

Neuropsychiatry of Sleep

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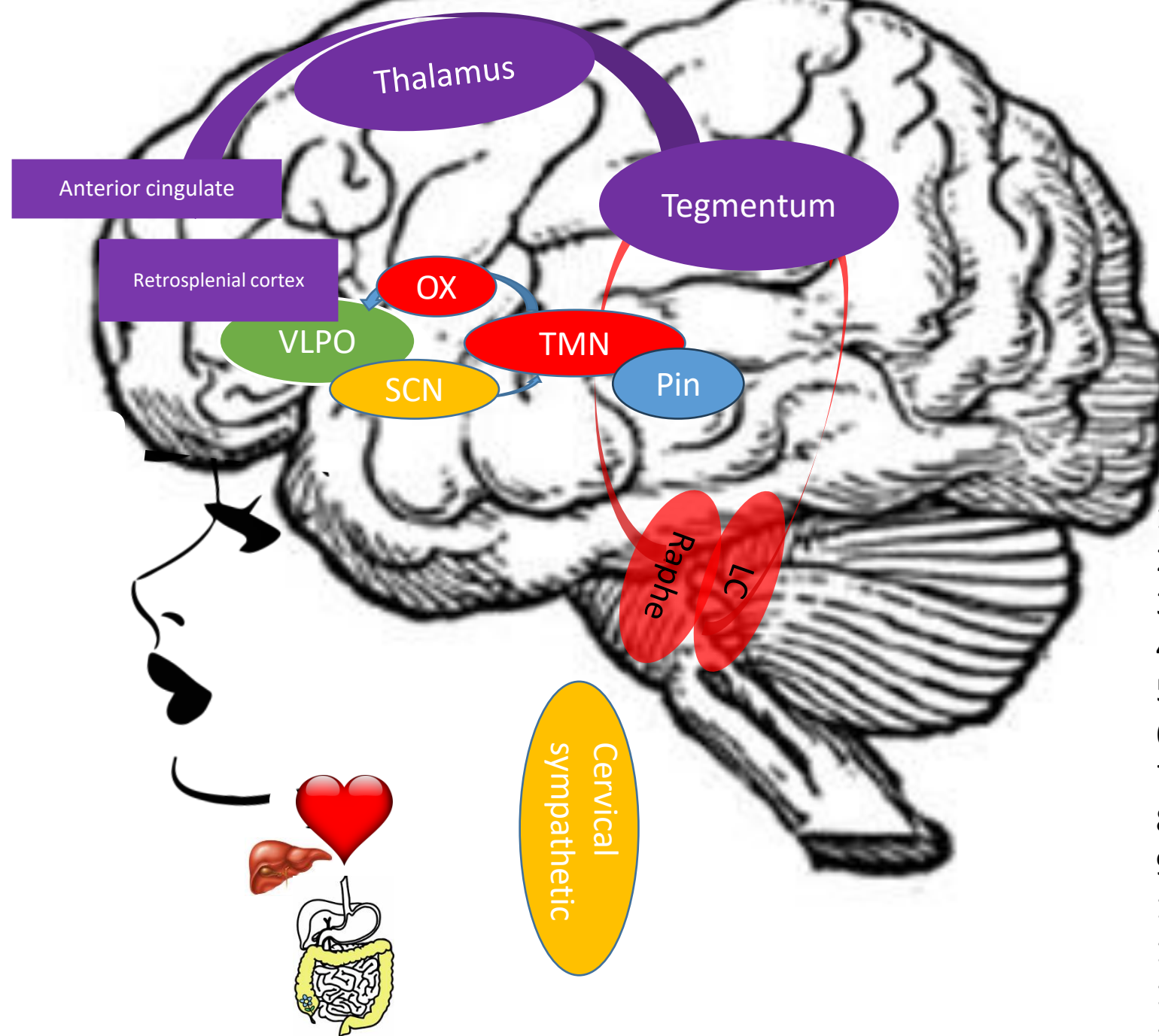
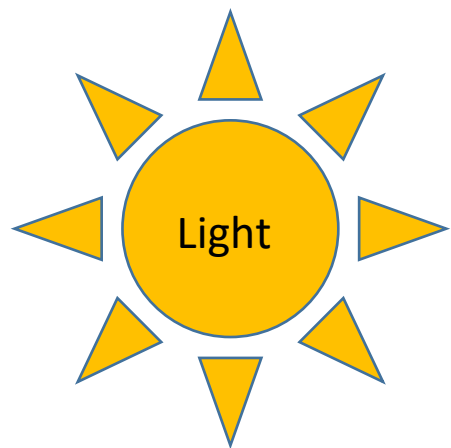
Medical Director, Faulkner Sleep and EEG Testing Center

Disclosures

- Jazz pharma (didactic presentation to the Jazz staff on sleep and epilepsy, consultation)
- Doximity
- Trustee foundation (philanthropy, via MGB epilepsy)

Objectives

- Gain understanding of basic sleep physiology
- Identify signs of sleep disorders
- Learn to initiate treatment for common sleep disorders.



1. Adenosine
2. GABA
3. Galanin
4. Histamine
5. Orexin
6. Monoamines
7. Epinephrine.
8. Norepinephrine
9. Serotonin
10. Acetylcholine
11. Dopamine
12. Melanopsin
13. Melatonin

Normal NREM physiology

Decrease in muscle tone, heart rate, overall oxygen demand

~2% decrease in measures SaO_2

Normal heart rate in sleep is slower (can be 40-90 bpm)

Regular respirations and heart rate

Primarily homeostatic regulation – SWS increases after sleep deprivation

Normal REM sleep physiology

EEG – with many features of wakefulness

Oxygen consumption, cerebral blood flow, and glucose utilization – all increased

Most dreams occur in REM

Eye movements – seen through eye lids

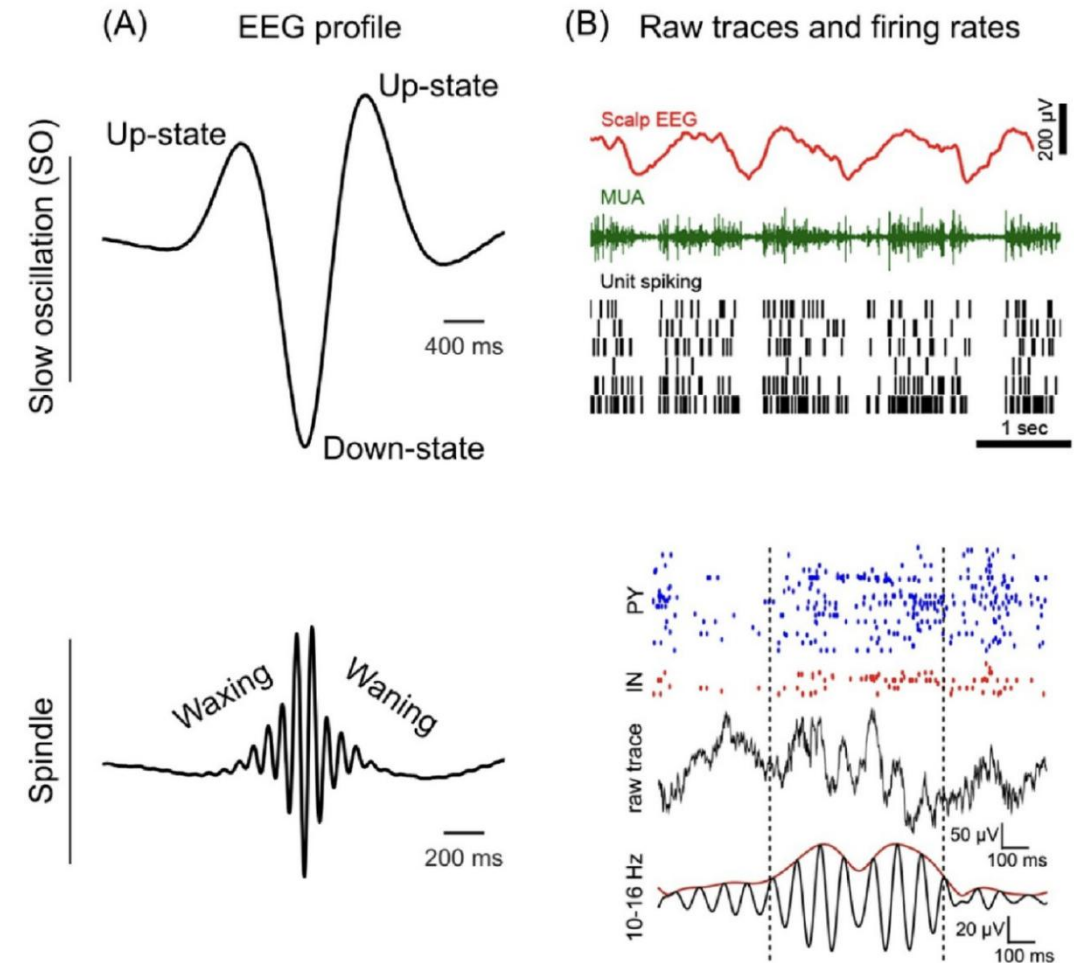
Motor output is blocked through active hyperpolarization of alpha motor neurons (REM atonia)

Primarily circadian regulation, closely linked to circadian phase with a peak a little after the nadir of the core body temperature

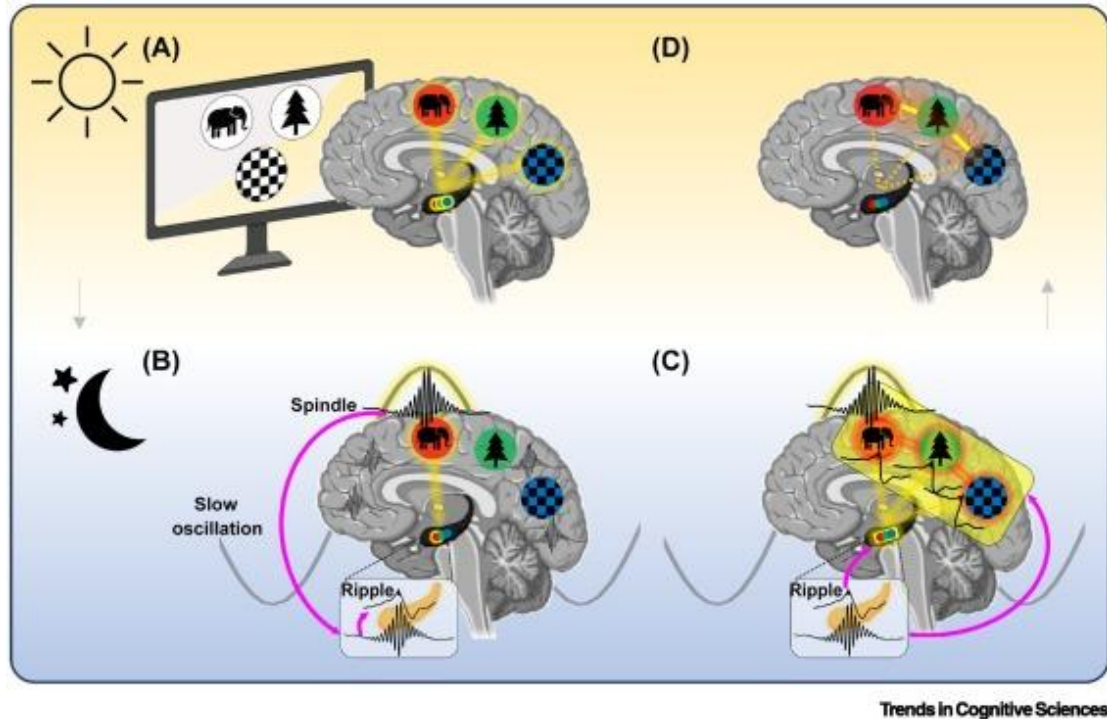
Microarchitecture

Spindle-slow oscillation coupling

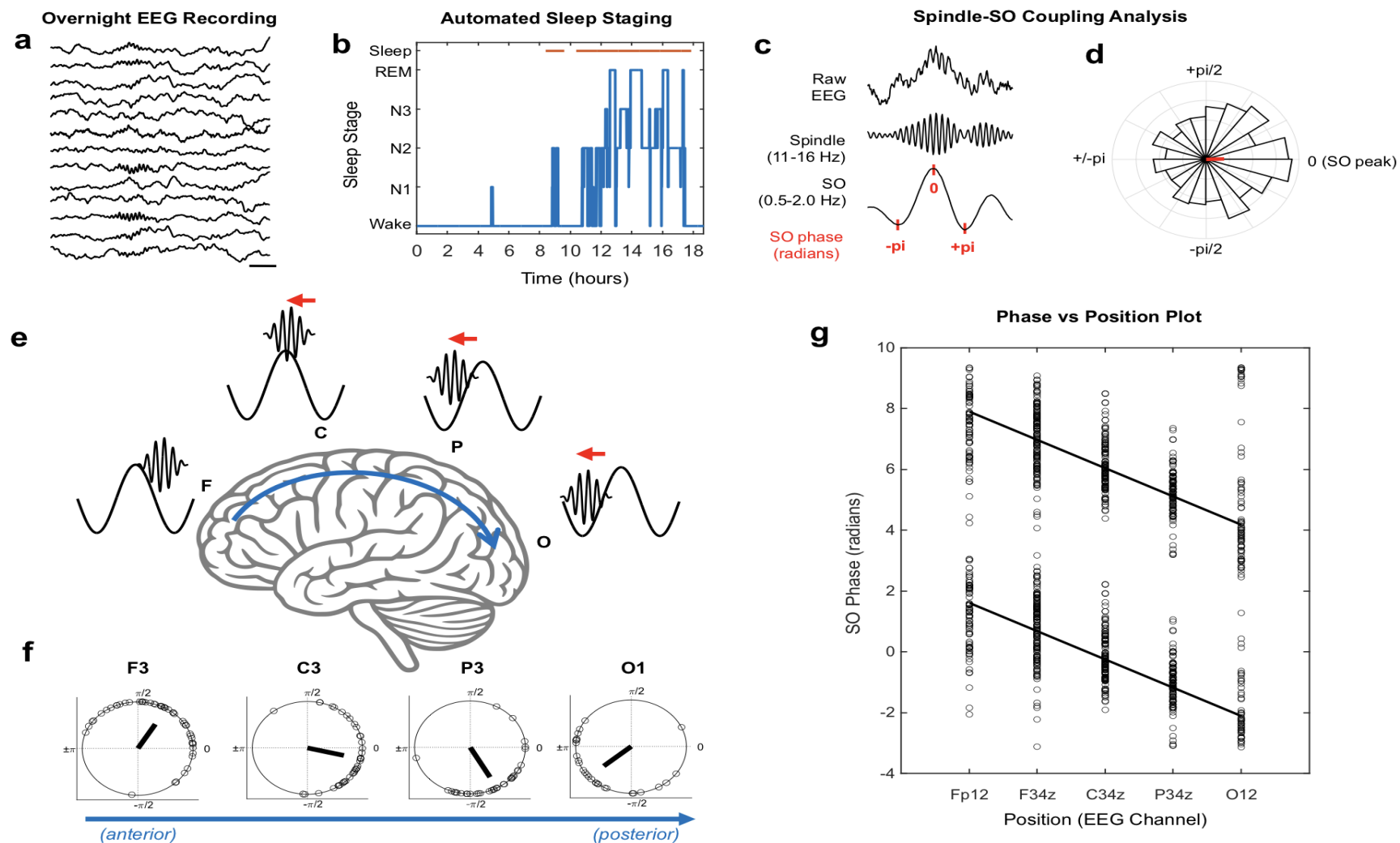
- Slow oscillations (SO)
 - Slow fluctuations (0.75 sec)
 - Travel from prefrontal cortex posteriorly
 - Reflect UP – increase, and Down -decrease in neuronal firing rates over broad fields
 - Rain wide coherence in up state increases after declarative task
- Spindles
 - 12-16 Hz, usually 0.5-1 sec
 - Thalamus to cortex connections
 - When on the UP state of SO ->memory consolidation
- Ripples
 - brief (~50–100 ms) high-frequency oscillations (110–200 Hz)
 - Usual recording from animal or intracranial human EEG
 - From hippocampus – CA1-3
 - Involved in replay, memory processing



Sleep microarchitecture – implications for memory processing



- (A) During learning, cortical nodes that represent different elements of our experience are synaptically tagged. Activation spreads to the hippocampus, where pointers (indices; small circles) to the cortical nodes are retained.
- (B) During sleep, spindles are broadcast widely during SO up-states and resonate most strongly at tagged sites engaged in prior learning (large spindle). This entrains hippocampal spindles which reactivate the corresponding hippocampal index and trigger ripples.
- (C) Hippocampal ripples facilitate intrahippocampal pattern completion of the engram and activate/propagate to corresponding (indexed) cortical target sites, triggering cortical pattern completion and strengthening cortical–cortical connections of the participating nodes.
- (D) Consolidated memories are reflected in strengthened cortical connections. Hippocampal contributions likely diminish with time (broken lines) but can be reintroduced by alterations to the memory trace.

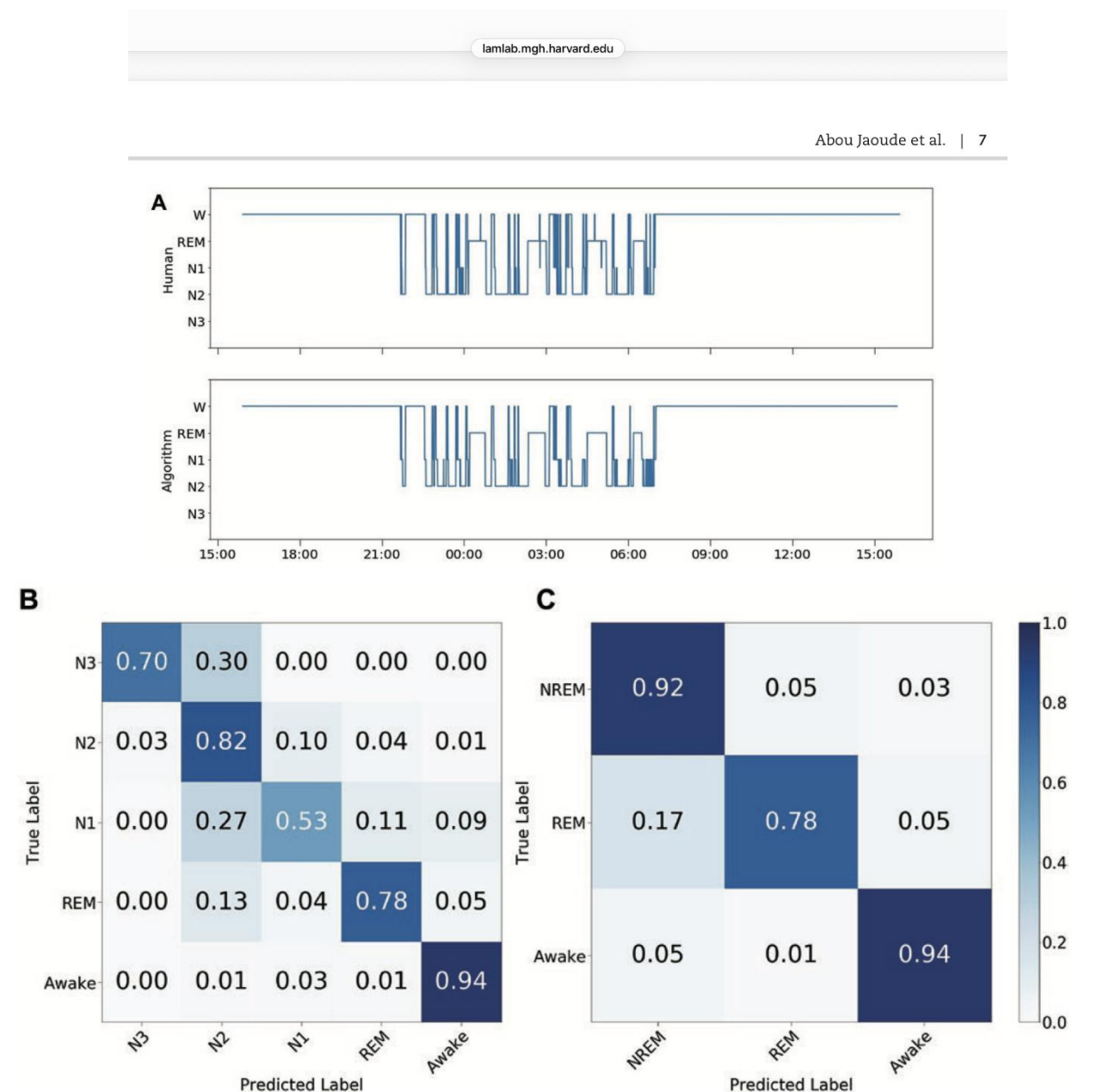


Autoscoring – ambulatory EEG – Persyst – sleep/wake



Auto scoring example from EMU

- Recordings – MGH sleep lab dataset (6 EEG channels)
- Ambulatory outpatient dataset – 18 EEG 24-72 hr recordings (research on insomnia)
- All manually scored for comparison



Therefore, we next sought to characterize CRNN_{EEG}'s performance – whereas transition outputs should be considered with some

Normal sleep macro-architecture

NREM

- N1 – 5-10%, “lighter sleep”
- N2 – 50-60%, K-complexes, sleep spindles
- N3 - ~10%, decreases with age deeper sleep; ‘slow wave sleep’

REM – Stage R, 15-25%

- Same apparent changes in consciousness, but eye movements, elaborate dreams (>80% of dreams in REM), atonia

Sleep cycles ~90 min in humans.





Recognizing sleep disorders

Recognizing sleep disorders

Chief complaint “I can’t sleep”

- “I haven’t slept since...”
- “I was never a good sleeper”
- “I fall asleep, but keep waking up every hour”

Chief complaint: “I fall asleep when I should not”

Culprits

- Medications/substances
 - Caffeine, alcohol, illicit
 - ADD medications, some antidepressants, some BP medications
- A medical/neurological disorder
 - Hyperthyroidism, anemia, bipolar disorder
 - Nocturnal seizures
- A primary sleep disorder
 - RLS,
 - circadian rhythm disorder
 - Parasomnia/ RBD
- Medications/substances
 - ASM, anxiolytics, neuroleptic, antidepressants, antihypertensive,
- A medical/neurological disorder
 - Frequent seizures, Hypothyroidism,
- A primary sleep disorder
 - OSA, PLMS, RBD
 - Narcolepsy, Idiopathic hypersomnia

Clinically useful sleep tests

Portable testing (home
sleep apnea test) – tests
for sleep apnea only

PSG – answers questions
about overall sleep
(limited EEG, breathing, leg
movement abnormalities)
gold standard

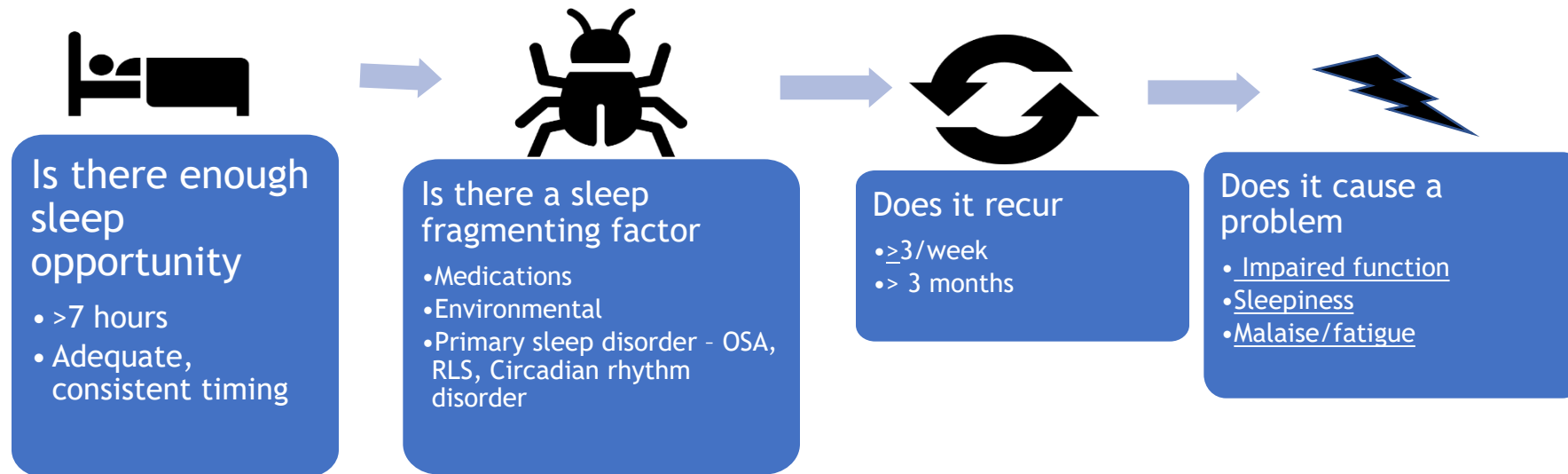
MSLT – night test +
daytime test – allows
monitoring of daytime
sleep in patients with
daytime sleepiness

MWT – tests ability to
stay awake

Full montage Video EEG-
PSG – allows monitoring
for abnormal behavior at
night – ideal for unusual
behaviors during the night
(parasomnia vs. seizure)

Activity based monitors

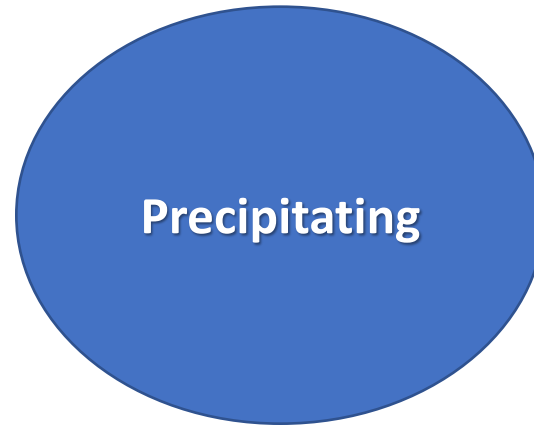
Diagnosing insomnia





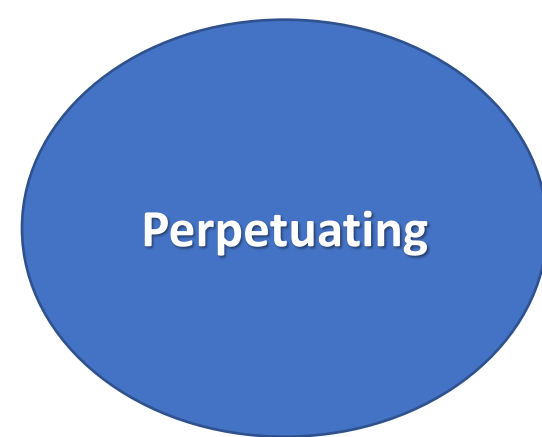
Predisposing

Inherited



Precipitating

Major stress
Illness
Other
physiologic
change



Perpetuating

Maladaptive behaviors, such as:

- Rumination
- Anxiety about not being able to fall asleep
- Substance use – caffeine to counteract the resulting fatigue, alcohol at bedtime

TREATMENT OF INSOMNIA

Counseling:

- Sleep hygiene
- Cognitive behavioral therapy
- Relaxation techniques

Medications:

- Benzodiazepines
- Other hypnotics
- Melatonin agonist
- Antidepressants
- Others

MEDICATIONS FOR INSOMNIA

Benzodiazepines

- Lorazepam, temazepam, oxazepam

Other hypnotics

- Zolpidem, zaleplon, eszopiclone

Melatonin agonists

- Ramelteon,

Orexin antagonists

- Suvorexant, Lemborexant, daridorexant

Antidepressants

- Mirtazapine, trazodone, amitriptyline, etc.

Others

Circadian rhythm disorders - typical complaints



DSWPD:

“I can’t wake up for school”

“I only get 4 hrs sleep because by the time I fall asleep, I have to wake up for school/work”

“I can’t sleep” – 10% of insomnia patient



ASWPD

“Don’t have a social life - too sleepy in the evenings”

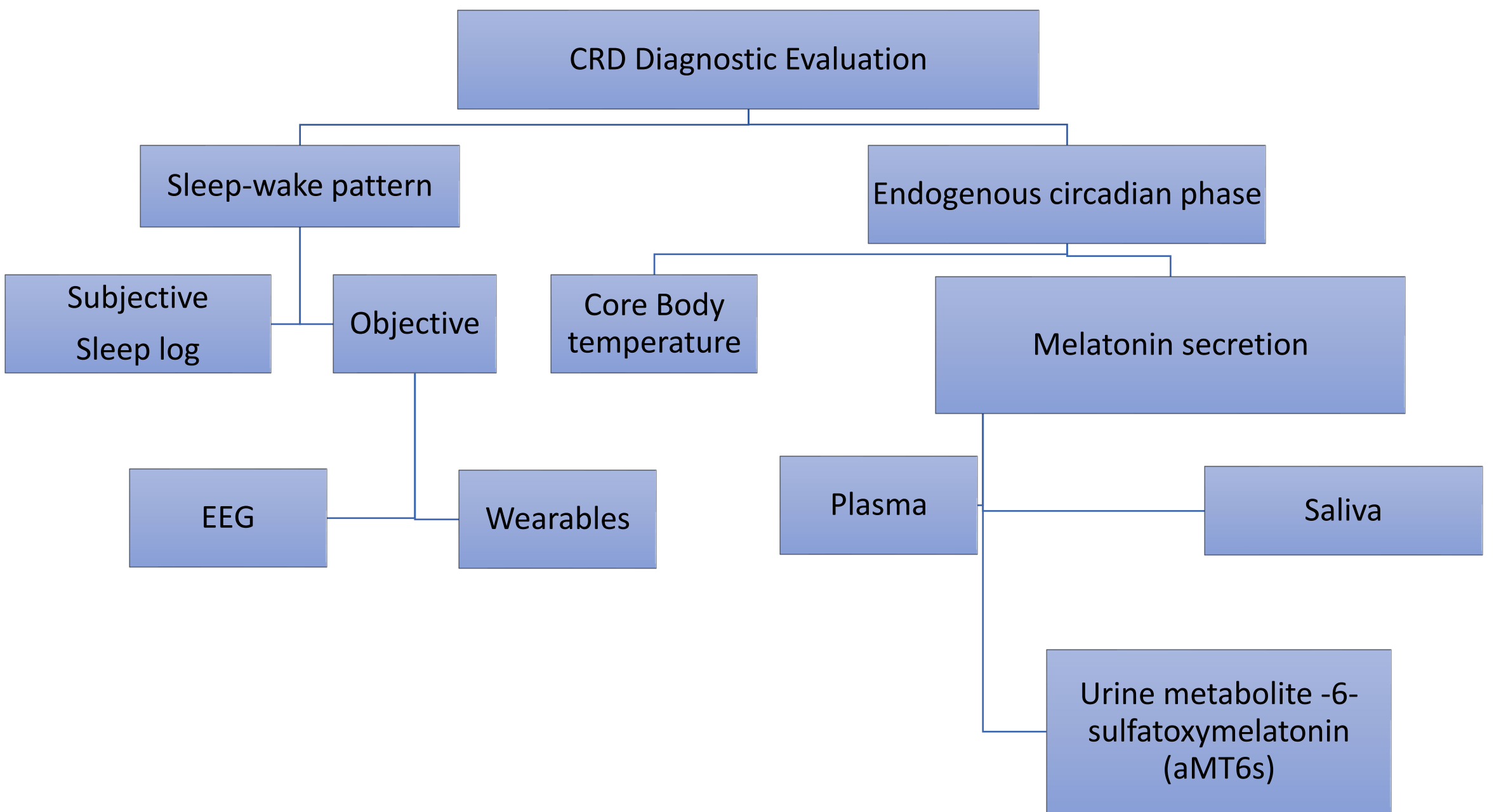
“I wake up in the middle of the night, can’t fall asleep again”



Non-24 hr – “each night I fall asleep later/earlier. Every 4-6 days I self-recalibrate”



Irregular – often in the context of neurodegeneration, irregular sleep-wake, multiple “cat-naps”, nocturnal wondering.



1. Write the date, day of the week, and type of day: Work, School, Day Off, or Vacation.
2. Put the letter "C" in the box when you have coffee, cola or tea. Put "M" when you take any medicine. Put "A" when you drink alcohol. Put "E" when you exercise.
3. Put a line (l) to show when you go to bed. Shade in the box that shows when you think you fell asleep.
4. Shade in all the boxes that show when you are asleep at night or when you take a nap during the day.
5. Leave boxes unshaded to show when you wake up at night and when you are awake during the day.

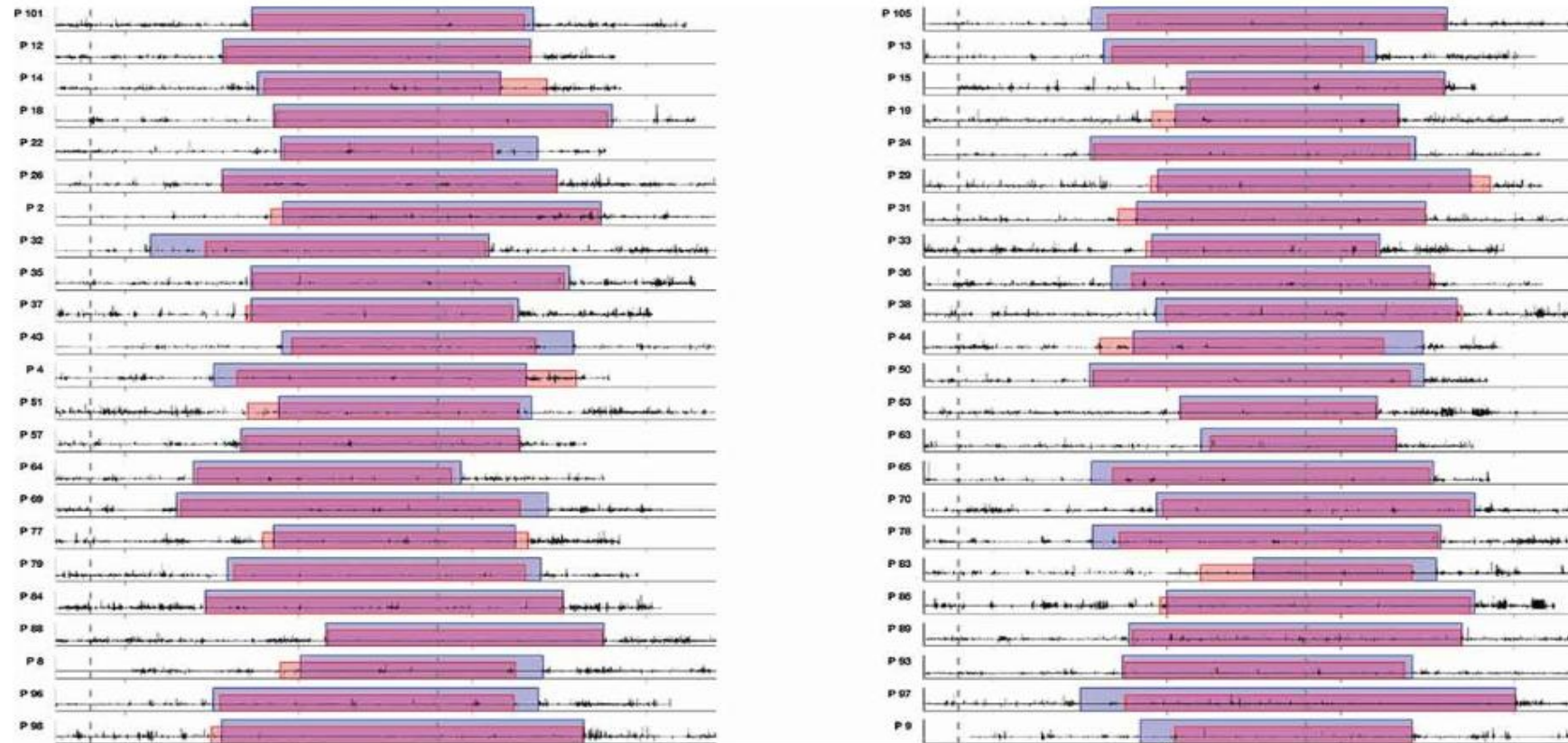
- Subjective assessment of sleep pattern

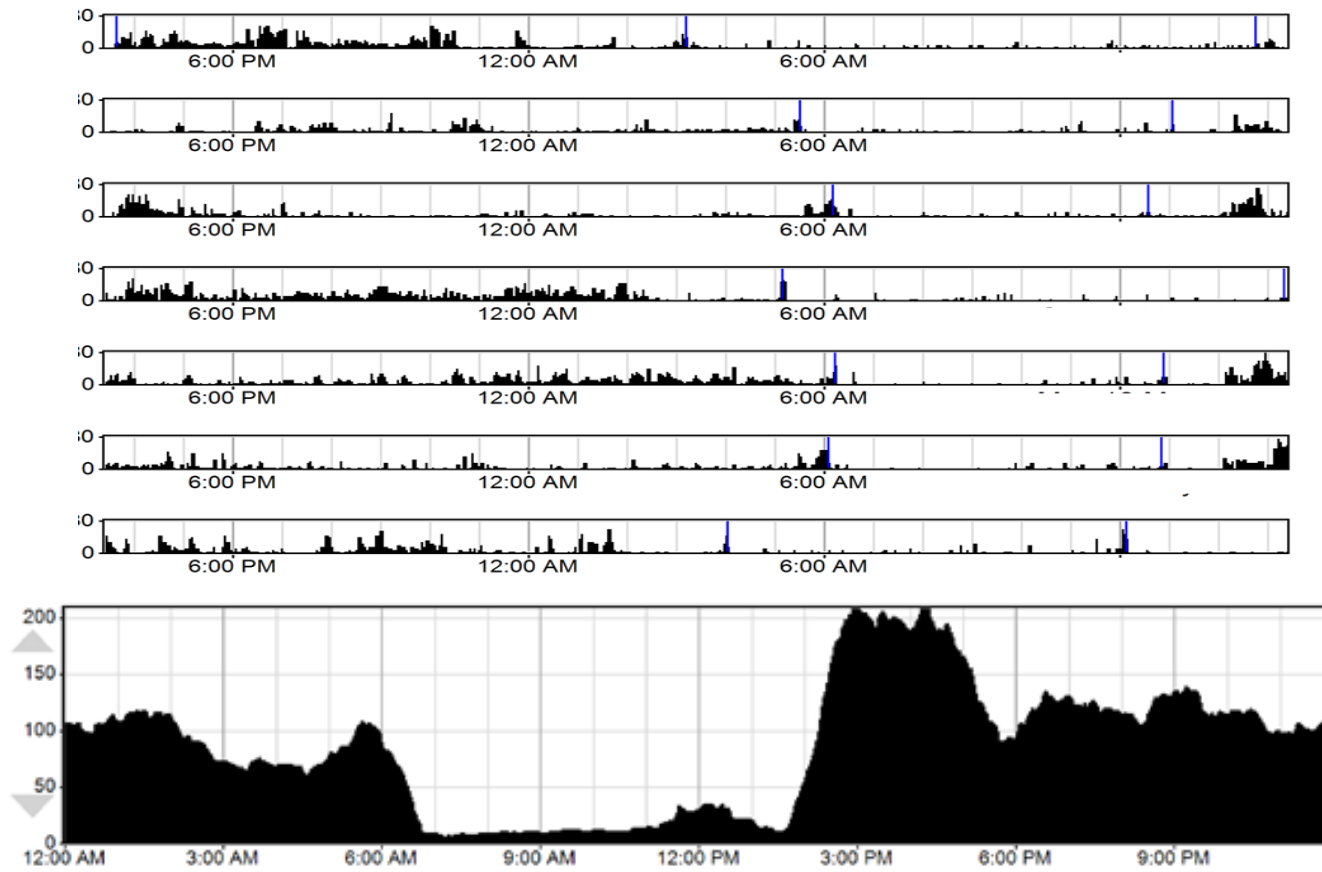
[illegible]

Objective assessment of sleep/activity patterns



Figure 2. Sleep period detection with ACT-S1 and PSG-EEG. Sleep period times automatically detected via ACT-S1 (blue areas) and manually detected via PSG-EEG (red areas) for each participant. The magnitude of 3-axes accelerometer data provided as input to the ACT-S1 is shown as black solid traces. Dashed vertical lines indicate the time-boundaries for PSG-EEG assessment of sleep, i.e., from 18:00 to 04:00 h the following morning.





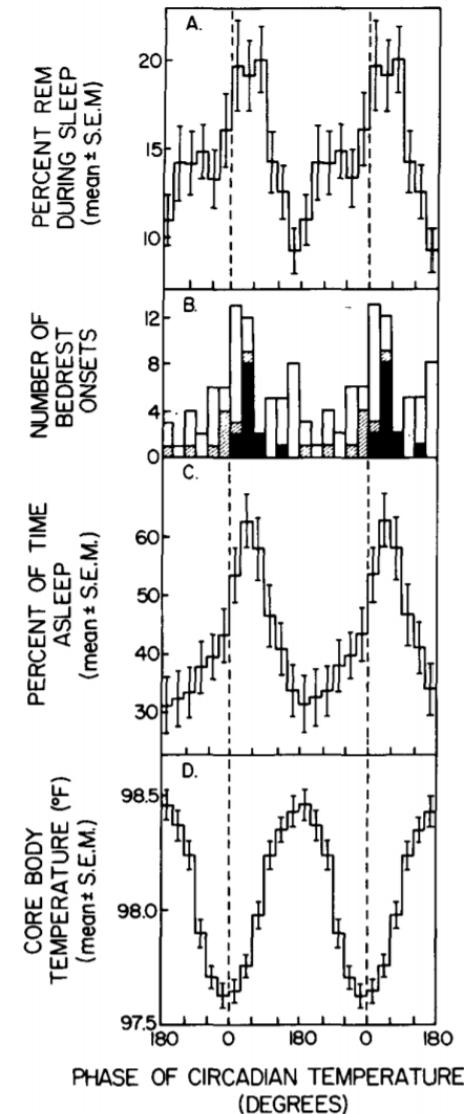
Giordano A, Pavlova MK. Objective Diagnosis of Circadian Rhythm Disorders. J Clin Neurophysiol. 2023 Mar 1;40(3):230-235. PMID: 36872502;

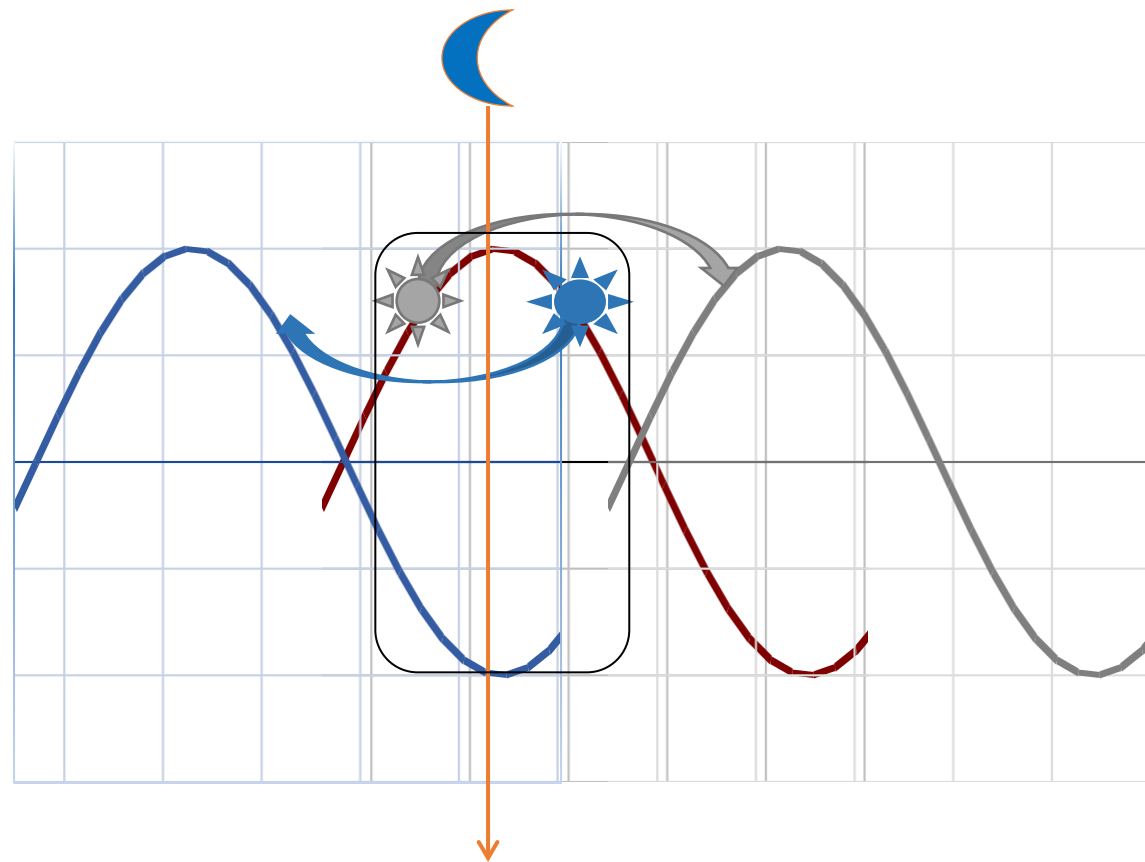


Measurement of circadian phase

Why measure circadian phase in clinic?

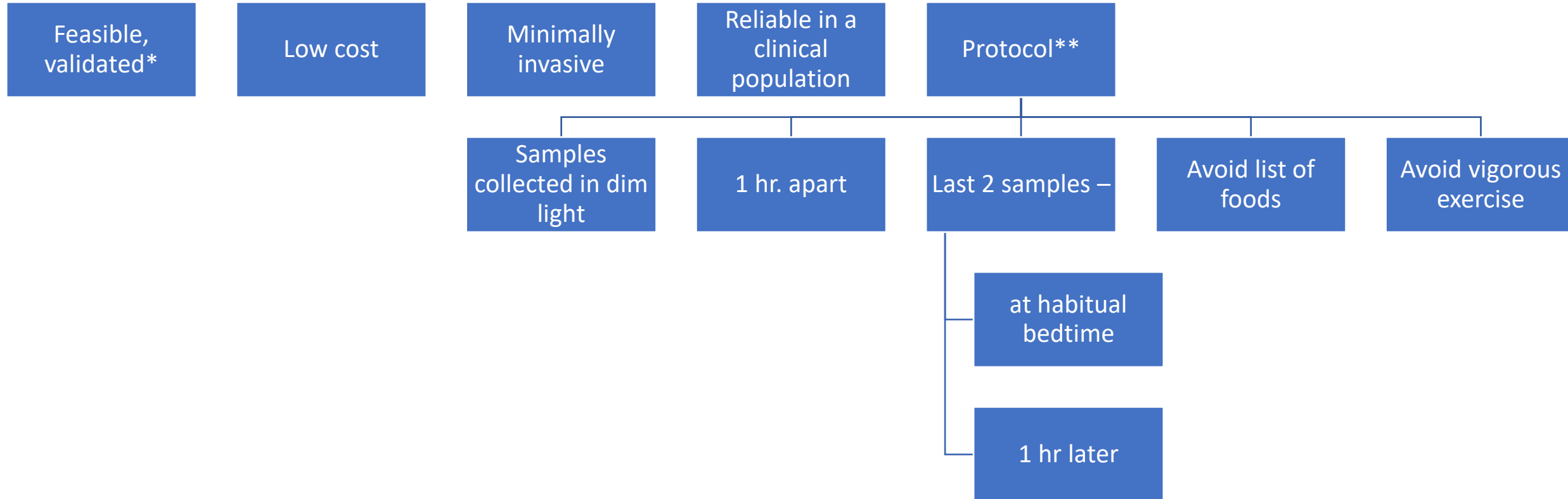
- Gives information of sleep propensity and sleep structure ->
- Circadian phase shifts in response to light
- Not all DSWPD patients have delayed melatonin secretion
- Treatment strategy may be affected
 - Timed melatonin may be ineffective depending on when it is given
 - Light exposure may have different effect depending on when it is given relative to the endogenous circadian phase





Core body temperature minimum

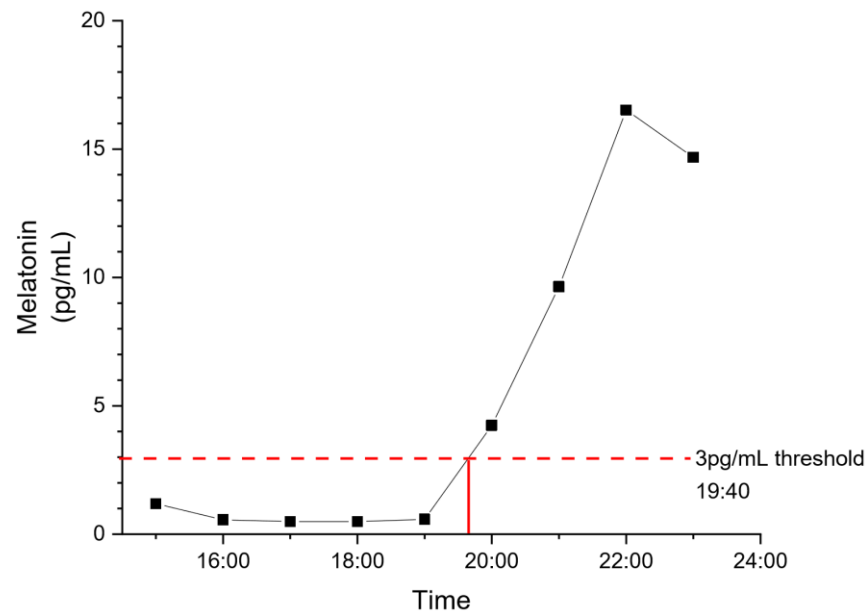
Outpatient salivary melatonin (DLMO) measurement



*Pullman RE, Roepke SE, Duffy JF. Laboratory validation of an in-home method for assessing circadian phase using dim light melatonin onset (DLMO). Sleep Med. 2012. PMID: 22445311;

**Murray. A Protocol to Determine Circadian Phase by At-Home Salivary Dim Light Melatonin Onset Assessment. J Pineal Res. 2024 Aug;76(5):e12994. PMID: 39158010.

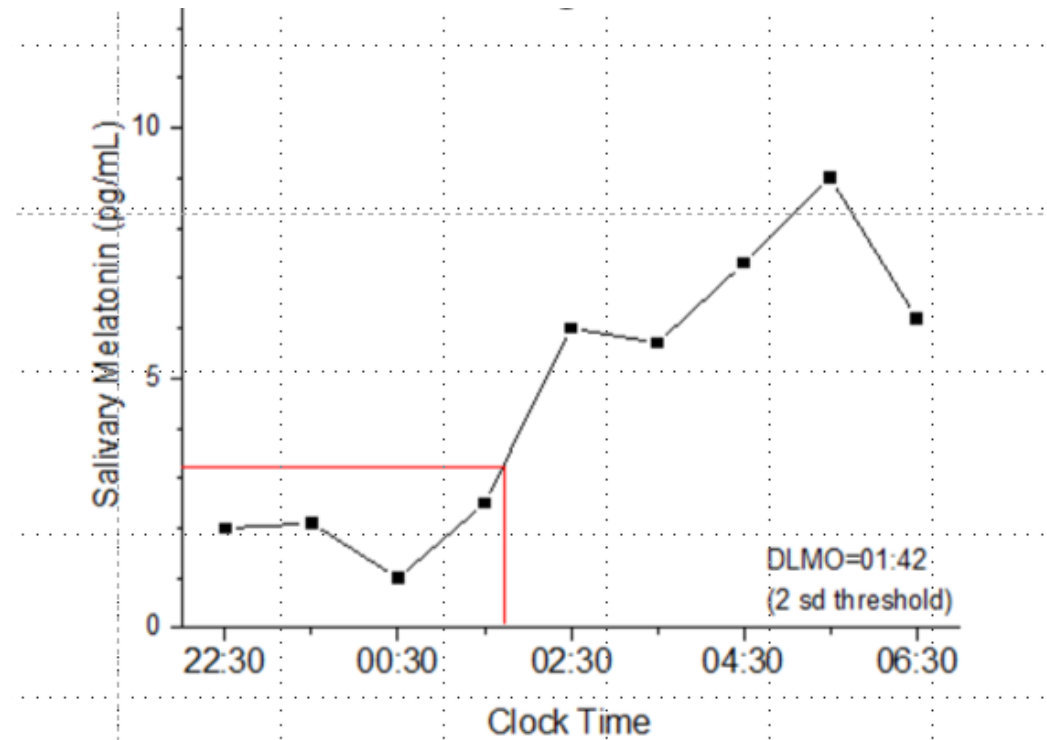
DLMO



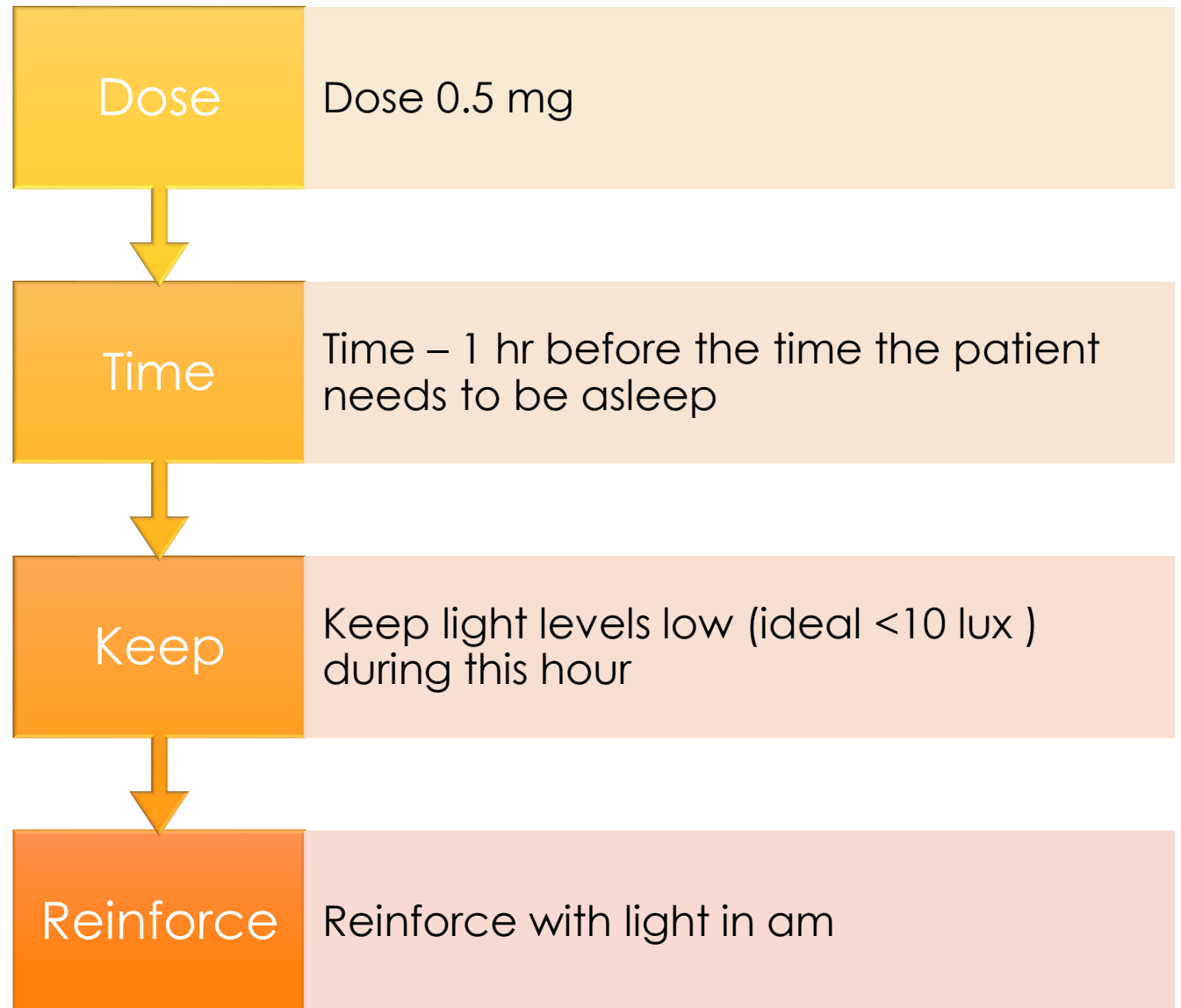
Murray et al; International Association of Circadian Health Clinics. A Protocol to Determine Circadian Phase by At-Home Salivary Dim Light Melatonin Onset Assessment. J Pineal Res. 2024 Aug;76(5):e12994. doi: 10.1111/jpi.12994. PMID: 39158010.

Patient AA

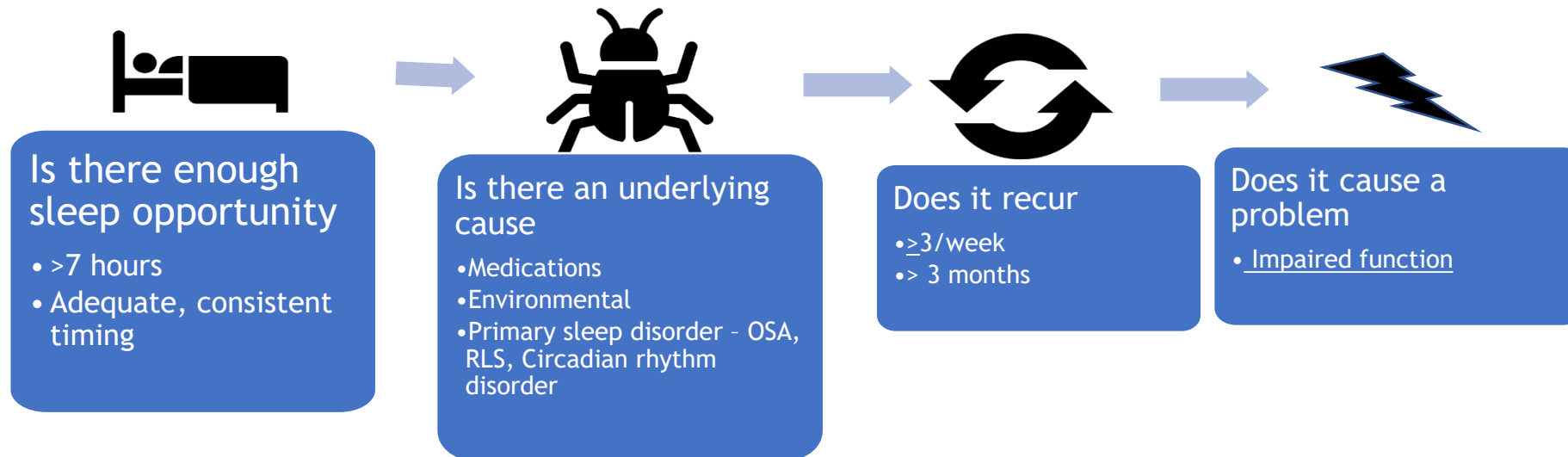
- Fatigue throughout the day
- Unintentional sleep
- Non-refreshing naps
- Abnormal MSLT
- Persistent symptoms despite treatment
- Late sleep



MELATONIN FOR DELAYED SLEEP WAKE PHASE DISORDERS

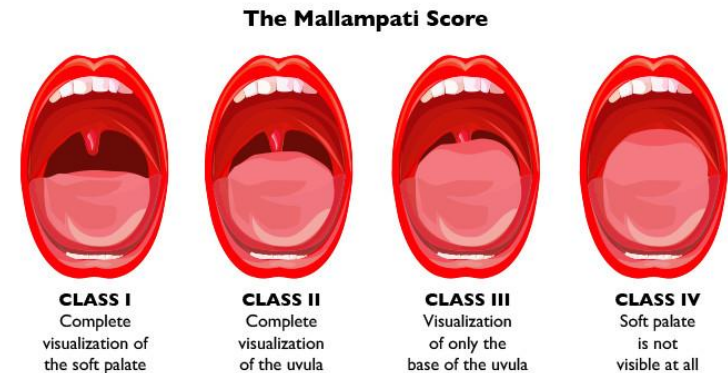


Diagnosing hypersomnia



Recognizing Obstructive sleep apnea

- Large neck
- Small chin
- Crowded upper airway
- Common symptoms
 - Asleep in the waiting room
 - Overall sleepiness/fragmented sleep
 - Concentration difficulties
 - High blood pressure



Obstructive Sleep Apnea

Typical symptoms - snoring/breathing pauses/gasping upon awakening

Insomnia – particularly in women,

Sleep fragmentation

Nonspecific symptoms

- Morning headache, better over the course of the day
- Panic attacks at night
- Attention deficits,
- Mood disturbance
- Others – nocturia, night sweats, erectile dysfunction, etc.
- Aggravation of other disease (e.g. recurrent seizures in a previously controlled epilepsy pt; new seizures in late adulthood)

Screening for OSA (STOP BANG)

- Snoring ?
 - Do you Snore Loudly (loud enough to be heard through closed doors or your bed-partner elbows you for snoring at night)?
- Tired ?
 - Do you often feel Tired, Fatigued, or Sleepy during the daytime (such as falling asleep during driving or talking to someone)?
- Observed ?
 - Has anyone Observed you Stop Breathing or Choking/Gasping during your sleep ?
- Pressure ?
 - Do you have or are being treated for High Blood Pressure ?
- Body Mass Index more than 35 kg/m²?
- Age older than 50 ?
- Neck size large ? (Measured around Adams apple)
 - For male, is your shirt collar 17 inches / 43cm or larger?
 - For female, is your shirt collar 16 inches / 41cm or larger?
- Gender = Male ?
- Yes on >3 questions – moderate to high risk of OSA

OSA – TREATMENTS



- PAP – CPAP/APAP, BiPAP, ASV
- Dental appliances
- Surgery –select cases
- Hypoglossal nerve stimulation (implant)
- Conservative measures – to use with another treatment or for few symptoms and $AHI < 15$
 - Sleep position
 - Weight loss
 - Avoidance of 'relaxants' close to bedtime



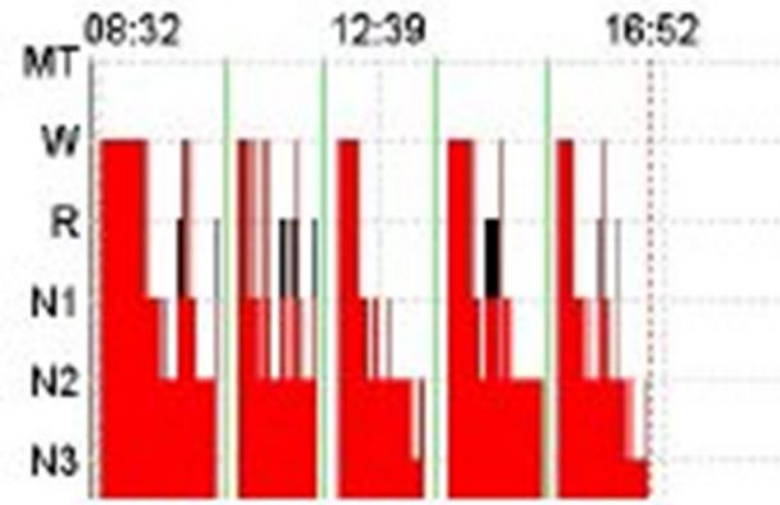
Central hypersomnia

- Narcolepsy type 1 (with cataplexy)
- Narcolepsy type 2 (no cataplexy)
- Idiopathic hypersomnia
 - With long sleep time
 - Without long sleep time
- Recurrent hypersomnia



Diagnosis

- Clinically
- Objective documentation - MSLT
 - on the day after a PSG
 - 5 nap opportunities x 20 min
 - short sleep latency (<8 min.)
 - 'SOREM': ≥ 2 naps containing REM
 - or REM in one nap and a REM latency on the preceding PSG <15 min.
- HLA typing
- CSF measurement of hypocretin





Movements at night

Restless Legs Syndrome and Periodic Limb Movements of Sleep

RLS: indescribable uncomfortable sensations that make the patient move limbs

PLMD – PLMS seen on PSG + symptoms (fragmented sleep, daytime sleepiness, etc.)

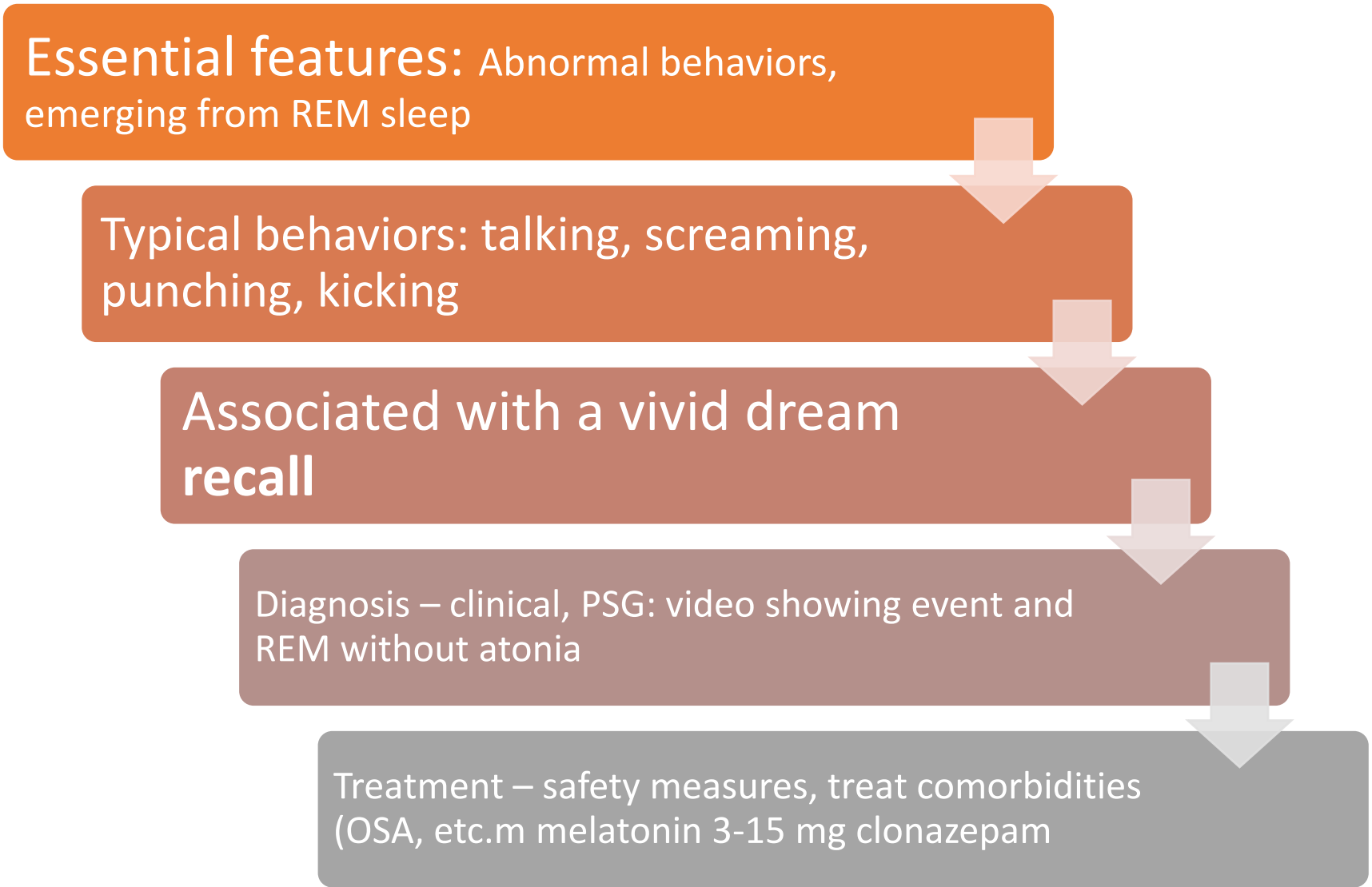
Diagnosis: by history; PSG can give confirmation of PLMS

Evaluation: other medical problems, sleep disorders, ferritin level

Treatment – iron supplementation if ferritin < 75, gabapentin

REM Behavior Disorder

Essential features: Abnormal behaviors, emerging from REM sleep



```
graph TD; A[Essential features: Abnormal behaviors, emerging from REM sleep] --> B[Typical behaviors: talking, screaming, punching, kicking]; B --> C[Associated with a vivid dream recall]; C --> D[Diagnosis – clinical, PSG: video showing event and REM without atonia]; D --> E[Treatment – safety measures, treat comorbidities (OSA, etc.) melatonin 3-15 mg clonazepam];
```

The diagram is a vertical flowchart with five rectangular boxes, each containing text. The boxes are arranged in a descending staircase pattern from top-left to bottom-right. The first box is orange, the second is a darker orange, the third is a reddish-brown, the fourth is a dark brown, and the fifth is a dark grey. Each box is connected to the one below it by a downward-pointing arrow. The arrows are light orange for the first three steps and light grey for the last two.

Typical behaviors: talking, screaming, punching, kicking

Associated with a vivid dream **recall**

Diagnosis – clinical, PSG: video showing event and REM without atonia

Treatment – safety measures, treat comorbidities (OSA, etc.) melatonin 3-15 mg clonazepam

1. Sleep Physiology Is Complex and Regulated by Multiple Systems

Sleep involves both **homeostatic** and **circadian** regulation.

NREM and REM sleep have distinct physiological profiles, with REM showing increased brain activity and metabolic demand.

Neurotransmitters like **GABA**, **orexin**, **melatonin**, and **monoamines** play critical roles in sleep-wake regulation.

2. Recognizing Sleep Disorders Requires a Multifactorial Approach

3. Diagnostic Tools Are Essential for Accurate Evaluation

4. Treatment Must Be Tailored to the Disorder



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Brigham and Women's Hospital

Founding Member, Mass General Brigham



HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

