

Bedside to Bench Conference
Sleep, Circadian Rhythms, and Aging: New Avenues for Improving Brain
Health, Physical Health and Functioning
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Sleep, Circadian Rhythms, and Aging: Translational Perspective



Phyllis C. Zee, MD, PhD
Benjamin and Virginia T. Boshes Professor of Neurology
Professor of Neurobiology
Director Center for Circadian and Sleep Medicine
Northwestern University Feinberg School of Medicine



Disclosures

Current research funding (Northwestern University)

- NIH
- DARPA
- Jazz
- Alzheimer's Association
- Dixon Family Foundation

Scientific Advisory Board (consultant)

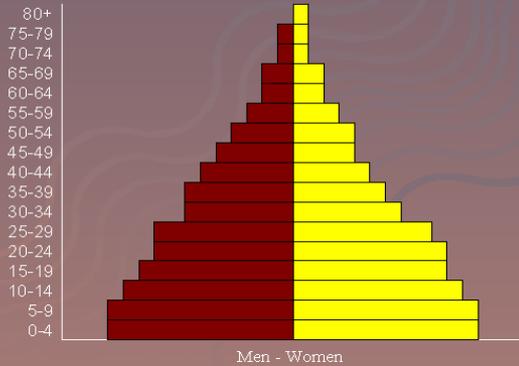
- Merck
- Philips

Other

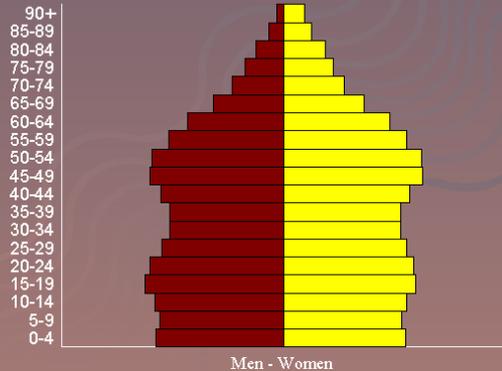
Stock ownership: Teva, Express Scripts

Demographics of Aging and Sleep Disturbance in America

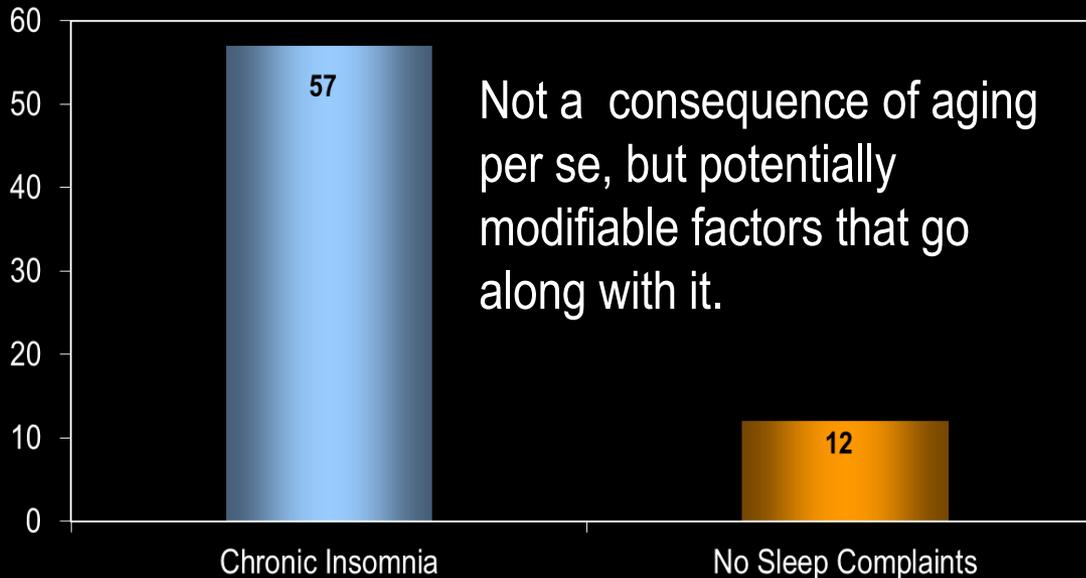
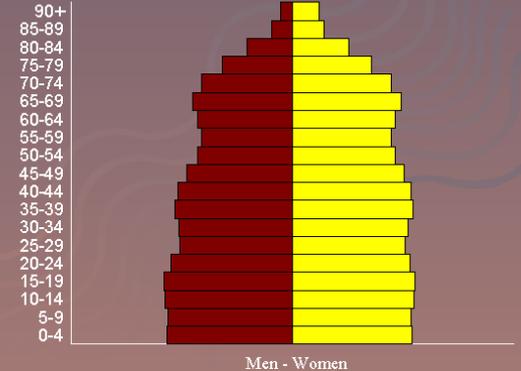
USA: 1900



USA: 2010



USA: 2030



Normal age associated changes in sleep and circadian rhythms contribute to vulnerability

NOT

primarily responsible for very high prevalence of sleep-wake disturbances in older adults

Highest contribution is physical, neurological mental health, socioeconomic and environmental factors.

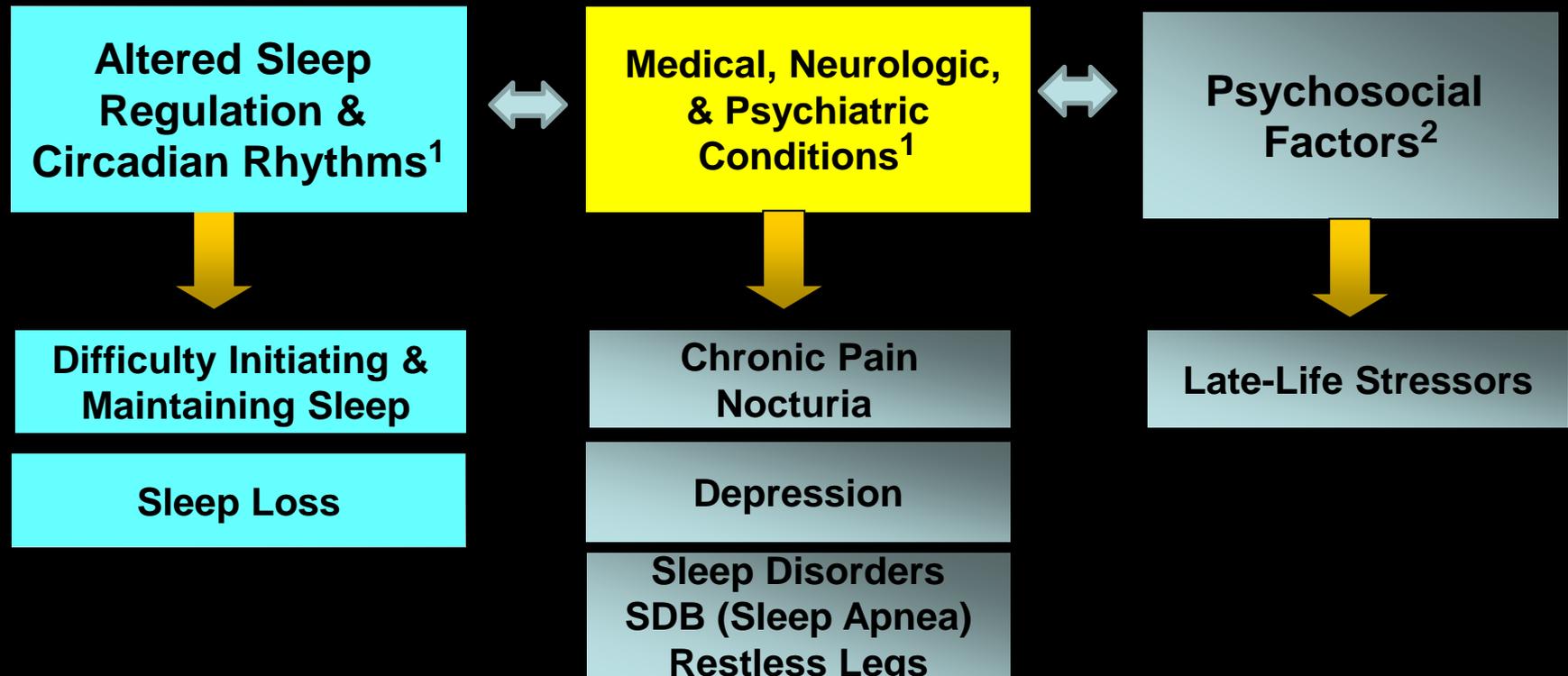
Not inevitable with aging!



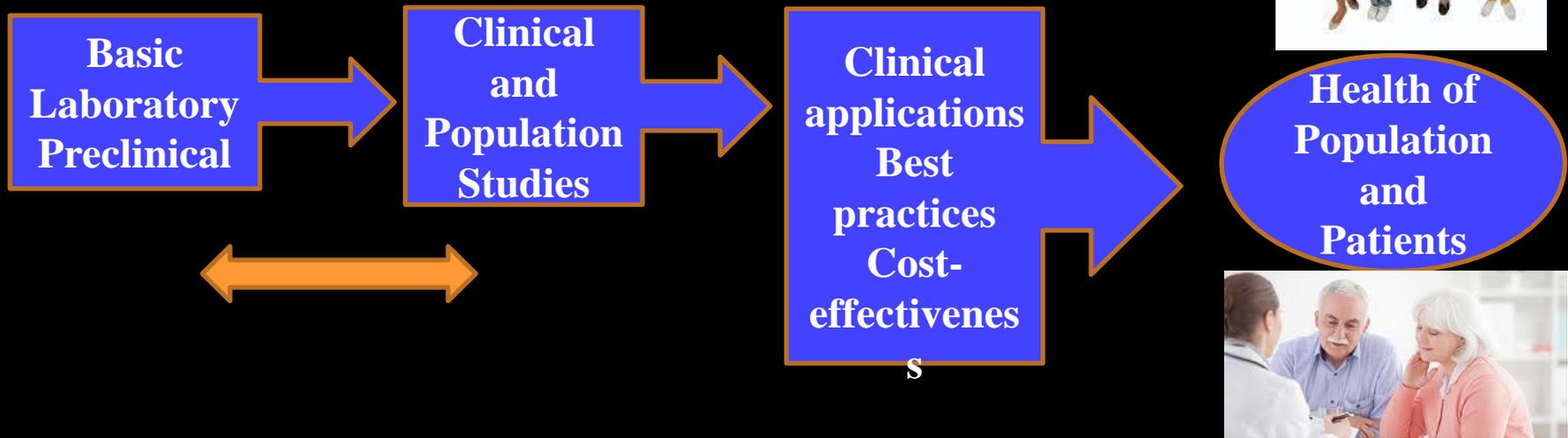
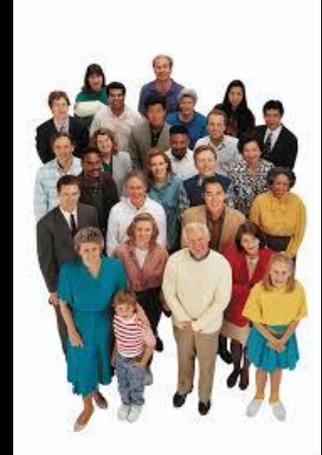
Foley DJ et al. *Sleep*. 1995;18:425-432; Foley D et al. *J Psychosom Res* 2004;56:497–502; Ohayon et al., *Sleep*. 2004 Nov 1;27(7):1255-73

Sleep-Wake Disturbance and Co-Morbidities

Common Conditions



What is Translational Research ? Does Definition Matter?

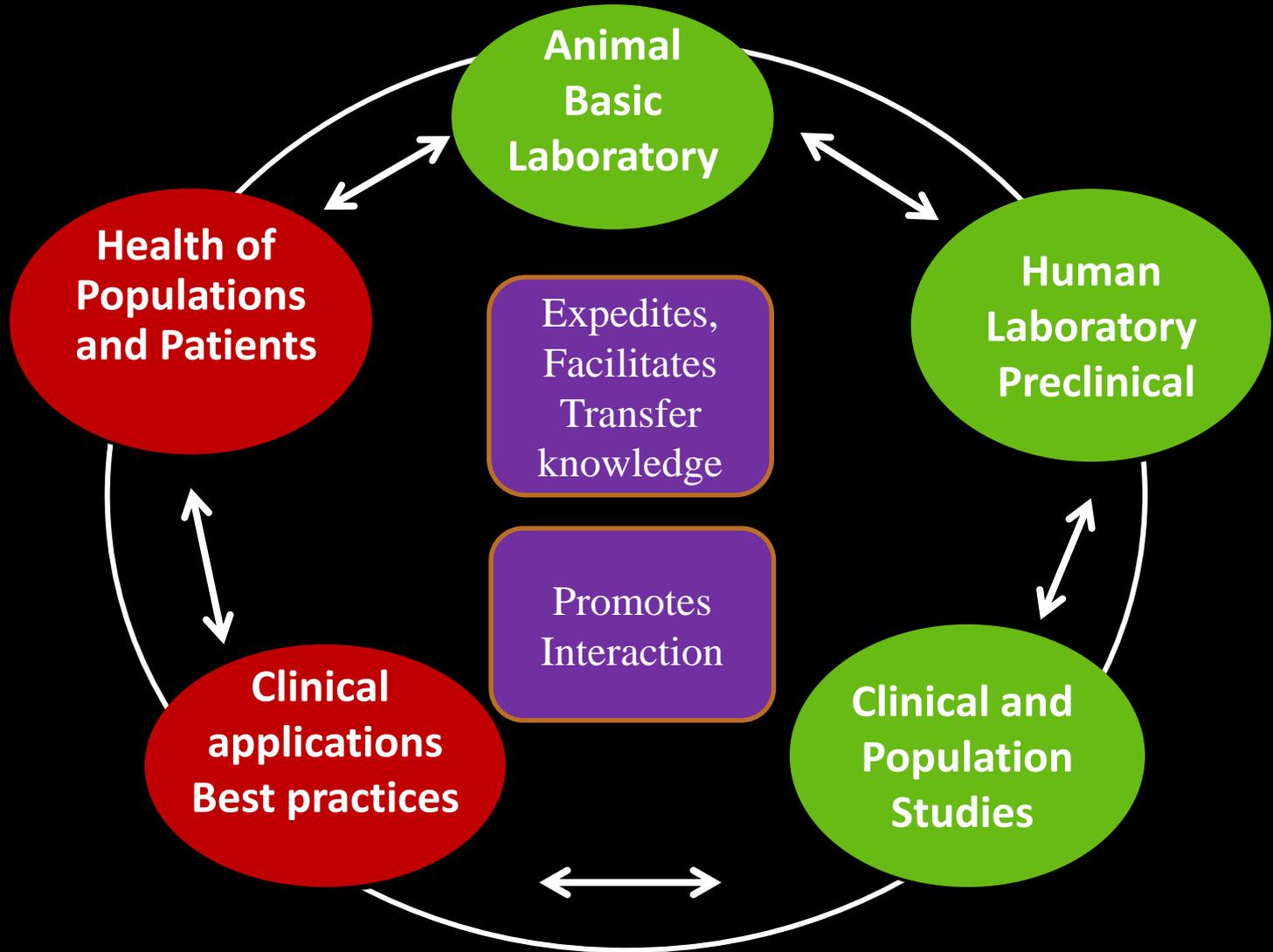


Translational research transforms scientific discoveries arising from laboratory, clinical, or population studies into clinical applications to reduce disease incidence, morbidity, and mortality.

Woolf SH. The meaning of translational research and why it matters. JAMA. 2008;299(2):211–213. National Cancer Institute. Translational Research Working Group Definition of “Translational Research”. <http://www.cancer.gov/trwg/TRWG-definition-and-TR-continuum>.

Translational Team Science

Multidirectional-Multidisciplinary Integration



Fundamental Basic Science Discoveries Have Changed How We Think About the Role of Sleep and Circadian Rhythms in Health and Disease

Sleep

- Sleep is a global brain activity AND sleep be a local brain phenomena
- Sleep is cellular, molecular in tissues and organs

Circadian Rhythm

- Clock genetic machinery exists in virtually all cells-tissues
- Clocks are integrated into metabolic, inflammatory, neural pathways....

It's about the interaction-alignment between these processes that determines health!

Sleep Upregulates Genes in Heart, Lung and Brain are Organ-Specific

Brain (cortex, hypothalamus):

- macromolecule biosynthesis
 - Heme synthesis, cholesterol synthesis, etc.

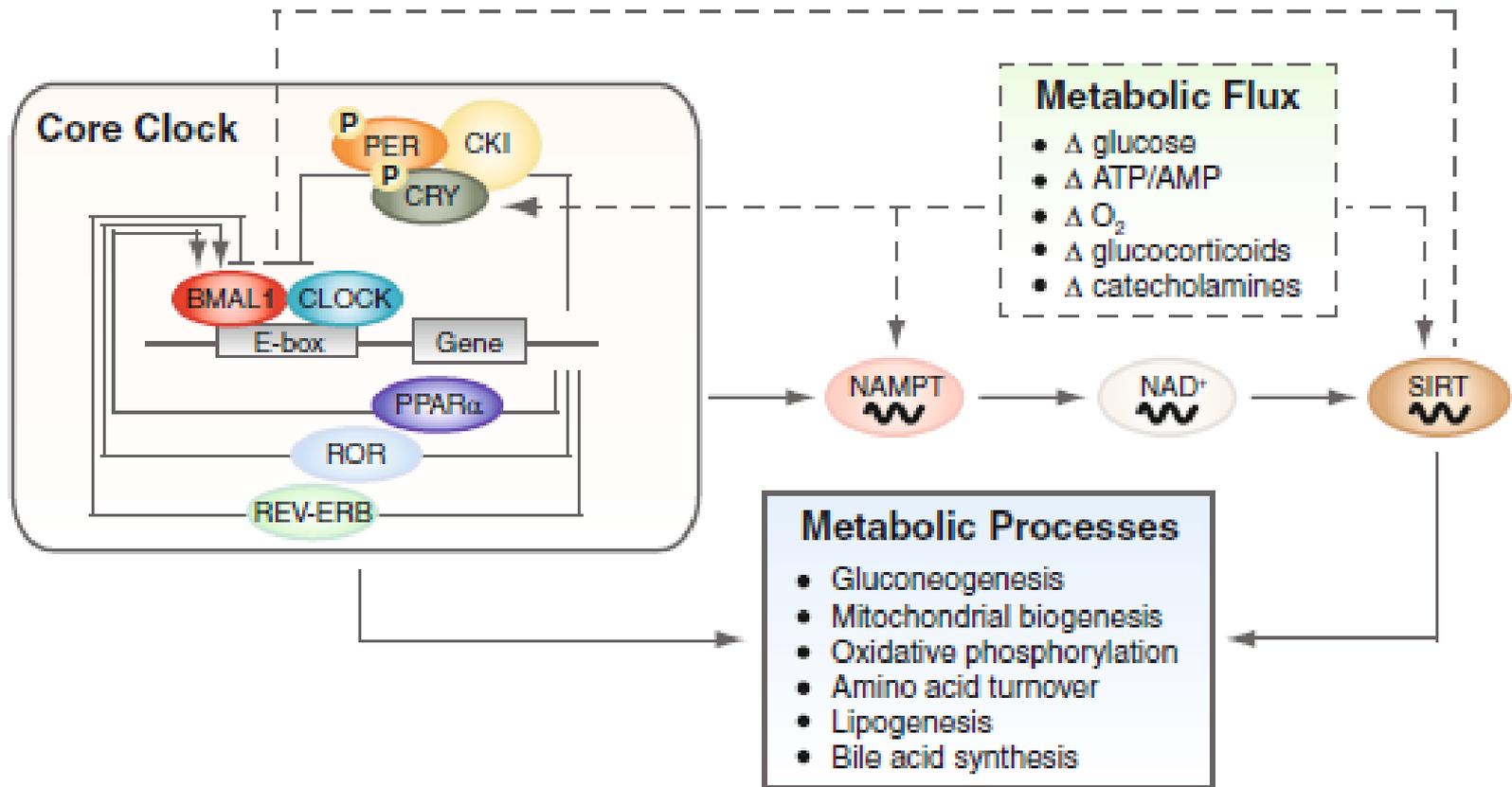
Heart:

- DNA repair
- ubiquitin-proteasome pathway

Lung:

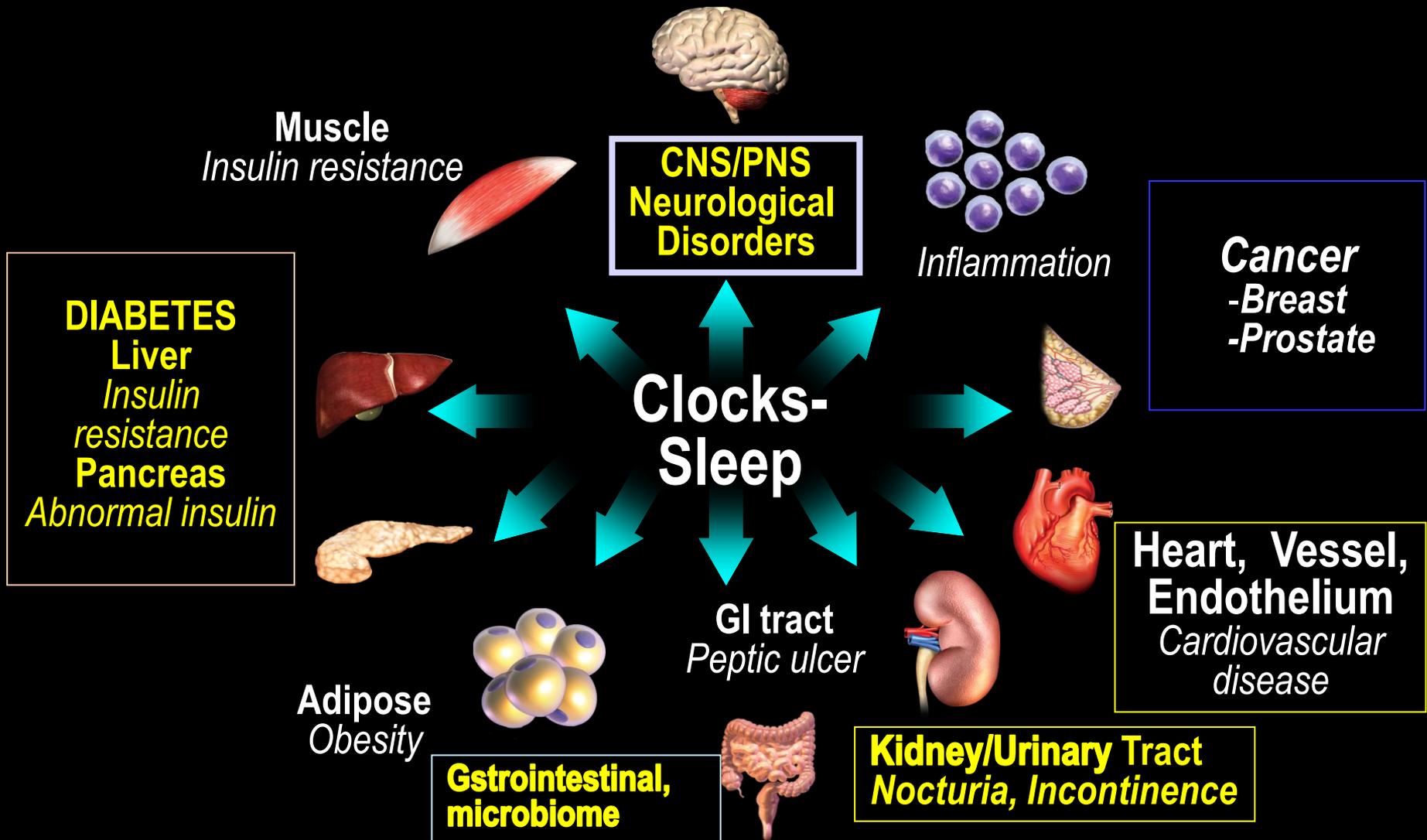
- Antioxidant enzymes

Clock Genes: Bi-Directional Regulation of Energy Balance



Sleep and Circadian Rhythms

Implications for Aging, Health and Disease

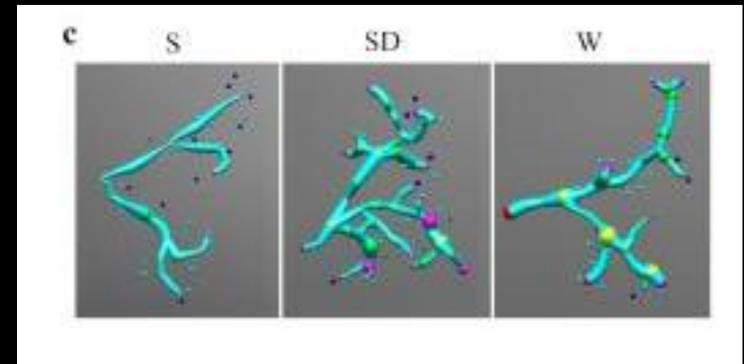
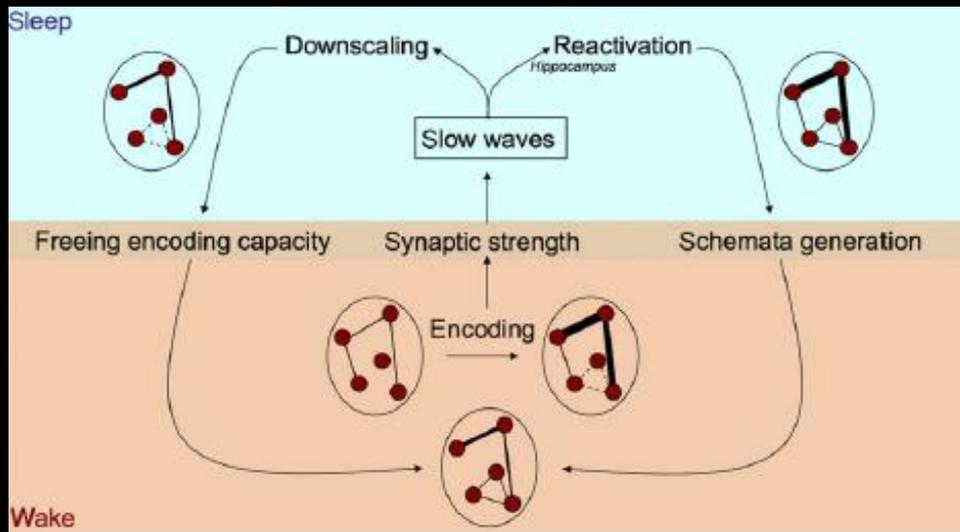


Memory Consolidation/Plasticity Hypotheses

Sleep enhances memory and plasticity

Consolidate memories

**Stimulate circuits, re-modeling
erase spurious memories**



Bassetti CL et al, Eur J Neurol, 2015

Born, 2006; Buzsaki, 1998; Giuditta, 1992;
Hennevin and Leconte, 1971; Maquet, 2001;
Sejnowski and Destexhe, 2001; Smith, 1995;
Steriade, 1999; Walker and Stickgold, 2006; Winson, 1993.

Kavanau, 1994; Krueger and Obal, 1993;
Roffwarg et al, 1966; Crick and Mitchison
1983; Davis 1985; Bushey D, et al, Science
332:1576, 2011

Local Increase in Slow Wave Sleep Correlates with Cognitive Training Induced Regional Plasticity

- EEG sleep slow-wave activity (SWA) is regulated globally and locally.
- Several studies have shown local learning- and use-dependent changes in SWA.
- Animal experiments and studies in humans indicate that these local changes in SWA reflect synaptic plasticity.
- Particularly important during development and aging.

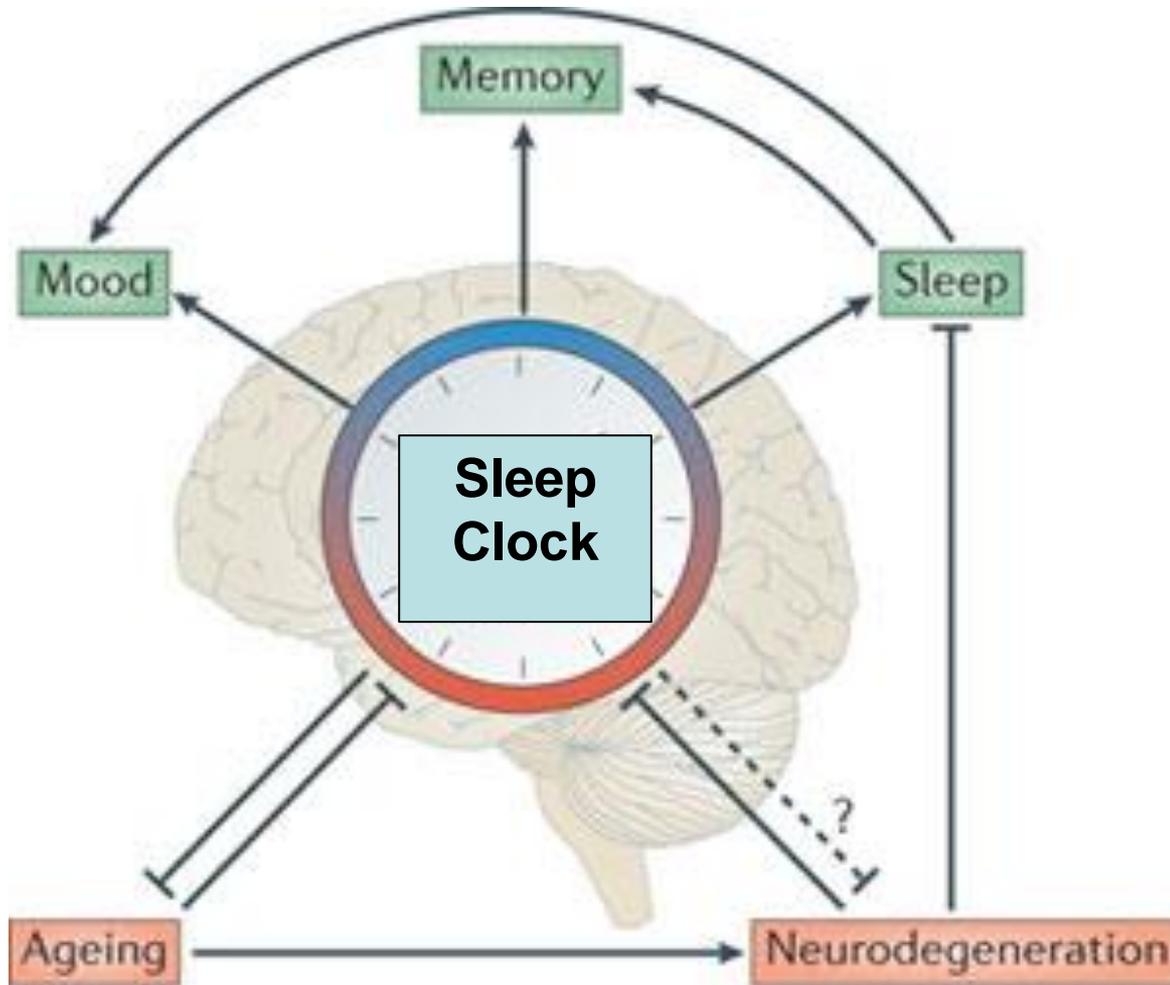
Classical View

Circadian rhythm and sleep-wake cycle disturbances are consequence of disease.

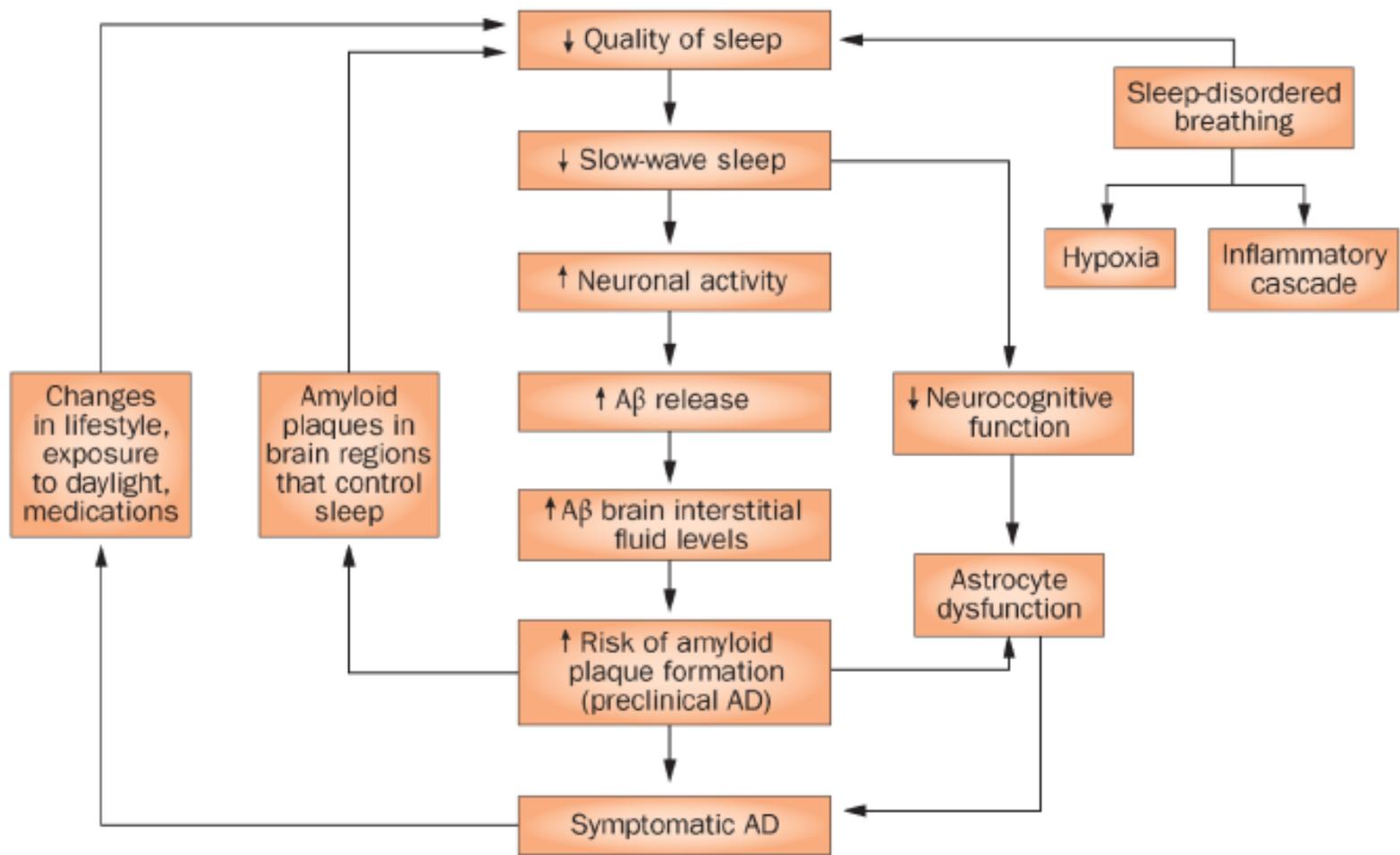
Circadian and sleep/wake disruption exacerbate symptoms of underlying disease.

Improving circadian rhythms and sleep are primarily symptomatic treatments

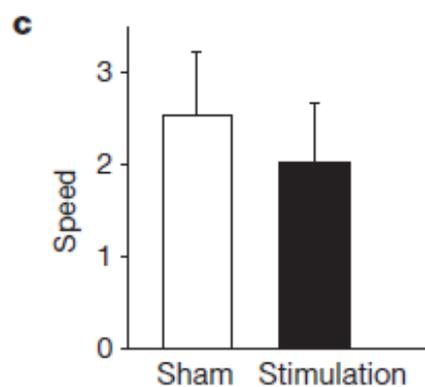
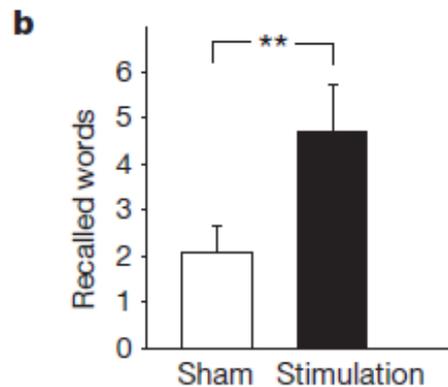
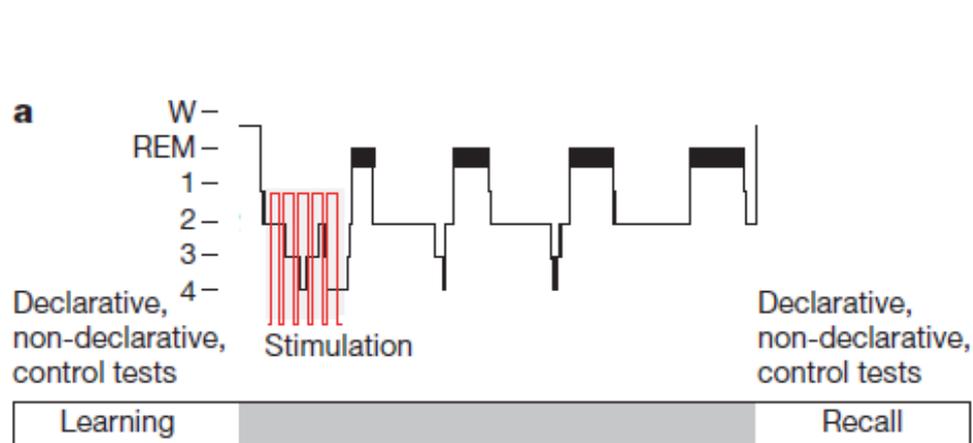
Emerging Evidence



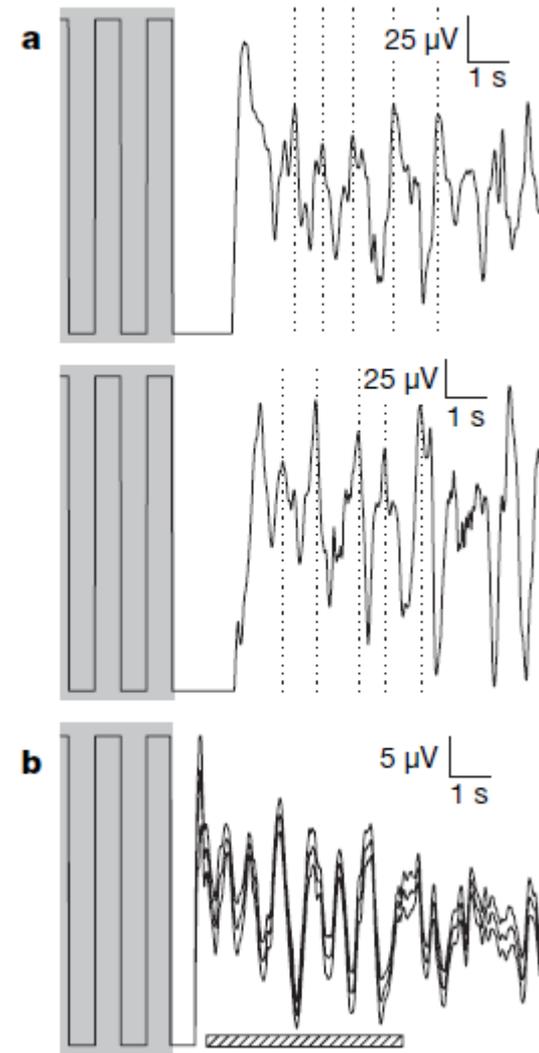
Sleep and Alzheimer's Disease



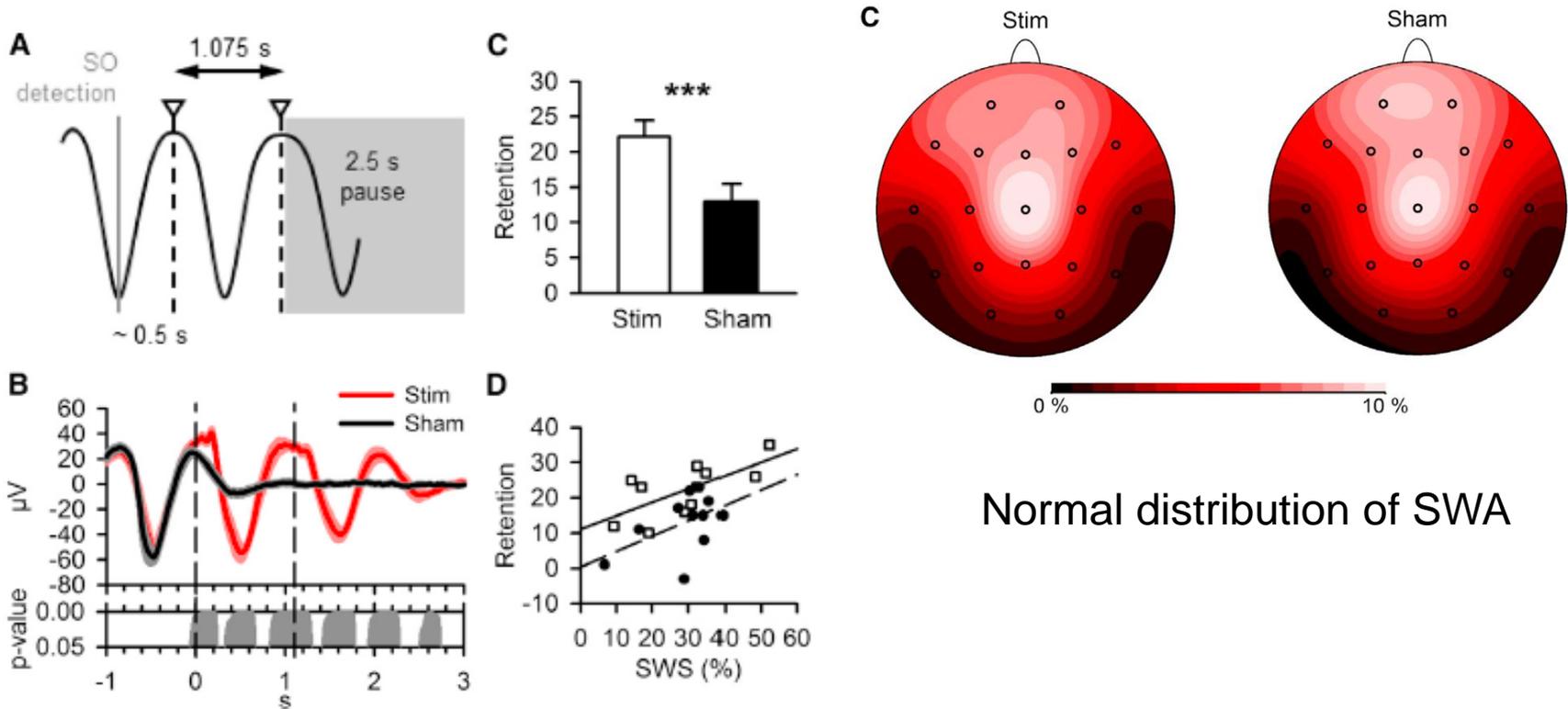
Enhancing SWA: Slow Oscillations in Sleep Potentiates Memory



Transcranial electrical oscillation (0.75 Hz)



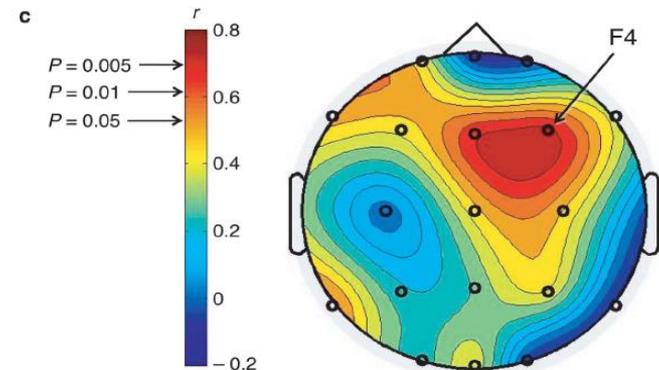
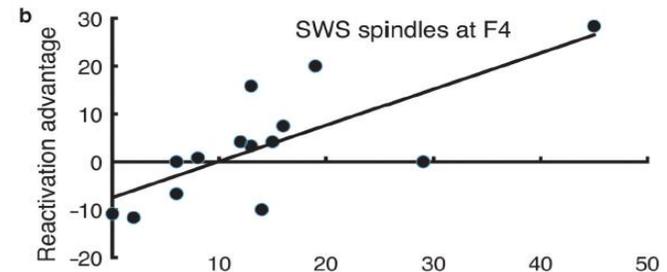
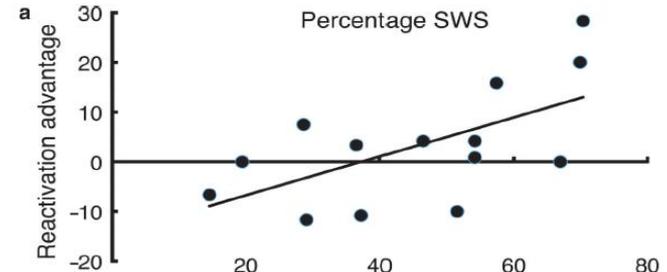
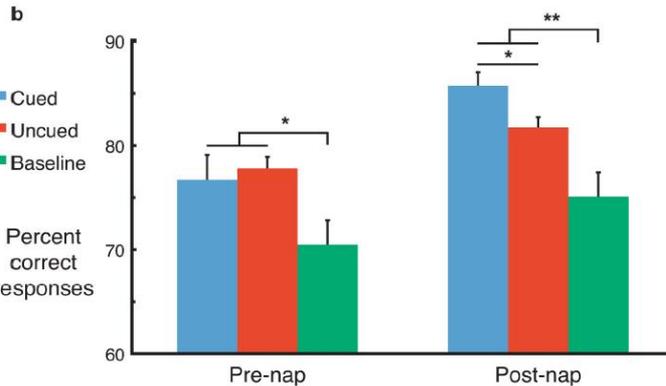
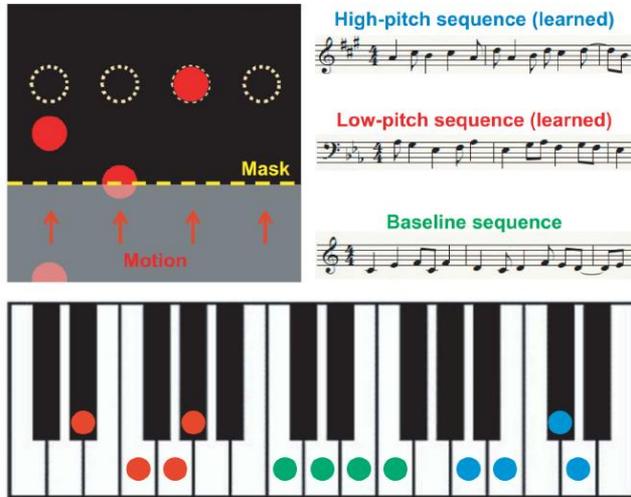
Acoustic Stimulation Enhances SWA and Declarative Memory in Sleep



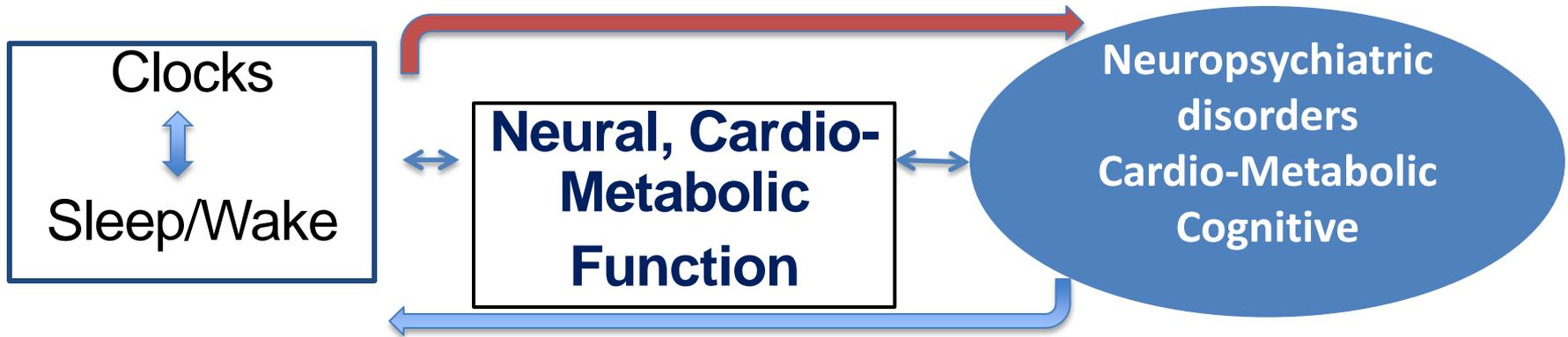
Effect of word pair retention correlated with magnitude of SWA and timing of acoustic stimulation in phase with SO in the up state.

Cued Memory Reactivation During Sleep and Learning

a Pre-nap training → 90-minute nap → Post-nap test



Updated View and: Implication for Metabolic and Cognitive Health in Aging



Circadian and sleep function essential for cell function, neural connectivity and plasticity

Circadian and sleep disruption contribute to cardio-metabolic and brain disorders common with aging

Improving circadian rhythms and sleep as targets for prevention and disease modification

Sleep and Circadian Research and Clinical Insights in Aging

Biology and genetics of sleep and circadian rhythms (global and local regulation)

- Bioenergetics, metabolism, inflammation
- Neuroplasticity: learning and memory
- Neuroprotection: neurotoxic substrates, recovery from injury

Sleep-wake and circadian disturbances and specific sleep disorders (SDB, Insomnia, RLS, shift work) as risk for:

- Cardio-metabolic disorders
- Gastrointestinal
- Neurodegenerative disorders
- Psychiatric disorders

Impact of treatment of sleep-wake disturbance/disorders on expression, course of common age-related disorders

- Sleep disordered breathing: cardiovascular and cerebrovascular disease
- REM Sleep Behavior: PD
- Circadian based treatments in neurodegeneration

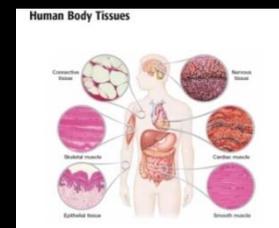
Perspectives for Translational Science

- Shared pathophysiology between sleep-wake disorders and common age-associated conditions require team science (interdisciplinary human/clinical and basic animal approaches) to elucidate mechanisms that can lead to precision in diagnostics and therapies.
- Sex differences in sleep and circadian regulation and impact of disruption generally not well studied and even less so in aging.
- Socioeconomic and environmental factors and ethnicity on sleep and circadian health disparity and access to care.
- Systematic sleep and circadian measures are needed in aging cohorts to define sleep health in older adults.
- **Clinical trials are needed to answer: Can sleep and circadian based strategies improve cognition and physical health or alter the development and expression of disease in older adults? How early?**

•

Moving New Methodological Approaches into Aging Research and Clinic for Older Adults

- More than routine PSG and Actigraphy (Biomarkers)
 - Quantitative EEG
 - Probing brain function using stimuli-High density EEG complemented by new imaging techniques
 - Cellular, Omics....
- Consolidation of clinical, behavioral, physiological electrophysiological, omics of sleep and circadian data.
- Self monitoring of sleep-wake behavior, environment, physiology with mobile devices
- Integrating various levels of data from different relevant tissues, phenotypes, genotypes under laboratory and free living conditions (bioinformatics, large data, computational science)



Sleep-Circadian Health

Sleep Disorder
Insomnia
Sleep apnea
Restless legs

Behavioral lifestyle
Psychological well-being
Socio-economic status
Work schedules
Physical activity level

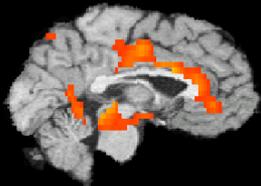
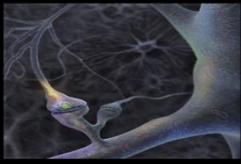
Genetic vulnerability
Age

Sleep/Circadian Rhythm

Inflammation
Metabolism
Autonomic
Oxidative stress
Synaptic plasticity/ connectivity

HEALTH and Disease

COGNITION, PERFORMANCE, SAFETY



Once we realize that we are eligible for senior discounts, healthy aging is what we hope for...

Good clocks, good sleep, good health

The importance of sleep to healthy aging is often overlooked in the medical community, but it's becoming increasingly apparent that good sleep could be a new vital sign.

Robert Butler

QUOTEHD.COM



Robert Neil Butler, MD
Founding Director of NIA 1975-1982
1927-2010

We've concluded that maybe sleep should be another one of the vital signs that doctors should check.

Robert Butler

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