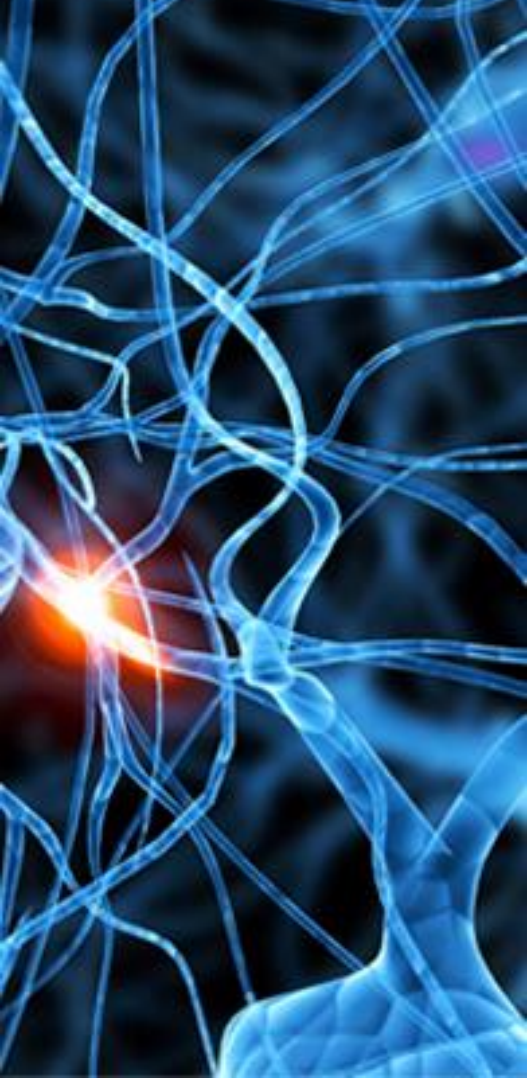


Adaptive, Personalized Enhancement of Deep Sleep and Memory for Optimal Aging

G.Santostasi, PhD

Chief Scientific Officer, DeepWave Tech.

AMMG Conference , Orlando Florida, 2018

Everybody sleeps: **tremendous** market opportunities



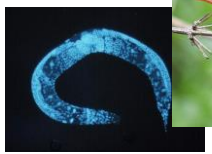






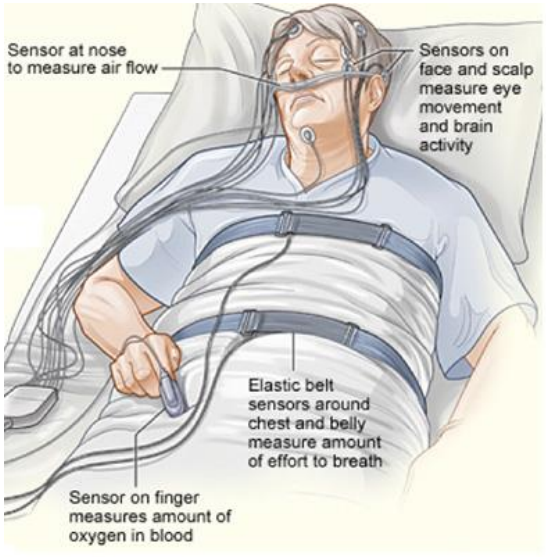


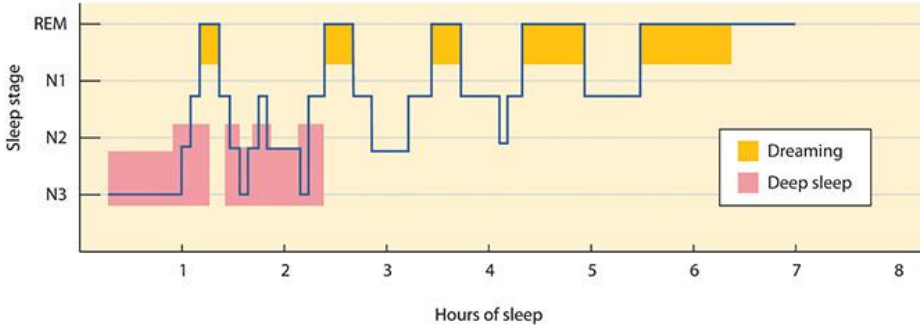


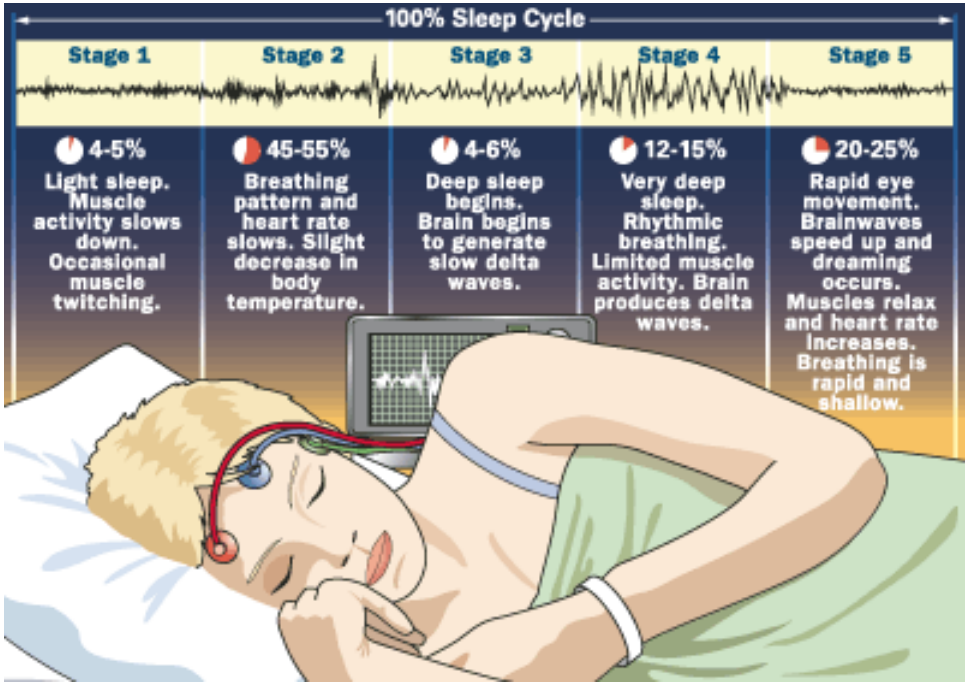




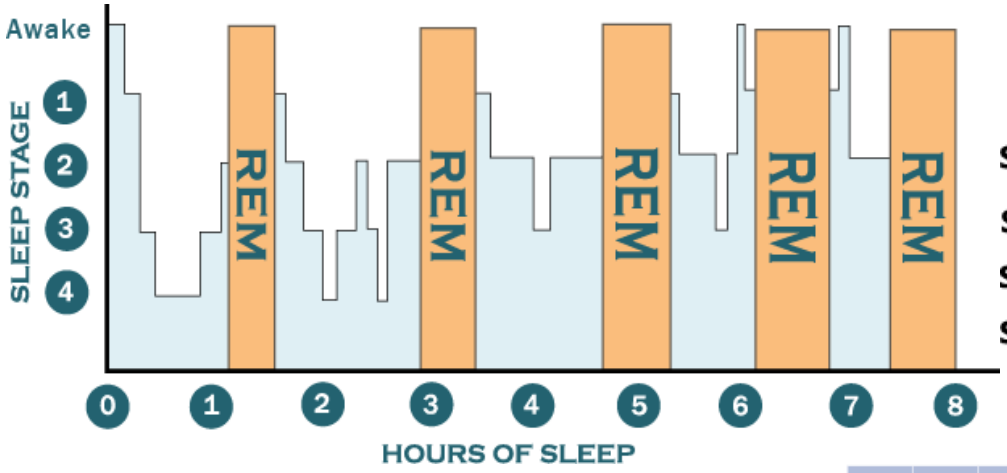


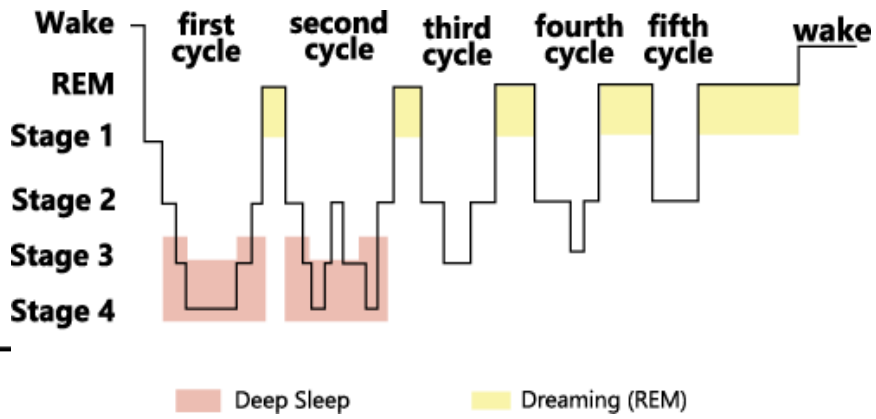

Sensor at nose to measure air flow
Sensors on face and scalp measure eye movement and brain activity
Elastic belt sensors around chest and belly measure amount of effort to breath
Sensor on finger measures amount of oxygen in blood
Awake
Beta waves
Drowsy, relaxed
Alpha waves
Stage N1 sleep
Theta waves
Stage N2 sleep
Sleep spindles
Stage N3 sleep
Delta waves
REM sleep
Fast, random

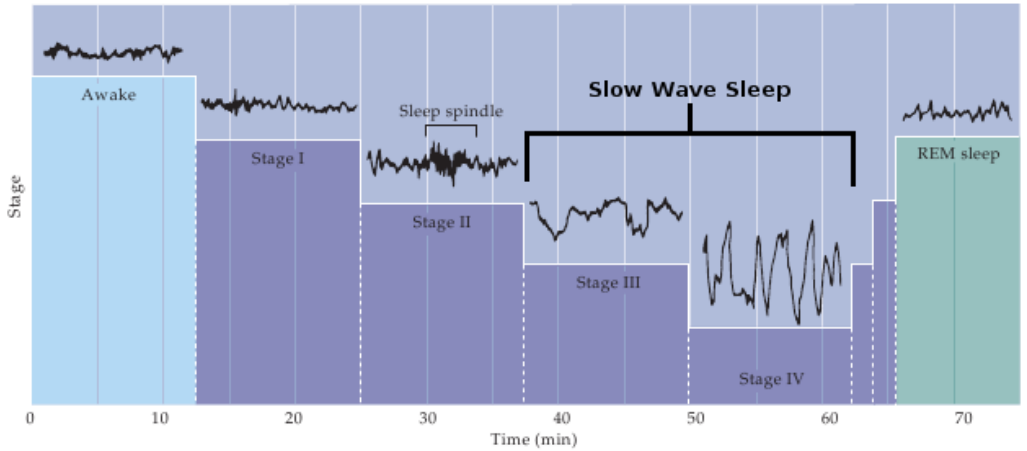

REM
N1
N2
N3
Sleep stage
Dreaming
Deep sleep
1
2
3
4
5
6
7
8
Hours of sleep


100% Sleep Cycle
Stage 1
Stage 2
Stage 3
Stage 4
Stage 5
4-5%
Light sleep. Muscle activity slows down. Occasional muscle twitching.
45-55%
Breathing pattern and heart rate slows. Slight decrease in body temperature.
4-6%
Deep sleep begins. Brain begins to generate slow delta waves.
12-15%
Very deep sleep. Rhythmic breathing. Limited muscle activity. Brain produces delta waves.
20-25%
Rapid eye movement. Brainwaves speed up and dreaming occurs. Muscles relax and heart rate increases. Breathing is rapid and shallow.

Stages of Healthy Sleep





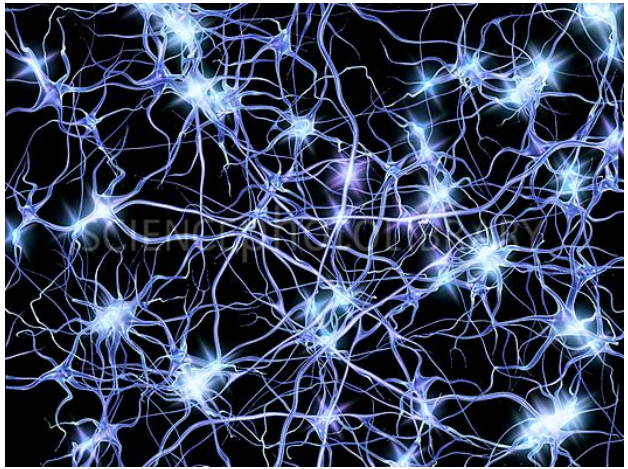


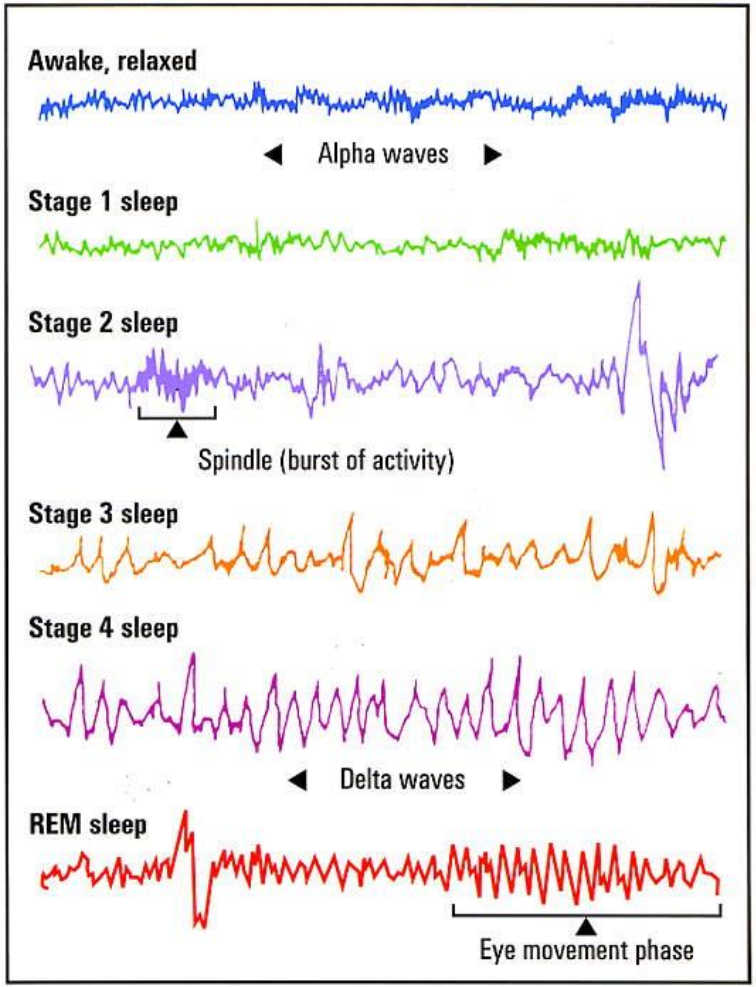
* REM = Rapid Eye Movement

**Deep Sleep = Slow Wave Sleep = Stages 3 and 4

Brain rhythms are the language of the brain.

- Neurons are communicating via chemical and electrical activity (firing).
- Different electrical activity rhythms are associated with different brain states and functions.
- The most reliable way to determine sleep stages is via an electroencephalogram (EEG)

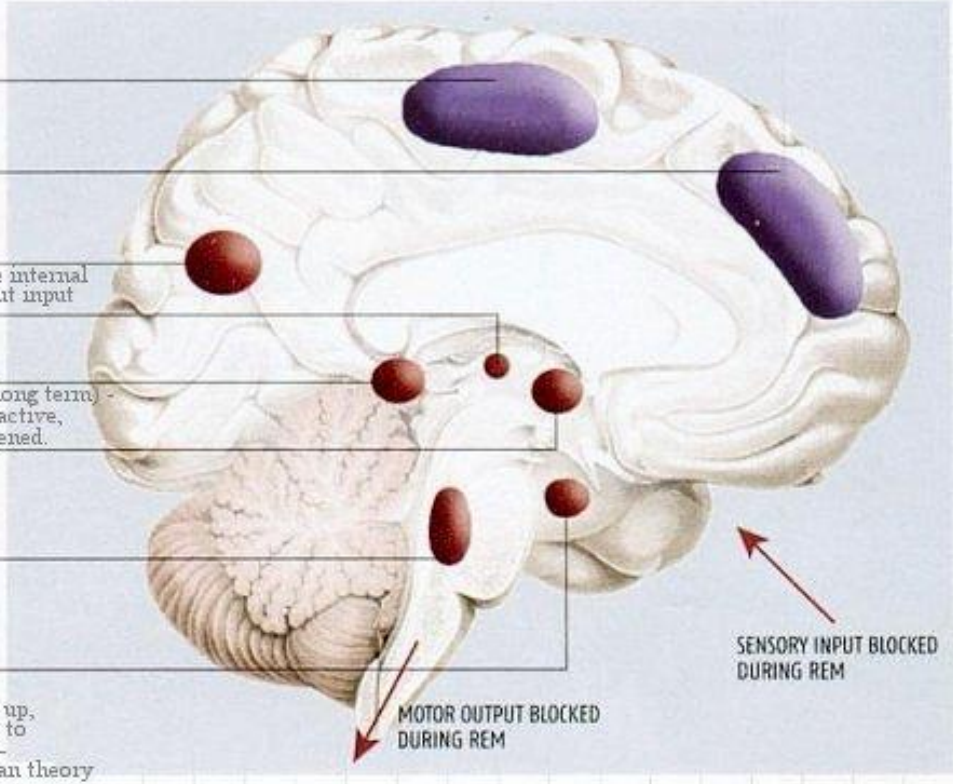




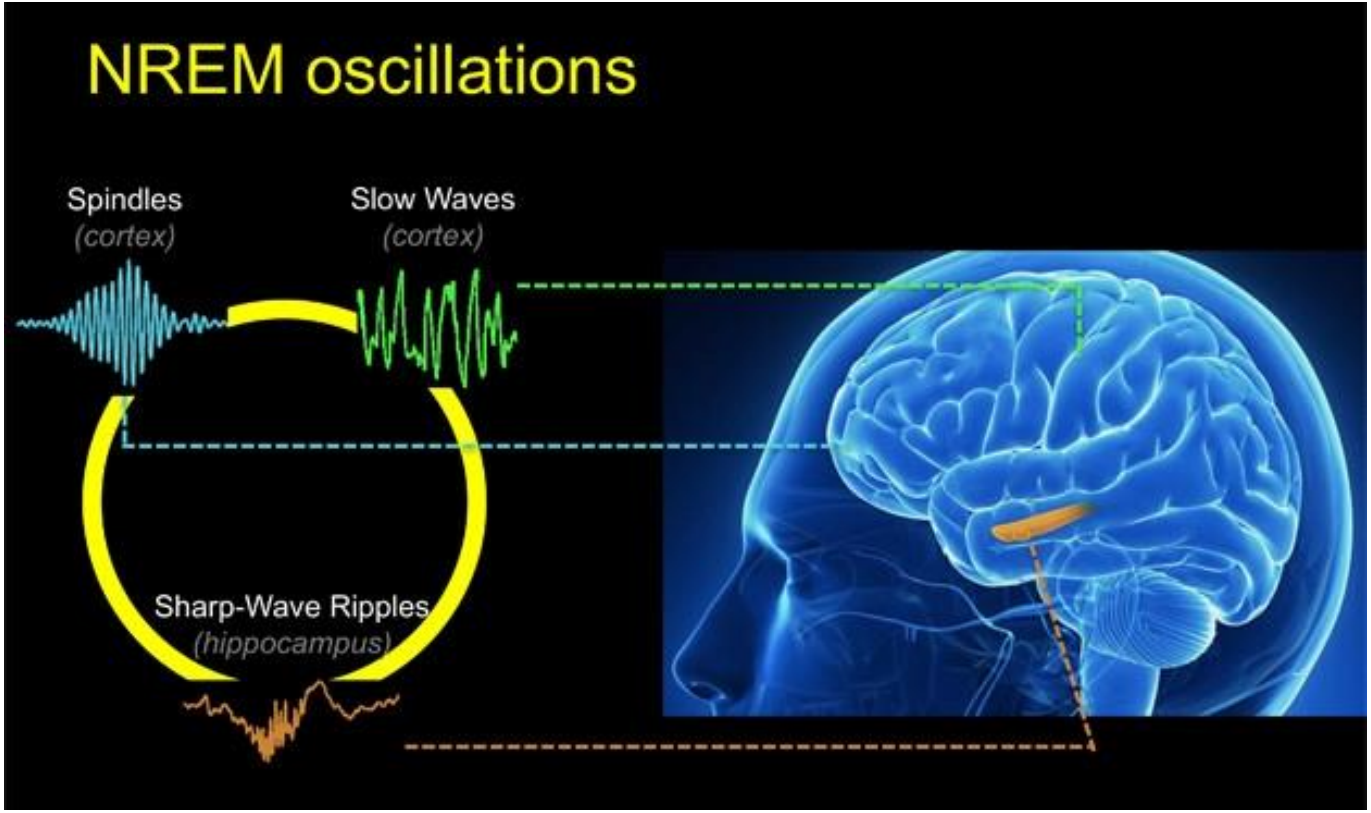
THE DREAMING BRAIN

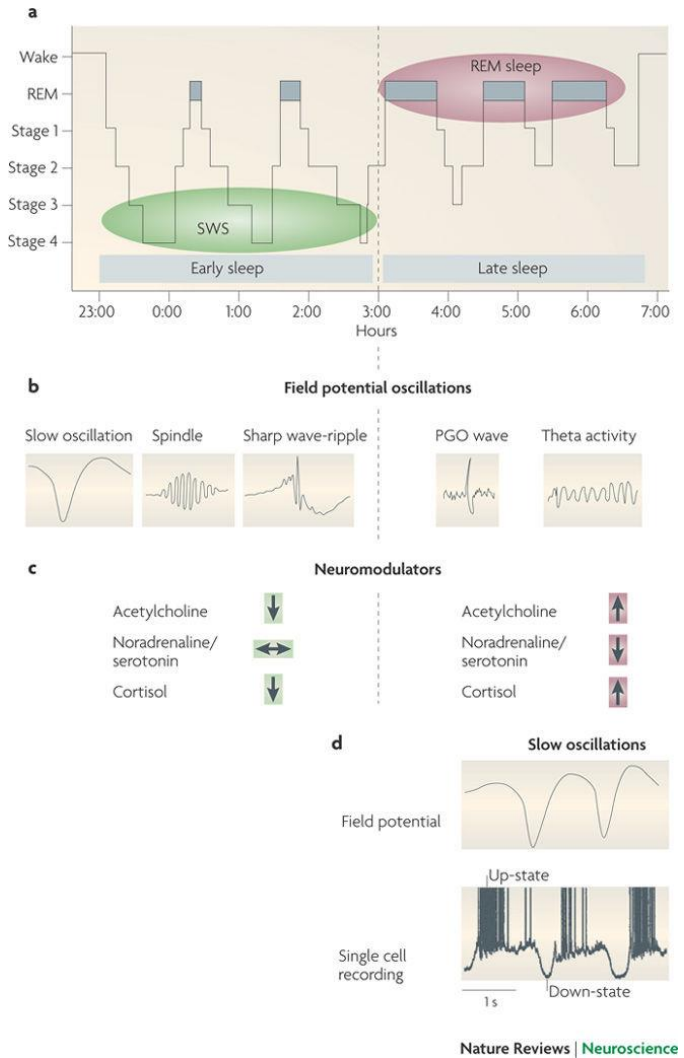
REM sleep produces a particular pattern of brain activity

● Active ● Inactive

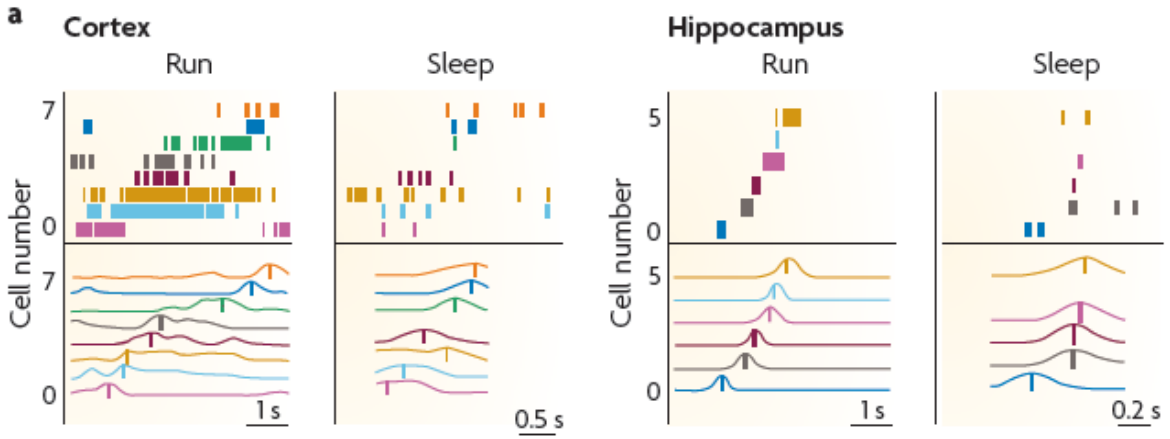


NREM oscillations



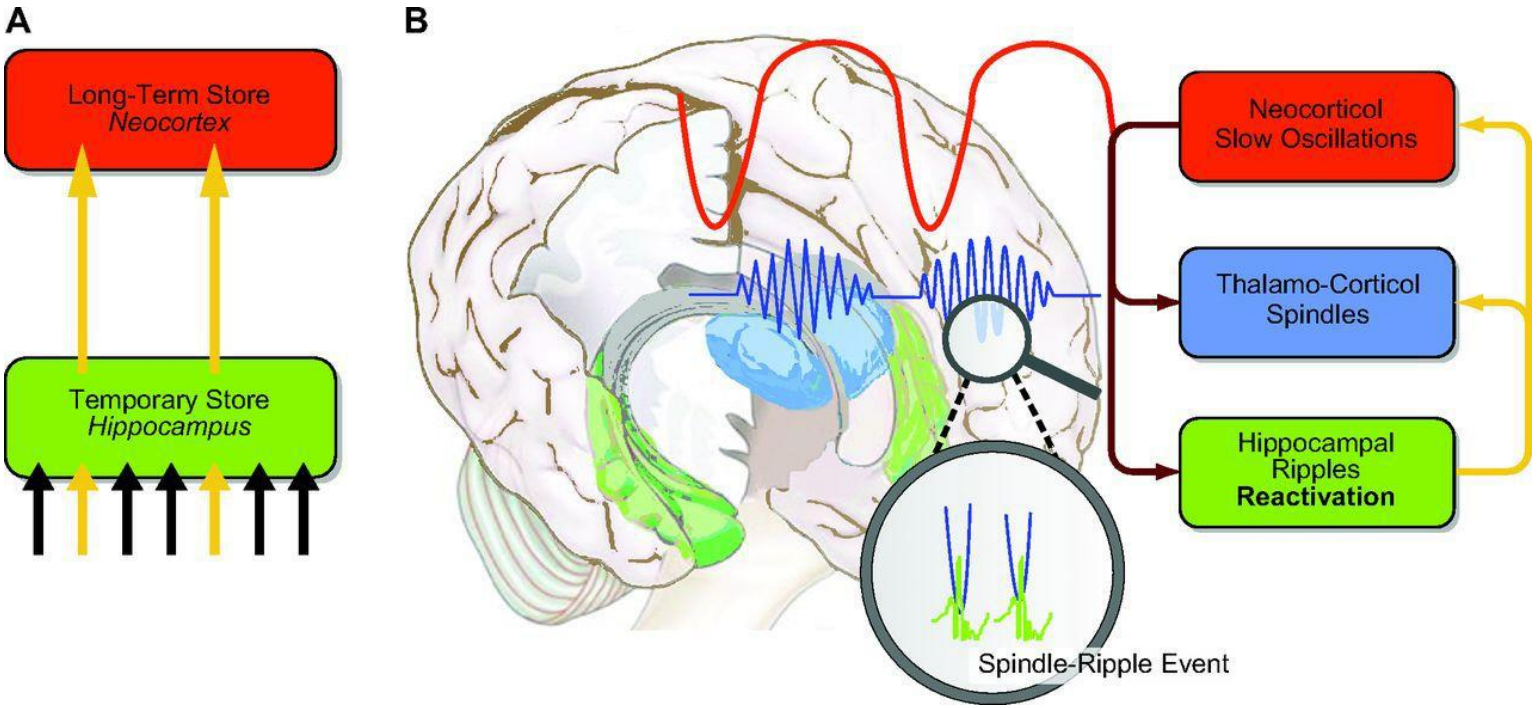

a
Wake
REM
Stage 1
Stage 2
Stage 3
Stage 4
REM sleep
SWS
Early sleep
Late sleep
23:00
0:00
1:00
2:00
3:00
4:00
5:00
6:00
7:00
Hours
b
Field potential oscillations
Slow oscillation
Spindle
Sharp wave-ripple
PGO wave
Theta activity
c
Neuromodulators
Acetylcholine
Noradrenaline/ serotonin
Cortisol
Acetylcholine
Noradrenaline/ serotonin
Cortisol
d
Slow oscillations
Field potential
Up-state
Single cell recording
1 s
Down-state

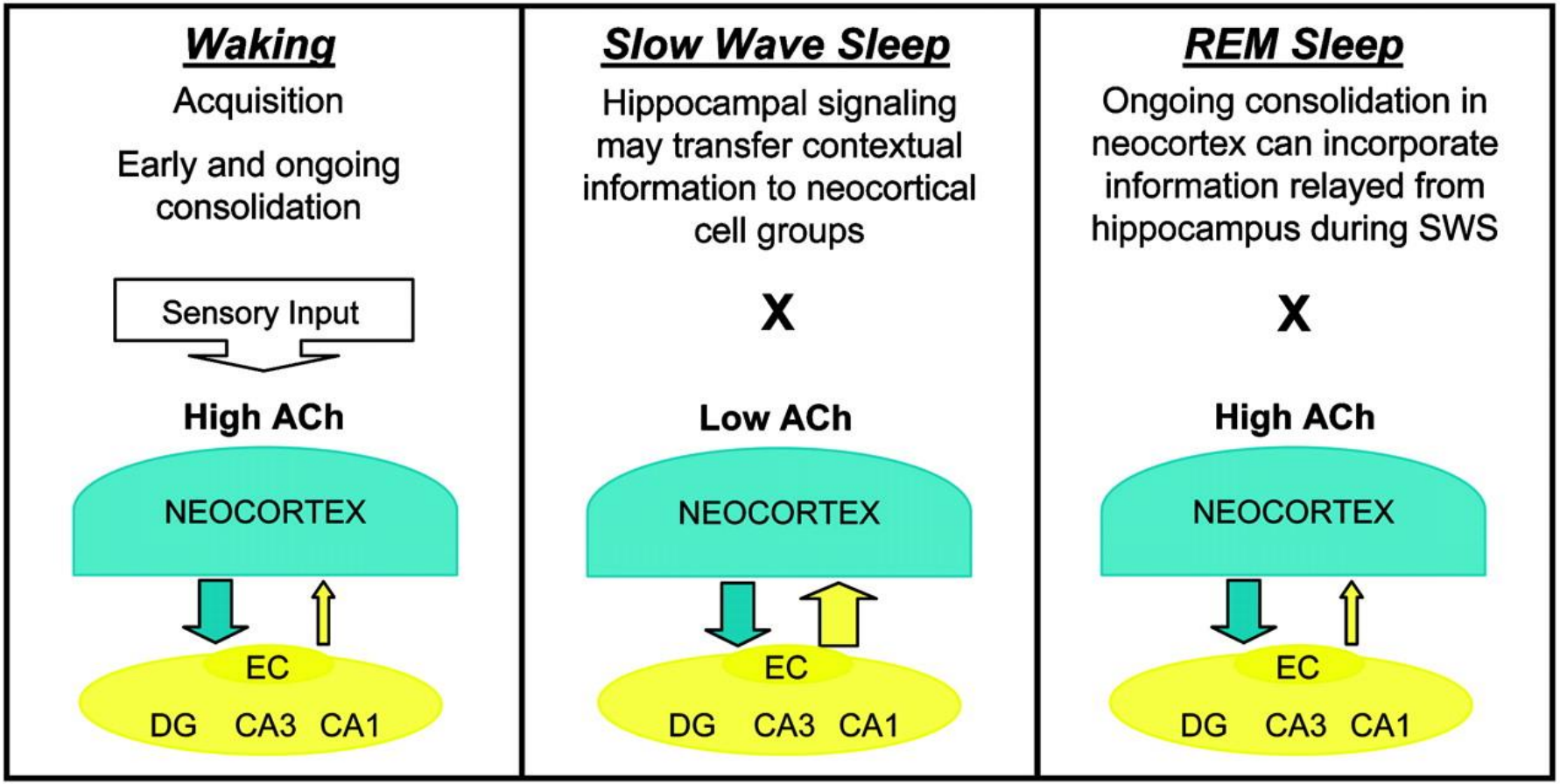
Memory re-activation during slow wave sleep



Key point: similarity of the temporal firing sequences
Illustration: Neuronal re-activation of ensemble activity mostly occurs during SWS and almost always occur in the order in which they were experienced.

Dialogue between different brain areas during slow-wave sleep




Waking
Acquisition
Early and ongoing consolidation
Sensory Input
High ACh
NEOCORTEX
EC
DG CA3 CA1
Slow Wave Sleep
Hippocampal signaling may transfer contextual information to neocortical cell groups
X
Low ACh
NEOCORTEX
EC
DG CA3 CA1
REM Sleep
Ongoing consolidation in neocortex can incorporate information relayed from hippocampus during SWS
X
High ACh
NEOCORTEX
EC
DG CA3 CA1

In humans, cats, and rats, spindle activity and ripples increase during the up-state, and become suppressed during the down-state of a slow oscillation.

Sharp-wave ripple complexes are also temporally coupled to spindles.

These ripple-spindle events provide a mechanism for hippocampal-neocortical information transfer.

Ripples and associated hippocampal memory re-activations feed into the excitatory phases of the spindle cycle.

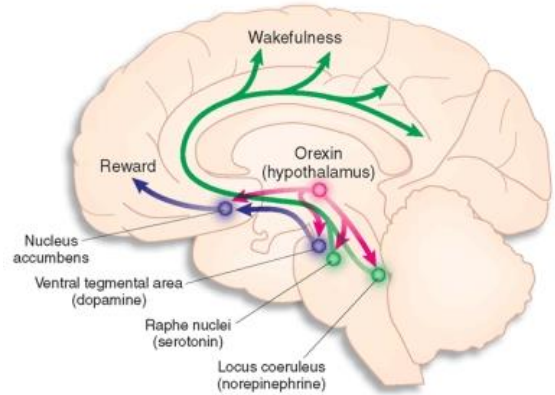
During the up-state, the feed-forward control of slow oscillations over ripples and spindles allows transferred information to reach the neocortex.

A whole cocktail of neurotransmitters are involved in driving wakefulness and sleep, including histamine, dopamine, norepinephrine, serotonin, glutamate, orexin and acetylcholine, among others.

While none of these neurotransmission processes is individually necessary, they all appear to contribute in some way. Histamine in particular is sometimes referred to as the “master” wakefulness-promoting neurotransmitter, exhibiting high activity during wakefulness, decreasing activity during non-REM sleep, and its lowest levels during REM sleep(which is why histamine-blocking antihistamine medications cause drowsiness and increase non-REM sleep).

Serotonin activity promotes wakefulness, increases sleep-onset latency (the length of time it takes to fall asleep) and decreases REM sleep. Acetylcholine activity in the reticular activating system of the brainstem stimulates activity in the forebrain and cerebral cortex, encouraging alertness and wakefulness, although it also appears to be active during REM sleep.

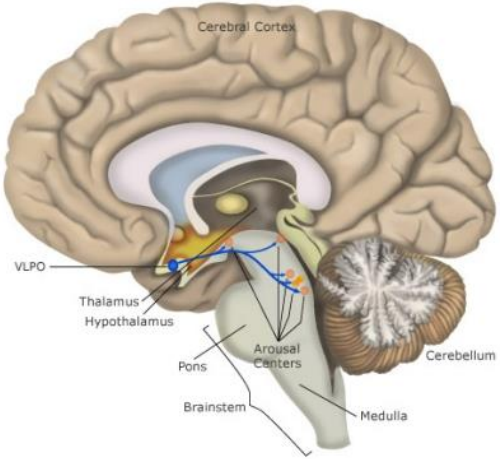
Dopamine activity sometimes seems to promote wakefulness and sometimes sleep (it is also involved in the process of dreaming), so its role is still far from clear.

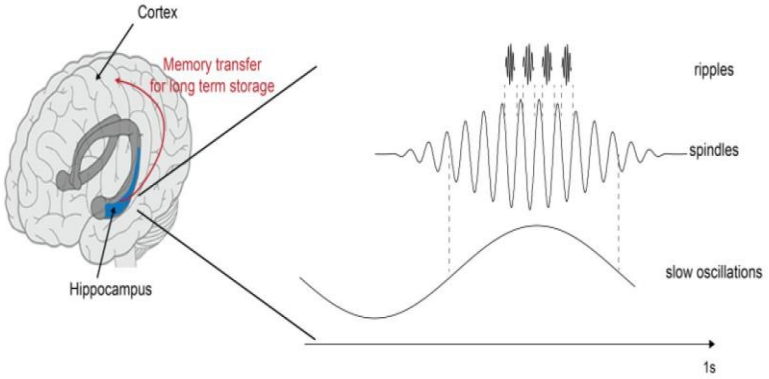


The ventrolateral preoptic nucleus (VLPO or VLPN) of the hypothalamus is one area of the brain that is particularly involved in the switch between wakefulness and sleep. Neurons in this small area help to promote sleep by inhibiting activity in areas of the brainstem that maintain wakefulness. Likewise, in a process of "**mutual** inhibition", during waking hours, those areas of the brain that are active in maintaining wakefulness by stimulating the cerebral cortex also work to inhibit the neurons of the VLPO.

For this reason, the VLPO is often referred to as the **"sleepswitch"**, although this is really a gross simplification. In fact, several different simultaneous and interactive processes are involved – some of which are described below – and there is as yet **no single unifying theory** that describes all their interactions.

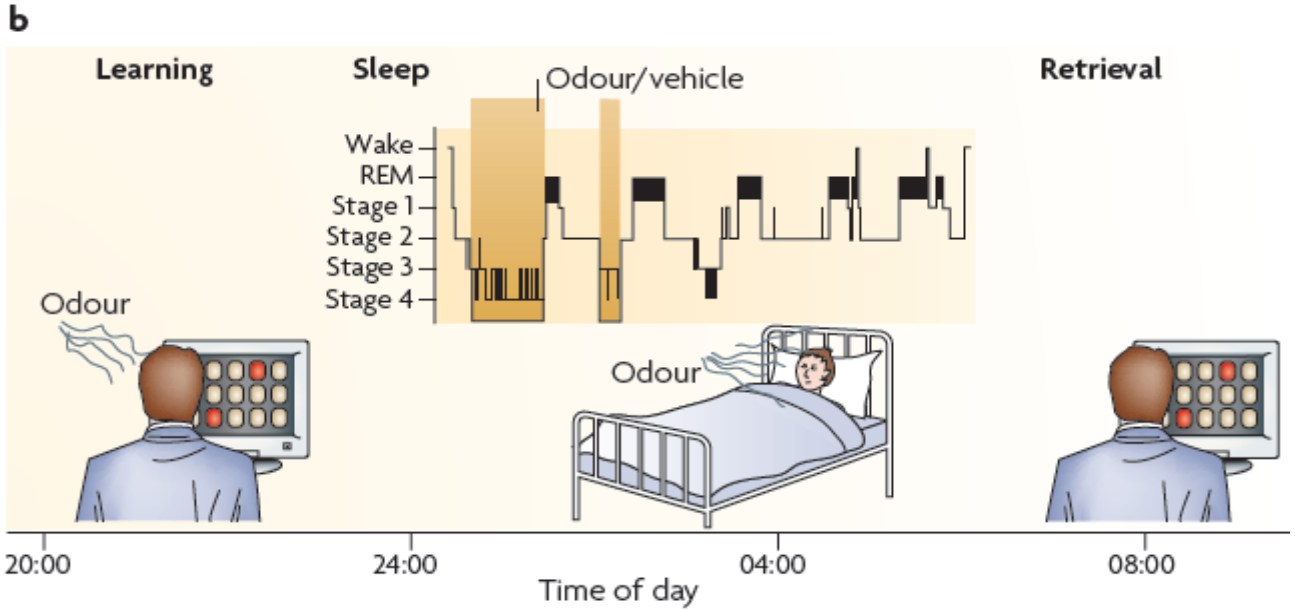
It sometimes seems that the more we discover about the complex physiological and neurological mechanisms of sleep and wakefulness, the more complications and interactions come to light, and the more questions arise.




Cortex
Memory transfer
for long term storage
Hippocampus
ripples
spindles
slow oscillations
1s


slow oscillation from the neocortex
spindle from the thalamus
ripple from the hippocampus

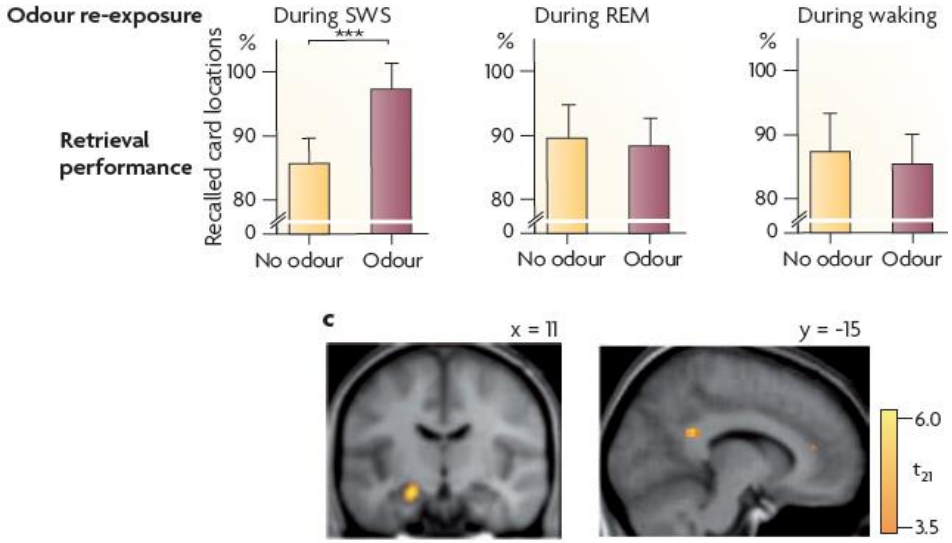
Memory re-activation during slow wave sleep



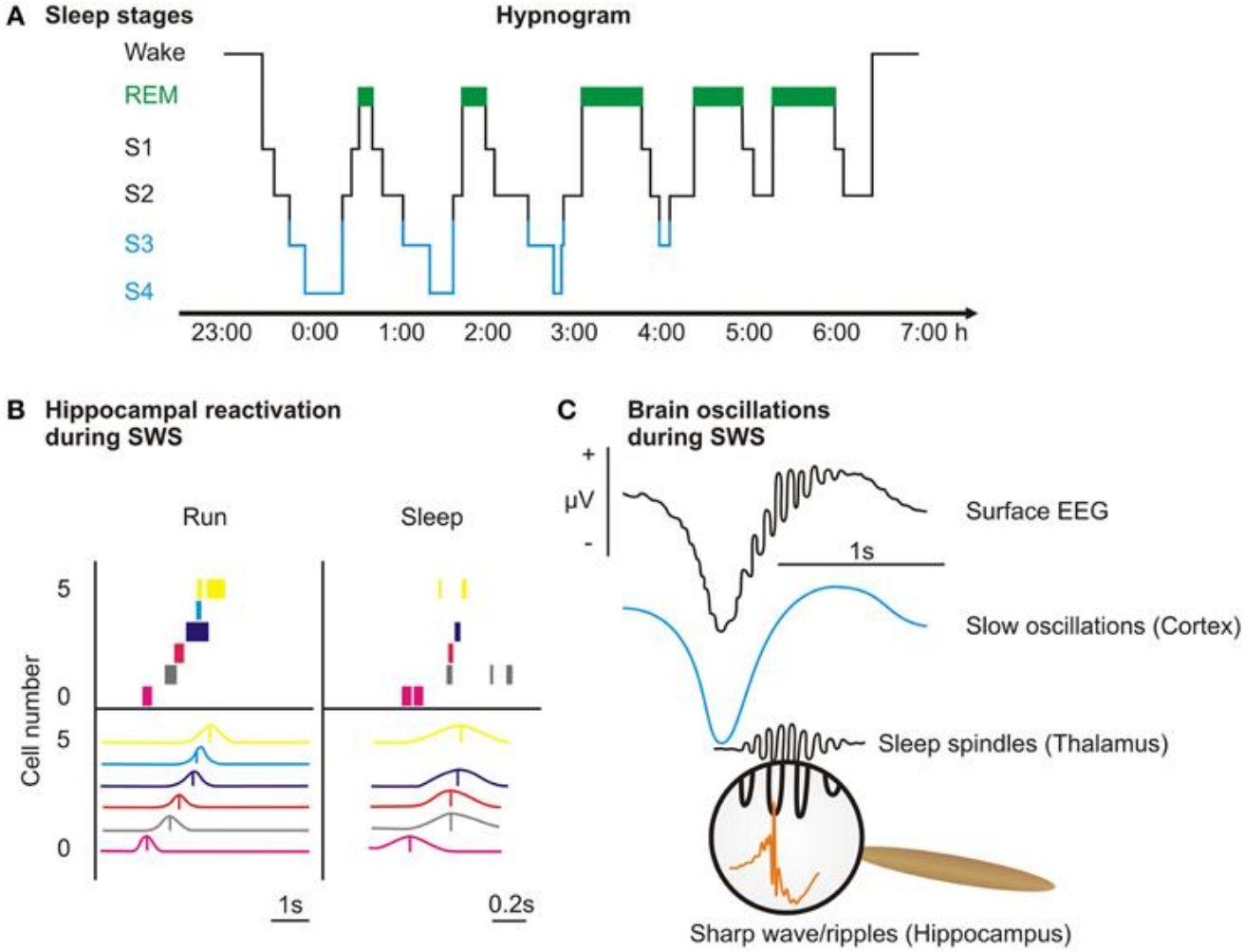
Key point: Odor re-exposed during SMS can potentiate memory.

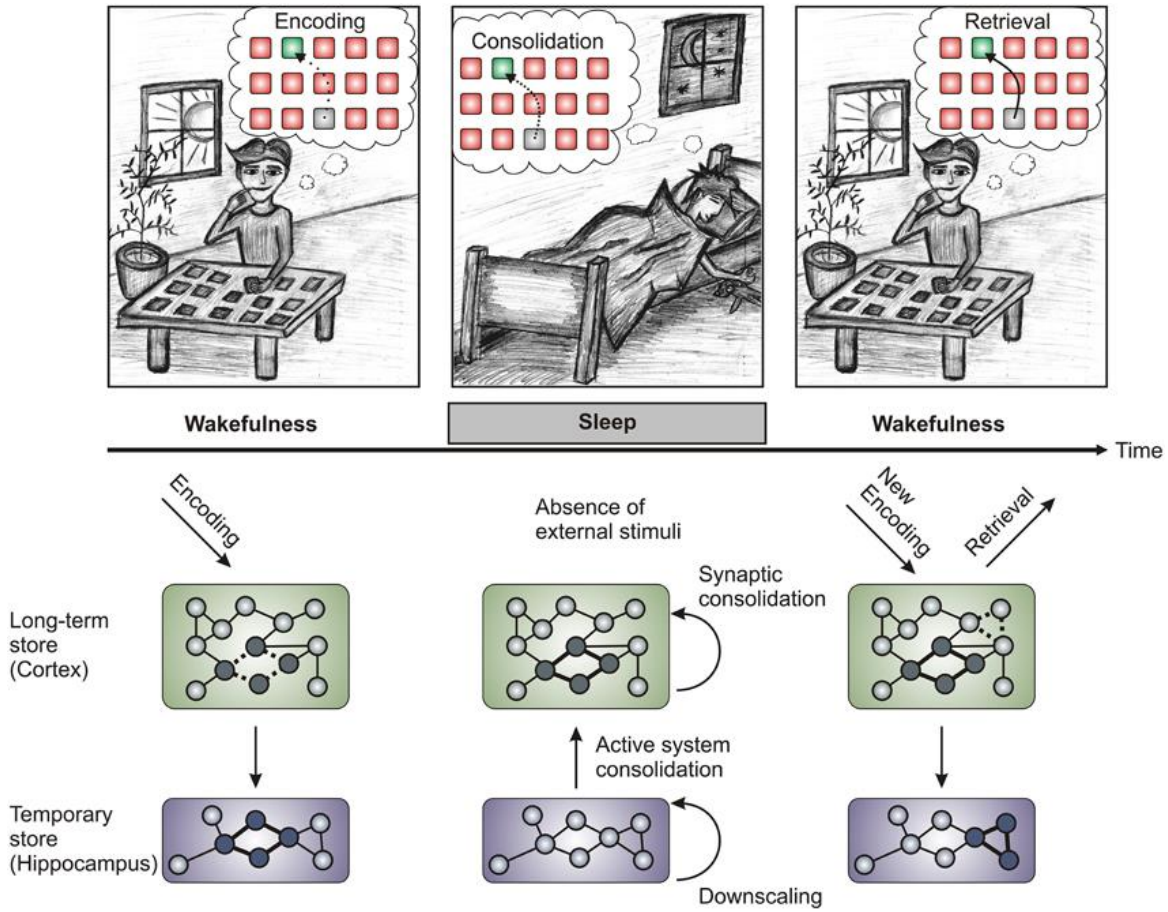
Illustration: Hippocampal networks are particularly sensitive to inputs that can re-activate memories during SMS, which supports the causal role of re-activation during SWS in memory consolidation.

Neurotransmitters	Location of Nuclear Group	Modulates
Acetylcholine	Dorsal Tegmentum of pons and midbrain	Wakefulness
	Basal forebrain	REM sleep
Monoamines		
Norepinephrine	Locus Ceruleus (from midbrain)	Wakefulness and attention
Serotonin	Raphe nuclei	Non- REM sleep
Histamine	Hypothalamus (posterior nucleus of hypothalamus)	Wakefulness



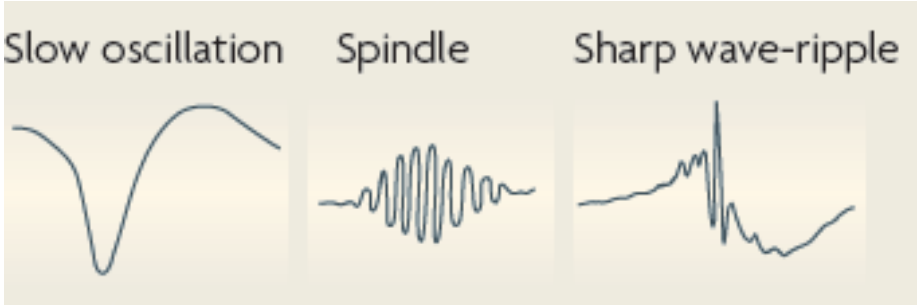
Key point: left anterior hippocampus and certain neocortical regions were activated specifically during SMS compared to other conditions.
Illustration: Support the theory that SMS's function is to transfer memory between hippocampus and neocortex.


A Sleep stages
Hypnogram
Wake
REM
S1
S2
S3
S4
23:00
0:00
1:00
2:00
3:00
4:00
5:00
6:00
7:00 h
B Hippocampal reactivation during SWS
Run
Sleep
Cell number
5
0
5
0
1s
0.2s
C Brain oscillations during SWS
+
μV
-
Surface EEG
1s
Slow oscillations (Cortex)
Sleep spindles (Thalamus)
Sharp wave/ripples (Hippocampus)


Encoding
Consolidation
Retrieval
Wakefulness
Sleep
Wakefulness
Time
Encoding
Absence of
external stimuli
New
Encoding
Retrieval
Synaptic
consolidation
Long-term
store
(Cortex)
Active system
consolidation
Temporary
store
(Hippocampus)
Downscaling

There is a fine-tuned temporal relationship between the occurrence of slow oscillations, spindles, and sharp wave-ripples during SWS that coordinate the bidirectional information flow between the neocortex and the hippocampus." Explain how "up-states" play a role here, and the excitatory phases of the spindle cycle.

The most prominent oscillations during SWS are slow oscillations, spindles, and sharp-wave ripples.



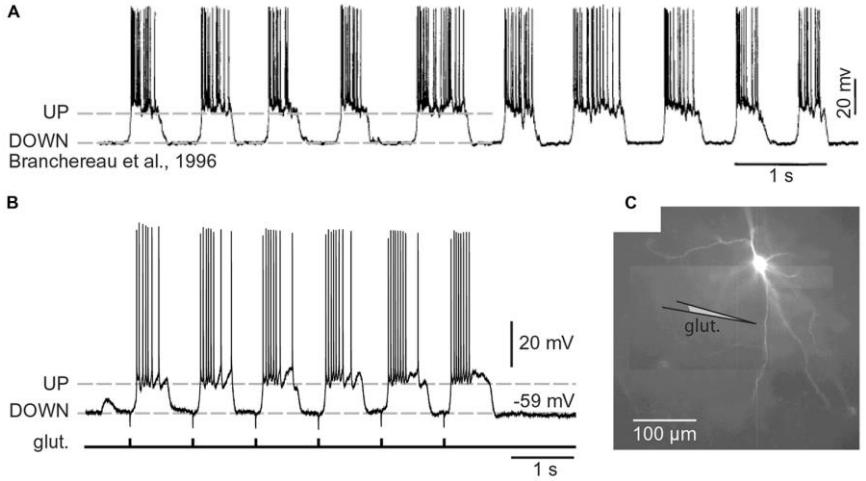
•Down-State – neurons'membranes are hyperpolarized, results in neuronal silence with an absence of spiking activity.

•Up-State – neurons'membranes are depolarized, resulting in strongly increased wake-like firing of large neuronal populations.

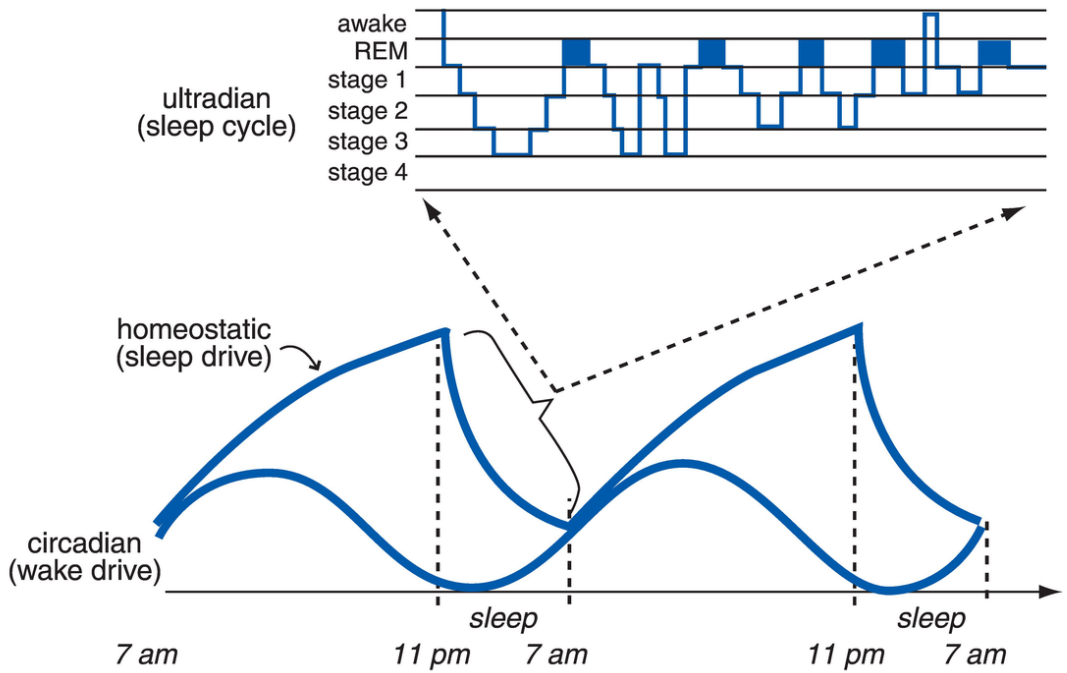
UP and DOWN states

- During slow oscillation the entire cortical network alternates between silent (Hyperpolarizing, or Down) and active (Depolarizing, or Up) states, each lasting 0.2-1 sec.

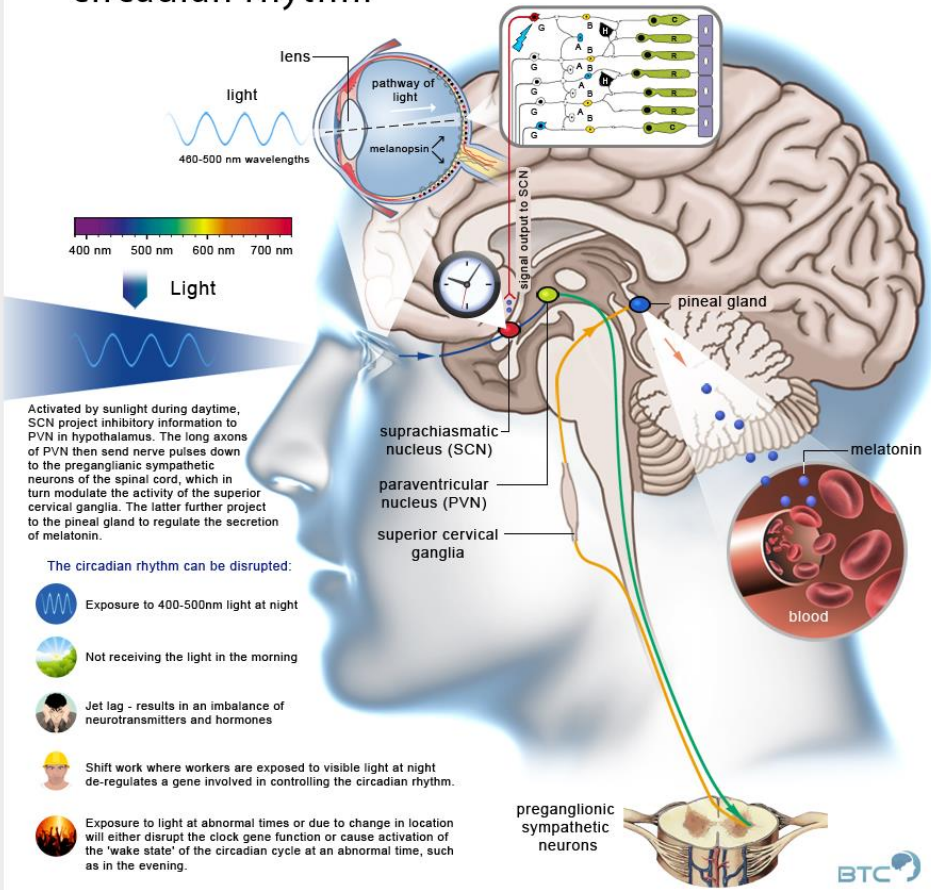
- At EEG level, the slow oscillation appears as periodic alterations of positive and negative waves (indicated by + and – signs in the figure).
- During EEG depth-positivity, cortical neurons remain in hyperpolarized, silent state.
- During EEG depth-negativity cortical neurons move to active states, reveal barrages of synaptic events and fire action potentials.



Processes Regulating Sleep



circadian rhythm

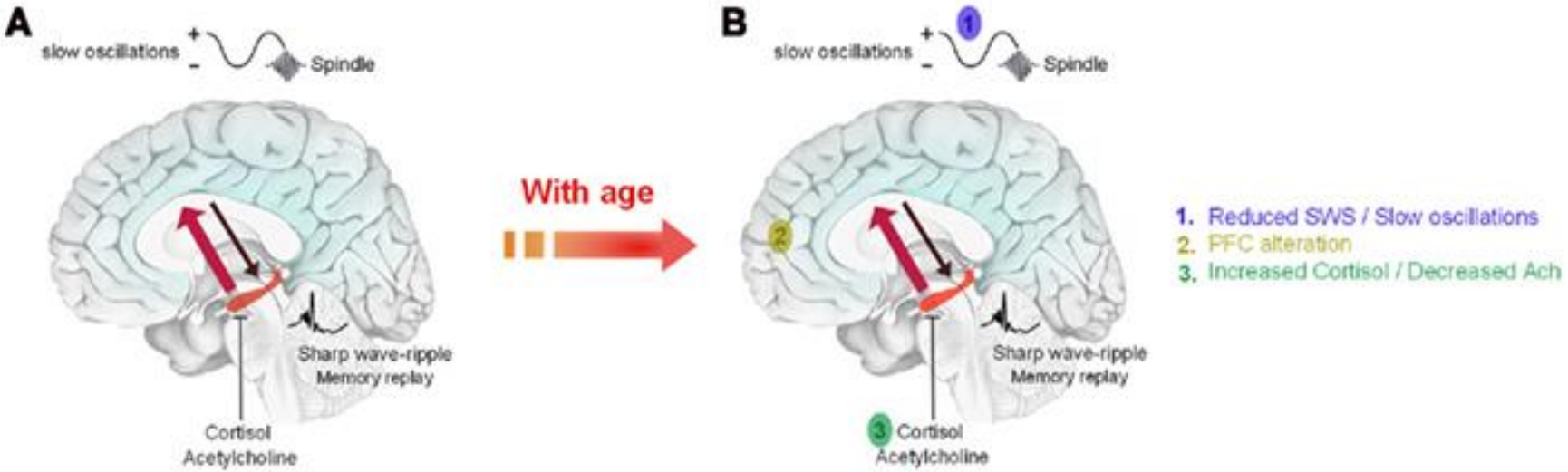


Activated by sunlight during daytime, SCN project inhibitory information to PVN in hypothalamus. The long axons of PVN then send nerve pulses down to the preganglianic sympathetic neurons of the spinal cord, which in turn modulate the activity of the superior cervical ganglia. The latter further project to the pineal gland to regulate the secretion of melatonin.

The circadian rhythm can be disrupted:

- Exposure to 400-500nm light at night
- Not receiving the light in the morning
- Jet lag - results in an imbalance of neurotransmitters and hormones
- Shift work where workers are exposed to visible light at night de-regulates a gene involved in controlling the circadian rhythm.
- Exposure to light at abnormal times or due to change in location will either disrupt the clock gene function or cause activation of the 'wake state' of the circadian cycle at an abnormal time, such as in the evening.

Sleep and Aging

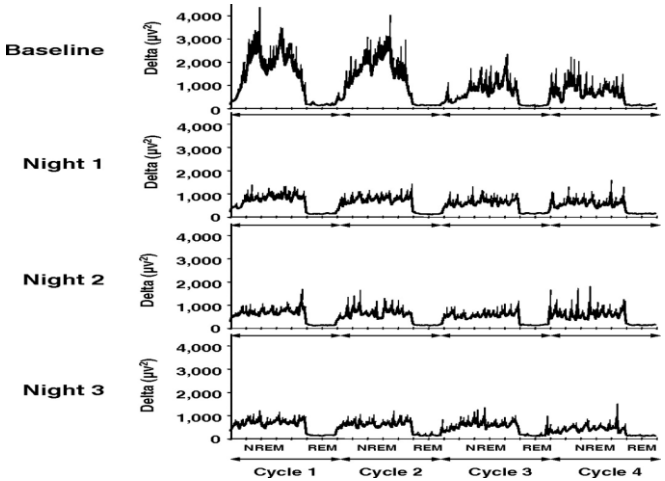


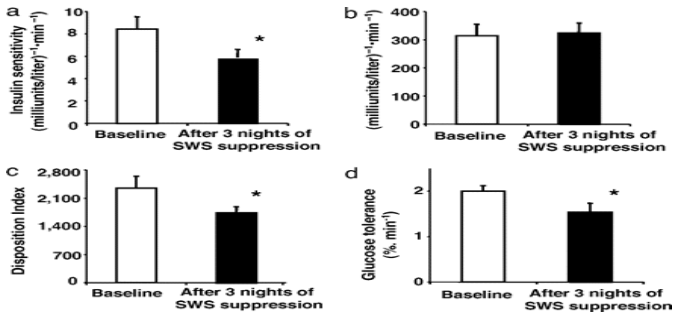
Slow-wave sleep and the risk of type 2 diabetes in humans

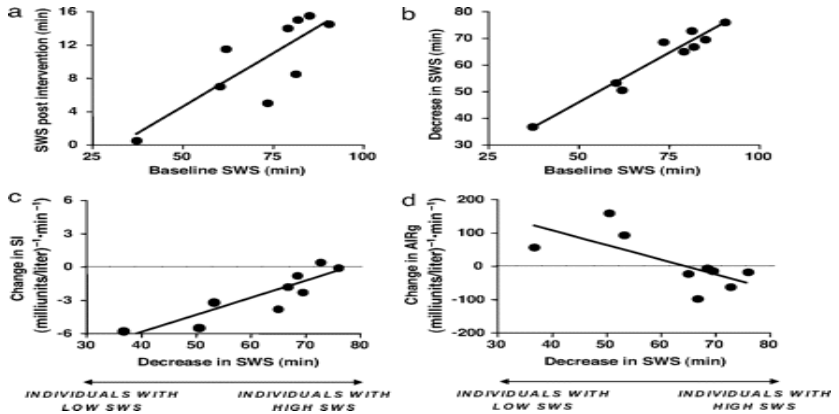
Esra Tasali, Rachel Leproult, David A. Ehrmann and Eve Van Cauter

PNAS January 22, 2008. 105 (3) 1044-1049; https://doi.org/10.1073/pnas.0706446105

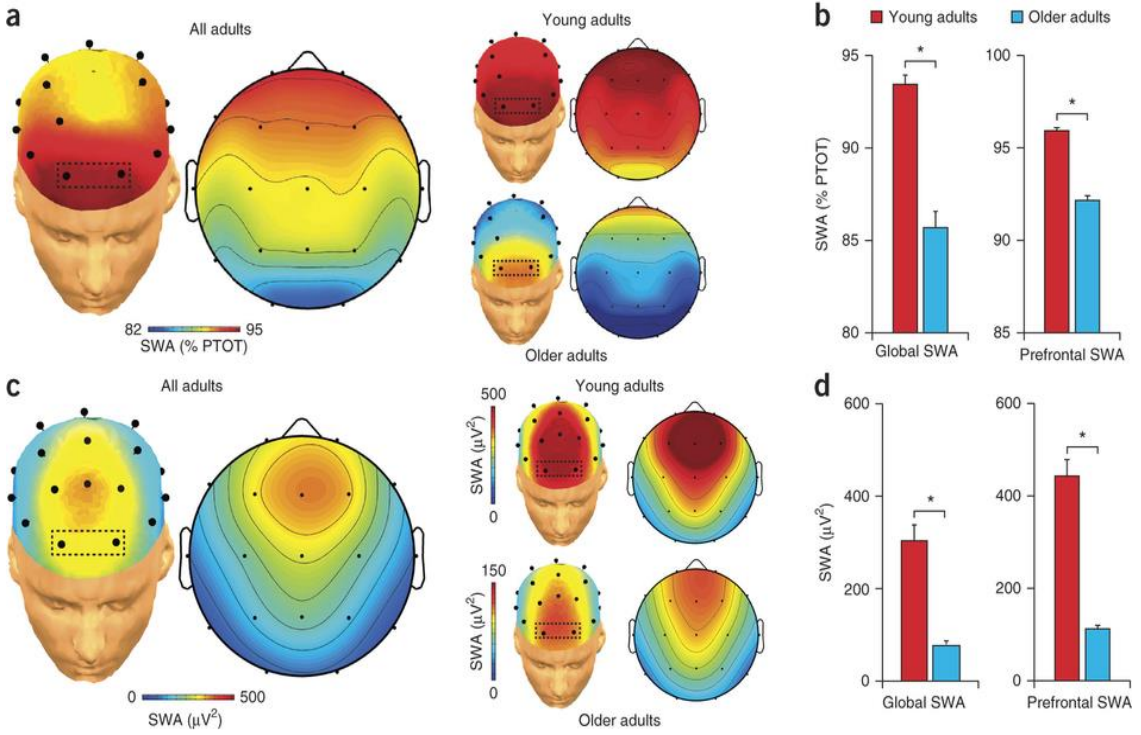
1.Edited by Donald F. Steiner, University of Chicago, Chicago, IL, and approved November 9, 2007 (received for review







Age differences in SWA (0.8-4.6 Hz) (a, b) and peak relative SWA (c,d)



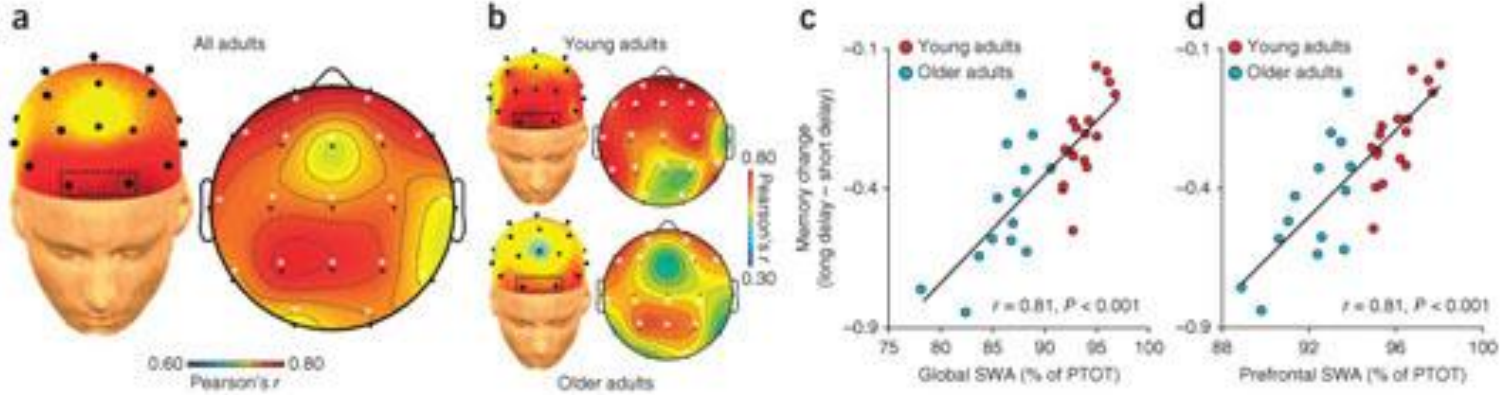
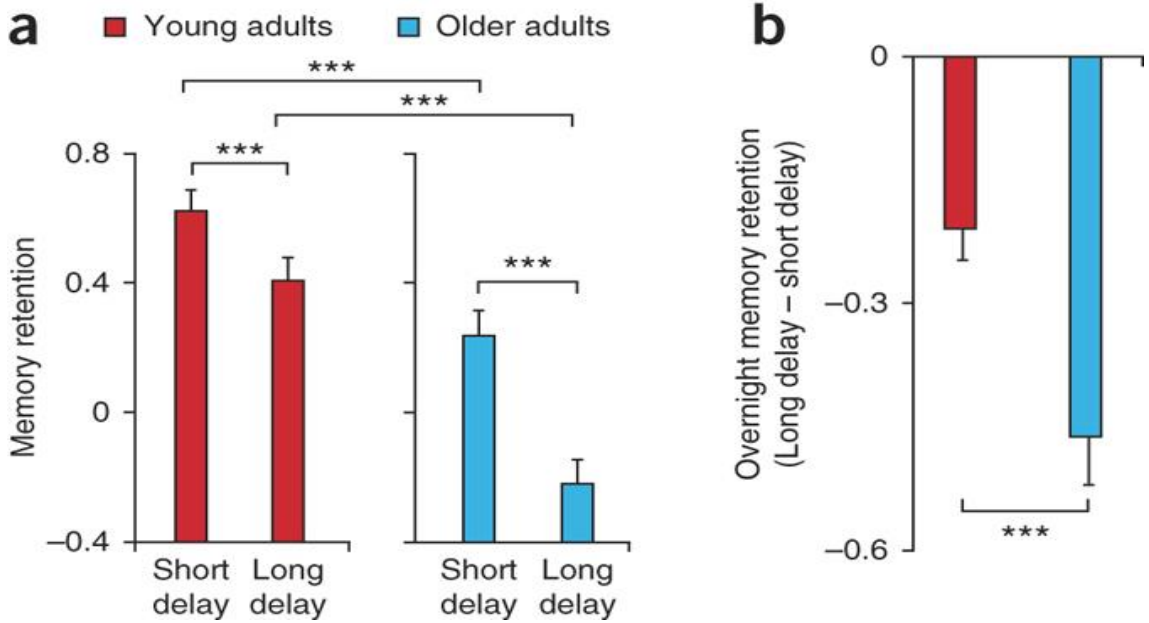


Figure 5 SWA predicts overnight memory change in young and older adults (**a**–**d**) Topographic plots of the association between relative SWA (0.8–4.6 Hz) during SWS and associative episodic memory change in all participants collapsed (**a**) and in young (top plots) and older (bottom plots) adults (**b**), with corresponding regressions for young (red) and older (blue) adults plotted for global relative SWA (**c**), defined as the average relative SWA across all electrode sites, and prefrontal SWA (**d**), defined as the average at prefrontal electrodes outlined in the box in **a** and **b** (Fp1 and Fp2), exhibiting peak relative SWA in both groups. Associations were specific to SWA, as measures of subjective sleepiness and alertness, objective alertness, circadian preference, neurocognitive status, fast spindle density during stage 2 sleep (**Supplementary Fig. 2**), TST, wake after sleep onset time, and sleep efficiency did not correlate with episodic memory change in either young or older adults separately (**Supplementary Table 3**). Similar to relative SWA, both global absolute SWA ($r = 0.57$, $P = 0.001$) and prefrontal absolute SWA (Fp1 and Fp2 mean; $r = 0.60$, $P < 0.001$) predicted episodic memory change across all participants. Although not significant in all cases, a similar association was detected in each group separately for both global (young adults, $r = 0.49$, $P = 0.045$; older adults, $r = 0.36$, $P = 0.21$) and prefrontal (young adults, $r = 0.56$, $P = 0.019$; older adults, $r = 0.24$, $P = 0.41$) absolute SWA. White asterisks, $P < 0.05$ corrected[22]. % PTOT denotes percentage of total spectral power (0.4–50 Hz).



Recognition performance (hit rate for originally studied word pairs – lure rate to originally studied word pairs – false alarm rate to new, unstudied words) reflects a measure of associative episodic memory consolidation. Age differences in recognition performance were the result of changes in hit rate (P<0,001) and not lure rate (P=0.16) or false alarm rate (P=0,17), suggesting that age differences in recognition performance were driven by differences in memory.

*** - P<0.001

Neuron
Article

Old Brains Come Uncoupled in Sleep: Slow Wave-Spindle Synchrony, Brain Atrophy, and Forgetting

Randolph F. Helfrich,[1,2,6,*] Bryce A. Mander,[3,4] William J. Jagust,[1,4] Robert T. Knight,[1,4,5] and Matthew P.
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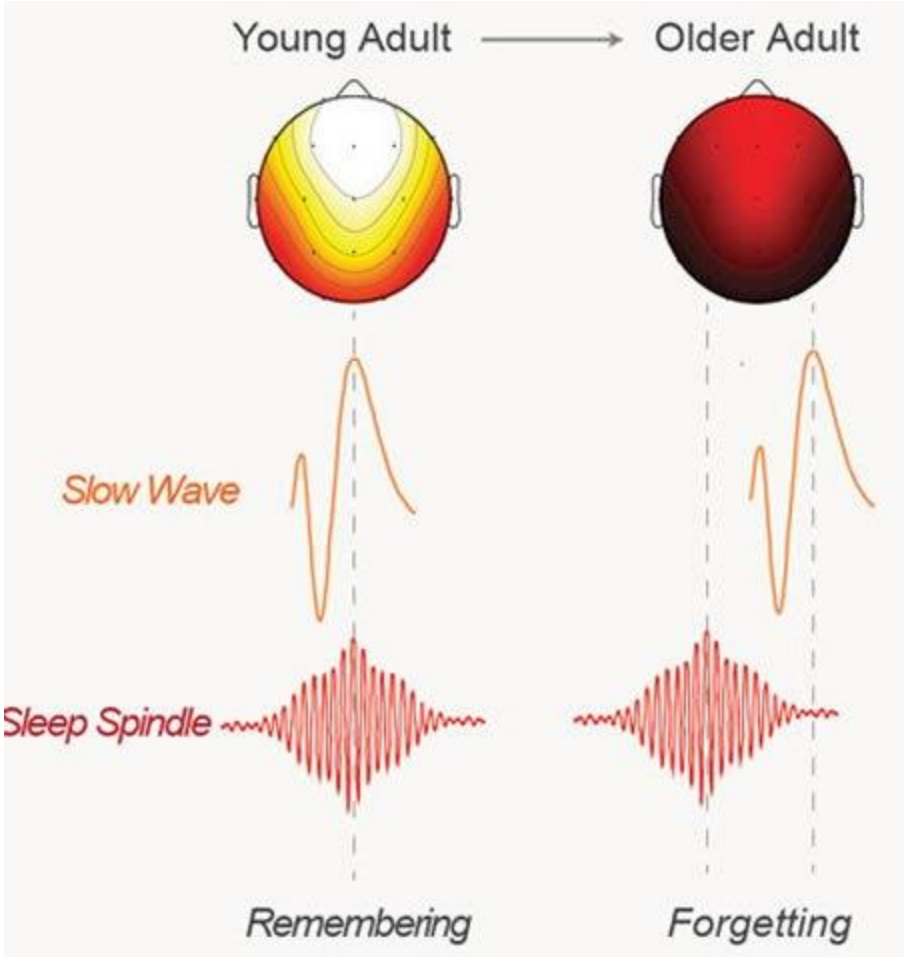
https://doi.org/10.1016/j.neuron.2017.11.020

The coupled interaction between slow-wave oscillations and sleep spindles during non-rapid-eye-movement (NREM) sleep has been proposed to support memory consolidation. However, little evidence in humans supports this theory. Moreover, whether such dynamic coupling is impaired as a consequence of brain aging in later life, contributing to cognitive and memory decline, is unknown. Combining electroencephalography (EEG), structural MRI, and sleep-dependent memory assessment, we addressed these questions in cognitively normal young and older adults. Directional cross-frequency coupling analyses demonstrated that the slow wave governs a precise temporal coordination of sleep spindles, the quality of which predicts overnight memory retention. Moreover, selective atrophy within the medial frontal cortex in older adults predicted a temporal dispersion of this slow wave-spindle coupling, impairing overnight memory consolidation and leading to forgetting. Prefrontal-dependent deficits in the spatiotemporal coordination of NREM sleep oscillations therefore represent one pathway explaining age-related memory decline.


Young Adult
Older Adult
Slow Wave
Sleep Spindle
Remembering
Forgetting

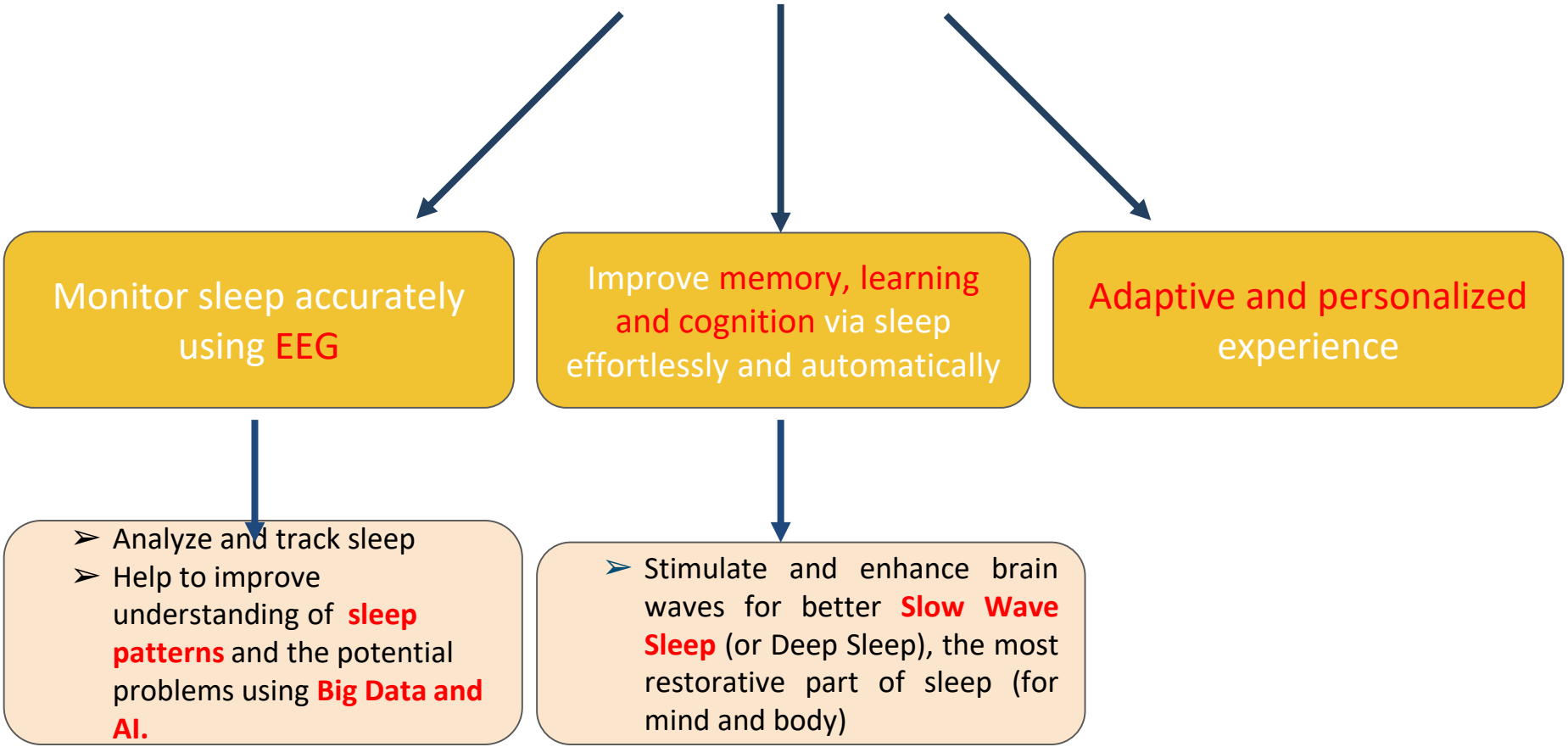


Improve cognition through Deep Sleep as a gateway to better mind and better health



Enhance memory, learning/education skills, and other cognitive functions

Sleep engineering



frontiers in Human Neuroscience

ORIGINAL RESEARCH
published: 08 March 2017
doi: 10.3389/fnhum.2017.00109

Acoustic Enhancement of Sleep Slow Oscillations and Concomitant Memory Improvement in Older Adults

*Nelly A. Papalambros[1], Giovanni Santostasi[1], Roneil G. Malkani[1], Rosemary Braun[2,3], Sandra Weintraub[4], Ken A. Paller[5] and Phyllis C. Zee[1]**

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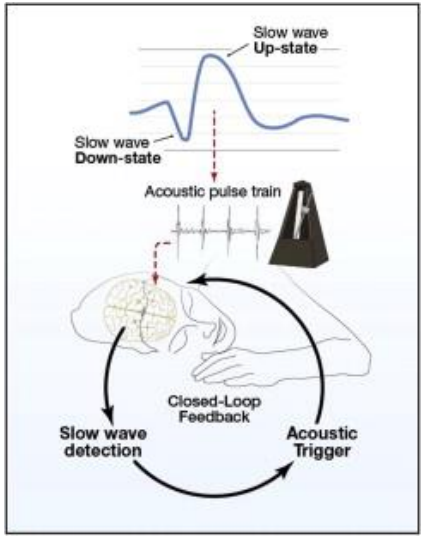
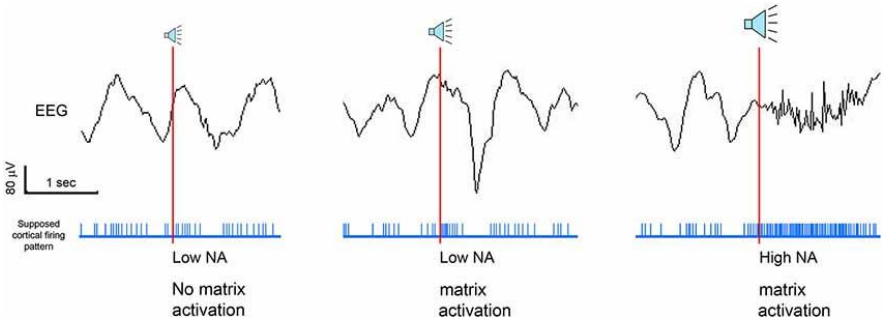
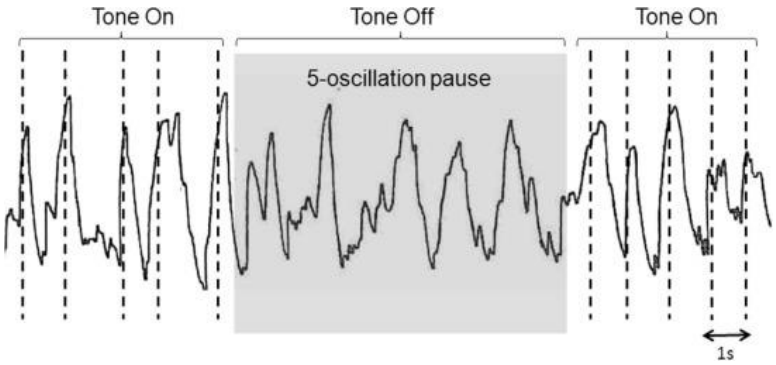
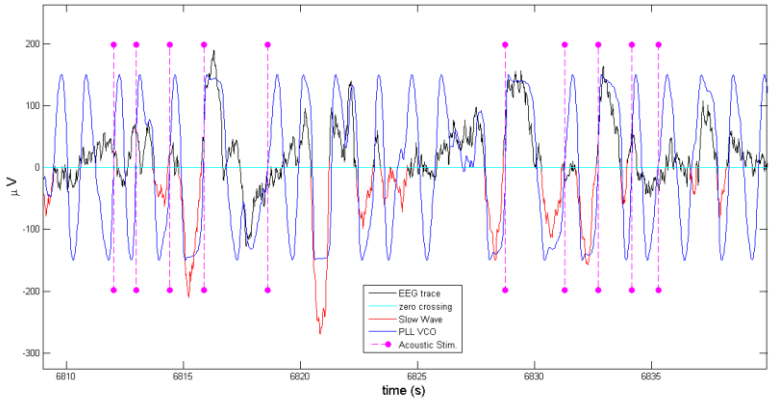


- Proprietary algorithm based on Phase Locked Loop (PLL) to follow each slow wave.
- Algorithm learns individual patterns of sleep and slow-wave activity using machine learning.



NA=noroadrenaline





Amplification of Slow-Waves by Acoustic Stimulation

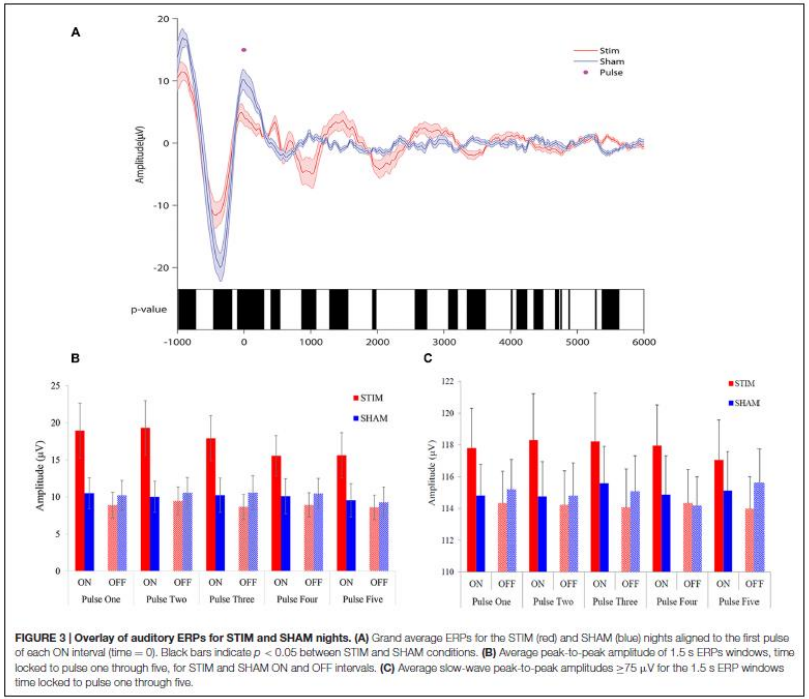
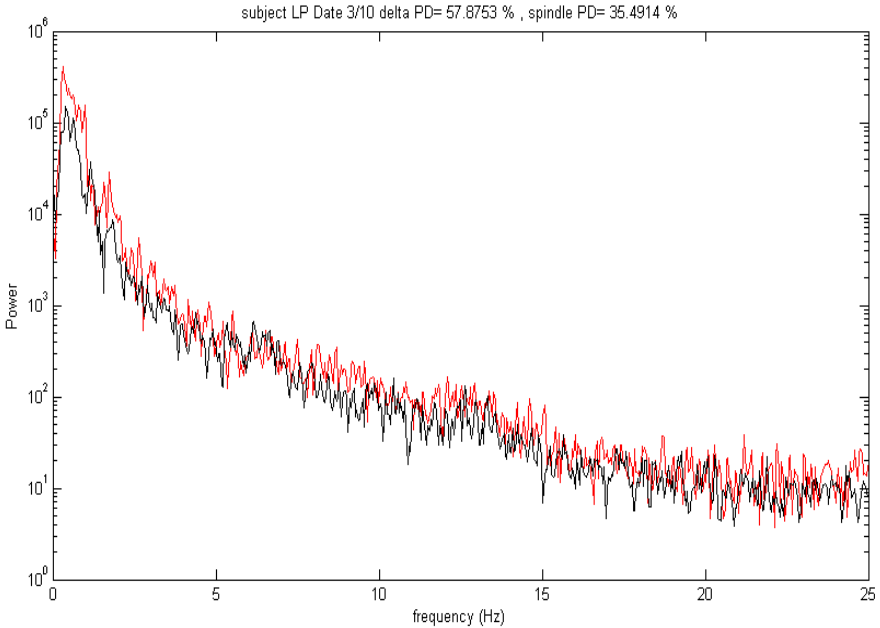


FIGURE 3 | Overlay of auditory ERPs for STIM and SHAM nights. (A) Grand average ERPs for the STIM (red) and SHAM (blue) nights aligned to the first pulse of each ON interval (time = 0). Black bars indicate $p < 0.05$ between STIM and SHAM conditions. **(B)** Average peak-to-peak amplitude of 1.5 s ERPs windows, time locked to pulse one through five, for STIM and SHAM ON and OFF intervals. **(C)** Average slow-wave peak-to-peak amplitudes $\geq$75 μV for the 1.5 s ERP windows time locked to pulse one through five.



Correlation between memory results and Slow-Wave Amplitude

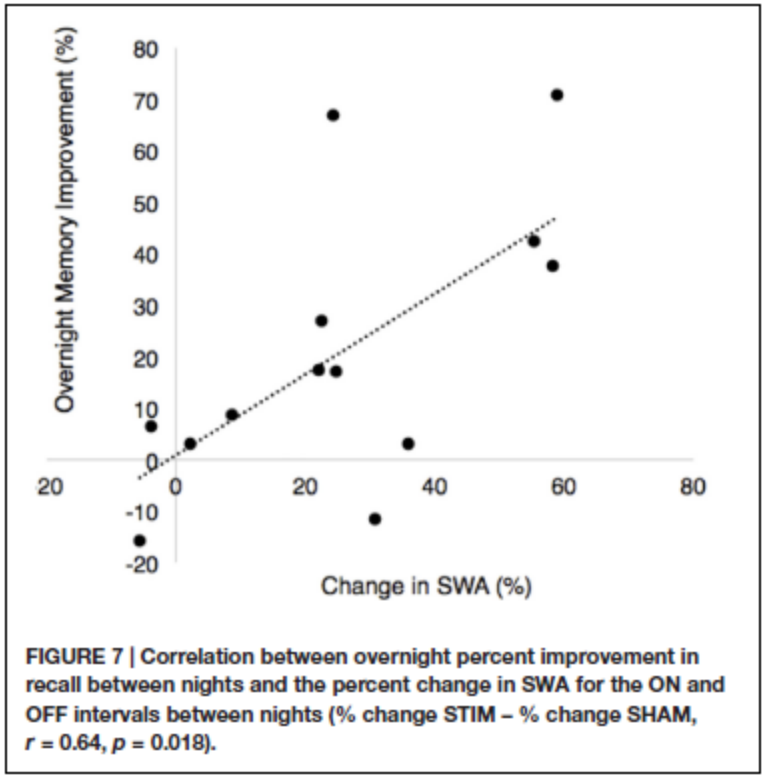


FIGURE 7 | Correlation between overnight percent improvement in recall between nights and the percent change in SWA for the ON and OFF intervals between nights (% change STIM – % change SHAM, $r = 0.64$, $p = 0.018$).

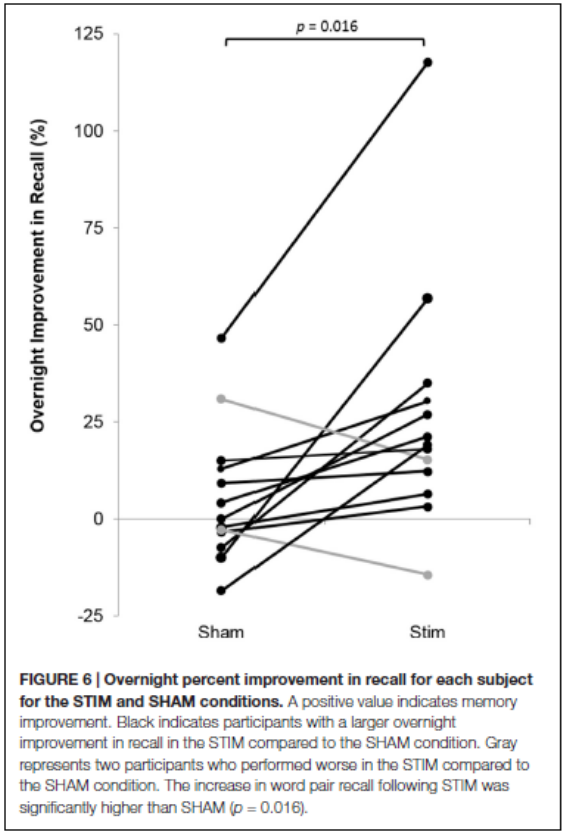


FIGURE 6 | Overnight percent improvement in recall for each subject for the STIM and SHAM conditions. A positive value indicates memory improvement. Black indicates participants with a larger overnight improvement in recall in the STIM compared to the SHAM condition. Gray represents two participants who performed worse in the STIM compared to the SHAM condition. The increase in word pair recall following STIM was significantly higher than SHAM ($p = 0.016$).

EEG wearable device to enhance slow wave sleep

Consumer devices at first (no precise medical claims - wellness, memory improvement similar to nutritional supplementation)



Core IP and Science

The research that led to this solution was funded via a cooperative agreement with DARPA as well as several grants from the United States government, American Alzheimer's Association, and others, totalling more than $10Million

A novel, non-pharmacological & non--invasive approach

- Analyzing the EEG signals
- Detecting the Slow Wave
- Delivering brain wave synchronized acoustic impulses

Restorative sleep

- Memory enhancement
- Metabolism regulation

- Pending patent application
  - Phase-locked loop to enhance Slow Wave Sleep, WO 2016028635 A1. *IP is being licensed to DeepWave Tech.*

- Published peer-review articles
  - Phase-Locked Loop for Precisely Timed Acoustic Stimulation during Sleep, Journal of Neuroscience Methods, December 2, 2015

Many Papers in Top Scientific Journals

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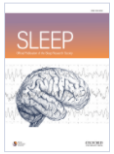

Volume 40, Issue 3
1 March 2017

Enhanced Memory Consolidation Via Automatic Sound Stimulation During Non-REM Sleep

Miika M. Leminen, MPsych, Jussi Virkkala, PhD, Emma Saure, MPsych, Teemu Paajanen, MPsych, Phyllis C. Zee, MD, PhD, Giovanni Santostasi, PhD, Christer Hublin, MD, PhD, Kiti Müller, MD, PhD, Tarja Porkka-Heiskanen, MD, PhD, Minna Huotilainen, DSc ... Show more

Sleep, Volume 40, Issue 3, 1 March 2017, zsx003, https://doi.org/10.1093/sleep/zsx003
Published: 31 January 2017

ELSEVIER

Journal of Neuroscience Methods

Volume 259, 1 February 2016, Pages 101-114



Phase-locked loop for precisely timed acoustic stimulation during sleep

Giovanni Santostasi [a], Roneil Malkani [a], Brady Riedner [b], Michele Bellesi [b], Giulio Tononi [b], Ken A. Paller [c], Phyllis C. Zee [a]

frontiers in Human Neuroscience

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Acoustic Enhancement of Sleep Slow Oscillations and Concomitant Memory Improvement in Older Adults

Nelly A. Papalambros[1], Giovanni Santostasi[1], Roneil G. Malkani[1], Rosemary Braun[2,3], Sandra Weintraub[4], Ken A. Paller[5] and Phyllis C. Zee[1*]

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Effects of phase-locked acoustic stimulation during a nap on EEG spectra and declarative memory consolidation

Ju Lynn Ong, June C. Lo, Nicholas I.Y.N. Chee, Giovanni Santostasi, Ken A. Paller, Phyllis C. Zee, Michael W.L. Chee

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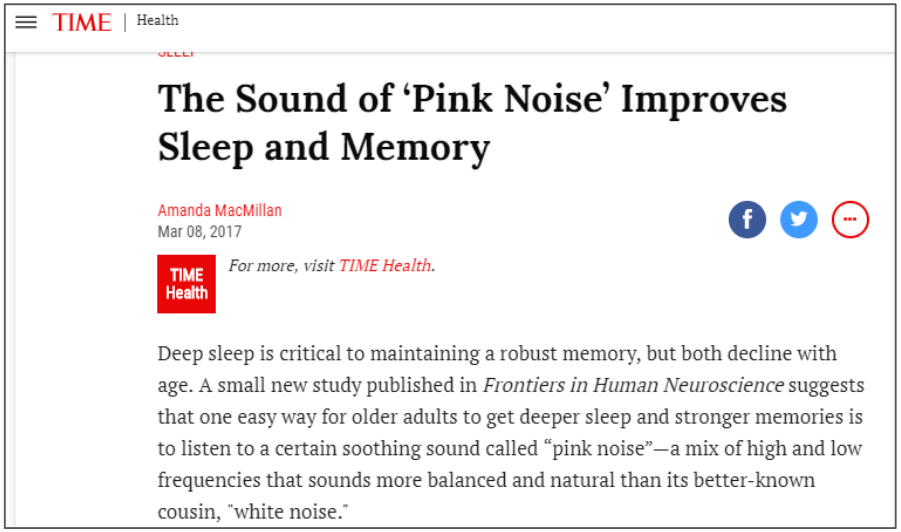
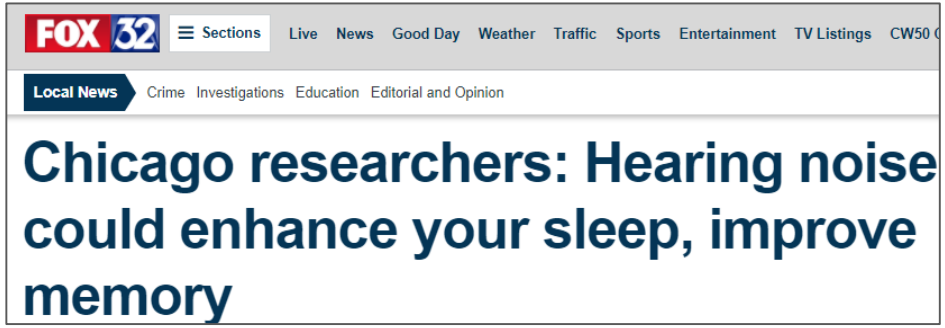
Positive press in Time Magazine , The Wall Street Journal, Smithsonian Magazine, FOX and more







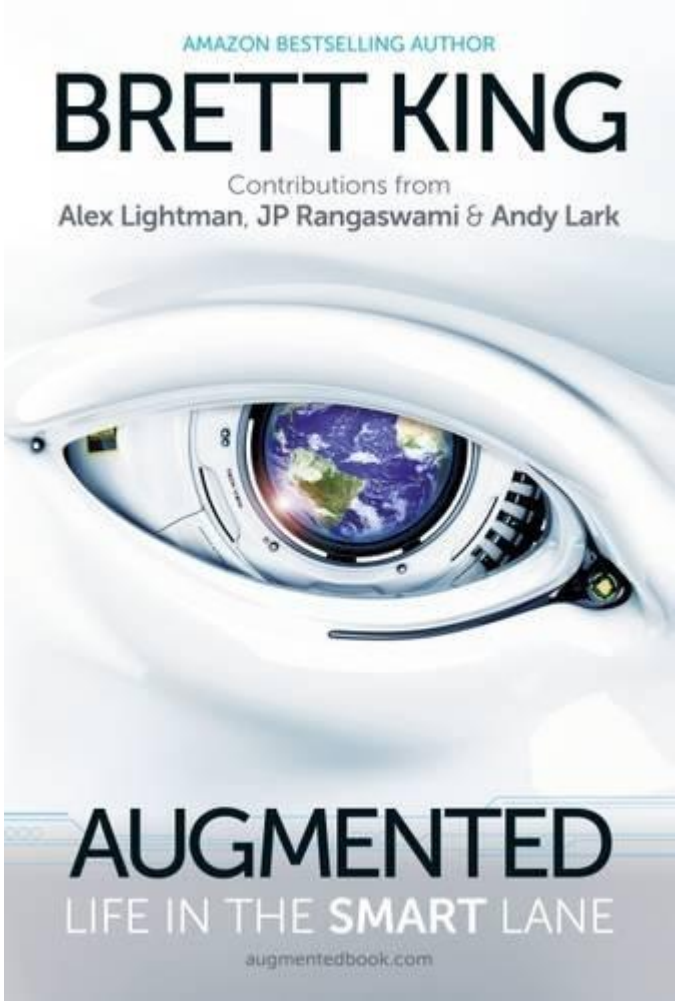




From Amazon Bestseller B. King "Augmented":

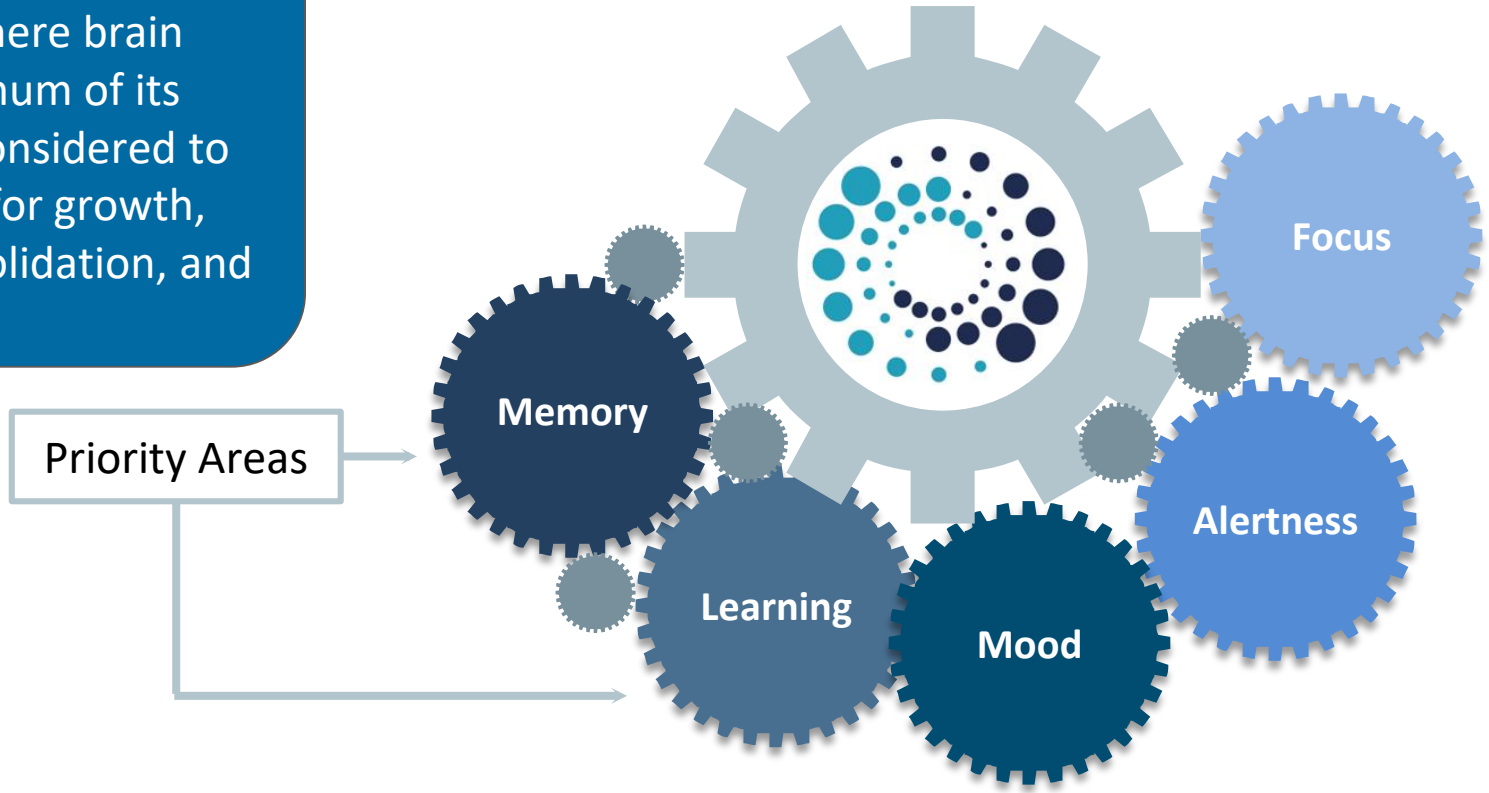
The quality of SWS decreases dramatically with age and this leads to significant age-related cognitive impairment." Dr Santostasi and his colleagues have developed a system that utilises acoustic stimulation of the brain to increase the duration and intensity of slow wave activity (SWA) so as to stabilise and increase the quality of sleep. It does this by synchronising the electrical activity of the brain regions responsible for facilitating SWA during SWS. "The new quantified self system utilises feedback algorithms that measure the duration and intensity of SWS as it is naturally occurring in the user's brain and modifies the amount with which SWA is enhanced in proportion to how much it is lacking, which is much more effective than increasing the duration and intensity of SWA by some unchanging baseline degree. This allows the system to adapt in accordance with the degree with which a user's SWS is impaired." Soon, you'll be able to put on headphones to go to sleep and enter an SWS state that will improve your brain, ability to learn, memory and ability to get to and/ or maintain a healthy weight. By using this method, you may also need less sleep each night. Imagine what you could do with 2 or 3 hours of wake up in better shape than you do today?

King, Brett; Lark, Andy; Lightman, Alex; Rangaswami, JP. Augmented: Life in The Smart Lane (Kindle Location 2394). Marshall Cavendish International (Asia) Pte Ltd.



The Promises of Slow Wave Sleep

Slow wave sleep is the sleep stage where brain shows a minimum of its activity. It is considered to be important for growth, memory consolidation, and brain renewal.



The Promises of Slow Wave Sleep



Alzheimer's disease	PTSD	ADHD	Diabetes	Depression	Bipolar disorder	Schizophrenia

Cognitive Performance → **Therapeutic Benefit**

SW is important for health in general, not just memory and auditory stimulation can enhance the benefits of SW sleep in a non-pharmacological and non-invasive way

nature COMMUNICATIONS

ARTICLE

DOI: 10.1038/s41467-017-02170-3 OPEN

Auditory closed-loop stimulation of EEG slow oscillations strengthens sleep and signs of its immune-supportive function

Luciana Besedovsky[1], Hong-Viet V. Ngo[1,2], Stoyan Dimitrov[1,3,4], Christoph Gassenmaier[5], Rainer Lehmann[3,4,6] & Jan Born[1,3,4,7]

Sleep is essential for health. Slow wave sleep (SWS), the deepest sleep stage hallmarked by electroencephalographic slow oscillations (SOs), appears of particular relevance here. SWS is associated with a unique endocrine milieu comprising minimum cortisol and high aldosterone, growth hormone (GH), and prolactin levels, thereby presumably fostering efficient adaptive immune responses. Yet, whether SWS causes these changes is unclear. Here we enhance SOs in men by auditory closed-loop stimulation, i.e., by delivering tones in synchrony with endogenous SOs. Stimulation intensifies the hormonal milieu characterizing SWS (mainly by further reducing cortisol and increasing aldosterone levels) and reduces T and B cell counts, likely reflecting a redistribution of these cells to lymphoid tissues. GH remains unchanged. In conclusion, closed-loop stimulation of SOs is an easy-to-use tool for probing SWS functions, and might also bear the potential to ameliorate conditions like depression and aging, where disturbed sleep coalesces with specific hormonal and immunological dysregulations.

[1] Institute of Medical Psychology and Behavioral Neurobiology, University of Tübingen, Otfried-Müller-Straße 25, 72076 Tübingen, Germany. [2] School of Psychology, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK. [3] German Center for Diabetes Research, Otfried-Müller-Straße 10, 72076 Tübingen, Germany. [4] Institute for Diabetes Research and Metabolic Diseases of the Helmholtz Center Munich at the University of Tübingen, Otfried-Müller-Straße 10, 72076 Tübingen, Germany. [5] Department of Internal Medicine IV, University of Tübingen, Otfried-Müller-Straße 10, 72076 Tübingen, Germany. [6] Central Laboratory, Department for Diagnostic Laboratory Medicine, University of Tübingen, Hoppe-Seyler-Straße 3, 72076 Tübingen, Germany. [7] Centre for Integrative Neuroscience, University of Tübingen, Otfried-Müller-Straße 25, 72076 Tübingen, Germany. Correspondence and requests for materials should be addressed to J.B. (email: jan.born@uni-tuebingen.de)

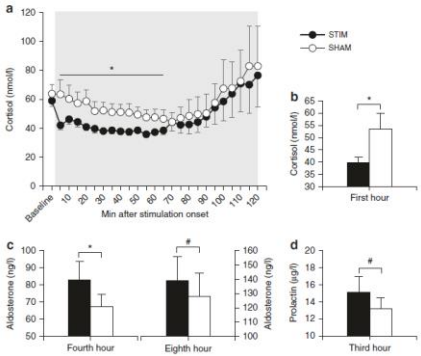


Fig. 2 Impact of auditory SO stimulation on cortisol, aldosterone, and prolactin levels. Means (±s.e.m.) of cortisol (**a**, **b**), aldosterone (**c**), and prolactin (**d**) levels calculated for 1-h bins. Gray area represents the 120-min stimulation period. $^{*}p < 0.05$, $^{\#}p < 0.1$ for pairwise comparisons between the Stimulation condition (STIM, black) and the Sham condition (SHAM, white) with Wilcoxon tests, two-sided. $n = 10$–14 (see "Methods" section for exact numbers)

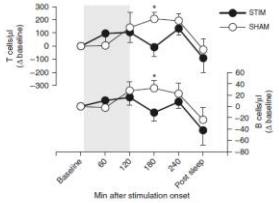
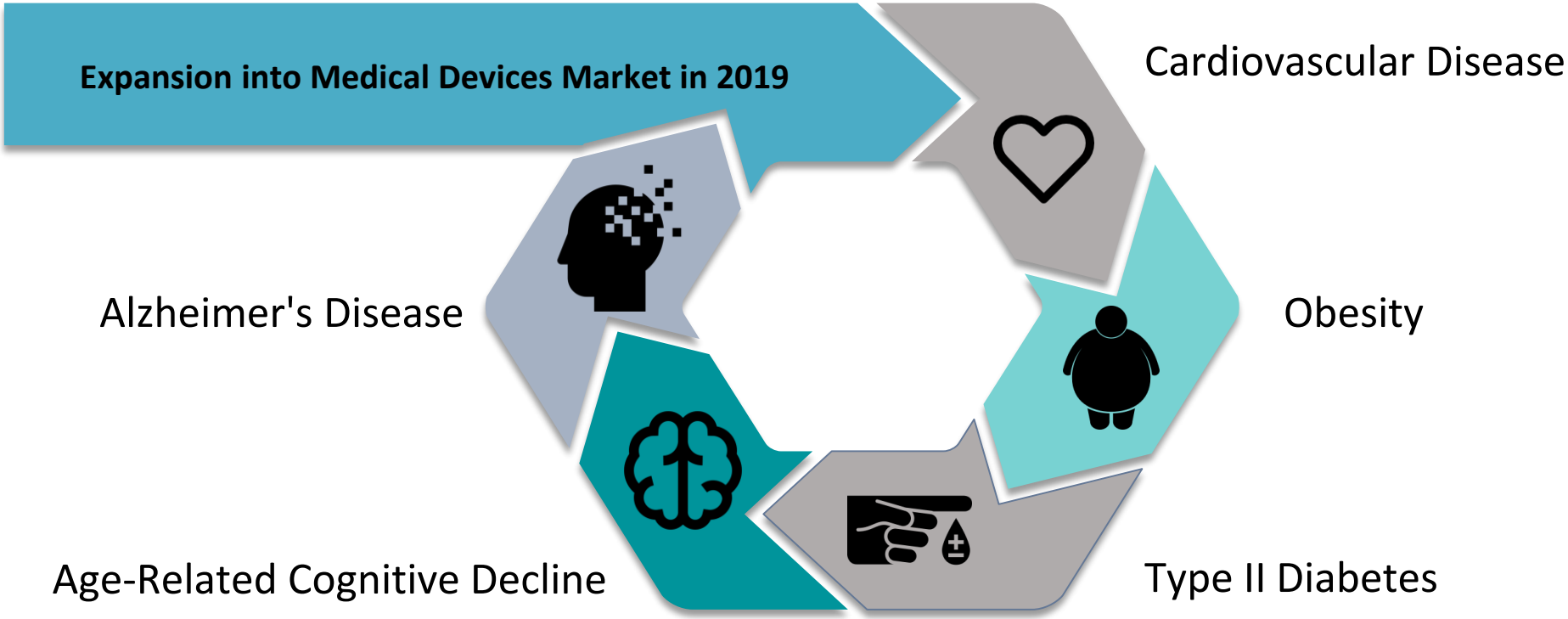


Fig. 3 Impact of auditory SO stimulation on lymphocyte counts. Means (±s.e.m.) of circulating T and B cell numbers (shown as difference from baseline). Gray area represents the 120-min stimulation period. $^{*}p < 0.05$ for pairwise comparisons between the Stimulation condition (STIM, black) and the Sham condition (SHAM, white) with Wilcoxon tests, two-sided. $n = 9$

Moreover, animal studies suggest that, during sleep, lymphocytes accumulate in lymph nodes[39,40]. Thus, the SO stimulation-induced decrease in circulating lymphocytes likely reflects a hormonally mediated redistribution of the cells to lymphoid tissues, where they can evolve their cell-specific immunological functions, eventually mediating the boosting effect of sleep on adaptive immune functions[3,14,36].

2019: Medical Grade Models



Sleep EEG, phenotypes, genomics, epigenetics

https://www.whatisepigenetics.com/



Short-Term Sleep Loss Alters DNA Methylation of Clock Genes



Could Poor Sleep and Histone Modification Degrade Your Memory?



Skipping Sleep Lowers the Body's Protective Antioxidant Levels and Induces Epigenetic Changes



Menopause and Insomnia Might Epigenetically Speed Up Aging



1. Sleep epigenetically Improves Immunity

DNA methylation, perhaps the most widely recognized epigenetic mechanism, is implicated in the connection between sleep and the body's ability to fight off infections and diseases. Research in the American Journal of Respiratory Critical Care Medicine showed that DNA methylation was increased in children suffering from OSA, or Obstructive Sleep Apnea (Kim et al., 2012).

2. Better sleep less stress

Recent research shows that histone modifications occur in the hippocampus as a result of acute stress, specifically hindering hippocampal neurogenesis via acetylation of histone H3K9. This may impair our ability to get a good night's sleep, according to Palagini et al. (2013).

3. Sleep to Reduce Cancer Risk

Not getting enough rest or disrupting your body's natural sleep rhythm could also lead to epigenetic changes to certain genes linked to immunity and tumor growth.

According to a study by Qureshi and Mehlerm (2014), people who were exposed to long term shiftwork had significant alterations in the levels of DNA methylation associated with circadian gene loci, immune system- and inflammation-related gene loci.

SUMMARY

Sleep supports the consolidation of memory.

• This is an active ‘system consolidation’ process in which memories are reactivated to be transferred from a temporary into a long-term store.

• Reactivation and transfer of memories take place during SWS under the control of the slow oscillation.

Additional Slides

The Sleep Homeostat

