SLEEP AND MEMORY

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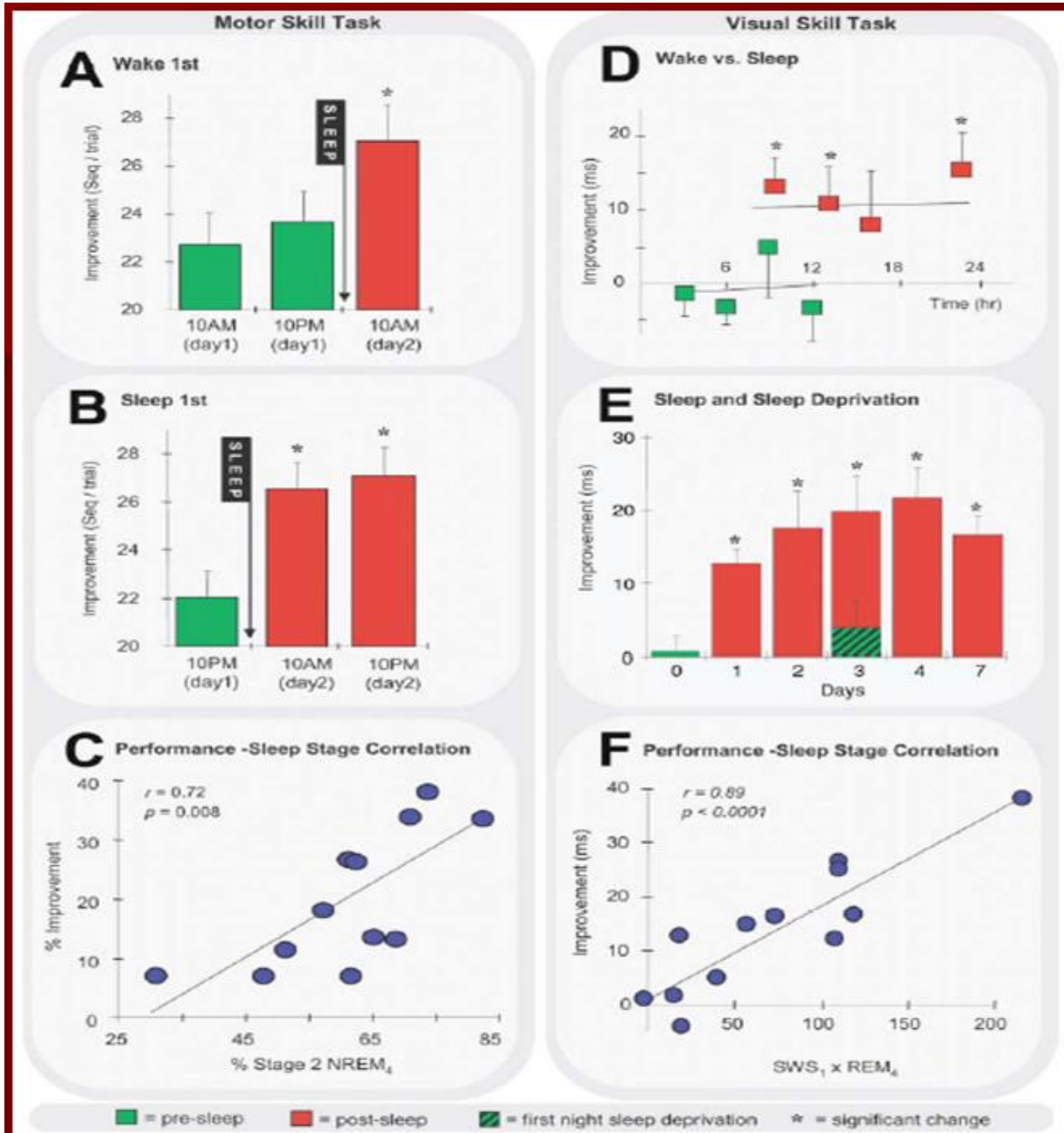


Figure 2. Sleep-Dependent Visual and Motor Skill Learning in the Human Brain

(A–C) Motor skill task. (A) Wake 1st—subjects (n = 15) trained at 10 AM showed no significant change in performance at retest following 12 hr of wake (day 1, green bars). However, by the second retest, following a night of sleep (day 2, red bar), performance improved significantly. (B) Sleep 1st—following evening training, subjects (n = 15) showed significant improvements in speed just 12 hr after training following a night of sleep (10 AM, red bar) but expressed no further significant change in performance following an additional 12 hr of wake (10 PM, red bar). (C) The amount of overnight improvement on the motor skill task correlated with the percentage of stage 2 NREM sleep in the last quartile of the night (% stage 2 NREM, fourth quartile).

(D–F) Visual skill task. Subjects were trained and then retested at a later time, with improvement (ms) in performance illustrated across time. Each subject was retested only once, and each point represents a separate group of subjects. (D) Wake versus sleep. Subjects trained and then retested on the same day (n = 33), after either 3, 6, 9, or 12 hr of subsequent wake (green squares), showed no significant improvement as a consequence of the passage of waking time for any of the four time intervals. In contrast, subjects (n = 39) trained and then retested 8, 12, 15, or 23 hr later, after a night's sleep (red squares), showed significant improvement. (E) Sleep deprivation. Subjects (n = 89) trained and retested 1–7 days later (red bars) continued to improve after the first night, without additional practice. Subjects (n = 11) sleep deprived the first night after training showed no improvement (green hatched bar), even after 2 nights of recovery sleep. (F) Overnight improvement was correlated with the percent of SWS in the first quarter of the night (SWS1) and REM sleep in the last quarter of the night (REM4). *$p < 0.05$; error bars, SEM.

Walker & Stickgold. Neuron 2004;44:121–133

Sleep and Memory

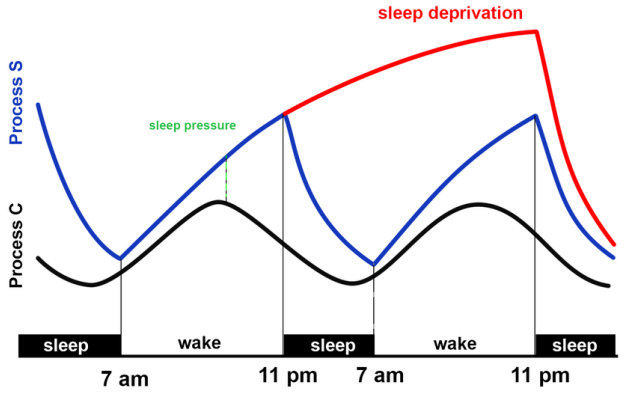
It is now well known that **sleep and memory consolidation** are connected, with a large amount of published evidence that sleep subserves the consolidation of learned information into long-term memory traces.

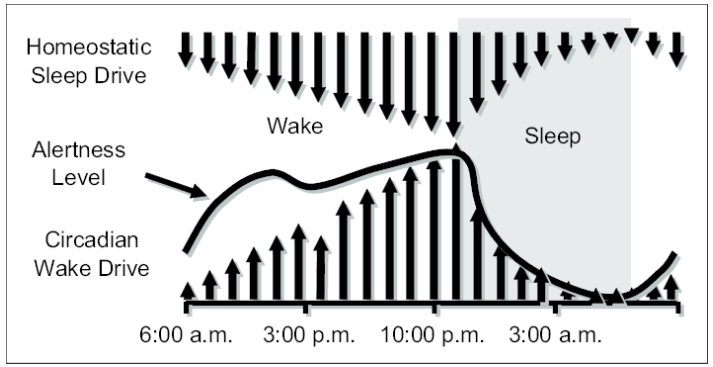
Two main different but non-exclusive comprehensive theoretical frameworks have been proposed for the relationship between sleep and memory consolidation:

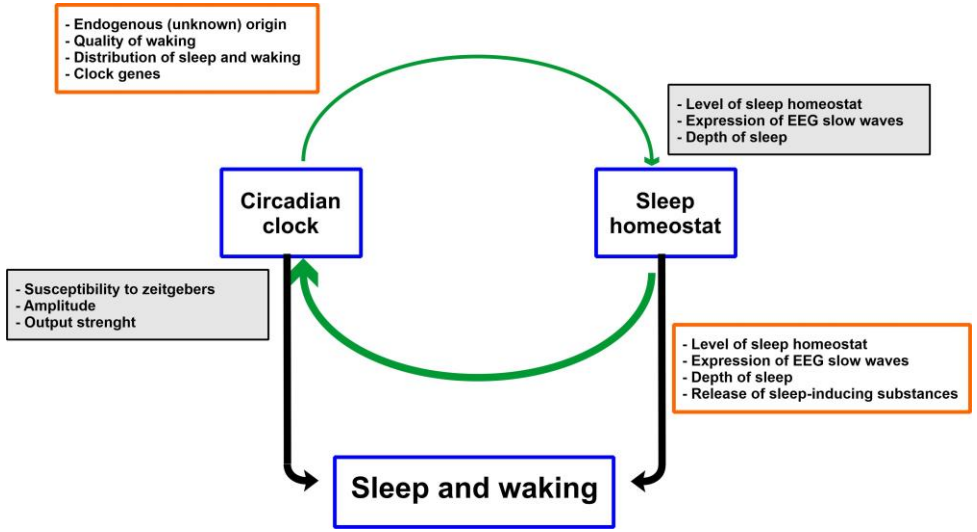
1. the **"synaptic homeostasis hypothesis"** - changes in the synaptic connectivity during learning might lead to an increasing need of space and energy; downscaling synaptic strength during sleep would save energy and eliminate unnecessary information (noise) from the previous day.

2. the **"dual process/sequential hypothesis"** - memory formation is dependent on different proportions of sleep stages, NREM-rich sleep during the first period of the night is beneficial for declarative memory, and REM-rich sleep of the last half of the night favors non-declarative, implicit or procedural memory.

Two-Process Model of Sleep Regulation







The circadian clock and the sleep homeostat both are thought to act on sleep and waking, shaping sleep-wake behavior.

Mechanistic influences of the circadian clock and of the sleep homeostat on the circadian clock exist.

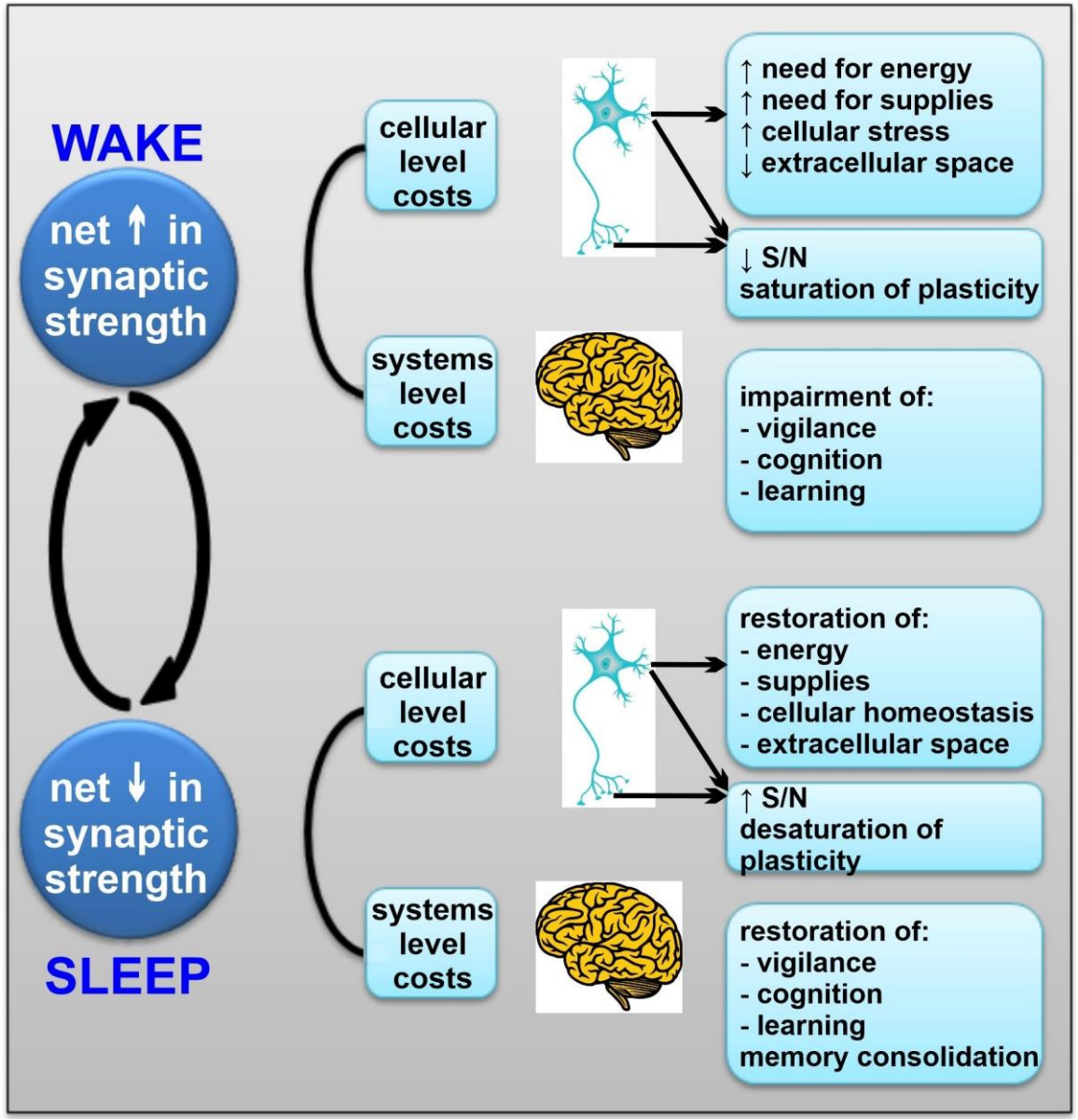
The clock and sleep homeostat also influence each other's functioning.

The influence of the sleep homeostat on the circadian clock seems to be larger than the reciprocal influence.

Adapted from Deboer, 2018

Synaptic Homeostasis Hypothesis (SHY)

SHY predicts that, by the end of a waking day, the synaptic connections of neural circuits undergo a net increase in synaptic strength due to ongoing learning, mediated by synaptic potentiation. Stronger synapses require more energy and supplies and are prone to saturation, creating the need for synaptic renormalization that mainly occurs during sleep, when the brain is dis-connected from the environment and neural circuits can be broadly reactivated offline to undergo a systematic synaptic down-selection represented by scalp-recorded SWA *(Tononi and Cirelli, 2020)*.



The down-scaling effect that SWA mediates would lead to the improved neural efficiency and functioning, as also confirmed by mathematical models *(Esser et al., 2007)*.

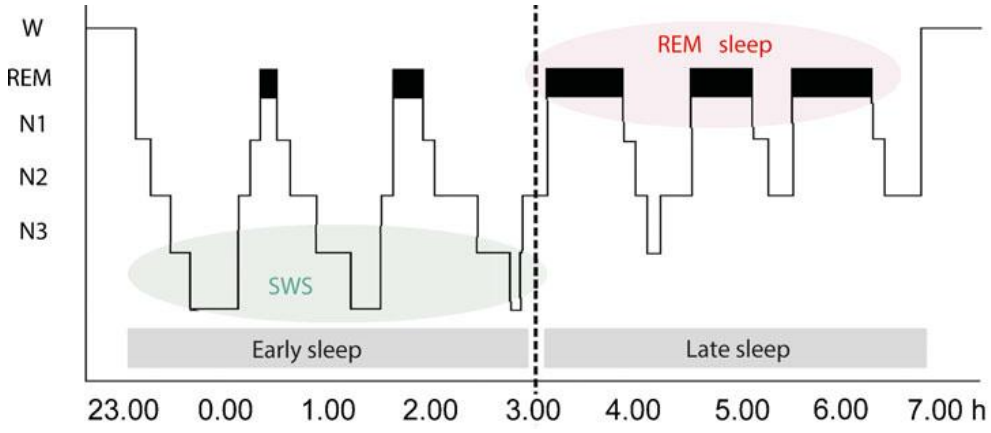
Synaptic Homeostasis Hypothesis (SHY)

The increase in synaptic strength during wake modulates the amount of SWA during slow wave sleep:

- ✓ wake time duration regulates the amplitude and duration of SWA: extended wakefulness leads to higher amplitude of the slow waves in NREM sleep with steeper slopes and fewer multi-peak waves *(Huber et al., 2000)*;
- ✓ the increase of SWA appears to be locally regulated, as behavioral tasks designed to activate a specific cortical region *(Ghilardi et al., 2000)* elevated the level of SWA in that region during slow wave sleep *(Huber et al., 2004)*;
- ✓ a procedure leading to synaptic depression (daytime arm immobilization) causes a local decrease, rather than an increase, in sleep SWA *(Huber et al., 2006)*.

SHY should be viewed as an attempt to identify an essential function of sleep, i.e. that sleep is needed to re-establish synaptic homeostasis, which is challenged by the remarkable plasticity of the brain. As such, it should be clear that SHY is a hypothesis not about specific mechanisms but about a universal, essential function of sleep. This function is the preservation of synaptic homeostasis in the face of a systematic bias toward a net increase in synaptic strength, a challenge that is posed by learning during adult wake and by massive synaptogenesis during development *(Tononi and Cirelli, 2012).*

Dual Process/Sequential Hypothesis



During early sleep slow-wave sleep (SWS) is prevailing, during late sleep rapid eye movement (REM) sleep predominates. Non-REM sleep encompasses SWS (N3), N2, and N1 with approximately equal amounts of N2 sleep during early and late sleep.

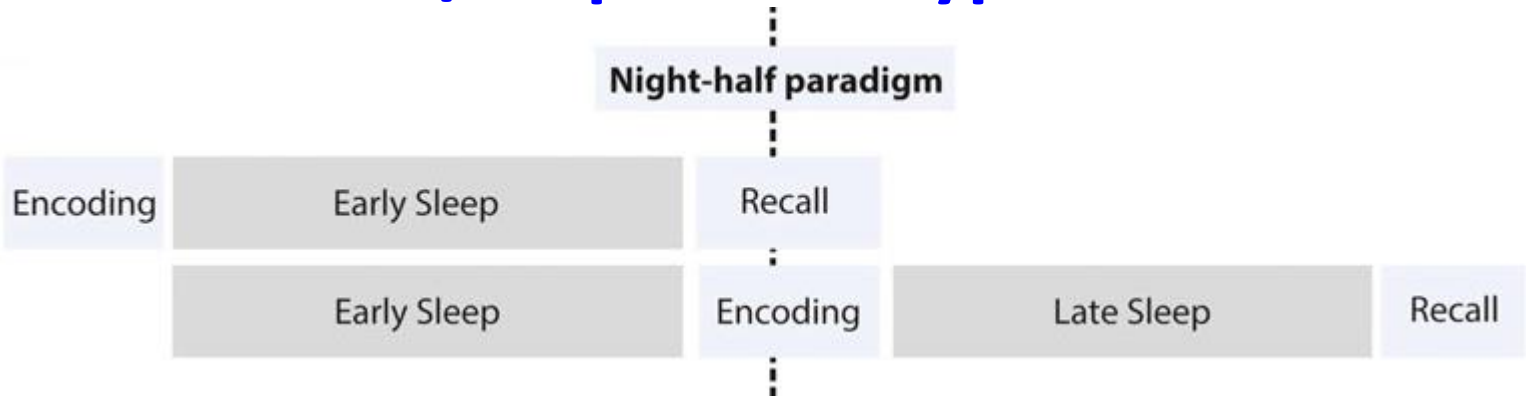
SWS mainly occurs in the first half of the night and is characterized by slowly oscillating brain activity reflecting alternating periods of neural activity and neural silence (i.e., up and down states) that are highly synchronized over widespread cortical brain areas.

In contrast, during REM sleep, occurring primarily in the second half of the night, the brain's oscillatory activity predominantly consists of mixed-frequency, low-amplitude oscillations resembling waking electroencephalographic activity combined with hippocampal theta oscillations, rapid-eye movements and reduced muscle tone.

The dual process hypothesis proposes that SWS preferentially benefits declarative memory, while REM sleep is of special importance for non-declarative memories.

(Smith 2001, Gais & Born 2004, Marshall & Born 2007)

Dual Process/Sequential Hypothesis



Participants either encode memories before (and recall after) a 3-h retention interval filled with early SWS-rich sleep (first night-half), or with late, REM-sleep-rich sleep *(Ackermann & Rasch 2014).*

NREM → Declarative memory **REM** → Procedural memory, Emotional memory

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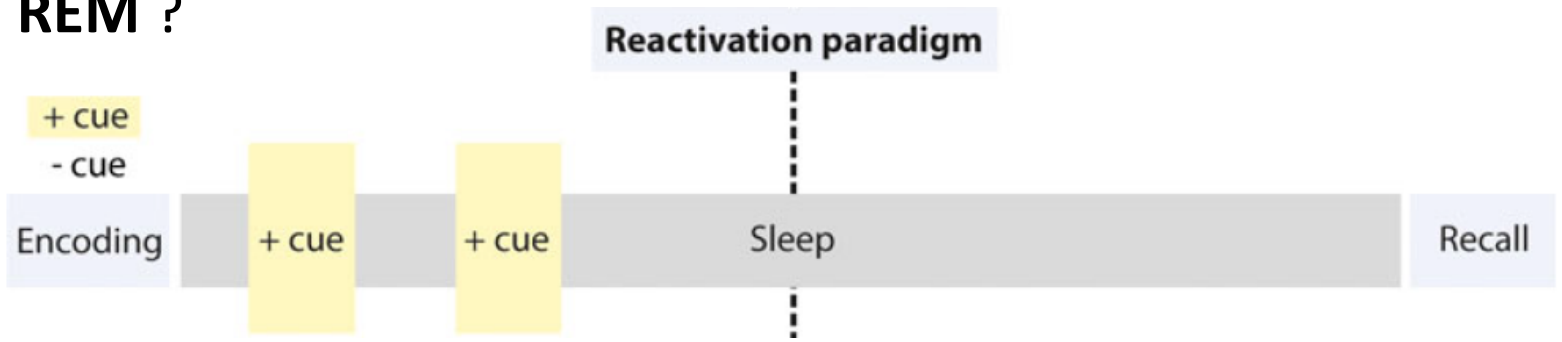
NREM →
Enhancement of declarative and procedural memory
Increase/decrease of emotional memory

REM ?



During encoding of a memory task, some stimuli are paired with a memory cue (e.g., odor or sound; + cue), while others are not (– cue). During post-learning sleep, the cue is presented again, typically during SWS, but other sleep stages would also be possible (e.g., early/late N2 sleep, REM sleep). Recall performance is tested after sleep and compared between cued and uncued stimuli *(Ackermann & Rasch 2014).*

Dual Process/Sequential Hypothesis

	Selective sleep stage deprivation	Oscillatory manipulation	Pharmacological manipulation
NREM	N2 → Impairs simple motor tasks N3 → No effects on declarative memory	Manipulating slow oscillations affects declarative memory	Effects on declarative memory only when increasing both SWA and spindles
REM	Impairs complex memories (procedural + declarative?)	?	No effects of REM sleep suppression on procedural memory

Adapted from Ackermann & Rasch 2014

Boosting slow oscillations during sleep potentiates memory

nature Vol 444|30 November 2006|doi:10.1038/nature05278

Lisa Marshall[1], Halla Helgadóttir[1], Matthias Mölle[1] & Jan Born[1]

- ✓ 13 volunteers learn 46 word-pairs in a training session before sleep
- ✓ Fluctuating electrical potentials applied to induce cortical slow oscillations
- ✓ The memory boost occurred **only if the electrical stimulation matched the oscillation frequency of cortical slow waves (0.75 Hz)** and not when the stimulation was at the theta frequency (5 Hz)
- ✓ The time chosen was crucial: no effect on recall if stimulation was during the last 45' of the night instead of the first 45'

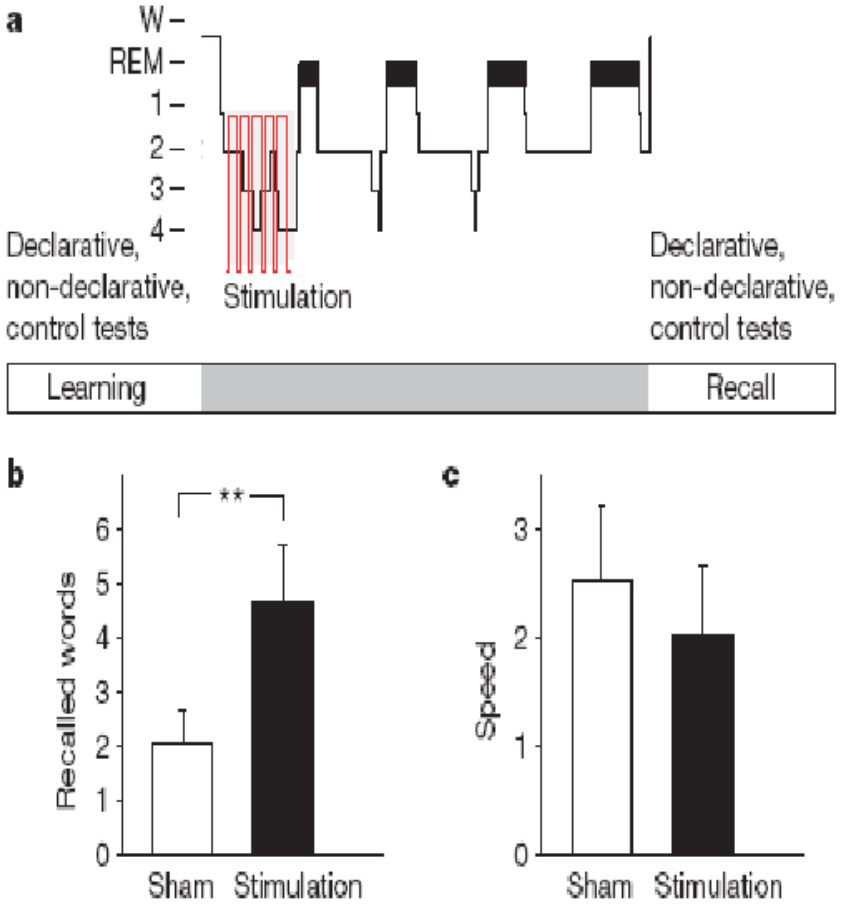


Figure 1 | Slow oscillatory stimulation enhances declarative memory

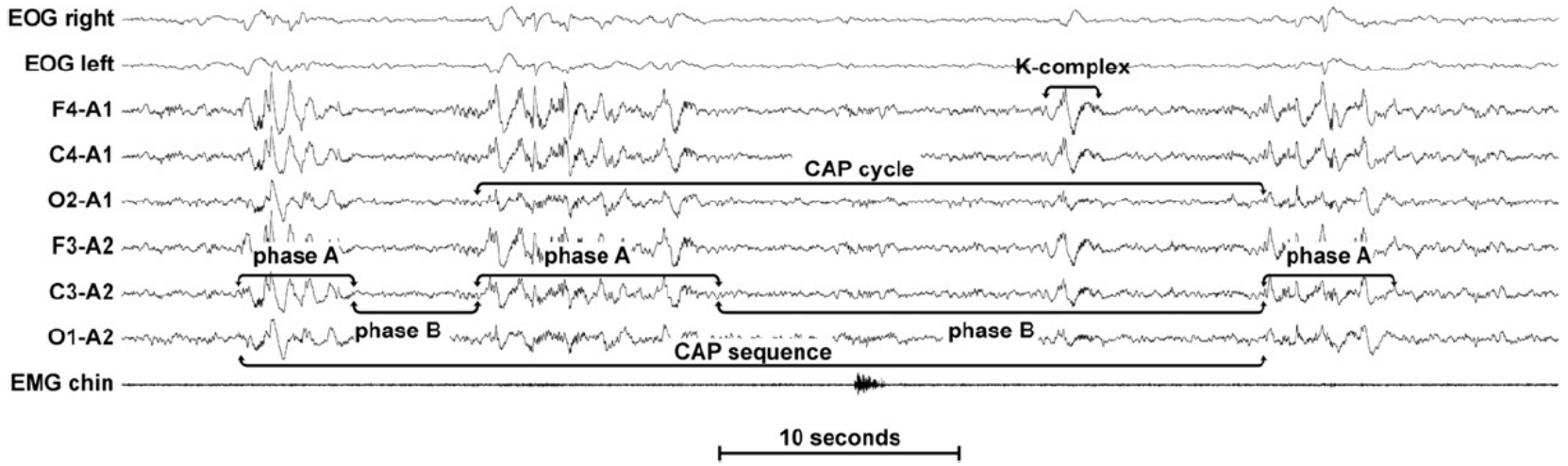


Fig. 2. A CAP cycle is defined as a sequence of 2 alternating stereotyped EEG patterns, each lasting more than 2 and less than 60 s, called phase A and phase B, which are the expression of a sustained fluctuation between "greater arousal" level (phase A: usually 8–12 s) and "lesser arousal" level (phase B: usually 16–25 s). At least 2 full CAP cycles in succession are needed to define a CAP sequence; thus, the minimum content of a sequence is A + B + A + B + A. Note that single K-complexes do not identify a CAP phase A.

The Role of Cyclic Alternating Pattern (CAP)

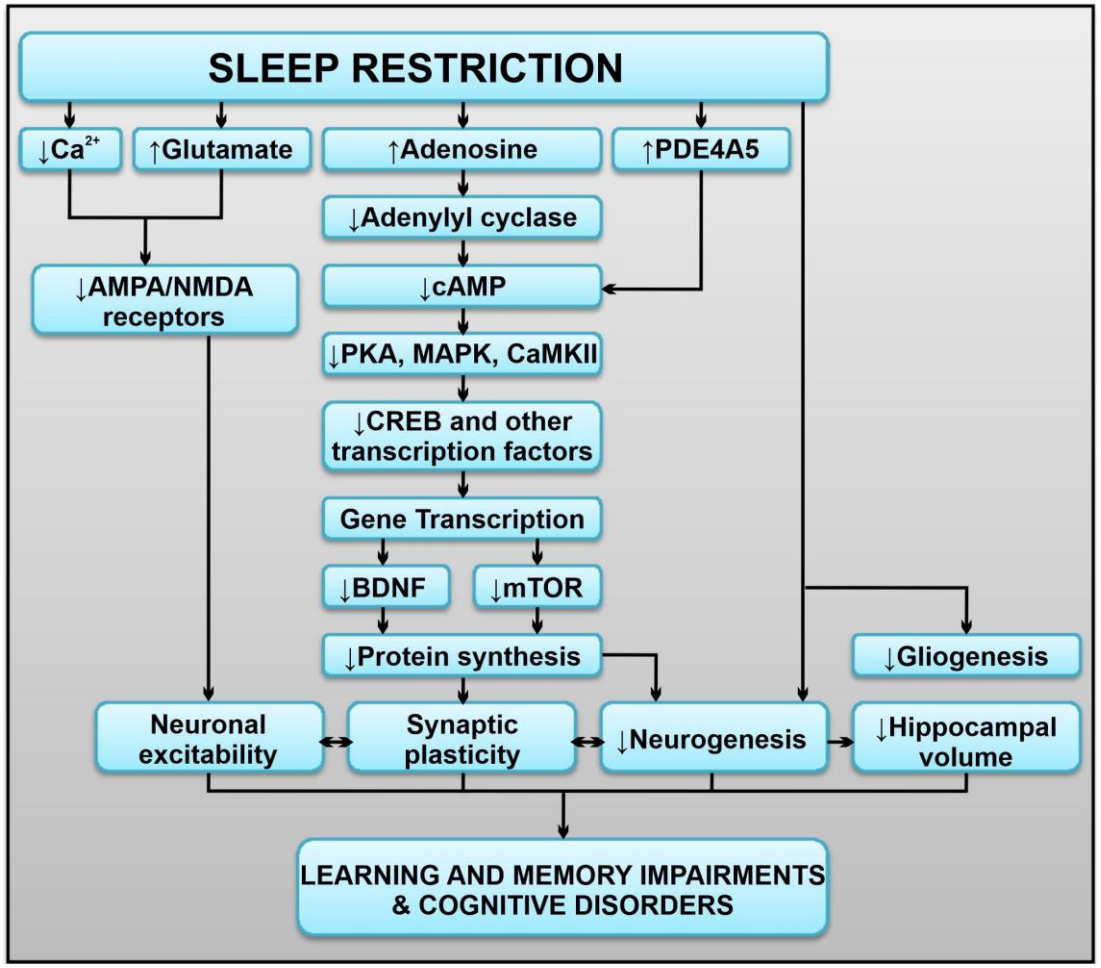
Ferri R, Huber R, Aricò D, Drago V, Rundo F, Massimini M, et al. The slow-wave components of the cyclic alternating pattern (CAP) have a role in sleep-related learning processes. Neurosci Lett 2008;432:228-231.

Ferri R, Drago V, Aricò D, Bruni O, Remington RW, Stamatakis K, et al. The effects of experimental sleep fragmentation on cognitive processing. Sleep Med 2010;11:378-385.

Aricò D, Drago V, Foster PS, Heilman KM, Williamson J, Ferri R. Effects of NREM sleep instability on cognitive processing. Sleep Med 2010;11:791-798.

Drago V, Foster PS, Heilman KM, Aricò D, Williamson J, Montagna P, et al. Cyclic alternating pattern in sleep and its relationship to creativity. Sleep Med 2011;12:361-366.

Sleep Restriction-Induced Impairments in Cognitive Function



Brief sleep deprivation suppresses cAMP-dependent protein kinase A (cAMP-PKA) signaling, which may directly affect glutamate receptor expression and function, but also reduces the activity of transcription factors, such as the cAMP response element-binding protein (CREB).

The latter leads to altered gene expression and protein synthesis, which impairs neuronal plasticity involved in learning and memory formation.

Chronically restricted or disrupted sleep may ultimately suppress neurogenesis and even lead to structural changes in the brain that can contribute to the development of cognitive disorders.

Adapted from Kreutzmann et al., 2015

"Some people talk in their sleep. Lecturers talk while other people sleep."
Albert Camus