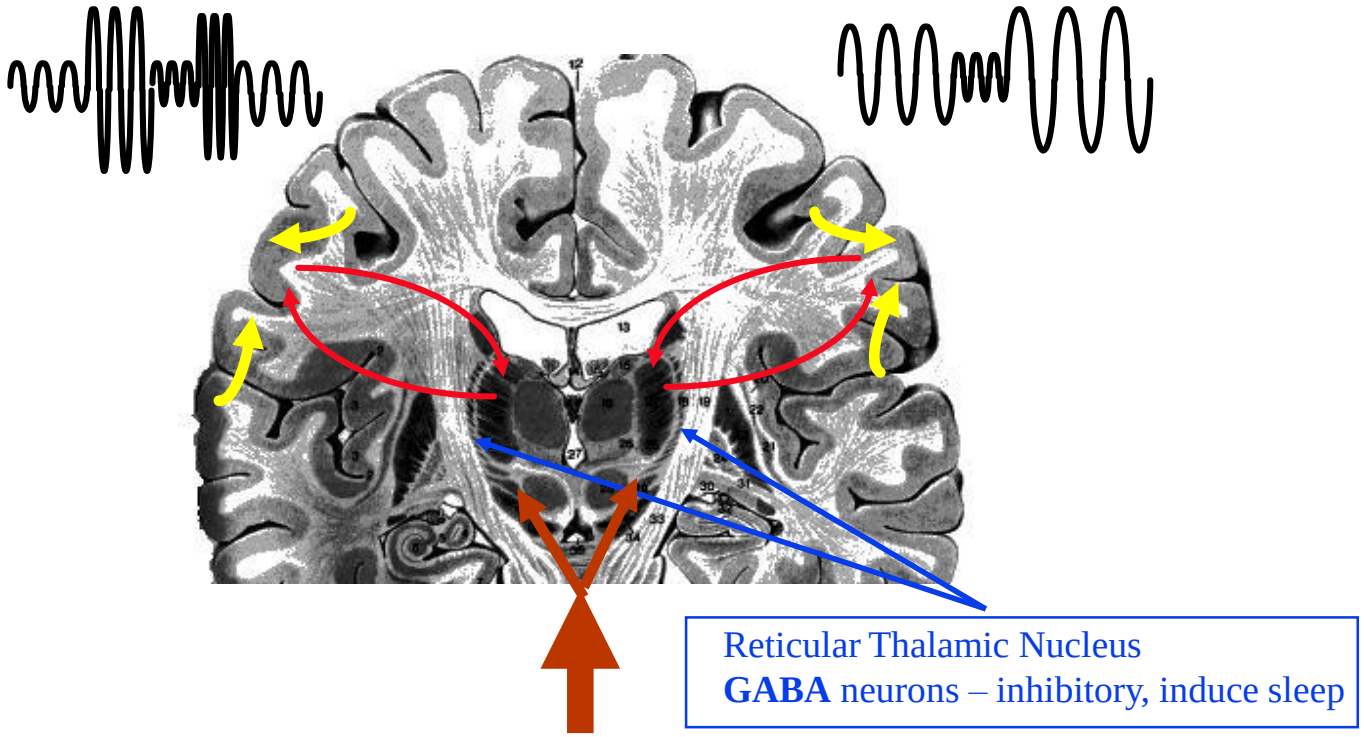


Reticular Thalamic Nucleus
GABA neurons – inhibitory, induce sleep

The Ascending Reticular Activating System Produces Desychronization of the EEG During Wakefullness by Inhibition of the Reticularthalamic Nucleus.

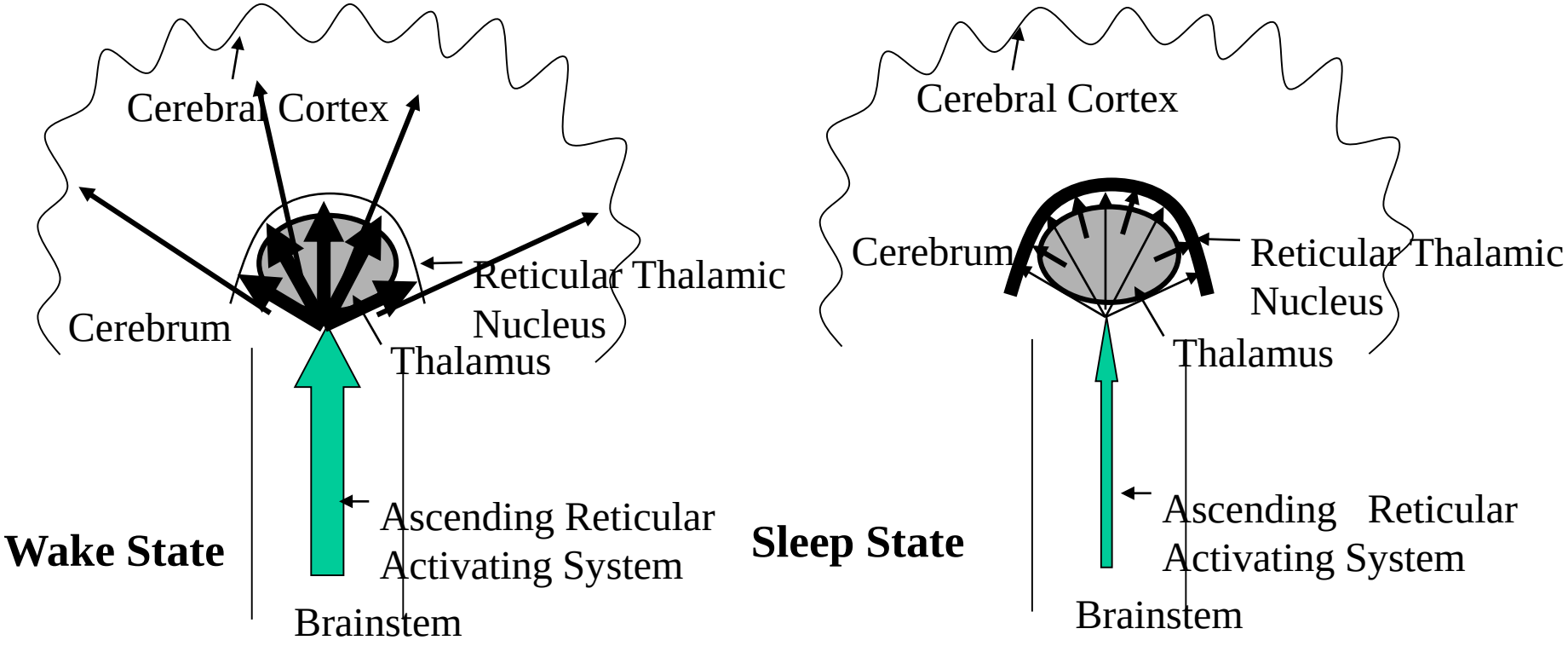
Wakefulness

The Ascending Reticular Activating System inhibits the Reticular Thalamic Nucleus allowing the cortex to be active during wakefulness



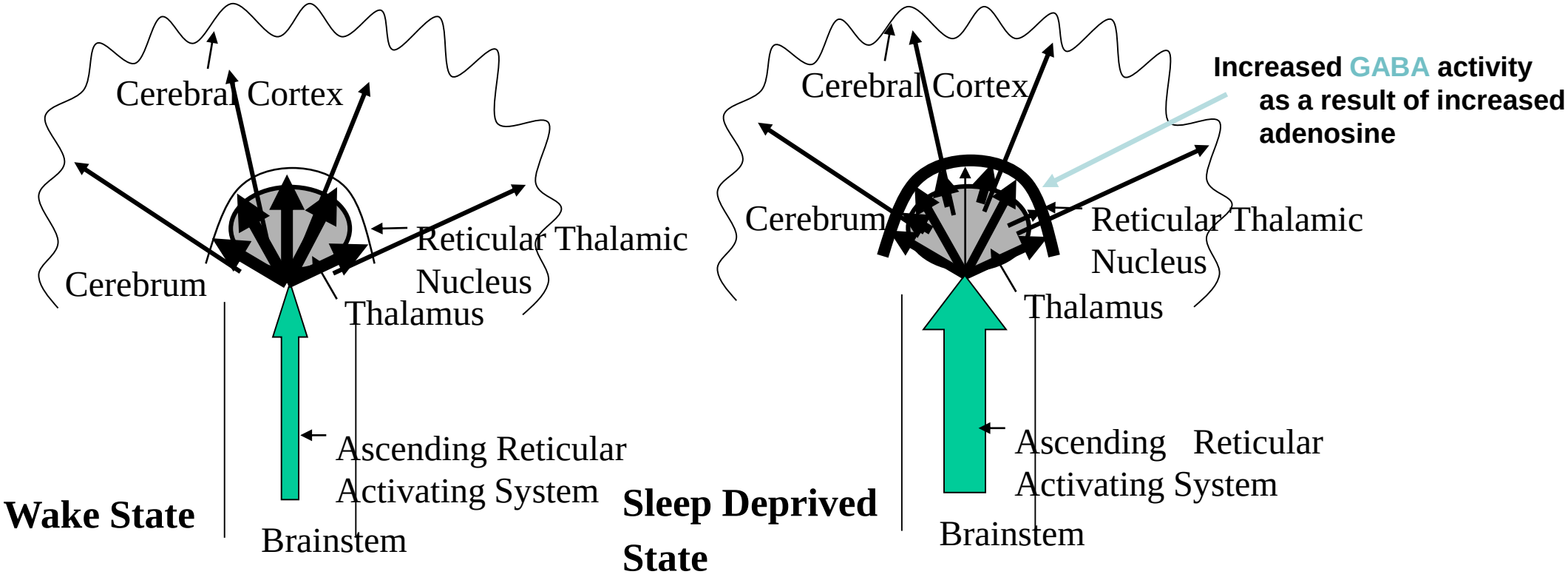
Reticular Thalamic Nucleus
GABA neurons – inhibitory, induce sleep

The Ascending Reticular Activating System Produces Desychronization of the EEG During Wakefullness by Inhibition of the Reticularthalamic Nucleus. **Acetylcholine and Histamine** – enhance wakefulness



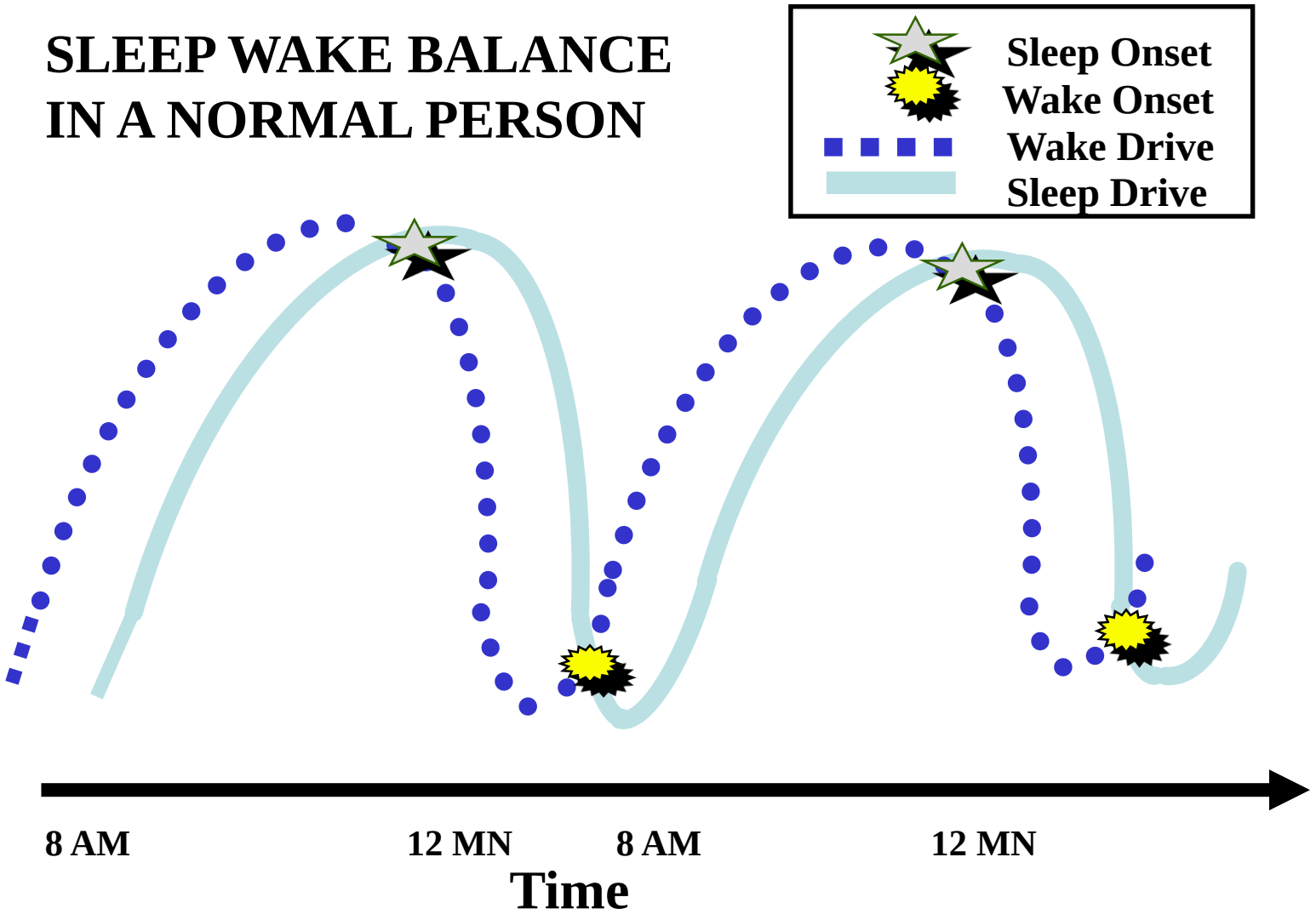
Physiologic Mechanism of the Sleep Drive / Wake Drive system and the balance between sleep and wake states

Physiologic Mechanism of the Sleep Drive / Wake Drive system and the changes between Wake and Sleep Deprived states

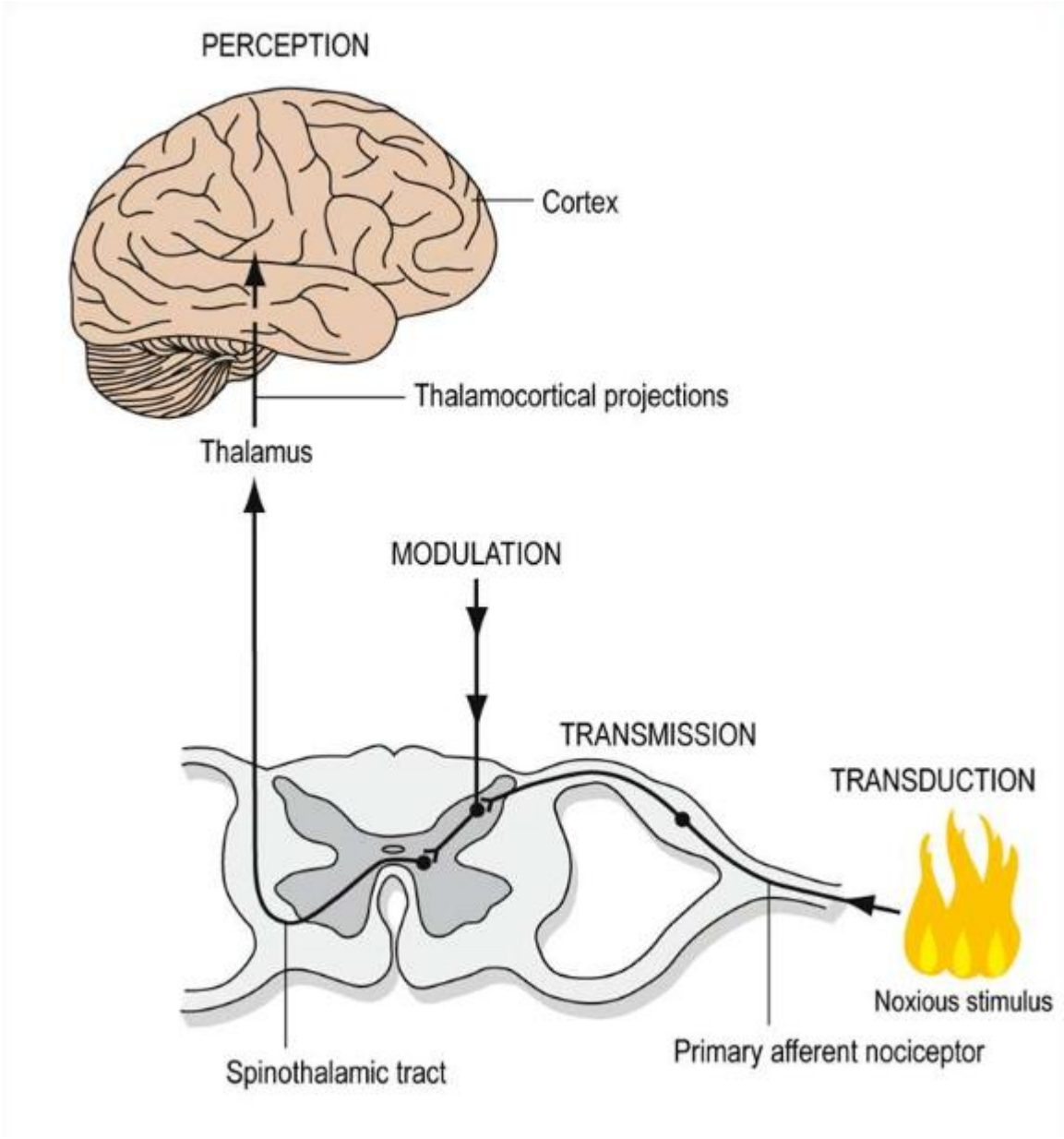


As a person becomes sleep deprived the reticular thalamic nucleus enhances its activity in attempts to shut down the cortex and induce sleep. Therefore it takes a greater degree of activity from the Ascending Reticular Activating System in order to overcome the Reticular Thalamic Nucleus activity and remain awake.

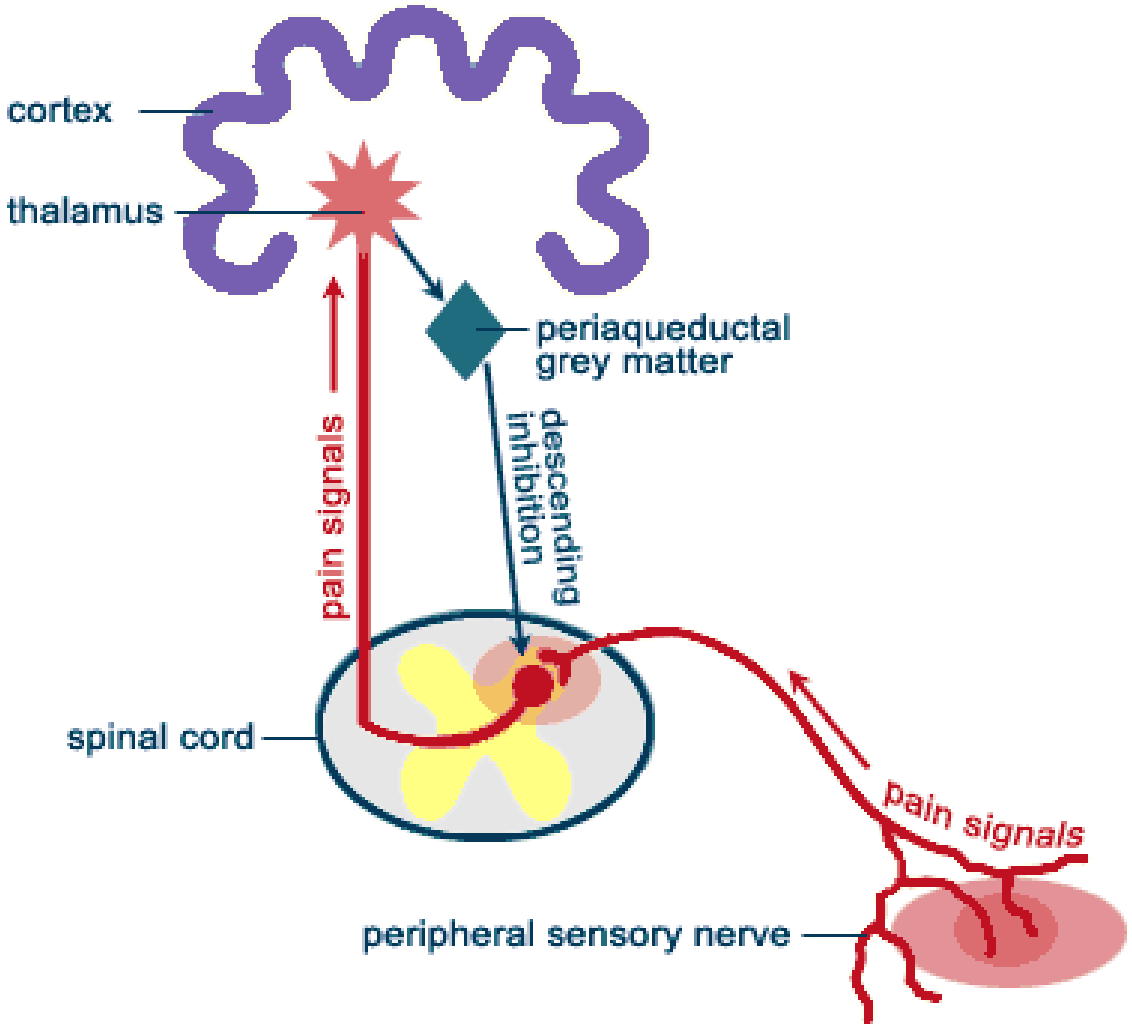
SLEEP WAKE BALANCE IN A NORMAL PERSON



Simplified depiction of ascending and descending pain signaling pathways.



Simplified depiction of ascending and descending pain signaling pathways.



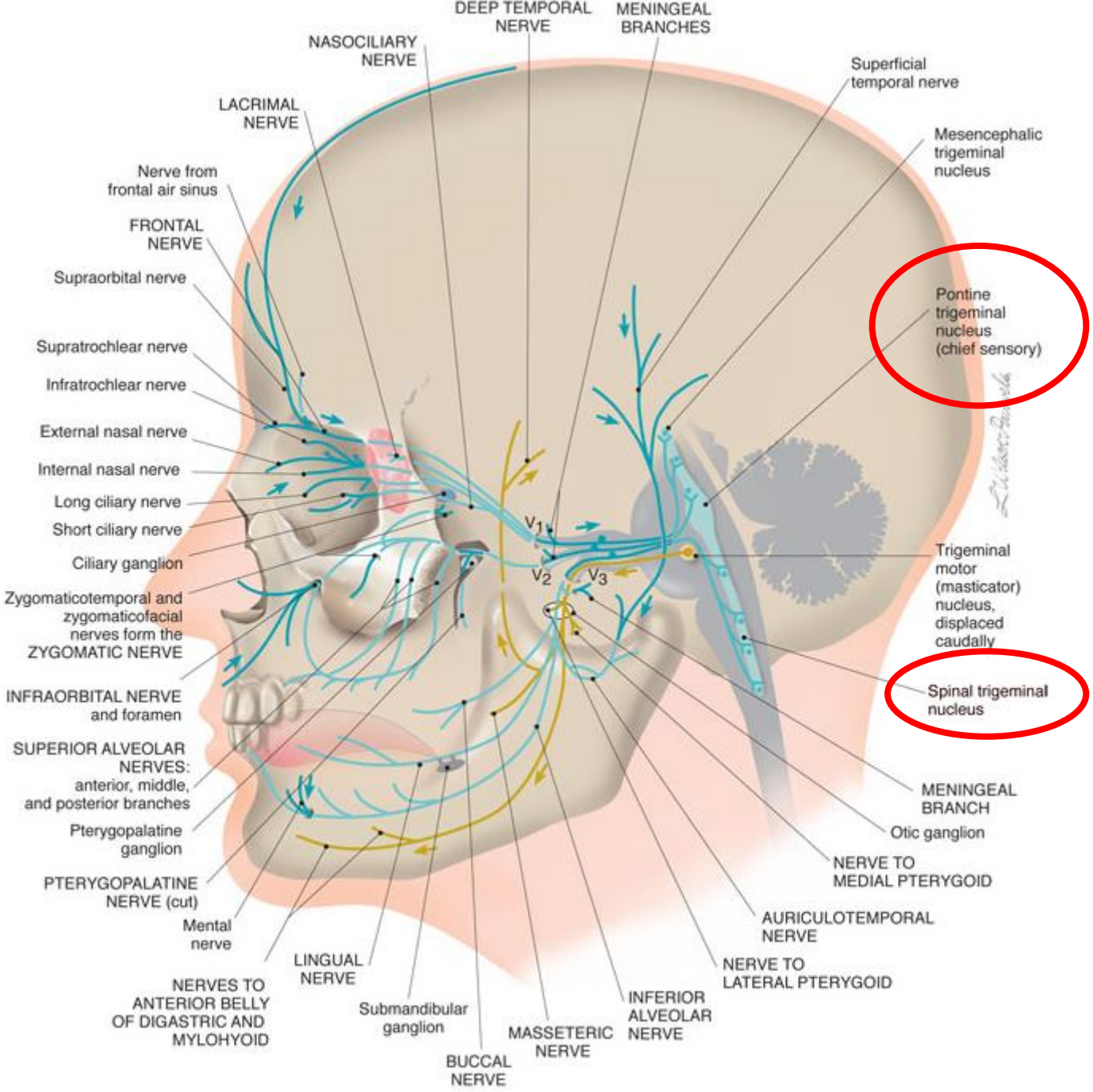
Ascending pain pathway = red;

Modulatory descending tracts = green.

Afferent nociceptive input enters the spinal cord via the Dorsal Root Ganglia.

Secondary order projection neurons ascend in the contralateral spinothalamic and spinorecticular tracts that relay the signal to the thalamus and then cortical centers.

Descending pathways projecting from the periaqueductal gray (PAG) in the midbrain and the rostral ventromedial medulla (RVM) to the dorsal horn and modulate pain transmission.


DEEP TEMPORAL NERVE
MENINGEAL BRANCHES
NASOCILIARY NERVE
Superficial temporal nerve
LACRIMAL NERVE
Mesencephalic trigeminal nucleus
Nerve from frontal air sinus
FRONTAL NERVE
Supraorbital nerve
Pontine trigeminal nucleus (chief sensory)
Supratrochlear nerve
Infratrochlear nerve
External nasal nerve
Internal nasal nerve
Long ciliary nerve
Short ciliary nerve
Ciliary ganglion
V1
V2
V3
Trigeminal motor (masticator) nucleus, displaced caudally
Zygomaticotemporal and zygomaticofacial nerves form the ZYGOMATIC NERVE
Spinal trigeminal nucleus
INFRAORBITAL NERVE and foramen
SUPERIOR ALVEOLAR NERVES: anterior, middle, and posterior branches
MENINGEAL BRANCH
Pterygopalatine ganglion
Otic ganglion
NERVE TO MEDIAL PTERYGOID
PTERYGOPALATINE NERVE (cut)
AURICULOTEMPORAL NERVE
Mental nerve
NERVE TO LATERAL PTERYGOID
LINGUAL NERVE
NERVES TO ANTERIOR BELLY OF DIGASTRIC AND MYLOHYOID
Submandibular ganglion
INFERIOR ALVEOLAR NERVE
MASSETERIC NERVE
BUCCAL NERVE

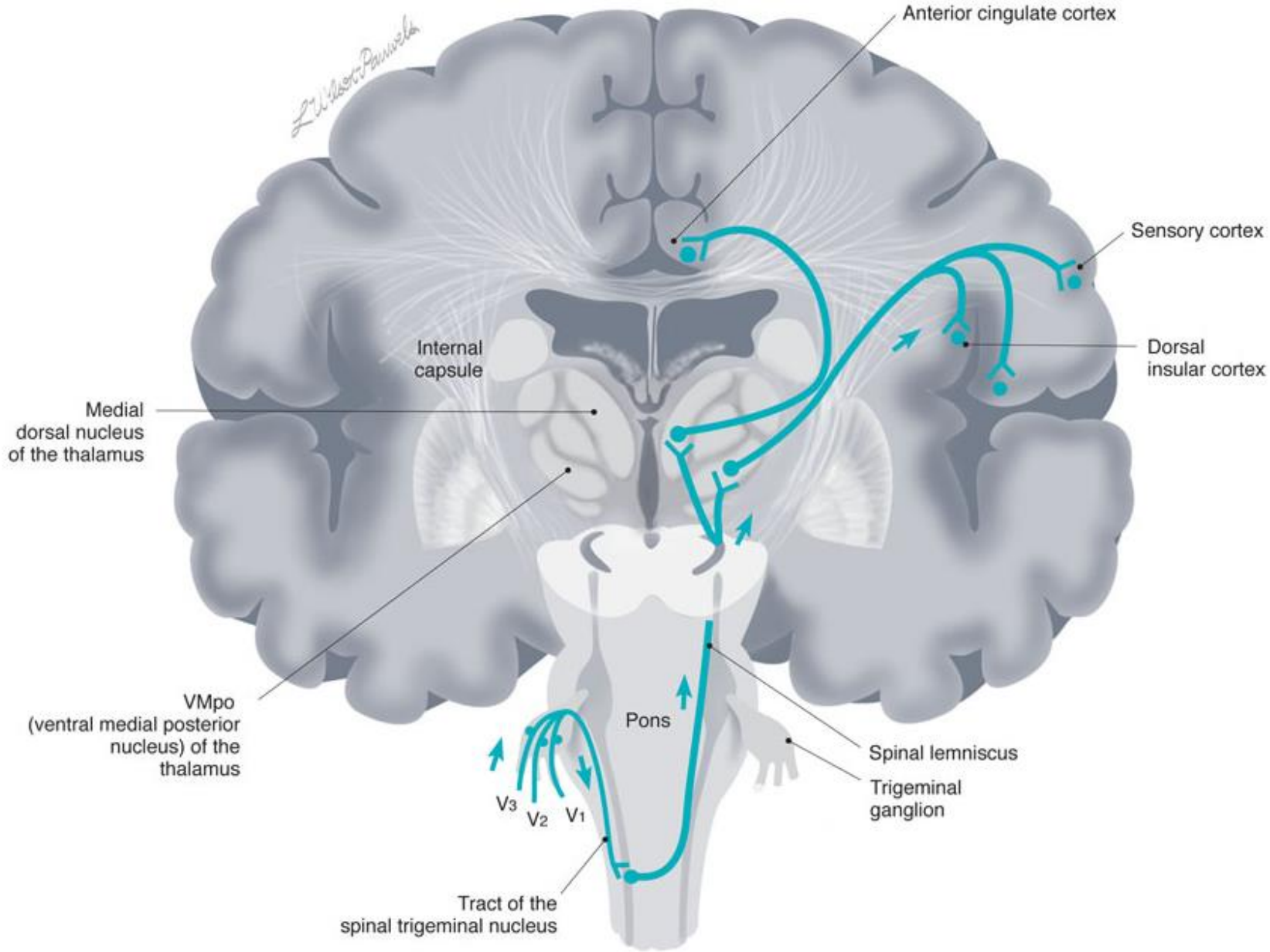
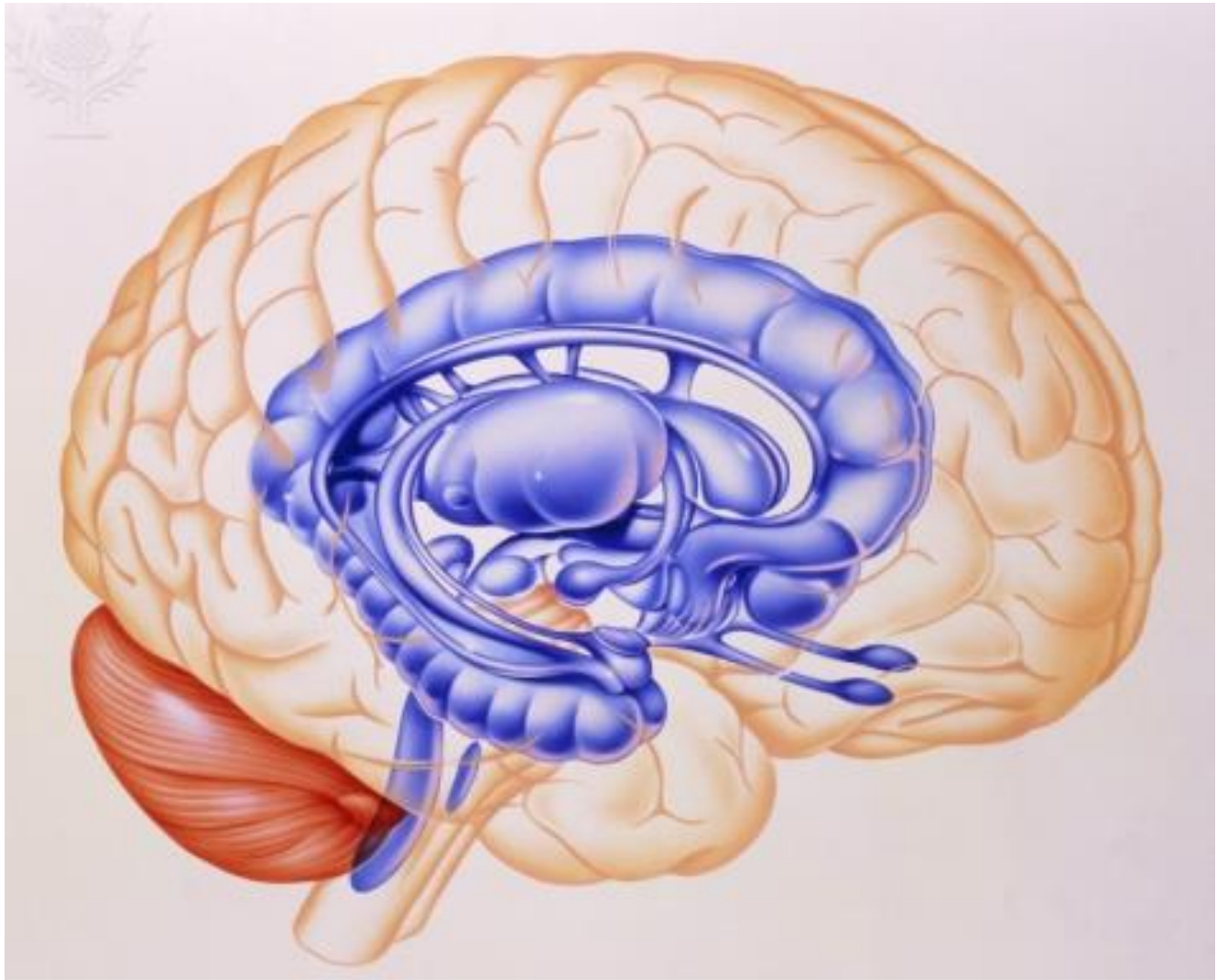


Figure V–13 Pain and temperature pathway from the head (pathways after Dostrovsky and Craig 2006).

Limbic system which regulates emotions has a strong influence on the filtering of incoming pain signals. Depression is associated with increase perception of pain. This factor is clearly recognized but is NOT covered in this lecture.



Effects of sleep on perception of pain

Randomized Controlled Trial > Sleep. 2007 Sep;30(9):1145-52. doi: 10.1093/sleep/30.9.1145.

Elevated inflammatory markers in response to prolonged sleep restriction are associated with increased pain experience in healthy volunteers

Monika Haack [1], Elsa Sanchez, Janet M Mullington

Affiliations + expand

PMID: 17910386 PMCID: PMC1978405 DOI: 10.1093/sleep/30.9.1145

Pain and Sleep

- Elevated inflammatory markers in response to prolonged sleep restriction are associated with increased pain experience in healthy volunteers.
  - Tissue necrosis factor
  - Interluken-6
  - C-Reactive protein
  - Prostaglandins

Central Sensitization: A Generator of Pain Hypersensitivity by Central Neural Plasticity

Alban Latremoliere and Clifford J. Woolf

The publisher's final edited version of this article is available at J Pain

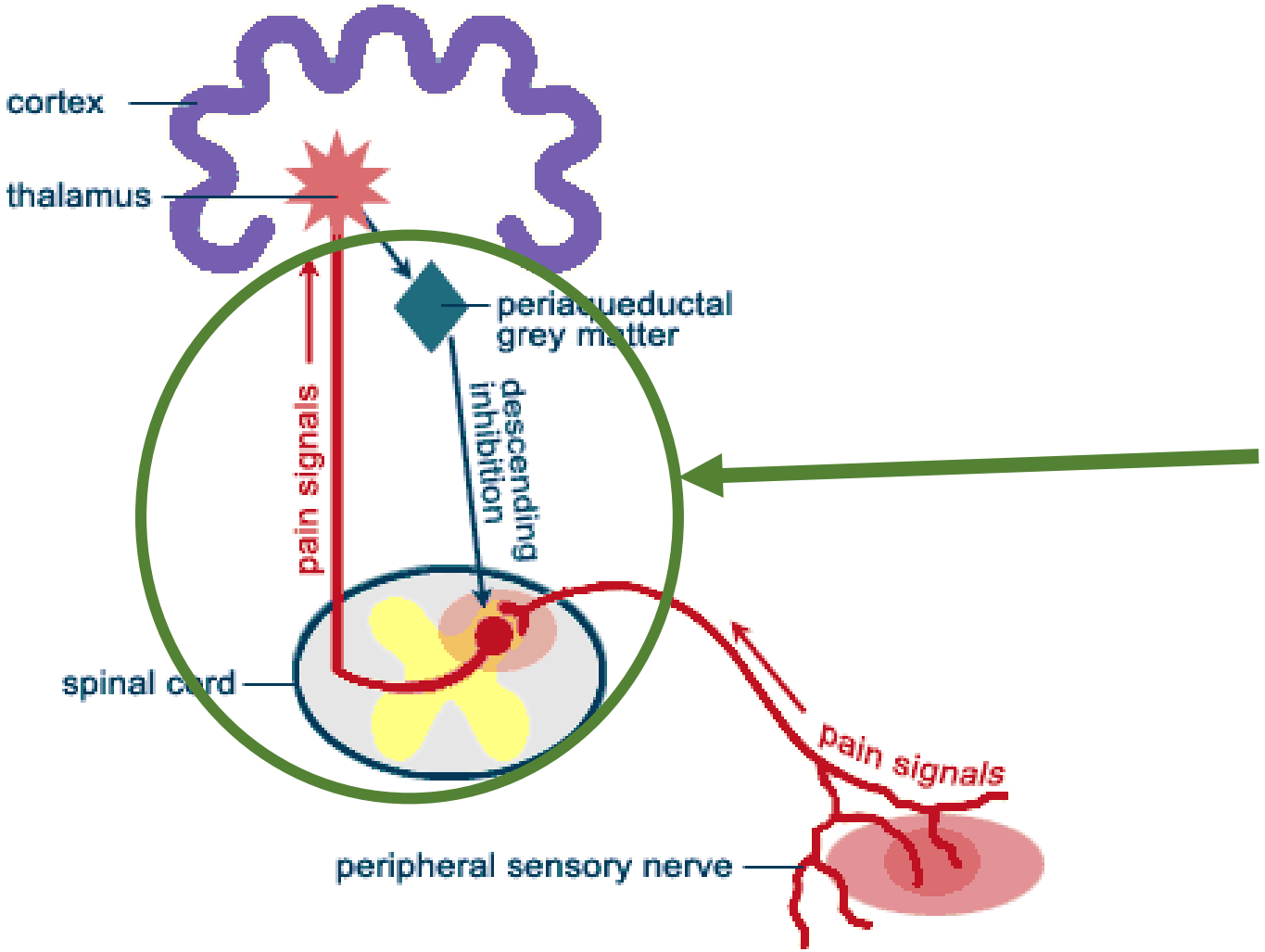
See commentary "Synaptic Plasticity and Central Sensitization: Author Reply" in *J Pain*, volume 11 on page 801.

Abstract

Go to: ▸

Central sensitization represents an enhancement in the function of neurons and circuits in nociceptive pathways caused by increases in membrane excitability and synaptic efficacy as well as to reduced inhibition and is a manifestation of the remarkable plasticity of the somatosensory nervous system in response to activity, inflammation, and neural injury. The net effect of central sensitization is to recruit previously subthreshold synaptic inputs to nociceptive neurons, generating an increased or augmented action potential output: a state of facilitation, potentiation, augmentation, or amplification. Central sensitization is responsible for many of the temporal, spatial, and threshold changes in pain sensibility in acute and chronic clinical pain settings and exemplifies the fundamental contribution of the central nervous system to the generation of pain hypersensitivity. Because central sensitization results from changes in the properties of neurons in the central nervous system, the pain is no longer coupled, as acute nociceptive pain is, to the presence, intensity, or duration of noxious peripheral stimuli. Instead, central sensitization produces pain hypersensitivity by changing the sensory response elicited by normal inputs, including those that usually evoke innocuous sensations.

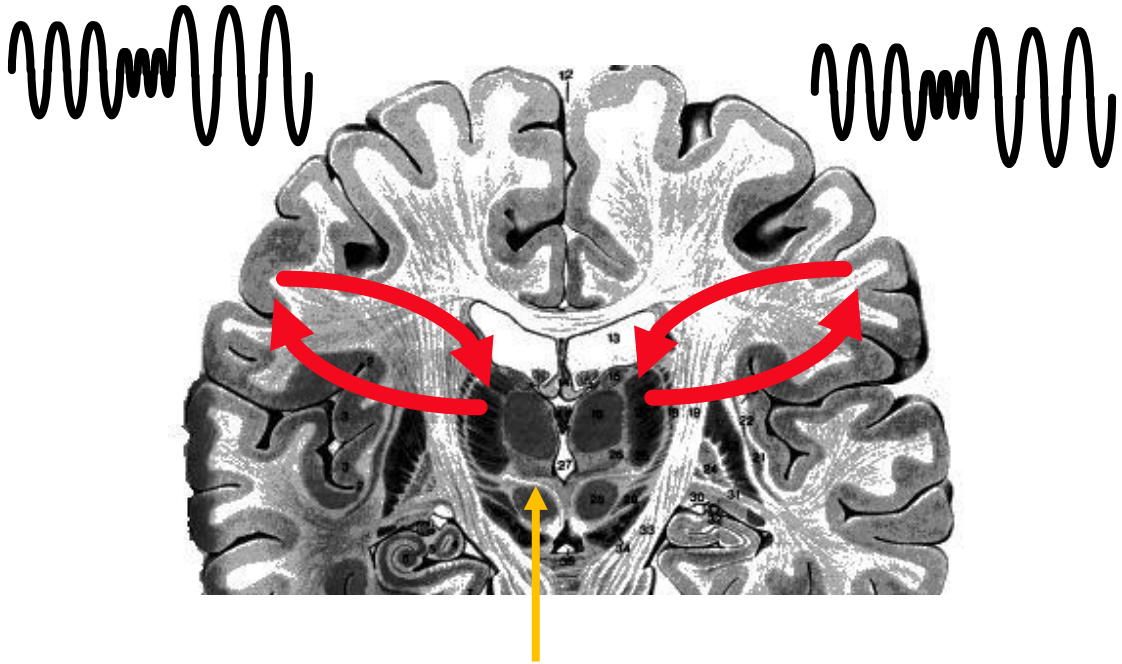
Simplified depiction of ascending and descending pain signaling pathways.



With Central Sensitization there is a change in the balance between the descending inhibition and ascending stimulation, resulting in less inhibition and increased pain from the same degree of stimulation prior to the Central Sensitization.

Non-REM Sleep

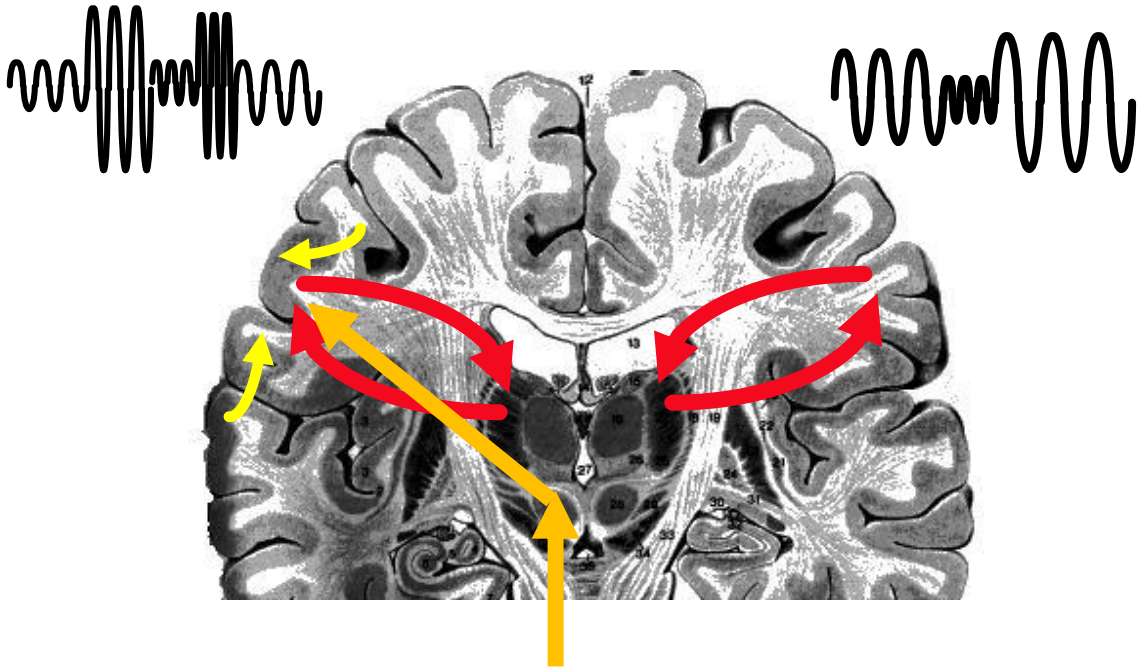
Sensory signals from the body typically are blocked during sleep and to not reach the cortex.



Sensory input from the body that passes through the descending inhibition is blocked at the thalamic level until a threshold is reached.

Non-REM Sleep

When the sensory signals from the body reach a certain threshold they breakthrough the thalamic inhibition and reach the cortex, causing arousals.



Sensory input from the body that passes through the descending inhibition is blocked at the thalamic level until a threshold is reached.

Stages of Sleep

N Sages – Somatic Restoration
Divided into N1, N2 and N3

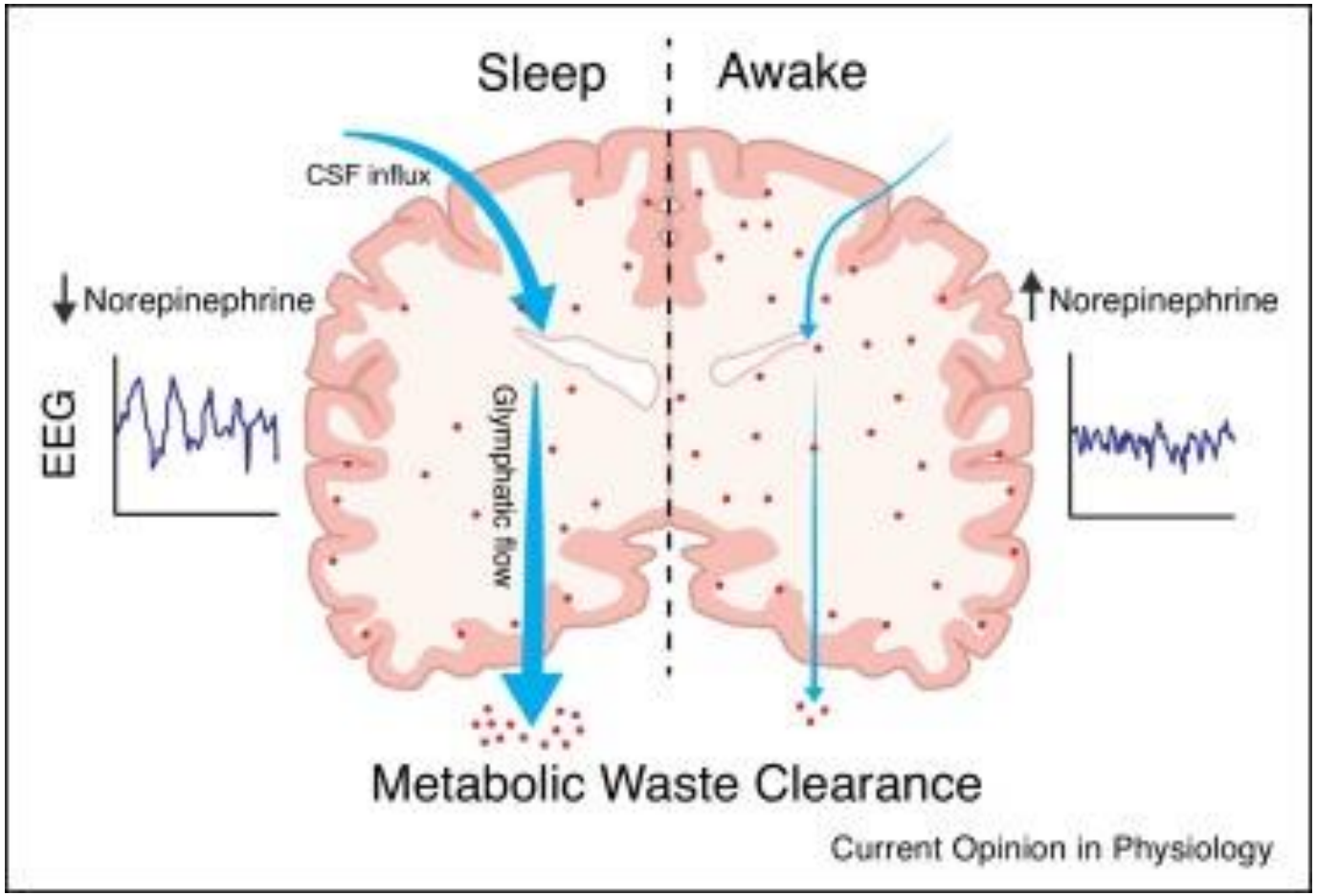
N3 is the stage in which there is the highest level of Growth Hormone release

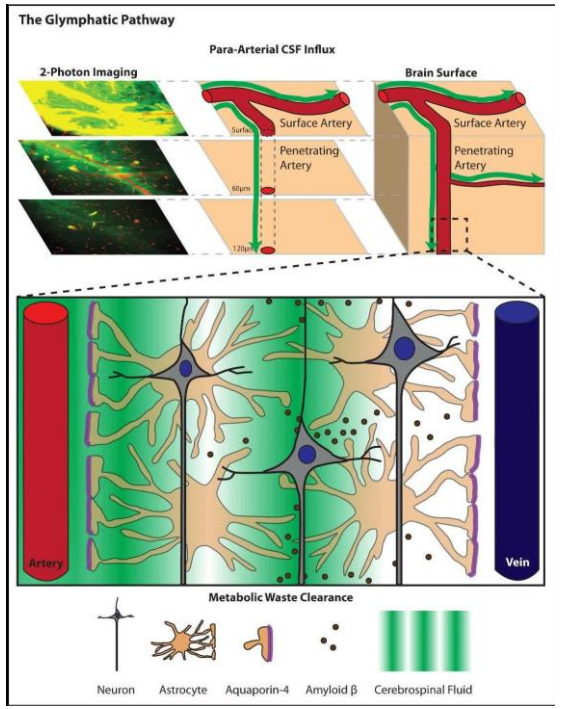
Pain threshold is thought to be influenced by N3 Sleep.

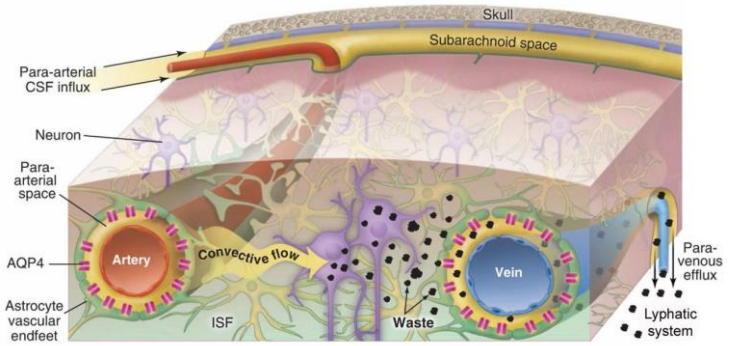
R Stage – (REM) – Limbic Restoration ---
Consolidation of Short Term Memory into Long Term Memory

Active (vivid) Dreaming, Rapid Eye Movements
Muscle Atonia

The Glymphatic System (Lymphatics of the brain) removes metabolic waist products such as amyloid proteins.
Glymphatic flow is greatest during Slow Wave Sleep







Clinical Trial > J Rheumatol. 1999 Jul;26(7):1586-92.

Effects of selective slow wave sleep disruption on musculoskeletal pain and fatigue in middle aged women

M J Lentz [1], C A Landis, J Rothermel, J L Shaver

Affiliations + expand

PMID: 10405949

Abstract

Objective: To determine whether disrupted slow wave sleep (SWS) would evoke musculoskeletal pain, fatigue, and an alpha electroencephalograph (EEG) sleep pattern. We selectively deprived 12 healthy, middle aged, sedentary women without muscle discomfort of SWS for 3 consecutive nights. Effects were assessed for the following measures: polysomnographic sleep, musculoskeletal tender point pain threshold, skinfold tenderness, reactive hyperemia (inflammatory flare response), somatic symptoms, and mood state.

Methods: Sleep was recorded and scored using standard methods. On selective SWS deprivation (SWSD) nights, when delta waves (indicative of SWS) were detected on EEG, a computer generated tone (maximum 85 decibels) was delivered until delta waves disappeared. Musculoskeletal tender points were measured by dolorimetry; skinfold tenderness was assessed by skin roll procedure; and reactive hyperemia was assessed with a cotton swab test. Subjects completed questionnaires on bodily feelings, symptoms, and mood.

Results: On each SWSD night, SWS was decreased significantly with minimal alterations in total sleep time, sleep efficiency, and other sleep stages. Subjects showed a 24% decrease in musculoskeletal pain threshold after the third SWSD night. They also reported increased discomfort, tiredness, fatigue, and reduced vigor. The flare response (area of vasodilatation) in skin was greater than baseline after the first, and again, after the third SWSD night. However, the automated program for SWSD did not evoke an alpha EEG sleep pattern.

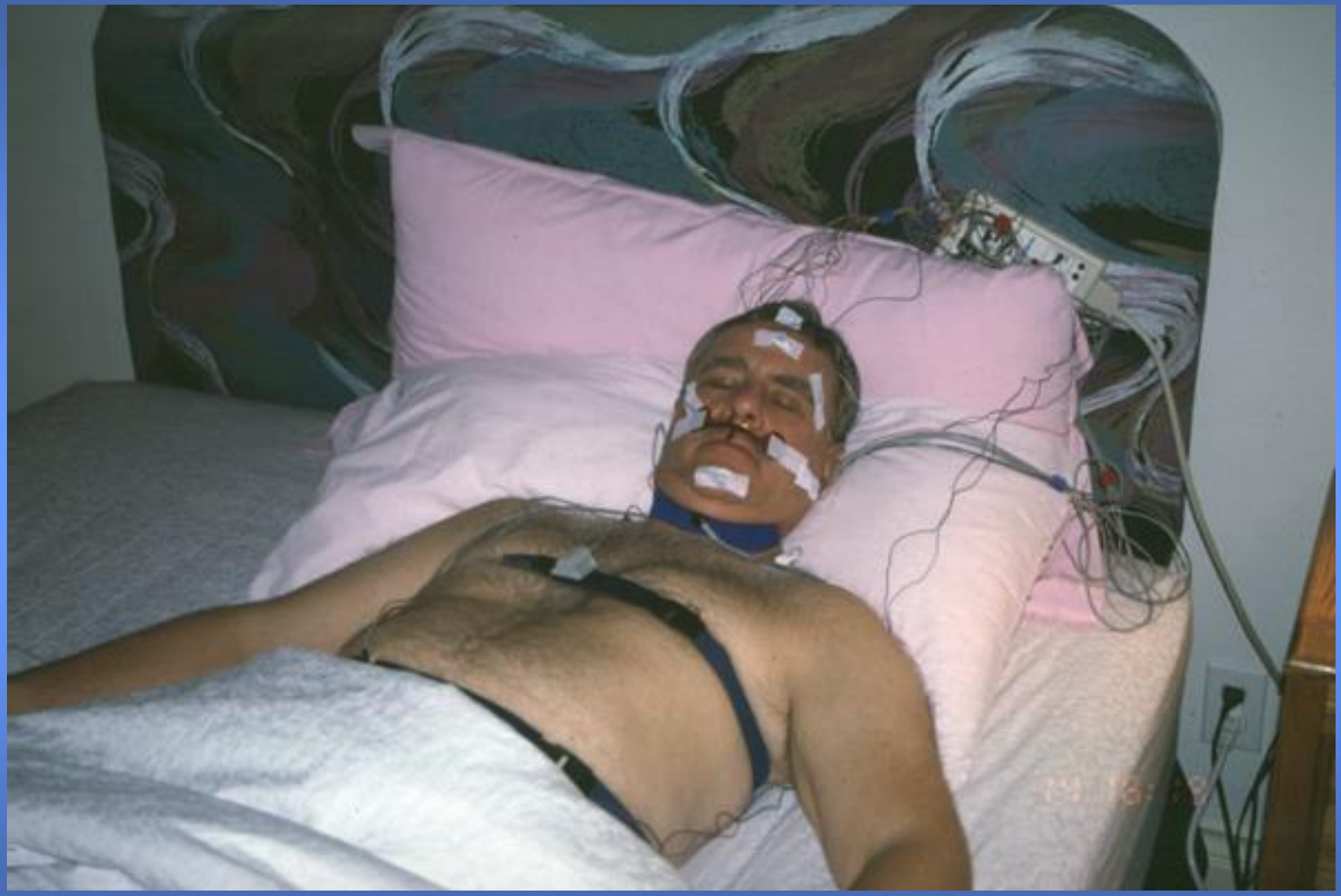
Conclusion: Disrupting SWS, without reducing total sleep or sleep efficiency, for several consecutive nights is associated with decreased pain threshold, increased discomfort, fatigue, and the inflammatory flare response in skin. These results suggest that disrupted sleep is probably an important factor in the pathophysiology of symptoms in fibromyalgia.

Principles of the relationship between pain and sleep

- Pain Threshold is influenced by sleep
- Many studies have demonstrated Slow Wave Sleep quality associated with the pain threshold
- Conditions that are associated with disturbed Slow Wave Sleep lower the pain threshold
- **Fibromyalgia** is know to be associated with Alpha Delta Sleep (disrupted slow wave sleep) and treatment of sleep pathology improves the pain in these patients.

Conditions of poor sleep cause a lower pain threshold and can lead to fibromyalgia.

- Rule out Contributing Factors
  - PLMS/RLS
  - Sleep Apnea
  - Altered Circadian Rhythm Disturbances
  - Poor sleep hygiene
  - Pre-existing Insomnia

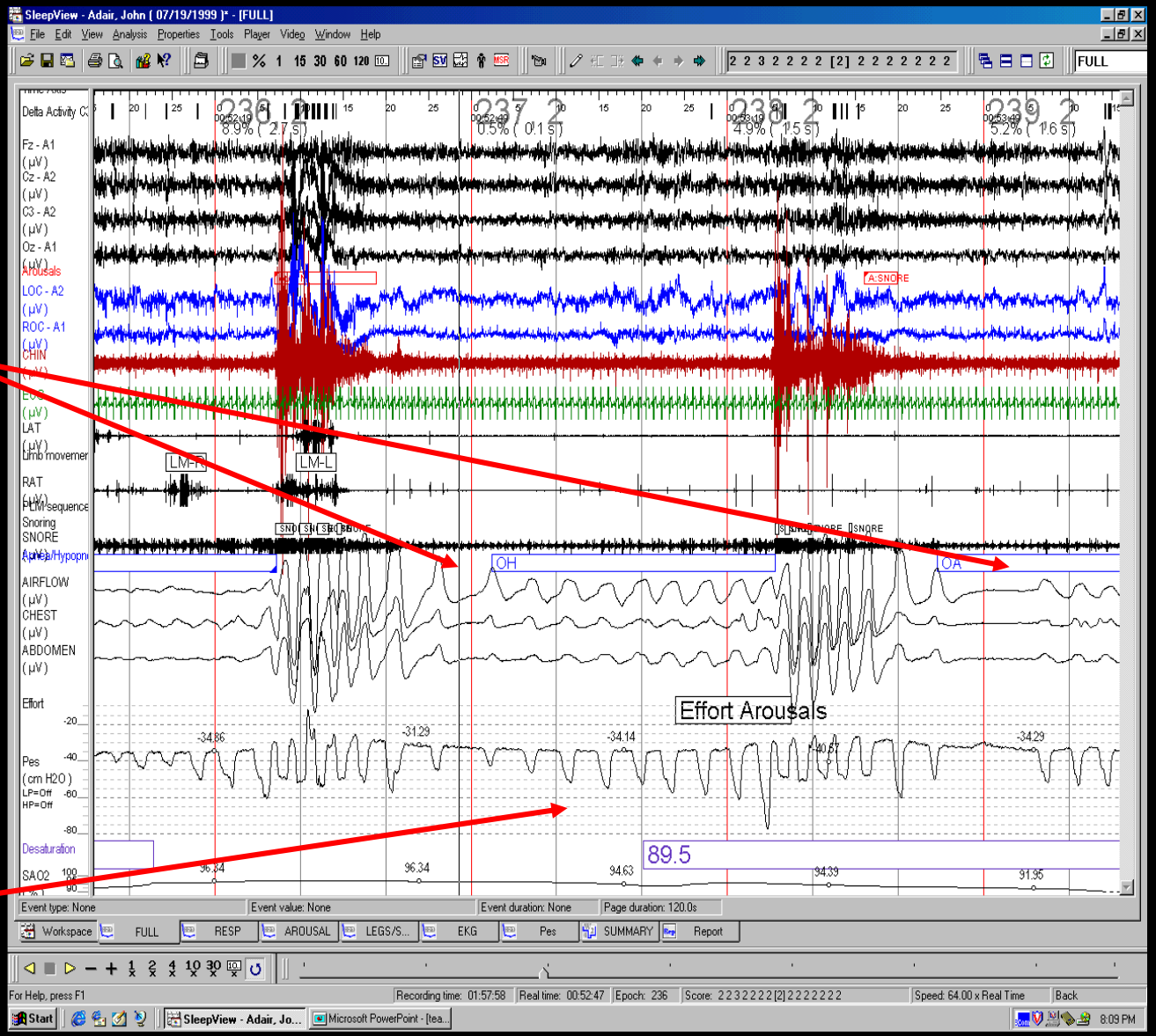


120 seconds of data sample of a sleep study

(This segment demonstrates arousals from obstructive breathing)

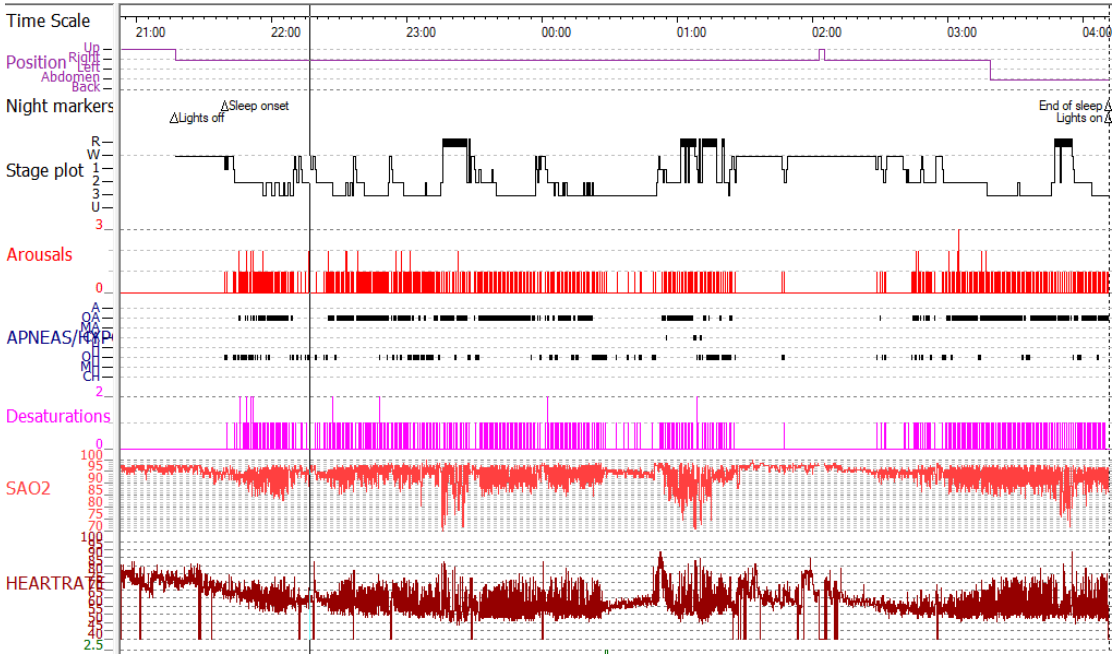
Hypopnea

Pes signal
(Pressure in the Esophagus)

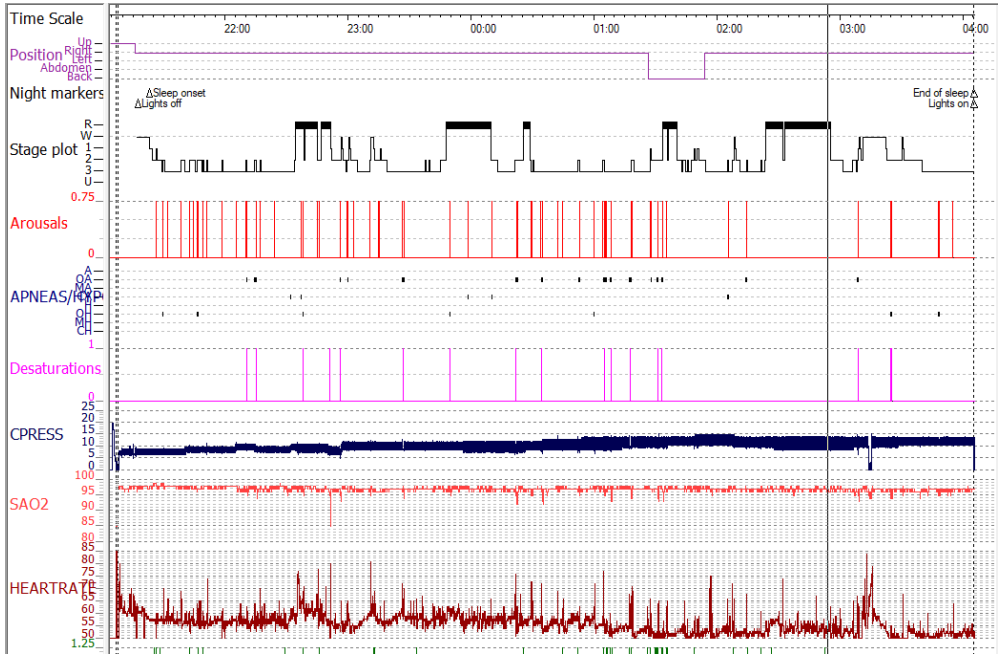


Patients with Fibromyalgia should have a good assessment of their sleep to determine if it is fragmented. If sleep is fragmented, then a cause for the fragmentation should be sought out and treated.

Fragmented Sleep (from OSA)



Improved Sleep (by treating OSA with PAP)



Home Sleep Apnea Testing Devices

(These are NOT equivalent to in-lab sleep studies)

These mainly identify moderate to severe OSA events

Apnea Link

Ring Oximeter with Cardiopulmonary Coupling Analysis (SleepImage)

These can not assess leg movements and also do not assess brain wave data.

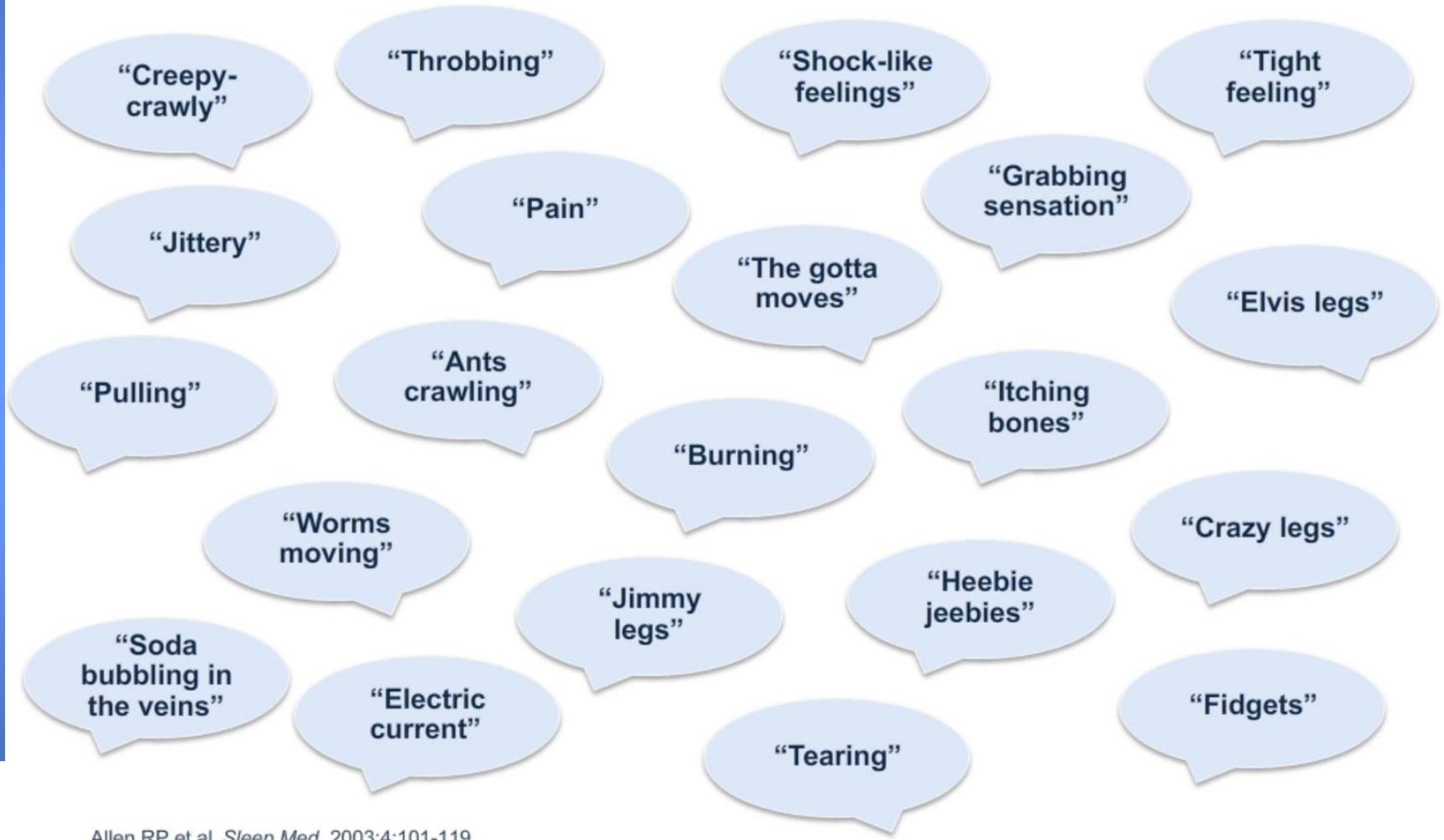
Restless Legs Syndrome
and
Periodic Leg Movements of Sleep (PLMS)

Restless Legs Syndrome (RLS)

- Neurological sensorimotor disorder characterized by[1]:
  - Urge to move usually associated with uncomfortable leg sensations
  - Symptoms that are worsened during periods of rest
  - Symptoms relieved by movement
  - Symptoms tend to be worse at night
- Occurs in >10 million adults[2]
  - More common in women[1]
- Underdiagnosed and misdiagnosed[1,3,4]
- Symptoms can occur during any period of rest[4-8]
- Patients often develop coping techniques to avoid/alleviate symptoms[9]

1. Allen RP et al. *Arch Intern Med.* 2005;165:1286-1292.
2. Hening W et al. *Geriatrics*. 2007;62:26-29.
3. Garcia-Borreguero D et al. *BMC Neurology*. 2011;11:28.
4. Hening W et al. *Sleep Med.* 2004;5:237-246.
5. Kushida CA et al. *Neurology*. 2009;72;439-446.
6. Tzonova D et al. *Sleep Med*. 2012;13:151-155.
7. Tison F et al. *Neurology*. 2005;65:239-246.
8. Allen RP, Earley CJ. *Sleep Med*. 2001;2:239-242.
9. Restless Legs Syndrome Foundation. Suggested coping methods for restless legs syndrome. http://www.rls.org/Document.Doc?id=1919. Accessed April 14, 2012.

Patients Often Have Difficulty Describing RLS Sensations



Allen RP et al. *Sleep Med.* 2003;4:101-119.

Key RLS Diagnostic Criteria

- **Urge to move the legs—usually accompanied or caused by uncomfortable leg sensations**
- **Temporary relief with movement—partial or total relief from discomfort by walking or stretching**
- **Onset or worsening of symptoms at rest or inactivity, such as when lying or sitting**
- **Worsening or onset of symptoms in the evening or at night**

Involuntary Leg Movements That Cause Arousal Associated With Restless Legs Syndrome (RLS)[1,2]

Background Information

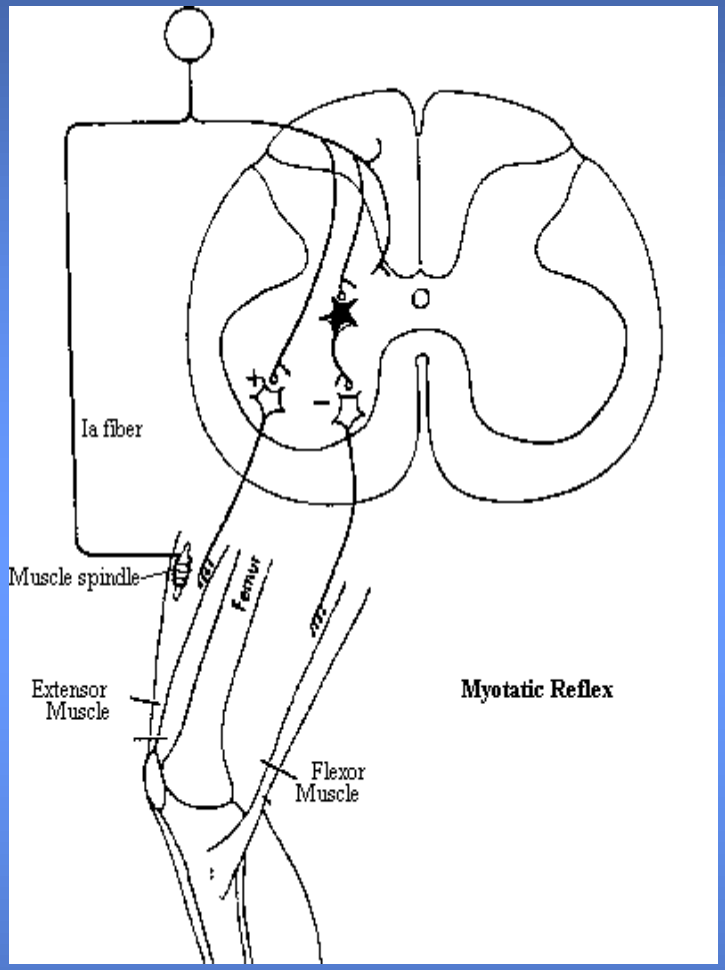
- Involuntary leg movements may cause arousal and further disrupt sleep[3]
- Involuntary leg movements are often a comorbid condition of RLS; however, patients may not be aware they are occurring[4]

1. Data on file, GlaxoSmithKline.
2. Saletu et al. *Neuropsychobiology*. 2000;41:190-199.
3. Montplaisir et al. *Mov Disord*. 997;12:61-65.
4. Allen et al. *Sleep Med*. 2003;4:101-119.

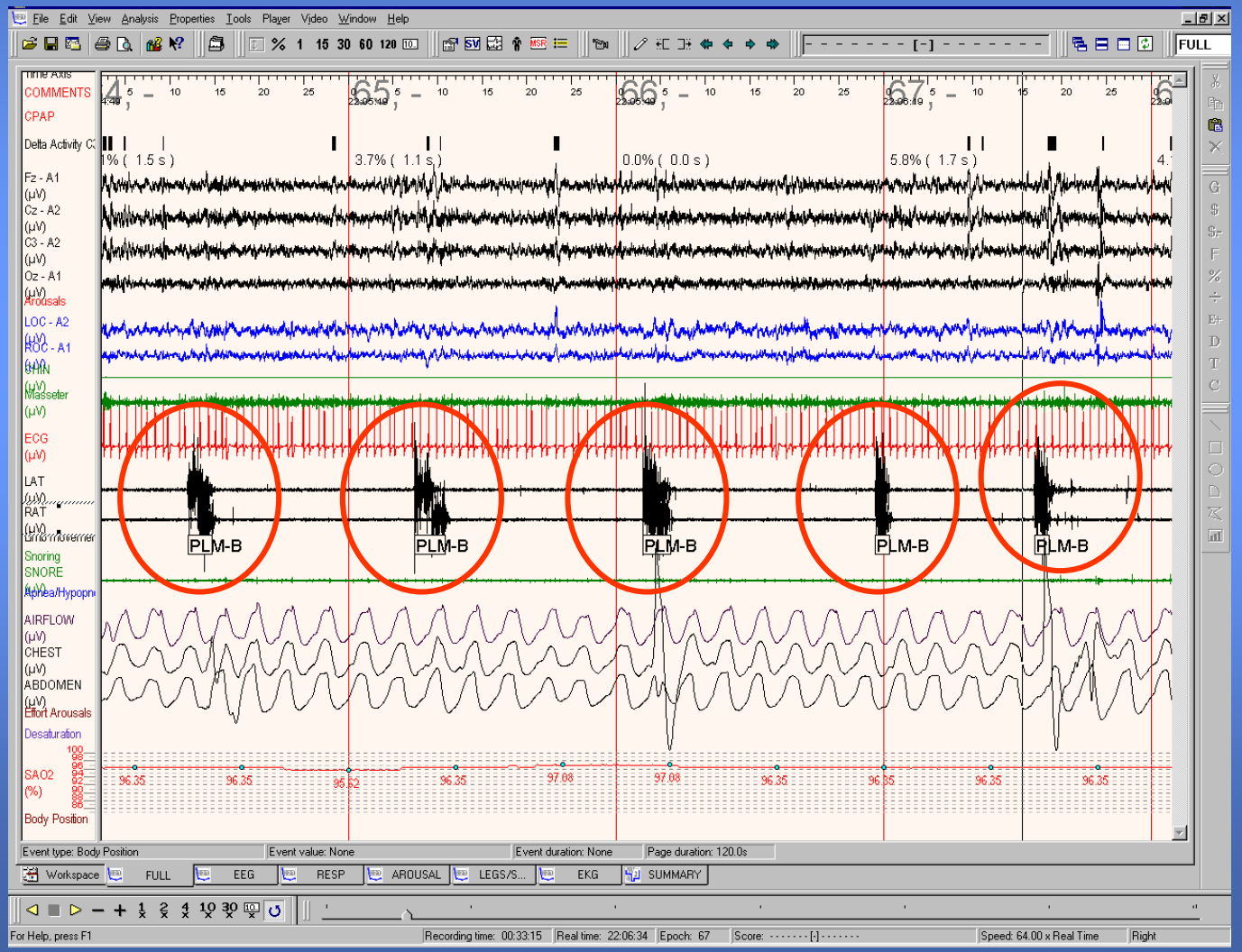
Dopamine is involved in the modulation of the motor reflex arc.

Low levels or decreased dopamine activity may cause a restless sensation in the limbs and may cause periodic leg movements during sleep.

Mild iron deficiency may interrupt dopamine availability and cause the Restless Legs Syndrome symptoms and Periodic Leg Movements of sleep. Ferritin level under 50 low in patients with RLS and worthy of treatment.



Periodic Leg Movements of Sleep (PLMS)
and
Periodic Leg Movement Disorder (PLMD)



Treatments for RLS / PLMS

- Iron supplementation (oral or IV)
- Dopamine agonist medications, such those also used to treat Parkinson’s

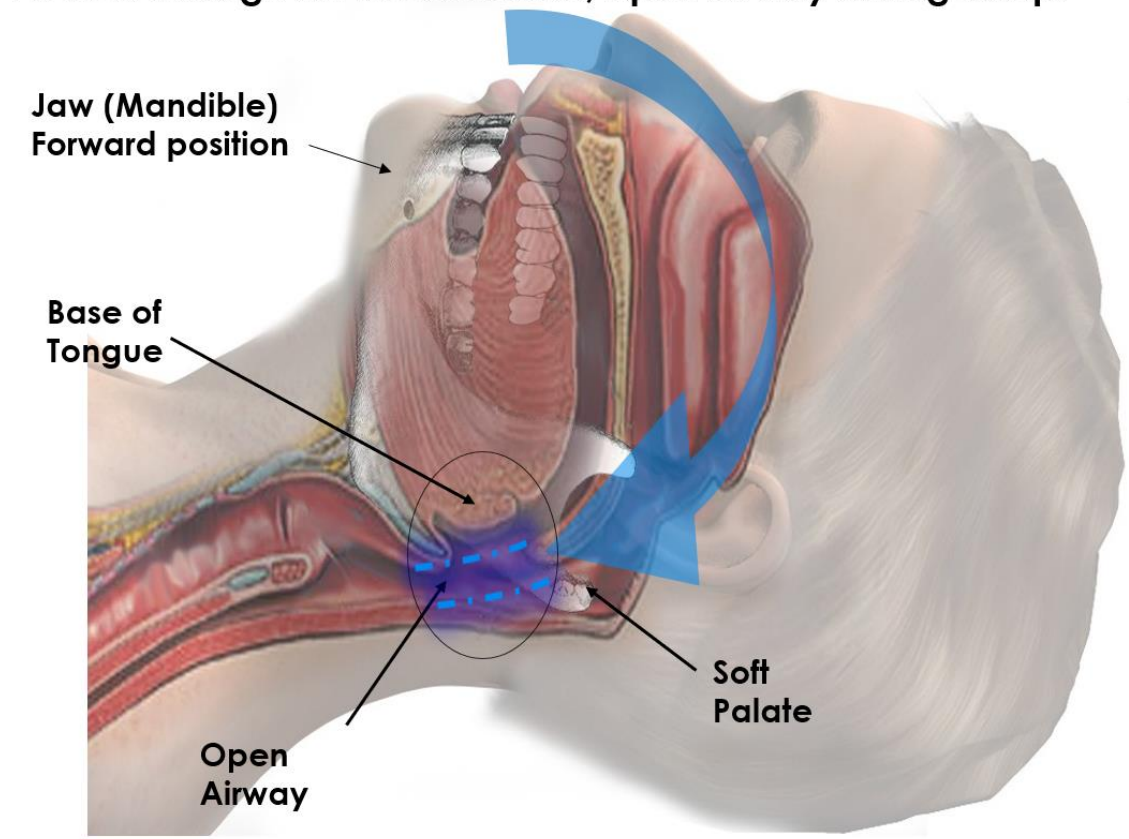
---

Treatments for RLS with little effect on decreasing PLMS

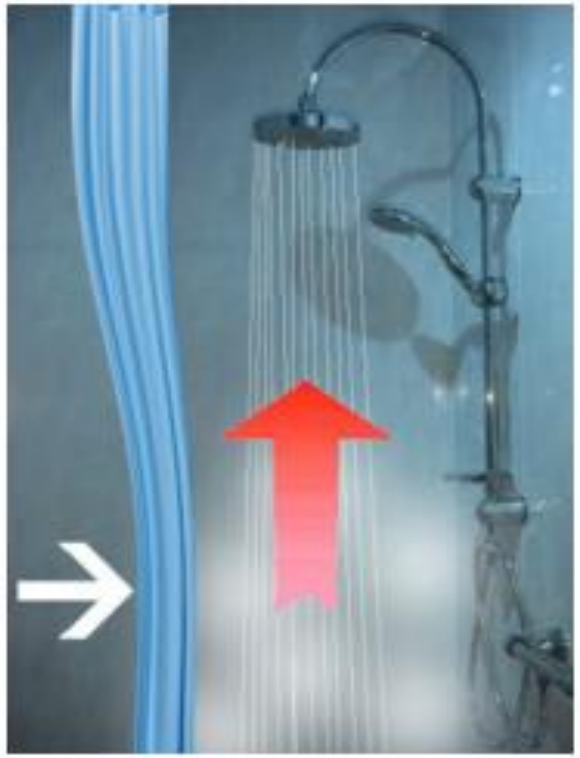
- Alpha 2 delta ligands (gabapentin, pregabalin)
- Opiates
- Benzodiazepines (Clonazepam)

Normal, Open Airway During Sleep

Air flow through an unobstructed, open airway during sleep.

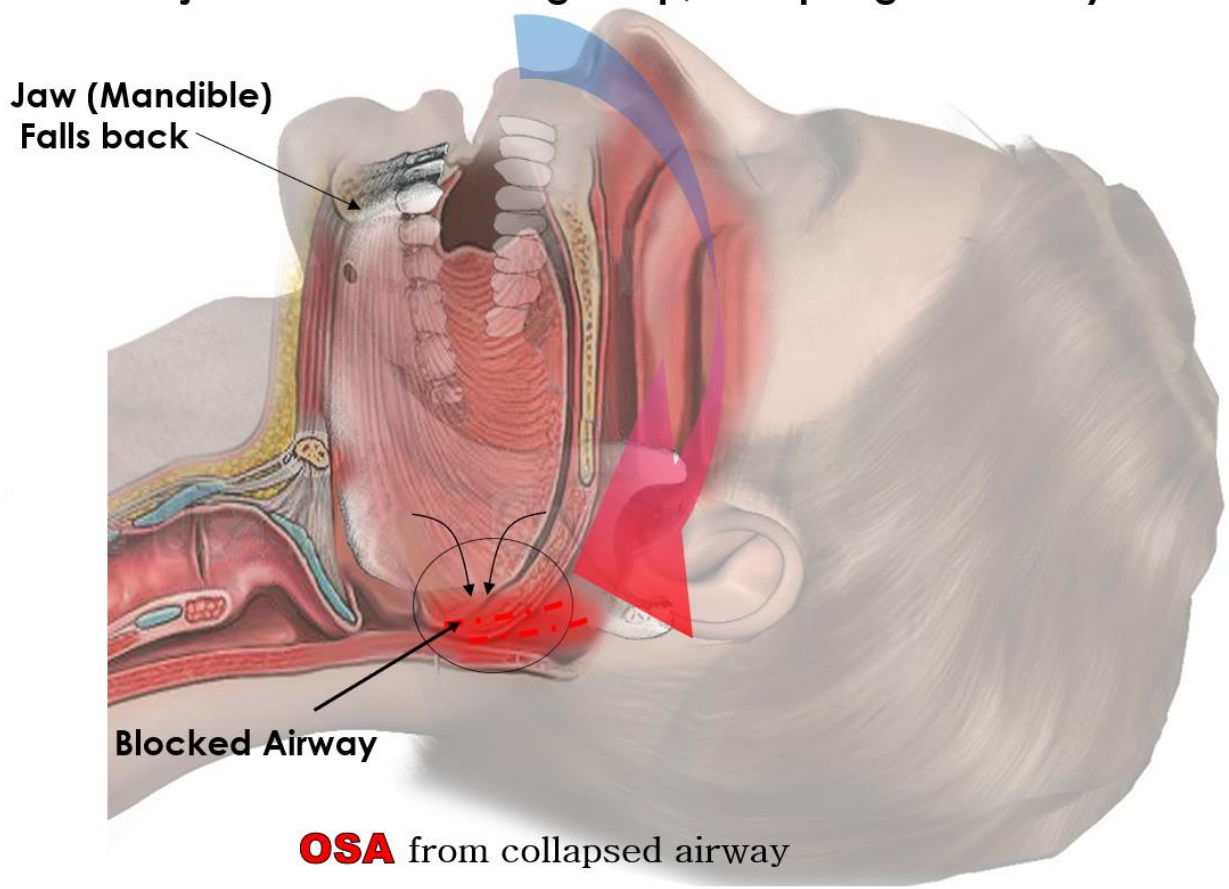


Flow and its relation to negative pressure (vacuum) – *The Bernoulli Effect*



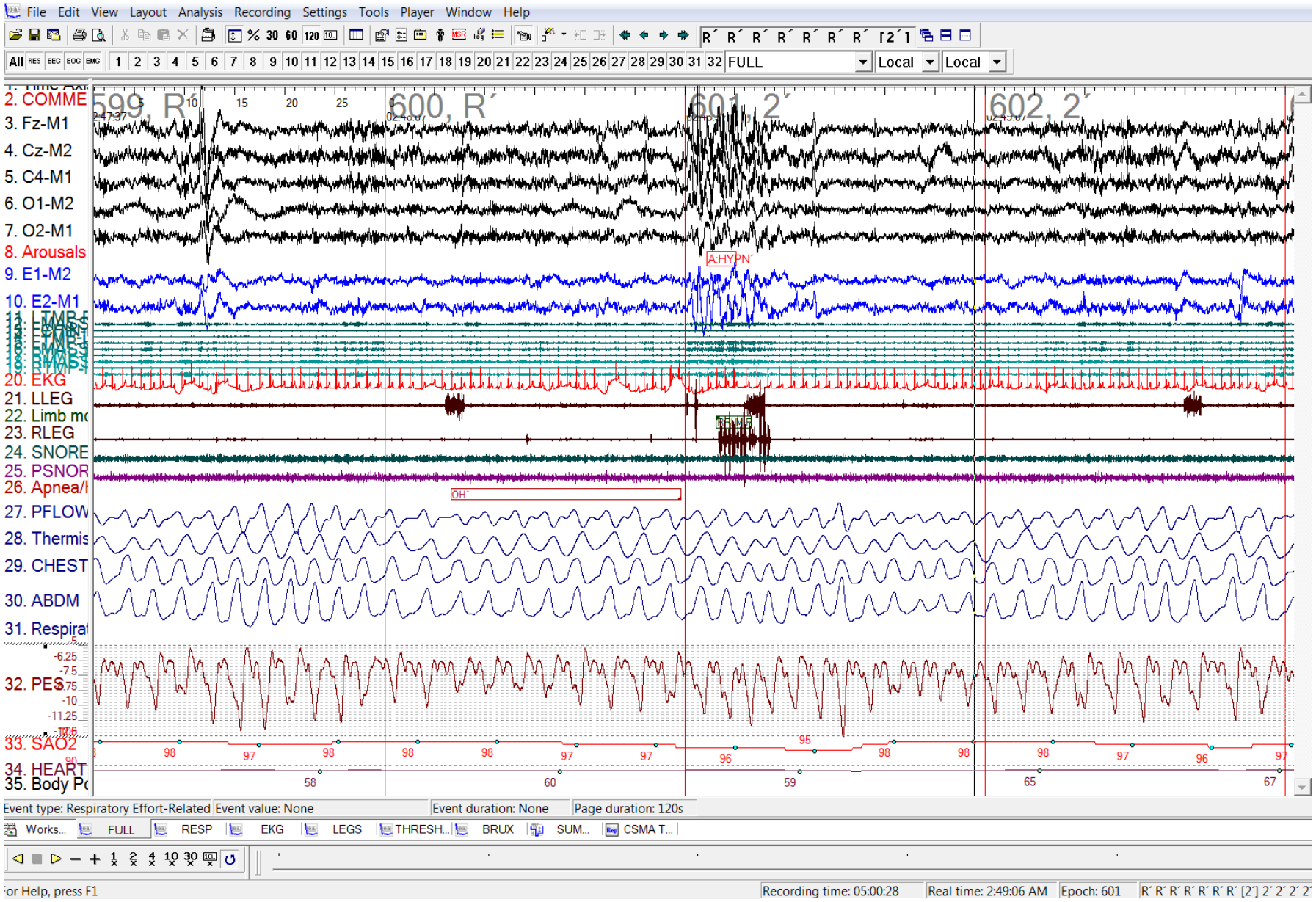
Abnormal, Obstructed Airway

The jaw falls back during sleep, collapsing the airway

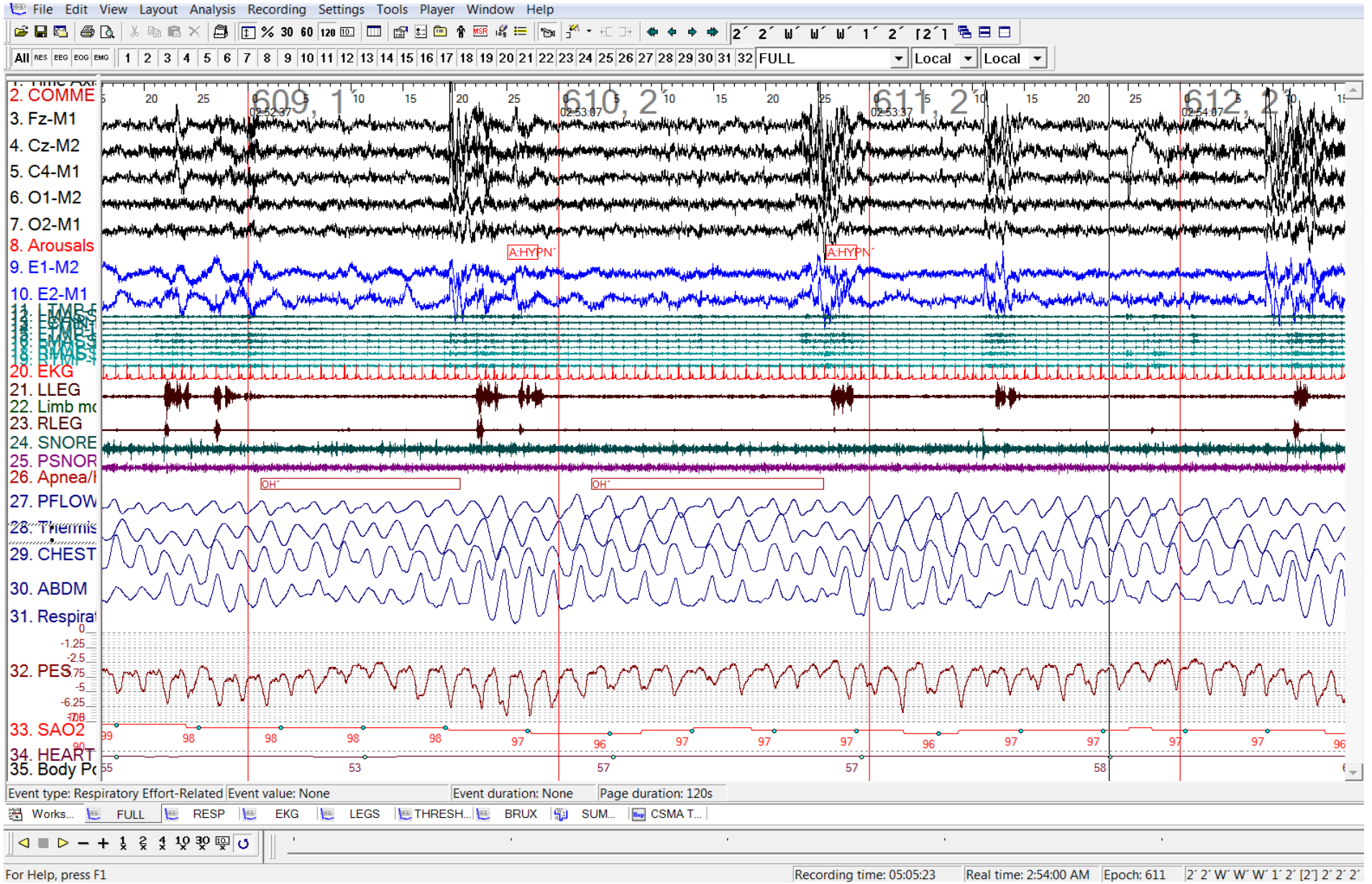


OSA from collapsed airway

NPSG on the same patient – clear hypopneas and PLMS



NPSG on the same patient – clear hypopneas and PLMS

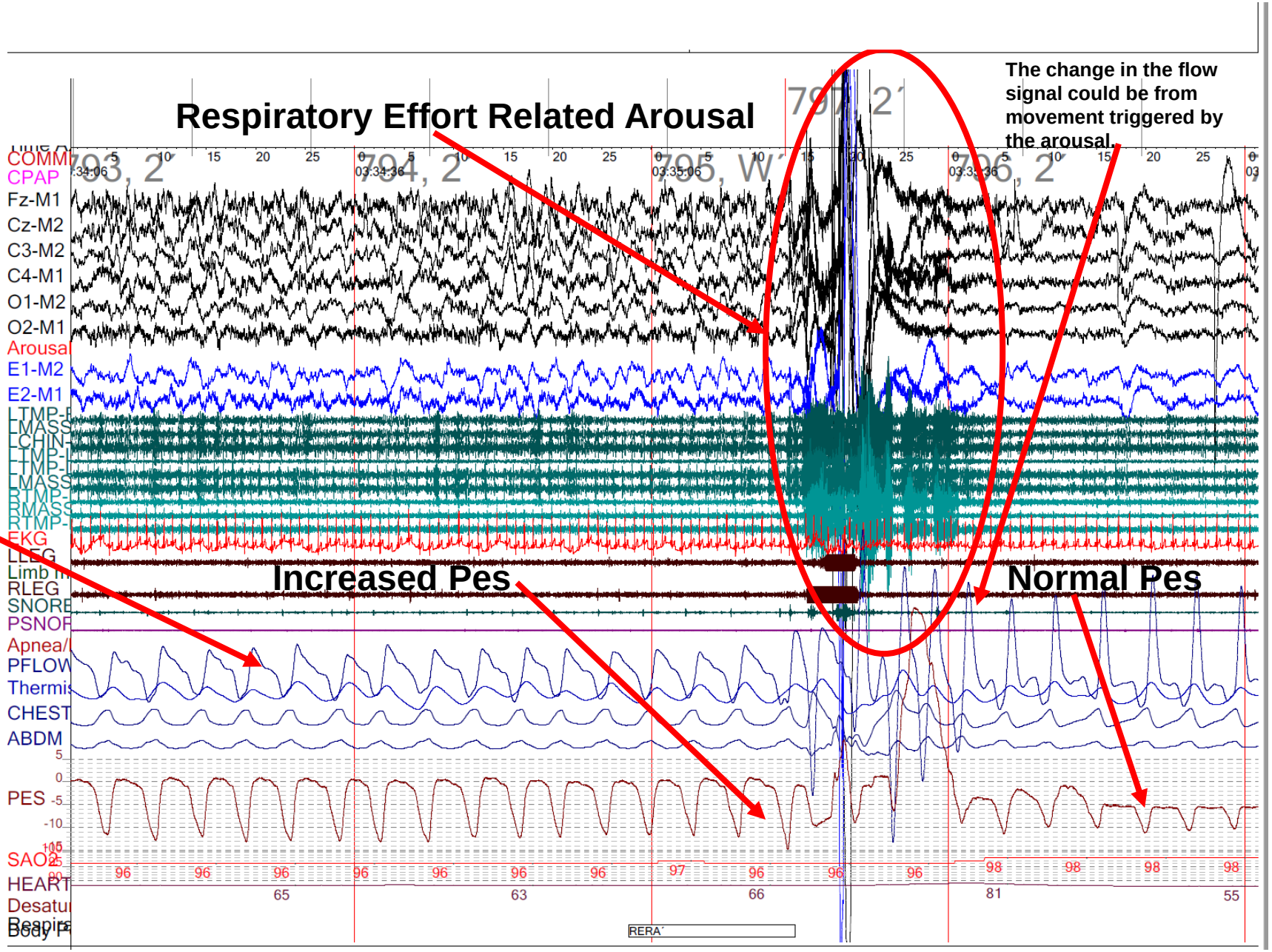


AHI = 6

RDI = 16

SaO2 94%

Nasal Pressure signal does not clearly show flow limitation.



Sleep, 15:S13–S16

From Obstructive Sleep Apnea Syndrome to Upper Airway Resistance Syndrome: Consistency of Daytime Sleepiness

Christian Guilleminault, Riccardo Stoohs, Alex Clerk, Jerald Simmons and Michael Labanowski

Stanford Sleep Research Center, Palo Alto, California, U.S.A.

Summary: Some patients with excessive daytime sleepiness who do not present the features of obstructive sleep apnea syndrome (OSAS) present a sleep fragmentation due to transient alpha EEG arousals lasting between three and 14 seconds. These transient EEG arousals are related to an abnormal amount of breathing effort, indicated by peak inspiratory esophageal pressure (Pes) nadir. In the studied population, these increased efforts were associated with snoring. Usage of nasal CPAP, titrated on Pes nadir values, for several weeks eliminated subjective daytime sleepiness and improved Multiple Sleep Latency Test scores from baseline evaluations. Patients suspected of CNS hypersomnia should be asked about continuous snoring, and their clinical evaluation should include a good review of maxillo-mandibular and upper airway anatomy.

Sleep, 1992; Vol 15, No 6, Supp. pp S13-S16.

Hypopnea Scoring Rules implemented by the AASM in 2013

Two different scoring rules currently exist, causing confusion.

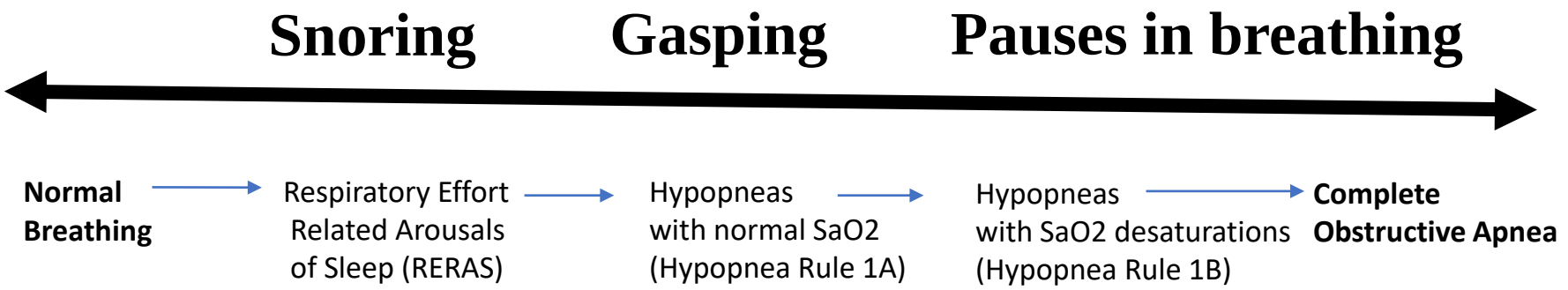
Rule 1A (Recommended rule)
Score a respiratory event as a hypopnea if ALL of the following criteria are met:

a. The peak signal excursions drop by ≥30% of pre-event baseline
b. The duration of the ≥30% drop in signal excursion is ≥10 seconds.
c. There is a ≥3% oxygen desaturation from pre-event baseline or the event is associated with an arousal. Note: No SaO2 desaturation required.

Rule 1B (Acceptable but not the recommended rule) Unfortunately many sleep facilities use this rule. Medicare only recognizes this rule.

Score a respiratory event as a hypopnea if
a. The peak signal excursions drop by ≥30% of pre-event baseline
b. The duration of the ≥30% drop in signal excursion is ≥10 seconds.
c. There is a ≥ 4% oxygen desaturation from pre-event baseline Note: No mention of arousals. Arousals are not part of 1B Hypopneas.

The Full Spectrum of Obstructive Breathing During Sleep.

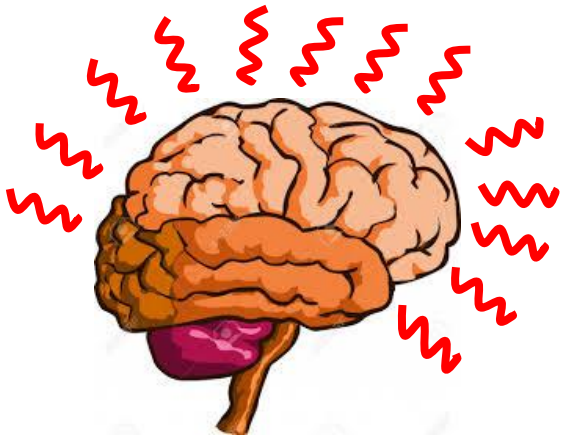


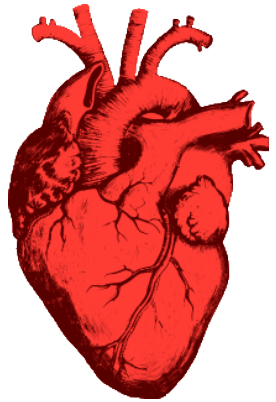
The Full Spectrum of Obstructive Breathing During Sleep.

Snoring **Gasping** **Pauses in breathing**

< - Bruxing / Clenching During Sleep - >

Normal Breathing → Respiratory Effort Related Arousals of Sleep (RERAS) → Hypopneas with normal SaO2 (Hypopnea Rule 1A) → Hypopneas with SaO2 desaturations (Hypopnea Rule 1B) → **Complete Obstructive Apnea**





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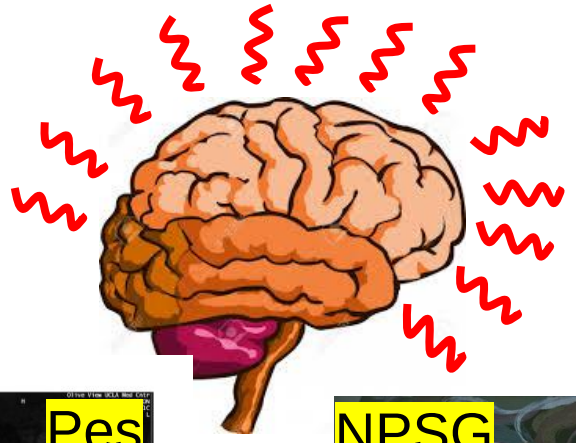
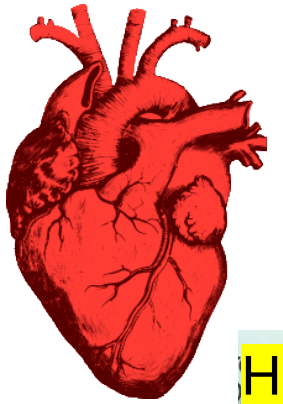
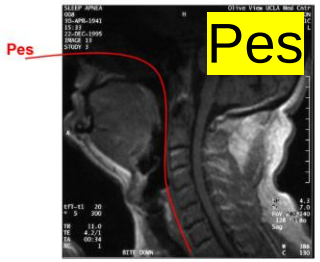
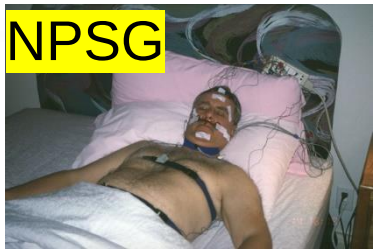








Sequence of evaluation and treatment

1. **Obtain a history / clinical exam**

2. **Perform a sleep study to assess for disturbances of sleep physiology**

3. **Treat obstructive respirations if the are occurring**

4. **Treatment Periodic Leg Movements of Sleep (PLMS) if they are occurring**

5. **If the patient is still having pain from fibromyalgia then consider medications.**

   Monoamine augmentation of descending inhibition:
   - Duloxetine (Cymbalta®)-SNRI (FDA approved for FM
   - Milnacipran (Savella®)-SNRI (FDA approved for FM)

   Pregabalin (Lyrica®) approved for FM
   - Alpha 2-delta subunit voltage gated calcium channel blocker
     - Decreases glutamate release

The Effects of Sodium Oxybate on Clinical Symptoms and Sleep Patterns in Patients with Fibromyalgia

MARTIN B. SCHARF, MARGARET BAUMANN, and DAVID V. BERKOWITZ

ABSTRACT. ***Objective.*** Fibromyalgia (FM) is associated with the sleep phenomenon of alpha intrusion, and with low growth hormone secretion. Sodium oxybate has been shown to increase both slow-wave sleep and growth hormone levels. This double blind, randomized, placebo controlled crossover trial was conducted to evaluate the effects of sodium oxybate on the subjective symptoms of pain, fatigue, and sleep quality and the objective polysomnographic (PSG) sleep variables of alpha intrusion, slow-wave (stage 3/4) sleep, and sleep efficiency in patients with FM.

Methods. Patients received either 6.0 g/day sodium oxybate or placebo for 1 month, with an intervening 2 week washout period. Efficacy measures included PSG evaluations, tender point index (TPI), and subjective measurements from daily diary entries. Safety measures included clinical laboratory values, vital signs, and adverse events.

Results. Twenty-four female patients were included in the study; 18 completed the trial. TPI was decreased from baseline by 8.5, compared with an increase of 0.4 for placebo ($p = 0.0079$). Six of the 7 pain/fatigue scores (overall pain, pain at rest, pain during movement, end of day fatigue, overall fatigue, and morning fatigue) were relieved by 29% to 33% with sodium oxybate, compared with 6% to 10% relief with placebo ($p < 0.005$). Alpha intrusion, sleep latency, and rapid-eye-movement sleep were significantly decreased, while slow-wave (stage 3/4) sleep was significantly increased, compared with placebo ($p < 0.005$). Two of the 5 subjective sleep related variables were significantly different from placebo: morning alertness (improved by 18% with sodium oxybate, compared with 2% for placebo; $p = 0.0033$) and quality of sleep (improved by 33% and 10%, respectively; $p = 0.0003$).

Conclusion. Sodium oxybate effectively reduced the symptoms of pain and fatigue in patients with FM, and dramatically reduced the sleep abnormalities (alpha intrusion and decreased slow-wave sleep) associated with the nonrestorative sleep characteristic of this disorder. (J Rheumatol 2003;30:1070–4)

The Journal of Rheumatology 2003; 30:5

Sodium oxybate: a potential new pharmacological option for the treatment of fibromyalgia syndrome

Ther Adv Musculoskel Dis
(2011) 3(4) 167–178
DOI: 10.1177/1759720X11411599

Todd J. Swick

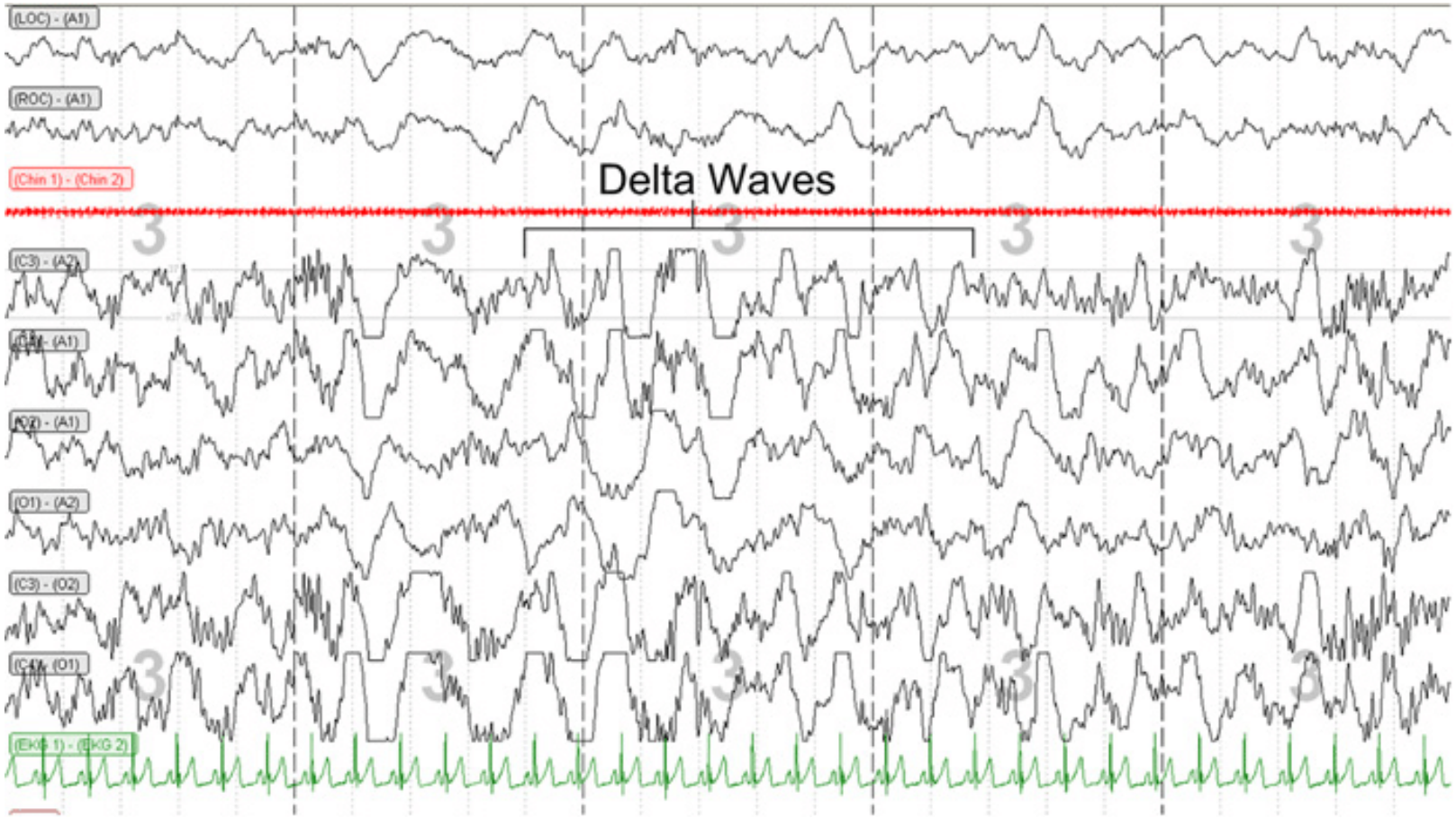
***Abstract*:** Fibromyalgia syndrome (FMS) is a common disorder, characterized by diffuse pain and tenderness, stiffness, fatigue, affective disorders and significant sleep pathology. A new set of diagnostic criteria have been developed which should make it easier for a busy clinician to diagnose the condition. US Food and Drug Administration (FDA) approved medications for the treatment of FMS have, for the most part, been geared to modulate the pain pathways to give the patient some degree of relief. A different kind of pharmacological agent, sodium oxybate (SXB), is described that is currently approved for the treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy. SXB, an endogenous metabolite of the inhibitory neurotransmitter gamma-hydroxybutyrate, is thought to act independently as a neurotransmitter with a presumed ability to modulate numerous other central nervous system neurotransmitters. In addition SXB has been shown to robustly increase slow wave sleep and decrease sleep fragmentation. Several large clinical trials have demonstrated SXB's ability to statistically improve pain, fatigue and a wide array of quality of life measurements of patients with fibromyalgia. SXB is not FDA approved to treat fibromyalgia.

***Keywords*:** fatigue, fibromyalgia, pain, polysomnography, sleep, sleep fragmentation, sodium oxybate

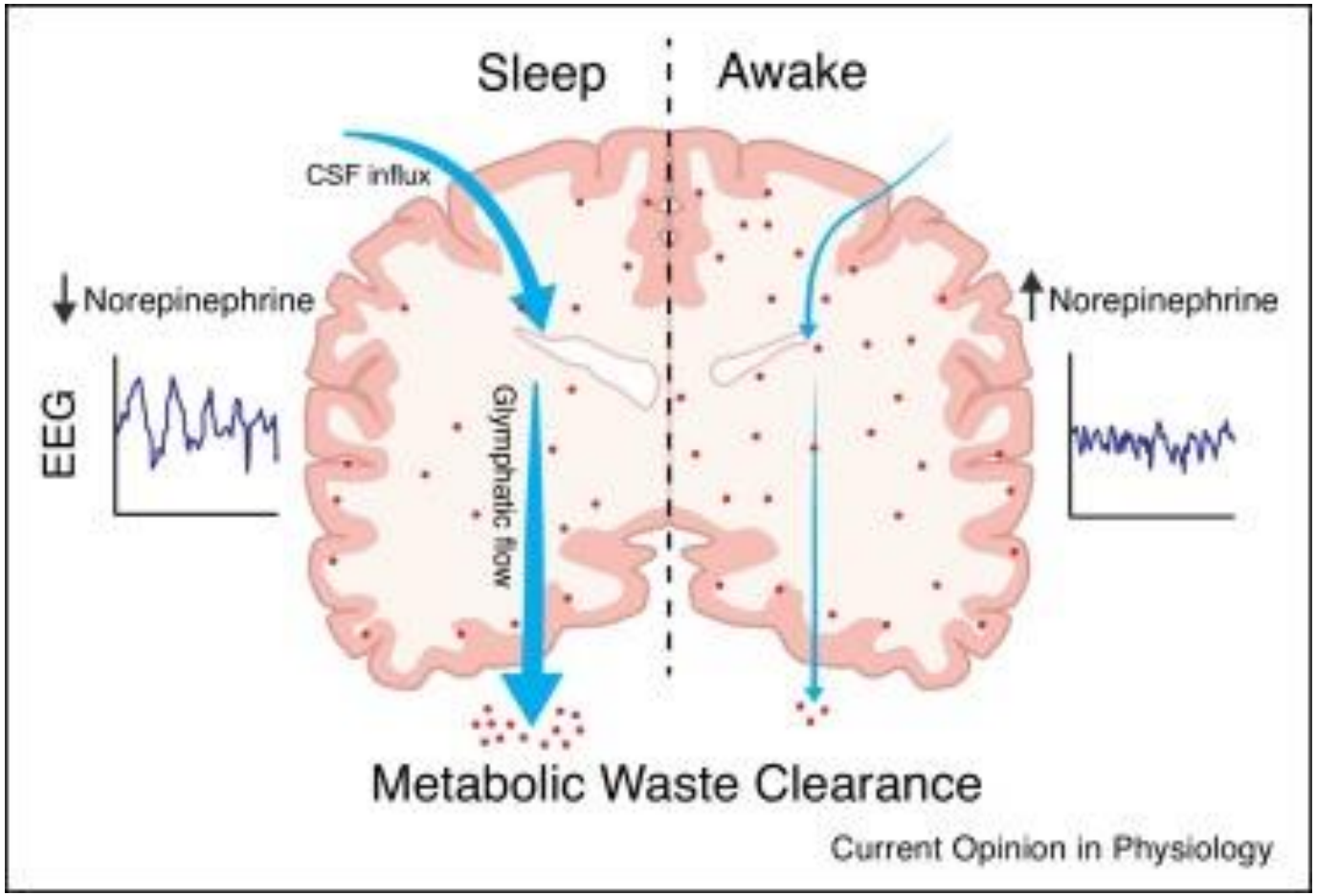
Oxybate and Fibromyalgia

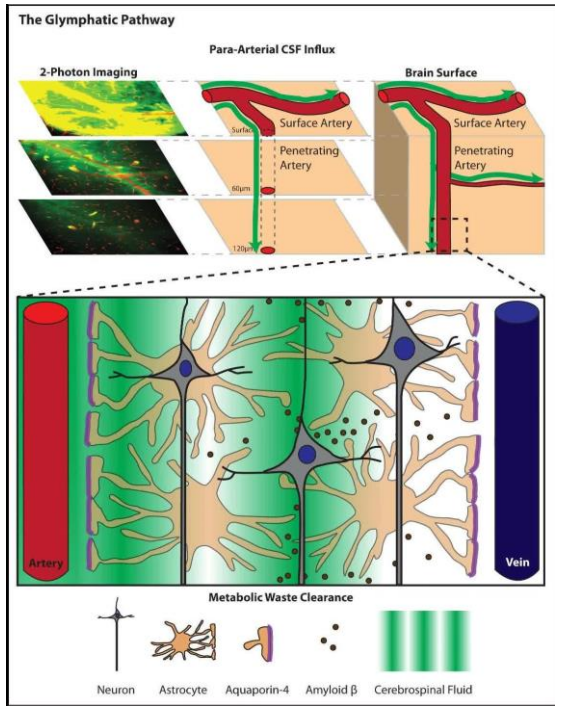
- Oxybate has been show to:
  - Decreases sleep onset latency
  - Decreases sleep fragmentation
  - Increases slow wave sleep (SWS) and increase Growth Hormone
- Two trials demonstrated improvement in pain, fatigue and sleep in Fibromyalgia patients
  - USA-548 patients with FM assigned to 3 groups; 4.5 Gm/Nt, 6.O Gm/Nt and Placebo
    - The active treatment arms demonstrated significantly greater improvement in pain VAS, Fatigue VAS and Jenkins Sleep Scale vs. placebo ($p = <0.001$)
  - International-573 patients with FM assigned to 3 groups; 4.5 Gm/Nt, 6.O Gm/Nt and Placebo
    - Similar results to the USA study.

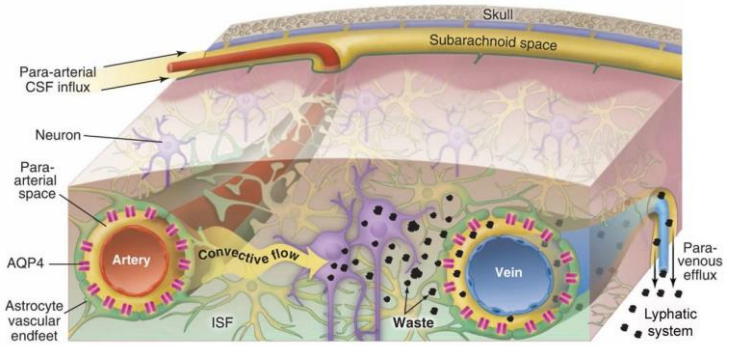
Oxybate increased Slow Wave (Delta) Sleep



The Glymphatic System (Lymphatics of the brain) removes metabolic waist products such as amyloid proteins.
Glymphatic flow is greatest during Slow Wave Sleep







REGULATORY NEWS - AMERICAS AUGUST 20, 2010 / 2:21 PM / UPDATED 13 YEARS AGO

UPDATE 3-US FDA panel rejects Jazz drug for fibromyalgia

By Lisa Richwine

5 MIN READ

* Committee votes 20-2 against recommending approval

* Drug contains “date rape” chemical

* Jazz shares drop sharply after hours (Adds company, panel member comment)

BETHESDA, Md., Aug 20 (Reuters) - A U.S. advisory panel on Friday rejected a Jazz Pharmaceuticals Inc JAZZ.O medicine to treat the pain disorder fibromyalgia amid concerns the product could be misused as a "date-rape" drug.

Sodium oxybate for the treatment of fibromyalgia

Roland Staud [1]

Affiliations + expand

PMID: 21679091 DOI: 10.1517/14656566.2011.589836

Abstract

Introduction: Gamma-hydroxybutyrate (GHB) is a short-chain fatty acid that is synthesized within the CNS, mostly from its parent compound gamma amino butyric acid (GABA). GHB acts as a neuromodulator/neurotransmitter to affect neuronal activity of other neurotransmitters and so, stimulate the release of growth hormone. Its sodium salt (sodium oxybate: SXB) was approved by the Food and Drug Administration (FDA) for the treatment of narcolepsy. SXB has shown to improve disrupted sleep and increase NR3 (slow-wave restorative) sleep in patients with narcolepsy. It is rapidly absorbed and has a plasma half-life of 30 - 60 min, necessitating twice-nightly dosing. Most of the observed effects of SXB result from binding to GABA-B receptors.

Areas covered: Several randomized, controlled trials demonstrated significantly improved fibromyalgia (FM) symptoms with SXB. As seen in narcolepsy trials, SXB improved sleep of FM patients, increased slow-wave sleep duration as well as delta power, and reduced frequent night-time awakenings. Furthermore, FM pain and fatigue was consistently reduced with nightly SXB over time. Commonly reported adverse events included headache, nausea, dizziness and somnolence. Despite its proven efficacy, SXB did not receive FDA approval for the management of FM in 2010, mostly because of concerns about abuse.

Expert opinion: Insomnia, fatigue and pain are important clinical FM symptoms that showed moderate improvements with SXB in several large, well-designed clinical trials. Because of the limited efficacy of currently available FM drugs additional treatment options are needed. In particular, drugs like SXB - which belong to a different drug class than other Food and Drug Administration (FDA)-approved FM medications such as pregabalin, duloxetine and milnacipran - would provide a much-needed addition to presently available treatment options. However, the FDA has set the bar high for future SXB re-submissions, with requirements of superior efficacy and improved risk mitigation strategies. At this time, no future FDA submission of SXB for the fibromyalgia indication is planned.

www.DentalSleepConference.com

www.MedicalSleepConference.com

www.SleepEducation.net

www.CSMA.Clinic – for clinical evaluation and treatment