from sleep to attention – lecture 6 – April 13, 2012

the function of sleep I - metabolism

a classic indicator of the link between sleep and metabolism - the post-thanksgiving nap

themes –

Brain mechanisms for sleep and attention overlap extensively. For example, the cerebral cortex, where conscious perception is realized, undergoes radical changes in the patterning of synaptic potentials (as revealed by EEG/LFP recordings) between the lowest-attention state (stage ¾ non-REM sleep) and high attention states (waking, REM sleep).

Changes in sleep/wake state and attention are sometimes mediated by groups of neurons that are highly interconnected (brainstem reticular and thalamic reticular neurons).

The classroom can be very hot.

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what do we know so far?

A definition for sleep that can be universally applied is difficult to come by. However, by combining the use of arousal thresholds, behavioral measurements (e.g., amount of movement or posture), and electrophysiological measurements a reasonably complete definition can be attained. Still, we end up with two very different forms of sleep which stand at opposite ends of the spectrum of attention.

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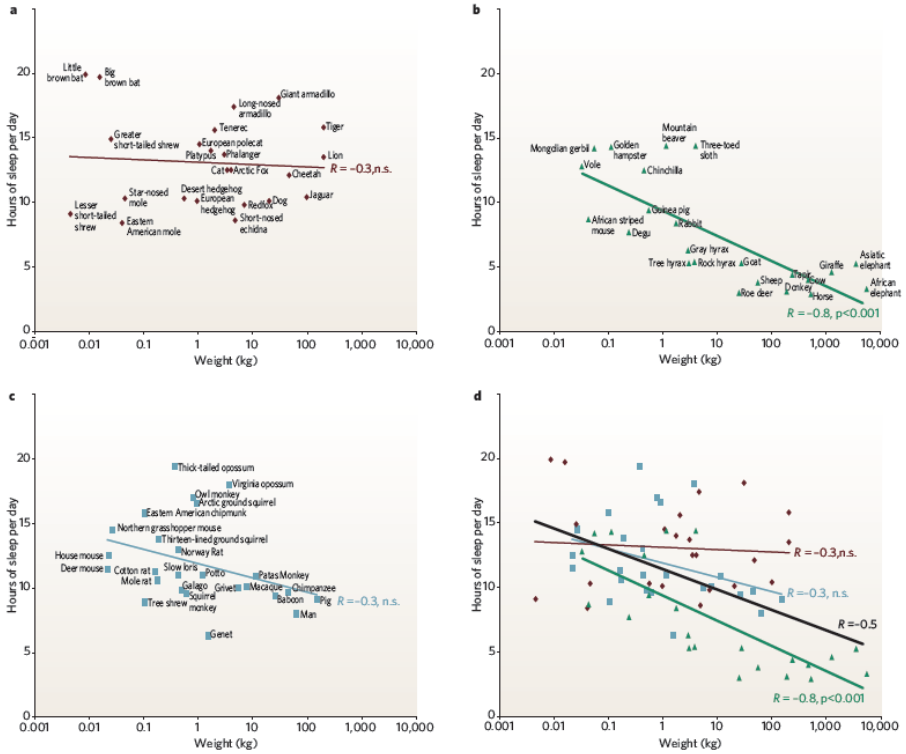
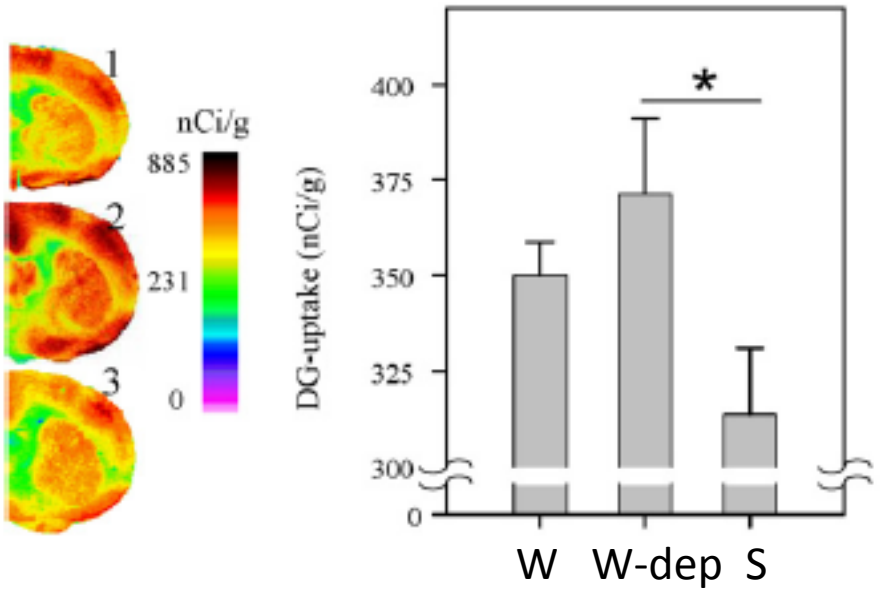
grandmaster snooze – the ferret sleeps approximately 18 hours per day

energy restoration vs. energy conservation

total daily sleep time across mammals is negatively correlated with body size which, in turn, is negatively correlated with metabolism. but…when body size is held constant, sleep time is poorly correlated with metabolism. so…given that body size is positively correlated with energy reserves, perhaps sleep simply enforces energy conservation



non-REM sleep is associated with decreased metabolism as measured by glucose utilization



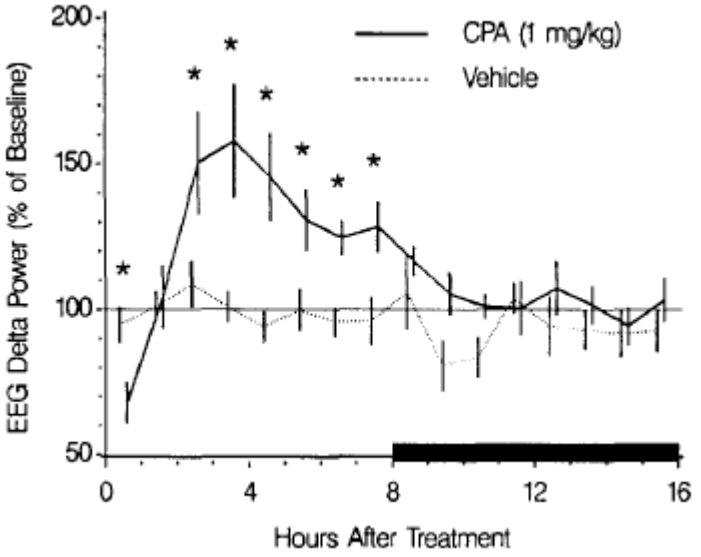
Vyazovskiy et al., Brain Res. Bull., 2008

but…compared to the reduced metabolism associated with a similar-length bout of quiet waking, a full night of sleep yields only a savings of approximately 120 calories (the equivalent of one hot-dog bun)

and…REM sleep, while only 20% of all sleep, is a high metabolism brain state

drugs (CPA) that mimic adenosine increase stage 3/4 non-REM sleep

caffeine acts to block the A1 type of adenosine receptor

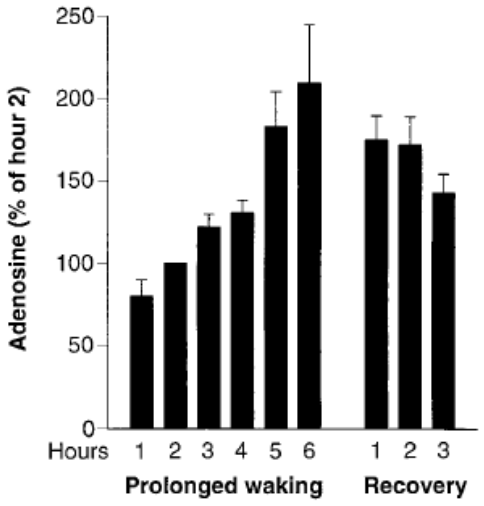


Benington et al., Brain Res., 1995

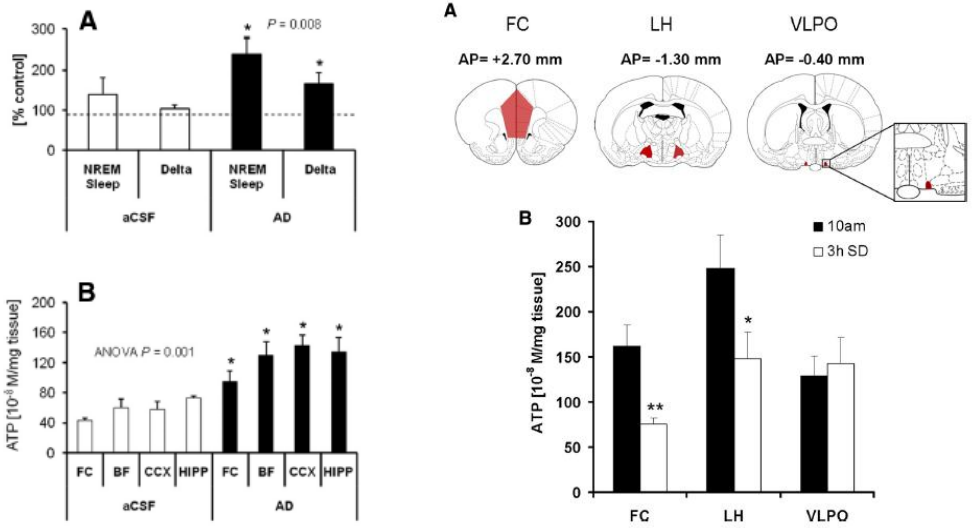
adenosine, the breakdown product of ATP utilization, increases during sleep deprivation

ATP stores increase during non-REM sleep induced by adenosine

sleep deprivation decreases ATP levels in brain



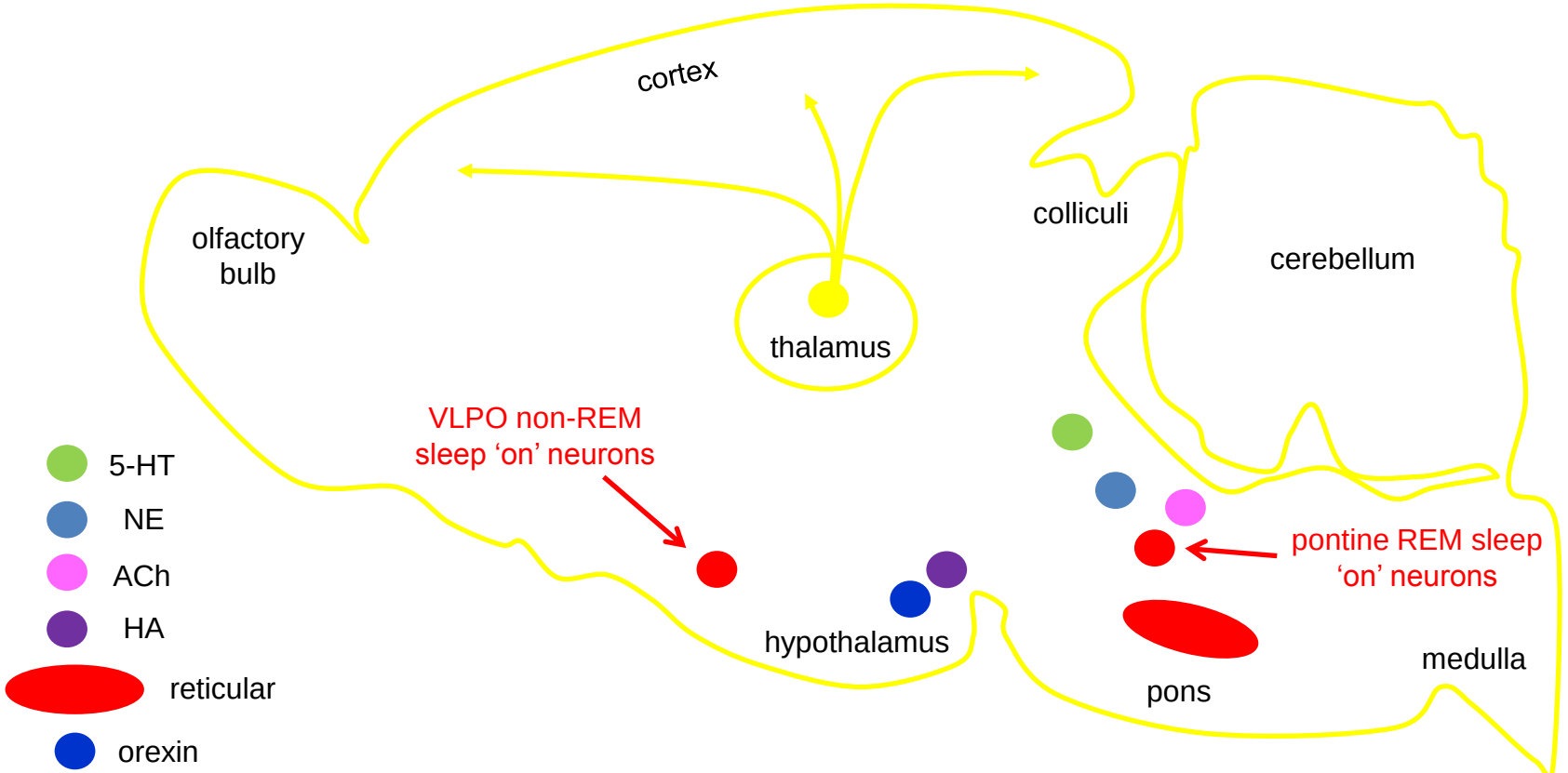
Porkka-Heiskanen et al., Science, 1997

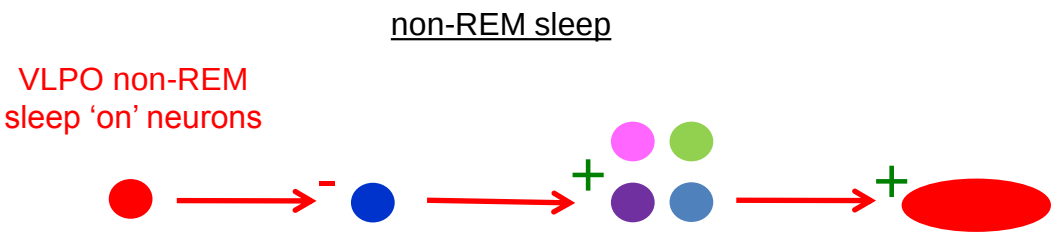


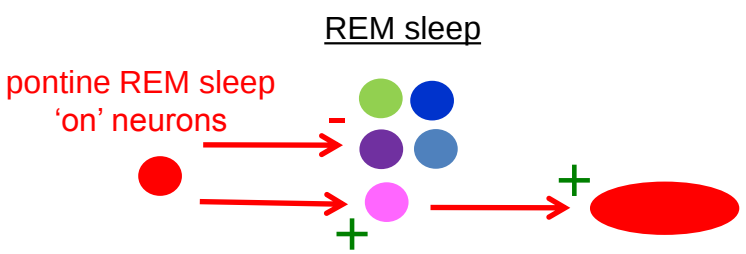
Dworak et al., J. Neuroscience, 1997

Q: What alters the activity of brainstem reticular neurons and neuromodulatory neurons to yield the patterns of thalamic and cortical activity that accompany wake, non-REM sleep, and REM sleep?

A: hypothalamic 'non-REM sleep on' and pontine 'REM sleep on' neurons
A: absence of movement and absence of environmental stimuli



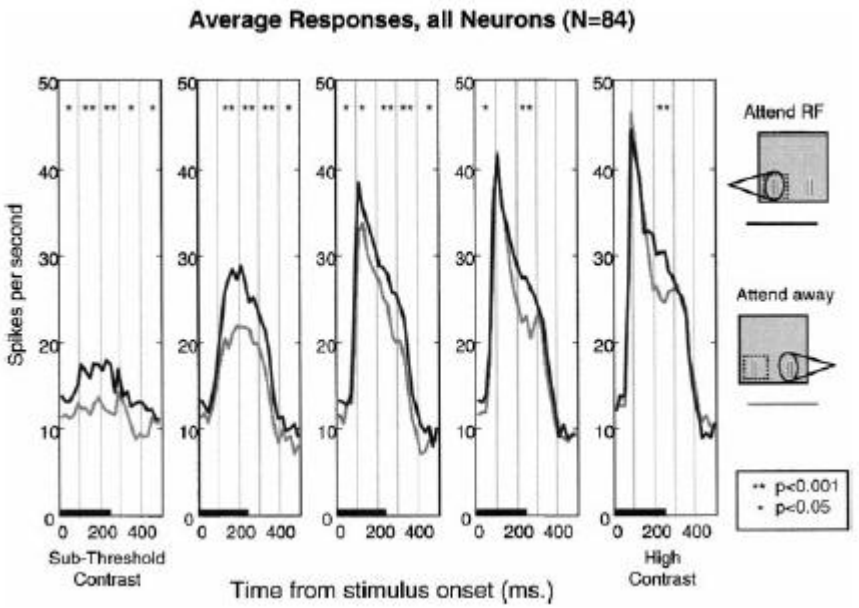




linking metabolism and sleep and attention:

the rate of action potentials is associated with the amount of glucose utilization

attention increases the observed number of action potentials of cortical neurons in response to a stimulus

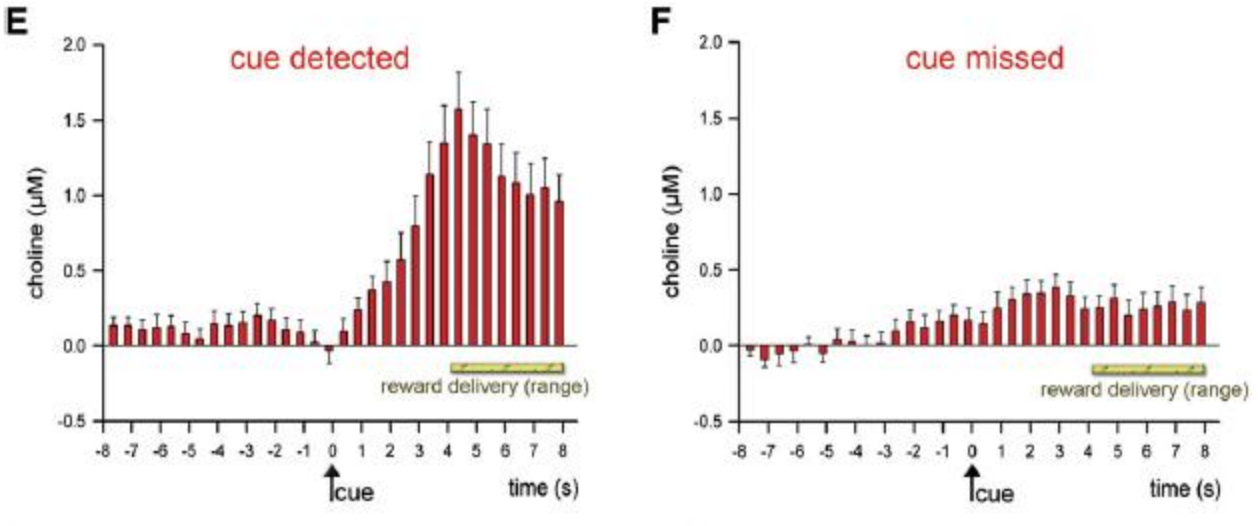


Reynolds et al., Neuron, 2000

linking metabolism and sleep and attention:

the rate of action potentials is associated with the amount of glucose utilization

neuromodulatory neurons which shut down in non-REM sleep are often more active during periods of increased attention in waking – thus, their own activity (and metaboloic) rates across a period of waking could signal a need for sleep



Parikh et al., Neuron, 2007

oddities – still yet to be explained is the fact that long-term sleep deprivation (2-4 weeks) drives rats to increase food intake and metabolism approximately four-fold – at the same time, such rats desire increasingly hotter environments (up to 120 degrees Fahrenheit !)

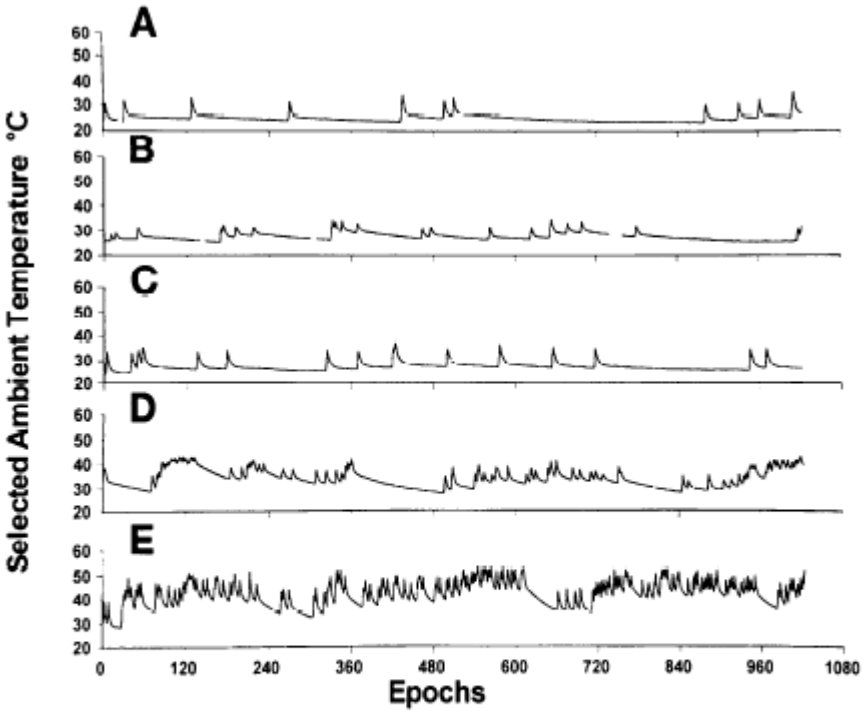


Fig. 1. Ambient temperature (T_{amb}) for 10 h of a representative day during each quarter of sleep deprivation for rats with total sleep deprivation (TSD). Pulses reflect T_{amb} increases after an operant response. *A*: baseline. *B*: 1st quarter (Q1). *C*: 2nd quarter (Q2). *D*: 3rd quarter (Q3). *E*: 4th quarter (Q4).

Shaw et al., Am. J. Physiol., 1997

from sleep to attention – lecture 7 – April 16, 2012

the function of sleep II - development

"you should have never told me horses sleep standing up…it gave me a mental block" – Mister Ed

themes –

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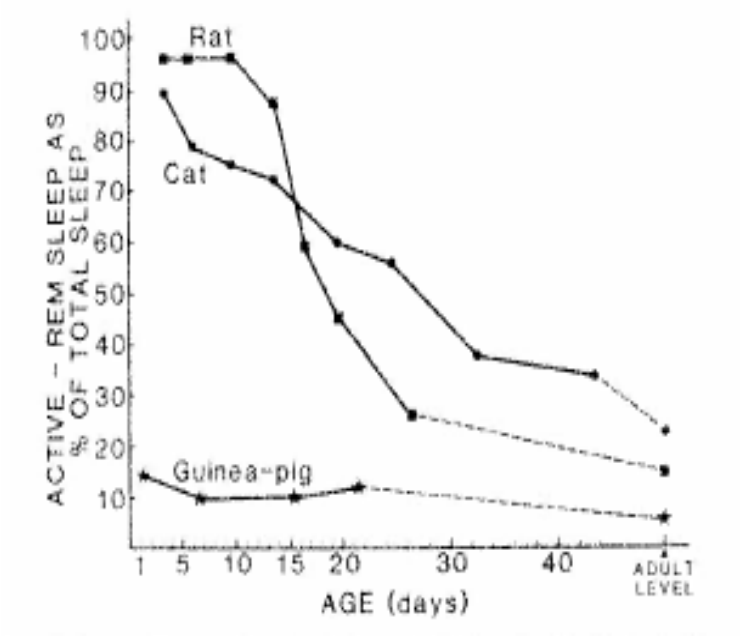
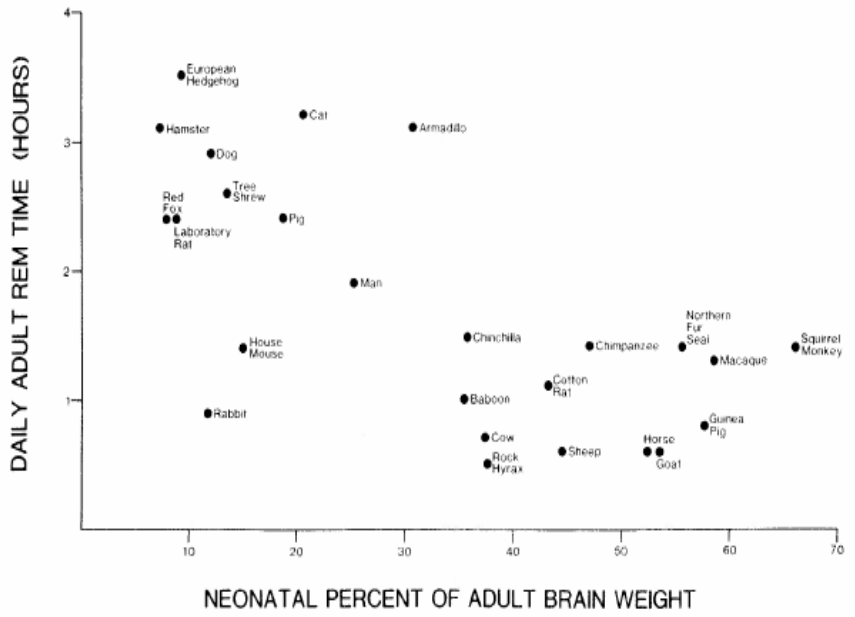
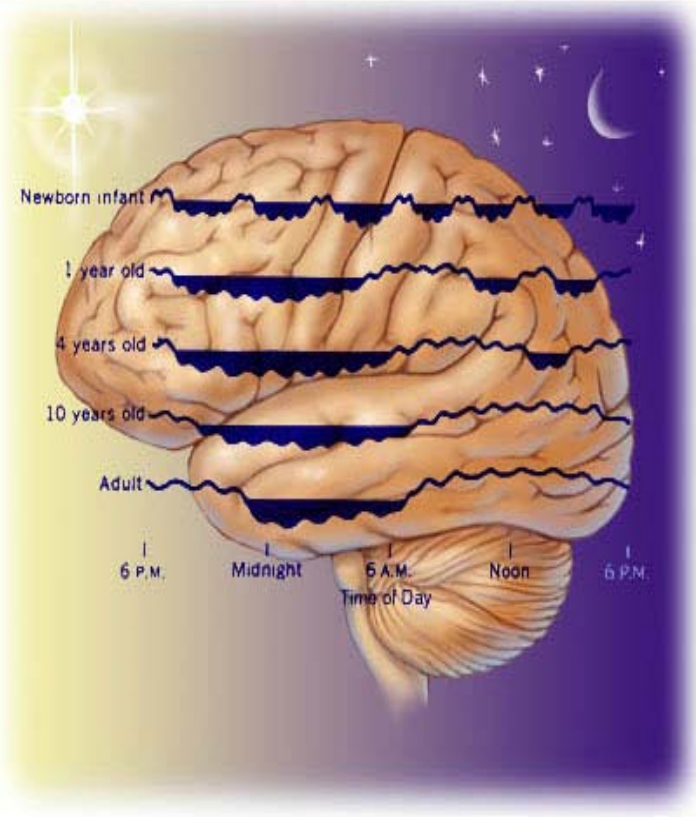
phylogeny: amount of REM sleep during development and adulthood is related to position along a precocial-altricial axis

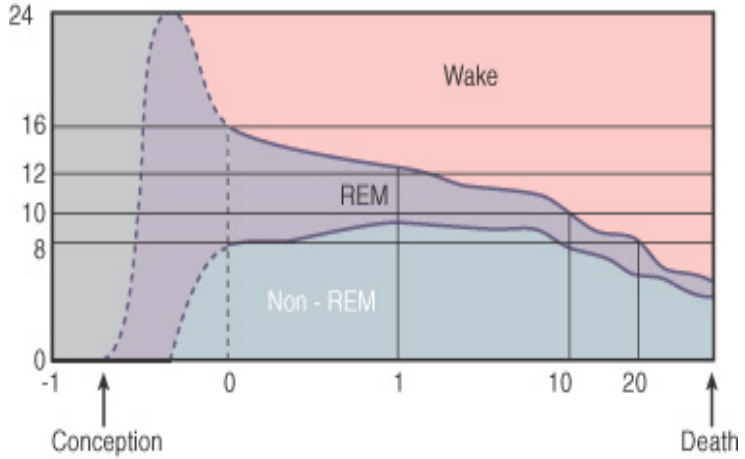




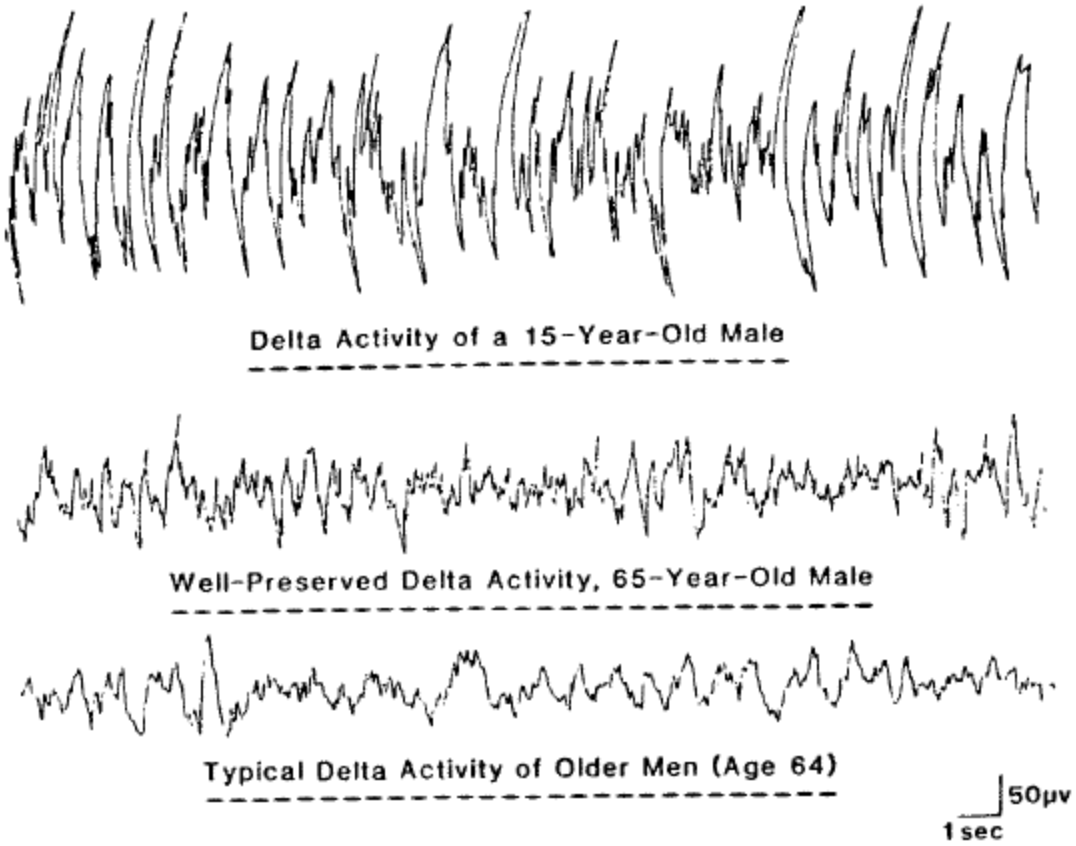
Zepelin (1994). In: Principles and Practice of Sleep Medicine (Kryger MH, Roth T, Dement WC, eds) p69-81. Philadelphia: W.B. Saunders, 1994

ontogeny: timing and amount of different types of sleep changes across the lifespan

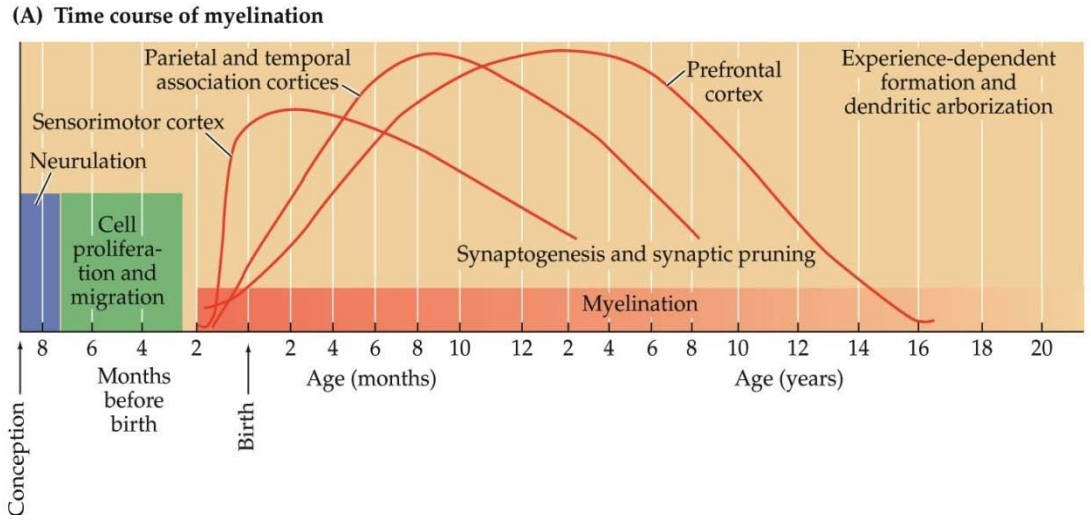


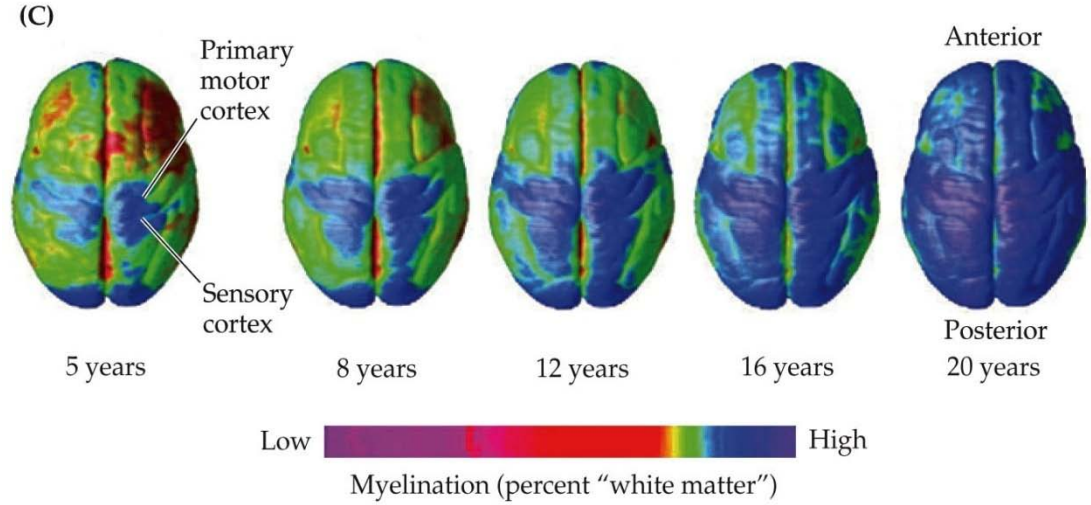


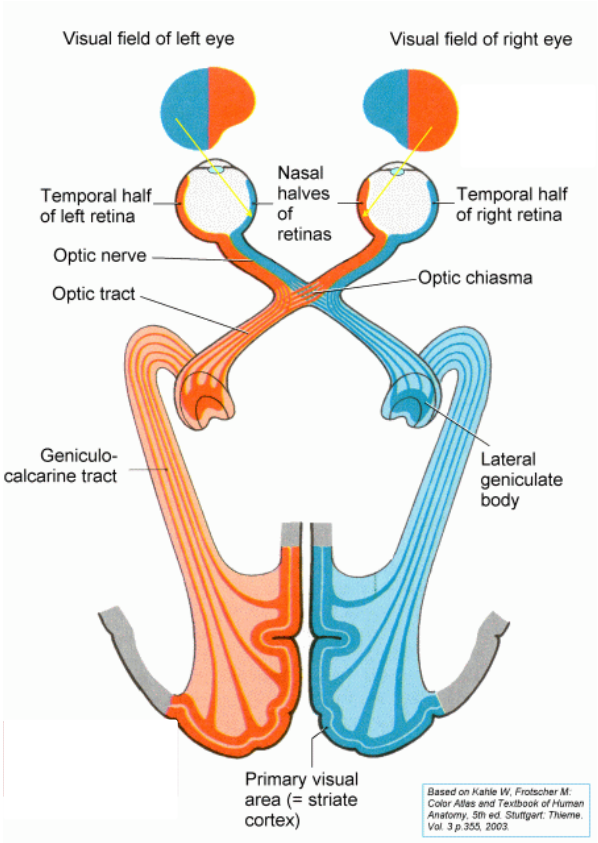
even slow-waves fizzle in old age

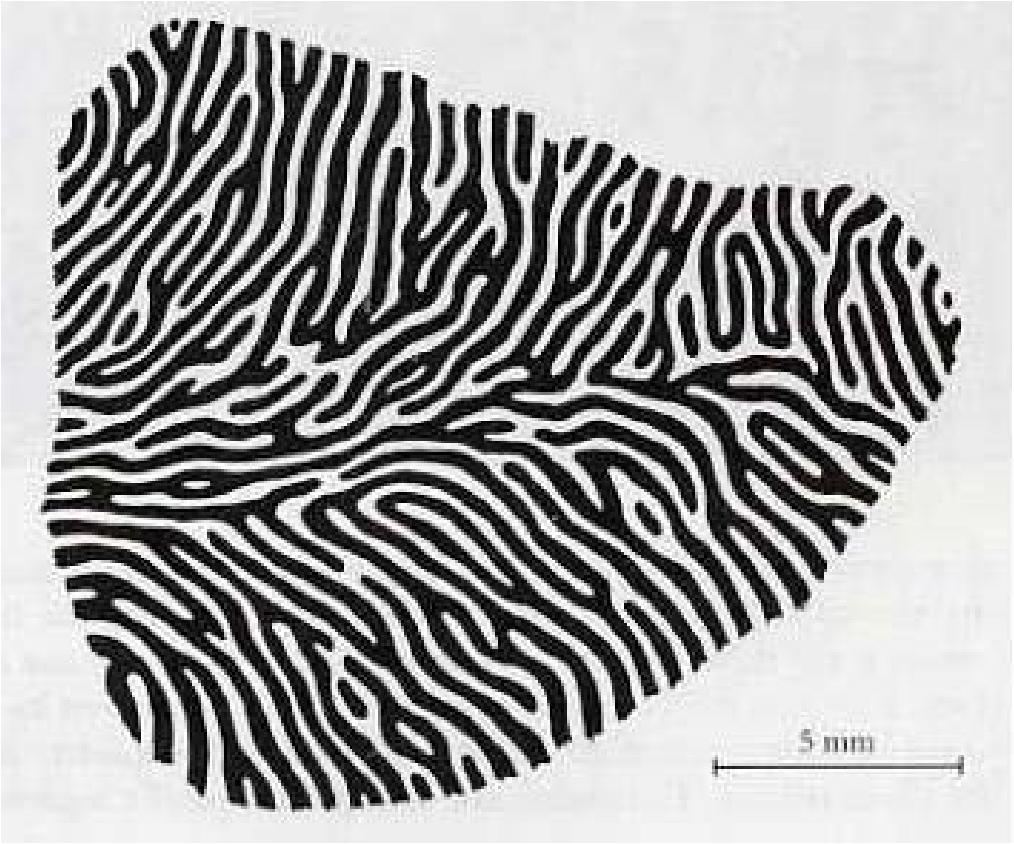


brain maturation patterns somewhat parallel changes in sleep

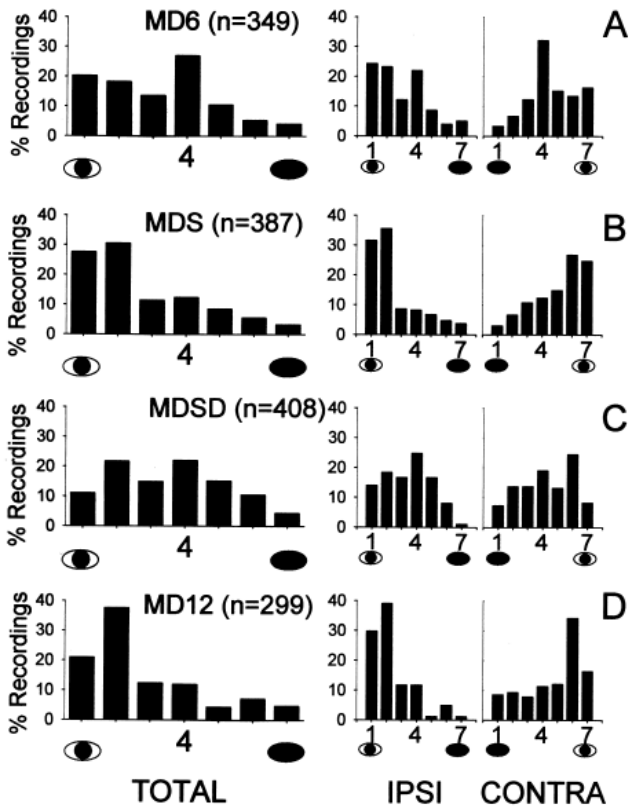


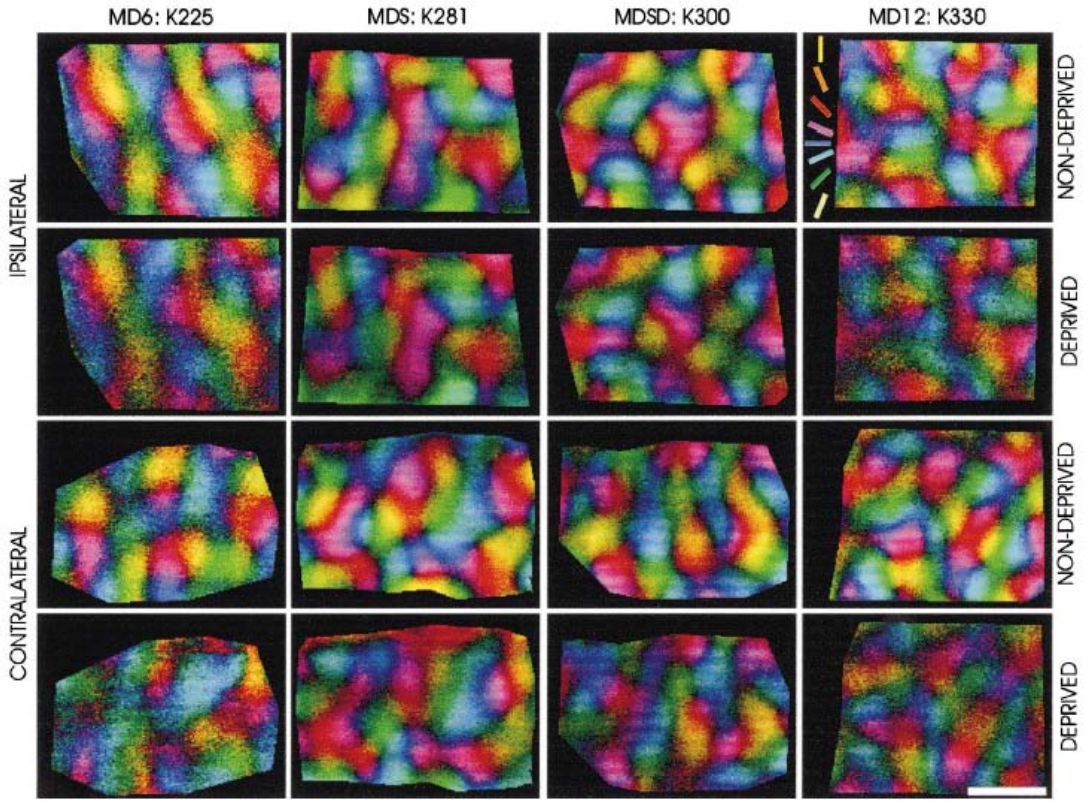



Visual field of left eye
Visual field of right eye
Temporal half of left retina
Nasal halves of retinas
Temporal half of right retina
Optic nerve
Optic chiasma
Optic tract
Geniculo-calcarine tract
Lateral geniculate body
Primary visual area (= striate cortex)
Based on Kahle W, Frotscher M: Color Atlas and Textbook of Human Anatomy. 5th ed. Stuttgart: Thieme. Vol. 3.p.355, 2003.

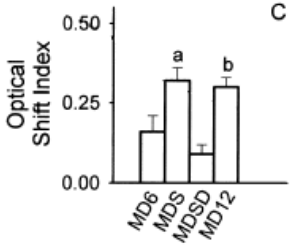

5 mm

sleep enhances changes in degree of ocular dominance in primary visual cortex induced by monocular deprivation





Following 6 hrs of monocular deprivation (MD6), a bias develops wherein more neurons respond more vigorously to input from the non-deprived eye ( ) than to the deprived eye ( ). Undisturbed sleep (MDS) in the dark for six hours after deprivation enhances this effect to the same extent as a full 12 hours of deprivation (MD12), but sleep-deprivation over the same six hours (MDSD) suppresses it.



Frank et al., Neuron, 2001

a newer, and certainly unproven, idea concerning the function of REM sleep as it relates to development

genetic reprogramming

here, activation of cortex by PGO waves is thought to strengthen connections in the brain that are genetically determined and which determine core attributes of the individual's personality, habits and perspectives

connections strengthened, during waking, as a result of interaction with the environment would be depressed during REM sleep

as a result, REM sleep would function to maintain differences among individuals despite extensive similarity in their environmental experience

from sleep to attention – lecture 8 – April 18, 2012

the function of sleep III – learning/memory

themes –

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what do we know so far (page 2)?

Supporting arguments for metabolism as a function of sleep include the increased accumulation of adenosine (an ATP breakdown product) during sleep deprivation, the accumulation of ATP during non-REM sleep, and the effects of adenosine in inhibiting ACH neurons whose activity supports the waking state. Still, the savings in energy associated with sleep seem relatively minor and REM sleep is actually associated with greater utilization of energy.

Supporting arguments for development as a function of sleep are given by the association of neonatal and adult REM sleep increases with the degree to which a species is born with an immature brain.

A role for sleep in learning and memory?

1. **Do REM sleep amounts correlate with intelligence?- arguments from comparison within or across species**

2. **Does sleep deprivation impact recall of learned material?**

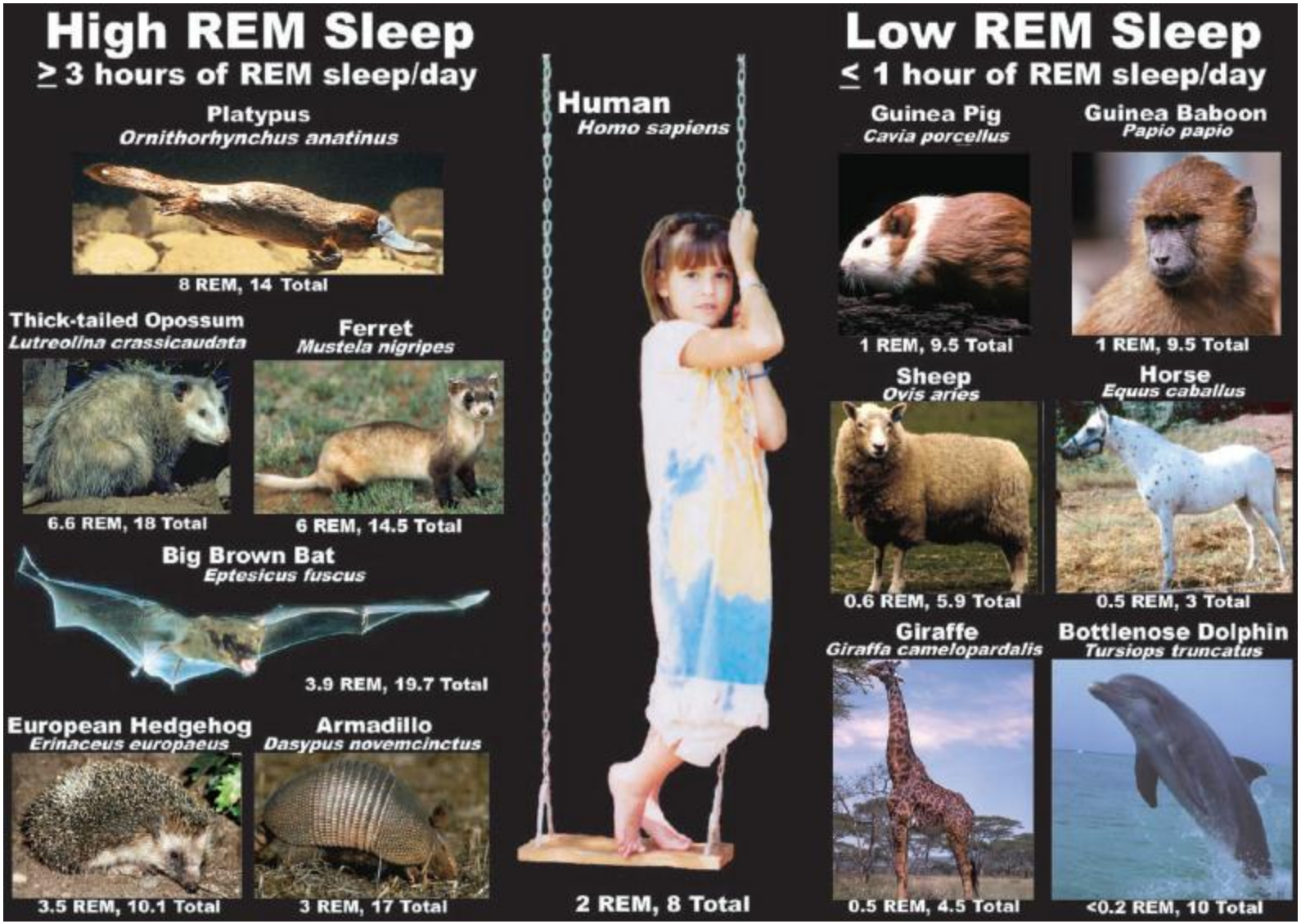
3. **Does the idea make sense neurobiologically? – is material learned during waking recalled in sleep and does the neurobiology of sleep support synaptic modification (the presumed basis for learning).**

4. **non-REM vs. REM sleep**

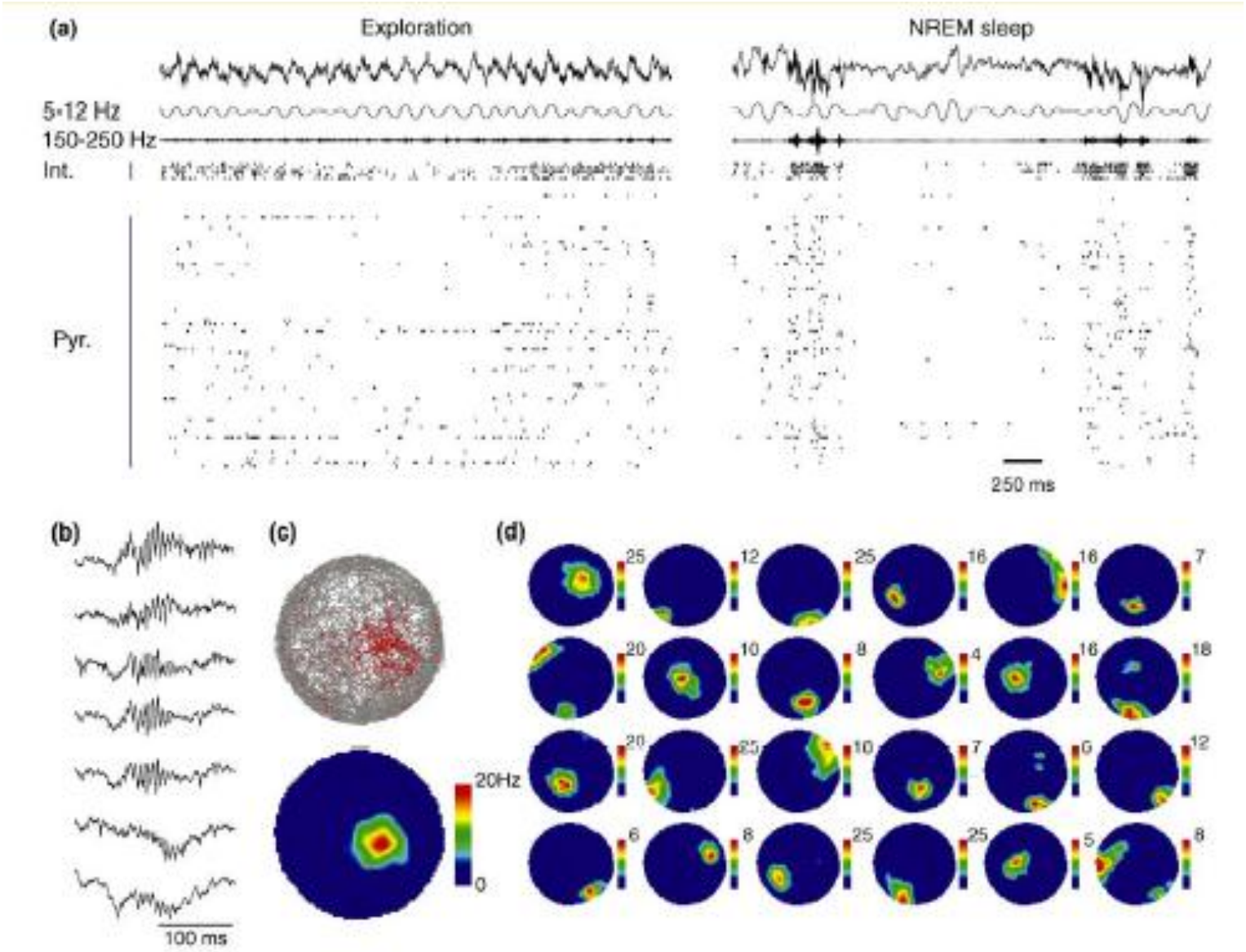
5. **procedural vs. declarative memory**

6. **consolidation vs. transfer vs. generalization**

REM sleep amounts are not related to intelligence either within or across species

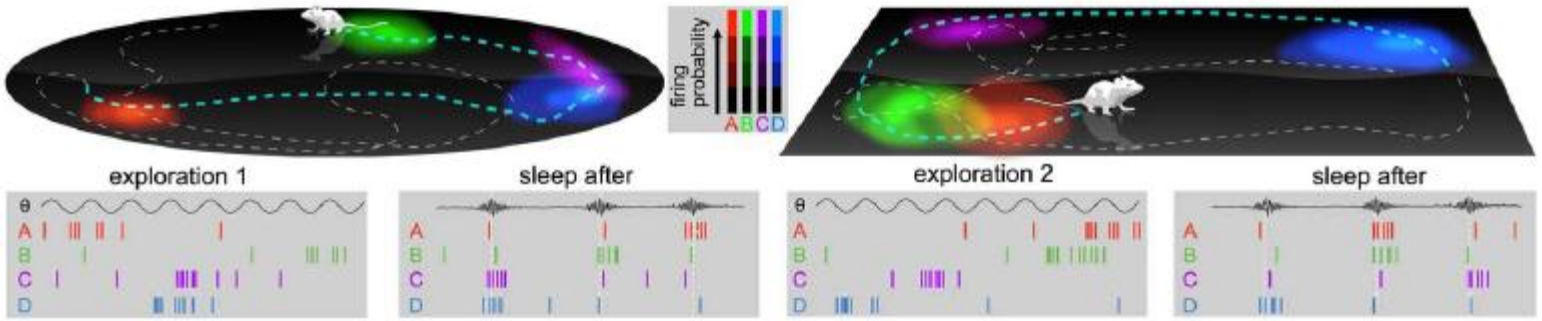


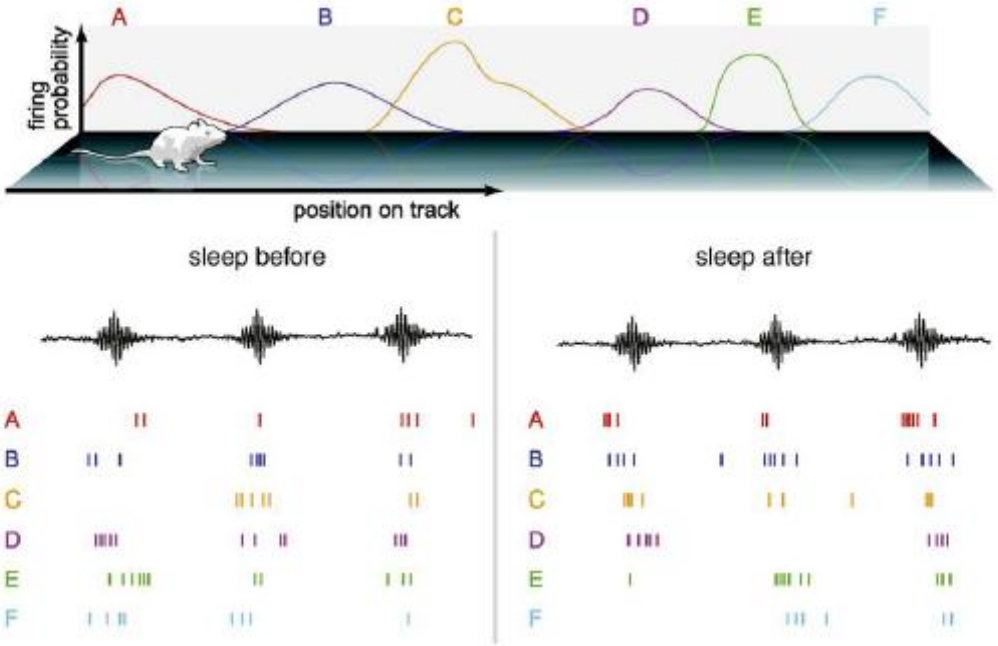
wake vs. non-REM LFPs in hippocampus



O'Neill et al., TINS, 2010

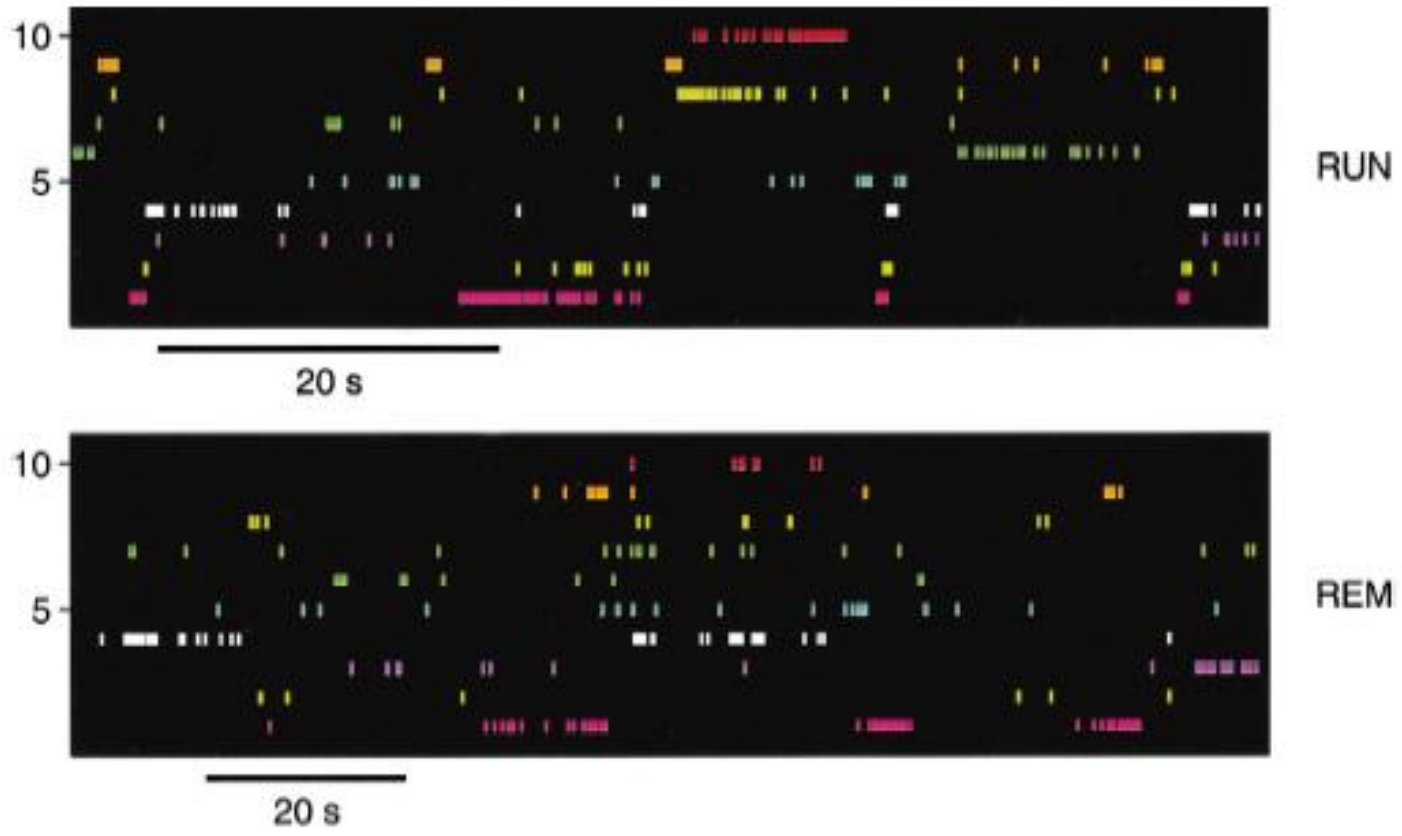
‘attention’ within sleep - sequences of hippocampal activity realized in waking are ‘reactivated’ during subsequent non-REM sleep





O’Neill et al., TINS, 2010

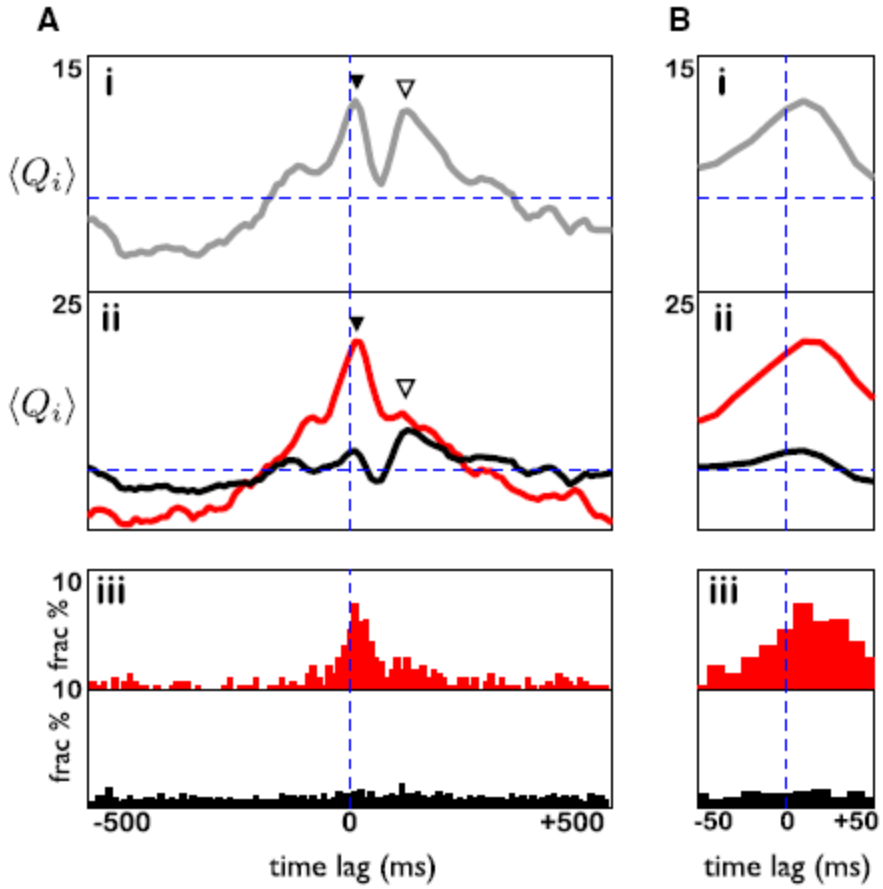
incomplete evidence for sequence replay during REM sleep



reactivation in the hippocampus is associated 100ms later by a burst of activity in the prefontal cortex – this supports the idea that hippocampal memories are transferred to cortex during sleep

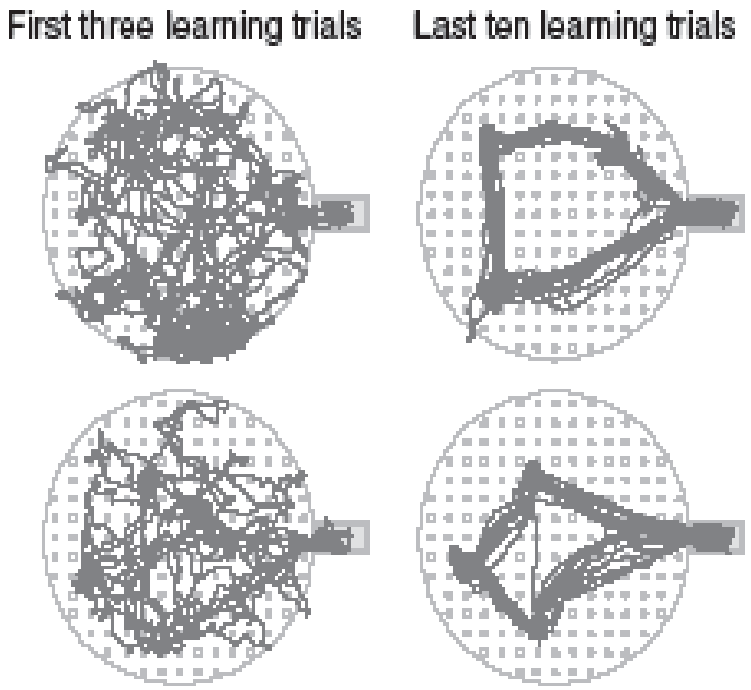
X-axis = time since burst of activity in hippocampus during non-REM sleep

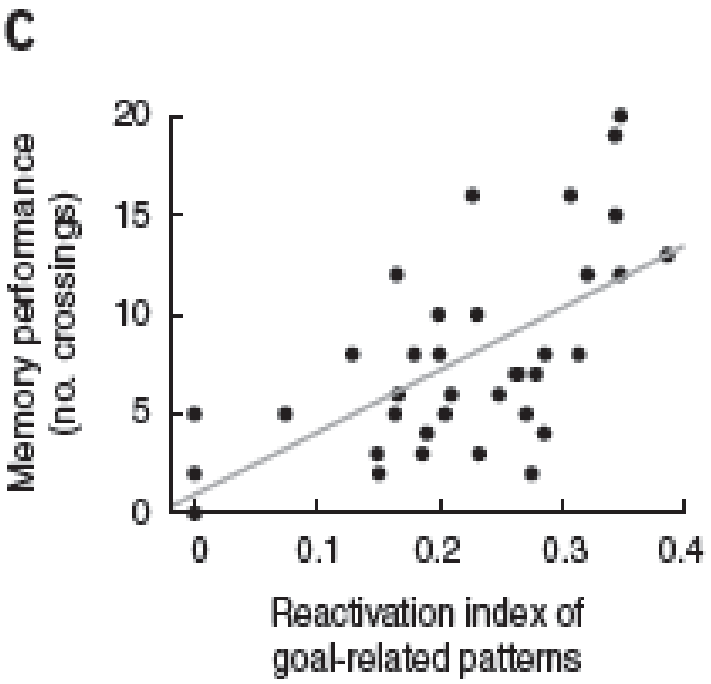
Y-axis = firing rate of all prefrontal cortex neurons (grey), rate of prefrontal cortex neurons with activity related to hippocampal activity during waking (red), and rate of prefrontal cortex neurons without activity related to hippocaampal activity during waking (black)



Wierzynski et al., 2009, Neuron

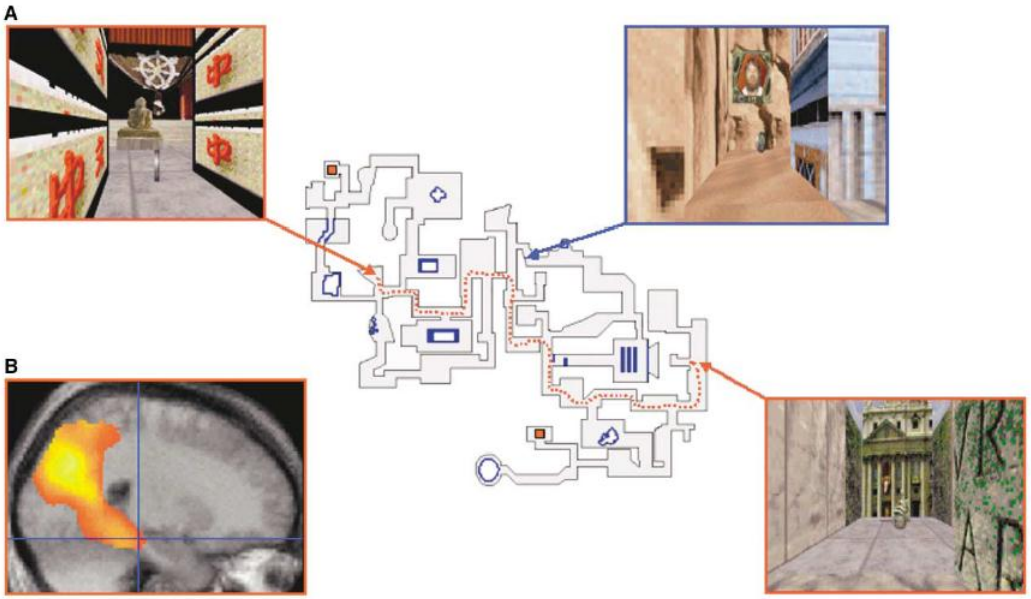
the first decent evidence that sleep reactivation matters





Dupret et al., Nature Neuroscience, 2010

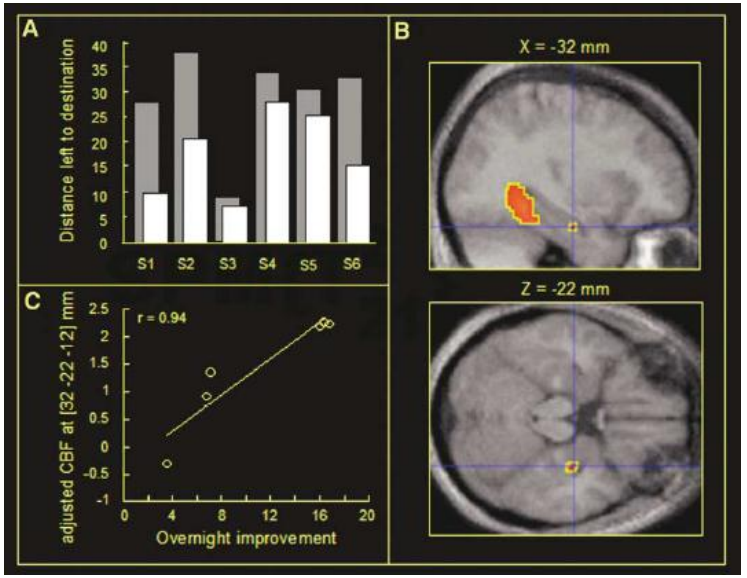
reactivation in humans



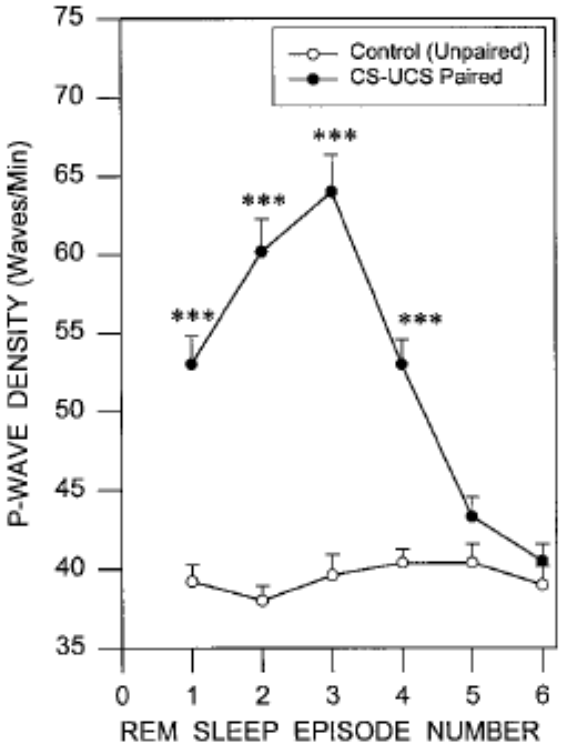
virtual navigation activates hippocampus and parietal cortex

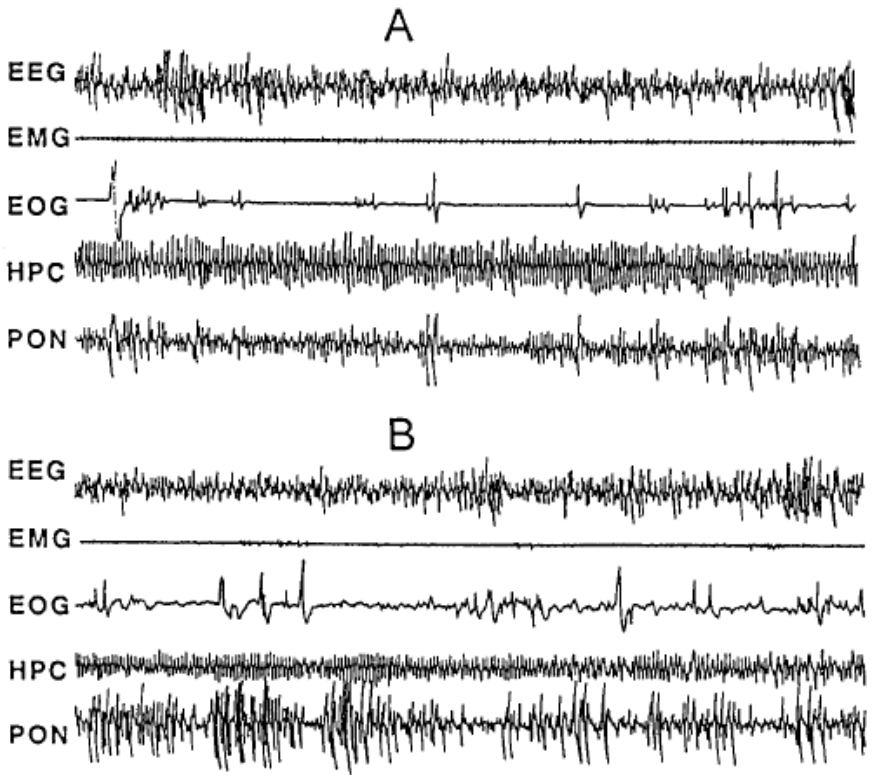
Peigneux et al., 2004 Neuron

post-sleep improvements in navigation correlate with hippocampal activation in sleep



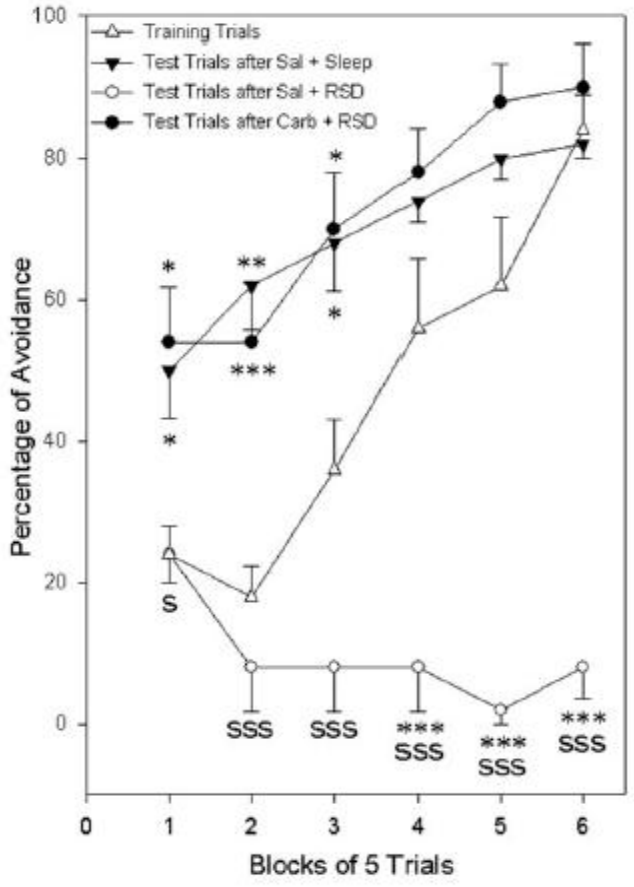
shock avoidance training increases PGO spike density in subsequent sleep

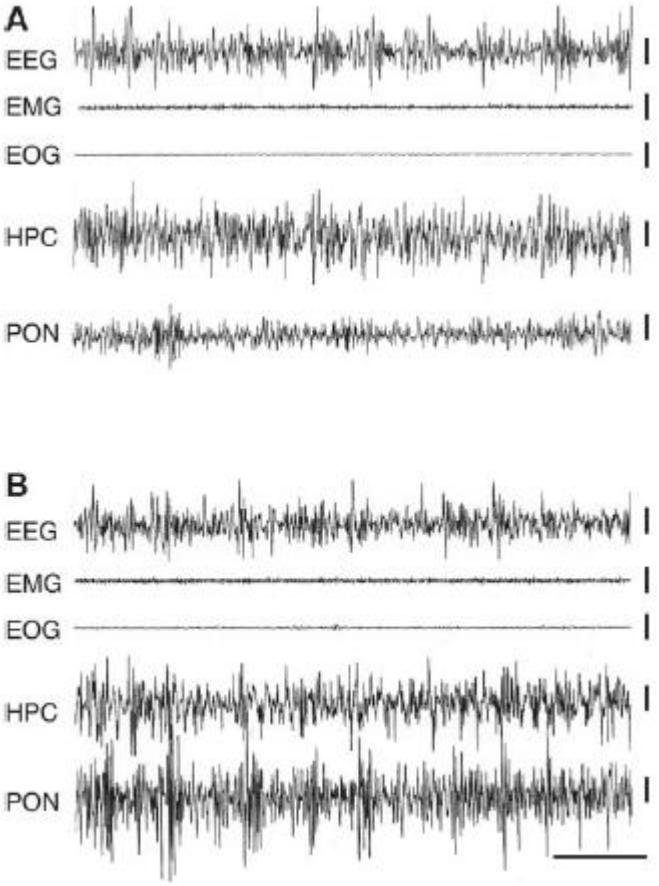




Datta, 2000 J. Neuroscience

REM sleep deprivation impairs two-way avoidance learning, but not if PGOs are induced within non-REM sleep





Datta, 2004 J. Neuroscience

from sleep to attention – lecture 9 – April 20, 2012

the function of sleep IV – cortical homeostasis

themes –

Brain mechanisms for sleep and attention overlap extensively. For example, the cerebral cortex, where conscious perception is realized, undergoes radical changes in the patterning of synaptic potentials (as revealed by EEG/LFP recordings) between the lowest-attention state (stage ¾ non-REM sleep) and high attention states (waking, REM sleep).

Changes in sleep/wake state and attention are sometimes mediated by groups of neurons that are highly interconnected (brainstem reticular and thalamic reticular neurons).

The classroom can be very hot.

REM sleep appears to be associated with a maximal frequency of events associated with reorientation of attention (as in a startle response) while non-REM sleep is associated with a minimal frequency of such events. The frequency of such events in the waking state lies between the two sleep states. Oddly enough, a similar pattern is observed for brain metabolism.

Work attempting to uncover the function of sleep typically takes either a species-comparison approach, a sleep-deprivation approach, or an approach involving recording of specific neurobiological characteristics of sleep.

what do we know so far?

A definition for sleep that can be universally applied is difficult to come by. However, by combining the use of arousal thresholds, behavioral measurements (e.g., amount of movement or posture), and electrophysiological measurements a reasonably complete definition can be attained. Still, we end up with two very different forms of sleep which stand at opposite ends of the spectrum of attention.

At the core of changes in the form of cortical EEG/LFPs that accompany changes in sleep/wake state (wake, non-REM sleep stages 1-4, REM sleep), are changes in the activity of brainstem reticular and thalamic reticular neurons.

Changes in thalamo-cortical activity patterns (as measured through cortical EEG) are brought about by changes in the activity of brainstem reticular neurons and neuromodulatory neurons (ACh, NE, HA, DA, 5-HT, orexin).

Dreams occur primarily during REM sleep when cortical EEG patterns are most like those of waking. Dreams themselves appear to arise from repeated bursts of activity in brainstem reticular neurons that drive bursts of activity in the thalamus and cortex and that resemble responses seen during attentional reorientation in waking (e.g., startle responses). One hypothesis is that dreams reflect the outcome of the cortex attempting to make sense of the noisy inputs it receives in REM sleep.

The lack of conscious experience in non-REM sleep appears to result from the repeated interruptions of cortical activity associated with spindles and slow-waves. Thus, conscious experience (essentially equivalent to that to which we have attention), demands a continuity of cortical activity across time.

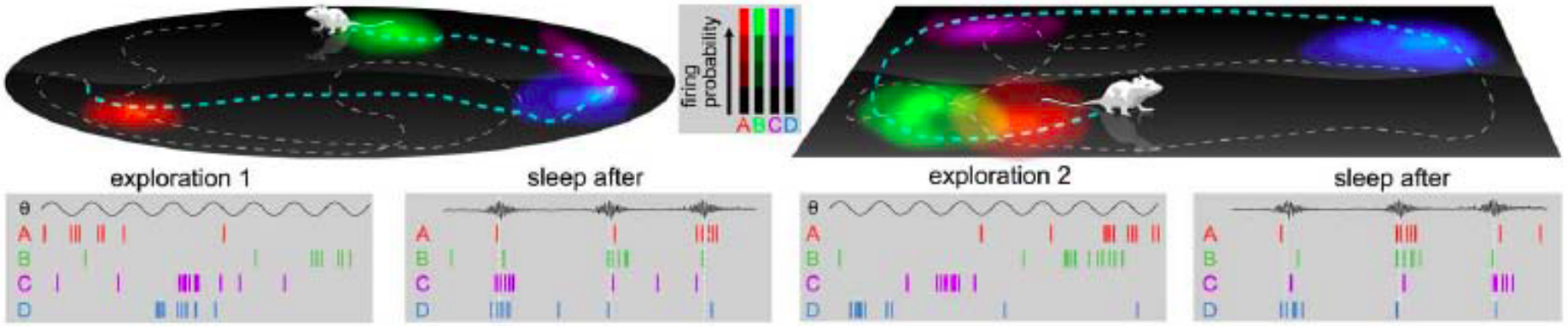
what do we know so far (page 2)?

Supporting arguments for metabolism as a function of sleep include the increased accumulation of adenosine (an ATP breakdown product) during sleep deprivation, the accumulation of ATP during non-REM sleep, and the effects of adenosine in inhibiting ACH neurons whose activity supports the waking state. Still, the savings in energy associated with sleep seem relatively minor and REM sleep is actually associated with greater utilization of energy.

Supporting arguments for development as a function of sleep are given by the association of neonatal and adult REM sleep increases with the degree to which a species is born with an immature brain.

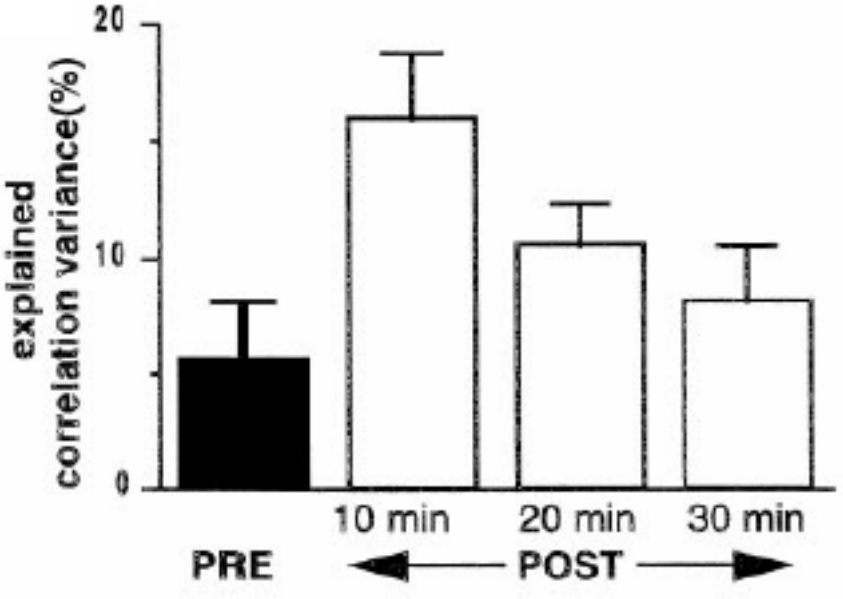
Studies using sleep deprivation as a method to show a relationship between sleep and learning/memory yield inconsistent results and suffer from potential confounds due to stress effects and interference. Recently, however, studies examining brain activity in sleep reveal 'reactivation' of some recent memories during non-REM sleep and suggest that the extent of such reactivation is related to positively related to subsequent tests of memory.

‘attention’ within sleep - sequences of hippocampal activity realized in waking are ‘reactivated’ during subsequent non-REM sleep

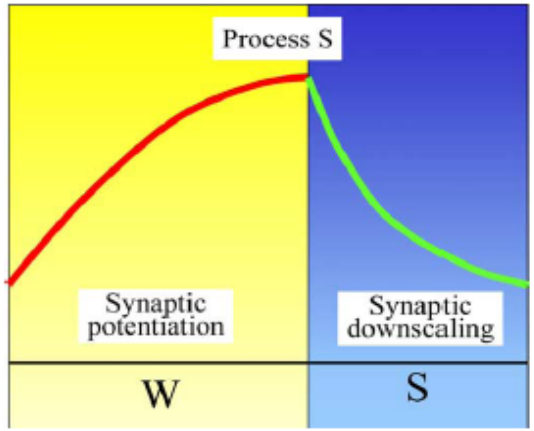


O’Neill et al., TINS, 2010

but…somehow…this effect fades rather quickly during the ensuing sleep period



Kudrimoti et al., J. Neuroscience, 2010

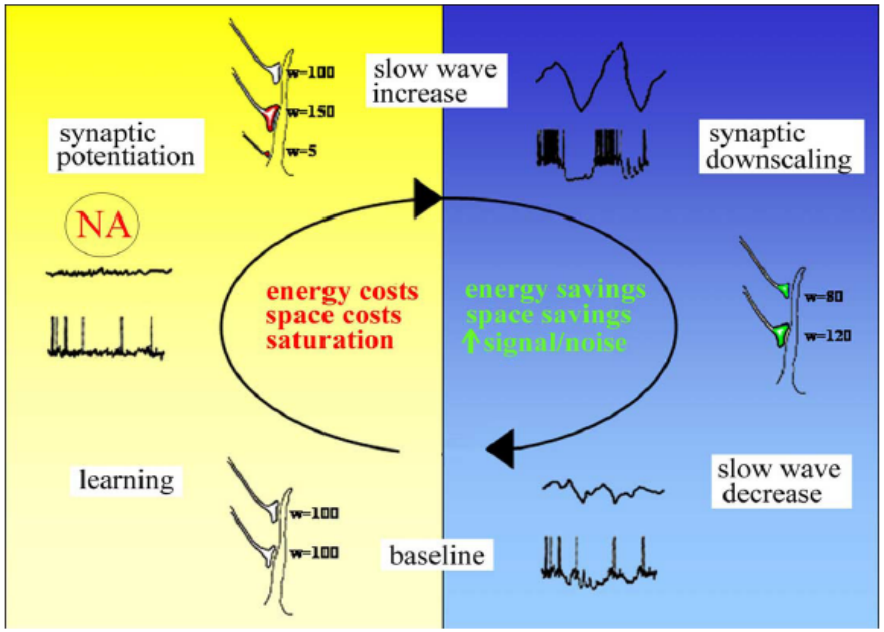


the need for sleep, thought to be necessary because of waking, has been modeled as a process, 'S', which builds during waking and is dissipated during sleep

but…what is process S? – Tononi proposes that it a net increase in strength of synapses during waking and that sleep is required to permit 'synaptic down-scaling'

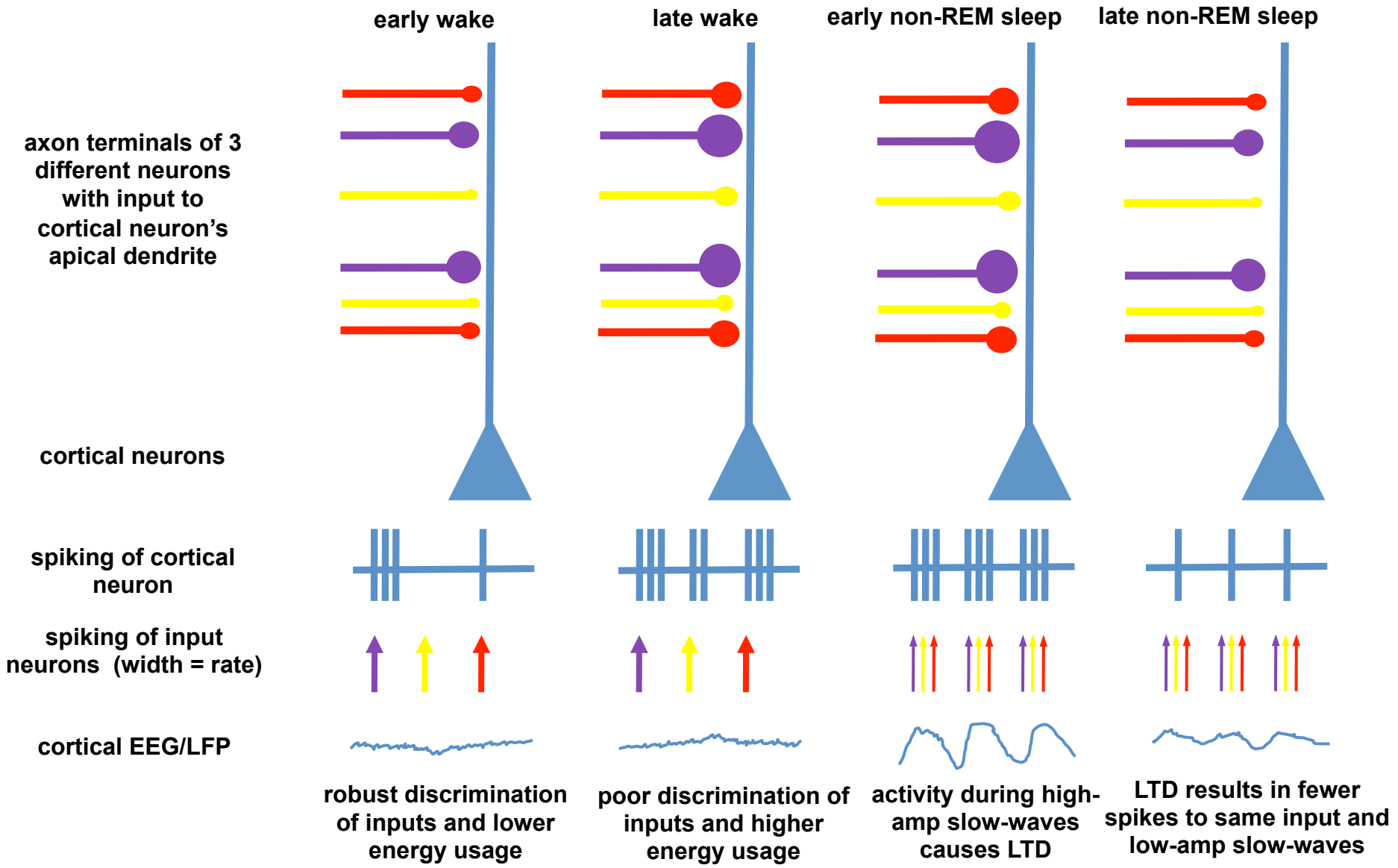
an overall bias of synaptic plasticity toward potentiation during waking is theorized to result in increased energy costs and decreased signal-to-noise ratios for neurons

during sleep, it is proposed that a wholesaled decrementing of synaptic strengths is realized and that this depends critically on the slow-waves associated with non-REM sleep

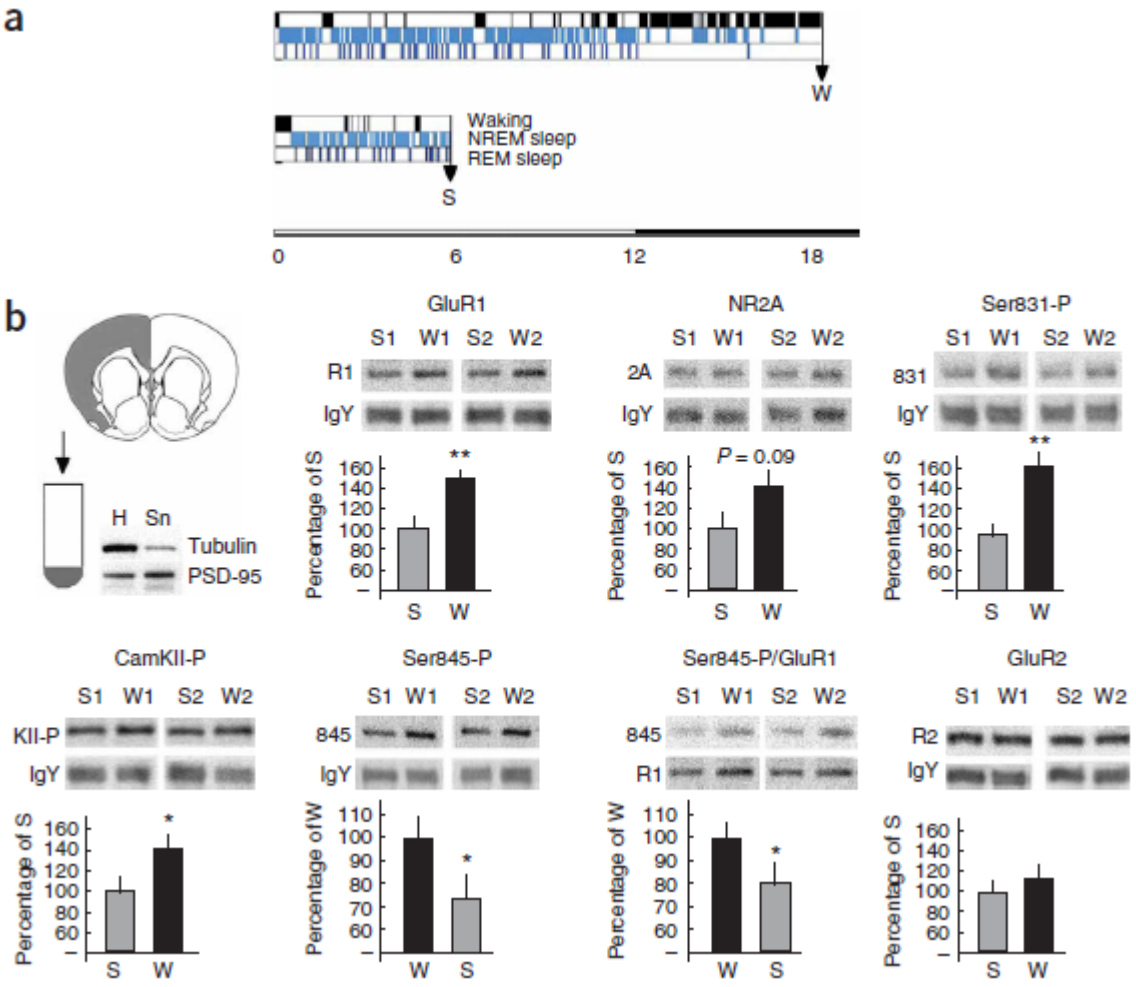


Tononi and Cirelli, Sleep Med. Rev., 2006

cortical homeostasis / synaptic down-scaling as a function for non-REM sleep – the basic notion

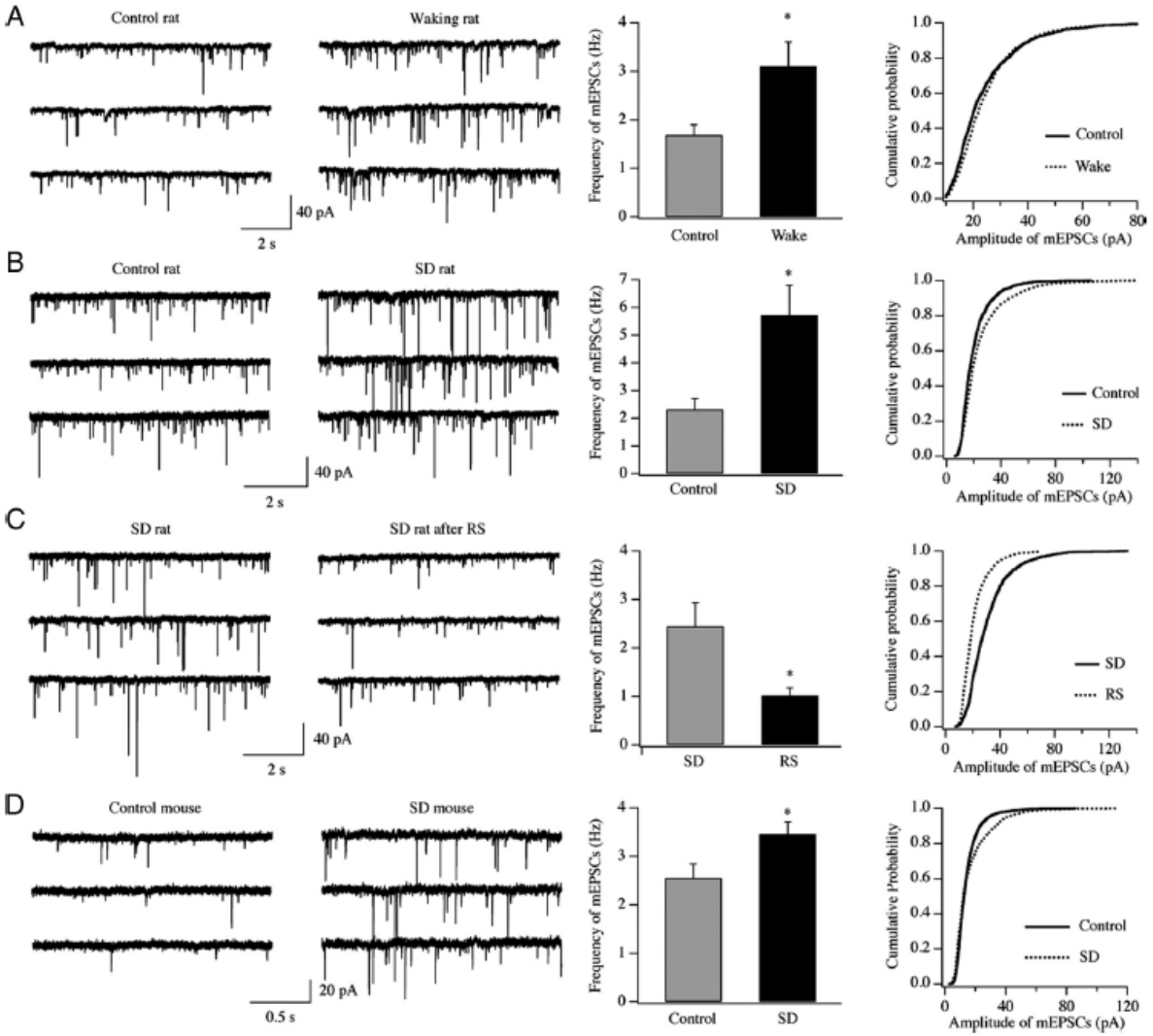


consistent with the 'synaptic down-scaling' / 'cortical homeostasis' theory of sleep function, markers for synaptic potentiation are indeed higher after a bout of waking than after a bout of sleep



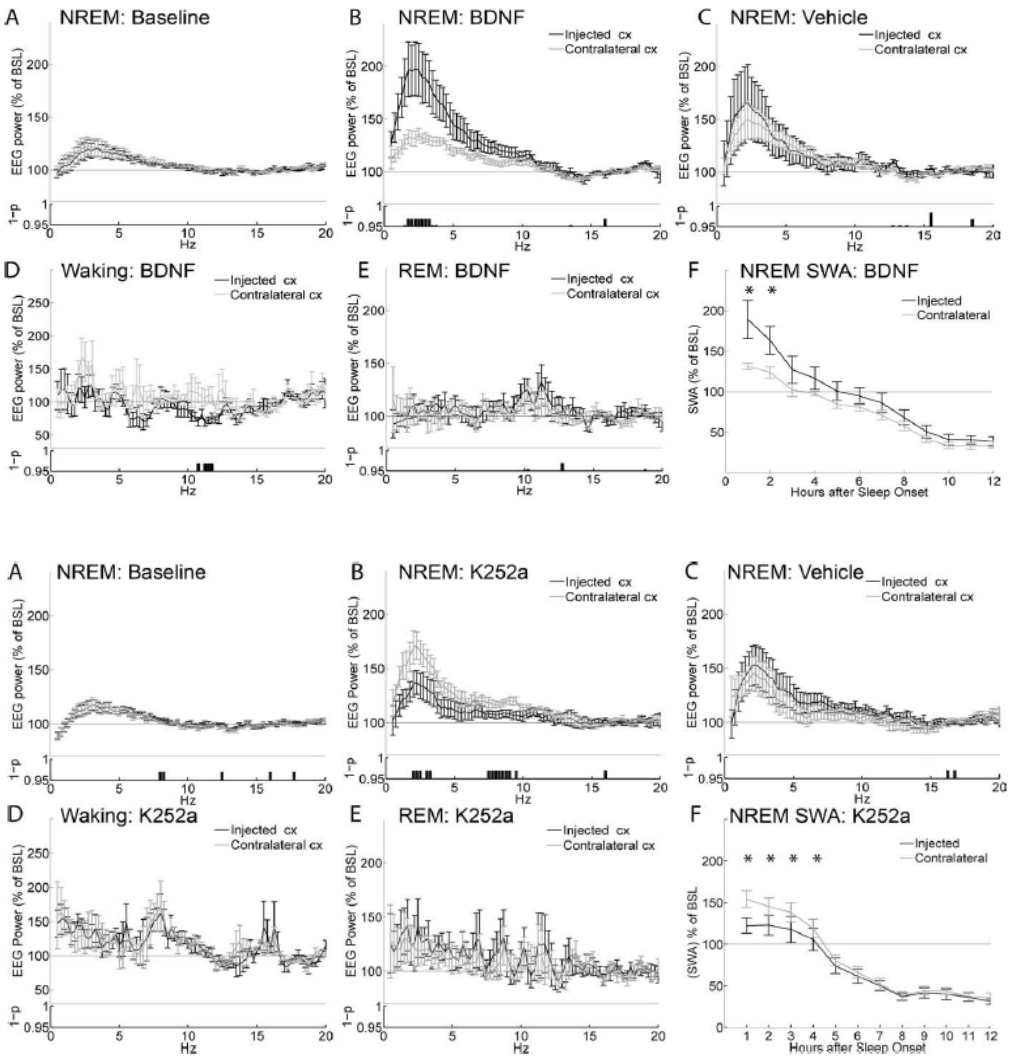
Vyazovskiy et al.,Nature Neuroscience, 2008

consistent with the 'synaptic down-scaling' / 'cortical homeostasis' theory of sleep function, the size and frequency of miniature epsp's are higher following a bout of waking and following sleep deprivation



Liu et al.,J. Neuroscience, 2010

consistent with the 'synaptic down-scaling' / 'cortical homeostasis' theory of sleep function…cortical microinjection of BDNF, which can increase synaptic strengths, results in subsequent increases in slow-wave activity within non-REM sleep



Faraguna et al.,J. Neuroscience, 2008