UCSF Weill Institute for Neurosciences

Memory and Aging Center

AWAKE THROUGH PSP

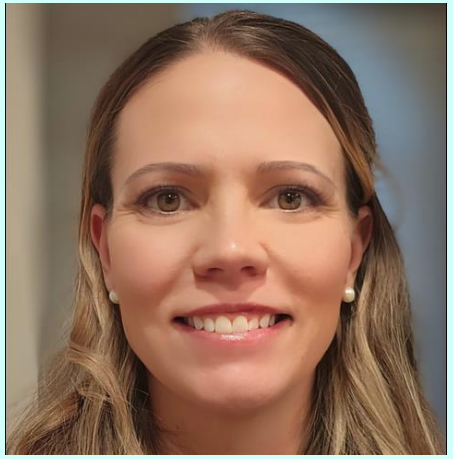
Christine M Walsh, PhD

Associate Professor

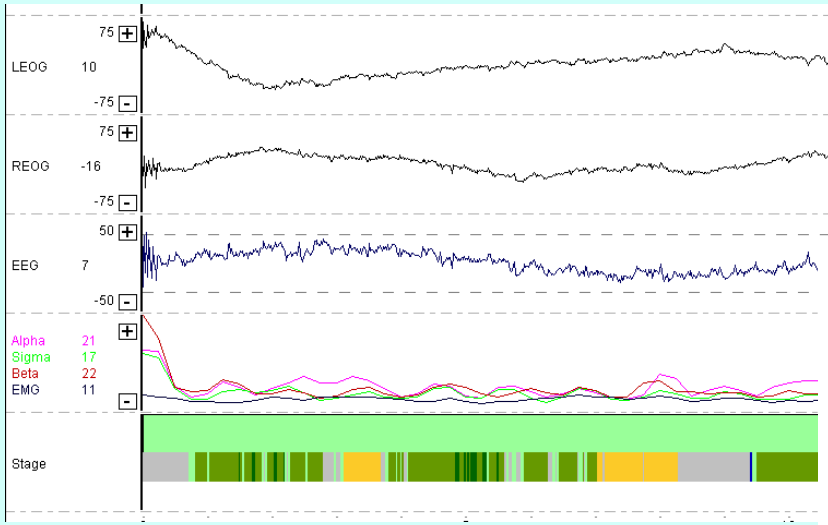
Sleep in Aging and Neurodegenerative Disease Lab

Memory & Aging Center, UCSF

Sleep Team

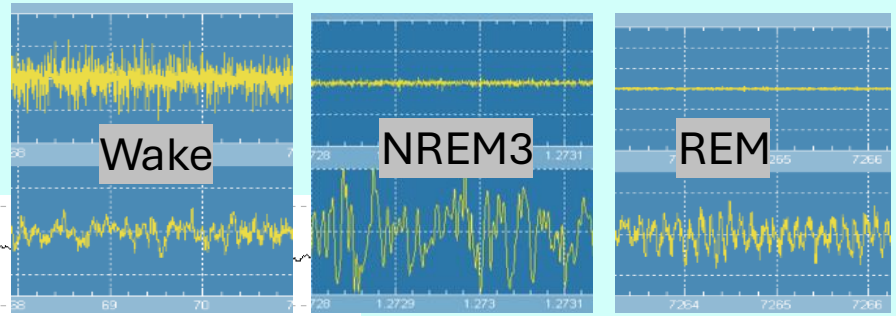


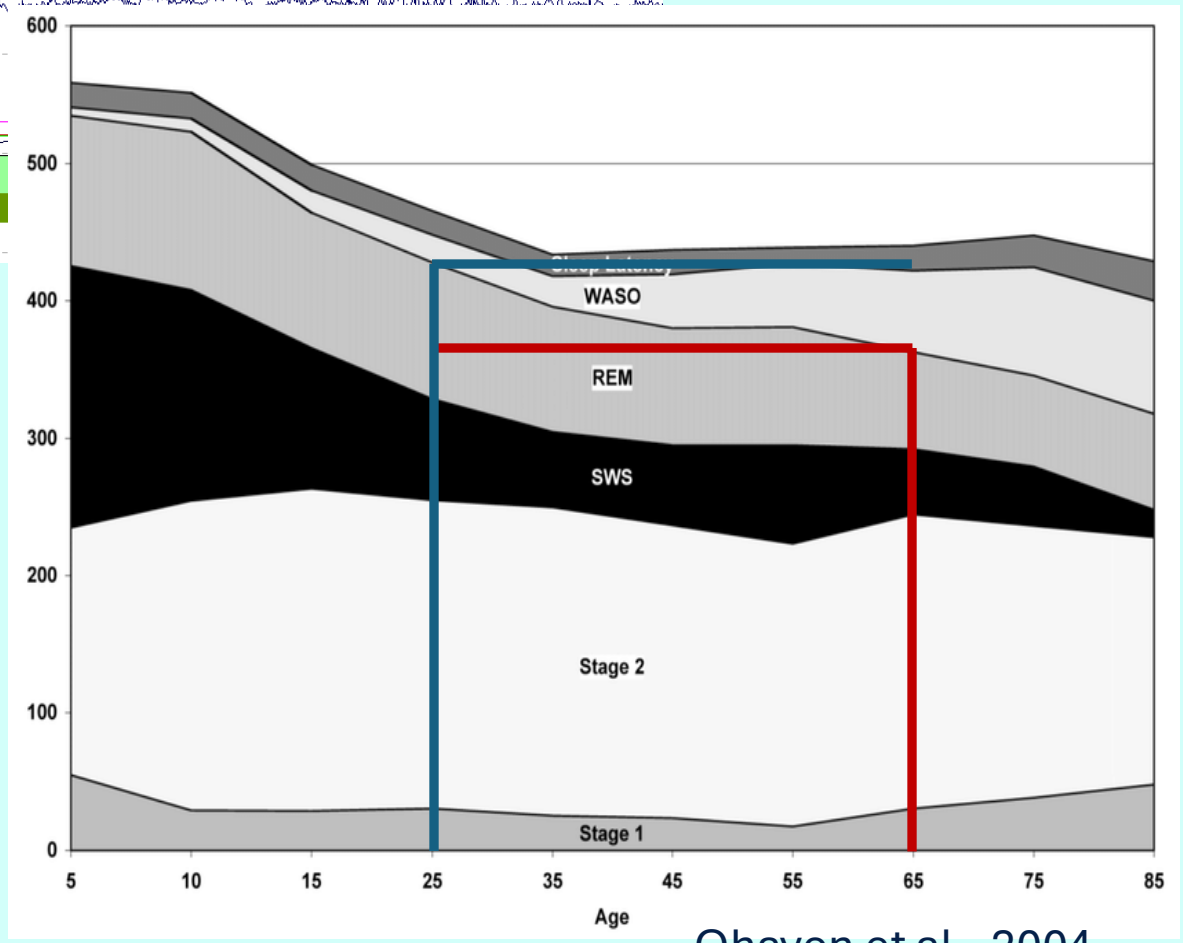
Tools we use in sleep studies



EMG

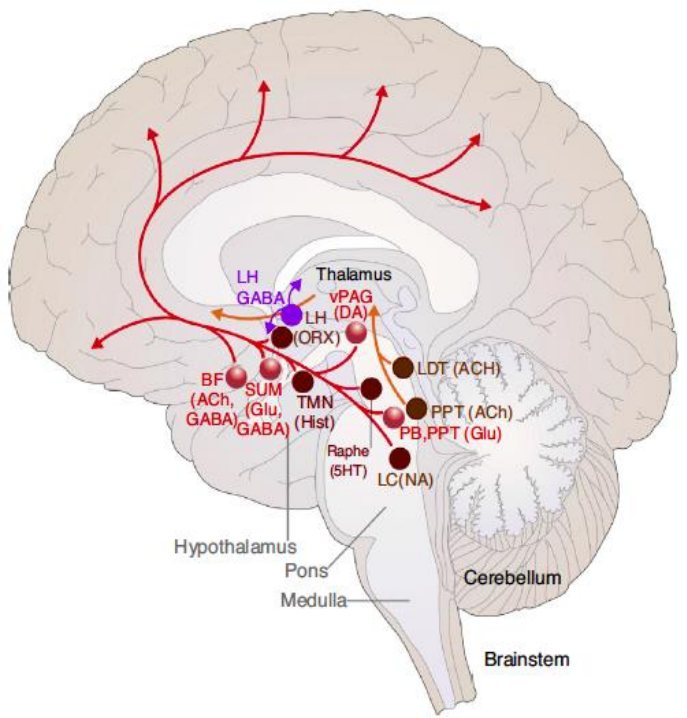
EEG



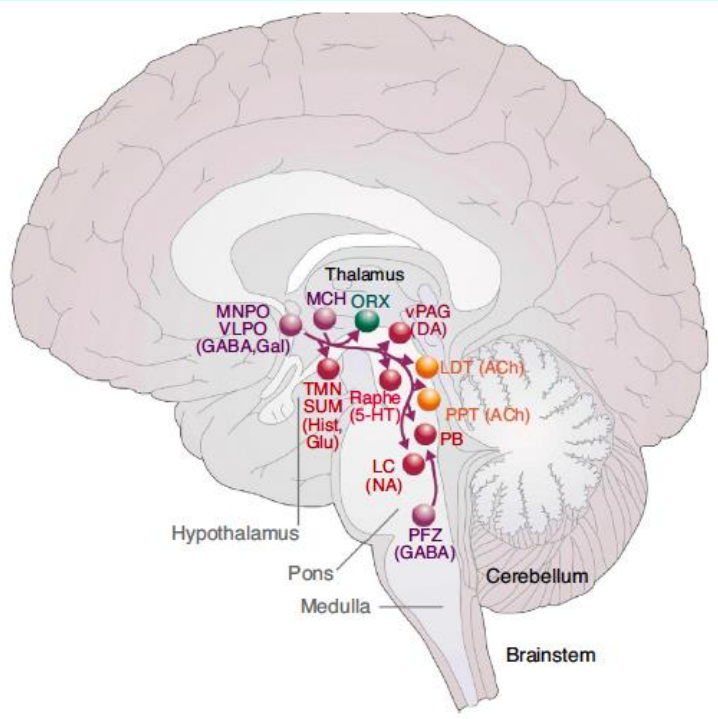


Ohayon et al., 2004

Wake Promoting



Sleep Promoting



14 days of 6hrs sleep/night
=
2 days of
complete sleep deprivation

van Dongen et al., 2003

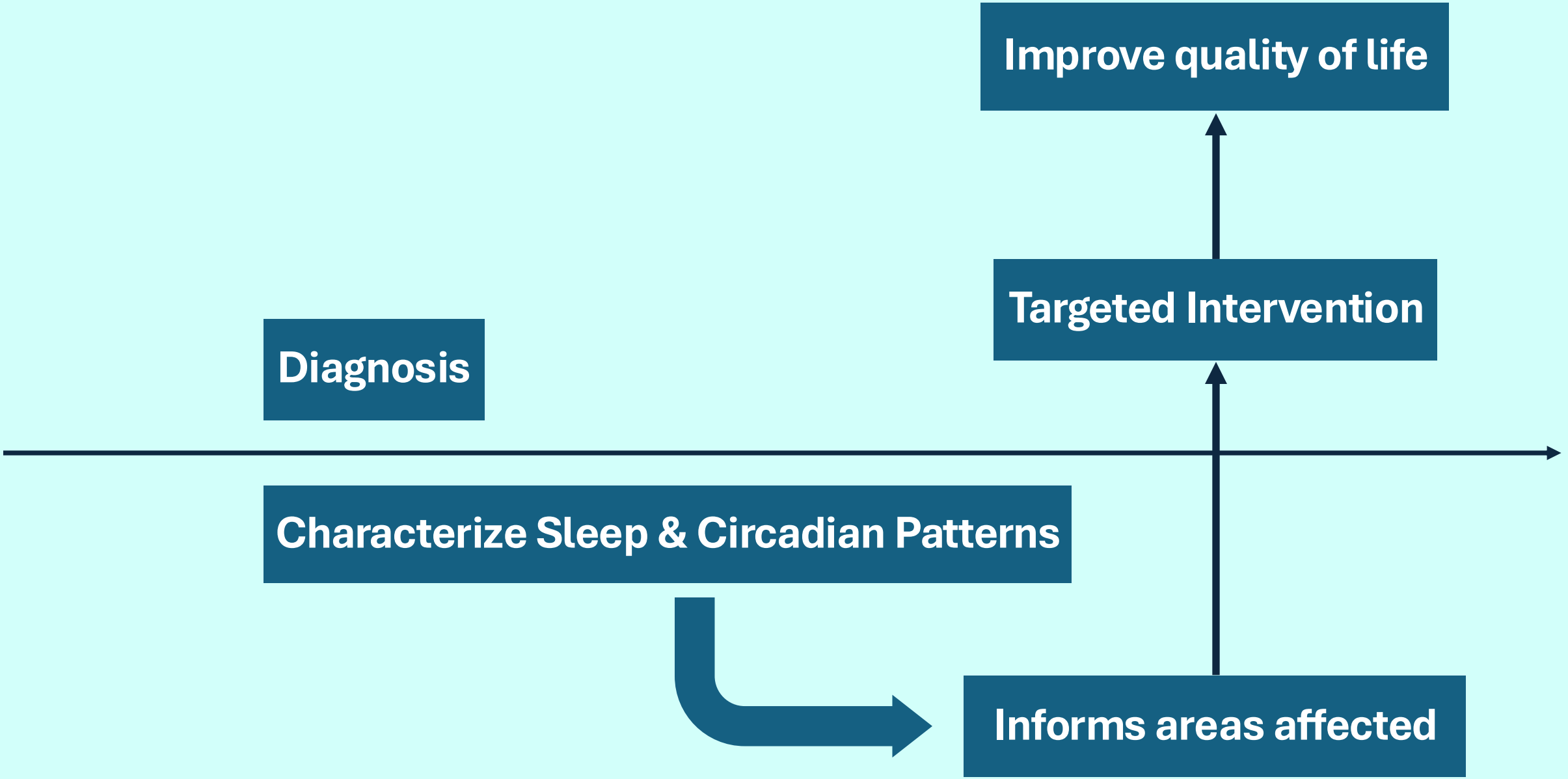
In young adults
reaction times after 24 hrs awake
=
0.085 % blood alcohol concentration

Dawson & Reid, 2007

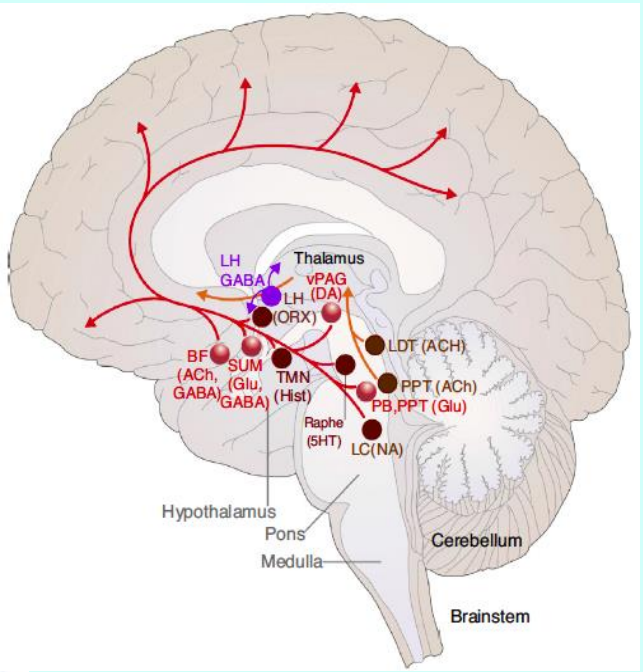
Saper, Scammell & Lu, 2005; Saper & Fuller, 2017

Insomnia

- Metabolic system
  - 
  - ↓ sugar break down
  - ↑ hunger
- Cardiovascular Health
- Immune system
- Sense of loneliness
- Emotional recognition and regulation
- Associated with increased neurodegenerative proteins
- Diminished grey volume
- Diminished white matter integrity
- Cognition


Improve quality of life
Targeted Intervention
Diagnosis
Characterize Sleep & Circadian Patterns
Informs areas affected

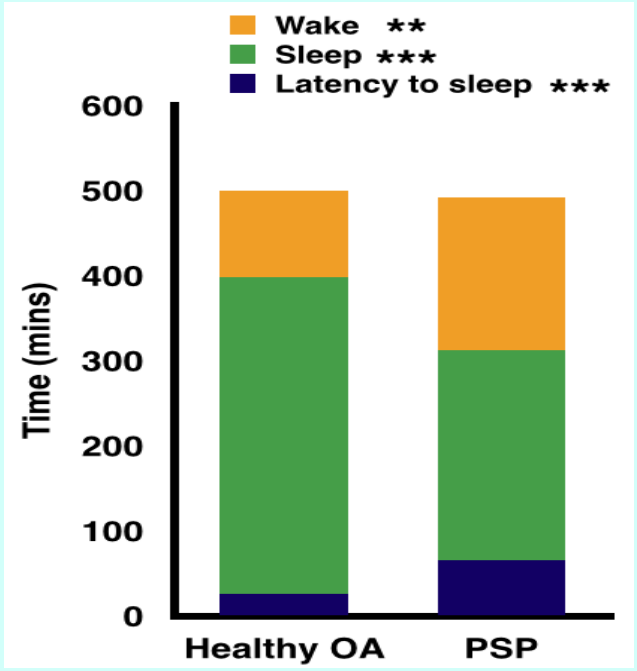
Progressive Supranuclear Palsy (PSP)

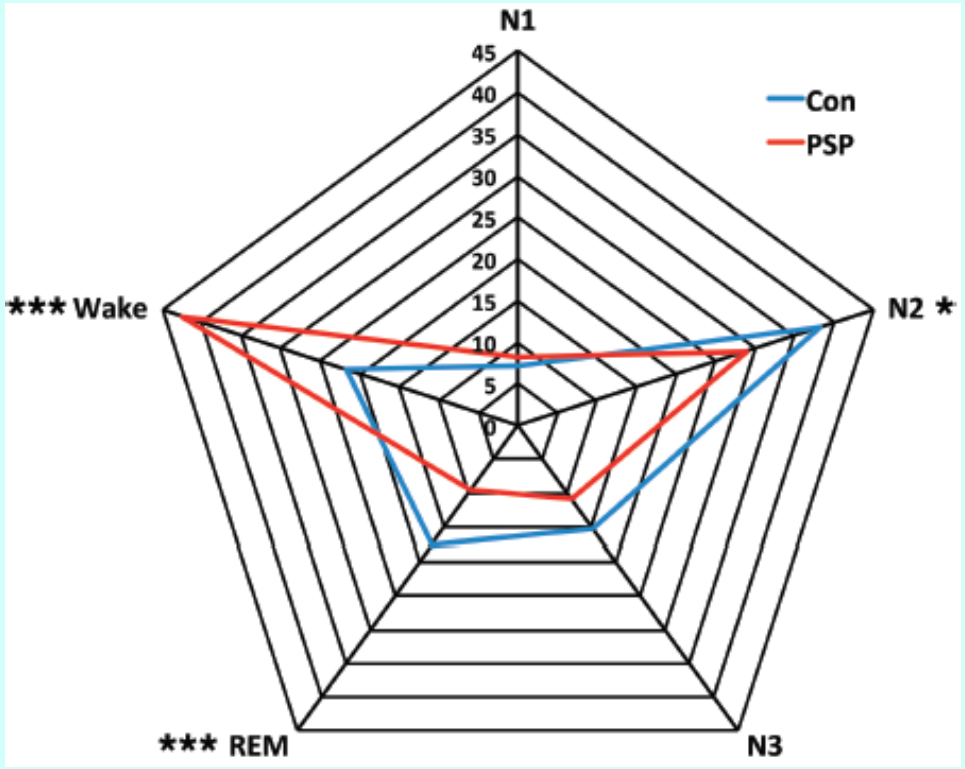


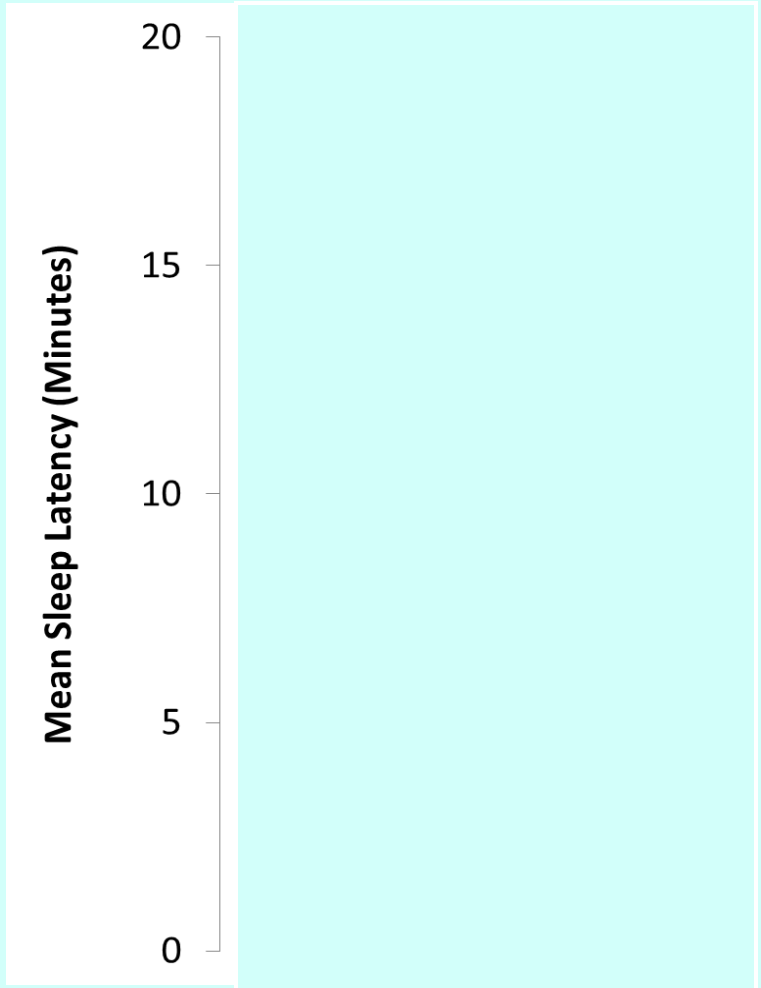
Williams et al., 2007

Saper, Scammell & Lu, 2005; Saper & Fuller, 2017

PSP have profound sleep loss







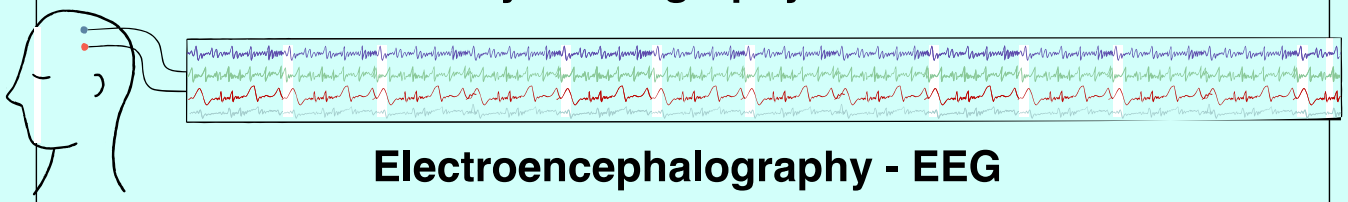
Little sleep day or night

Walsh et al., 2017

18
Clinical Sleep Control

20
Progressive Supra-nuclear Palsy

Polysomnography - PSG



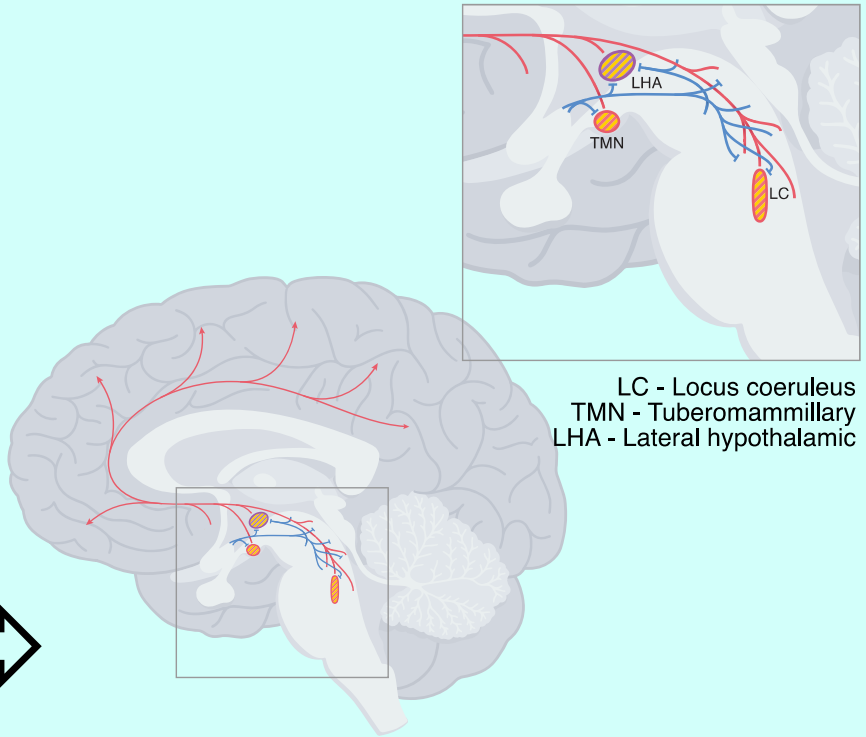
Electroencephalography - EEG

14
Clinical Sleep Control

33
Alzheimer's disease

19
Postmortem Neuronal Counting Analysis

x9 x10



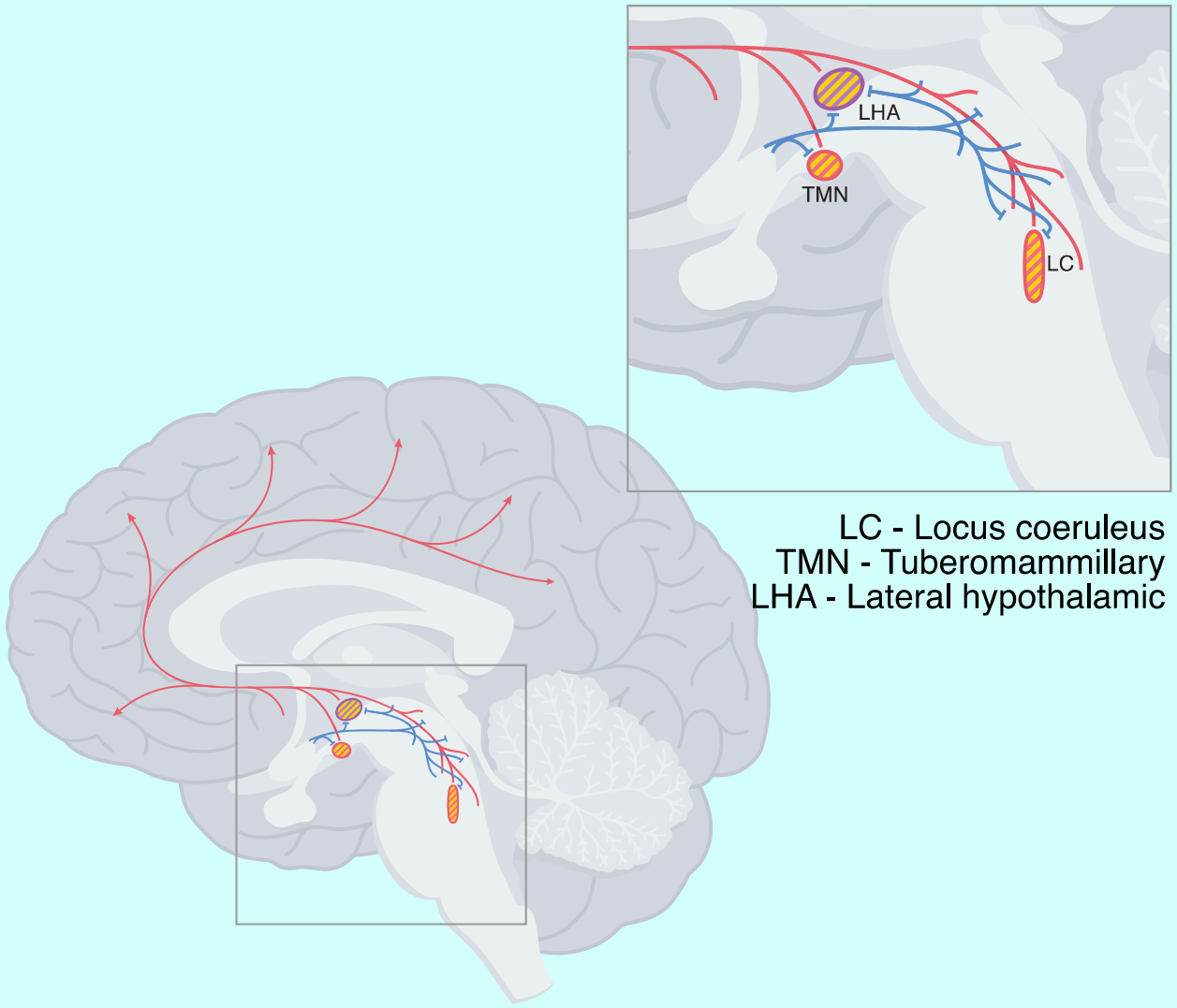
LC - Locus coeruleus
TMN - Tuberomammillary
LHA - Lateral hypothalamic

Oh, Walsh et al, 2022

Key take-aways

- Wake Promoting Neuronal count was associated with –
  - Loss of sleep drive
  - Increased sleep fragmentation

- Number of subcortical wake-promoting neurons relates to sleep phenotypes
- -> tau accumulation is sufficient to disrupt sleep/wake balances in neurodegenerative diseases

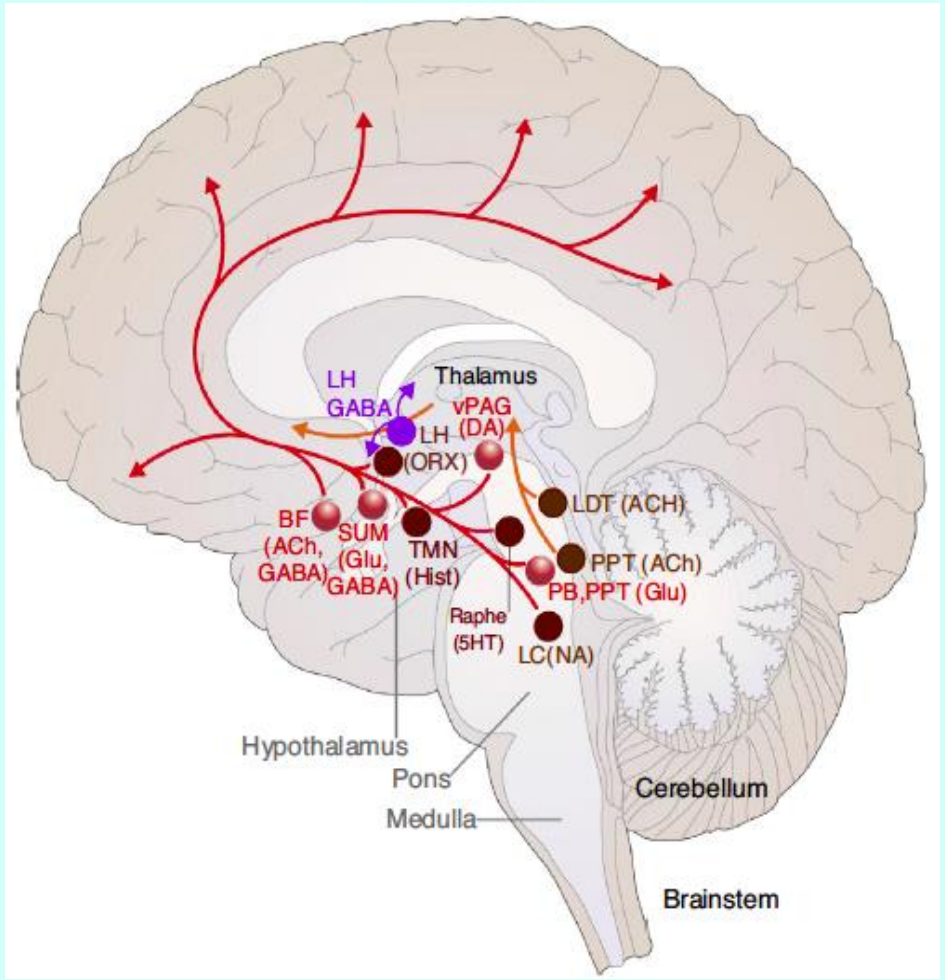


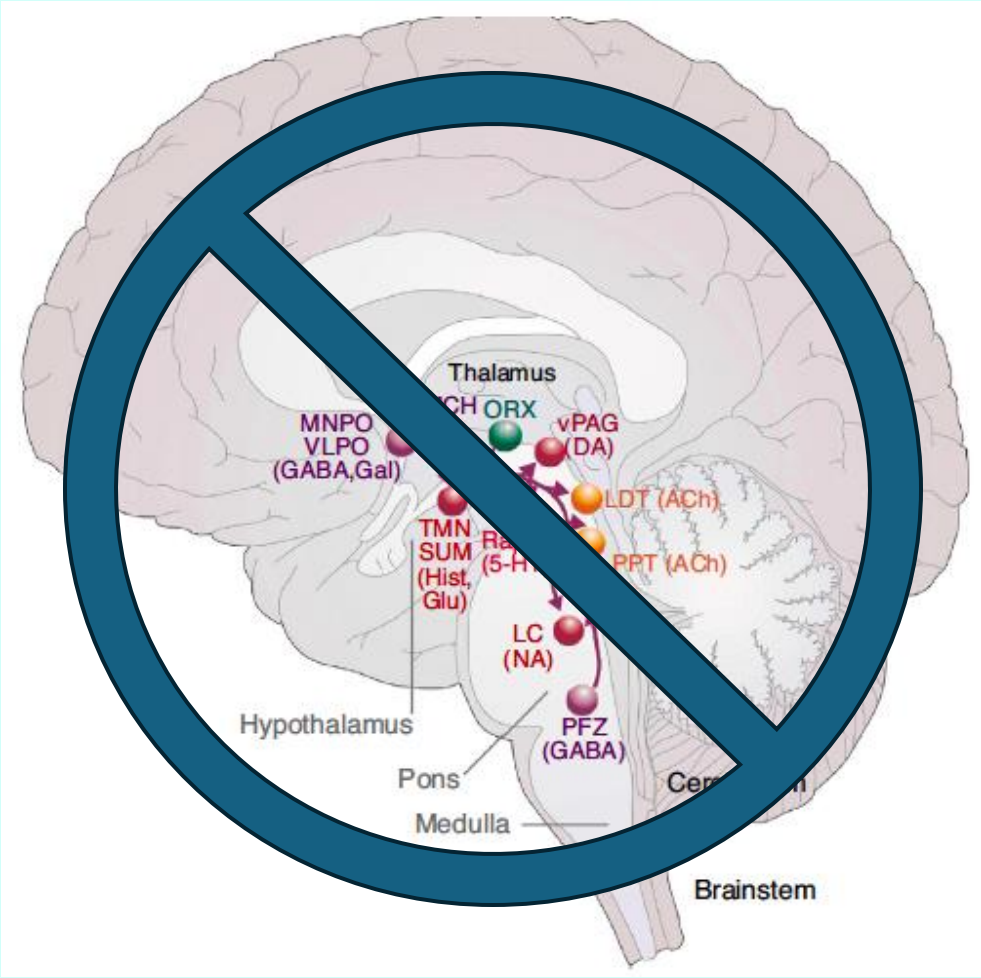
LC - Locus coeruleus
TMN - Tuberomammillary
LHA - Lateral hypothalamic

Oh, Walsh et al, 2022

Wake Promoting

Sleep Promoting





Saper, Scammell & Lu, 2005; Saper & Fuller, 2017

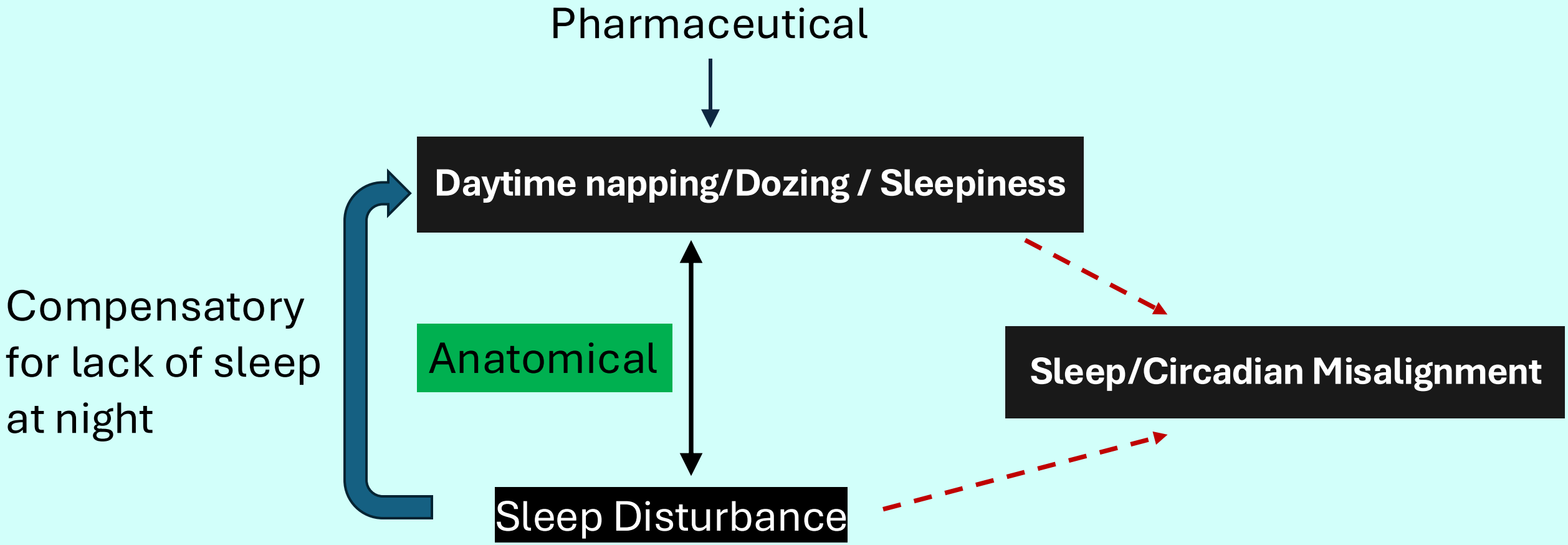
Development of targeted sleep interventions

- Profound loss of sleep in PSP & relative sparing of orexinergic wake-promoting nuclei

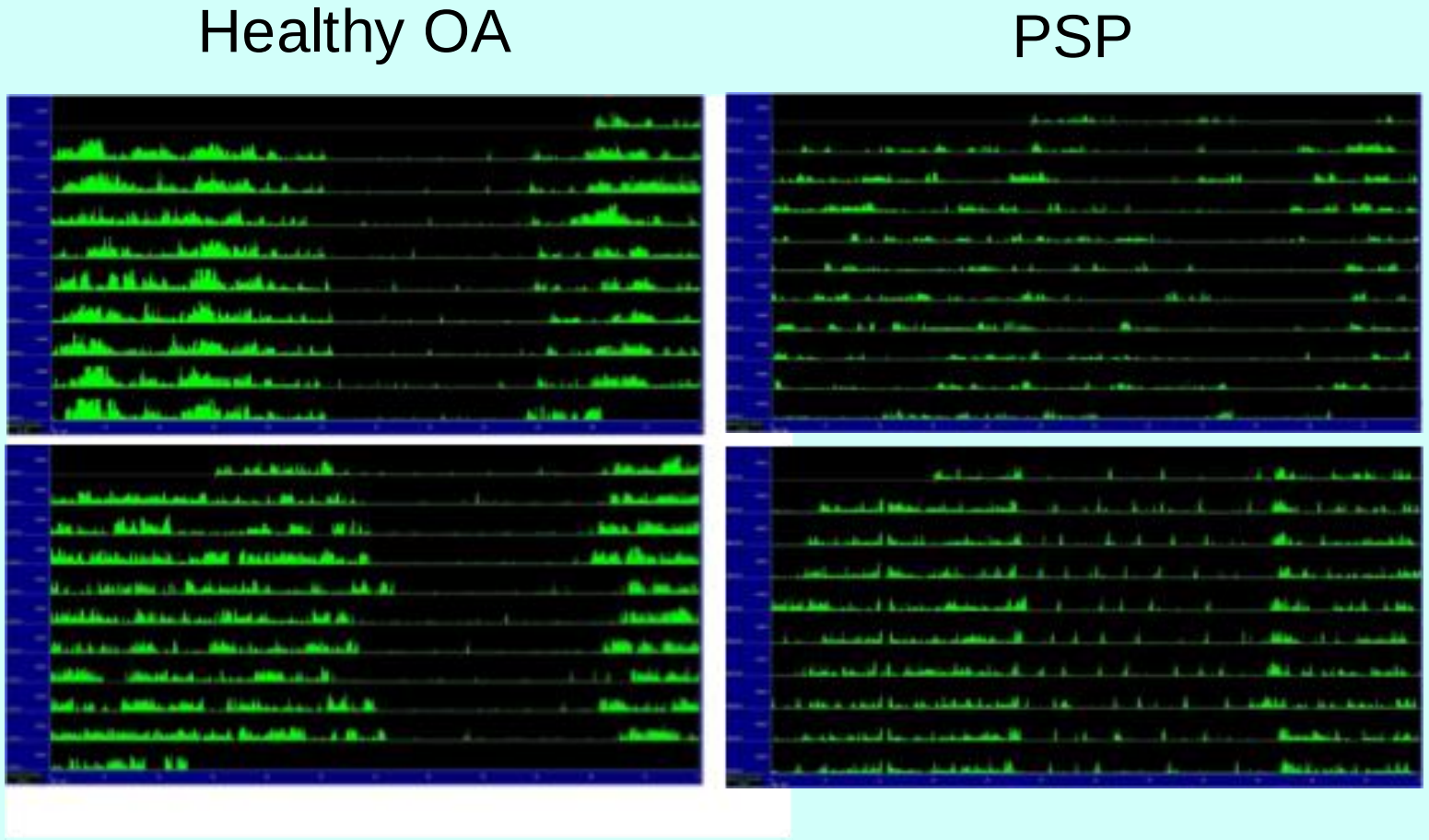
- 6-week cross-over study in PSP using 2 FDA-approved hypnotics
  - Zolpidem – GABAergic agonist, targets sleep regulating system
  - Suvorexant – Orexin antagonist, targets wake regulating system

- Aims:
  - To examine the efficacy and safety of a) zolpidem and b) suvorexant on objectively measured sleep and clinical global ratings of change in symptomatic severity in subjects with PSP.
  - Compare and contrast the effects of suvorexant and zolpidem on efficacy and safety in subjects with PSP.
  - Test the acceptability and feasibility of conducting a remote randomized clinical trial

- Remote to reduce participant/caregiver burden
- Does not preclude future enrollment in any therapeutic trials
- Trial ID: NCT04014387.
- Email: pspsleepstudy@ucsf.edu

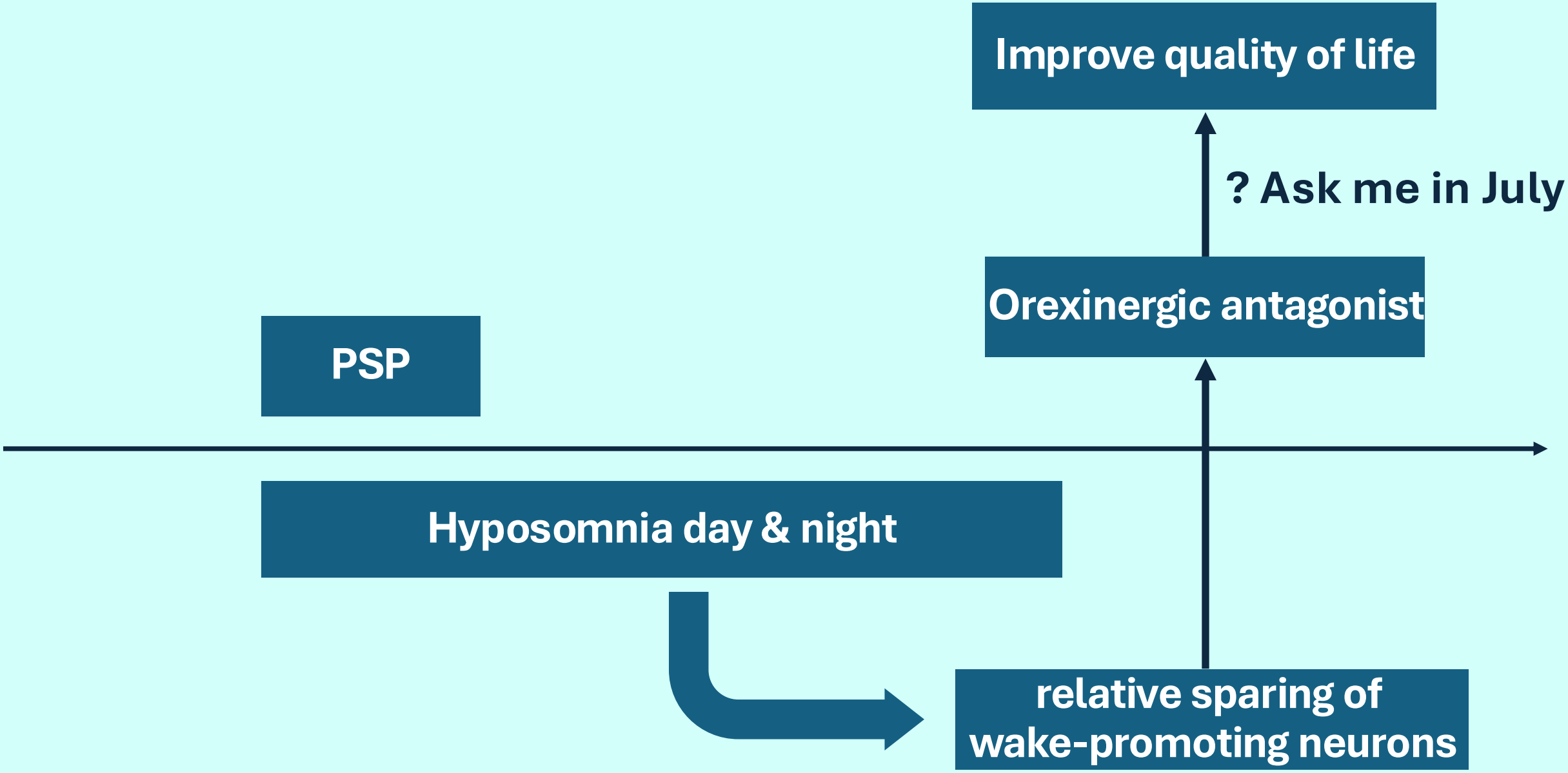

Pharmaceutical
Daytime napping/Dozing / Sleepiness
Compensatory for lack of sleep at night
Anatomical
Sleep/Circadian Misalignment
Sleep Disturbance

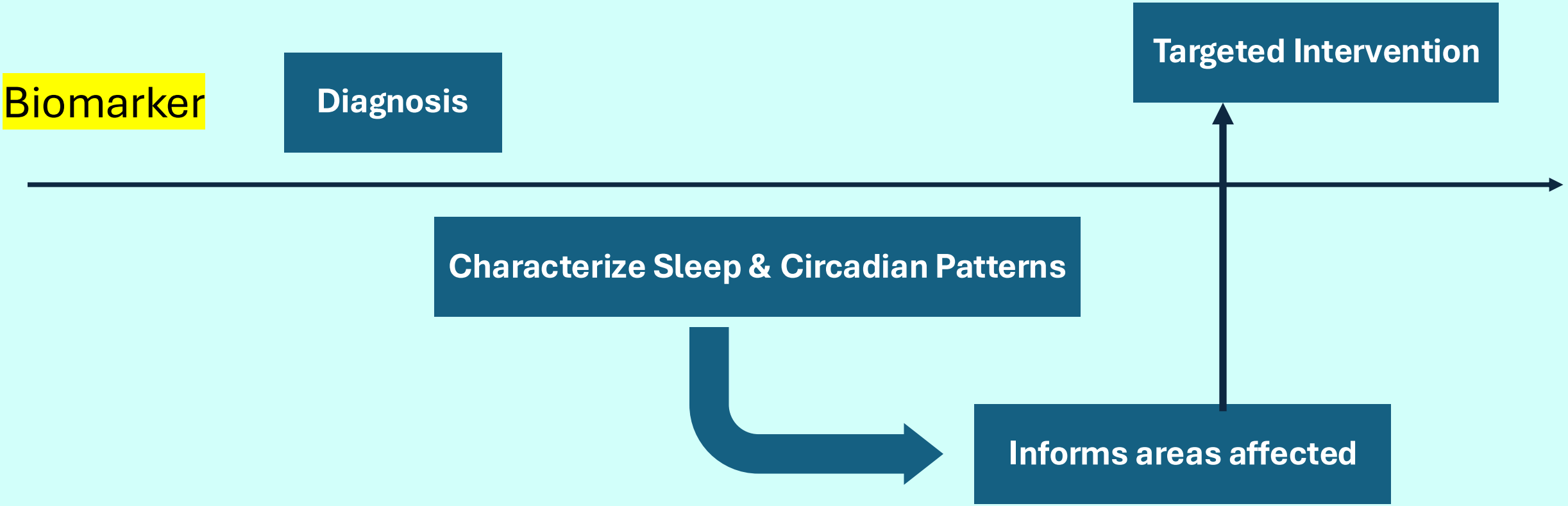
Weakened rest-activity-rhythms in Progressive Supranuclear Palsy (PSP)



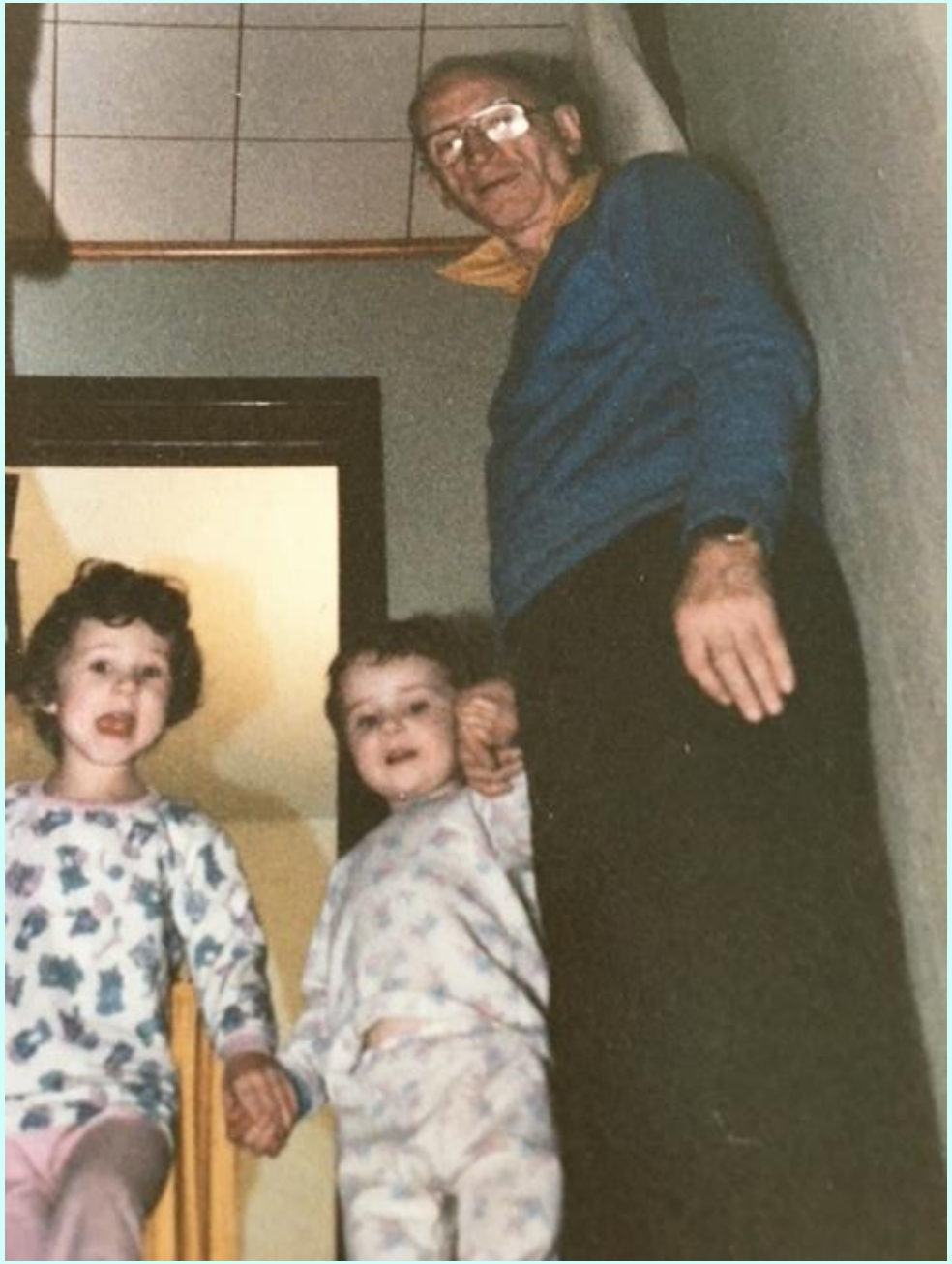
Weaker rest-activity rhythms in PSP after controlling for sleep fragmentation, cognitive impairment & depression

Walsh et al., 2016


Improve quality of life
? Ask me in July
Orexinergic antagonist
PSP
Hyposomnia day & night
relative sparing of
wake-promoting neurons


Biomarker
Diagnosis
Targeted Intervention
Characterize Sleep & Circadian Patterns
Informs areas affected

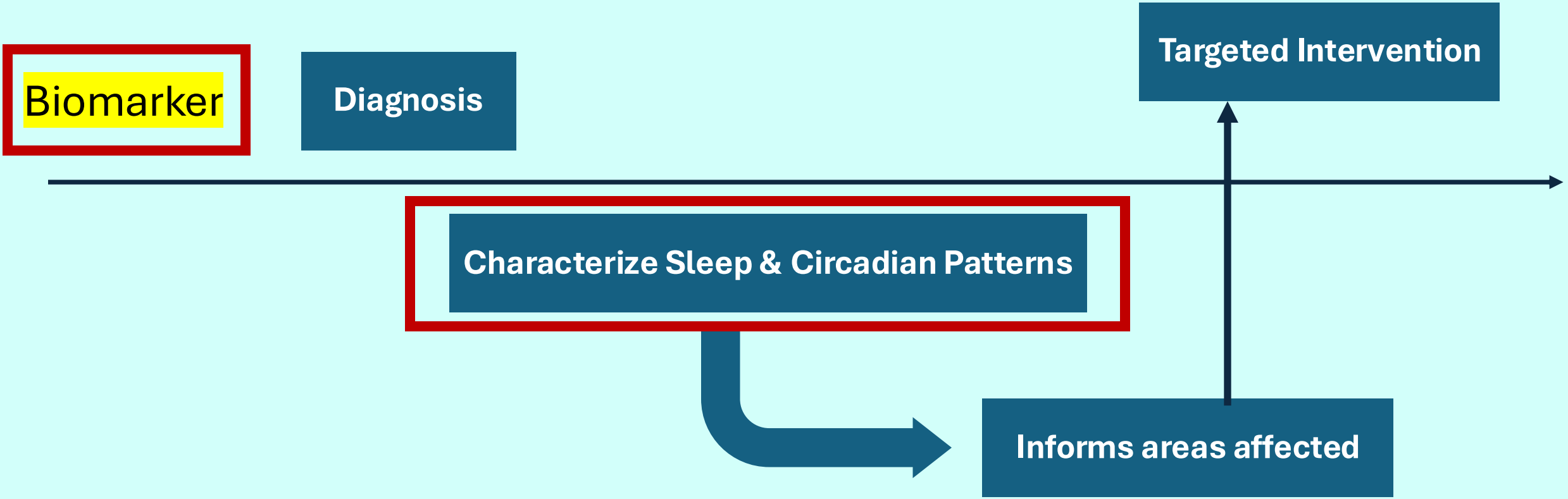
Hints inside our sleep



Sleep disorders as a predictor of NDDs

- REM sleep behavior disorder (RBD)
  - Dream enactment
  - Synucleinopathies
    - **20 years** prior to PD / LBD diagnosis
    - 1 of the core criteria listed for LBD

Huge credit to many including:
Jacques Montplaisir, Carlos Schenck, Mark Mahowald, Ron Postuma, Erik St Louis, Brad Boeve, Alex Iranzo


Biomarker
Diagnosis
Targeted Intervention
Characterize Sleep & Circadian Patterns
Informs areas affected

Insomnia

- Metabolic system
  - Insulin ↓
  - Ghrelin ↑
- Cardiovascular Health
- Immune system
- Sense of loneliness
- Emotional recognition and regulation
- Associated with increased p-tau, aβ, syunclein
- Diminished grey volume
- Diminished white matter integrity
- Cognition

Factors that alter sleep in neurodegenerative diseases

- Physiological changes
  - E.g. weight change
- Occurrence of sleep disorders
- Medical and psychiatric morbidity
  - Hypertension; congestive heart failure; diabetes; depression….
- Medication side effects
- Environmental and behavioral factors

(Deschenes & McCurry, 2009)

Good Sleep Hygiene

- Maintain regular bedtime and rise time throughout the week
- Limit time in bed to sleeping
- Avoid or reduce napping
- Exercise before 2pm
- Spend time in natural light
- Avoid caffeine, nicotine and alcohol close to bedtime
- Establish a comfortable sleep environment
- Establish a calming nighttime routine

Caregiving through the night

- Caregivers have lower sleep durations (~ 2.4 – 3.5hrs less/wk; Gao et al., 2019)
- Sleep helps mood and emotions
  - reduce stress / anxiety
  - can reduce depression
  - helps regulate emotions
  - helps in reading emotions
  - helps in risk-assessment
  - helps in judgement and negotiating
- Sleep helps overall health
  - the immune system
  - insulin / ghrelin regulation
  - neural health

How can a caregiver sleep?

The “Try Tos”

- reduce likelihood of un-checked sleep disorders for you and your loved-one
  - (also talk to dr about medication schedule)
- maintain a stable sleep pattern (bedtime and final rise time)
- exercise or get some daylight in the morning
- reduce your level of alertness during the night
  - use a patient bed monitor or door monitor
  - or set an alarm if needed for nighttime care
- follow general sleep hygiene guidelines as best you can
- continue being social, including attending groups like this

Acknowledgements

Participants & Their Families

UCSF SAND lab
Thomas Neylan
Lea Grinberg
Esther Li
Natalie Pandher
Leslie Yack
Grinberg Lab

MAC UCSF teams
ADRC, BrANCH, ALLFTD, RabLab, Grinberg Lab, PPG, RPD, Trials

UCSF
Adam Boxer
Kaitlin Casaletto
Joseph Chen
Adam Gazzaley
Michael Geschwind
Hilary Heuer
Joel Kramer
Bruce Miller
Joseph Oh
Emily Paolillo
Igor Pruffer
Gil Rabinovici
Kamalini Ranasinghe
Julio Rojas
Rowan Saloner
Wade Smith
Adam Staffaroni
Lawren VandeVerde
David Ziegler

Mayo Clinic- Rochester
Erik St Louis
Bradley Boeve

UCLA
Keith Vossel

Stanford University
Emannuel Mignot

UCSD
Sara Banks

Vanderbilt University
Ciaran Considine
Ryan Darby

Advanced Brain Monitoring, Inc

University of Cambridge
Zanna Voysey
Roger Barker

Sapienza University of Rome
Susanna Lopez
Claudio Babiloni

Hospital Clinic, Barcelona
Neus Falgàs

Funding:
Rainwater Charitable Foundation
NIA R01 AG032289 (Kramer)
NIA RO1 AG038791 (Boxer)
NIA U54NS092089 (Boxer)
NIA R01AG060477 (Neylan, Grinberg)
NIA R01 AG064314 (Grinberg, Neylan)

UCSF Weill Institute for Neurosciences

Memory and Aging Center

THANK YOU

PSPsleepstudy@ucsf.edu

Christine.walsh@ucsf.edu