Healthy Sleep, Healthy Brain

Canadian Consortium on Neurodegeneration in Aging / Alzheimer's Society of Canada Webinar
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Andrew S.P. Lim MD
Neurologist, Sunnybrook Health Sciences Centre
Associate Professor, Division of Neurology
University of Toronto, Toronto, Canada

Sleep is seen throughout the animal world…

… so it must be doing something important…. and that thing might be maintaining brain health.

Outline

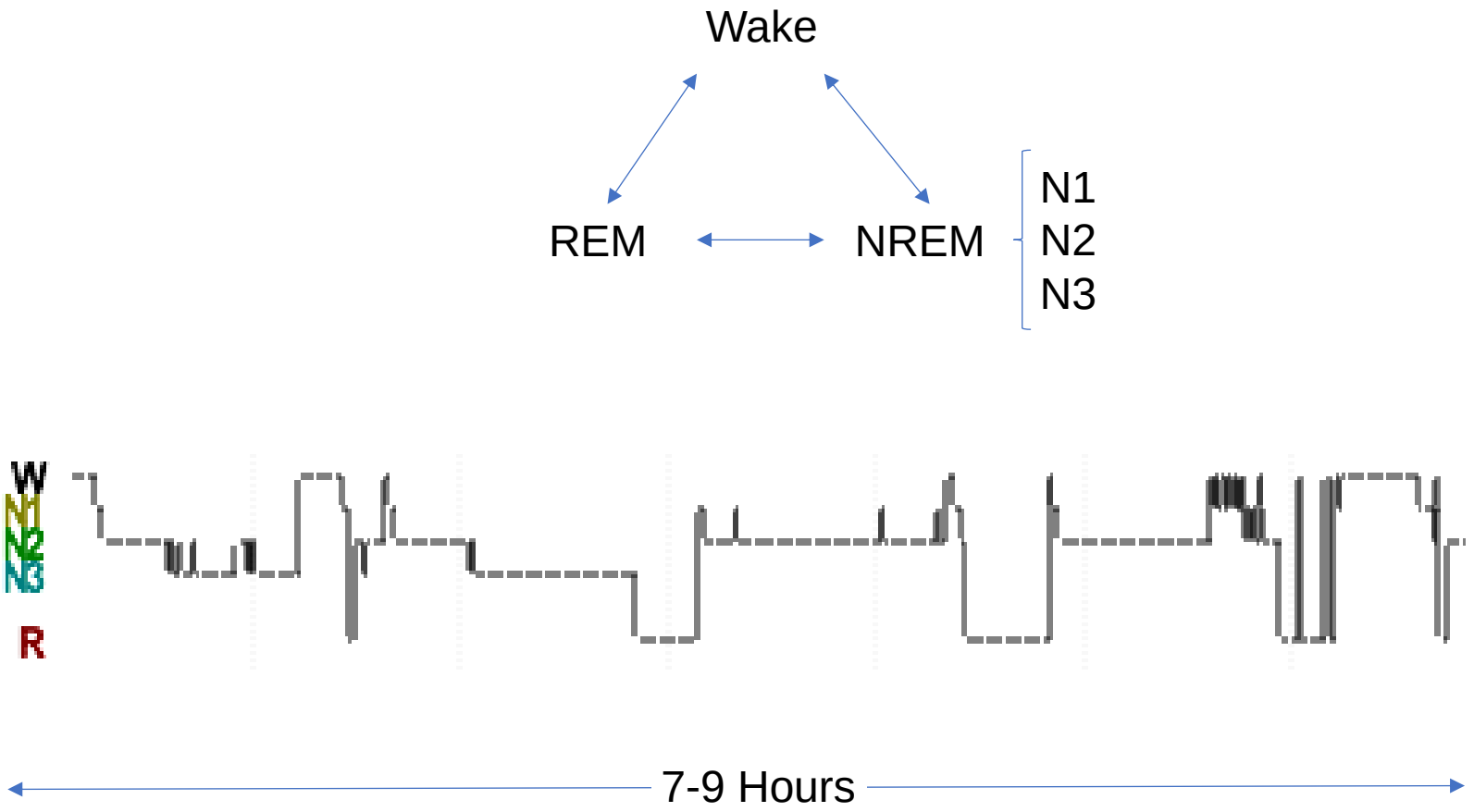
Part I: ABCs of Sleep
- 1.1 Normal Sleep
- 1.2 Functions of Sleep
- 1.3 Measurement of Sleep
- 1.4 Types and Burden of Sleep Disruption

Part II: Sleep and Dementia
- 2.1 Hypothetical Framework
- 2.2 Epidemiology
- 2.3 Neurobiology

Part III: Sleep in the Geriatric Clinic
- 3.1 Cardinal Sleep Symptoms
- 3.2 Neurobiology of Sleep and Wake Regulation
- 3.3 Disrupted Nighttime Sleep
- 3.4 Excessive Daytime Sleepiness

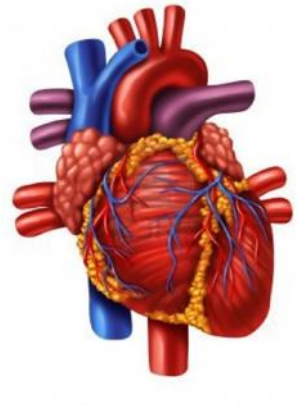
Part I: ABC’s of Sleep

1.1 Normal Sleep

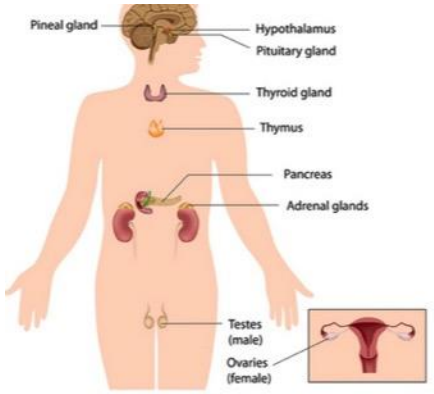


1.2 Functions of Sleep

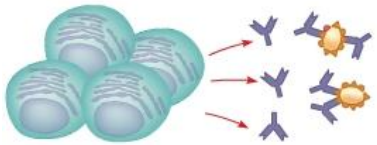
Cardiovascular Health



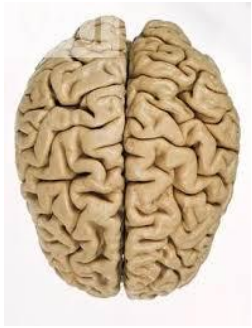
Hormonal Regulation



Immune Function

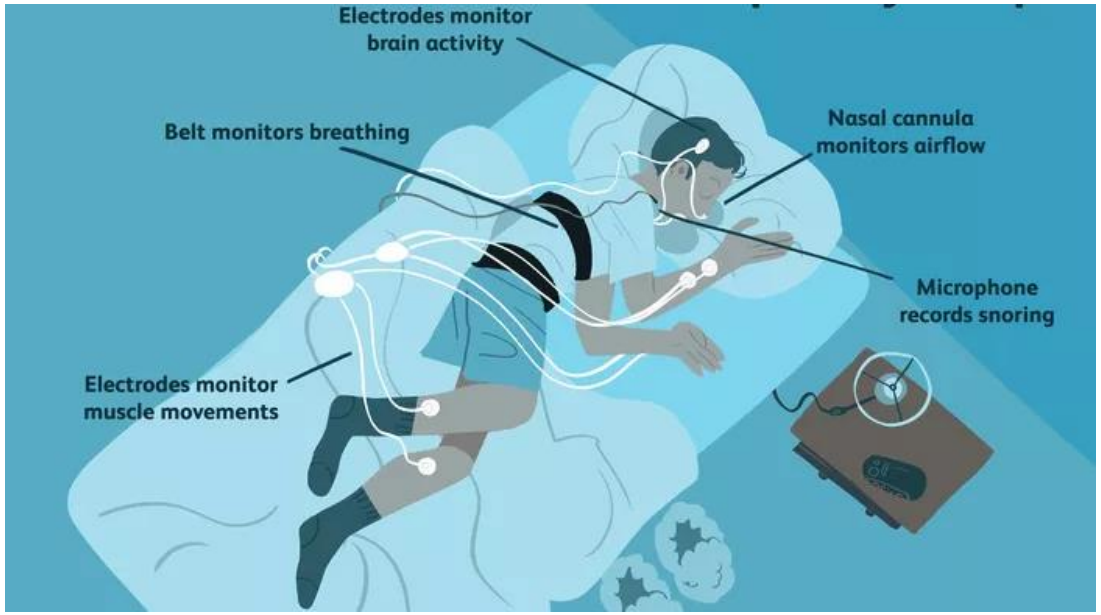


Brain Health



1.3 Measurement of Sleep

In the Sleep Lab



At Home

Actigraphy

Finger Plethysmo-graphy

Home Sleep Apnea Testing

Wireless Adhesive ECG/sound/resp /PTT/SpO2/accel

Ambulatory EEG

1.4 Types and Burden of Sleep Disruption

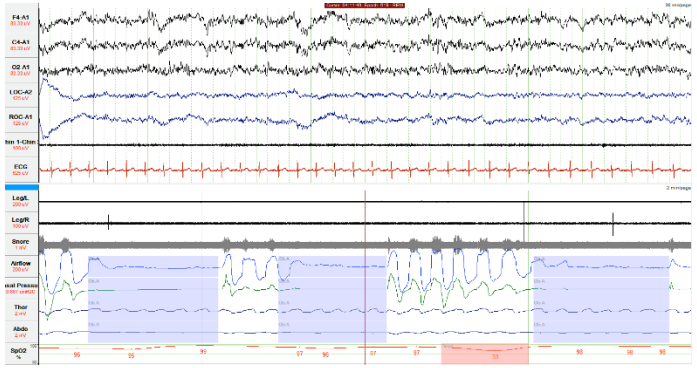
Sleep Deprivation

15% of employed Americans report getting less than 6 hours a night of sleep

Poor Sleep Quality (e.g. Fragmentation, sleep stage distribution)

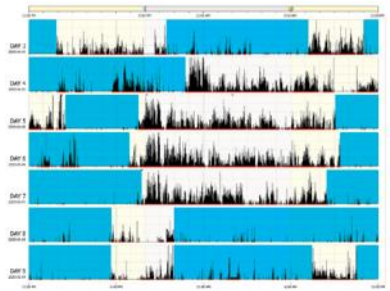
30-40% of older Americans complain of excessive awakenings at night

Disrupted Sleep Physiology (e.g. Apnea, RLS)



Up to 5% of middle-aged and 9-17% of older American adults has sleep apnea

Circadian Rhythm Disruption (e.g. Shift-Work)



~15 million Americans (~10% of workforce) are engaged in regular night work or rotating shift work

The Ontario Sleep Health Study

3200 Adults Aged 35-70 (mean age 58)

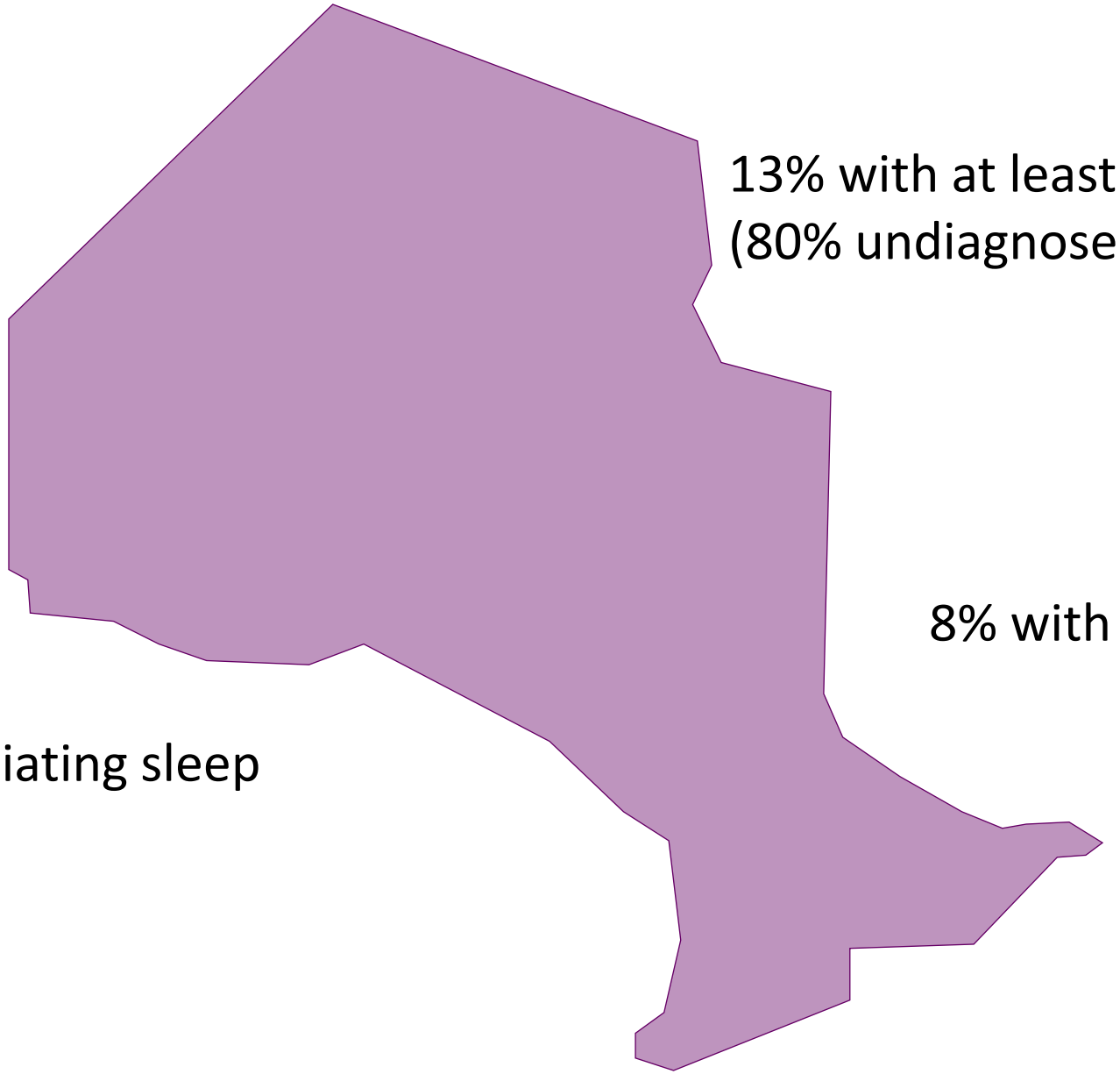
38% with excessive sleepiness

13% with at least moderate sleep apnea (80% undiagnosed)

64% with difficulty maintaining sleep

8% with restless legs syndrome

13% with difficulty initiating sleep



Part II: Sleep and Dementia

Sleep Problems are Common and Have a Huge Impact on Health

65% of men and
35% of women aged
60-85 have SLEEP APNEA

35-45% of older adults report INSOMNIA

Older adults with SLEEP APNEA have 1.5-2.5x the risk of DEMENTIA

INSOMNIA is associated with 1.5x the risk of DEMENTIA

Older adults SLEEPING <5 HOURS per night have 2.6x the risk of DEMENTIA

Hypothetical Framework

Sleep and Circadian Rhythm Disruption

Hypothetical Framework

Sleep and Circadian Rhythm Disruption

Molecular, Cellular, Network-Level Brain Changes

Hypothetical Framework

Sleep and Circadian Rhythm Disruption

Molecular, Cellular, Network-Level Brain Changes

Cognitive, Motor, Functional Impairment

Hypothetical Framework

Sleep and Circadian Rhythm Disruption

Molecular, Cellular, Network-Level Brain Changes

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Cognitive, Motor, Functional Impairment

Sleep fragmentation is associated with a higher risk of incident Alzheimer's disease and more rapid cognitive decline

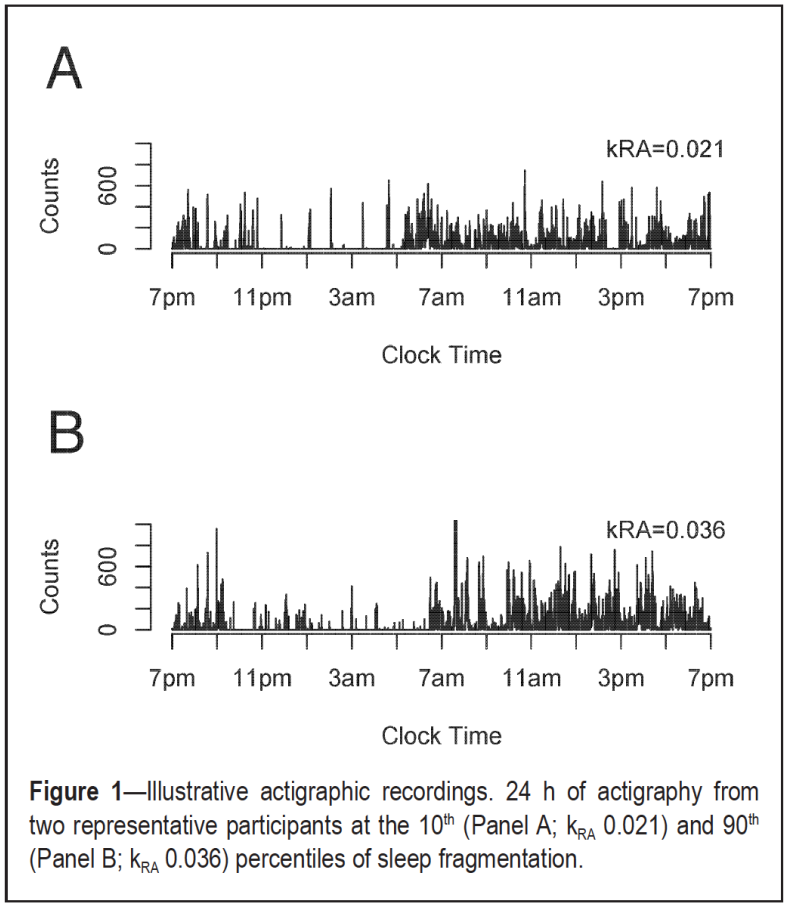
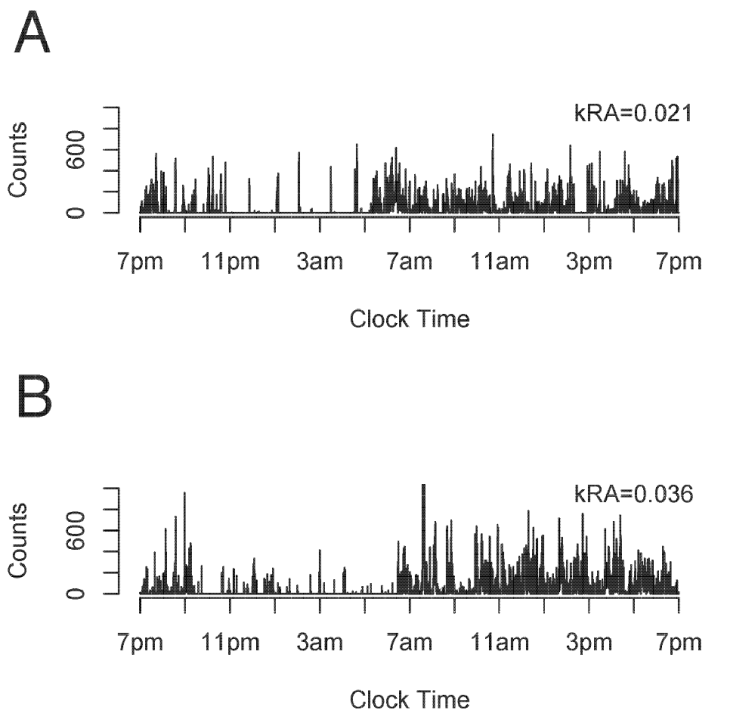


Figure 1—Illustrative actigraphic recordings. 24 h of actigraphy from two representative participants at the 10th (Panel A; k_{RA} 0.021) and 90th (Panel B; k_{RA} 0.036) percentiles of sleep fragmentation.

Lim et al, Sleep, 2013 (n=737; Rush Memory and Aging Project)

Sleep fragmentation is associated with a higher risk of incident Alzheimer's disease and more rapid cognitive decline



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Incident Alzheimer's Disease

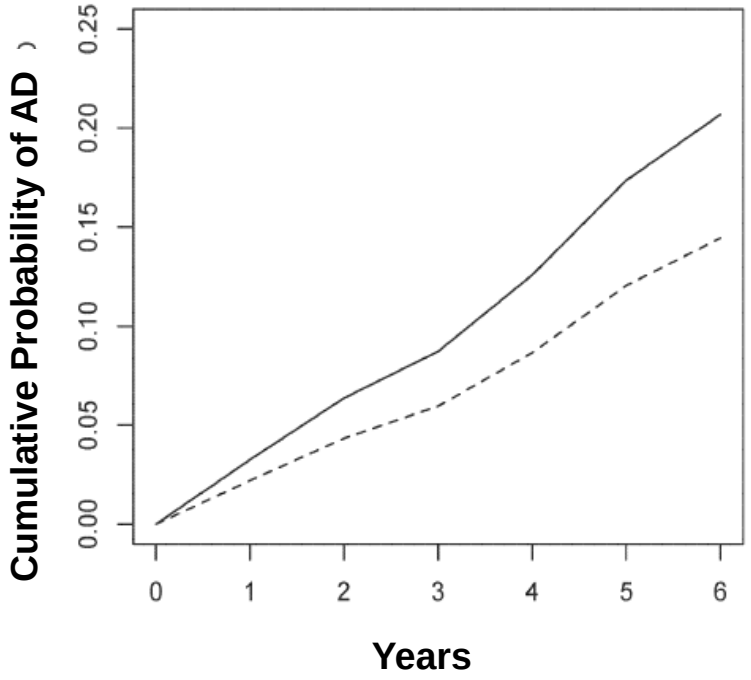

Figure 2—Expected risk of AD. The model predicted risk of AD based on the entire cohort is illustrated for two hypothetical average participants with high (Solid line: 90th percentile; k_{RA} = 0.036) and low (Dotted line: 10th percentile; k_{RA} = 0.021) levels of sleep fragmentation.

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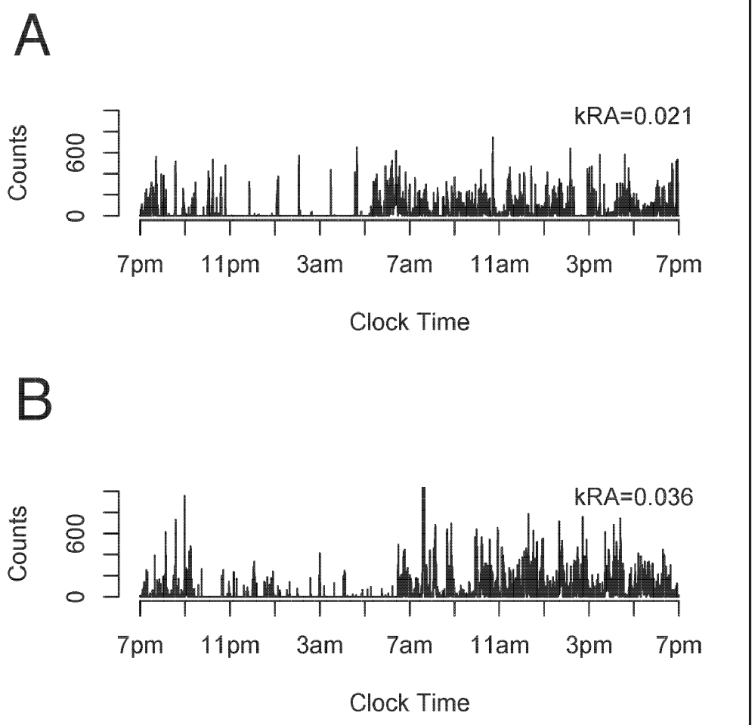

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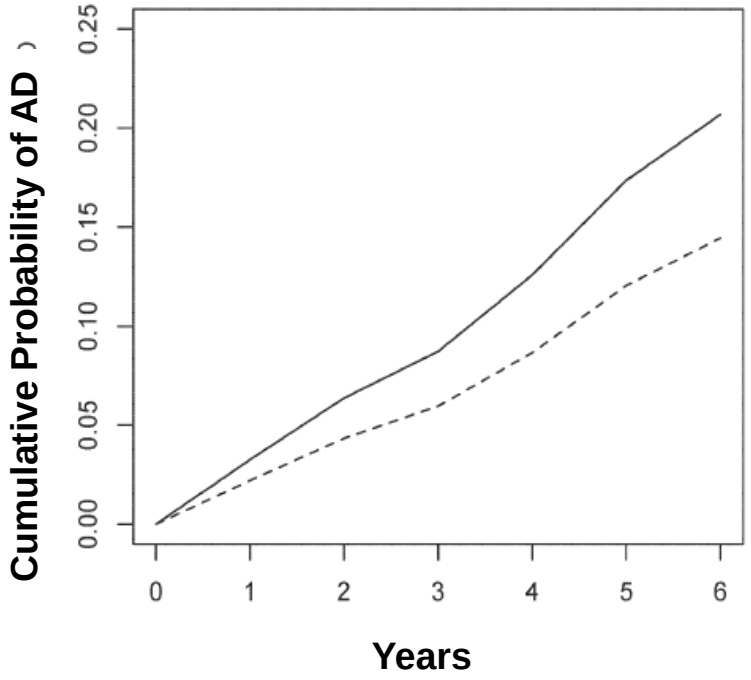

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Cognitive Decline

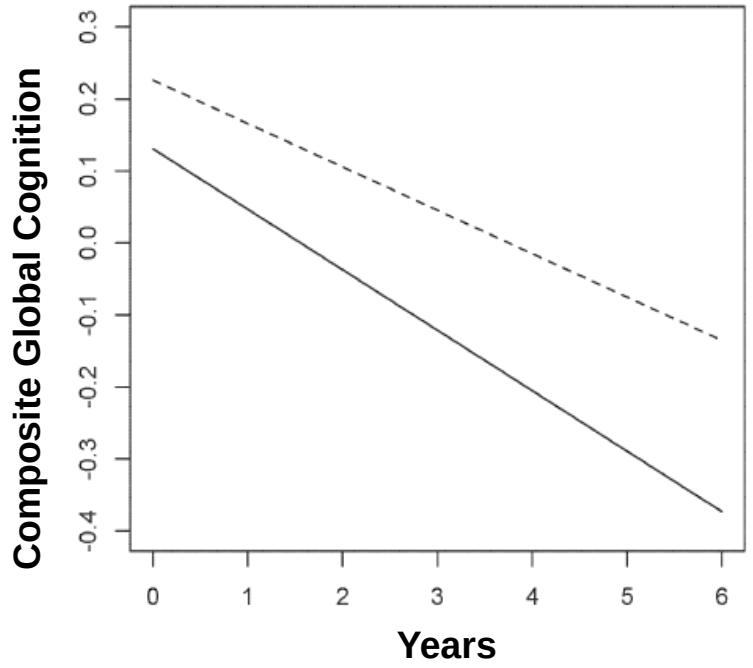

Figure 3—Expected cognitive decline. The model predicted rate of global cognitive decline based on the entire cohort is illustrated for 2 hypothetical average participants with high (Solid line: 90th percentile; k_{RA} = 0.036) and low (Dotted line: 10th percentile; k_{RA} = 0.021) levels of sleep fragmentation.

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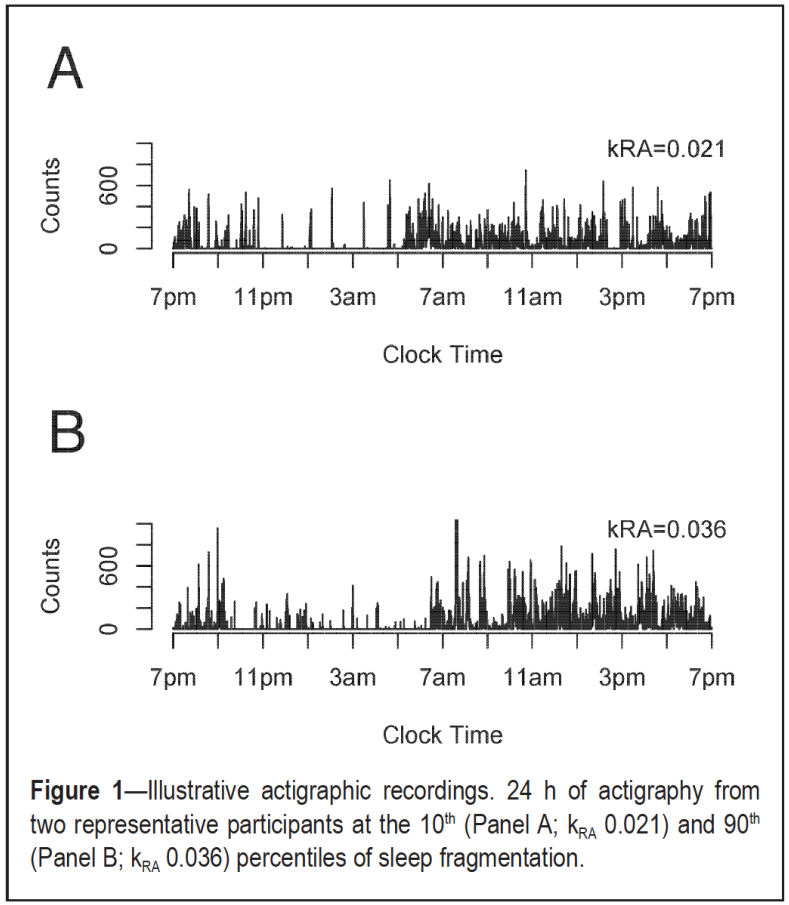
Adults with the APOE e4 genotype are particularly susceptible to the adverse effects of sleep fragmentation



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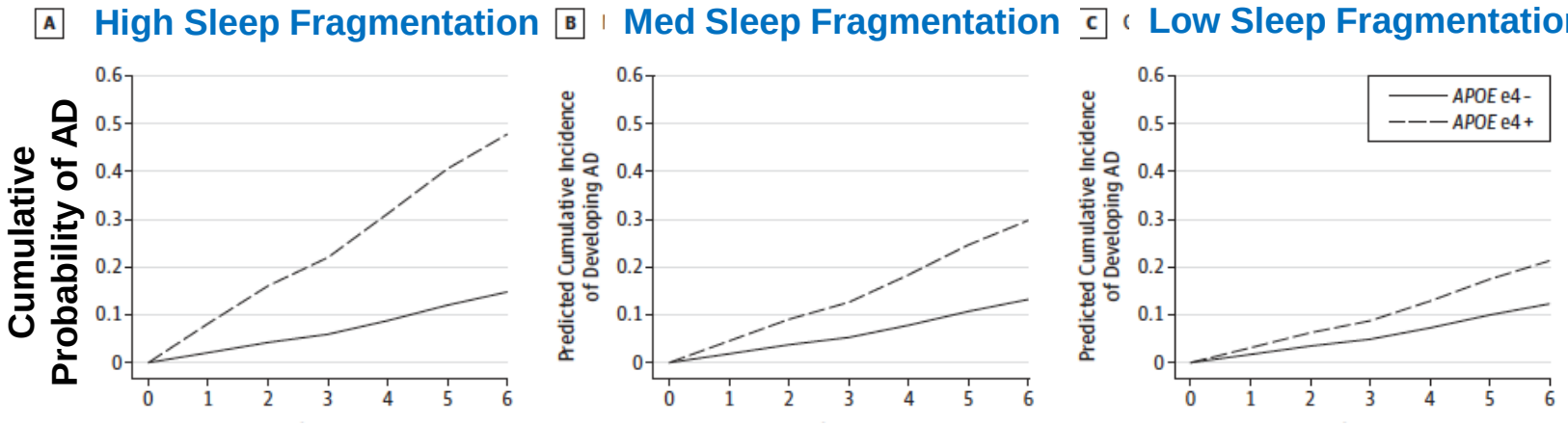

The model-predicted cumulative incidence of Alzheimer disease (AD) and rate of cognitive decline based on the entire cohort are illustrated for hypothetical average *APOE* ε4+ and ε4− participants with poor (A,D: 10th percentile), median (B,E: 50th percentile), and good (C,F: 90th percentile) sleep consolidation (k_{RA} = 0.037, 0.027, and 0.021, respectively).

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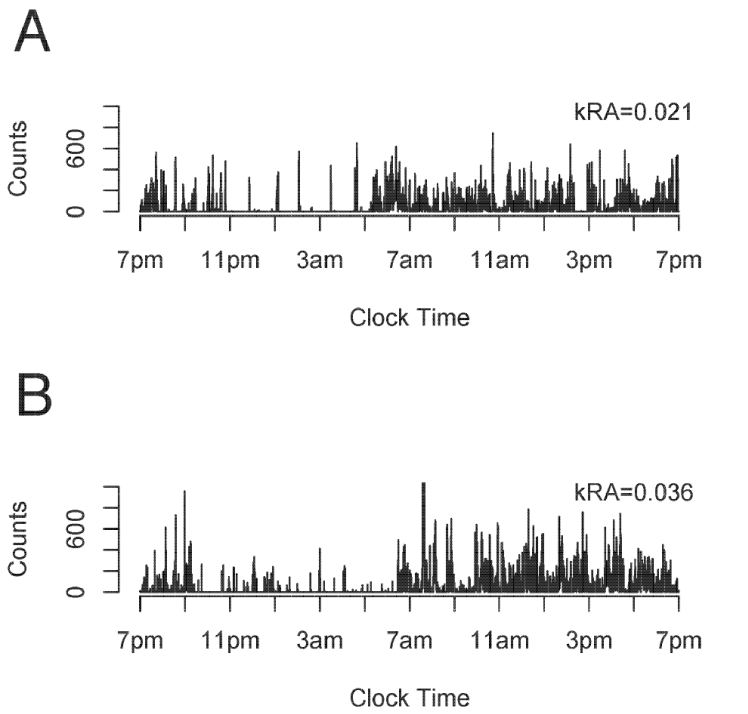

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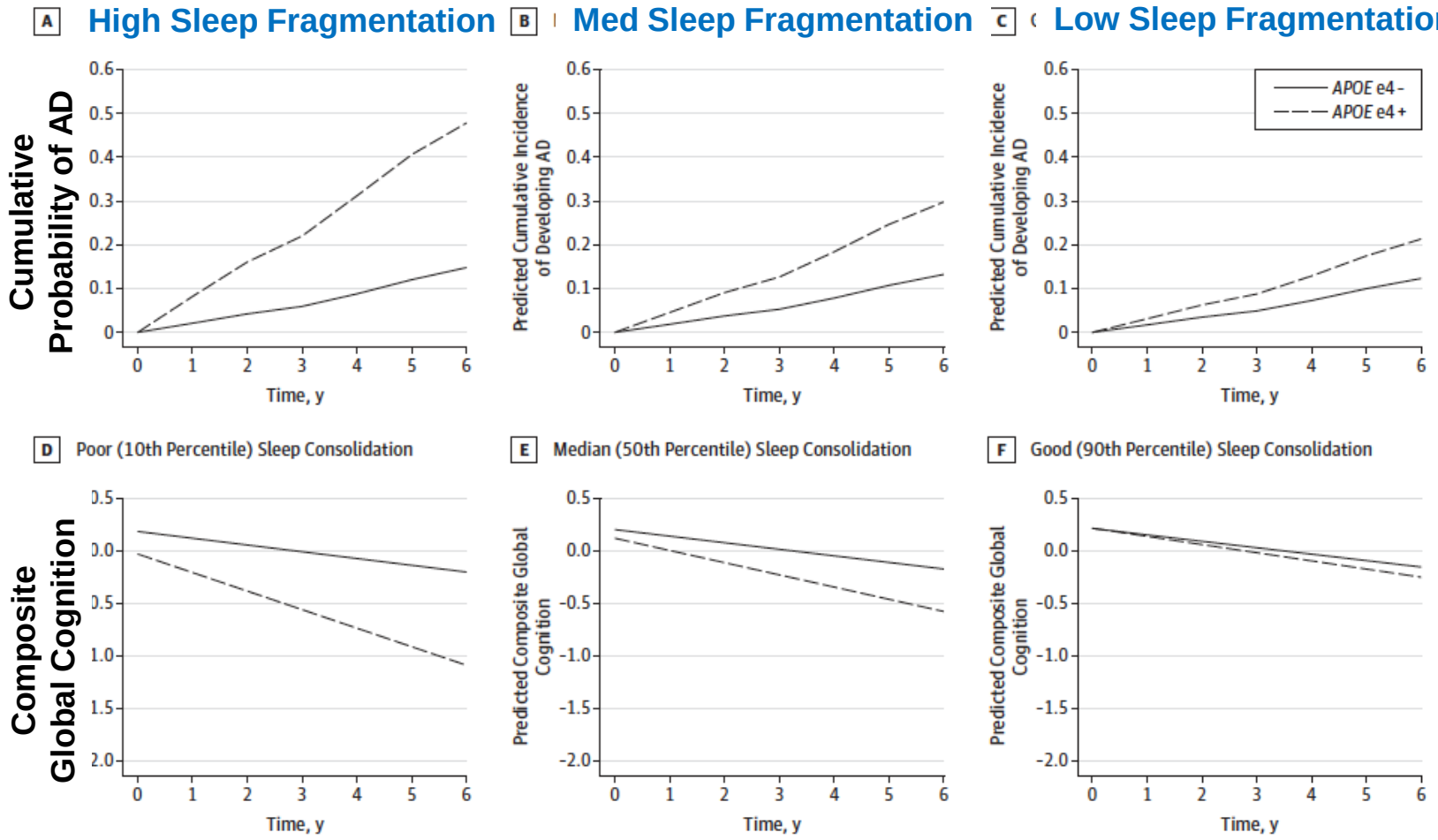

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Why is this?

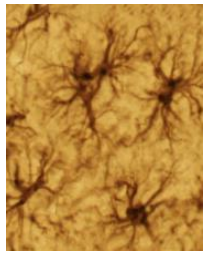
What Mediates these Associations?

Sleep and Circadian Rhythm Disruption

Molecular, Cellular, Network-Level Brain Changes

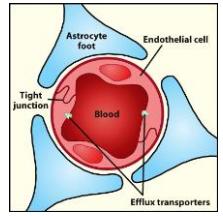
Cognitive, Motor, Functional Impairment

Brain Effects of Sleep and Circadian Disruption in Model Organisms

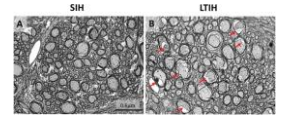


Astrocytosis[1]

Synaptic Dysfunction[1,3,4,5]



BBB[10]



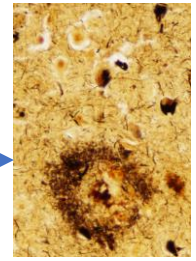
White Matter[11]

Hippocampal Neurogenesis[2]

Circadian Disruption

Sleep Disruption

↑Amyloid Production[12]

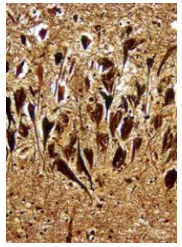


Amyloid[15]

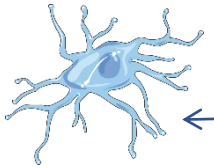
↓Interstitial Clearance[13]

Neuronal Oxidative Stress[1,7]

Autophagy[14]



Tau[16]



Microglia and Inflammation[8,9]

1 Musiek et al, J Clin Invest, 2013
2 Gibson et al, PLoS One, 2010
3 Kincheski et al, Brain Behav Immun, 2017
4 Di Meco et al, Neurobiol Aging, 2014
5 Arrigoni et al, Eur J Neurosci, 2009
6 Silva et al, Neuropharmacol, 2014
7 Zhang and Veasy, J Neurosci, 2014
8 Bellesi et al, J Neurosci, 2017
9 Fonken et al, Brain Behav Immun, 2015
10 He et al, J Neurosci, 2014
11 Veasy et al, Sleep, 2013
12 Cirrito et al, Neuron, 2005
13 Xie et al, Science, 2013
14 He et al, Chronobiol Int, 2016
15 Kang et al, Science, 2009
16 Rothman. Brain Res, 2013

What happens in humans?

Sleep Fragmentation is Accompanied by Focal Brain Atrophy in Older Adults

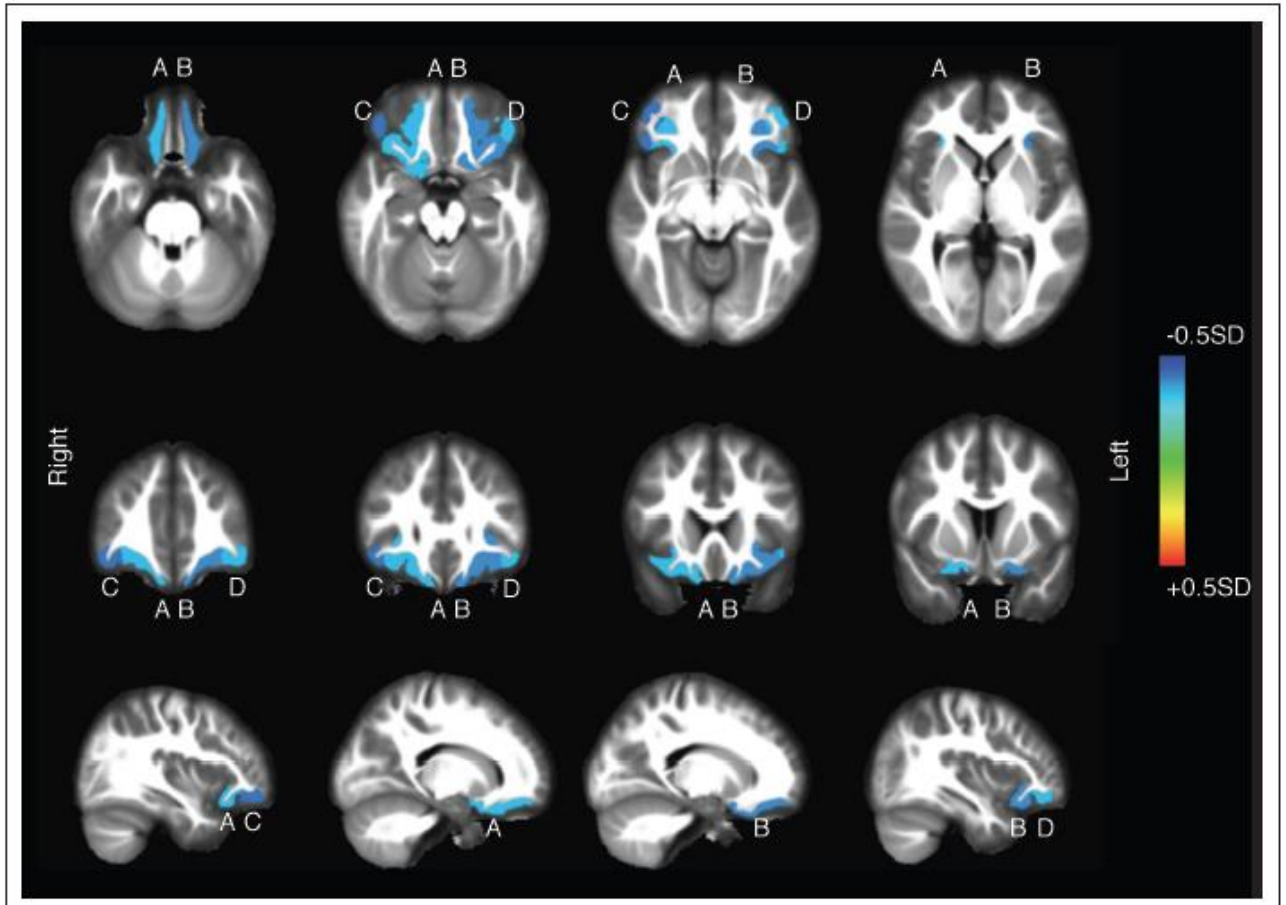
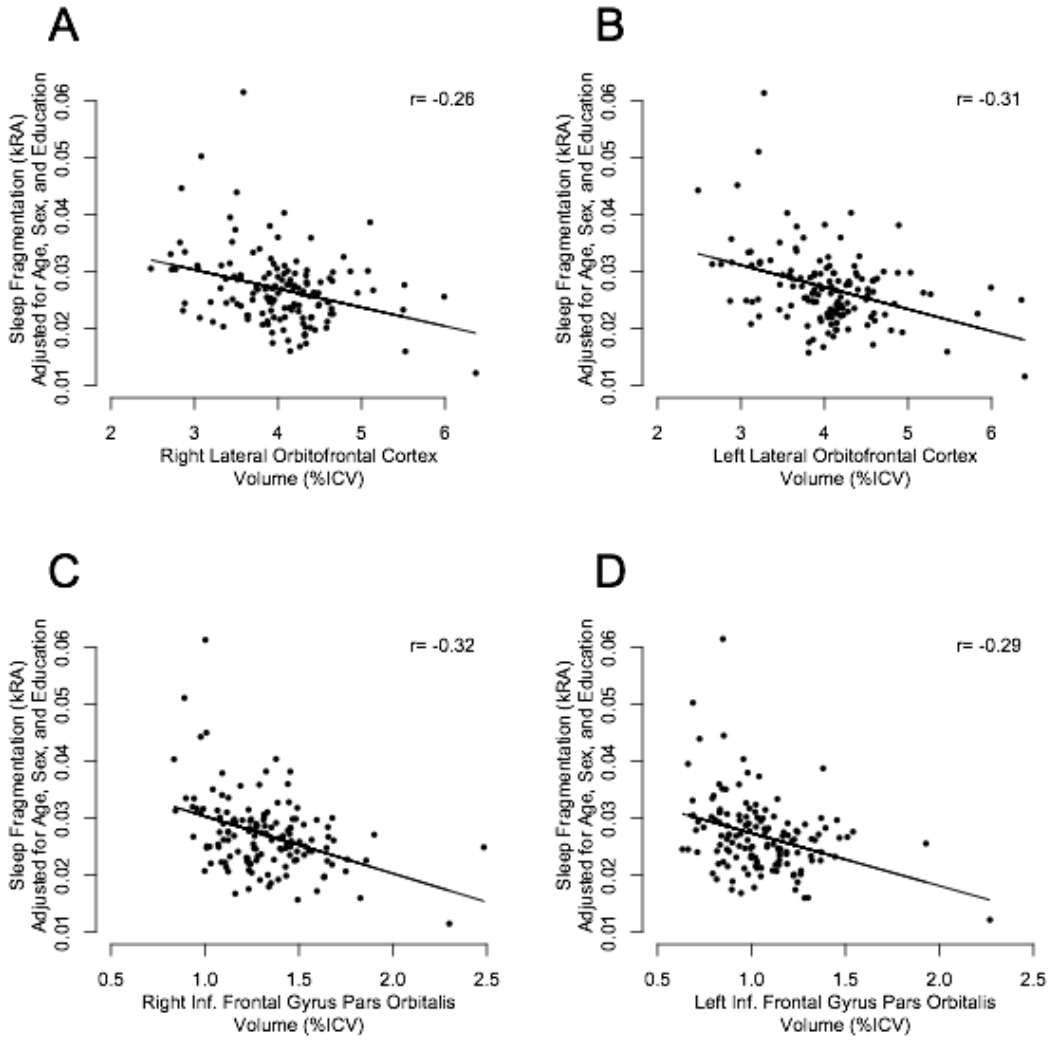


Figure 1—Cortical regional volumes associated with sleep fragmentation at a false discovery rate < 0.05. Color indicates standard deviation (SD) increase in sleep fragmentation per 1 SD decrease in regional cortical volume, overlaid on the mean T1-weighted template and gray matter labels of the IIT Human Brain Atlas (www.nitrc.org/projects/iit2). **(A)** Right lateral orbitofrontal cortex. **(B)** Left lateral orbitofrontal cortex. **(C)** Right inferior frontal gyrus pars orbitalis. **(D)** Left inferior frontal gyrus pars orbitalis.



Lim et al, Sleep, 2016 (n=141; Memory and Aging Project)

Sleep fragmentation is accompanied by greater neurofibrillary tangle pathology, particularly in APOE e4 carriers

Figure 2. Apolipoprotein E (*APOE*) Genotype, Sleep Consolidation, Alzheimer Disease Pathology, and Cognitive Function Proximate to Death

The model-predicted composite global cognitive function proximate to death (A), β-amyloid pathology at autopsy (B), and neurofibrillary tangle density at autopsy (C) based on participants who died during the study period are illustrated for hypothetical average *APOE* ε4⁺ and ε4⁻ participants with poor (10th percentile), median (50th percentile), and good (90th percentile) sleep consolidation. Vertical bars indicate 95% CIs. Composite global function, β-amyloid pathology, and neurofibrillary tangle pathology were assessed as described in the Supplement (eMethods).

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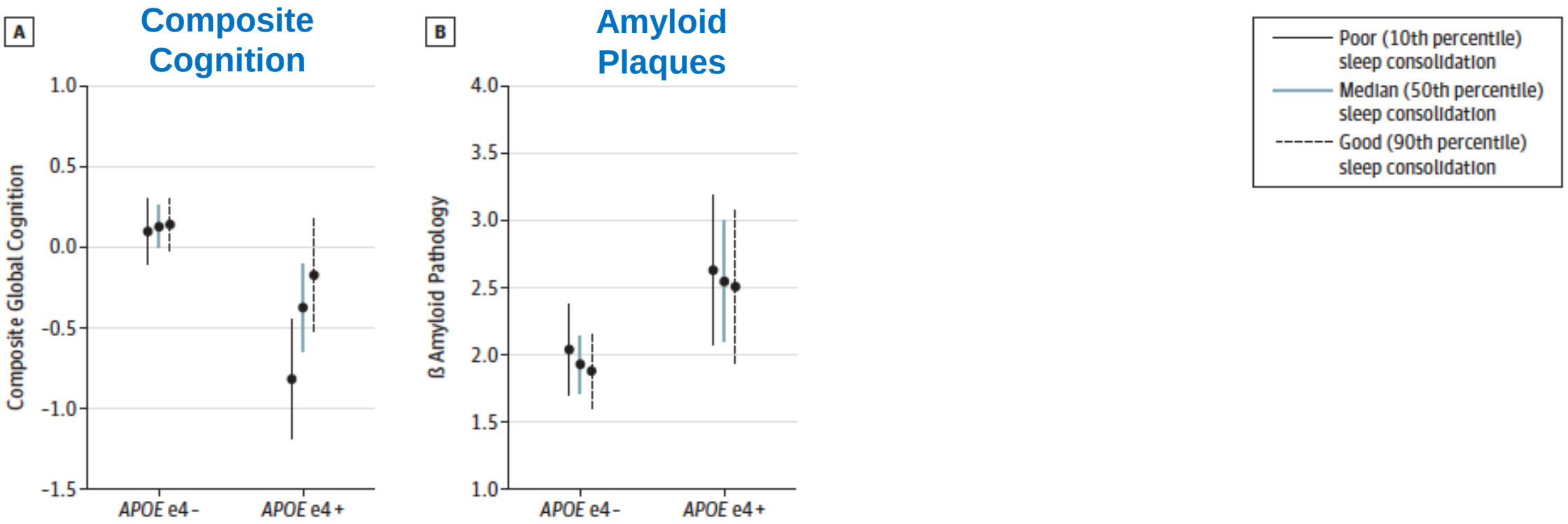

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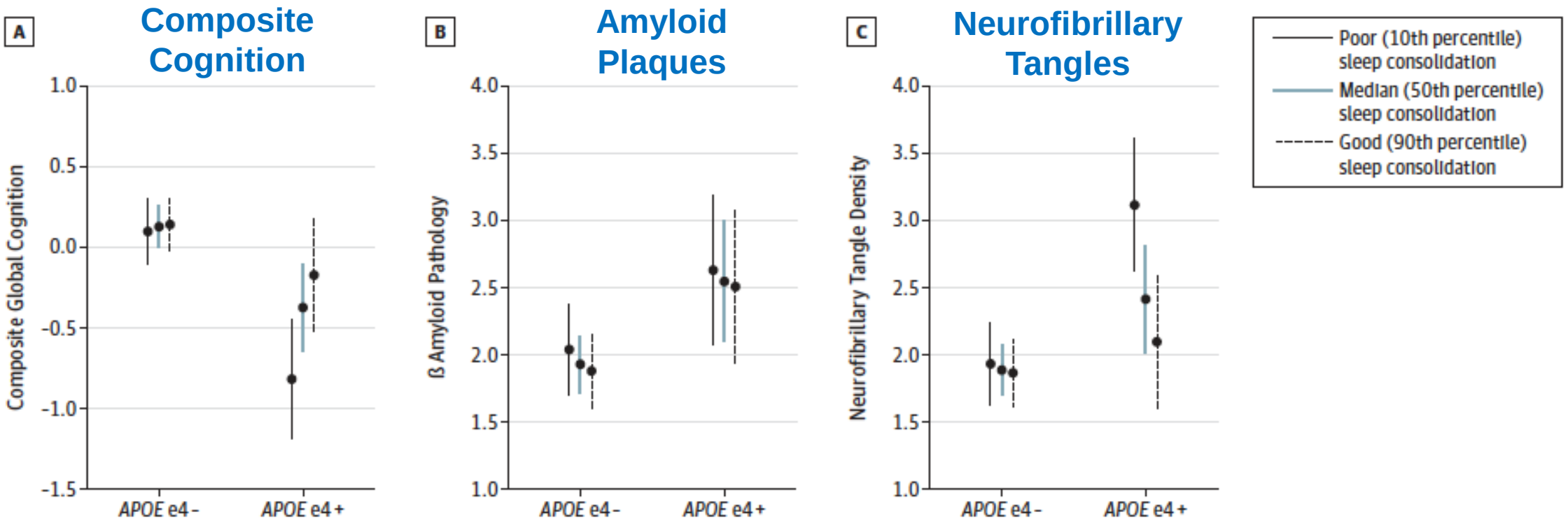

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Sleep fragmentation is accompanied by greater Parkinson disease pathology in adults without Parkinson disease

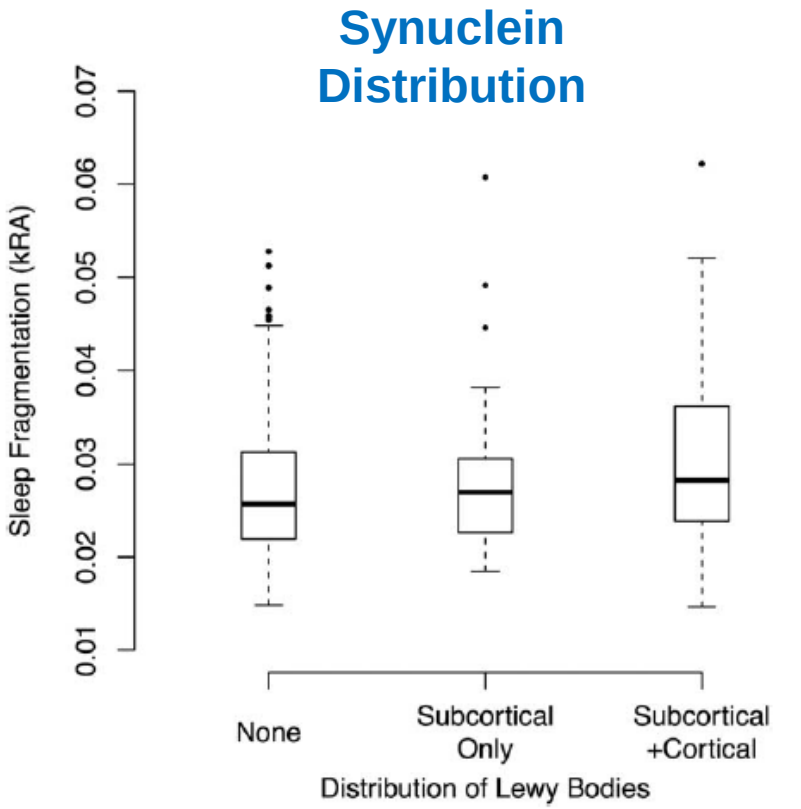

FIG. 1. Sleep fragmentation and severity of Lewy body pathology in adults without Parkinson's disease. Solid bars indicate medians. Boxes indicate interquartile ranges.

Sohail et al, Mov Disord, 2017 (n=269; Rush Memory and Aging Project)

Sleep fragmentation is accompanied by greater Parkinson disease pathology in adults without Parkinson disease

Synuclein Distribution

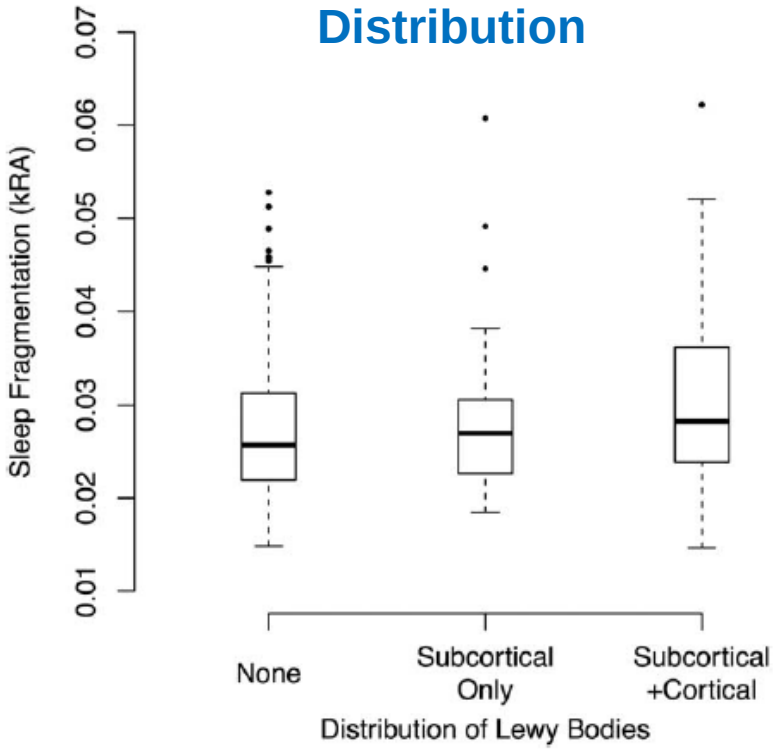

FIG. 1. Sleep fragmentation and severity of Lewy body pathology adults without Parkinson's disease. Solid bars indicate median Boxes indicate interquartile ranges.

Nigral Cell Loss

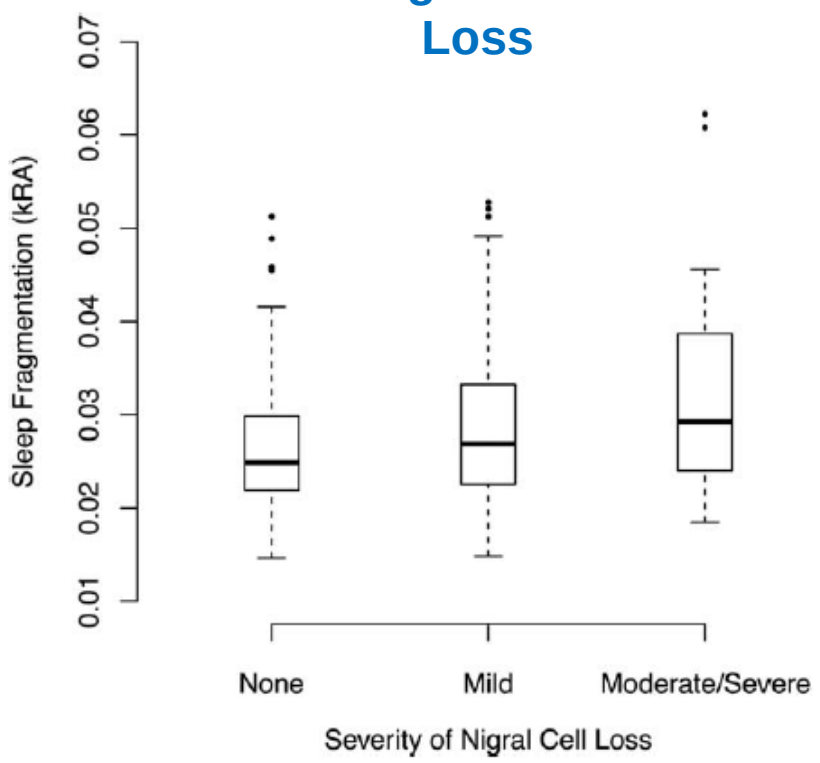

FIG. 2. Sleep fragmentation and severity of substantia nigra cell loss in adults without Parkinson's disease. Solid bars indicate medians. Boxes indicate interquartile ranges.

Sohail et al, Mov Disord, 2017 (n=269; Rush Memory and Aging Project)

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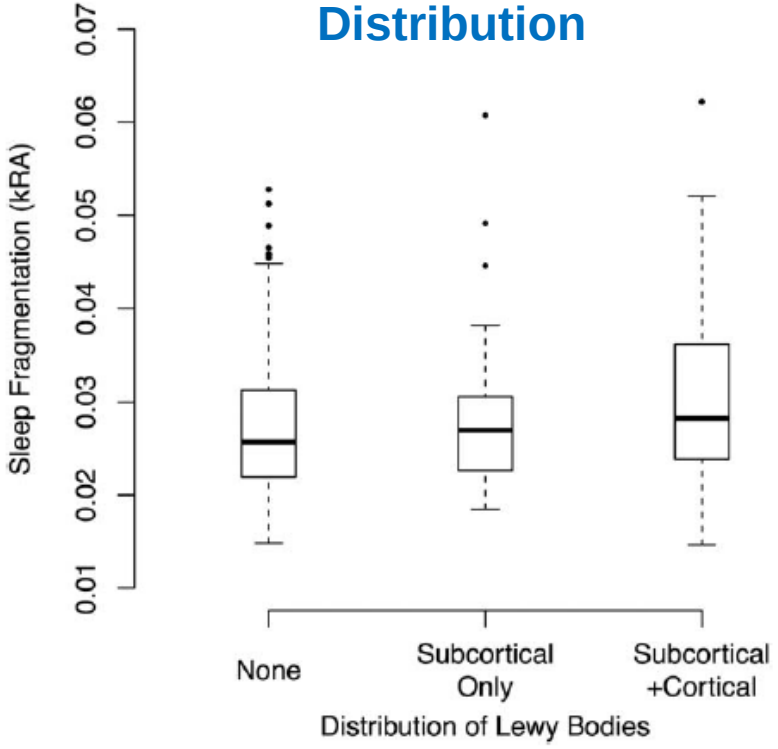

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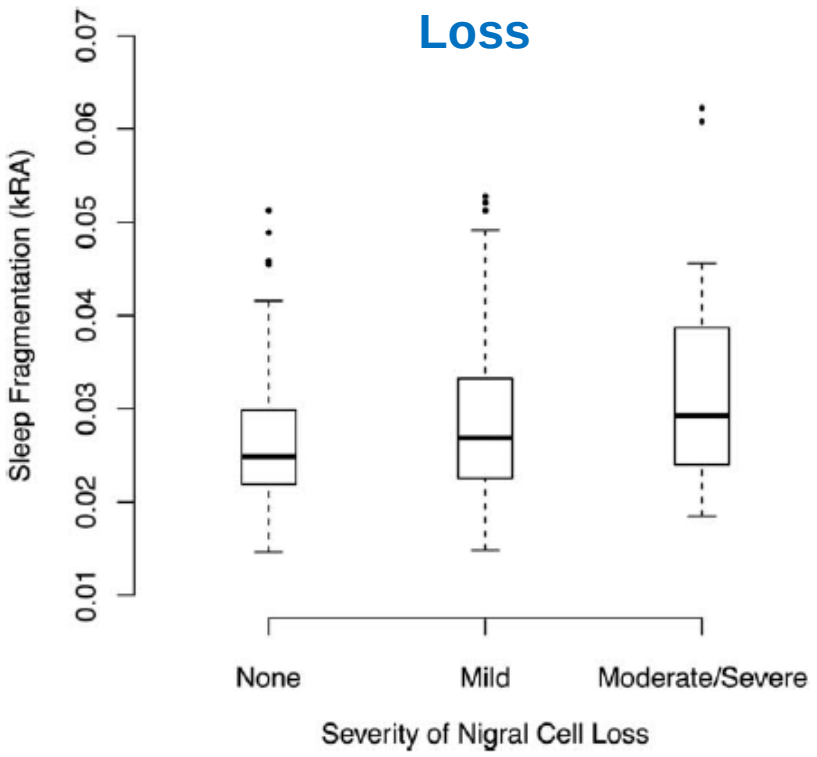

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Pathological Diagnosis PD

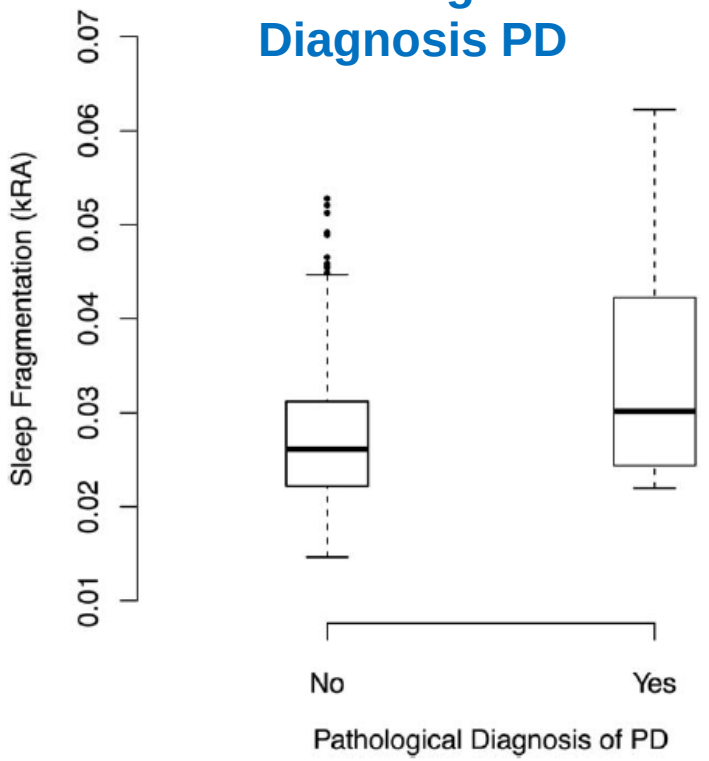


FIG. 3. Sleep fragmentation and pathological diagnosis of PD in adults without Parkinson's disease. Solid bars indicate medians. Boxes indicate interquartile ranges.

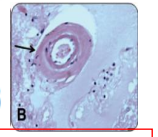
Sohail et al, Mov Disord, 2017 (n=269; Rush Memory and Aging Project)

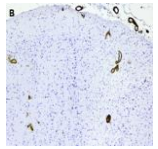
Sleep fragmentation is accompanied by a greater burden of arteriolosclerosis and subcortical infarcts

Table 1. Sleep Fragmentation and Vessel Pathology

	OR for More Severe Vascular Pathology (95% CI) *P* Value		
	Arteriolosclerosis	Atherosclerosis	Amyloid Angiopathy
Age at death (per year)	1.04 (1.00–1.07) 0.05	1.06 (1.02–1.10) 0.001	1.03 (1.00–1.07) 0.08
Male sex	0.53 (0.33–0.85) 0.01	1.31 (0.80–2.13) 0.28	0.65 (0.65–1.71) 0.83
Education (per year)	1.04 (0.97–1.13) 0.26	0.91 (0.84–0.98) 0.02	0.97 (0.90–1.05) 0.46
Sleep fragmentation (per 1 SD)	1.27 (1.02–1.59) 0.03	1.15 (0.92–1.42) 0.22	1.10 (0.88–1.37) 0.42

CI indicates confidence interval; and OR, odds ratio.



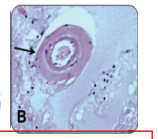


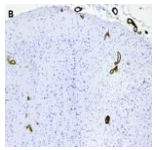
Lim et al, Stroke, 2016 (n=315; Rush Memory and Aging Project)

Sleep fragmentation is accompanied by a greater burden of arteriolosclerosis and subcortical infarcts

Table 1. Sleep Fragmentation and Vessel Pathology

	OR for More Severe Vascular Pathology (95% CI) *P* Value		
	Arteriolosclerosis	Atherosclerosis	Amyloid Angiopathy
Age at death (per year)	1.04 (1.00–1.07) 0.05	1.06 (1.02–1.10) 0.001	1.03 (1.00–1.07) 0.08
Male sex	0.53 (0.33–0.85) 0.01	1.31 (0.80–2.13) 0.28	0.65 (0.65–1.71) 0.83
Education (per year)	1.04 (0.97–1.13) 0.26	0.91 (0.84–0.98) 0.02	0.97 (0.90–1.05) 0.46
Sleep fragmentation (per 1 SD)	1.27 (1.02–1.59) 0.03	1.15 (0.92–1.42) 0.22	1.10 (0.88–1.37) 0.42

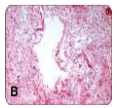




CI indicates confidence interval; and OR, odds ratio.

Table 2. Sleep Fragmentation and Number of Infarcts

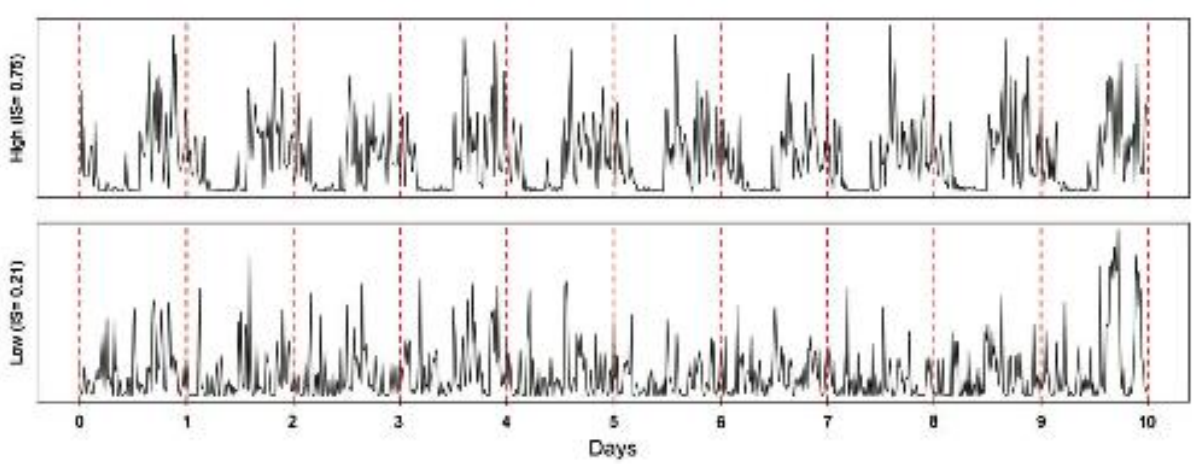
	OR for Greater Number of Infarcts (95% CI) *P* Value			
	Macroscopic		Microscopic	
	Subcortical	Cortical	Subcortical	Cortical
Age at death (per year)	1.04 (1.00–1.09) 0.06	1.00 (0.95–1.06) 0.95	1.00 (0.95–1.06) 0.96	1.03 (0.98–1.08) 0.21
Male sex	0.98 (0.54–1.75) 0.96	1.83 (0.90–3.66) 0.09	0.67 (0.29–1.42) 0.32	1.01 (0.53–1.87) 0.98
Education (per year)	0.87 (0.79–0.96) 0.01	0.98 (0.87–1.10) 0.73	0.95 (0.84–1.07) 0.41	0.98 (0.89–1.08) 0.72
Sleep fragmentation (per 1 SD)	1.31 (1.01–1.68) 0.04	0.94 (0.65–1.29) 0.72	0.87 (0.58–1.22) 0.45	1.14 (0.86–1.48) 0.36

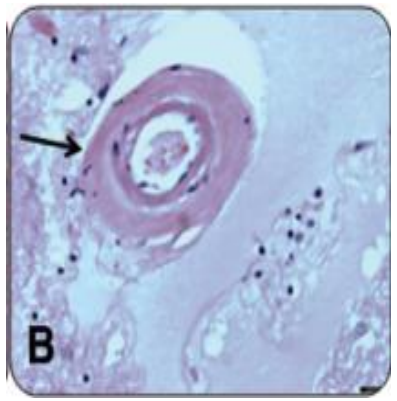



CI indicates confidence interval; and OR, odds ratio.

Lim et al, Stroke, 2016 (n=315; Rush Memory and Aging Project)

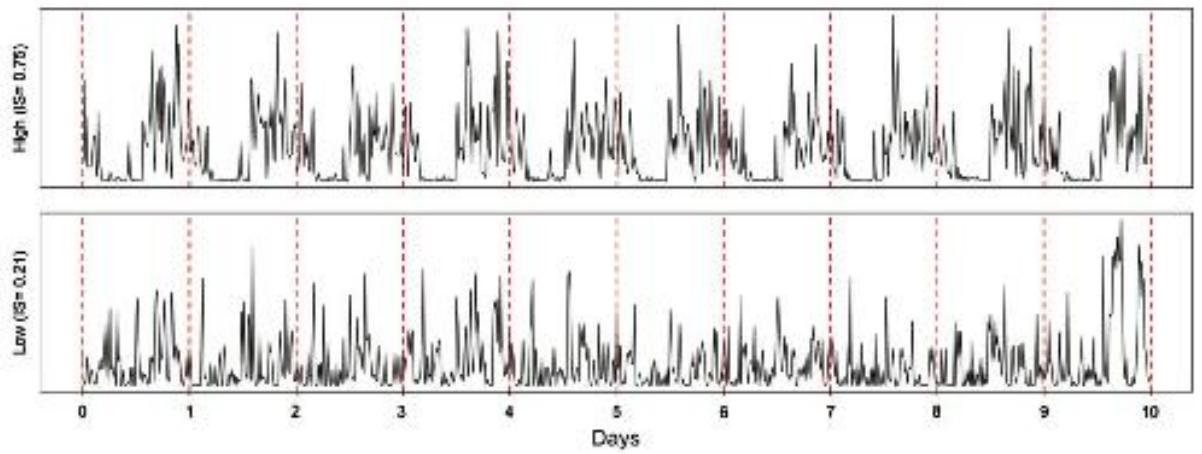
Irregular rest-activity rhythms are associated with increased severity of arteriolosclerosis

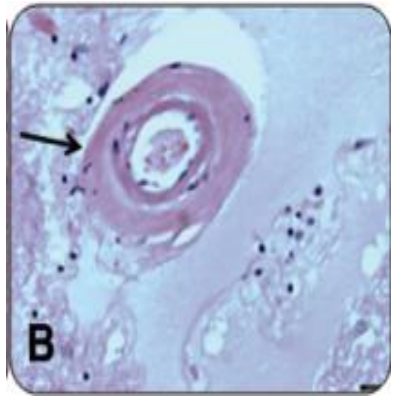


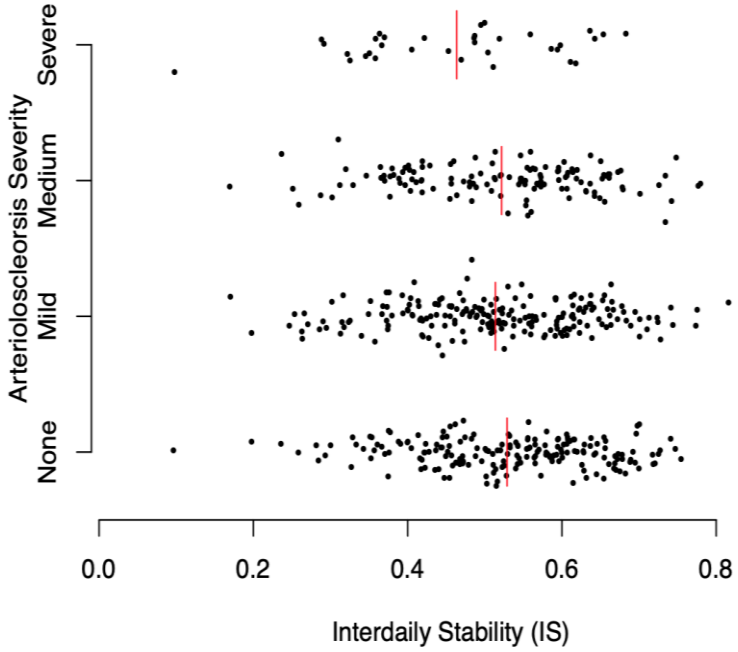


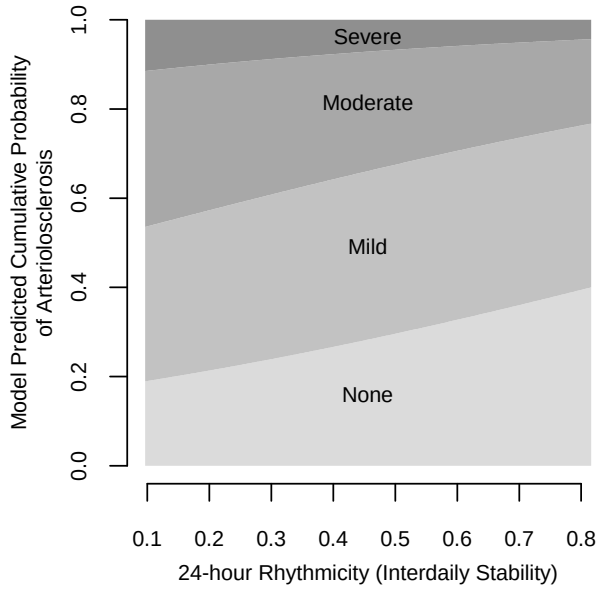
(Sommer et al, Stroke, 2021: Memory and Aging Project)

Irregular rest-activity rhythms are associated with increased severity of arteriolosclerosis



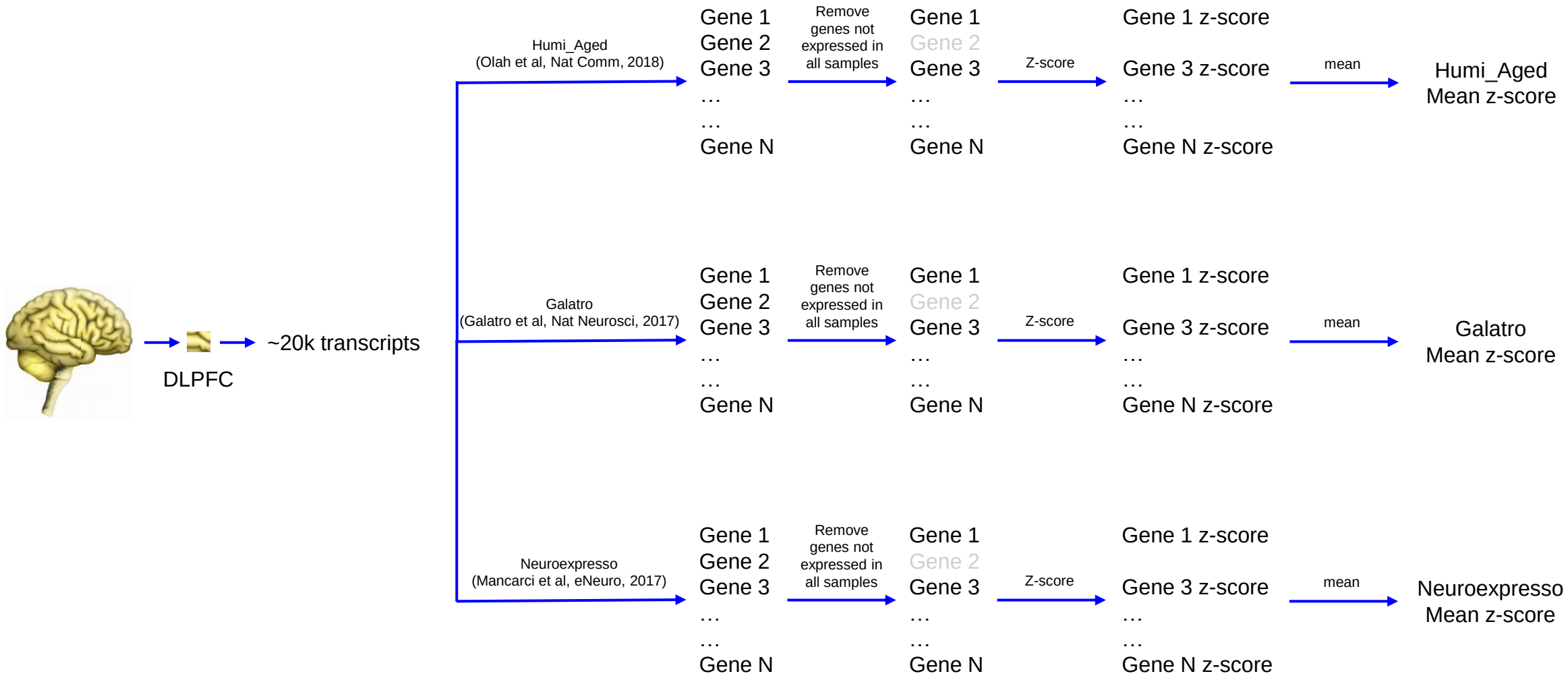




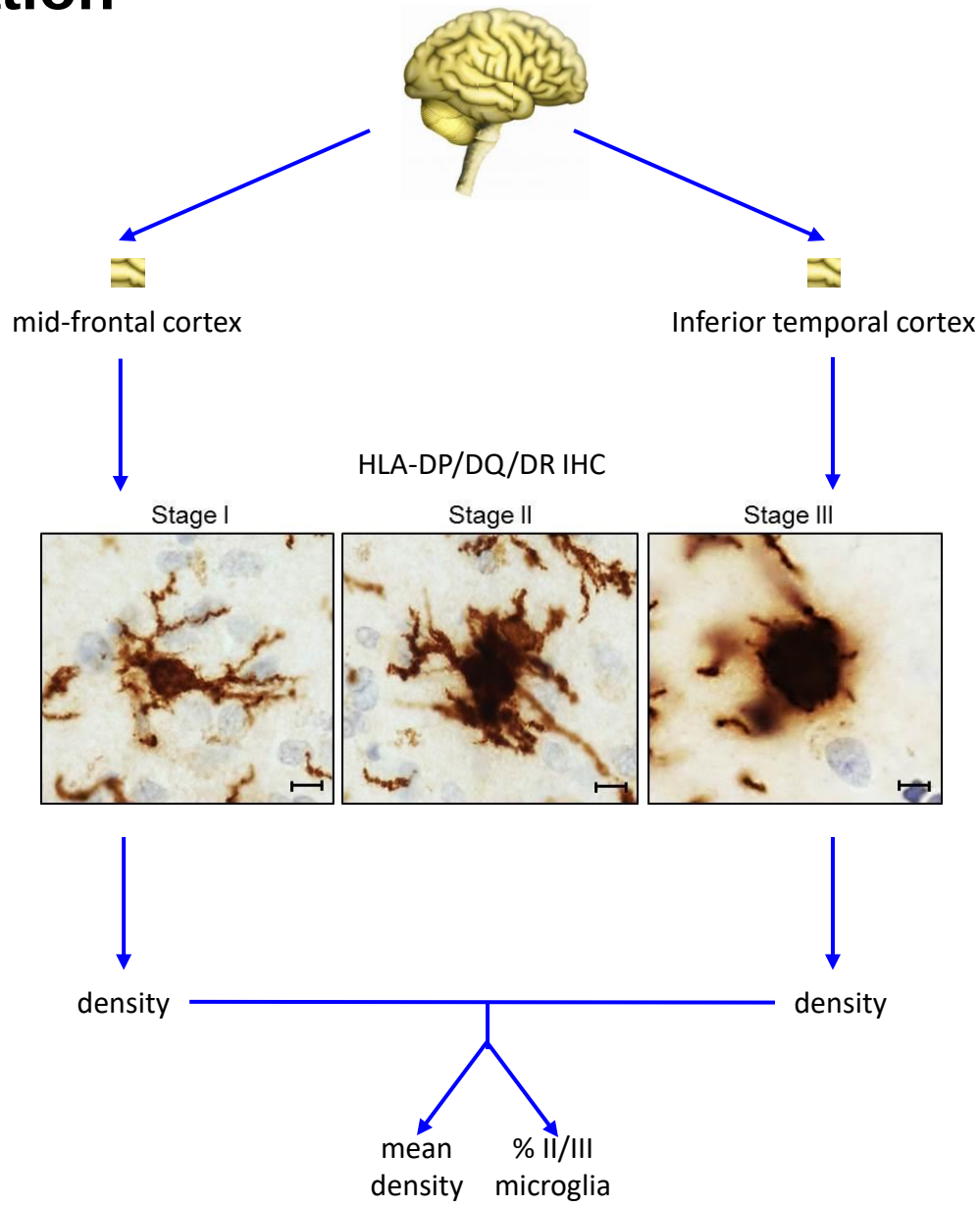


(Sommer et al, Stroke, 2021: Memory and Aging Project)

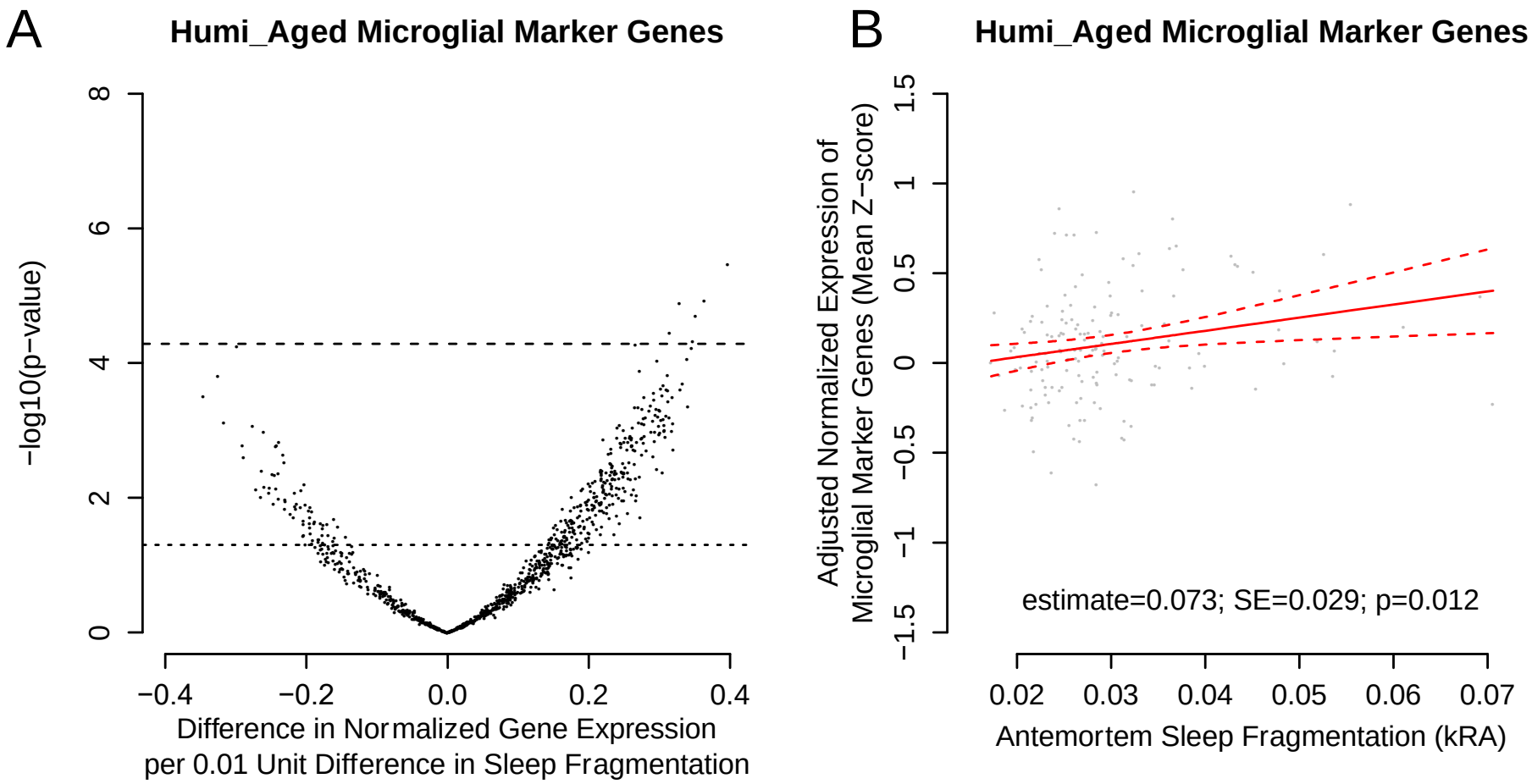
Sleep fragmentation is associated with microglial transcriptional aging and morphological activation



Sleep fragmentation is associated with microglial transcriptional aging and morphological activation

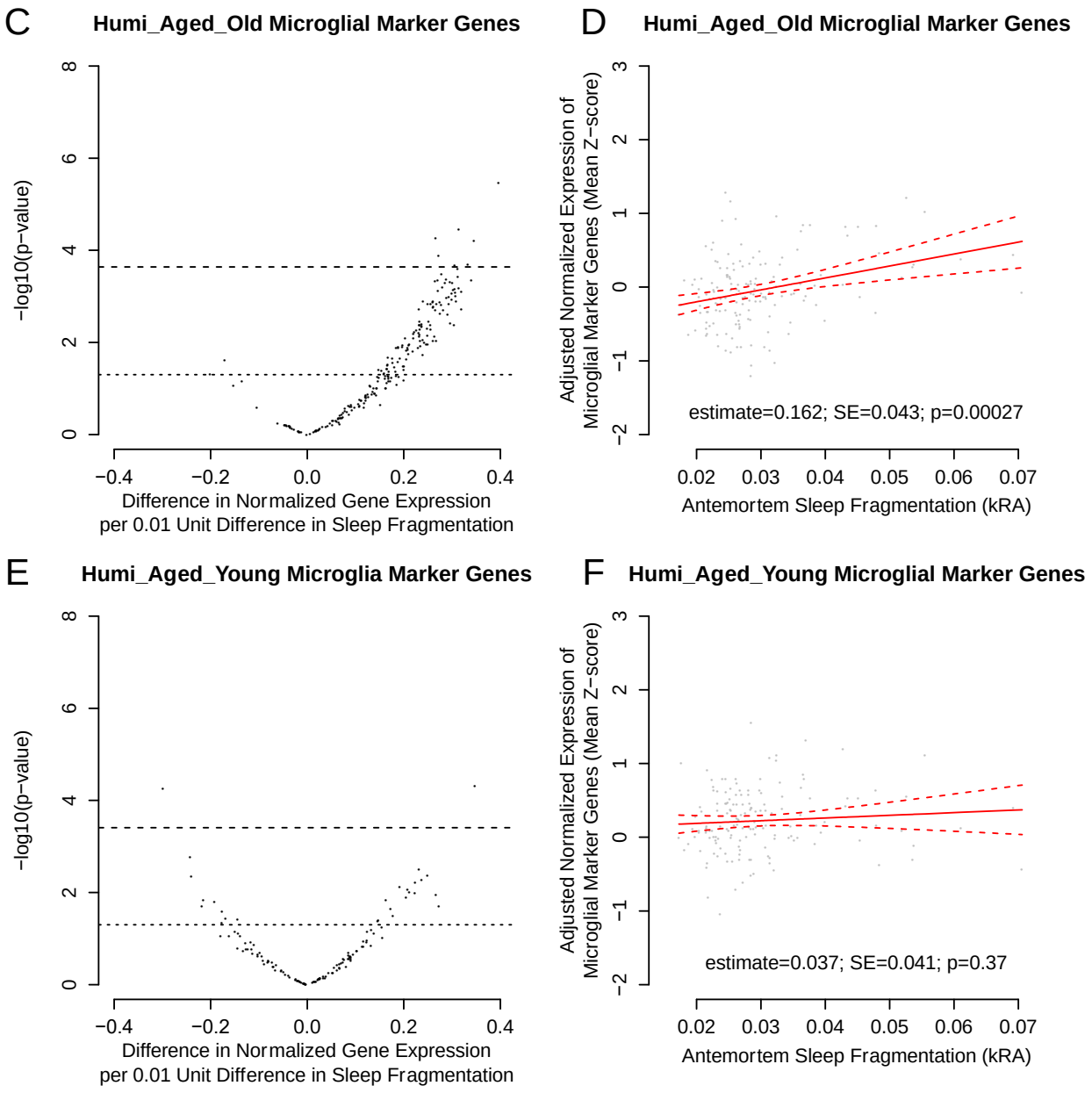


Sleep fragmentation is associated with elevated expression of microglial marker genes



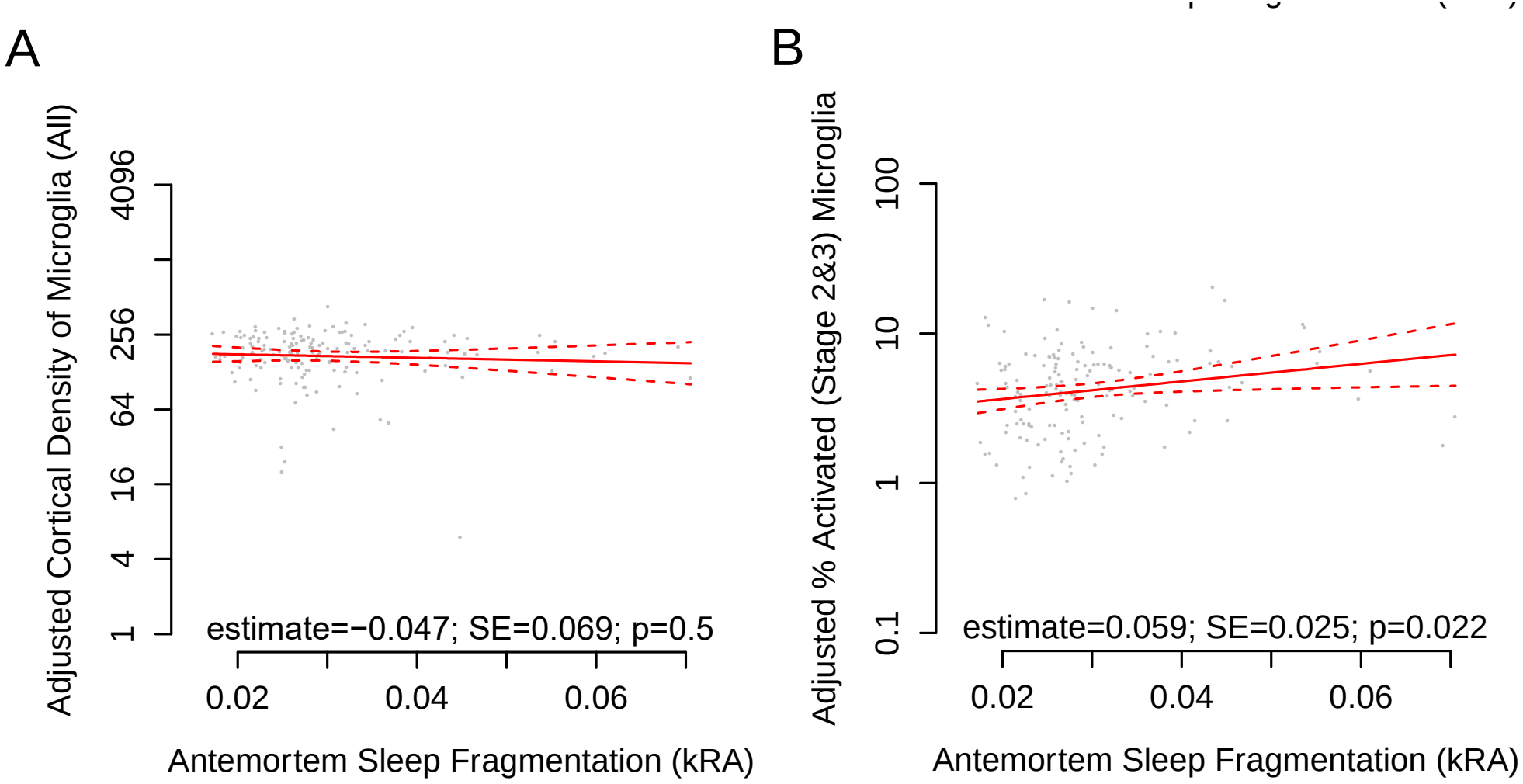
(Kaneshwaran et al, Sci Adv, 2019)

Sleep fragmentation is specifically associated with elevated expression of genes characteristic of aged microglia



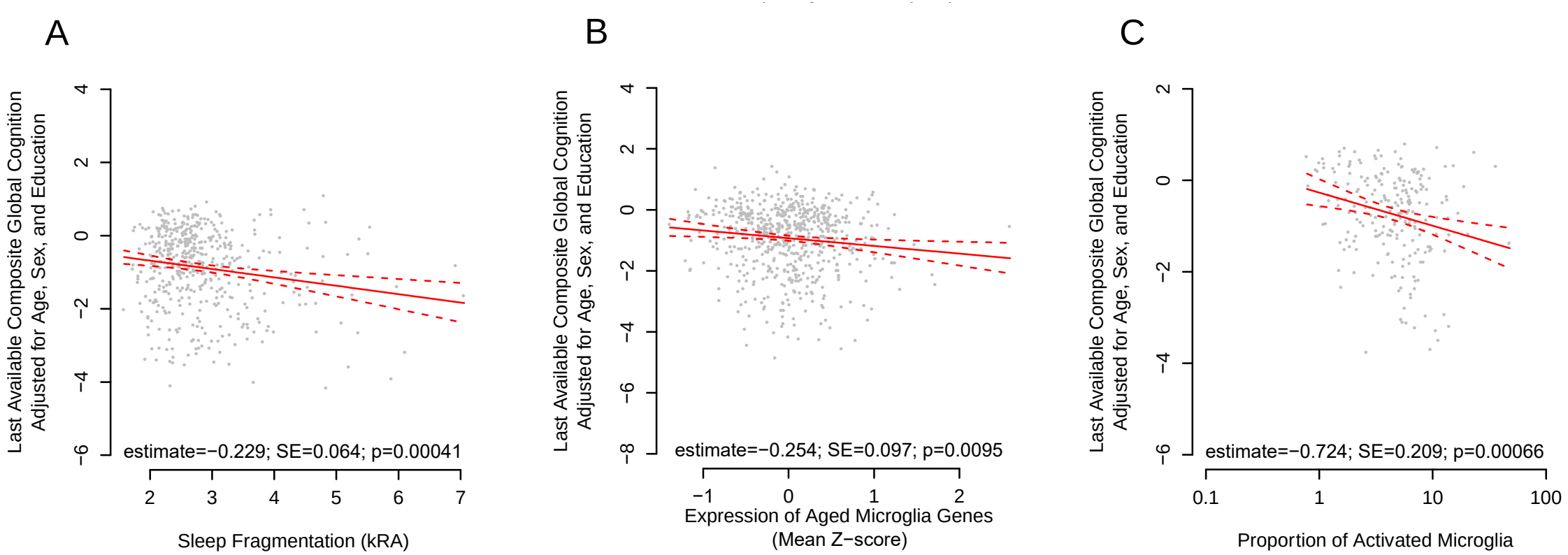
(Kaneshwaran et al, Sci Adv, 2019)

Sleep fragmentation is also associated with a greater proportion of morphologically activated microglia



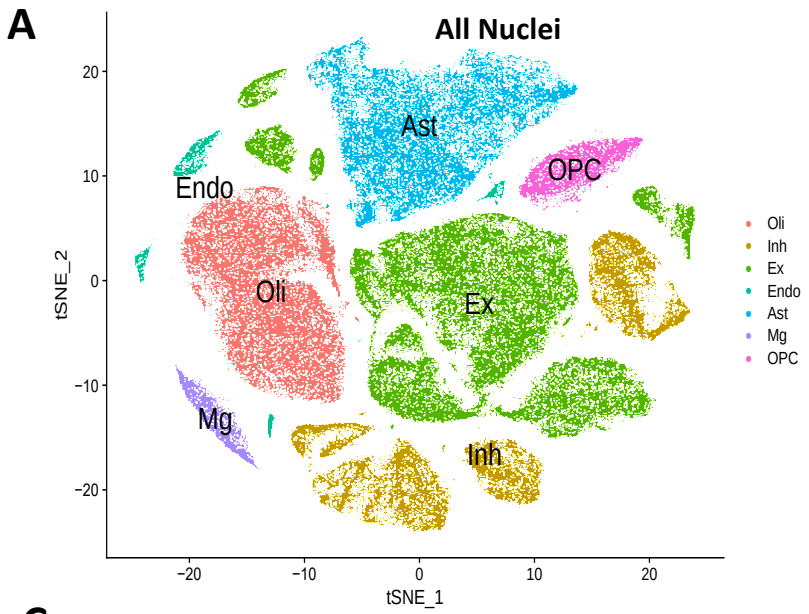
(Kaneshwaran et al, Sci Adv, 2019)

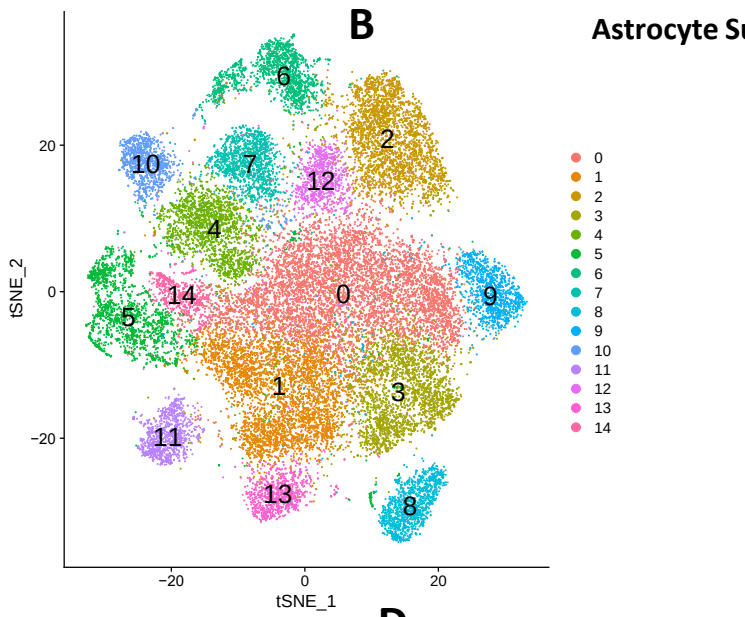
Sleep fragmentation, microglial transcriptional aging, and microglial activation are all associated with cognitive impairment

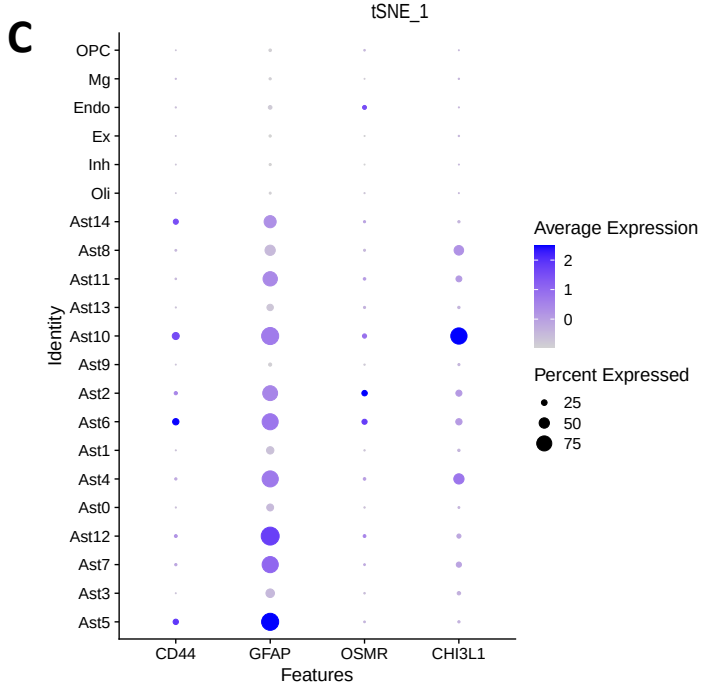


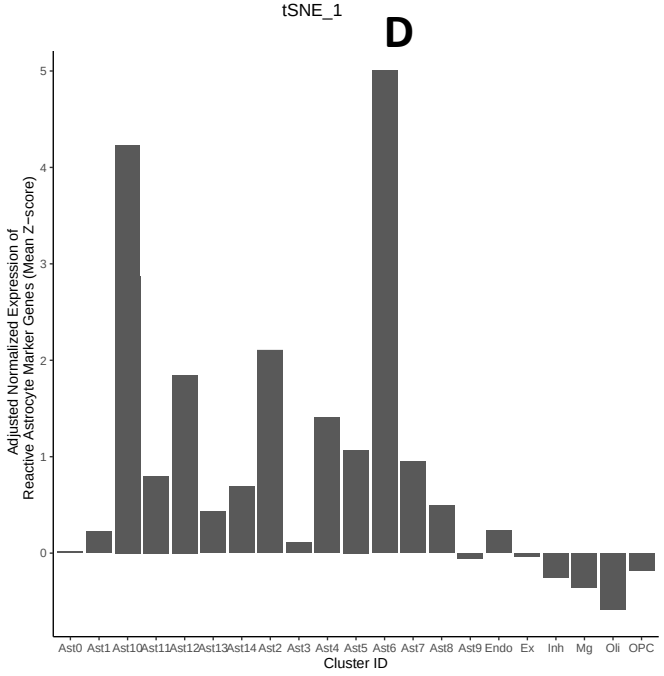
(Kaneshwaran et al, Sci Adv, 2019)

Analysis of human snRNAseq data
identifies marker genes for human activated astrocytes







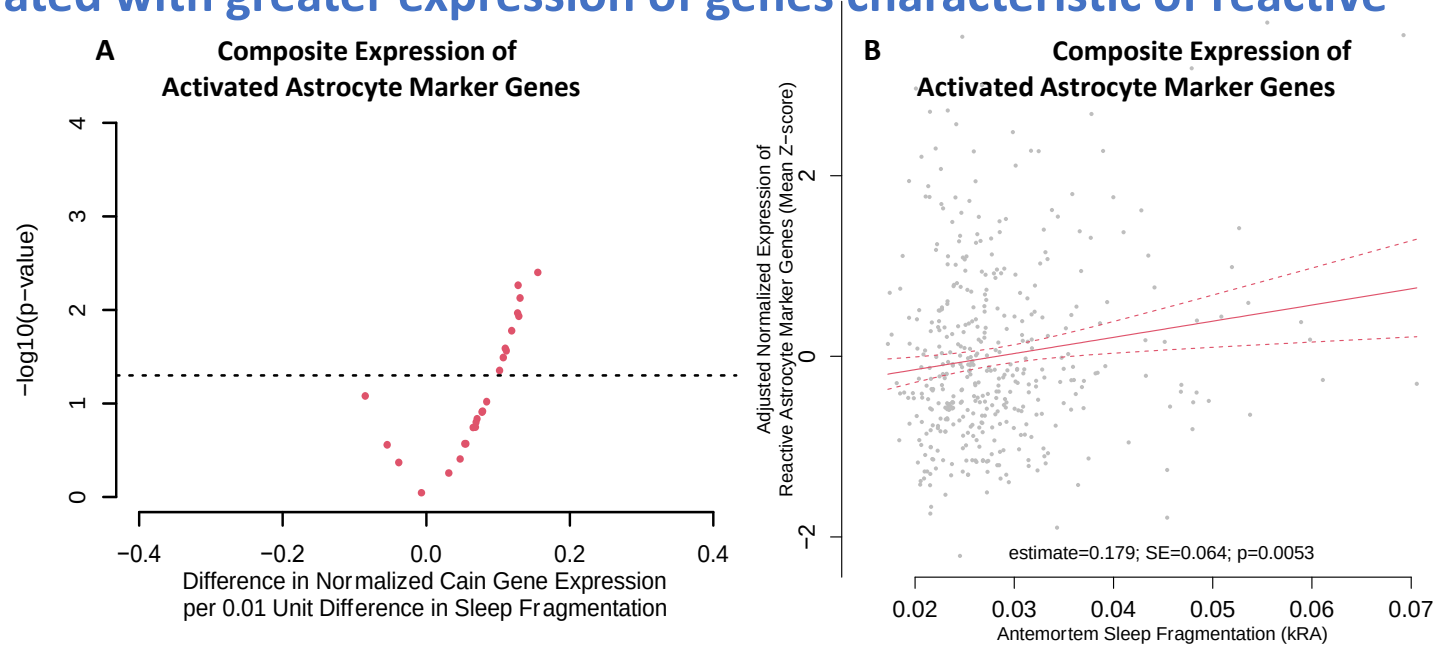


1. *bioRxiv 2020*

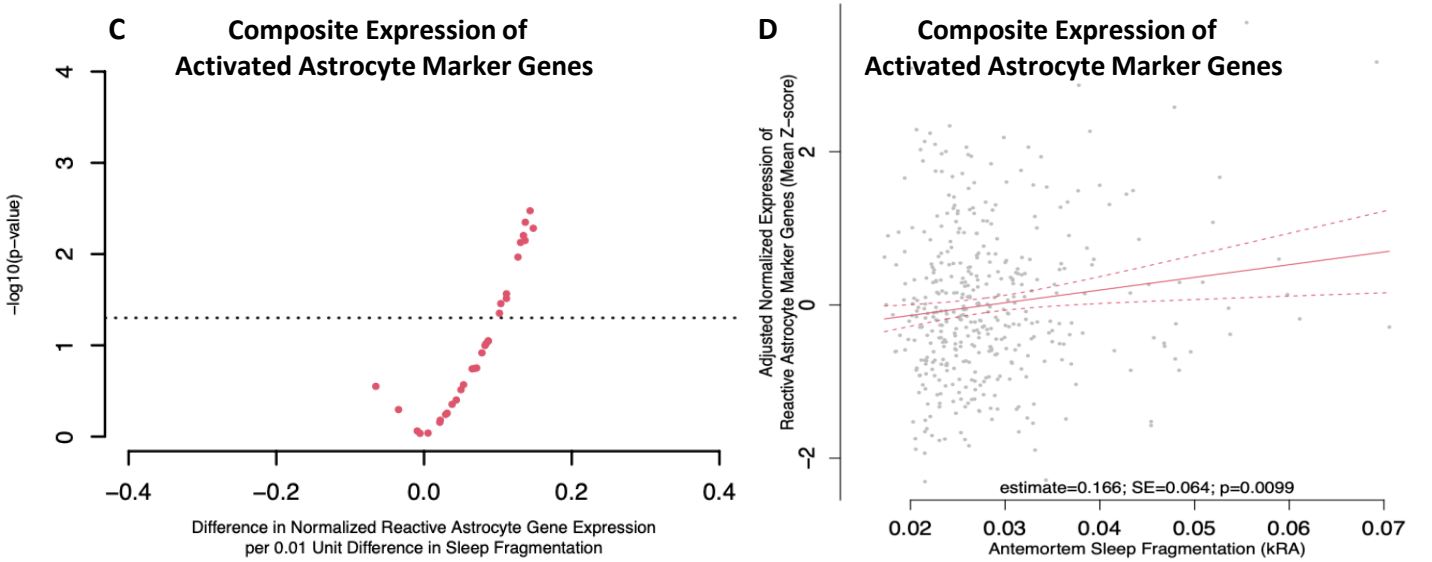
(Rebecca Wu)

Worse sleep fragmentation is associated with greater expression of genes characteristic of reactive astrocytes

Primary Activated Astrocyte Gene Set



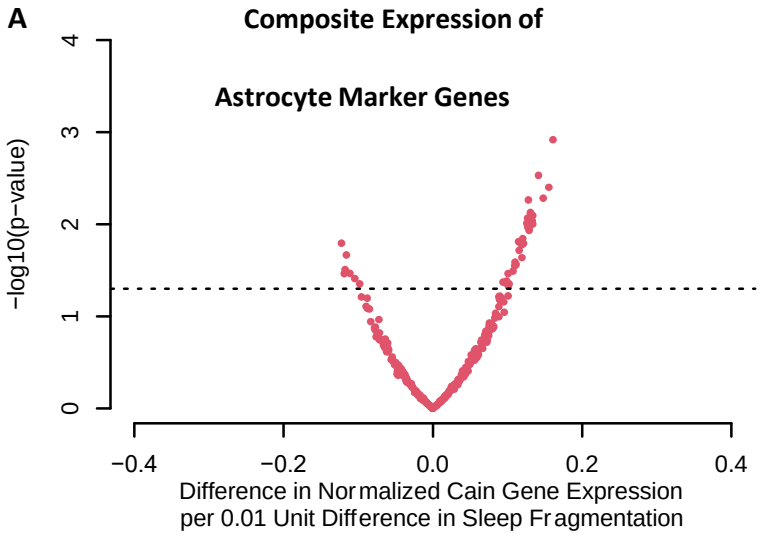
Secondary Activated Astrocyte Gene Set

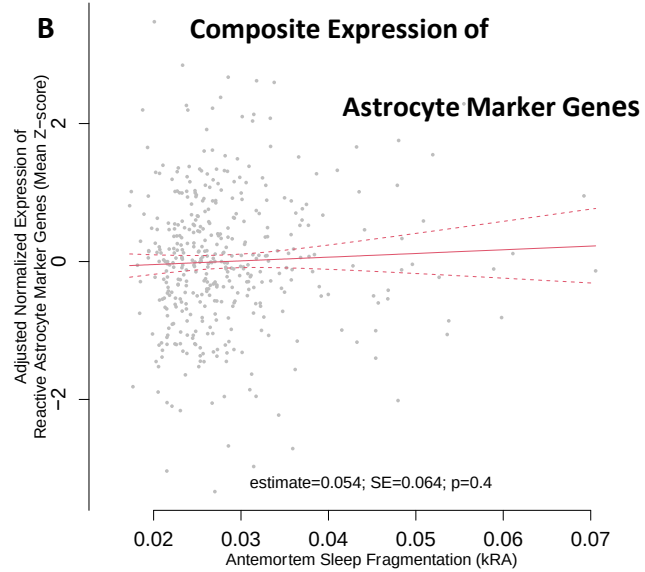


(Rebecca Wu; Memory and Aging Project; N=408)

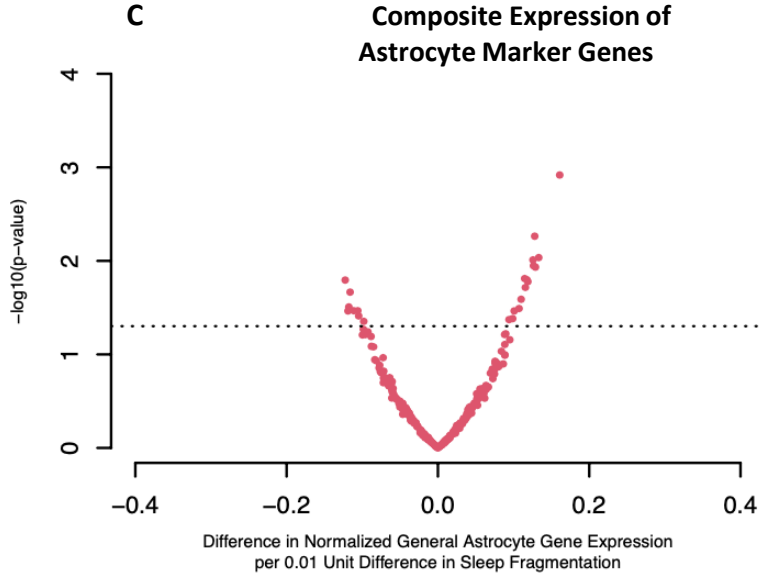
Sleep fragmentation is not associated with expression of genes characteristic of astrocytes in general

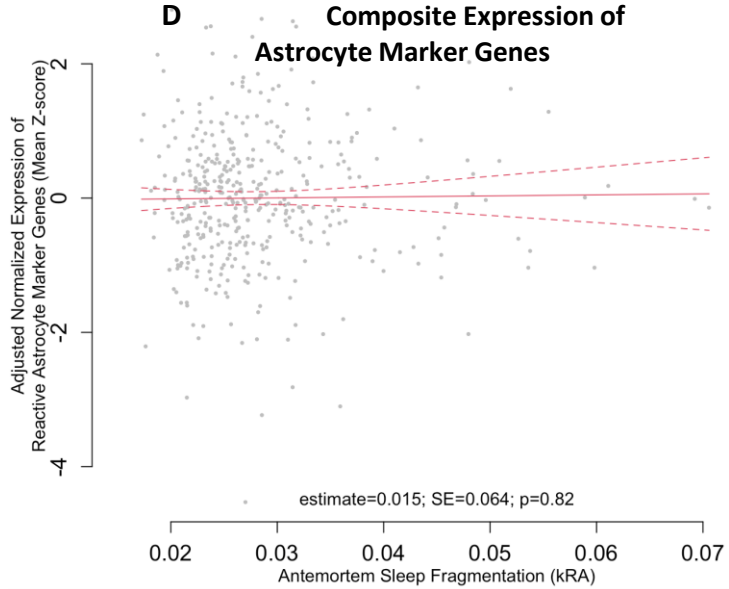
Primary Astrocyte Gene Set





Secondary Astrocyte Gene Set





(Rebecca Wu; Memory and Aging Project; N=408)

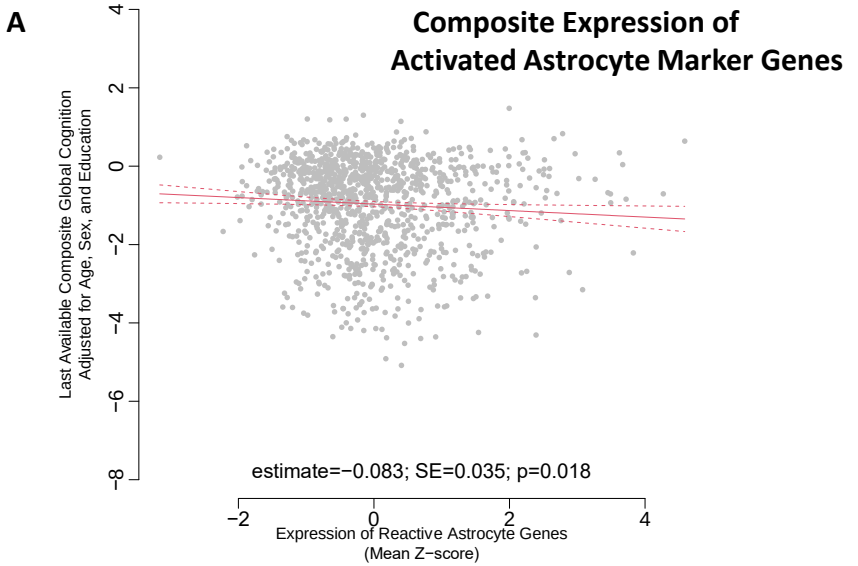
This association with activated astrocytes is not accounted for by Dementia associated pathology

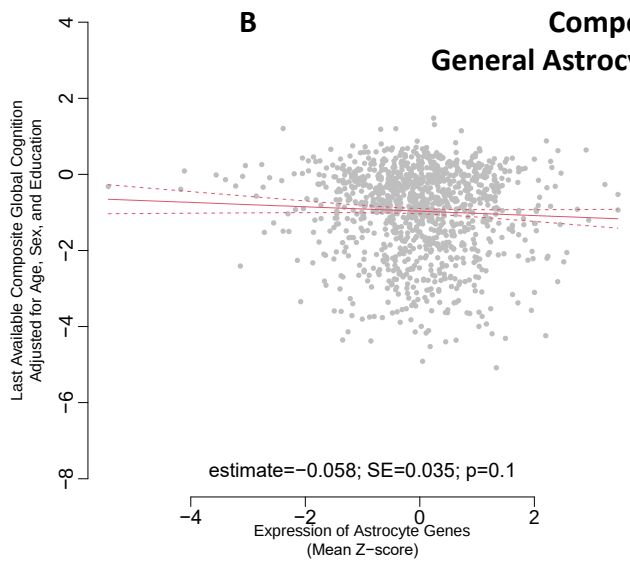
Model	Covariates	Predictor	Estimate	SE	Pval
A	Age+Sex+Education+Technical	Sleep	0.13	0.05	9.94E-03
B	A+AD Pathology	Sleep	0.14	0.05	6.63E-03
C	A+Lewy Body Pathology	Sleep	0.13	0.05	8.33E-03
D	A+Gross Infarcts	Sleep	0.13	0.05	8.56E-03
E	A+Micro Infarcts	Sleep	0.13	0.05	1.01E-02
F	A+TDP43	Sleep	0.13	0.05	1.14E-02
G	A+Hippocampal Sclerosis	Sleep	0.13	0.05	9.90E-03
H	A+All Pathologies	Sleep	0.15	0.05	4.37E-03

(Rebecca Wu; Memory and Aging Project; N=408)

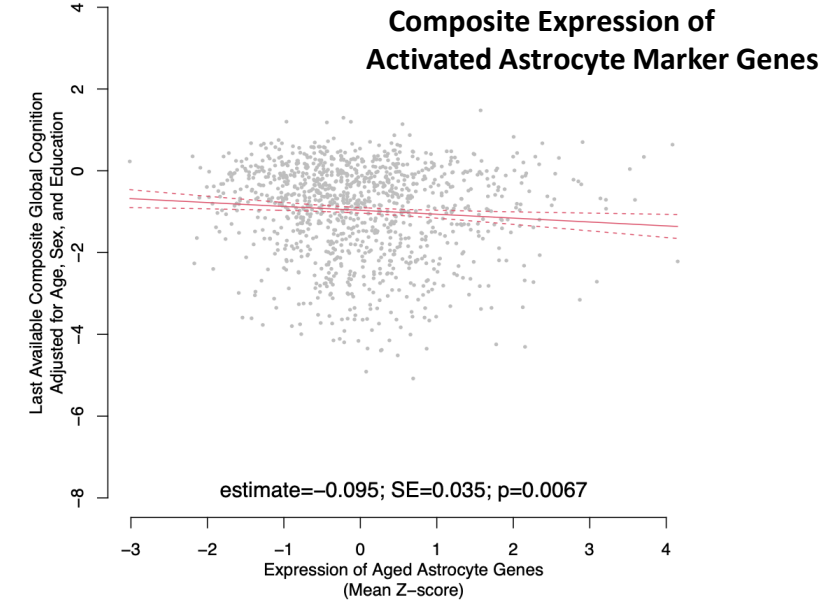
Reactive astrocytes are associated with impaired global cognition

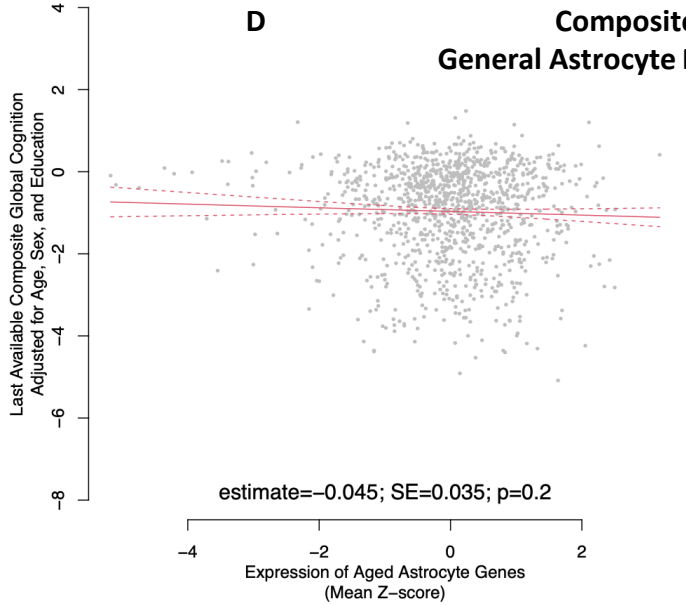
Primary Activated Astrocyte Gene Set





Secondary Activated Astrocyte Gene Set





(Rebecca Wu; Memory and Aging Project; N=408)

This association between reactive astrocytes and cognition is not accounted for by Dementia associated pathology

Model	Outcome	Covariates	Predictor	Est	SE	Pval
A	Cognition	Age+Sex+Education+Technical	Composite Activated Astrocytes	-0.08	0.04	1.81E-02
B	Cognition	A+AD Pathology	Composite Activated Astrocytes	-0.09	0.03	6.48E-03
C	Cognition	A+Lewy Body Pathology	Composite Activated Astrocytes	-0.07	0.03	4.23E-02
D	Cognition	A+Gross Infarcts	Composite Activated Astrocytes	-0.08	0.03	2.01E-02
E	Cognition	A+Micro Infarcts	Composite Activated Astrocytes	-0.08	0.04	1.74E-02
F	Cognition	A+TDP43	Composite Activated Astrocytes	-0.07	0.04	4.12E-02
G	Cognition	A+Hippocampal Sclerosis	Composite Activated Astrocytes	-0.08	0.03	2.84E-02
H	Cognition	A+All Pathologies	Composite Activated Astrocytes	-0.06	0.03	3.98E-02

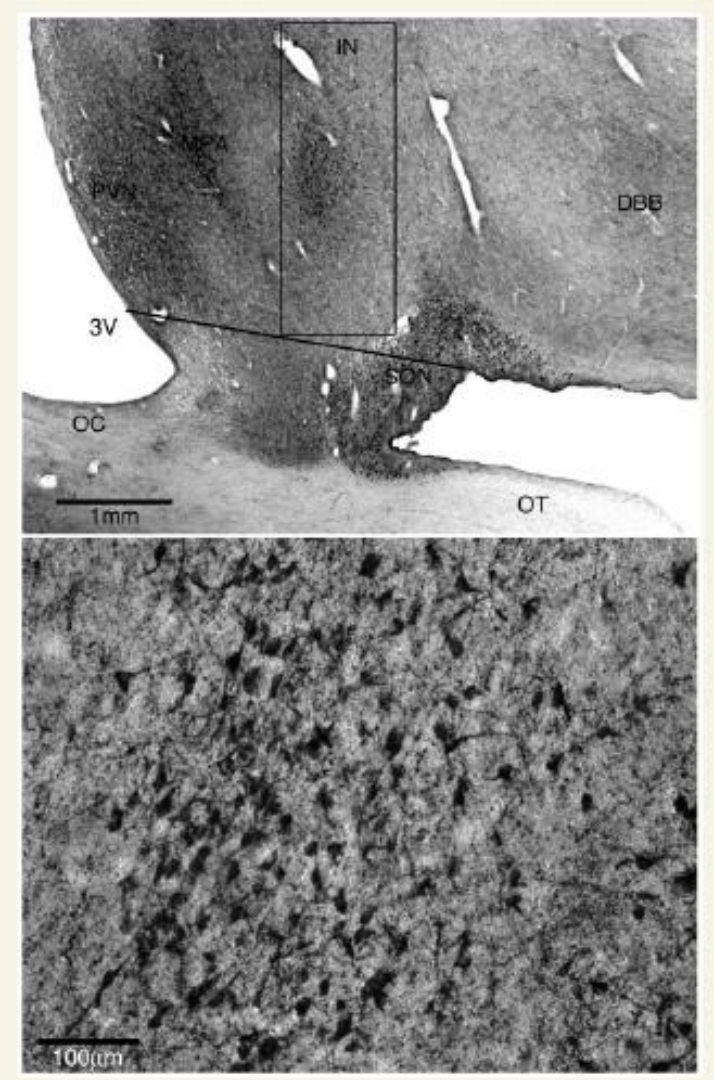
(Rebecca Wu; Memory and Aging Project; N=408)

How might brain pathology affect sleep?

Sleep and Circadian Rhythm Disruption

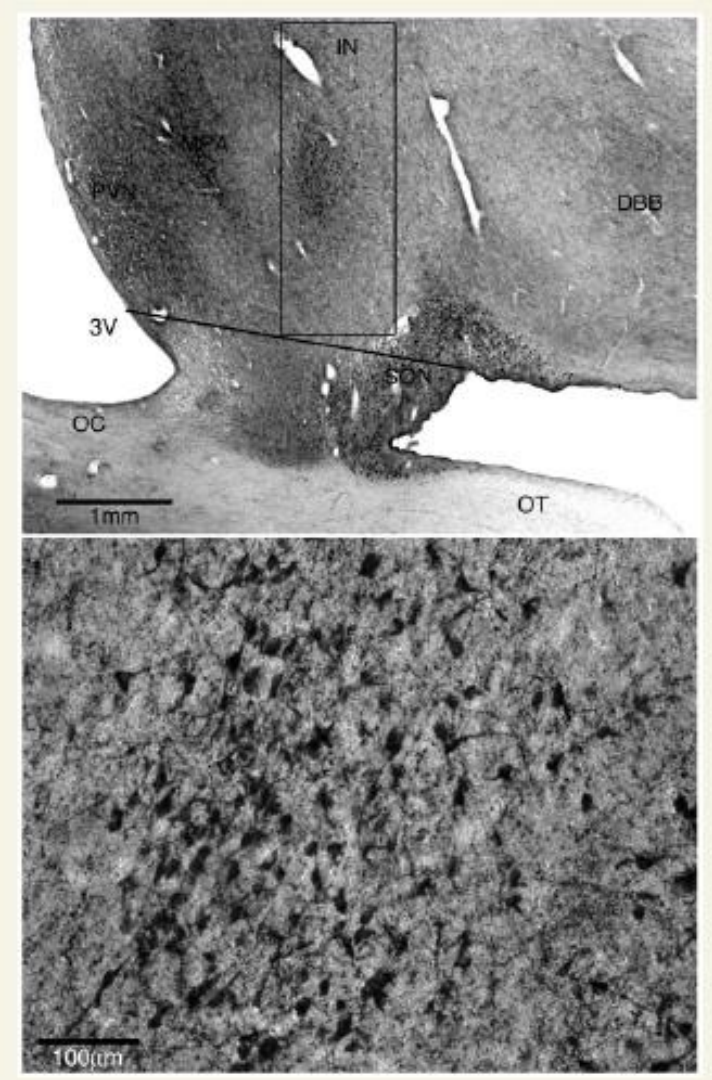
Molecular, Cellular, Network-Level Brain Changes

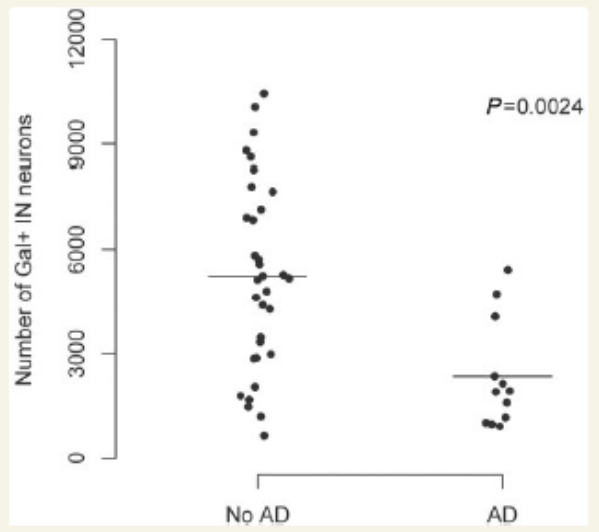
Alzheimer’s disease is accompanied by neuron loss in the intermediate nucleus of the hypothalamus, which correlates with sleep fragmentation



Lim et al, Brain, 2014 (n=45; Rush Memory and Aging Project)

Alzheimer’s disease is accompanied by neuron loss in the intermediate nucleus of the hypothalamus, which correlates with sleep fragmentation





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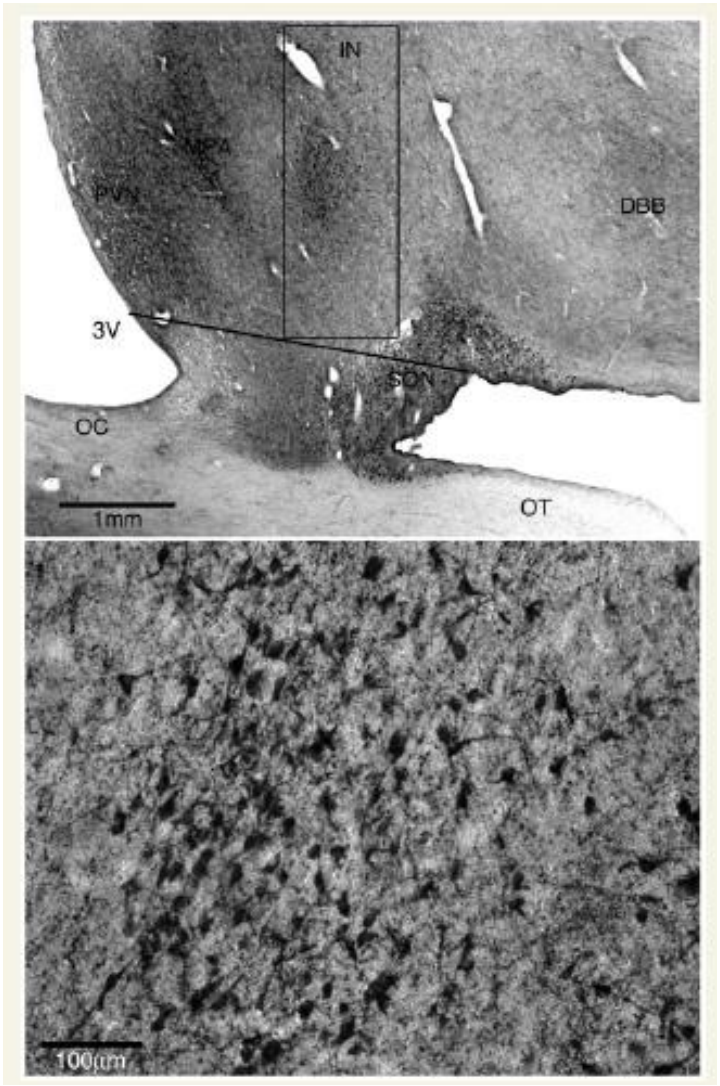
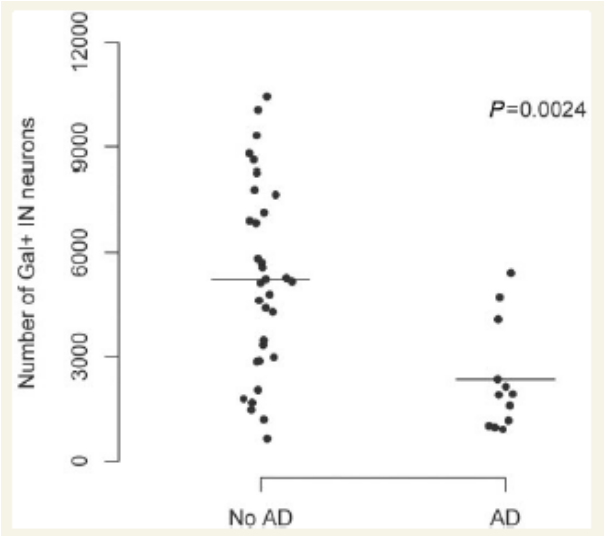
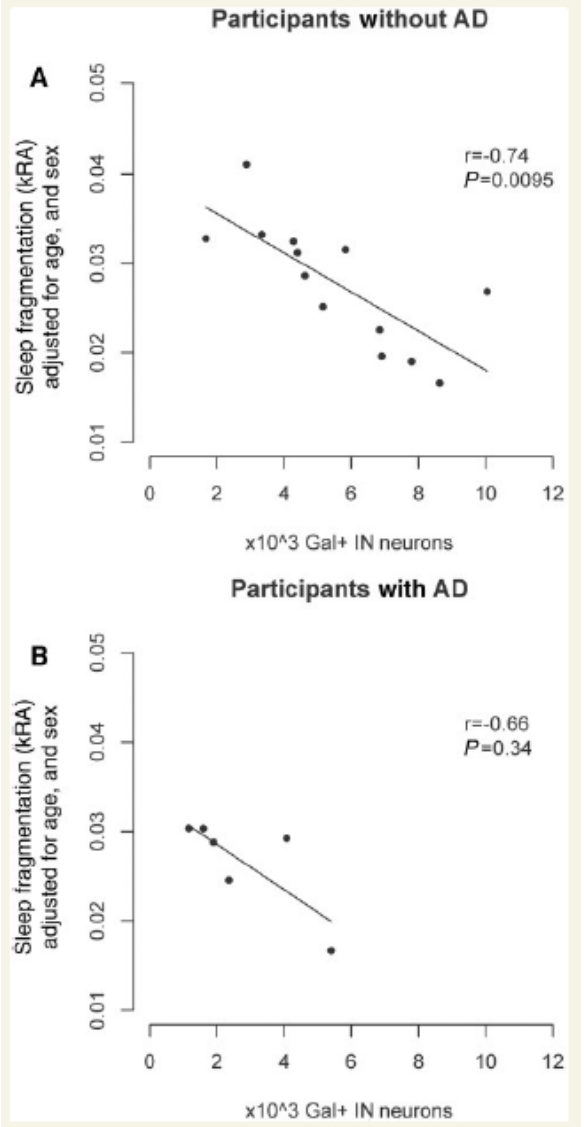
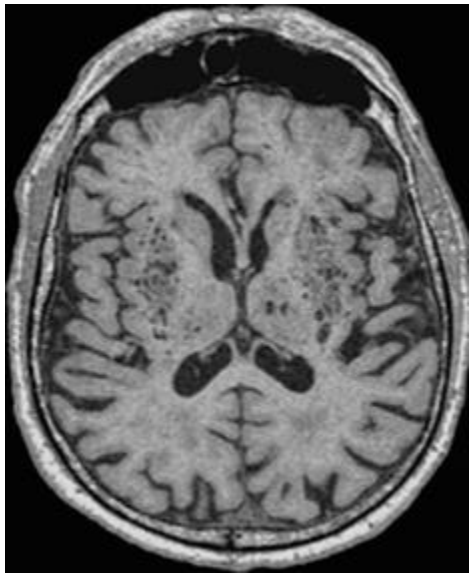


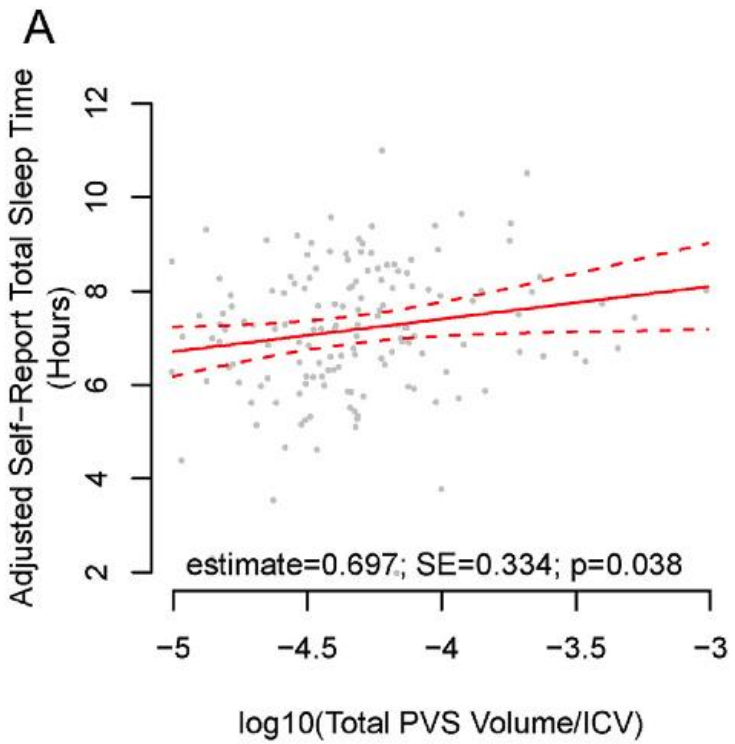


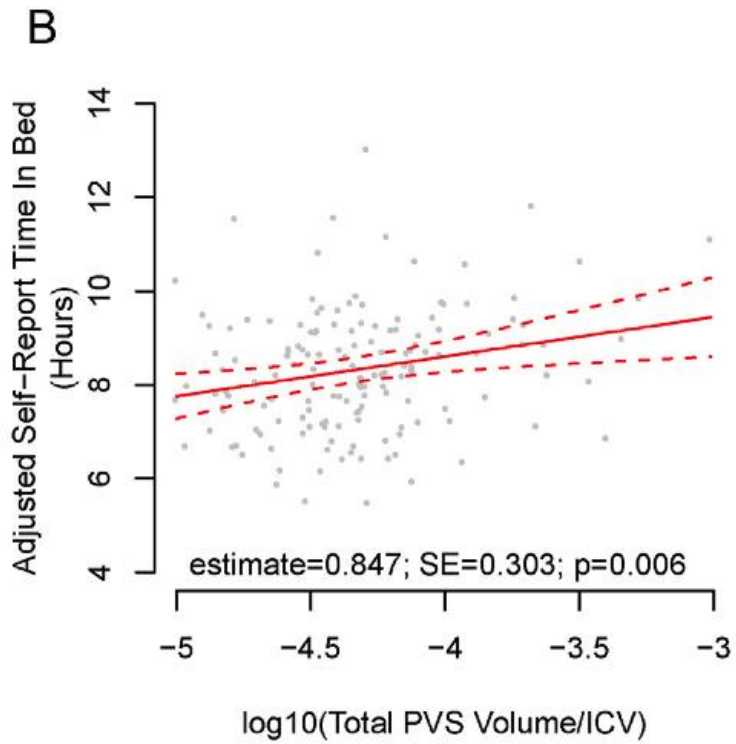


Lim et al, Brain, 2014 (n=45; Rush Memory and Aging Project)

Enlarged Perivascular Spaces are Associated with Long Sleep Time in Patients with Cerebrovascular Disease



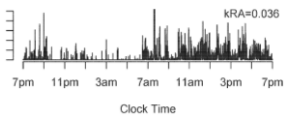




(Ramirez et al, Sleep Medicine, 2021: ONDRI cohort; n=152)

Overall Summary

Sleep and Circadian Disruption



Sleep Fragmentation

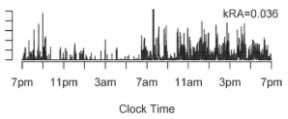
Circadian Disruption

Clinical Outcomes

Dementia

Overall Summary

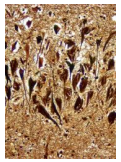
Sleep and Circadian Disruption



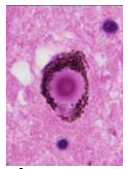
Sleep Fragmentation

Circadian Disruption

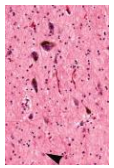
Structural Cognitive Substrates



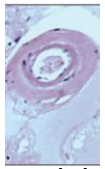
NFT



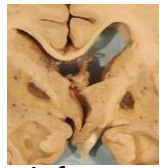
Lewy Bodies



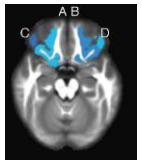
Neuron Loss



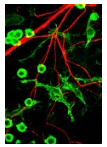
Arteriolo-sclerosis



Infarcts



Atrophy



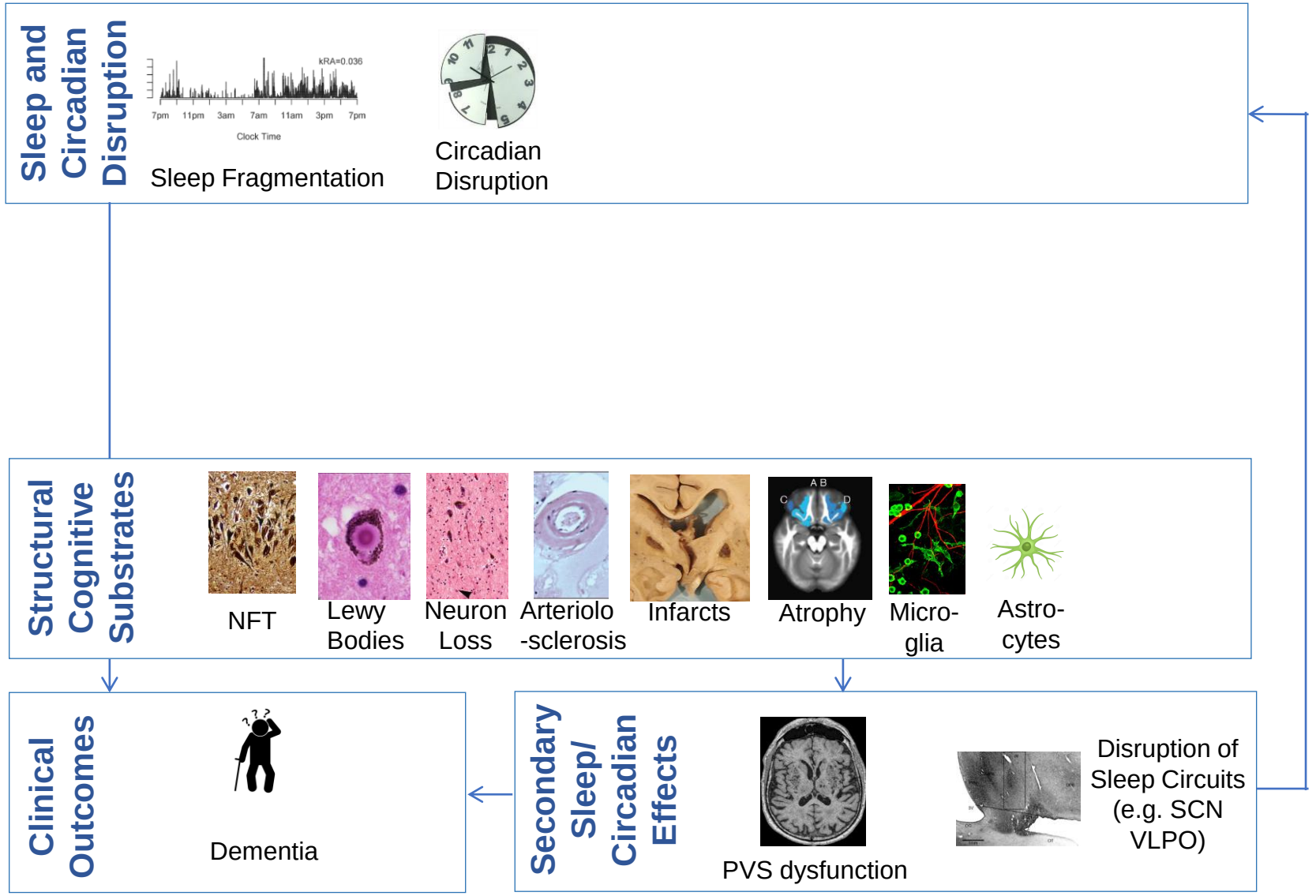
Micro-glia

Astro-cytes

Clinical Outcomes

Dementia

Overall Summary



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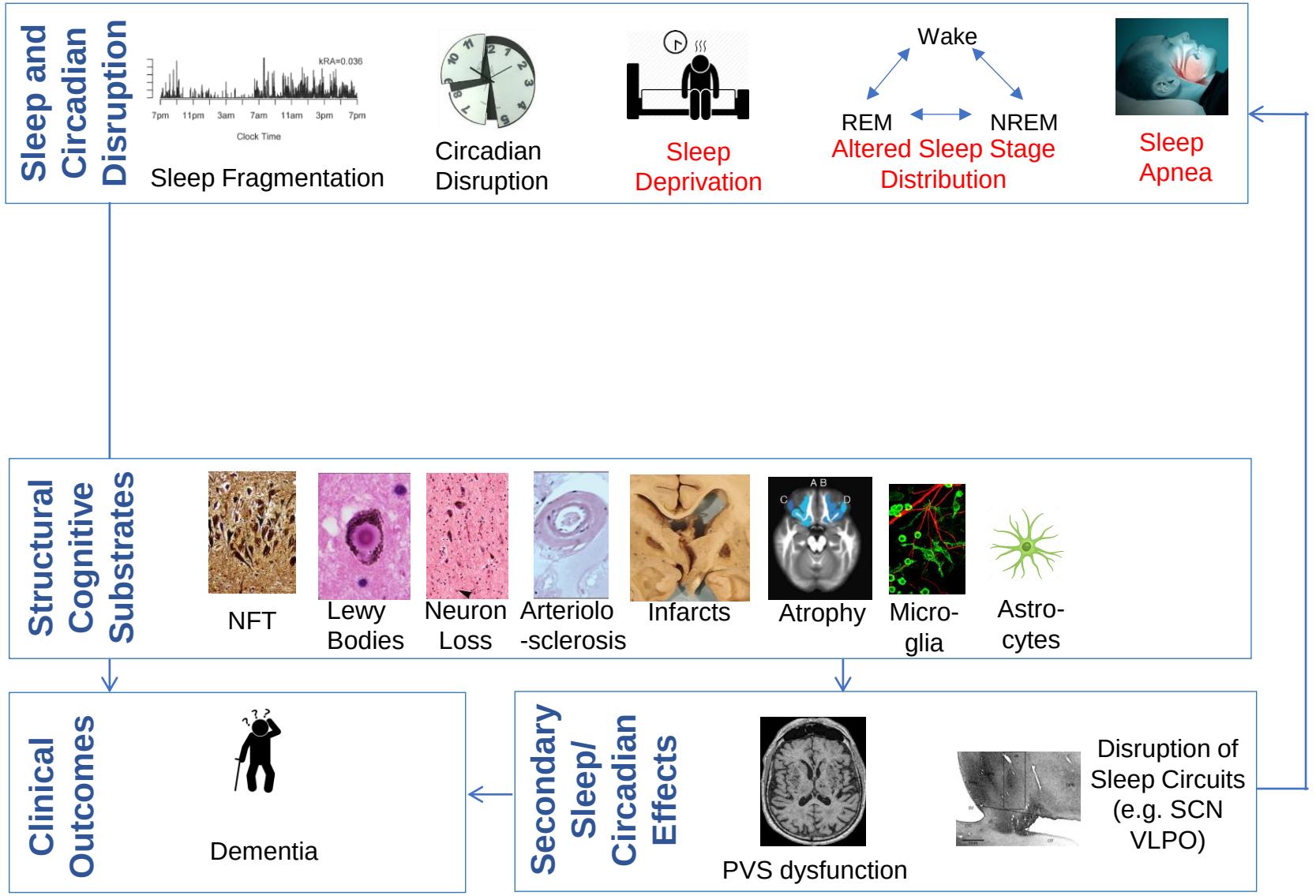

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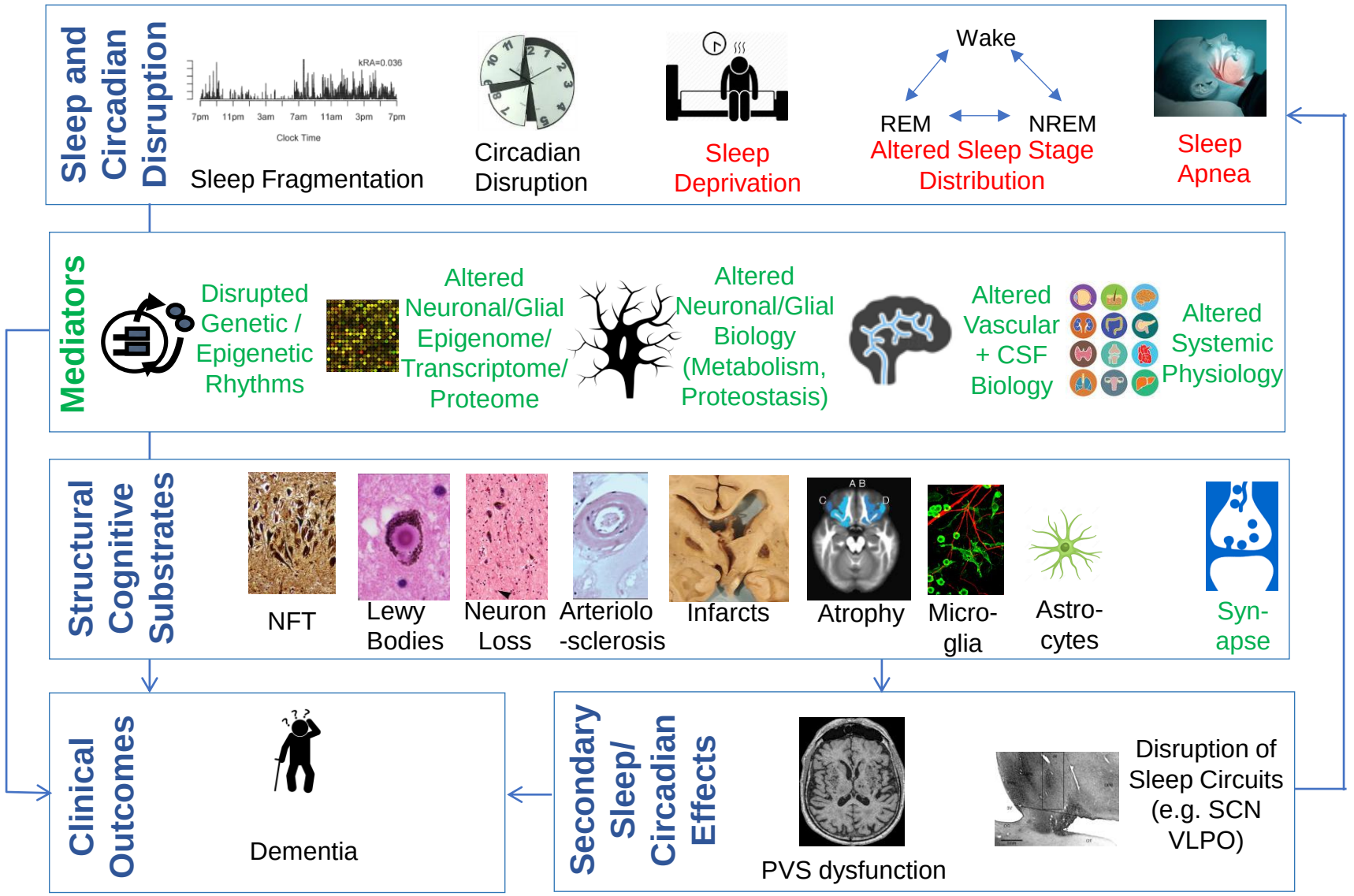

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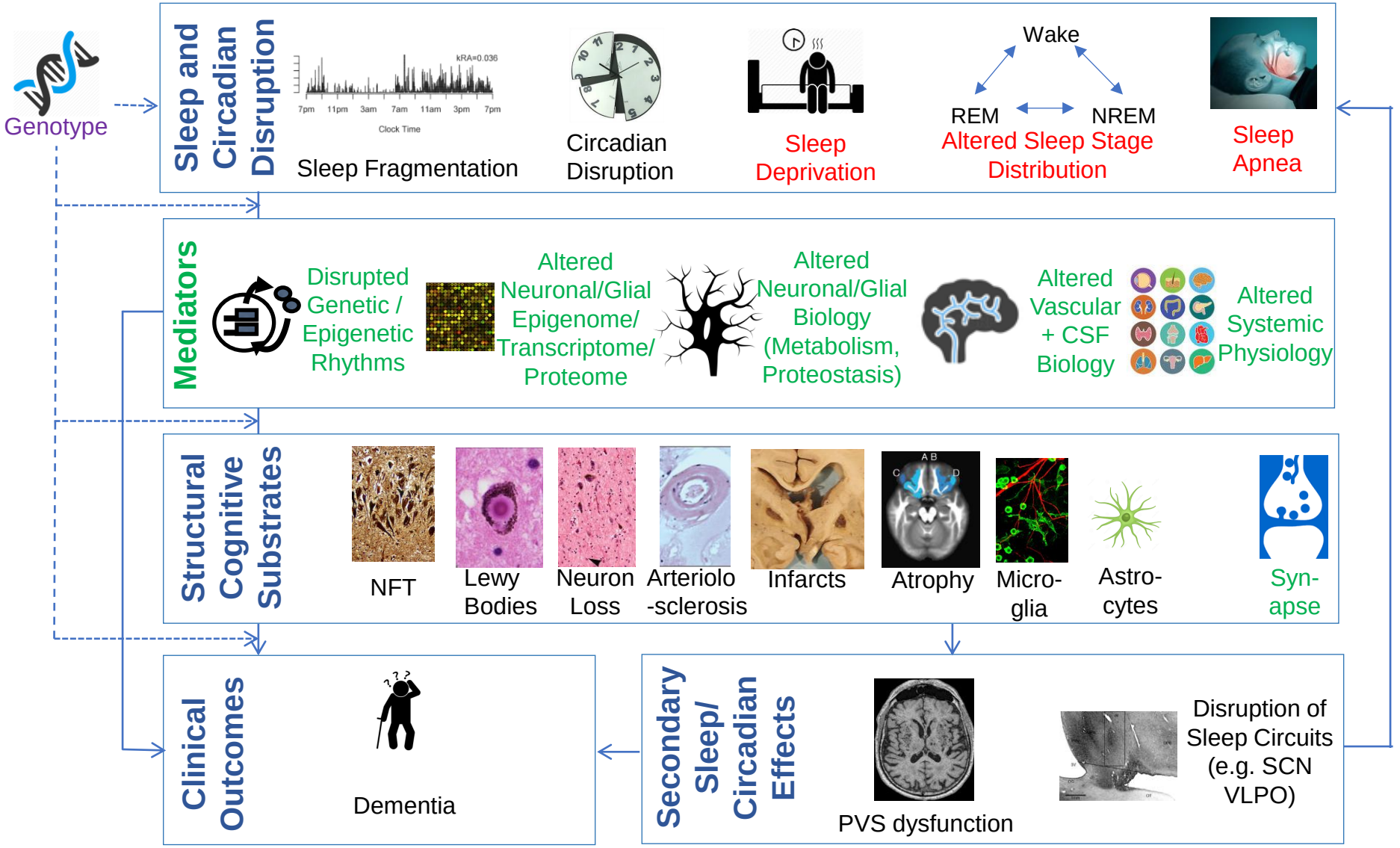

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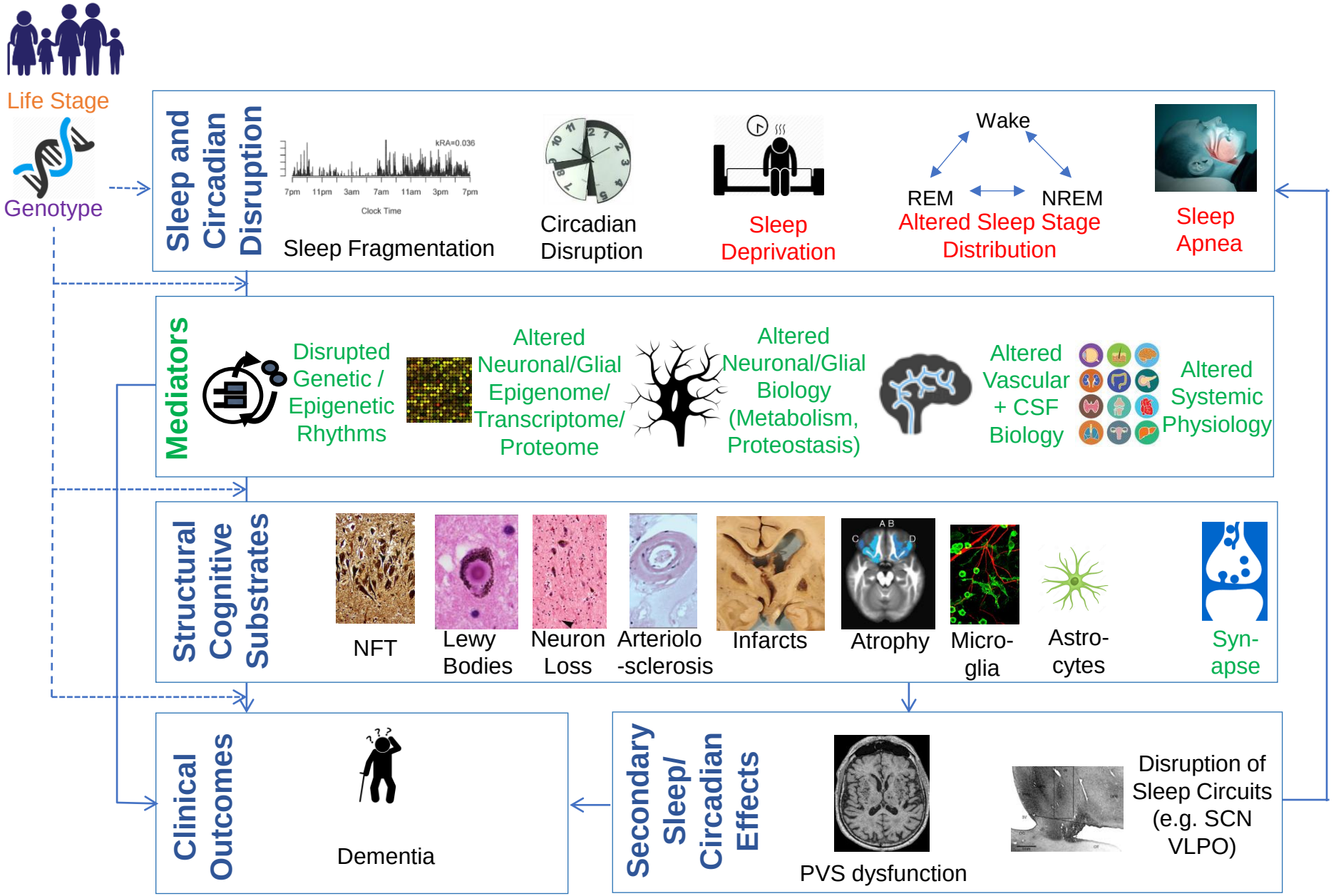
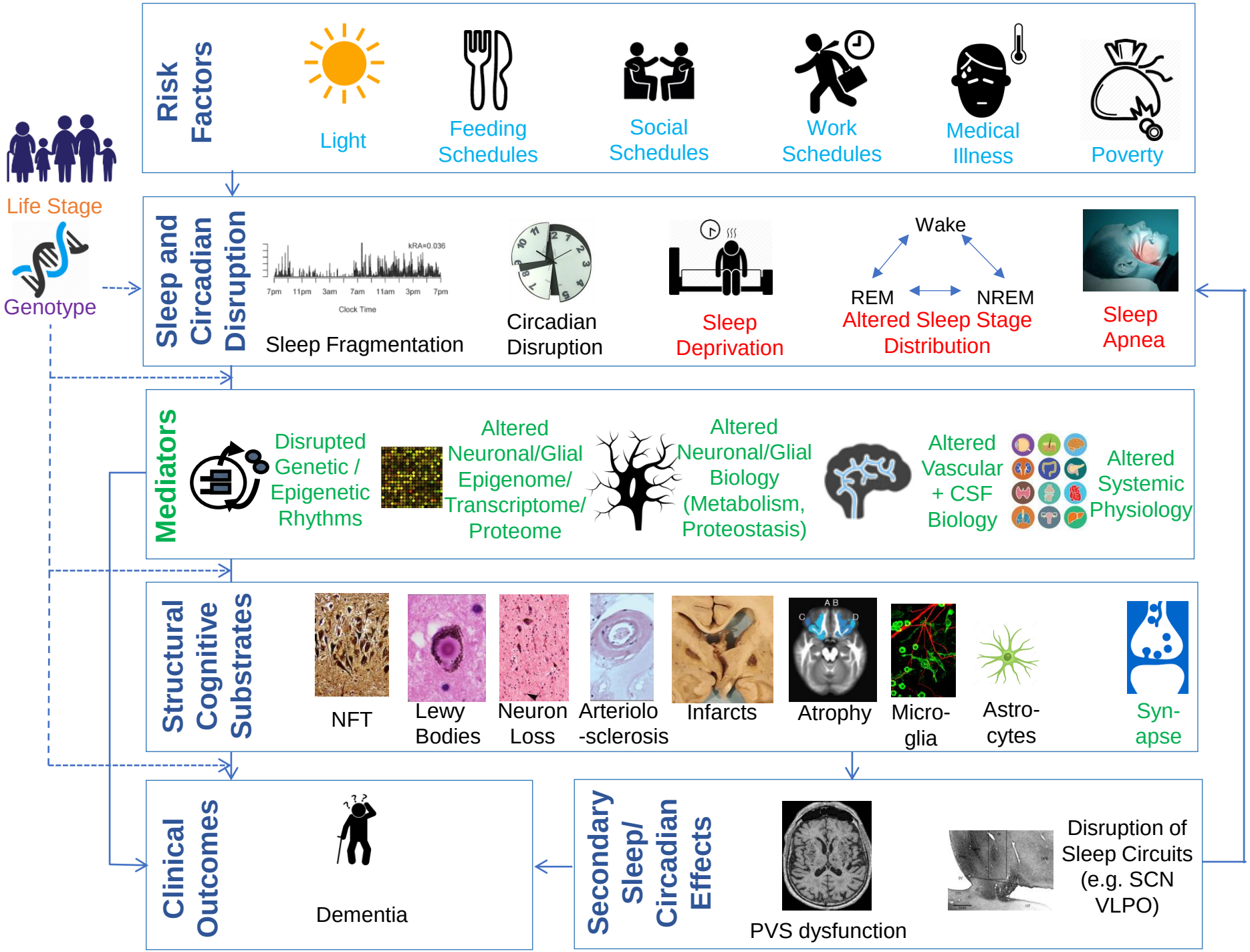


Overall Summary



Part III – Managing Sleep Difficulties in Older Adults

Sleep Problems are Common and Have a Huge Impact on Health

65% of men and
35% of women aged
60-85 have SLEEP APNEA

35-45% of older adults
report INSOMNIA

Older adults with SLEEP APNEA have 1.5-2.5x the risk of DEMENTIA

INSOMNIA is associated with 1.5x the risk of DEMENTIA

Older adults SLEEPING <5 HOURS per night have 2.6x the risk of DEMENTIA

3.1 Normal Sleep

The older adult with healthy sleep…

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..falls asleep easily and stays asleep 6-9 hours with no more than 1-2 awakenings and….

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The older adult with healthy sleep…

..falls asleep easily and stays asleep 6-9 hours with no more than 1-2 awakenings and….

…has no trouble staying awake during the day even in sedentary situations (e.g. TV, meetings, passenger in car)

3.1 Keys to Healthy Sleep

3.1 Keys to Healthy Sleep

- Establish a relaxing pre-sleep routine
- Keep a quiet, dark sleep environment
- Don’t use the bed for anything other than sleep and sex
  - No electronic devices
  - No TV
  - No work
- Avoid eating in the middle of the night

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- Get regular moderate exercise
- Get adequate outside time
- Avoid excessive napping

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- Avoid eating in the middle of the night

- Get regular moderate exercise
- Get adequate outside time
- Avoid excessive napping

- **Regularity is key** – try to keep the same bedtime, wake time, and mealtimes every day

3.1 Common Pitfalls

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- **Pre-sleep Melatonin**: can be helpful for older adults with circadian phase delay (i.e. sleep late and wake up late) but actually harmful for those with sleep maintenance problems due to circadian phase advance

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- **Pre-sleep Melatonin**: can be helpful for older adults with circadian phase delay (i.e. sleep late and wake up late) but actually harmful for those with sleep maintenance problems due to circadian phase advance

- **Excessive Morning Light:** can be harmful for those with sleep maintenance problems due to circadian phase advance

3.1 Cardinal Sleep Symptoms

3.1 Cardinal Sleep Symptoms

Trouble Falling or Staying Asleep

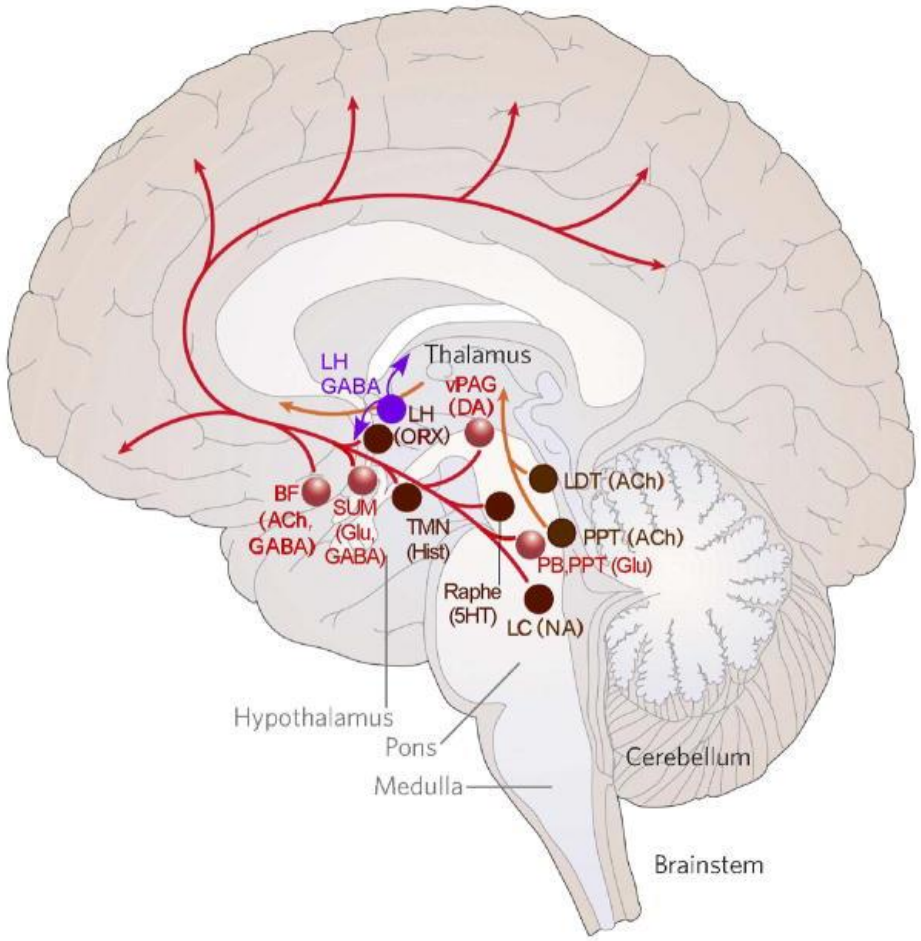
3.1 Cardinal Sleep Symptoms

Trouble Falling or Staying Asleep

Excessive Daytime Sleepiness

3.2 Control of Sleep – Sleep and Wake Nodes

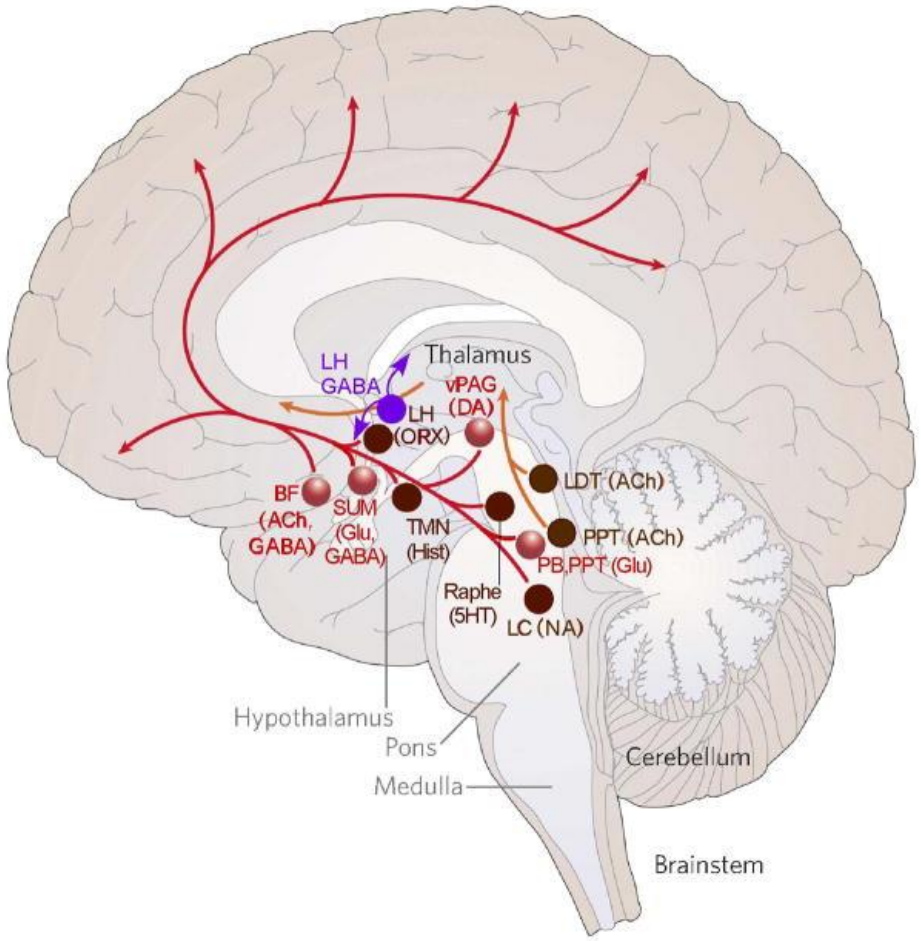
Wake Promoting Areas



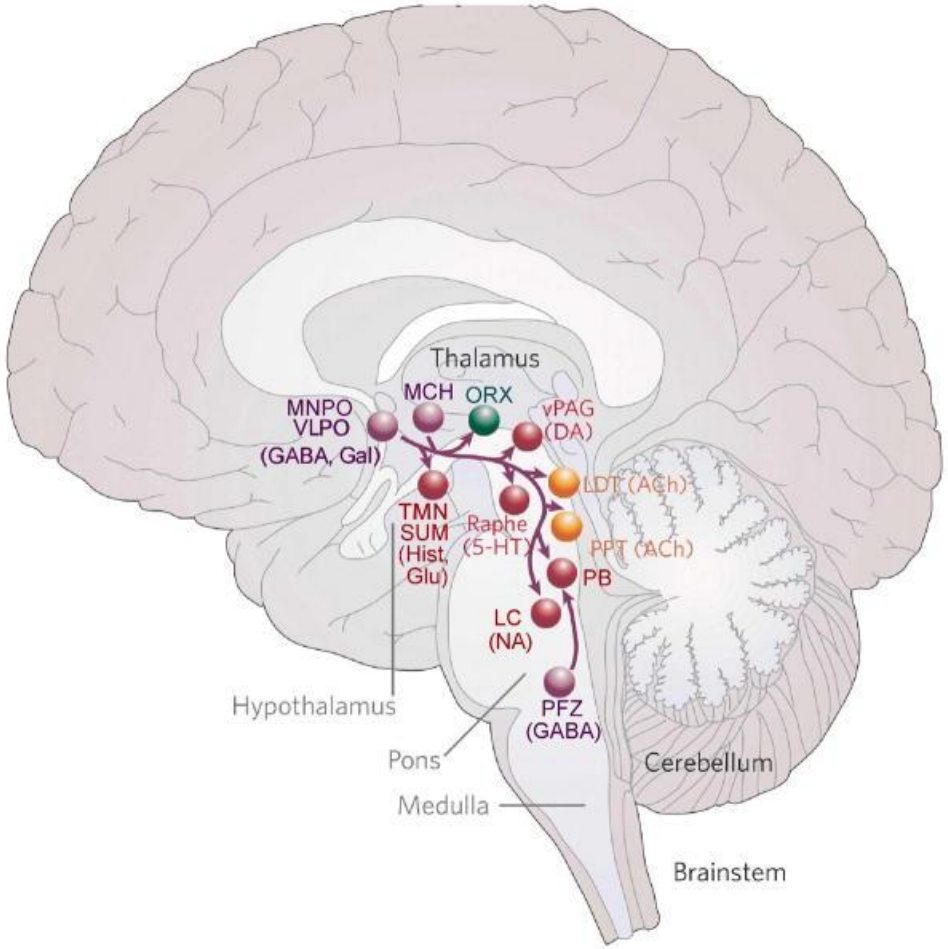
(Saper and Fuller et al, Curr Opin Neurobiol, 2017)

3.2 Control of Sleep – Sleep and Wake Nodes

Wake Promoting Areas



Sleep Promoting Areas



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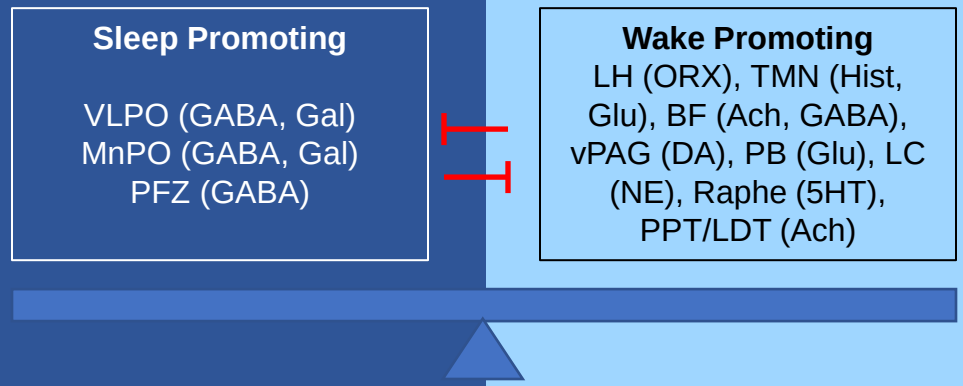
3.2 Control of Sleep – The Core Flip Flop Switch



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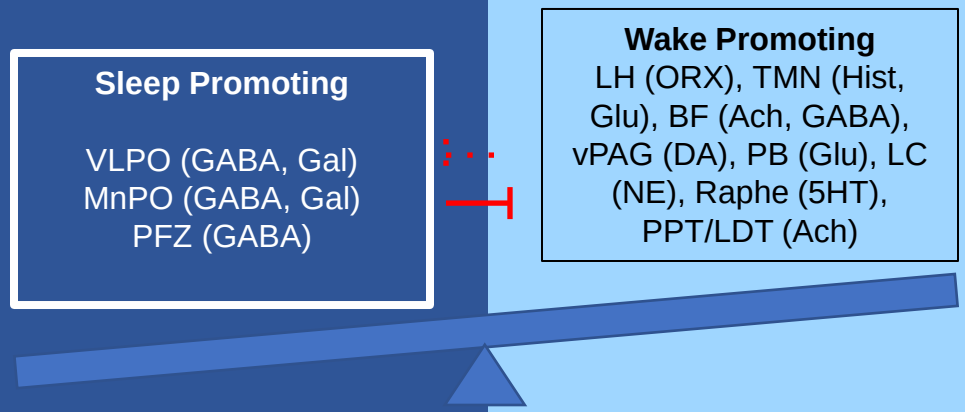

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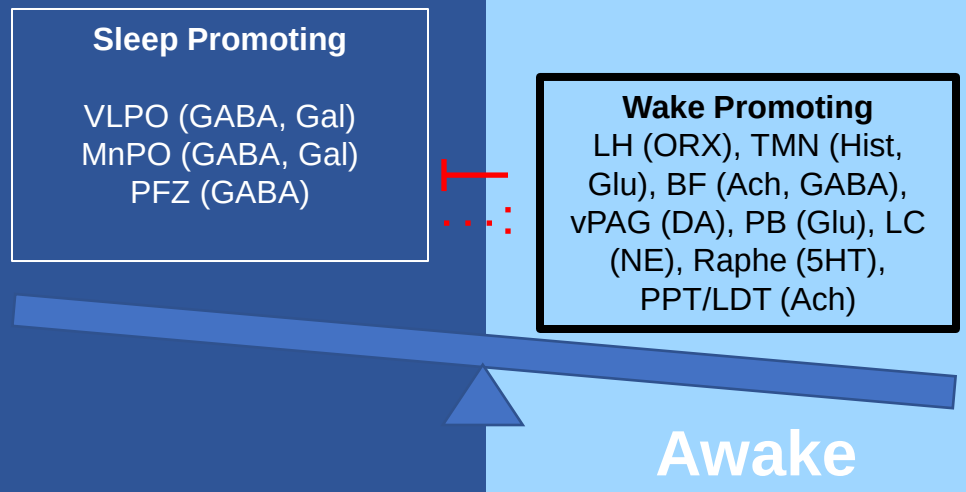


3.2 Control of Sleep – The Two Process Model

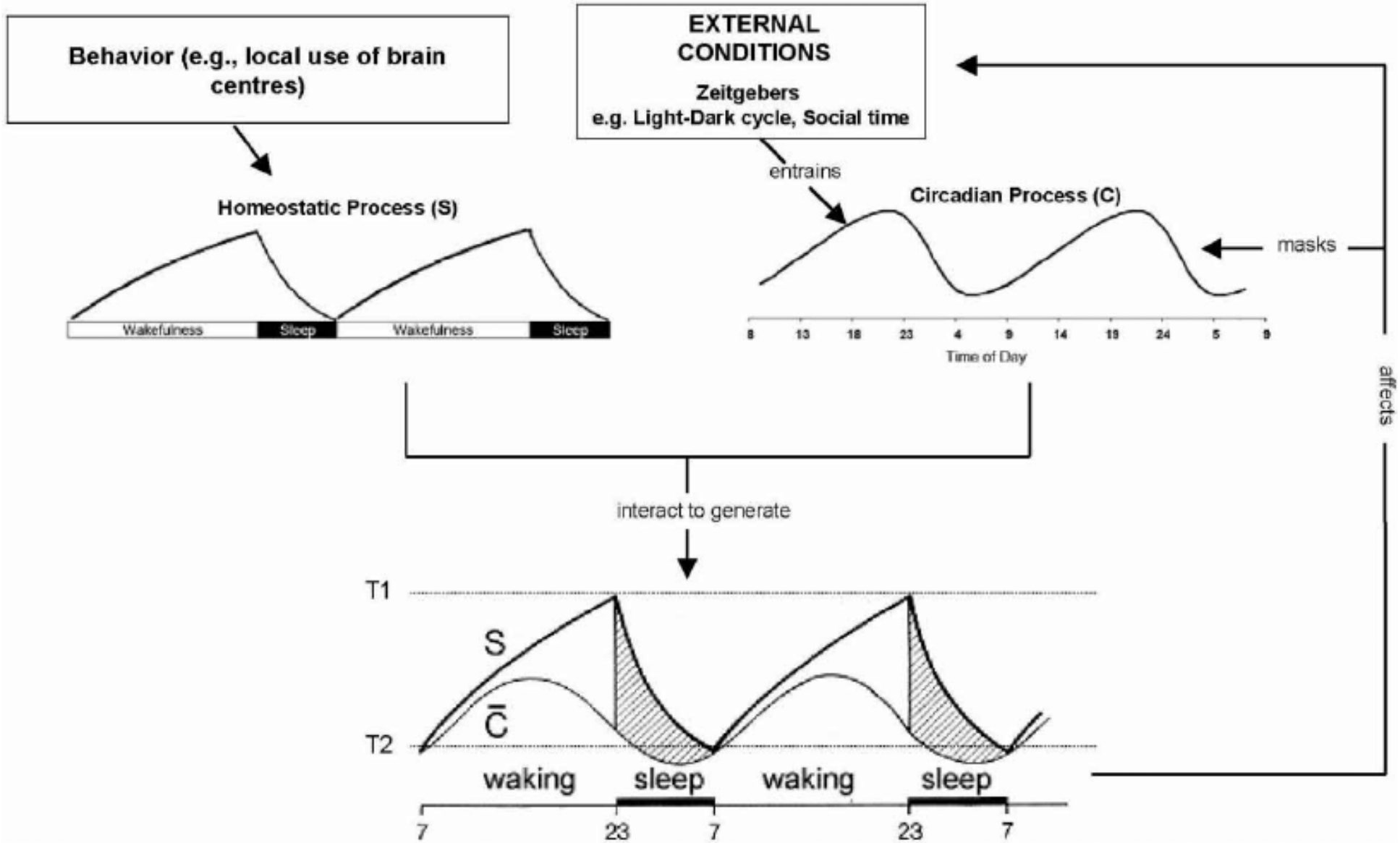
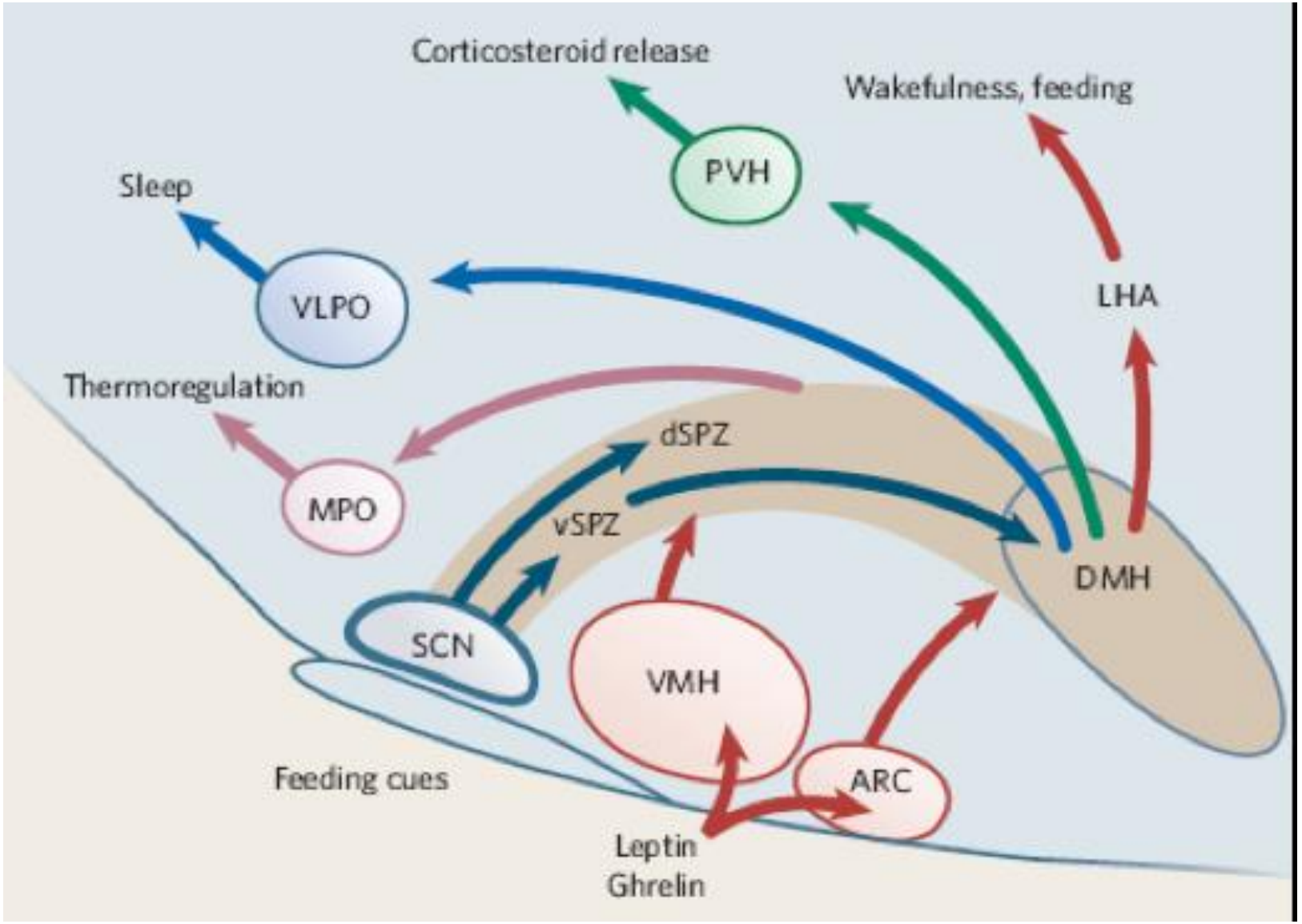


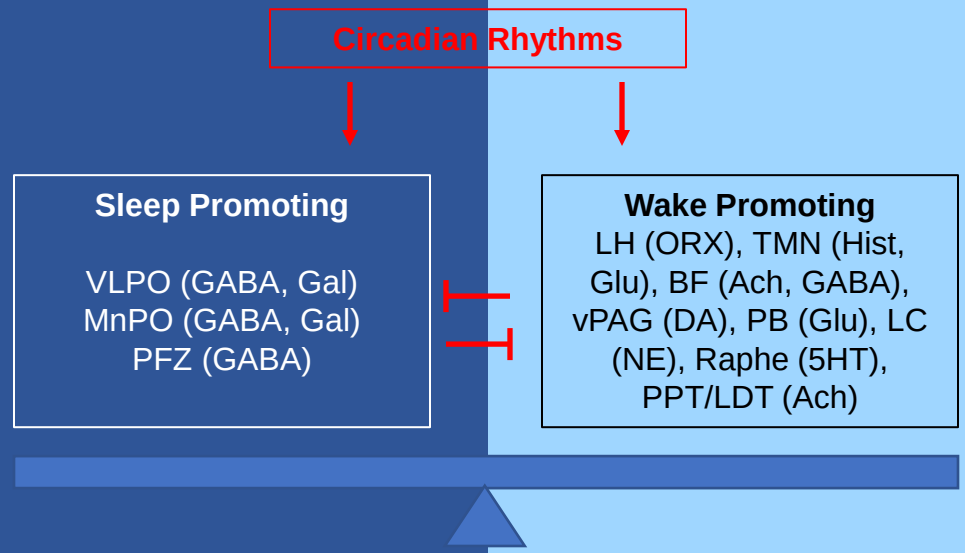
Figure from Schmidt et al, 2007 based on model first proposed by Borbely

3.2 Control of Sleep – Circadian Control



(Saper, 2005)

3.2 Control of Sleep – Additional Levels of Control



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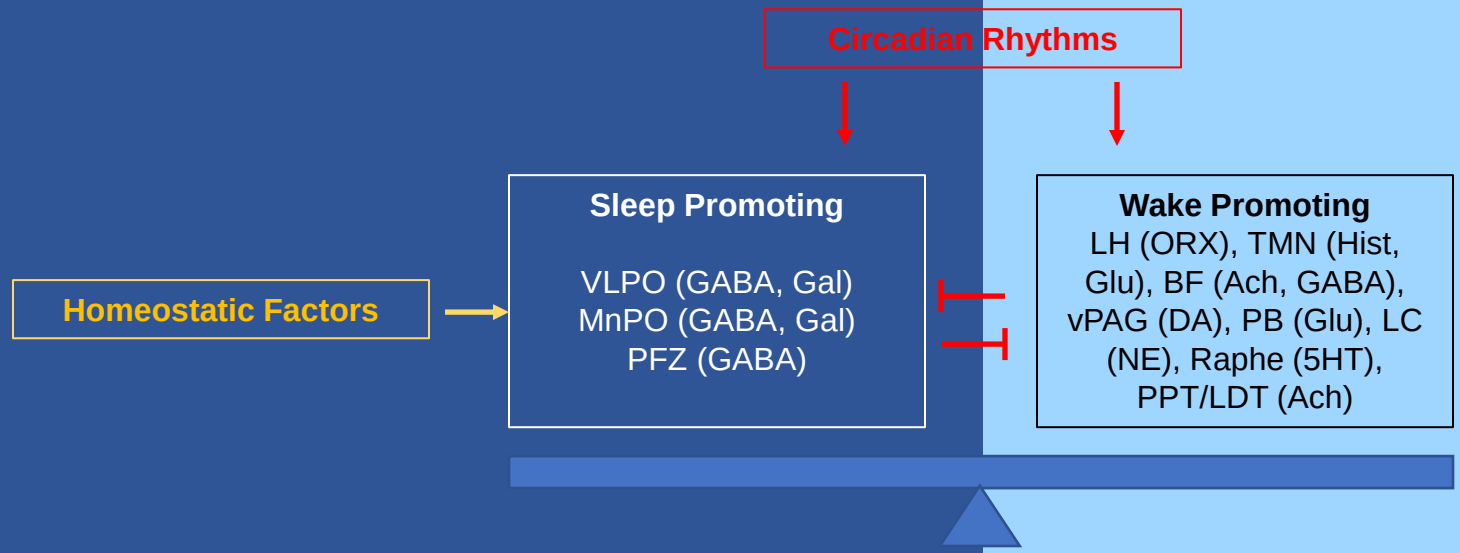

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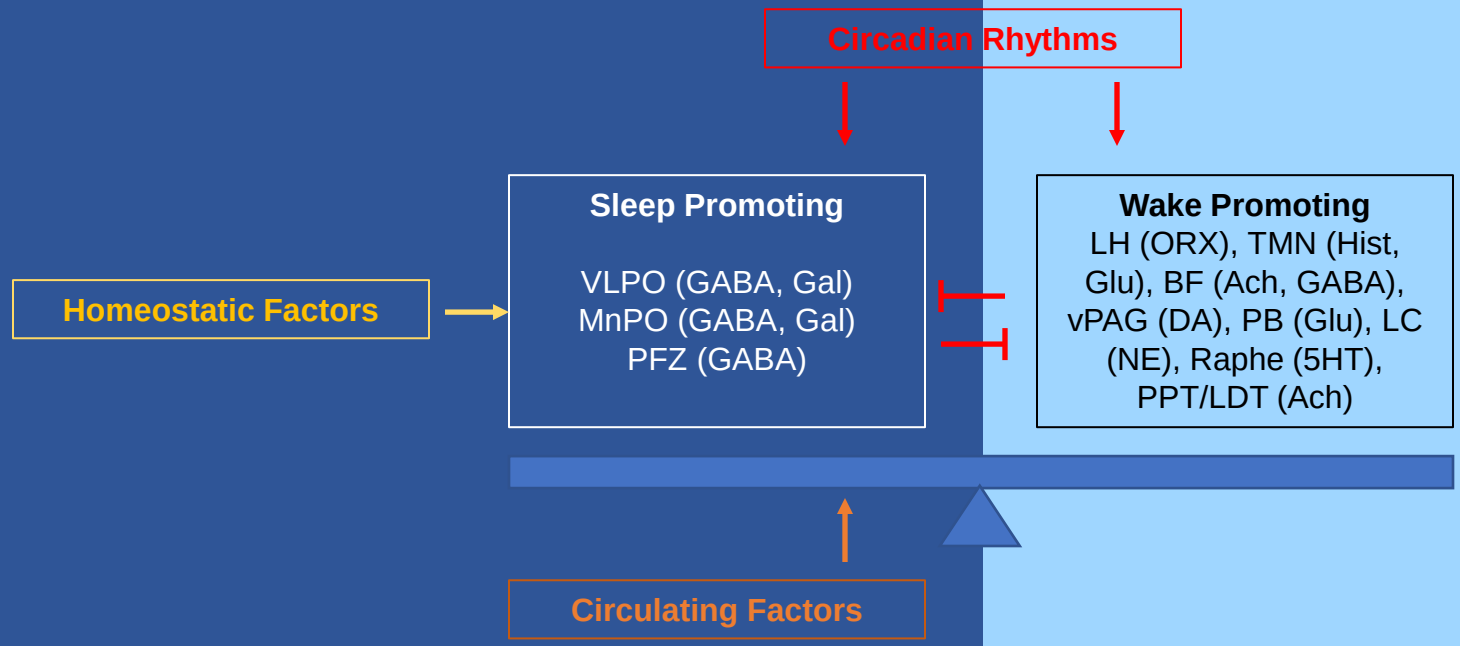

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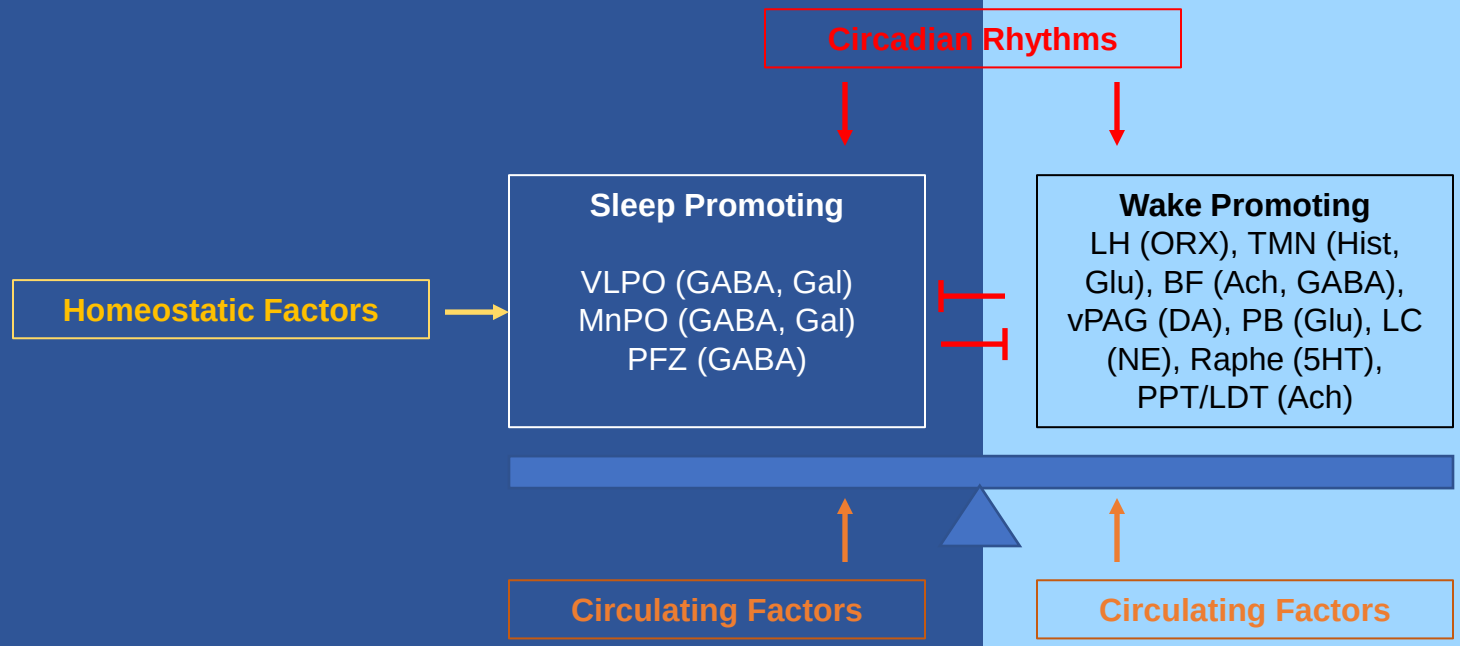
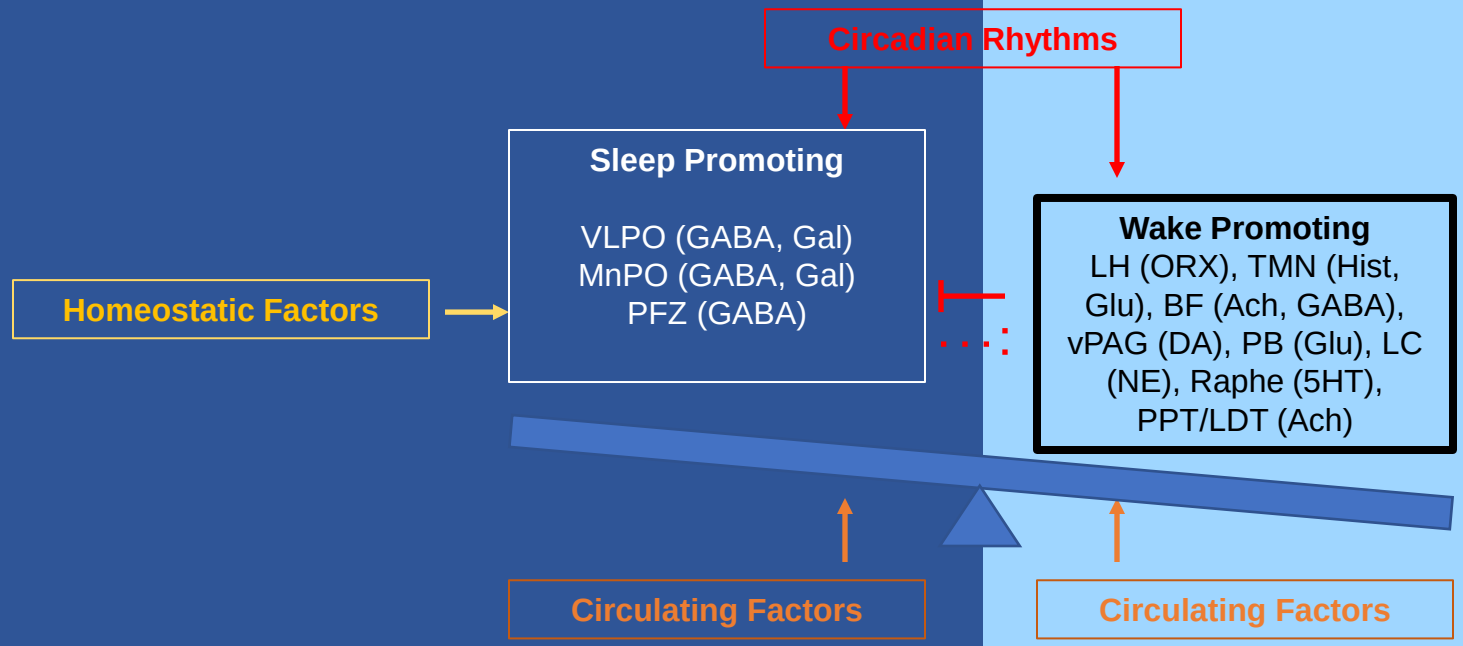


3.3 Insomnia – Assessment and Management



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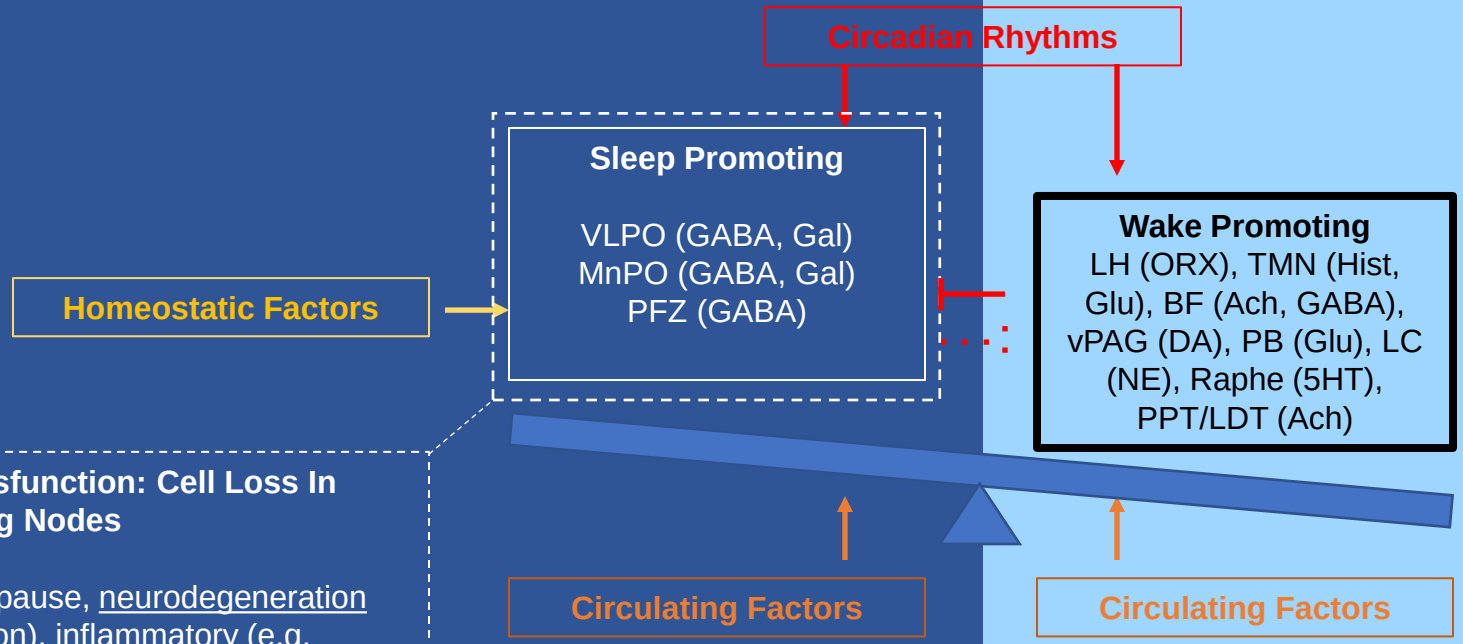

Core Circuit Dysfunction: Cell Loss In Sleep Promoting Nodes

DDx: age, menopause, neurodegeneration (e.g. PD, AD, prion), inflammatory (e.g. demyelination, NMDA encephalitis)
Hx: sleep maintenance>initiation; other neurological symptoms
Ix: PSG – arousals/fragmentation; imaging
Rx: GABA-acting hypnotics

3.3 Insomnia – Assessment and Management

Process C: Circadian Dysfunction
DDx: environmental, phase advance/delay, ocular (cataract, retina), SCN (neurodegeneration)
Hx: light, activity, feeding schedule; constrained vs. ad lib
Ix: actigraphy under ad-lib sleep conditions
Rx: sleep/wake scheduling, phototherapy, melatonin, light/dark scheduling

Circadian Rhythms

Sleep Promoting

VLPO (GABA, Gal)
MnPO (GABA, Gal)
PFZ (GABA)

Homeostatic Factors

Wake Promoting
LH (ORX), TMN (Hist, Glu), BF (Ach, GABA), vPAG (DA), PB (Glu), LC (NE), Raphe (5HT), PPT/LDT (Ach)

Circulating Factors

Circulating Factors

Core Circuit Dysfunction: Cell Loss In Sleep Promoting Nodes

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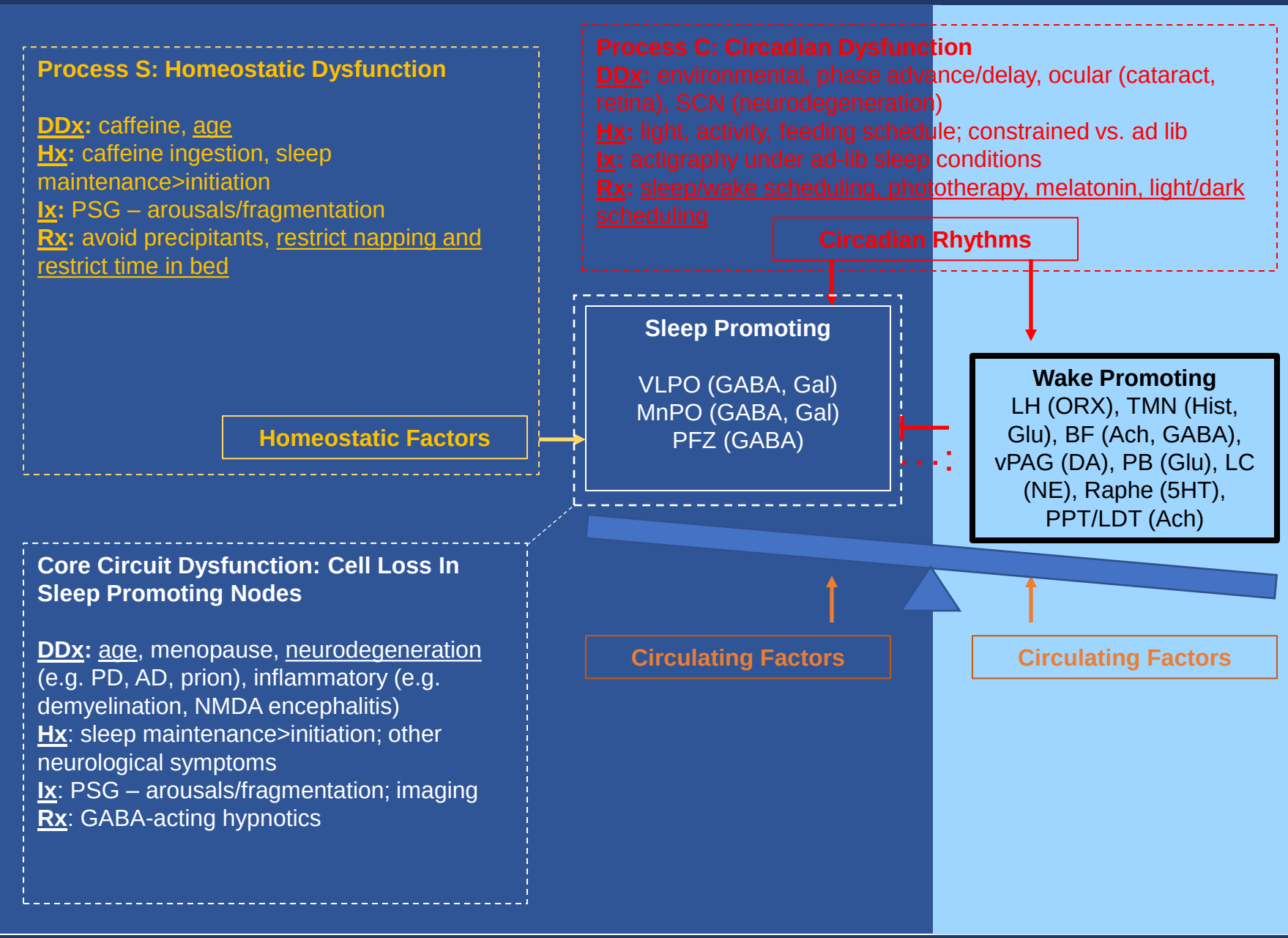
3.3 Insomnia – Assessment and Management



3.3 Insomnia – Assessment and Management

Process S: Homeostatic Dysfunction

DDx: caffeine, age
Hx: caffeine ingestion, sleep maintenance>initiation
Ix: PSG – arousals/fragmentation
Rx: avoid precipitants, restrict napping and restrict time in bed

Homeostatic Factors

Process C: Circadian Dysfunction

DDx: environmental, phase advance/delay, ocular (cataract, retina), SCN (neurodegeneration)
Hx: light, activity, feeding schedule; constrained vs. ad lib
Ix: actigraphy under ad-lib sleep conditions
Rx: sleep/wake scheduling, phototherapy, melatonin, light/dark scheduling

Circadian Rhythms

Wake Activation: Psychiatric

DDx: anxiety (general and sleep), mood, conditioning
Hx: psych symptoms, sleep pre-occupation/anxiety, situational dependence
Rx: CBT, sedating antidepressants

Psychiatric

Sleep Promoting

VLPO (GABA, Gal)
MnPO (GABA, Gal)
PFZ (GABA)

Wake Promoting

LH (ORX), TMN (Hist, Glu), BF (Ach, GABA), vPAG (DA), PB (Glu), LC (NE), Raphe (5HT), PPT/LDT (Ach)

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Circulating Factors

Circulating Factors

3.3 Insomnia – Assessment and Management

Process S: Homeostatic Dysfunction

DDx: caffeine, age
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VLPO (GABA, Gal)
MnPO (GABA, Gal)
PFZ (GABA)

Wake Promoting

LH (ORX), TMN (Hist, Glu), BF (Ach, GABA), vPAG (DA), PB (Glu), LC (NE), Raphe (5HT), PPT/LDT (Ach)

Wake Activation: Psychiatric

DDx: anxiety (general and sleep), mood, conditioning
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Psychiatric

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Hx: sleep maintenance>initiation; other neurological symptoms
Ix: PSG – arousals/fragmentation; imaging
Rx: GABA-acting hypnotics

Circulating Factors

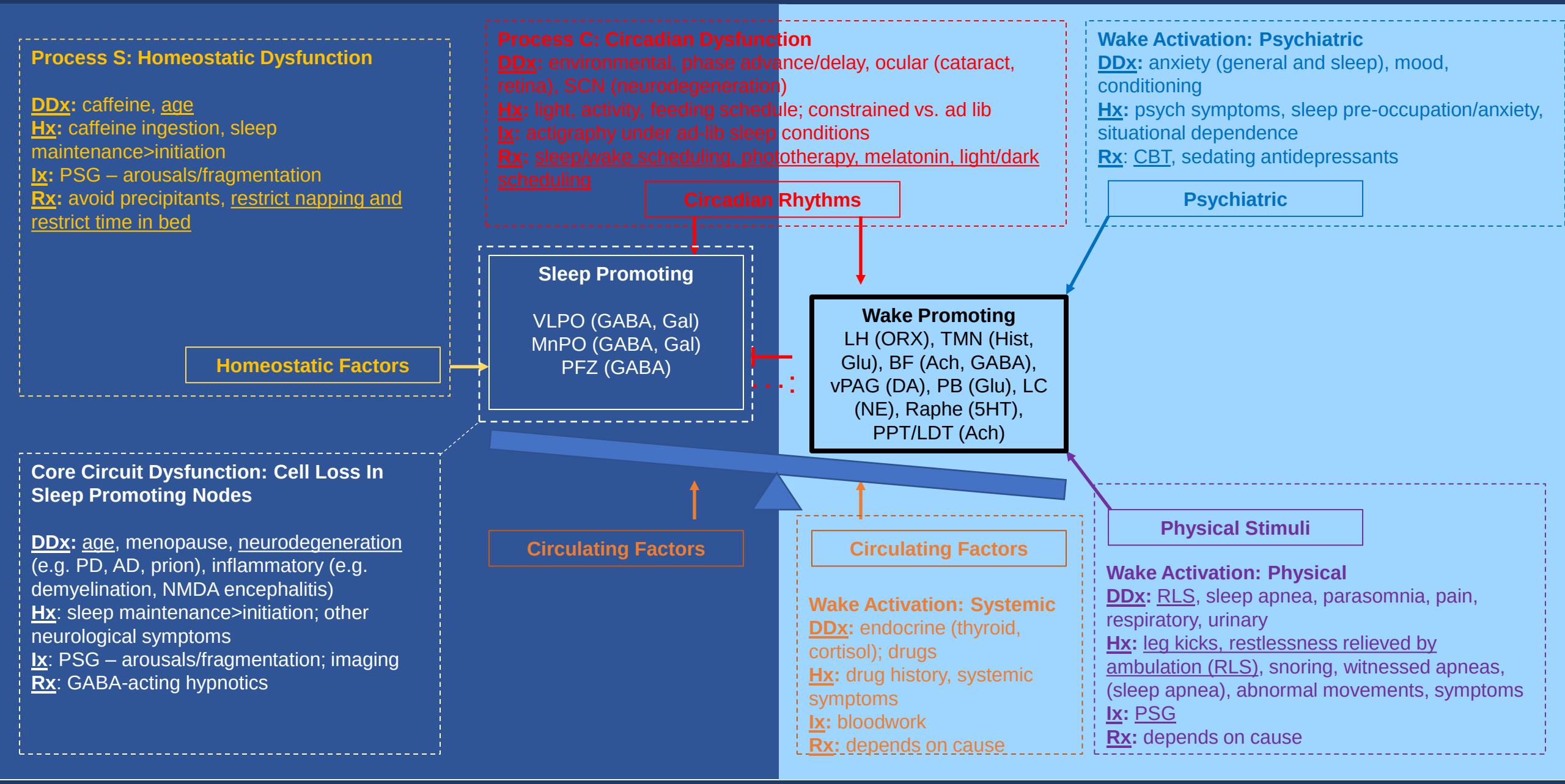
Circulating Factors

Physical Stimuli

Wake Activation: Physical

DDx: RLS, sleep apnea, parasomnia, pain, respiratory, urinary
Hx: leg kicks, restlessness relieved by ambulation (RLS), snoring, witnessed apneas, (sleep apnea), abnormal movements, symptoms
Ix: PSG
Rx: depends on cause

3.3 Insomnia – Assessment and Management



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Process S: Homeostatic Dysfunction

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Homeostatic Factors

Process C: Circadian Dysfunction

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Circadian Rhythms

Wake Activation: Psychiatric

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Psychiatric

Sleep Promoting

VLPO (GABA, Gal)
MnPO (GABA, Gal)
PFZ (GABA)

Wake Promoting

LH (ORX), TMN (Hist, Glu), BF (Ach, GABA), vPAG (DA), PB (Glu), LC (NE), Raphe (5HT), PPT/LDT (Ach)

Other Wake-Suppressing Medications

Anti-adrenergic, anti-histaminergic, orexin antagonists

Core Circuit Dysfunction: Cell Loss In Sleep Promoting Nodes

DDx: age, menopause, neurodegeneration (e.g. PD, AD, prion), inflammatory (e.g. demyelination, NMDA encephalitis)
Hx: sleep maintenance>initiation; other neurological symptoms
Ix: PSG – arousals/fragmentation; imaging
Rx: GABA-acting hypnotics

Circulating Factors

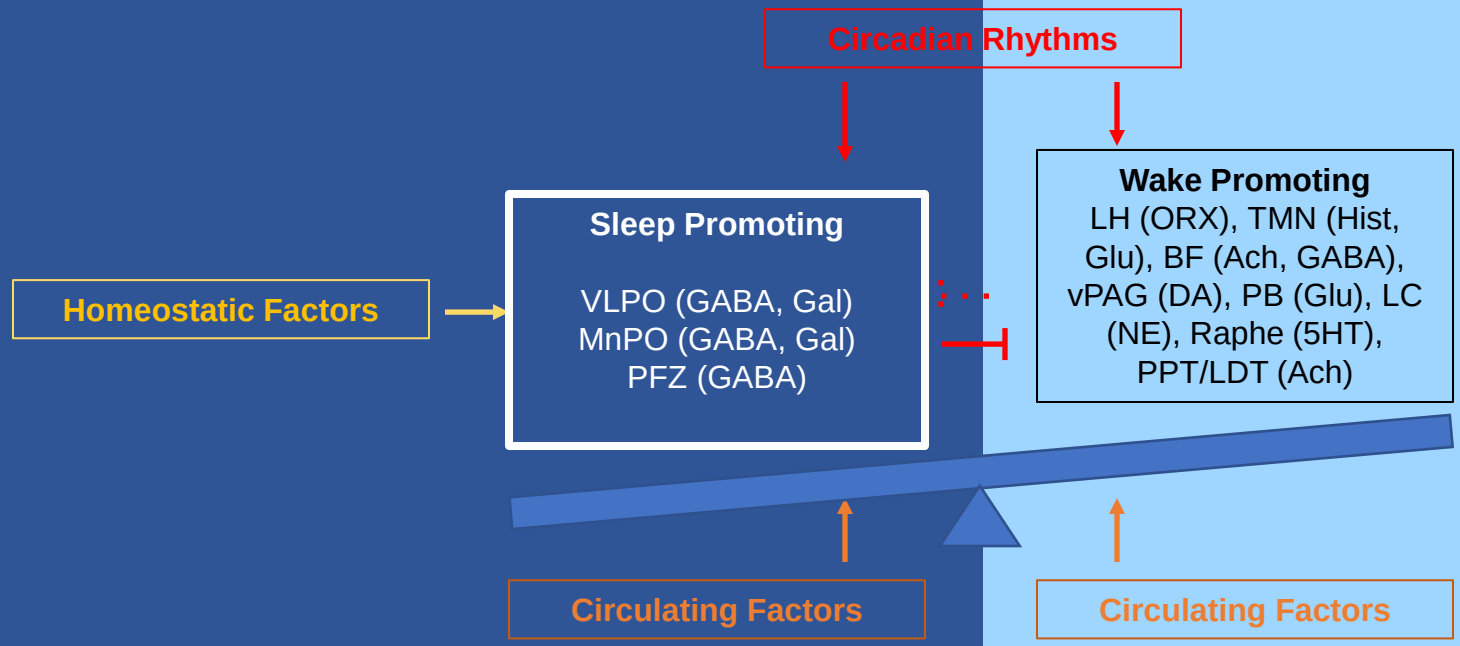
Circulating Factors

Wake Activation: Systemic
DDx: endocrine (thyroid, cortisol); drugs
Hx: drug history, systemic symptoms
Ix: bloodwork
Rx: depends on cause

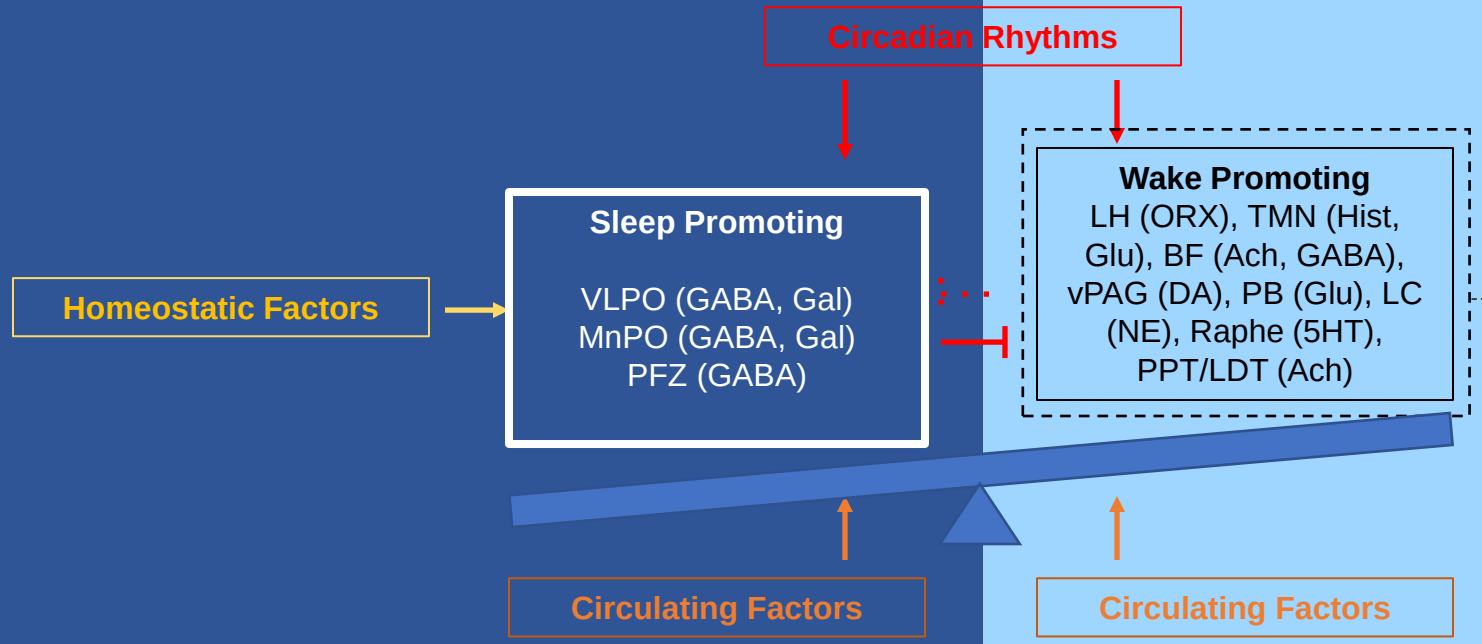
Physical Stimuli

Wake Activation: Physical
DDx: RLS, sleep apnea, parasomnia, pain, respiratory, urinary
Hx: leg kicks, restlessness relieved by ambulation (RLS), snoring, witnessed apneas, (sleep apnea), abnormal movements, symptoms
Ix: PSG
Rx: depends on cause

3.4 Excessive Daytime Sleepiness – Assessment and Management



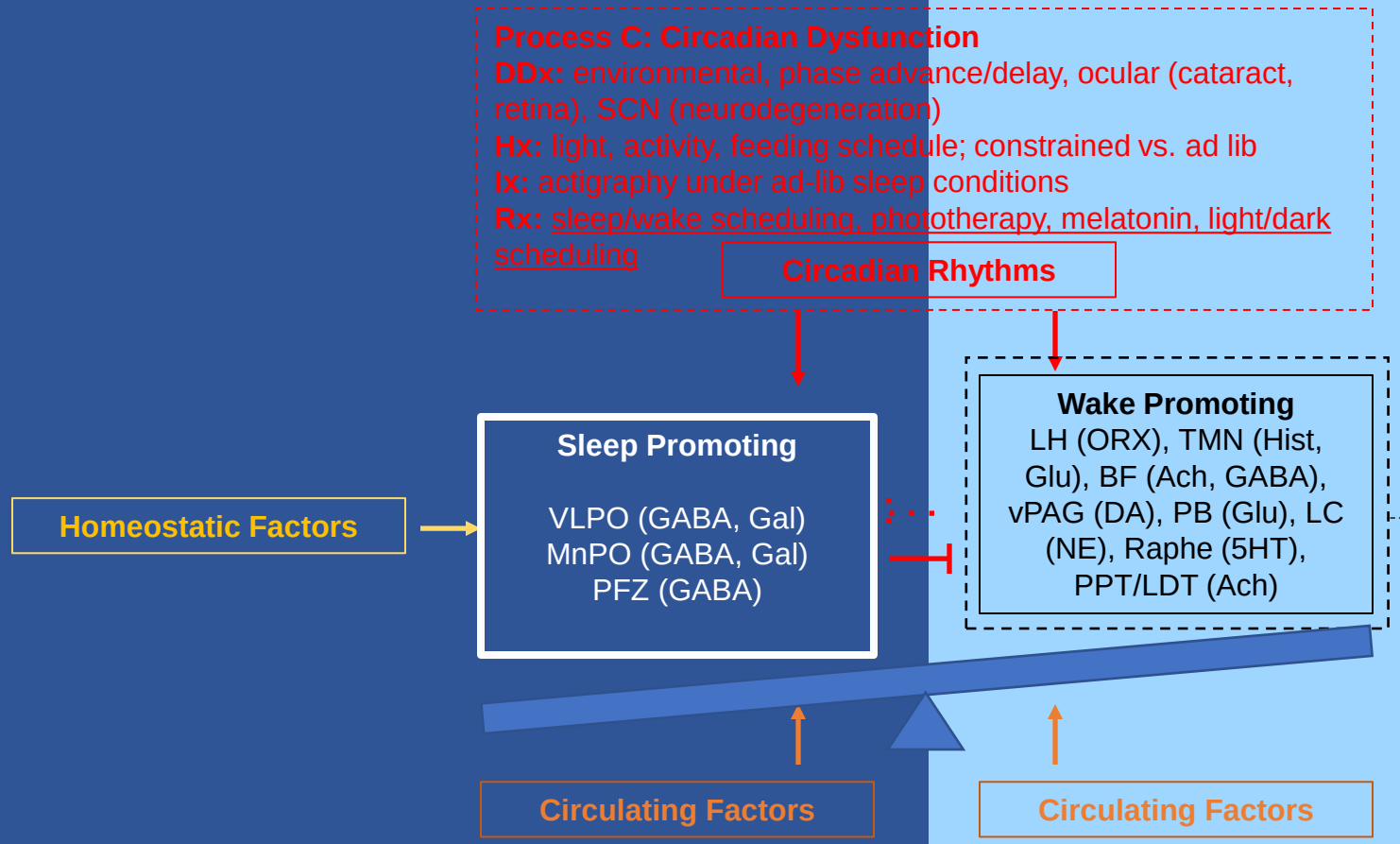
3.4 Excessive Daytime Sleepiness – Assessment and Management



Core Circuit Dysfunction: Cell Loss In Wake Promoting Nodes

DDx: neurodegeneration (e.g. PD, AD, prion), inflammatory (e.g. demyelination), narcolepsy, idiopathic hypersomnia
Hx: total 24-hour sleep time, fragmented vs. consolidated, refreshing naps?, other Sx state boundary dyscontrol (hypnagogic hallucinations, sleep paralysis, cataplexy)
Ix: multiple sleep latency test
Rx: stimulants (modafinil, methylphenidate, amphetamines, pitolisant)

3.4 Excessive Daytime Sleepiness – Assessment and Management



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Rx: stimulants (modafinil, methylphenidate, amphetamines, pitolisant)

3.4 Excessive Daytime Sleepiness – Assessment and Management

Process S: Homeostatic Dysfunction

DDx: sleep deprivation, sleep disruption (sleep apnea, other)
Hx: sleep timing, effect of sleep extension (e.g. multi-day holiday), snoring, witnessed apneas, (sleep apnea),
Ix: PSG, home sleep testing
Rx: sleep extension, treat cause of disrupted sleep (e.g. apnea)

Homeostatic Factors

Process C: Circadian Dysfunction
DDx: environmental, phase advance/delay, ocular (cataract, retina), SCN (neurodegeneration)
Hx: light, activity, feeding schedule; constrained vs. ad lib
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Circulating Factors

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Ix: actigraphy under ad-lib sleep conditions
Rx: sleep/wake scheduling, phototherapy, melatonin, light/dark scheduling

Circadian Rhythms

Insufficient Wake Promotion: Psychiatric

DDx: depression, bipolar
Hx: psych symptoms,
Rx: CBT, stimulating antidepressants

Psychiatric

Sleep Promoting

VLPO (GABA, Gal)
MnPO (GABA, Gal)
PFZ (GABA)

Wake Promoting
LH (ORX), TMN (Hist, Glu), BF (Ach, GABA), vPAG (DA), PB (Glu), LC (NE), Raphe (5HT), PPT/LDT (Ach)

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Hx: sleep timing, effect of sleep extension (e.g. multi-day holiday), snoring, witnessed apneas, (sleep apnea),
Ix: PSG, home sleep testing
Rx: sleep extension, treat cause of disrupted sleep (e.g. apnea)

Homeostatic Factors

Process C: Circadian Dysfunction
DDx: environmental, phase advance/delay, ocular (cataract, retina), SCN (neurodegeneration)
Hx: light, activity, feeding schedule; constrained vs. ad lib
Ix: actigraphy under ad-lib sleep conditions
Rx: sleep/wake scheduling, phototherapy, melatonin, light/dark scheduling

Circadian Rhythms

Sleep Promoting

VLPO (GABA, Gal)
MnPO (GABA, Gal)
PFZ (GABA)

Wake Promoting
LH (ORX), TMN (Hist, Glu), BF (Ach, GABA), vPAG (DA), PB (Glu), LC (NE), Raphe (5HT), PPT/LDT (Ach)

Insufficient Wake Promotion: Psychiatric

DDx: depression, bipolar
Hx: psych symptoms,
Rx: CBT, stimulating antidepressants

Psychiatric

Core Circuit Dysfunction: Cell Loss In Wake Promoting Nodes

DDx: neurodegeneration (e.g. PD, AD, prion), inflammatory (e.g. demyelination), narcolepsy, idiopathic hypersomnia
Hx: total 24-hour sleep time, fragmented vs. consolidated, refreshing naps?, other Sx state boundary dyscontrol (hypnagogic hallucinations, sleep paralysis, cataplexy)
Ix: multiple sleep latency test
Rx: stimulants (modafinil, methylphenidate, amphetamines, pitolisant)

Circulating Factors

Circulating Factors

Insufficient Wake Promotion: Systemic
DDx: endocrine (thyroid, cortisol); drugs
Hx: drug history, systemic symptoms
Ix: bloodwork
Rx: depends on cause

3.4 Excessive Daytime Sleepiness – Assessment and Management

Process S: Homeostatic Dysfunction

DDx: sleep deprivation, sleep disruption (sleep apnea, other)
Hx: sleep timing, effect of sleep extension (e.g. multi-day holiday), snoring, witnessed apneas, (sleep apnea),
Ix: PSG, home sleep testing
Rx: sleep extension, treat cause of disrupted sleep (e.g. apnea)

Homeostatic Factors

Process C: Circadian Dysfunction
DDx: environmental, phase advance/delay, ocular (cataract, retina), SCN (neurodegeneration)
Hx: light, activity, feeding schedule; constrained vs. ad lib
Ix: actigraphy under ad-lib sleep conditions
Rx: sleep/wake scheduling, phototherapy, melatonin, light/dark scheduling

Circadian Rhythms

Insufficient Wake Promotion: Psychiatric

DDx: depression, bipolar
Hx: psych symptoms,
Rx: CBT, stimulating antidepressants

Psychiatric

Sleep Promoting

VLPO (GABA, Gal)
MnPO (GABA, Gal)
PFZ (GABA)

Wake Promoting
LH (ORX), TMN (Hist, Glu), BF (Ach, GABA), vPAG (DA), PB (Glu), LC (NE), Raphe (5HT), PPT/LDT (Ach)

Core Circuit Dysfunction: Cell Loss In Wake Promoting Nodes

DDx: neurodegeneration (e.g. PD, AD, prion), inflammatory (e.g. demyelination), narcolepsy, idiopathic hypersomnia
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Ix: multiple sleep latency test
Rx: stimulants (modafinil, methylphenidate, amphetamines, pitolisant)

Circulating Factors

Sleep Activation: Systemic

DDx: inflammation;
Hx: drug history, systemic symptoms
Ix: bloodwork
Rx: depends on cause

Circulating Factors

Insufficient Wake Promotion: Systemic
DDx: endocrine (thyroid, cortisol); drugs
Hx: drug history, systemic symptoms
Ix: bloodwork
Rx: depends on cause

3.5 Summary of Sleep Assessment

History

Sleep/Wake Schedule

- ❑ Lights-out, sleep latency, wake time, arousals, return latency, naps
- ❑ Light/dark timing
- ❑ Meal and physical activity timing
- ❑ Weekday vs. weekend vs. holiday
- ❑ At home vs. holiday

Sleep Symptoms

- ❑ Snoring, apneas, gasping, headaches, diaphoresis
- ❑ Restless legs
- ❑ Other movements/vocalizations
- ❑ Thoughts/anxieties
- ❑ Nightmares
- ❑ Sleep paralysis / hallucinations / cataplexy

Daytime Sleepiness

- ❑ Naps (short/long); refreshing?
- ❑ Sedentary situation
- ❑ Effect of sleep extension
- ❑ Home vs. holidays

Other

- ❑ Co-morbidities
- ❑ Psychiatric
- ❑ Medications/Drugs/Alcohol
- ❑ School/work schedule

3.5 Summary of Sleep Assessment

History

Sleep/Wake Schedule

- ❑ Lights-out, sleep latency, wake time, arousals, return latency, naps
- ❑ Light/dark timing
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- ❑ Home vs. holidays

Other

- ❑ Co-morbidities
- ❑ Psychiatric
- ❑ Medications/Drugs/Alcohol
- ❑ School/work schedule

Physical Exam

Sleep Apnea Risk

- ❑ Body habitus
- ❑ Neck circumference
- ❑ Size of mandible
- ❑ Tonsils / upper airway
- ❑ General cardiac and respiratory exam

Neurodegeneration

- ❑ Cognition
- ❑ Parkinsonism

Ocular

- ❑ Cataracts
- ❑ Visual function

3.5 Summary of Sleep Assessment

History

Sleep/Wake Schedule

- ❑ Lights-out, sleep latency, wake time, arousals, return latency, naps
- ❑ Light/dark timing
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Sleep Symptoms

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Neurodegeneration

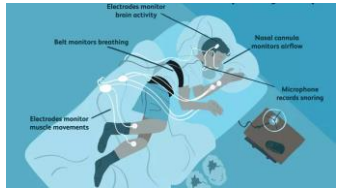
- ❑ Cognition
- ❑ Parkinsonism

Ocular

- ❑ Cataracts
- ❑ Visual function

Investigations

Sleep Assessments



Polysomngoraphy

Home Sleep Apnea Testing

Actigraphy

Wireless Adhesive ECG/sound/resp /PTT/SpO2/accel

Ambulatory EEG

Imaging

- ❑ If lesion suspected on history/physical examination, or specific neurodegenerative diagnosis

Bloodwork

- ❑ Hormonal, others, as indicated by history and physical examination

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Co-Op (CS)

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Rose Yan
Andrei Chuson
Shreni Patel
Saskia Tjioe
Kirusanthy Kaneshwaran
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Contact Information:
andrew.lim@utoronto.ca