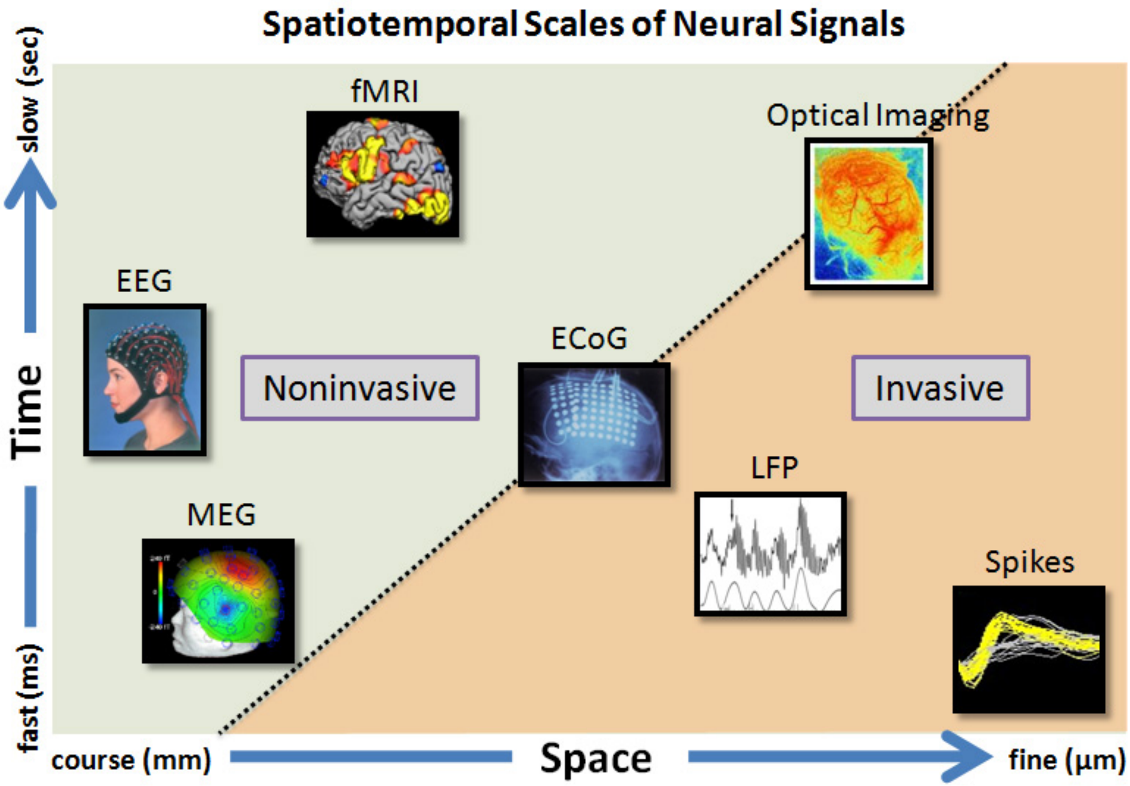
Jan Wikgren, University of Jyväskylä

Animal models of cognition

1. Basic methodology
2. Learning and memory in general
3. Hippocampal oscillations and learning

Neural recordings

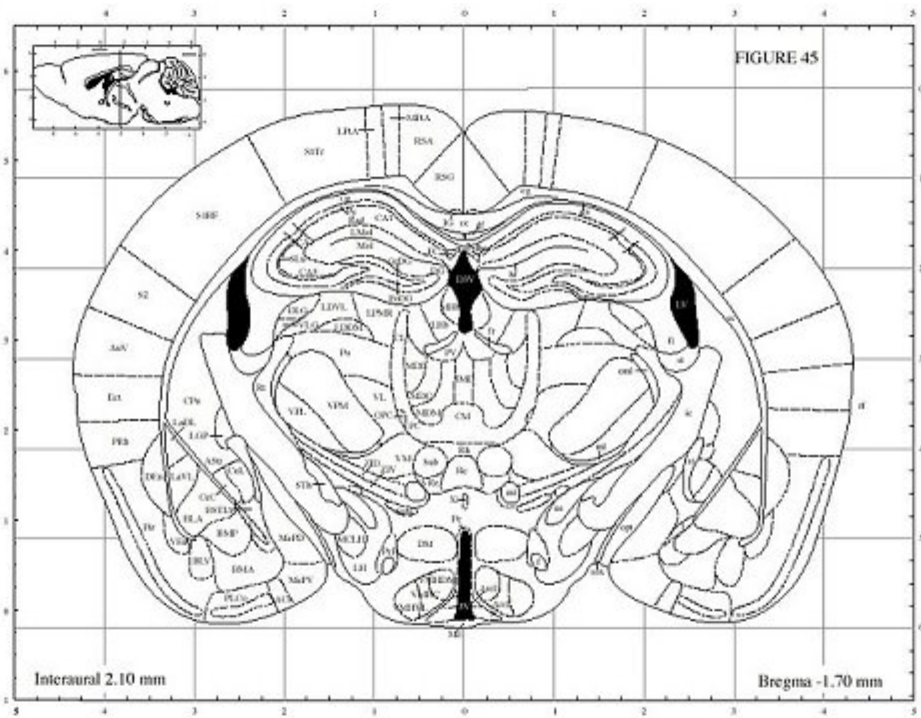


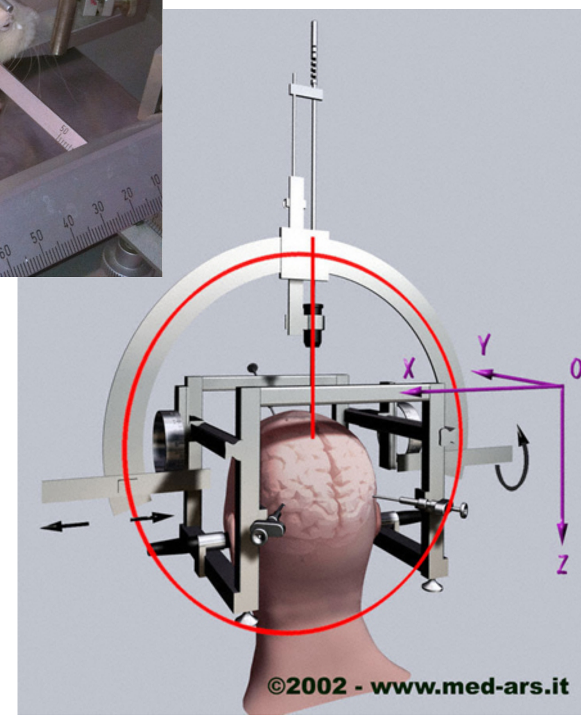
- In non-invasive recordings, there is a trade-off between spatial and temporal resolution
- Intracranial recordings do not have such a shortcoming
- …(although there is a risk of not seeing the forest from the trees)

Intracranial recordings

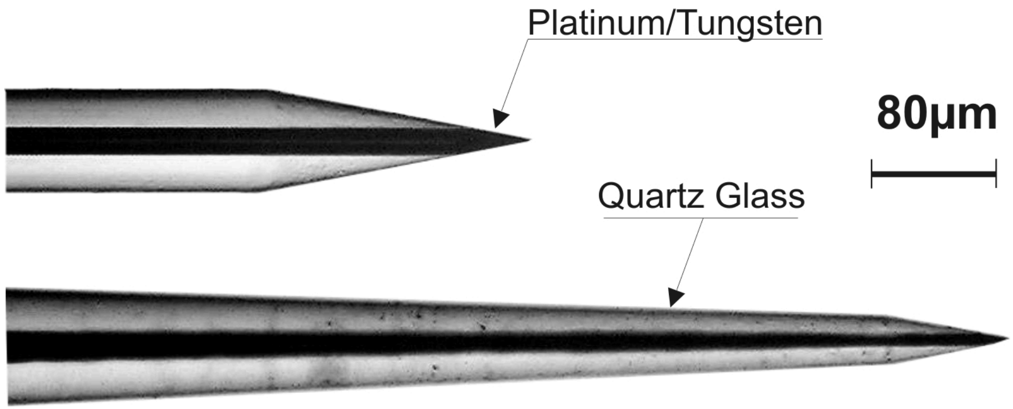
- Done also in humans (how, when?) but obviously mostly in animals (why?)

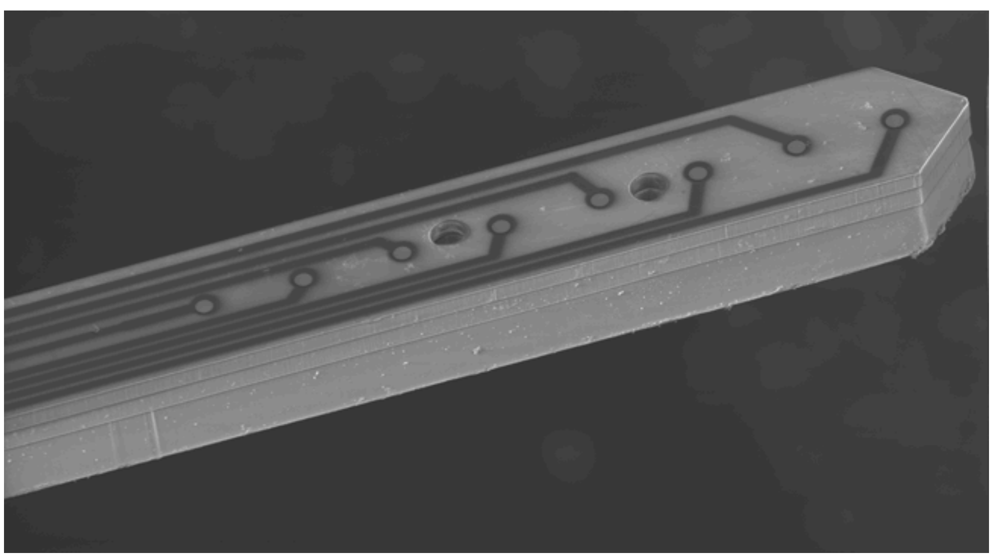
Stereotaxic frame

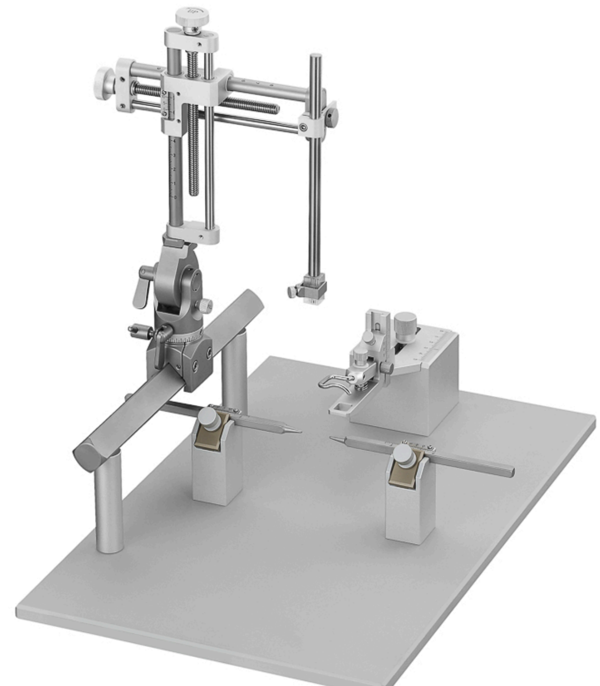




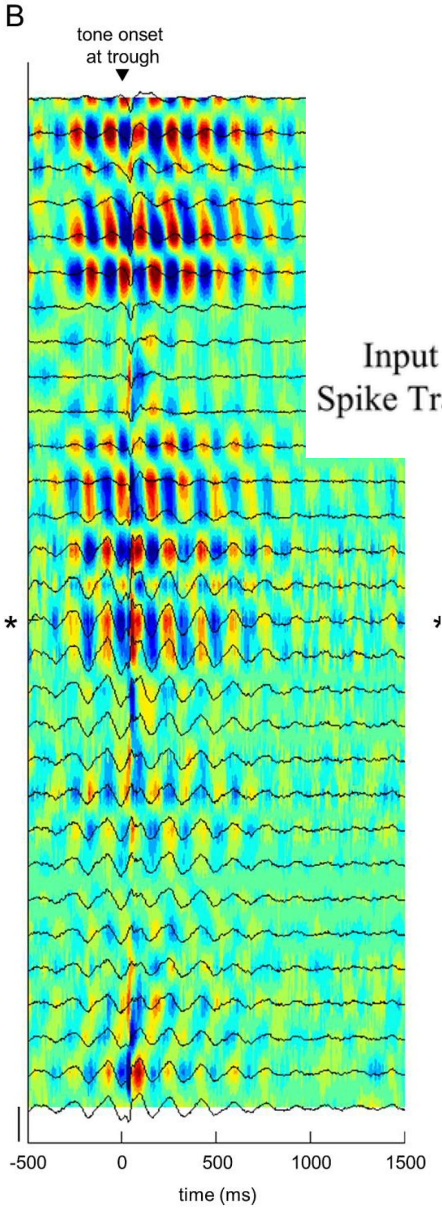
Electrodes

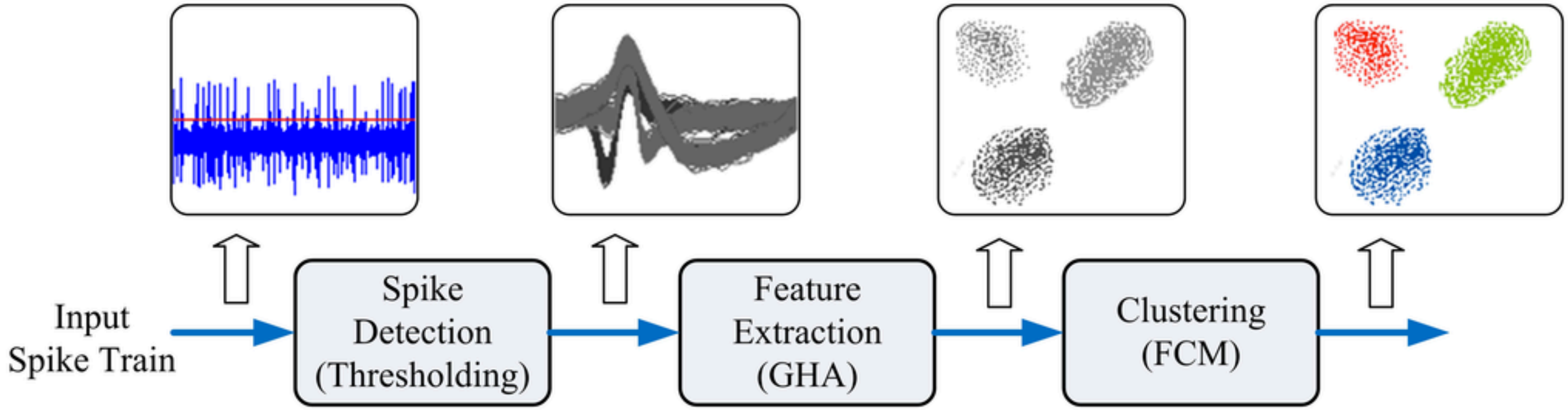






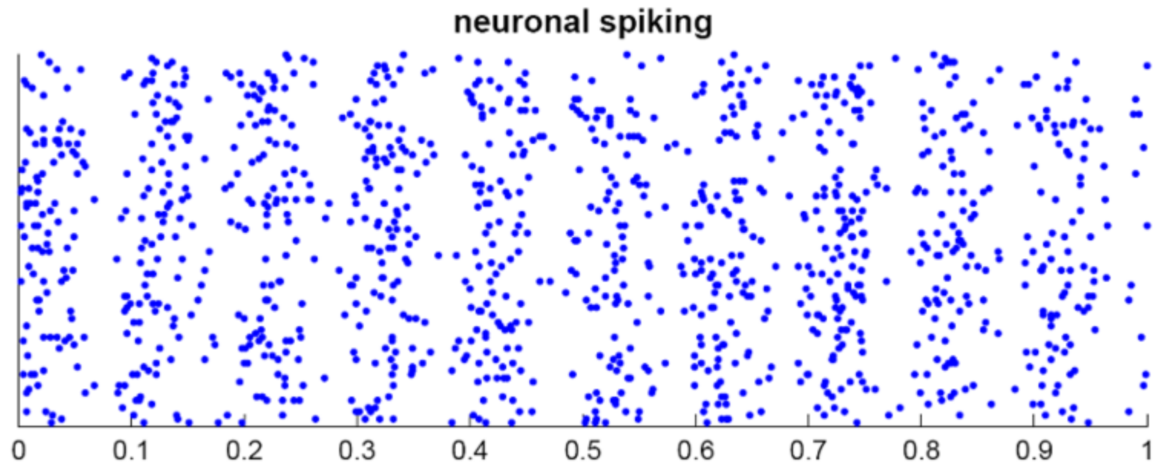
Recordings

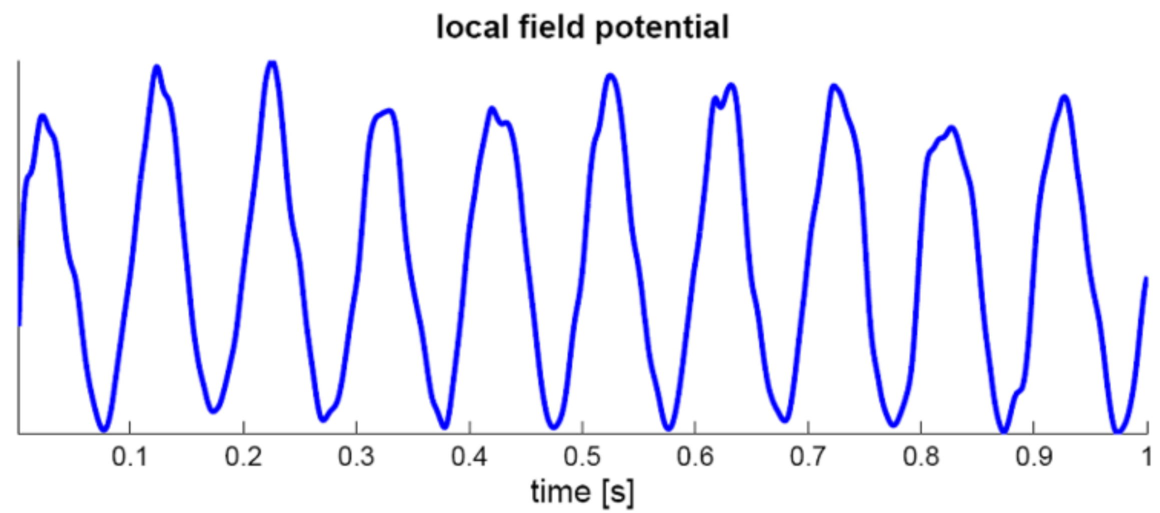




- Oscillations (EEG-like local field potentials, LFP)
- Multi-unit activity
- Single-unit activity

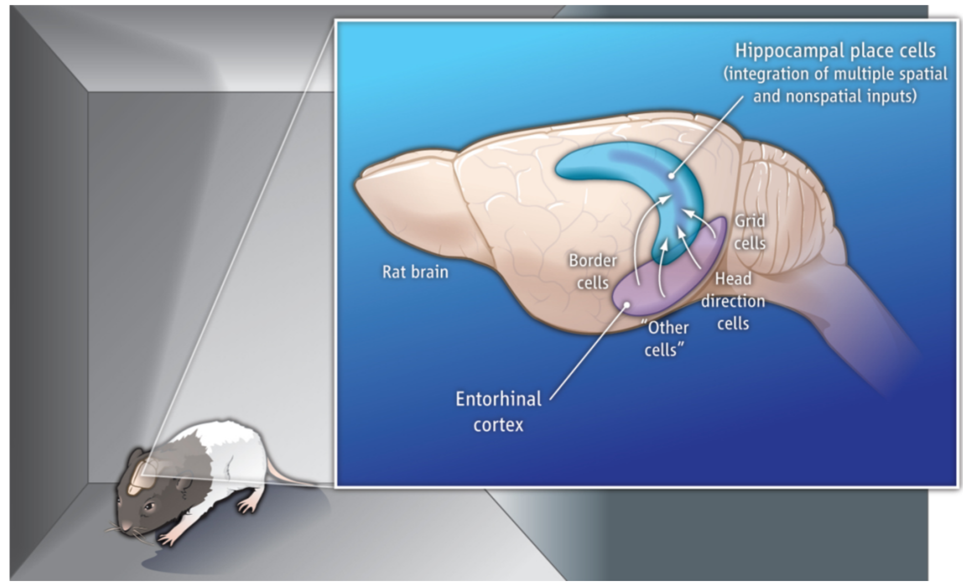
Neurophysiological recordings



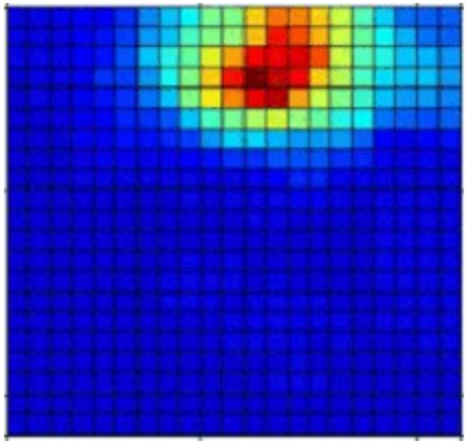


Neurophysiological studies on the hippocampus

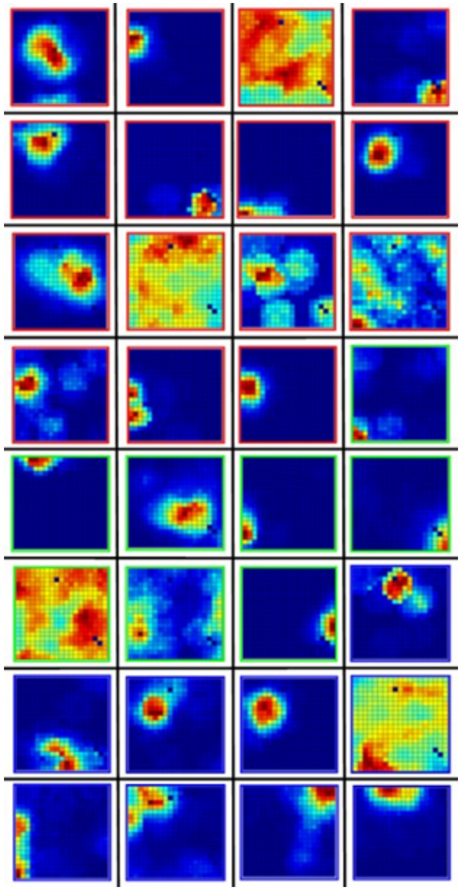
Neural activity can be recorded in an awake, behaving animal



Place cells (O'Keefe)

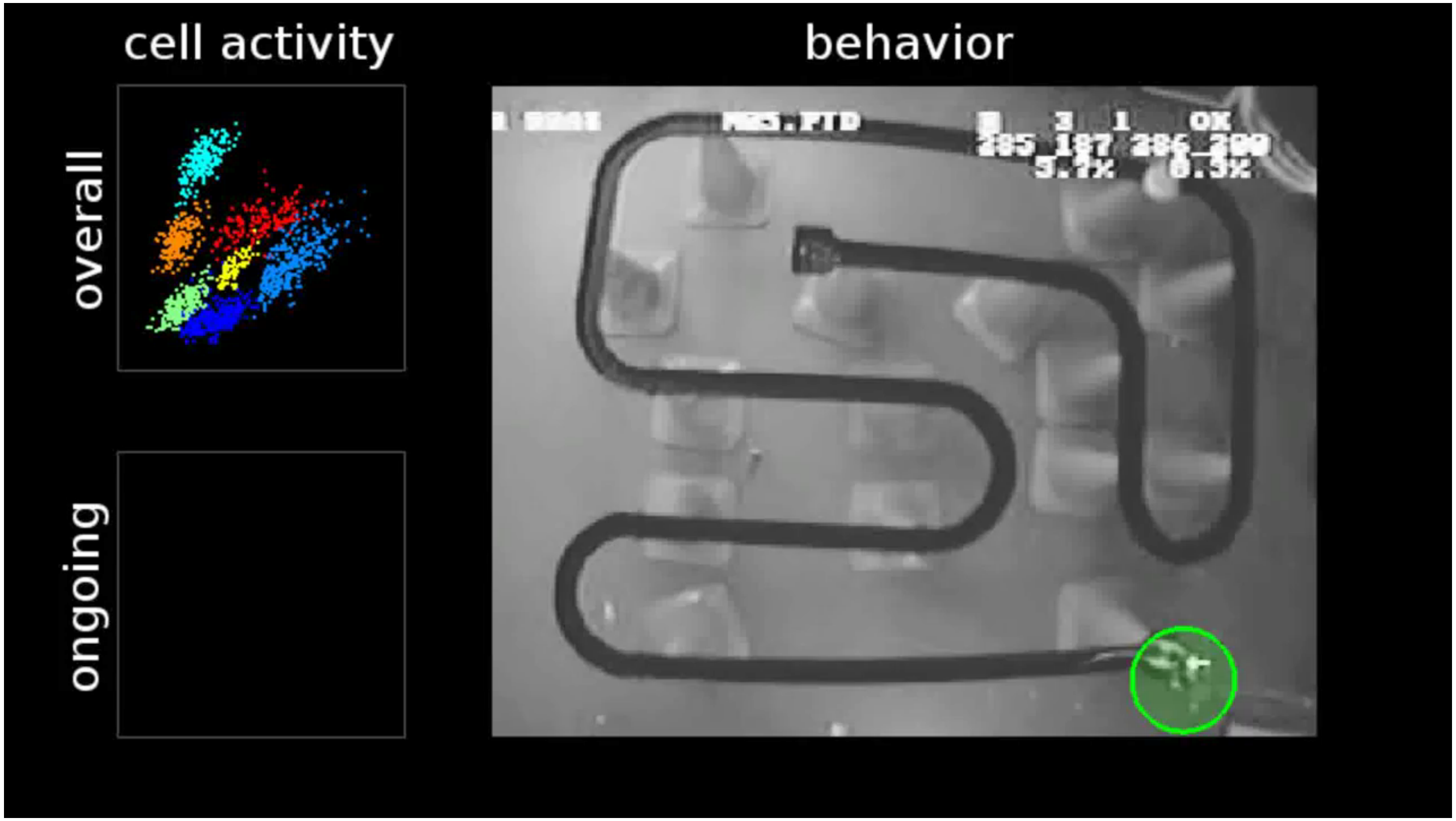


Firing frequency of one cell as rat moves about in a square-shaped arena



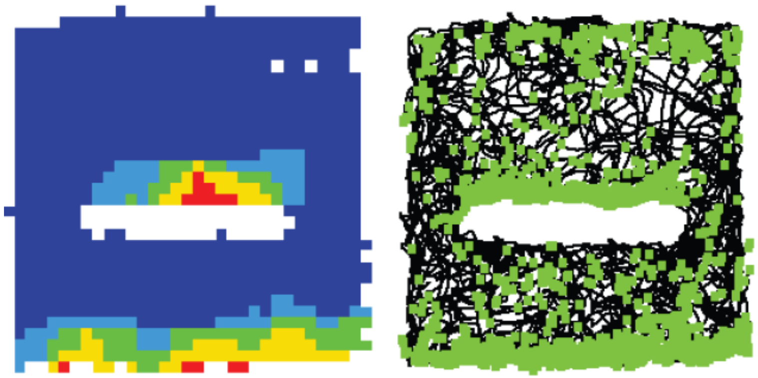
Different cells fire in different areas of the arena

Place cells



Together, the firing pattern of the hippocampal cells tells the rest of the brain where the animal is at a given moment

Boundary cells

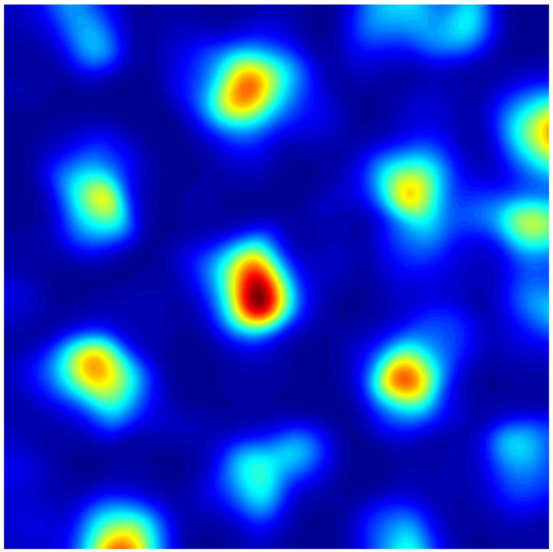


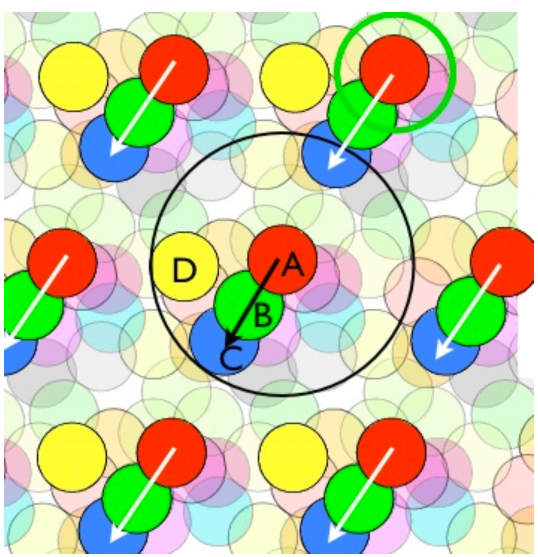
If a barrier is added on the arena, some cells that are active near the ”bottom” wall, also become active when the animal encounters a barrier of the same orientation

Place cells in humans

- Recordings in epilepsy patients show the existence of place in humans too
- Experiments with intracranial recordings are rare, though

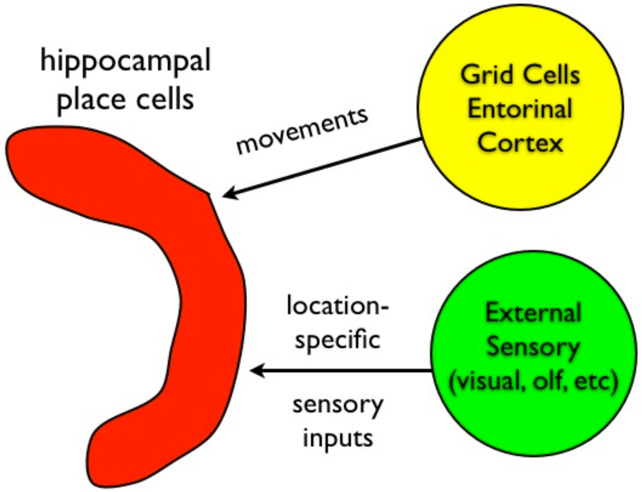
Grid cells (E and M-B Moser)

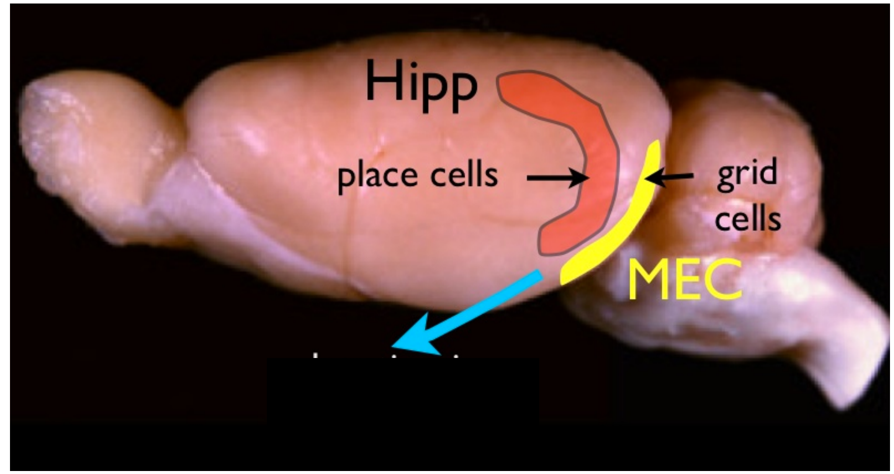




- Grid cells, found in the entorhinal cortex, are like place cells, but they have multiple place fields
- Curiously, these place fields are very strictly organized as hexagonal patterns
- Another grid cell may form a pattern that is exactly like that of another cell but the pattern is shifted slightly to some direction
- Thus, activation pattern of grid cells tells the how fast and to what direction the animal is going

The emerging picture





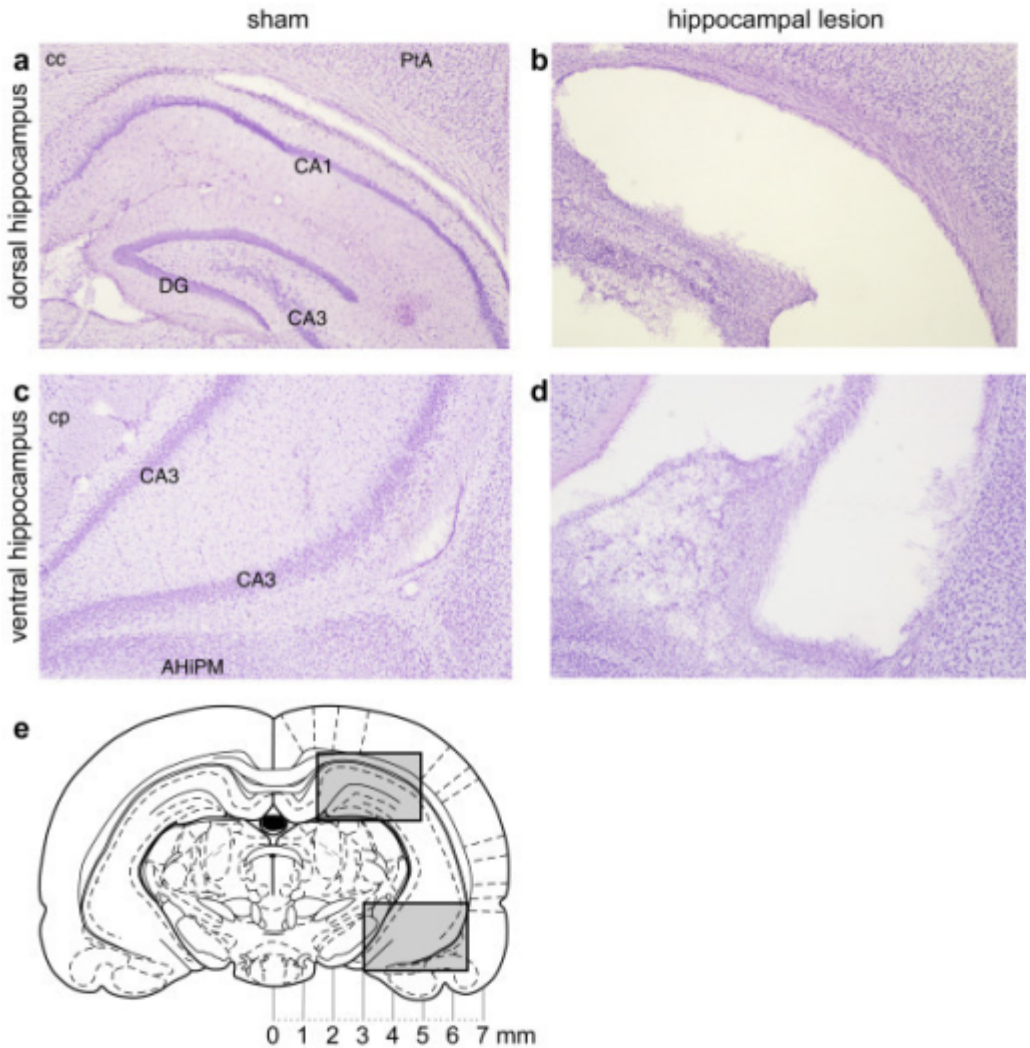
Hippocampal place cells converge information coming from different sources in order to represent where we are

Entorhinal grid cells aid the organism in determining where it is going and how fast

Significance of the findings

- The neural navigation system is one of the most comprehensive descriptions of how the brain represents something
- These findings also imply that people have *a priori* sense of space (cf. Immanuel Kant)
- Some researchers are now working on the idea that how the hippocampal system represents space and our own point-of-view in it, would actually be the governing principle of how we represent autobiographical and semantic knowledge

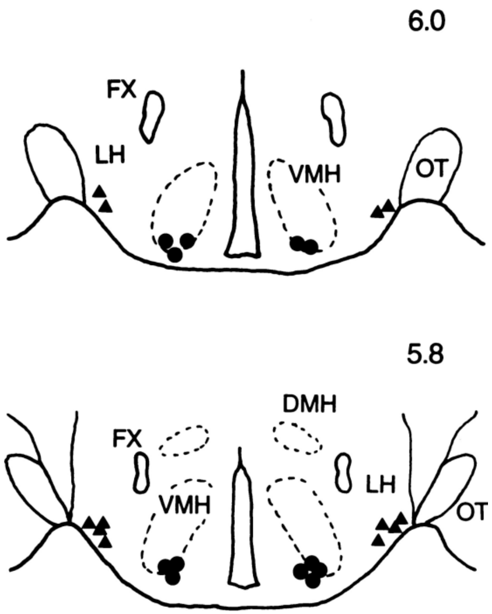
Lesions and inactivations

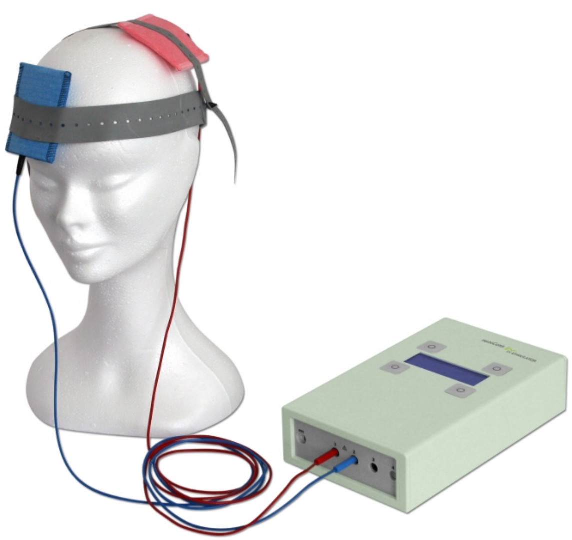


- Lesions are spatially confined, irreversible damage made e.g., by
  - Electric current
  - Ablation
  - Cutting of fibers of passage
  - Chemical substances
- Reversible inactivation can be accomplished by
  - Chemical substances
  - Cooling

Remember the case of HM? How does he relate to this?

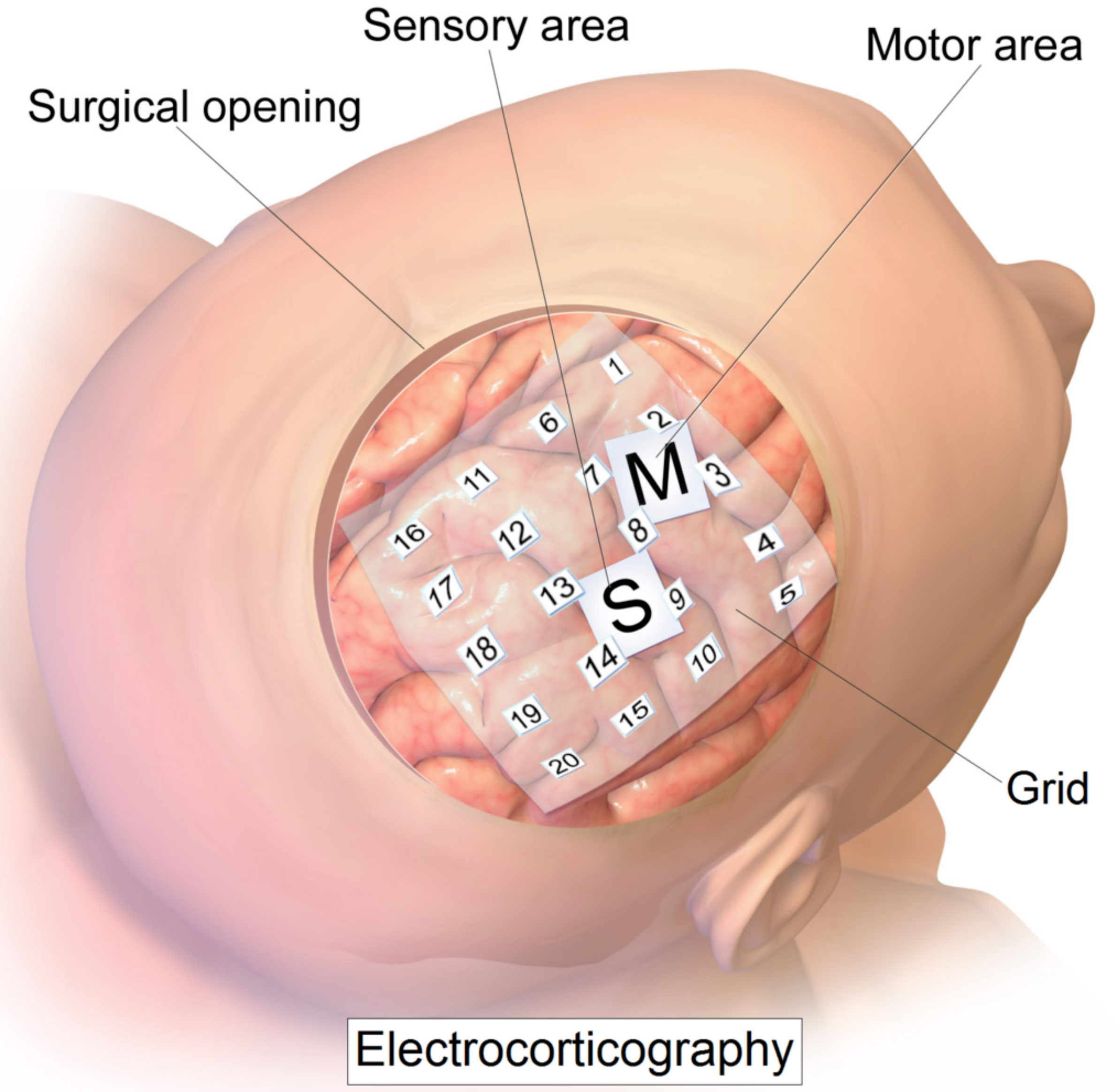
Brain stimulation





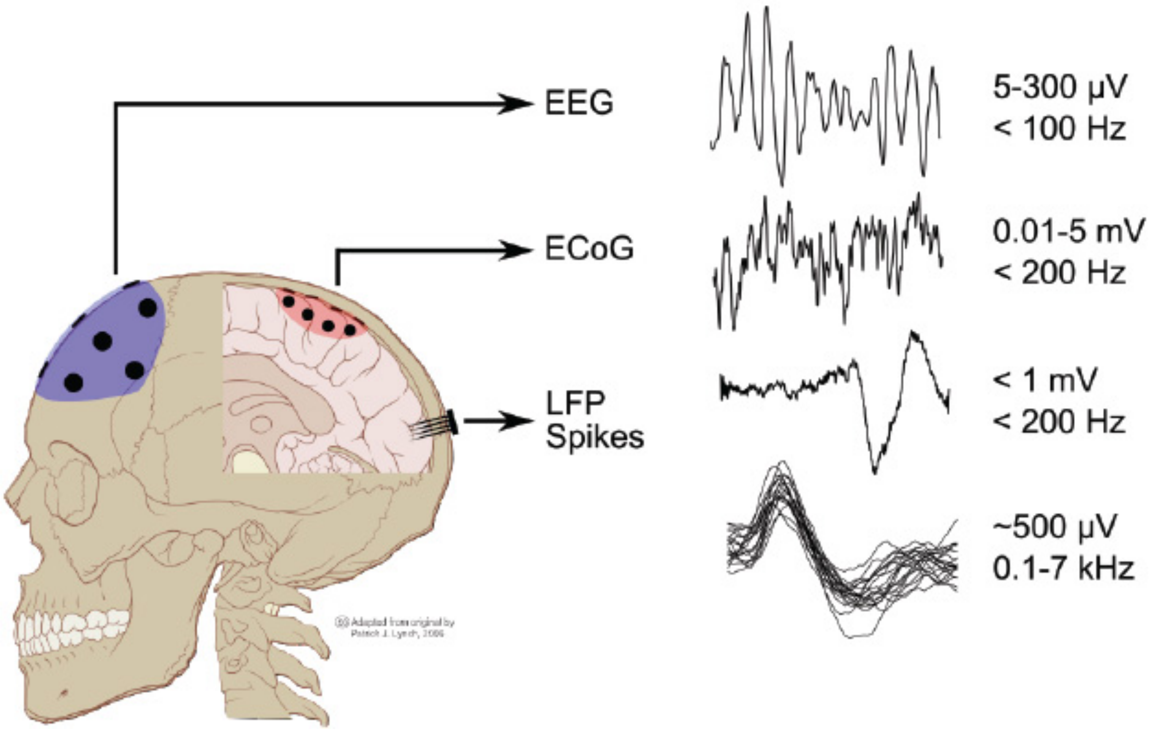
- The neural tissue can also be stimulated by weak electric current
- By using intracranial electrodes this can be done on the level of nuclei
- Non-invasive counterparts are tDCS and TMS, the effect of which is restricted on cortical areas

- *Optogenetics is a promising new tool for both inducing and blocking brain activity in certain neurons in a given area*



The weaknesses of non-invasive recordings (at least part of them) can be avoided byt recording brain activity from within the brain

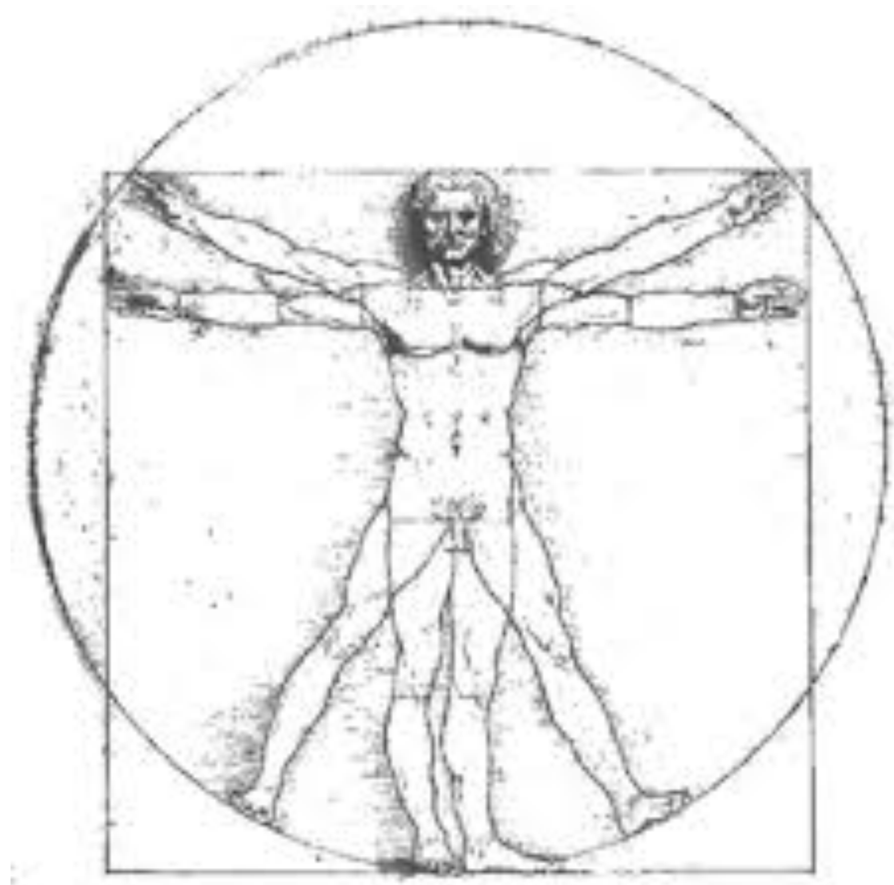
ECoG - electrocorticography



- Like EEG, but the electrodes are implanted under the dura

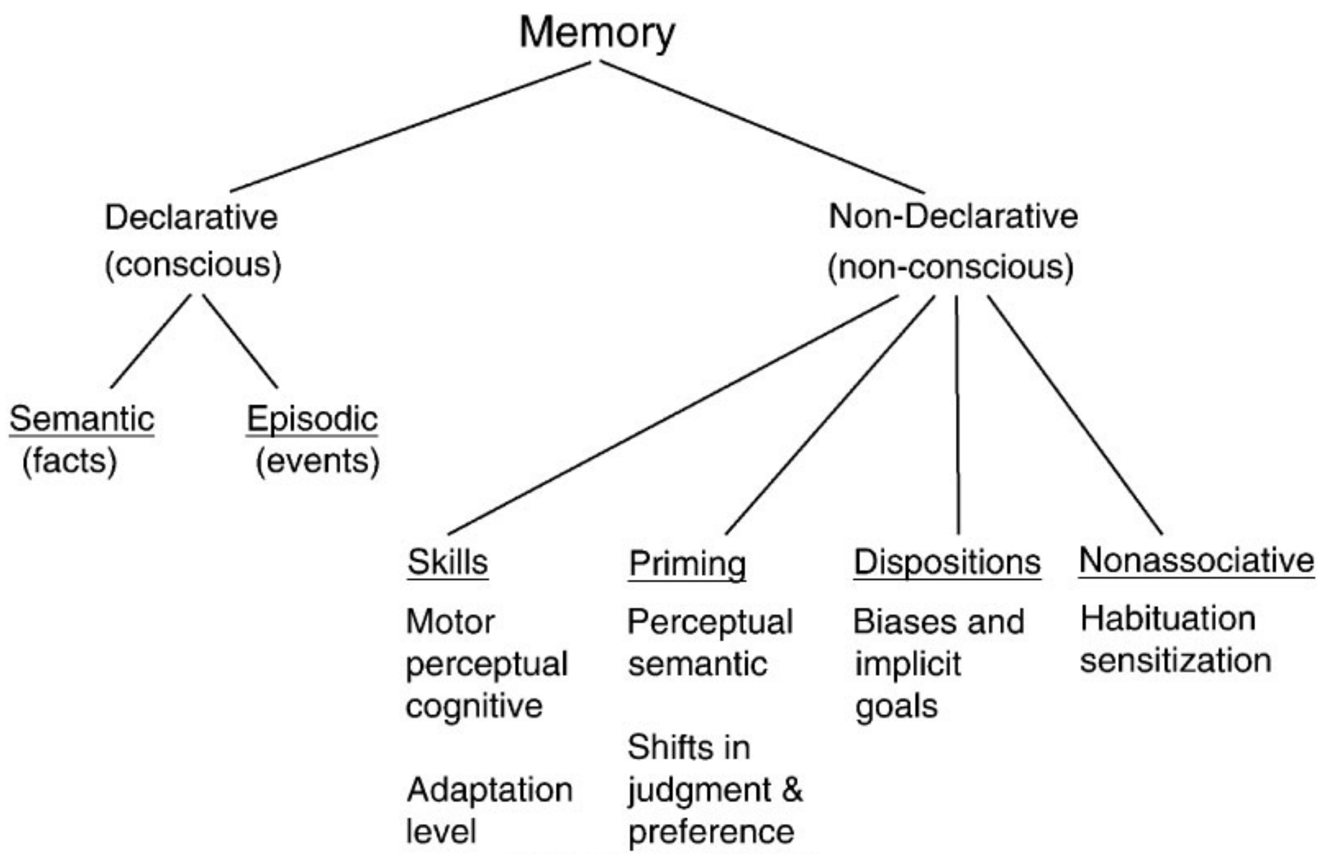
Katsotaan tähän väliin video:

Part II: Learning and memory (in humans)



Varieties of memory

Memory is not unitary: the Schacter-Tulving classification of memory types

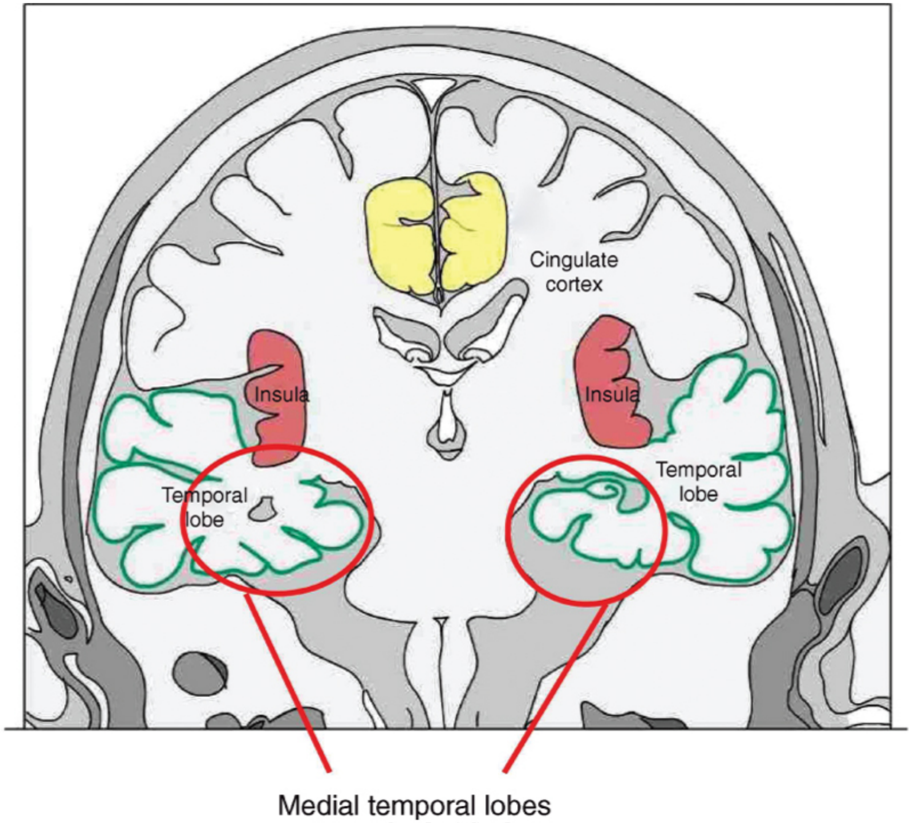


Source: Adapted from Schacter and Tulving, 1994.

Important brain structures in the study of memory are the cortex and the medial temporal lobes (MTL), which contain the two hippocampi and their surrounding tissue.

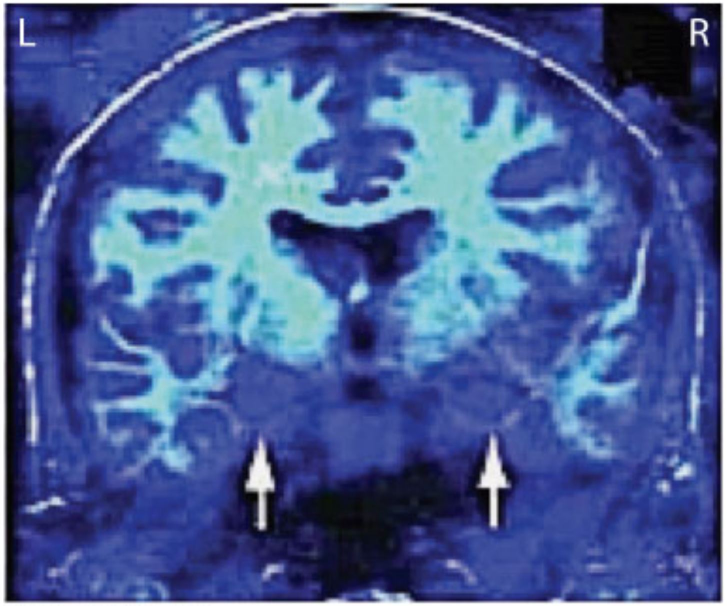
The MTL encodes information across sensory domains such as smell, vision, and touch.

The MTL is a highly interactive crossroads, well-placed for integrating multiple brain inputs, and for coordinating learning and retrieval in many parts of the cortex. It is a 'hub of hubs'.



Source: Drawn by Shawn Fu.

HM: the best-studied amnesia patient



3; *right*, Corkin *et al.*, 1997.

The white arrows show lesions where the MTL was removed.

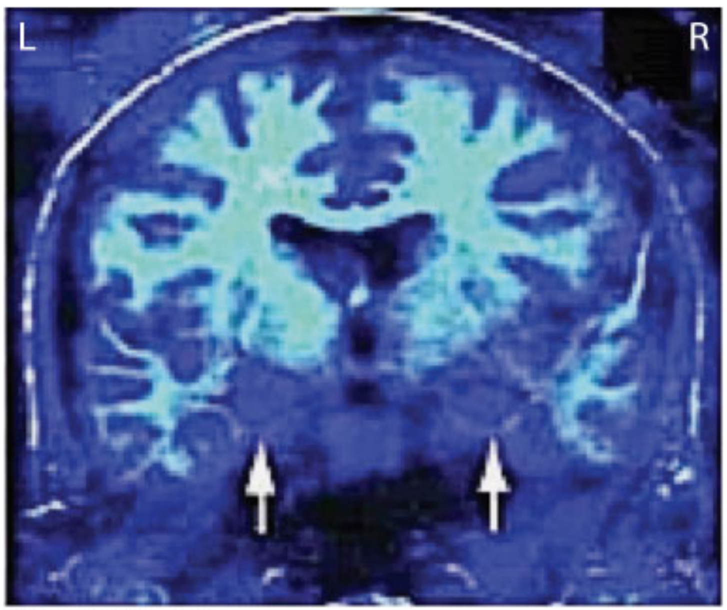
HM had MTL in both hemispheres removed surgically in an attempt to relieve his epileptic seizures. The surgery was successful in reducing the seizures, but it had a profound and unexpected impact on his memory.

HM could not remember any of the events in his life thereafter -- the people he met, the things he did. Even today, he cannot keep track of his age, and can no longer recognize himself in the mirror because he is unfamiliar with his changed image since the surgery in the 1950’s.

HM: the best-studied amnesia patient -- bilateral surgical removal of the hippocampi

Read more about HM …"The Day His World Stood Still"

http://www.brainconnection.com/topics/?main=fa/hm-memory



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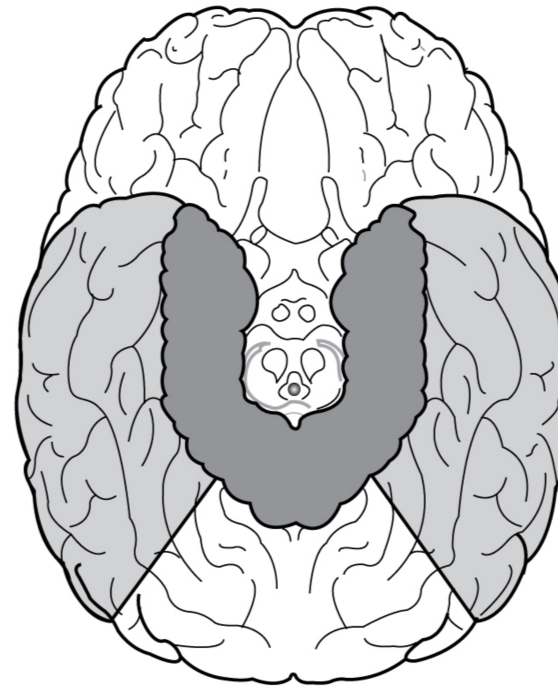
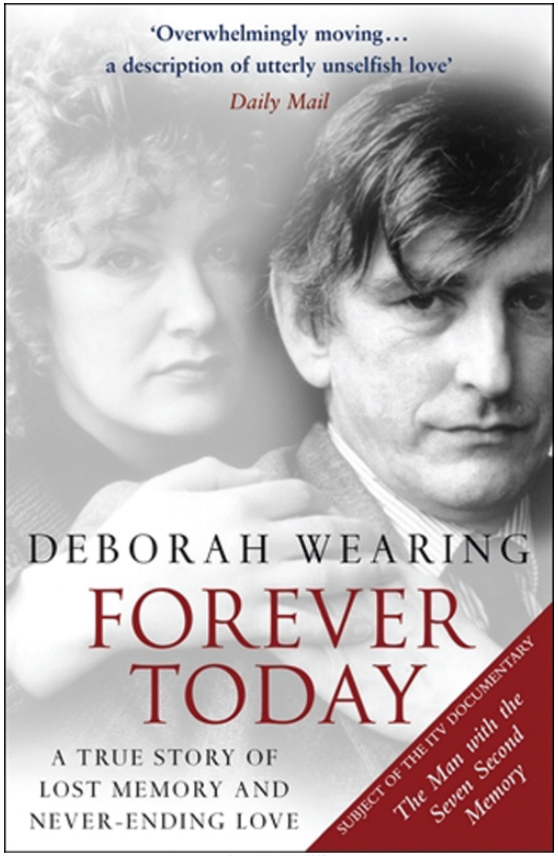


A bottom view of the brain shows the regions removed by surgery for HM.

Only a fleeting moment … the story of Clive Wearing, a rising young musician in Britain who was suddenly struck with a rare type of brain damage.

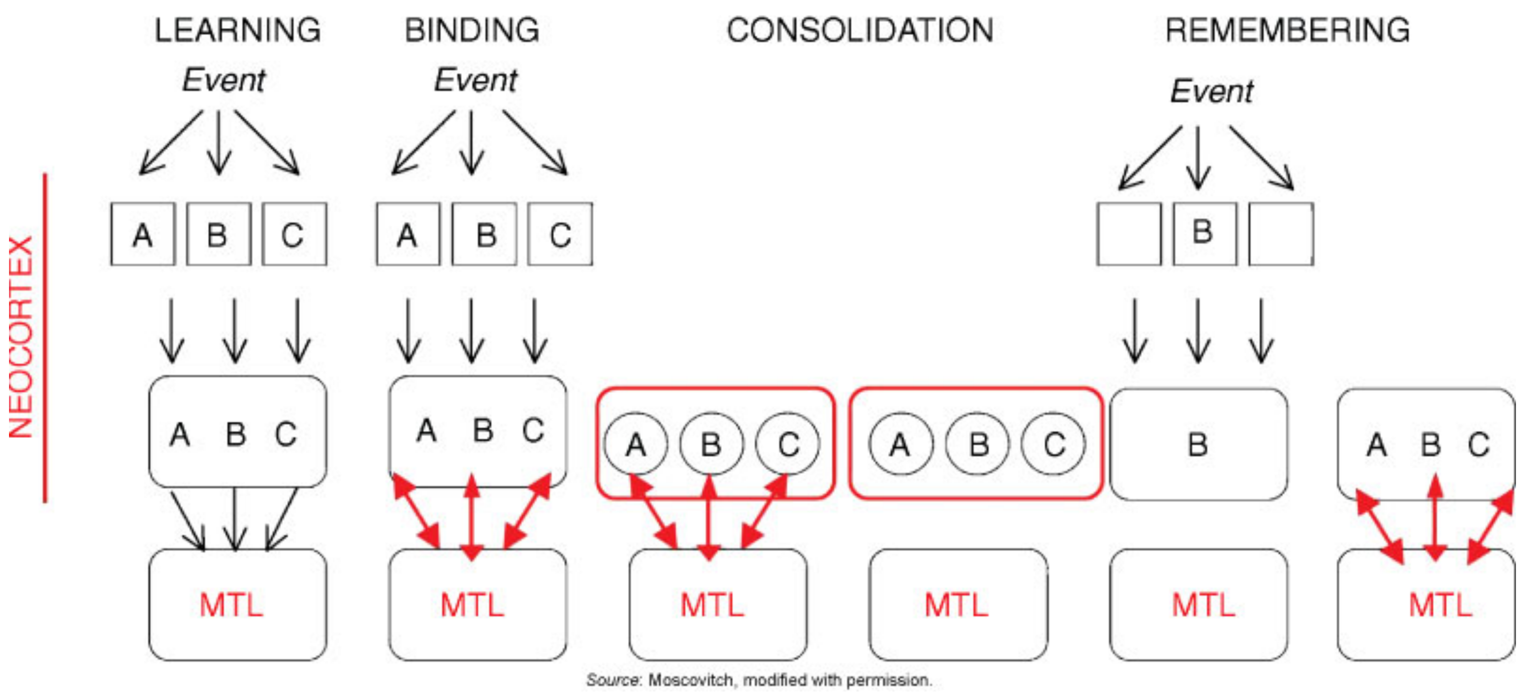
Part 1a
http://www.youtube.com/watch?feature=player_detailpage&v=WmzU47i2xgw

Part 2d
http://www.youtube.com/watch?v=UKxr08GEE54



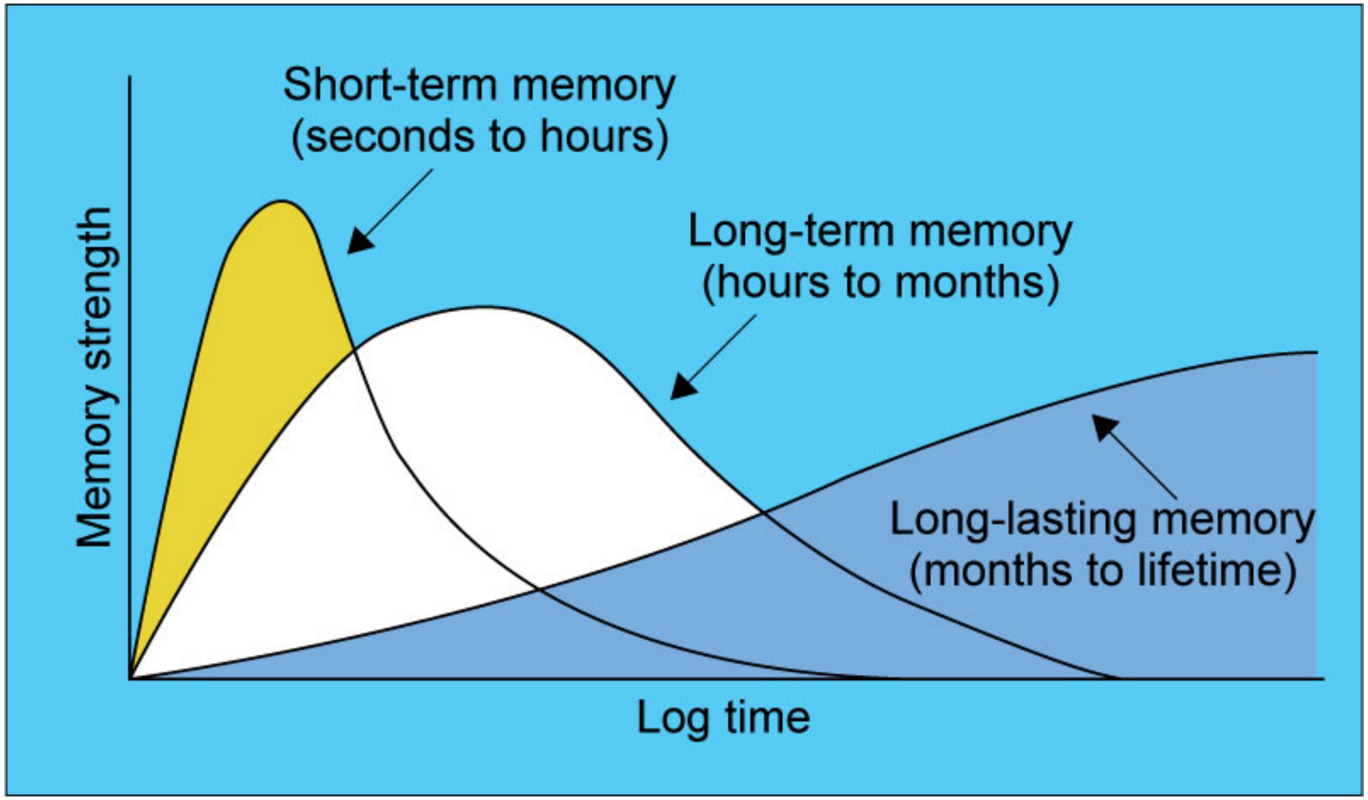
Source: Wearing, 2005.

Consolidation: from temporary to permanent storage



The steps of learning, binding, consolidating, and remembering an event

Rapid consolidation: synaptic mechanisms



Source: McGaugh, 2000.

Three overlapping time courses for consolidation proposed by James McGaugh

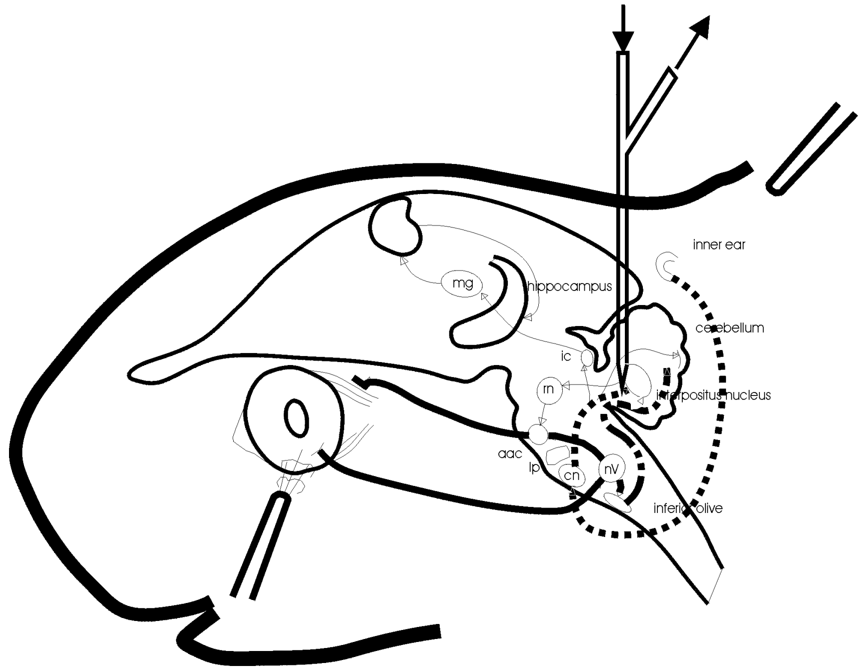
Interim summary

There are many different kinds of learning: the most fundamental distinction is between conscious (declarative or explicit) and non-conscious (implicit, e.g. procedural) learning.

Selective brain damages can lead to very selective deficits in learning.

Learning process itself consists of temporally distinct phases of which the most important are training and consolidation.

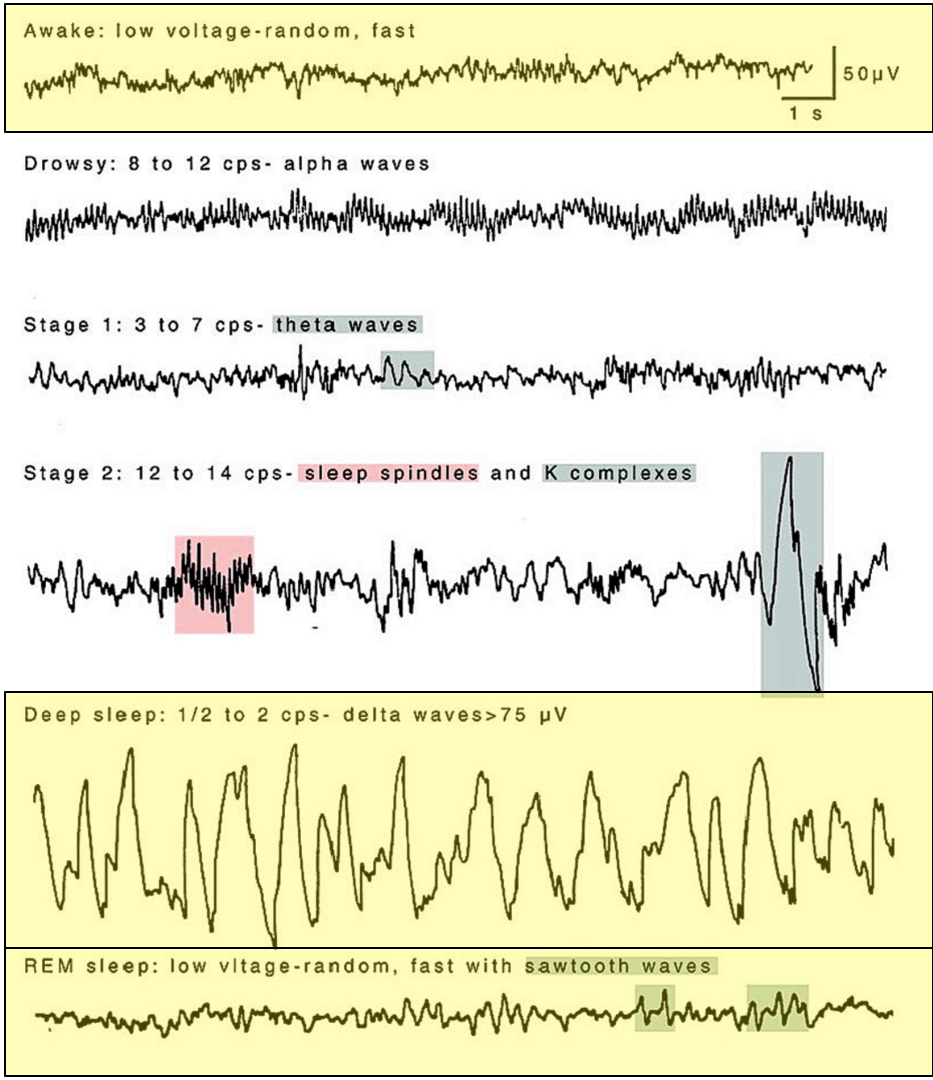
Part III. Psychological states and neural oscillations



Global rhythms of circadian states

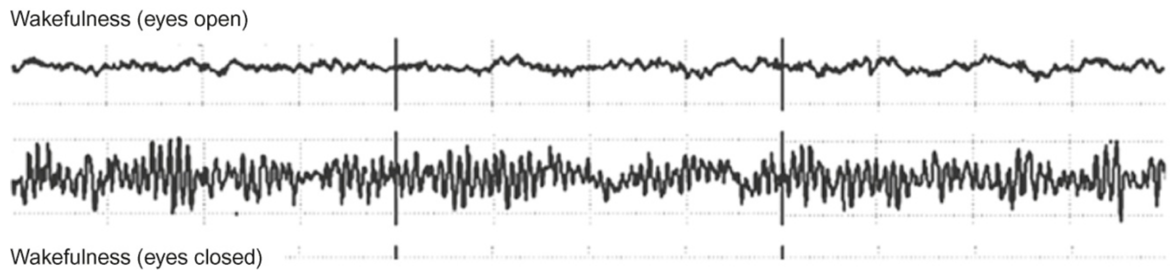
You are likely aware of how different you feel in an alert, wakeful state vs. a sleepy state vs. an exhausted sleep-deprived state. Your brain rhythms are also quite different in these states. EEG has long been used to study steady state brain rhythms in awake and asleep humans and animals.

In the figure, note the difference in the amplitude of the EEG brain waves from awake (top) to deep sleep and REM sleep (bottom).

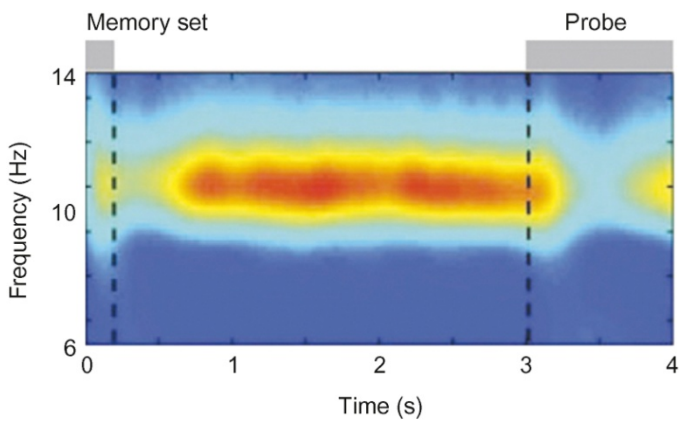


Alpha rhythms

In 1929, a German psychiatrist named Hans Berger made the first human EEG recordings by placing an electrode on his young son's head just above the occipital cortex. Berger asked his son to open and close his eyes and found that with eyes closed, a a small sinusoidal wave could be picked up. Berger called it the *alpha* wave.



A recent hypothesis for the role of alpha in cognition is alpha serves to coordinate other rhythms for the selection and maintenance of object representations during perception, working memory, and consciousness (Palva & Palva, 2007). Note the strong burst of alpha oscillations centered at 12 Hz in this working memory task.



Theta rhythms have multiple roles

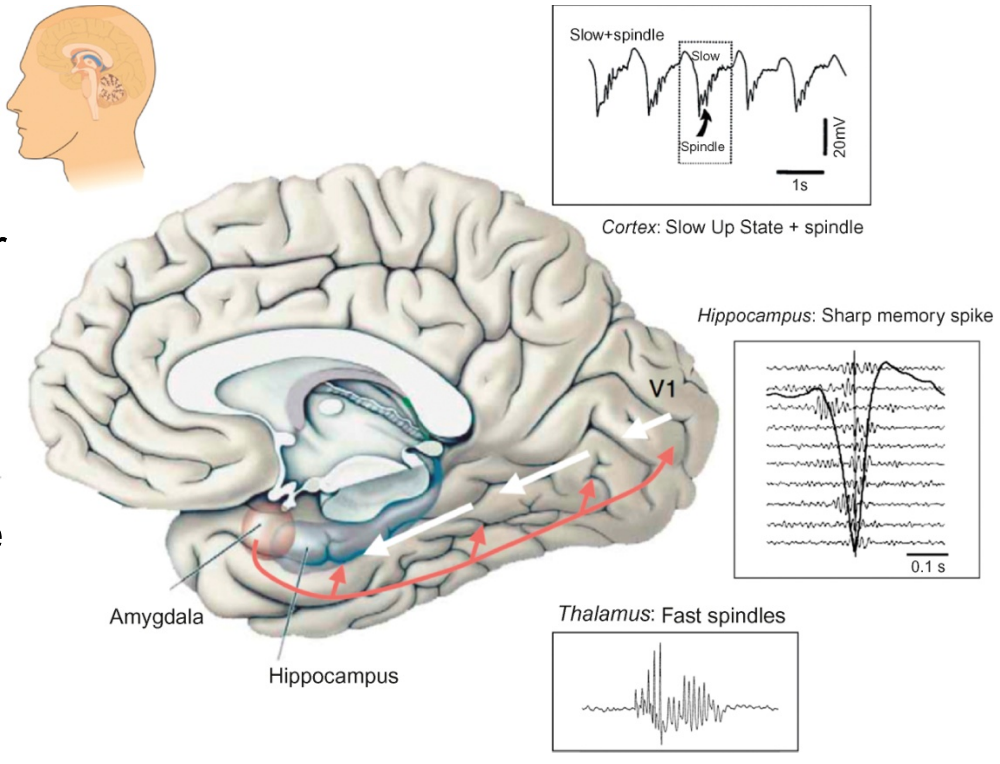
The theta rhythm is one of the slowest oscillations in the normal waking state, cycling 4-7 Hz, just above the delta rhythm that dominates slow wave sleep.

Theta is thought to play a key role in episodic memory and frontal lobe activities. Theta is one of the basic carrier frequencies of the hippocampus, observable during both episodic memory encoding and recall. Theta is believed to enable the coding and decoding of hippocampal learning in the cortex, especially the frontal lobes.

Some mental activity occurs in slow-wave sleep

Not all mental activity occurs in REM sleep. There has long been evidence of dream mentation in slow-wave sleep (SWS). There are key differences however: dreams in SWS are rational and repetitive while dreams in REM sleep are vivid but illogical with higher emotional intensities.

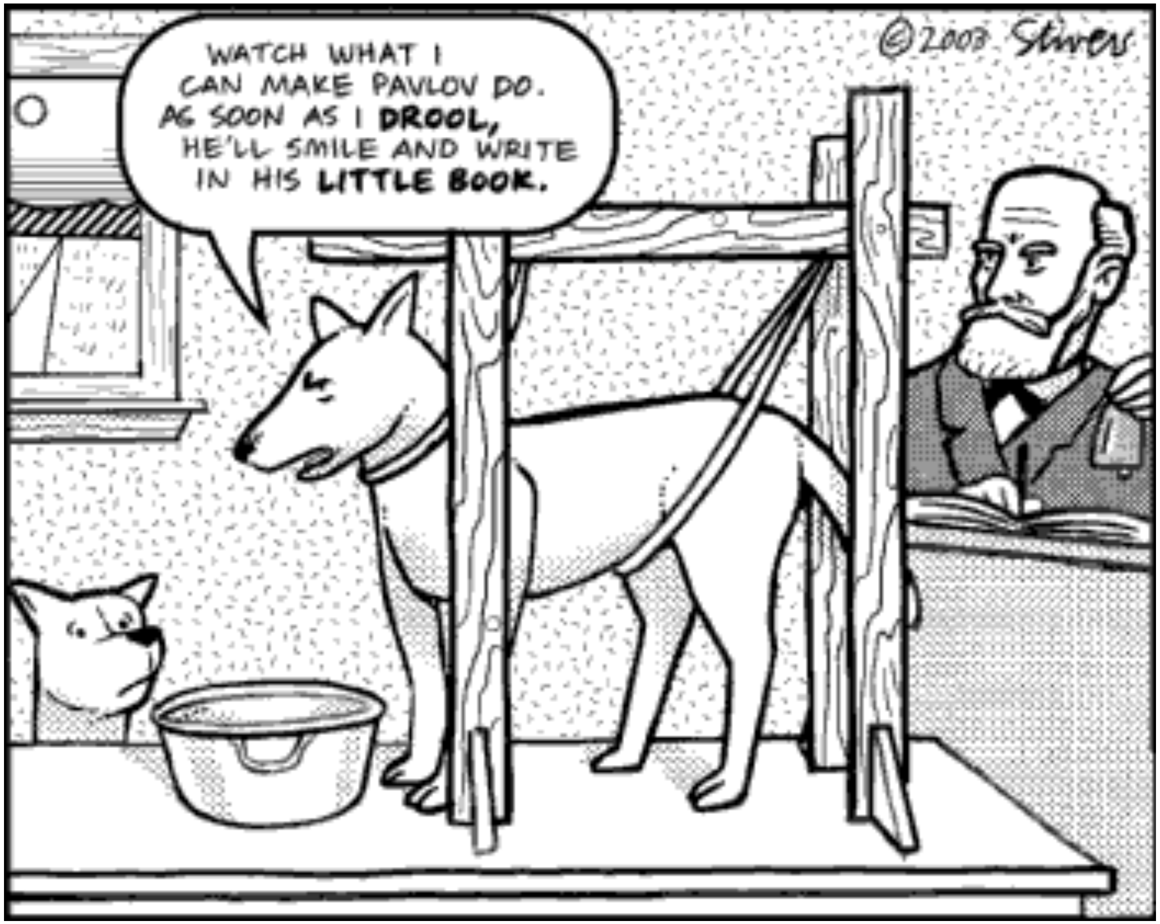
A key role for SWS is to enable memory consolidation during its 'Up States': thalamic spindles ignite these Up States which trigger hippocampal sharp spikes which are believed to activate memory traces in the hippocampus, leading to memory consolidation.

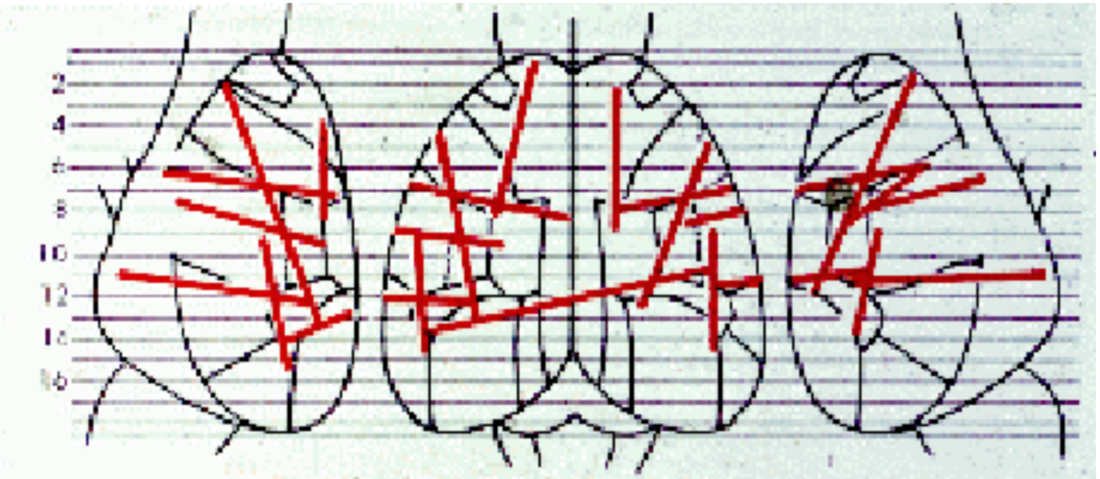


Interim summary

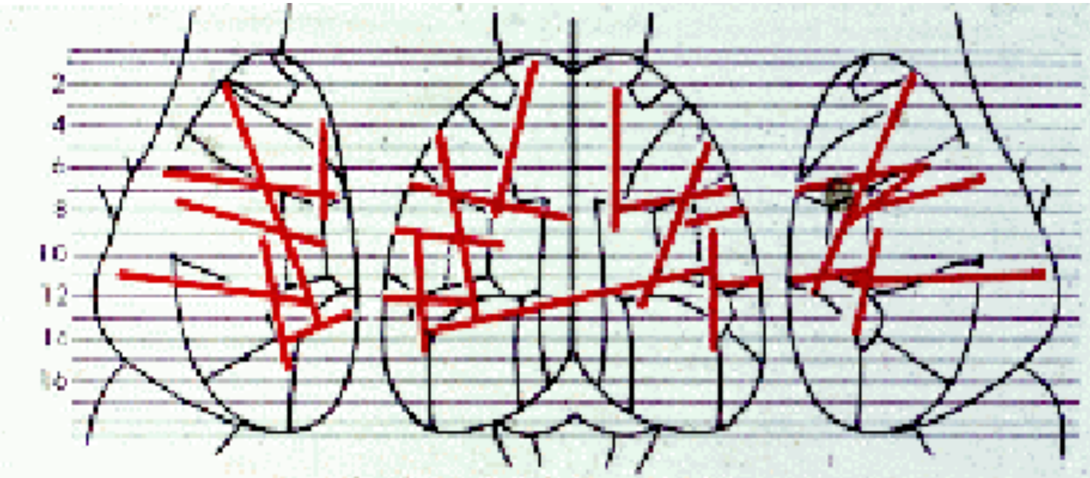
Different oscillatory states are related to different psychological states (levels of arousal, different cognitive operations)

Part 3. Classical conditioning as a research model of learning and memory





Karl Lashley tried to localize memory traces in rats



I sometimes feel that learning just is not possible

He never succeeded. After 30 years of effort…

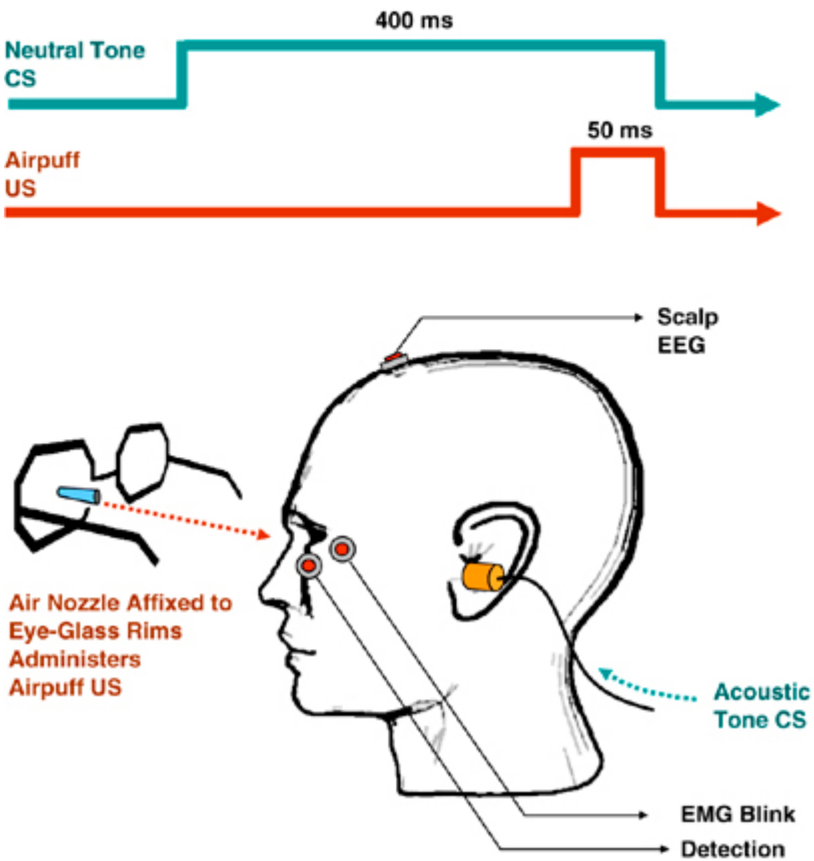
Instrumental- vs. classical conditioning

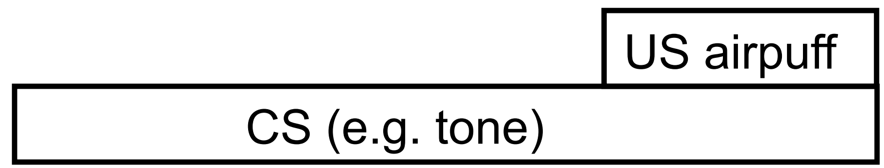
- Operant (instrumental) conditioning
  - The target’s own actions are reinforced by either a reward or punishment
- Classical (Pavlovian) conditioning
  - The target gets a reward/punishment during a certain stimulus irrespective of its own action

Classical eyeblink conditioning

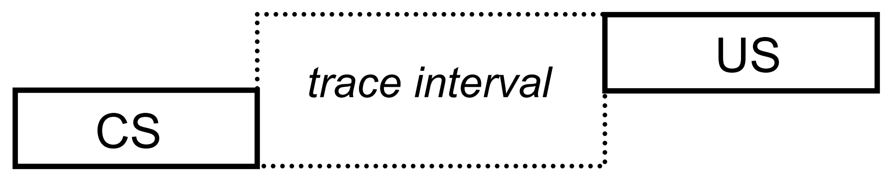
- In classical conditioning, the target is presented with an initially meaningless *conditioned stimulus (CS)* followed by reflex-evoking or otherwised biologically significant *unconditioned stimulus (US)*
- In eyeblink conditioning the CS is typically a neutral tone which does not evoke any behavioral responses
- The US is typically a mild airpuff towards the eye, which causes an eyeblink
- After many paired presentations of the CS and US, the subject blinks already as a response to the tone alone

Classical eyeblink conditioning

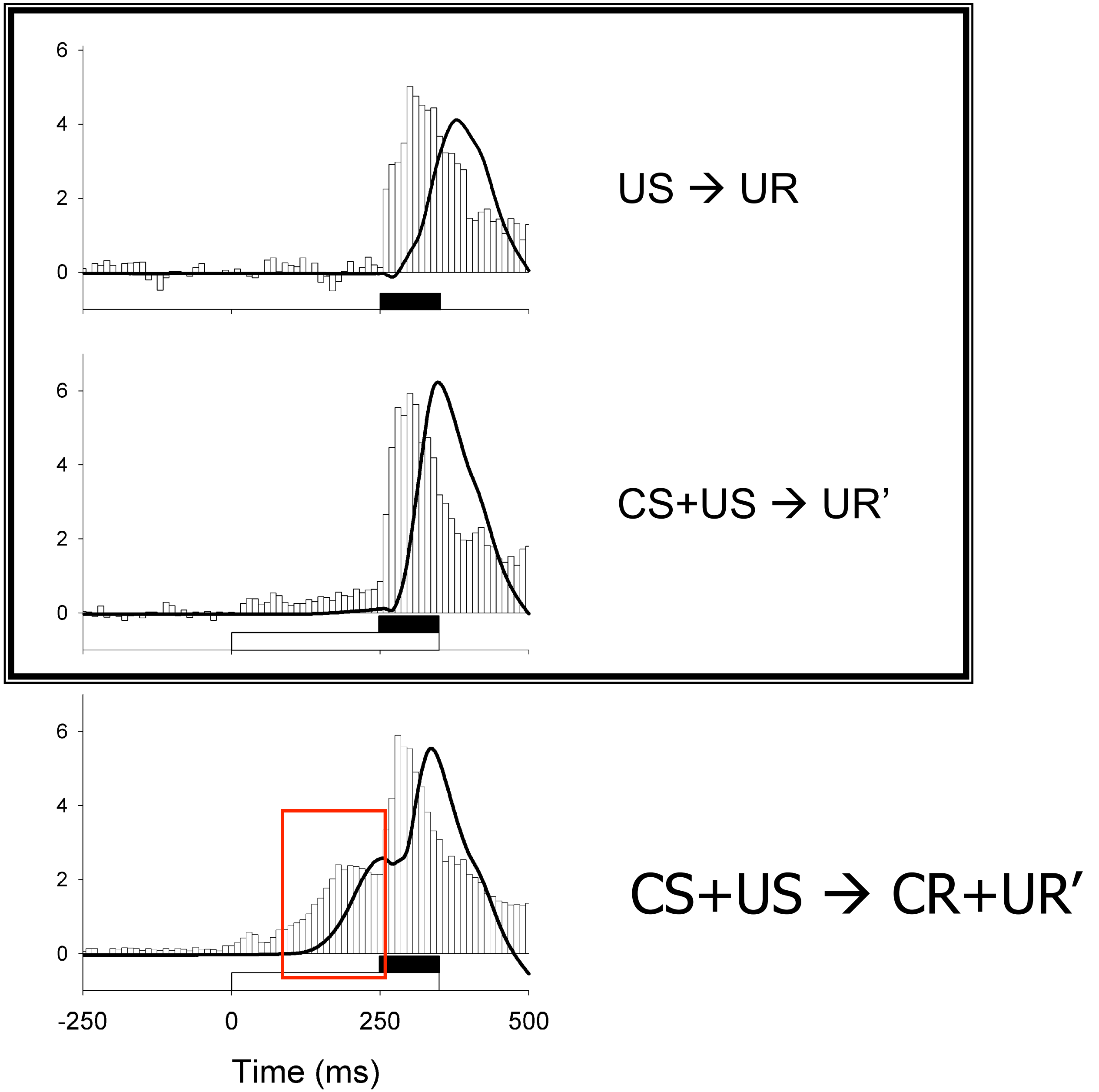




Delay conditioning

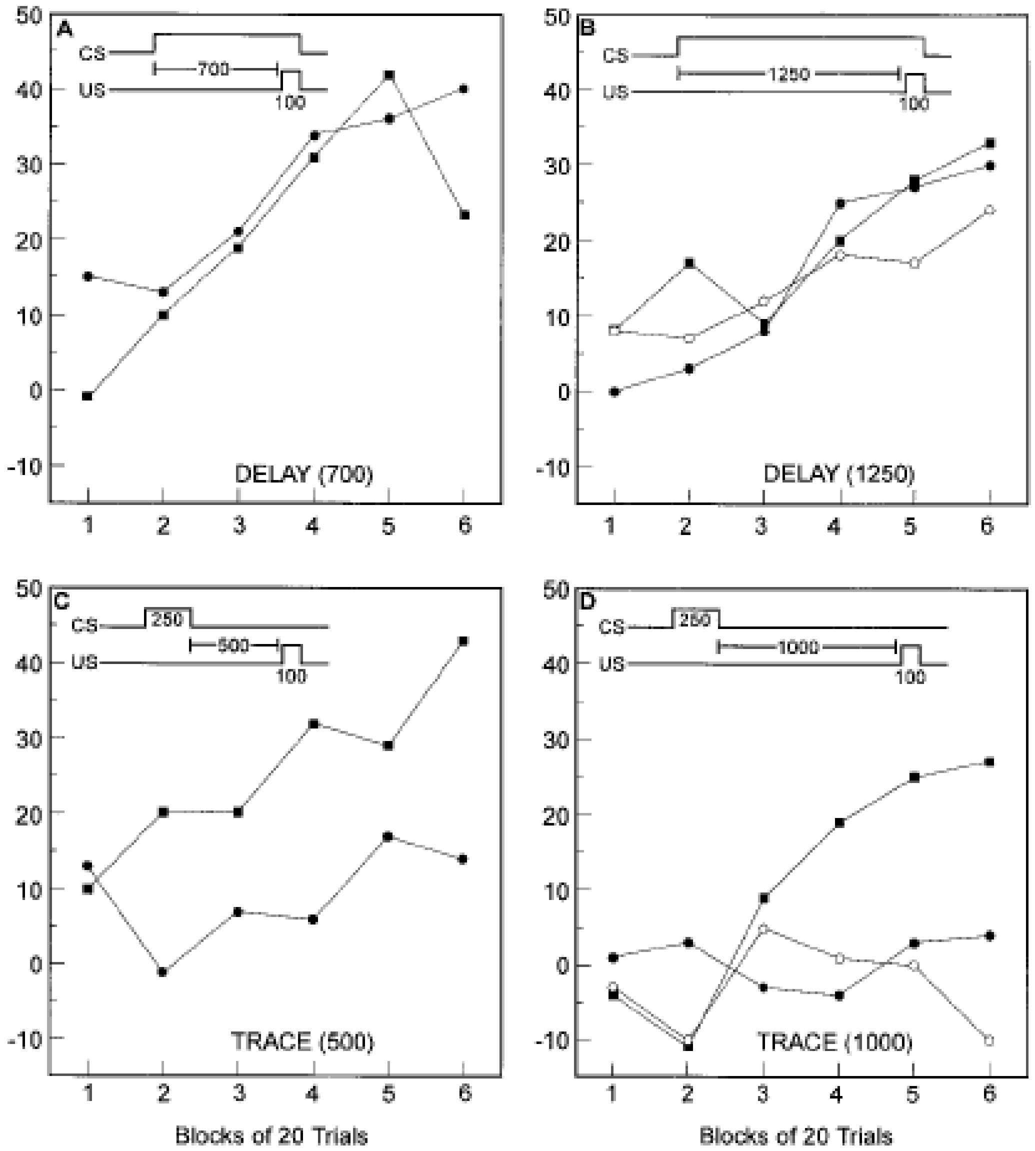


Trace conditioning



US → UR
CS+US → UR’
CS+US → CR+UR’
6
4
2
0
-250
0
250
500
Time (ms)

Effect of contingency awareness on learning
(Clark & Squire, 1998, Science)



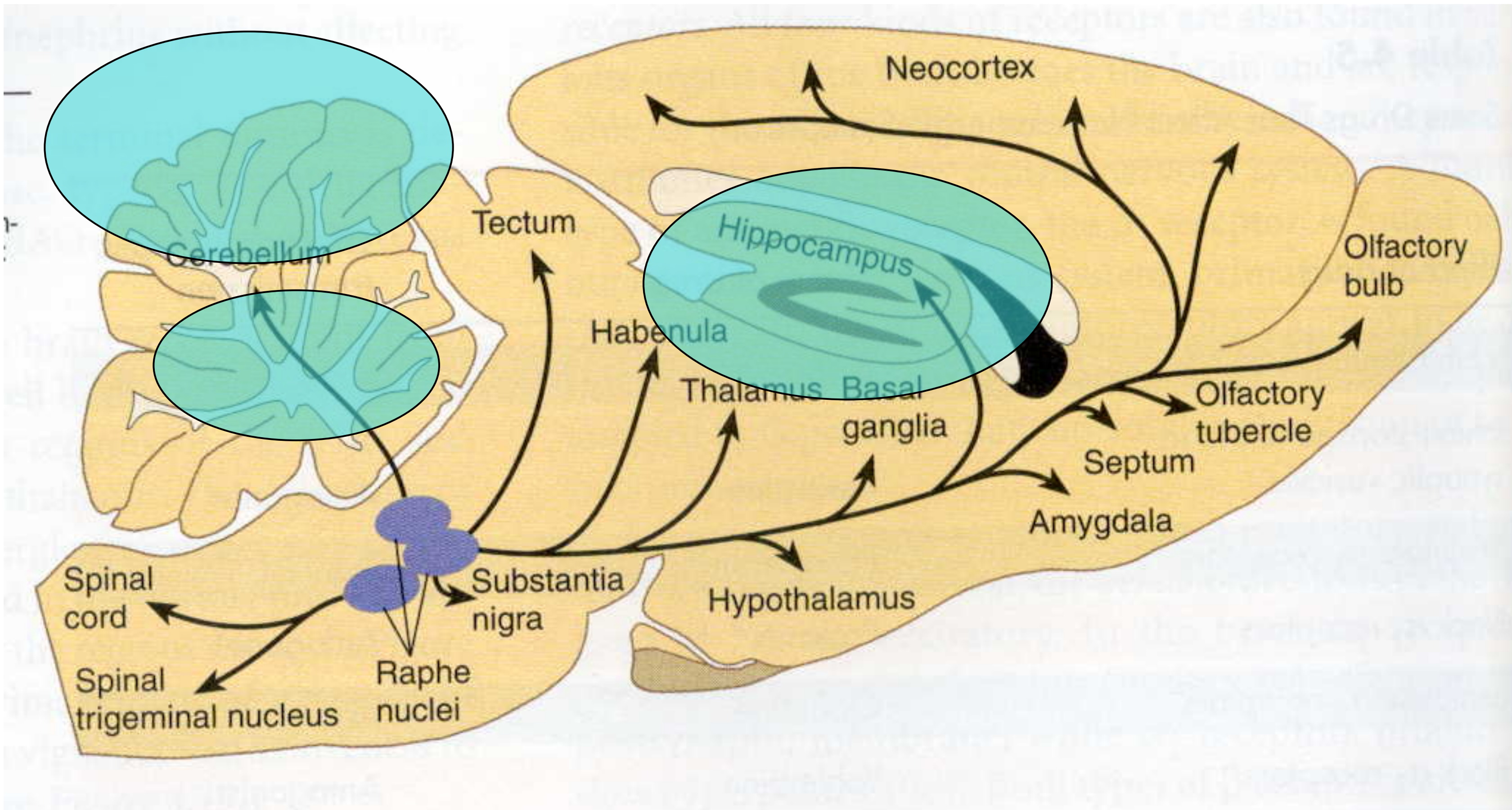
In delay conditioning, both groups (and amnesic patients) learn equally well

In trace conditioning, non-aware people (and amnesic patients) do not learn anything

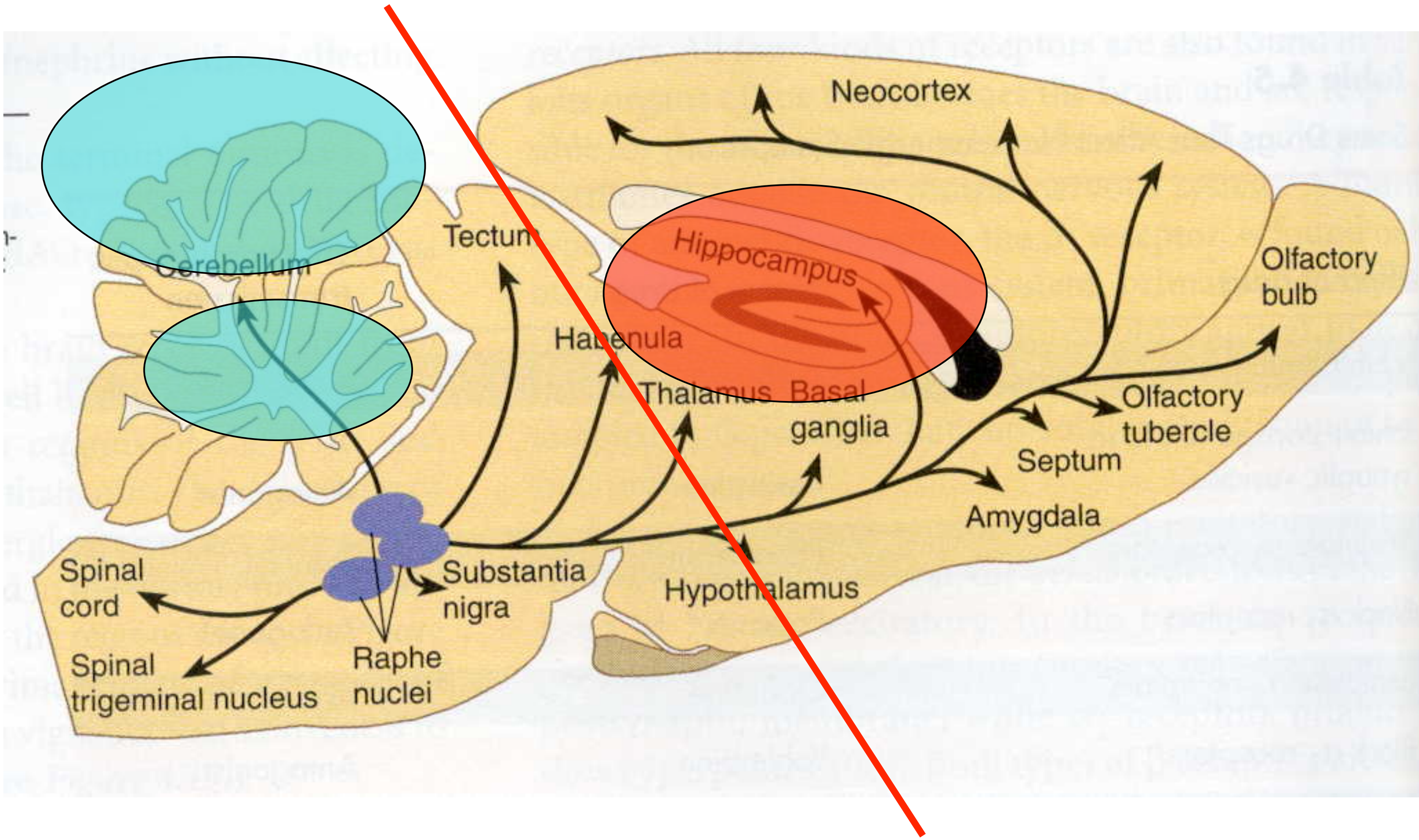
There are at least three distinct associations forming during the course of conditioning

- Emotional association
  - The subject learns that the CS predicts something that should be avoided
- Cognitive association
  - ”awareness” of belonginess of the CS and US
- Sensorimotor association
  - The ”skill” itself I. adaptive eyeblink just before the airpuff

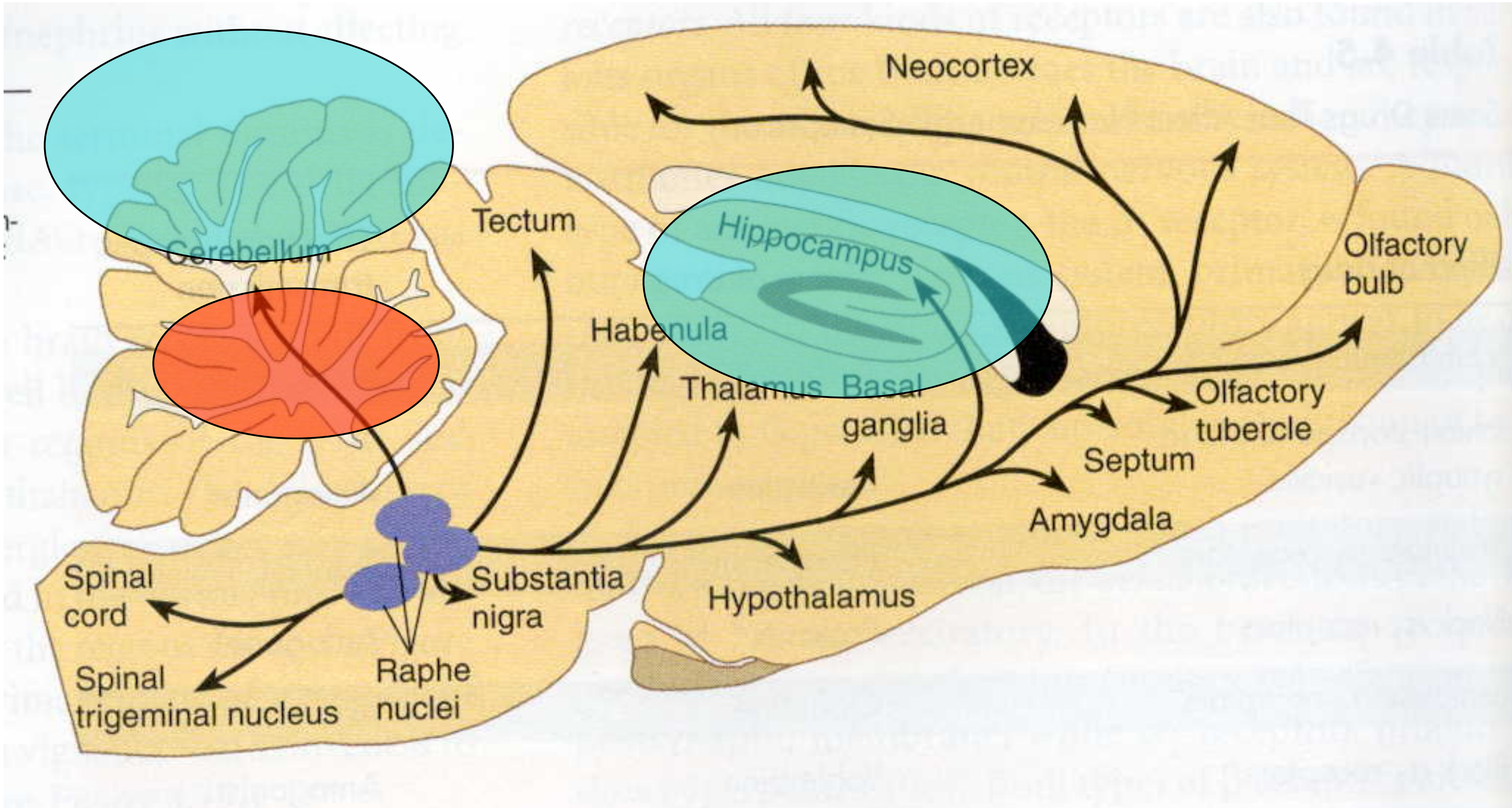
The crucial areas for development of conditioned eyeblink response are the cerebellar cortex and deep nuclei as well as the hippocampus (+ amygdala)



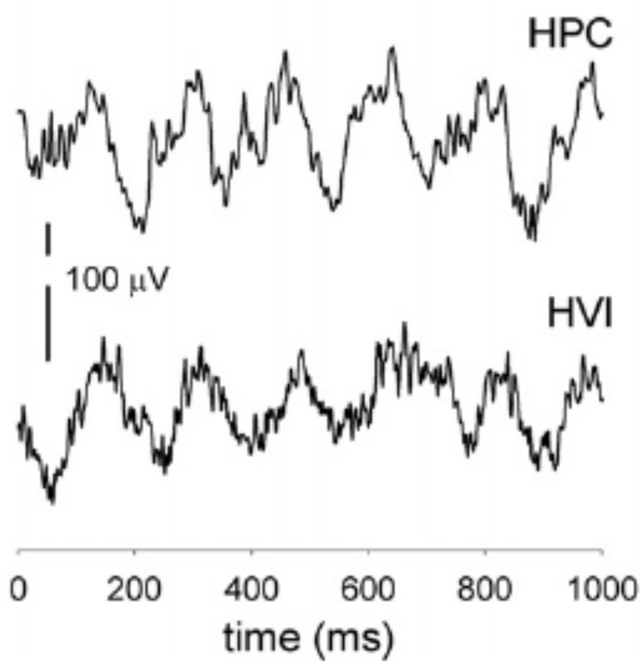
Cutting neural connections above the level of thalamus prevents learning of trace- but not delay EBCC



A small lesion in the cerebellar interpositus nucleus prevents learning in any kind of EBCC

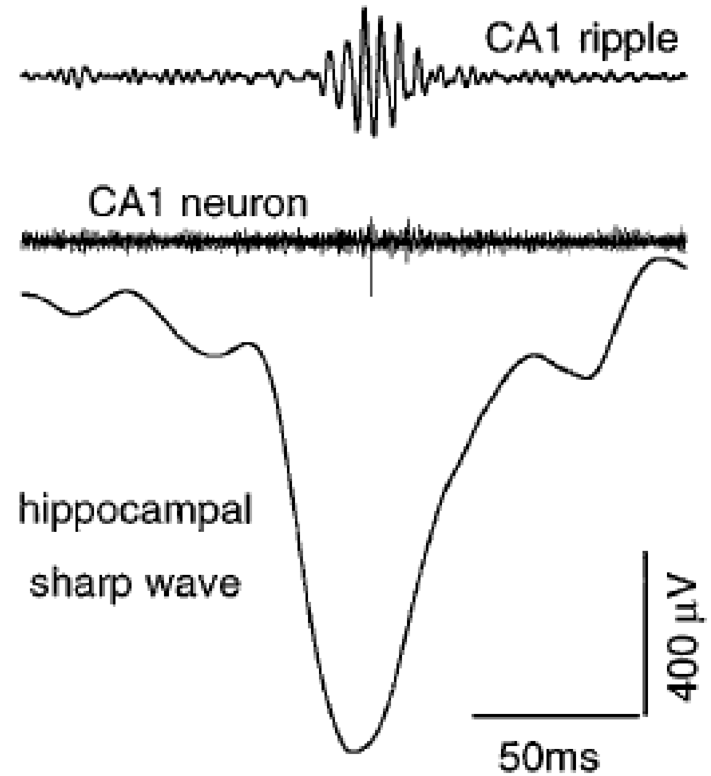


Hippocampal states have their behavioral counterparts



Dominant oscillatory pattern of the rabbit hippocampus is the theta oscillation, which is usually related to being alert.

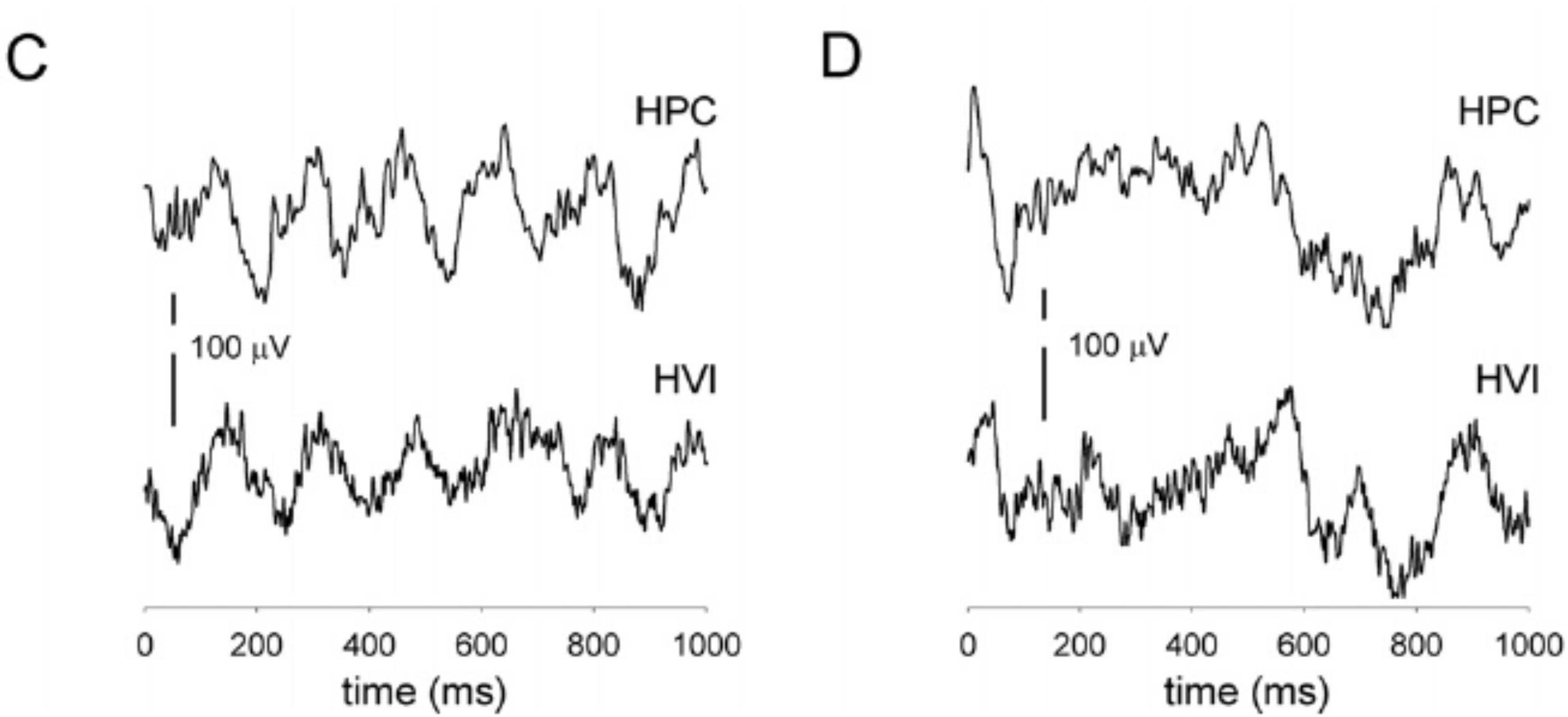
(From Wikgren et al, 2010)



In sharp-wave state, the animal is usually 'minding its own business' and ripple-events can be see.

(From Chrobak & Buzsaki, 1996)

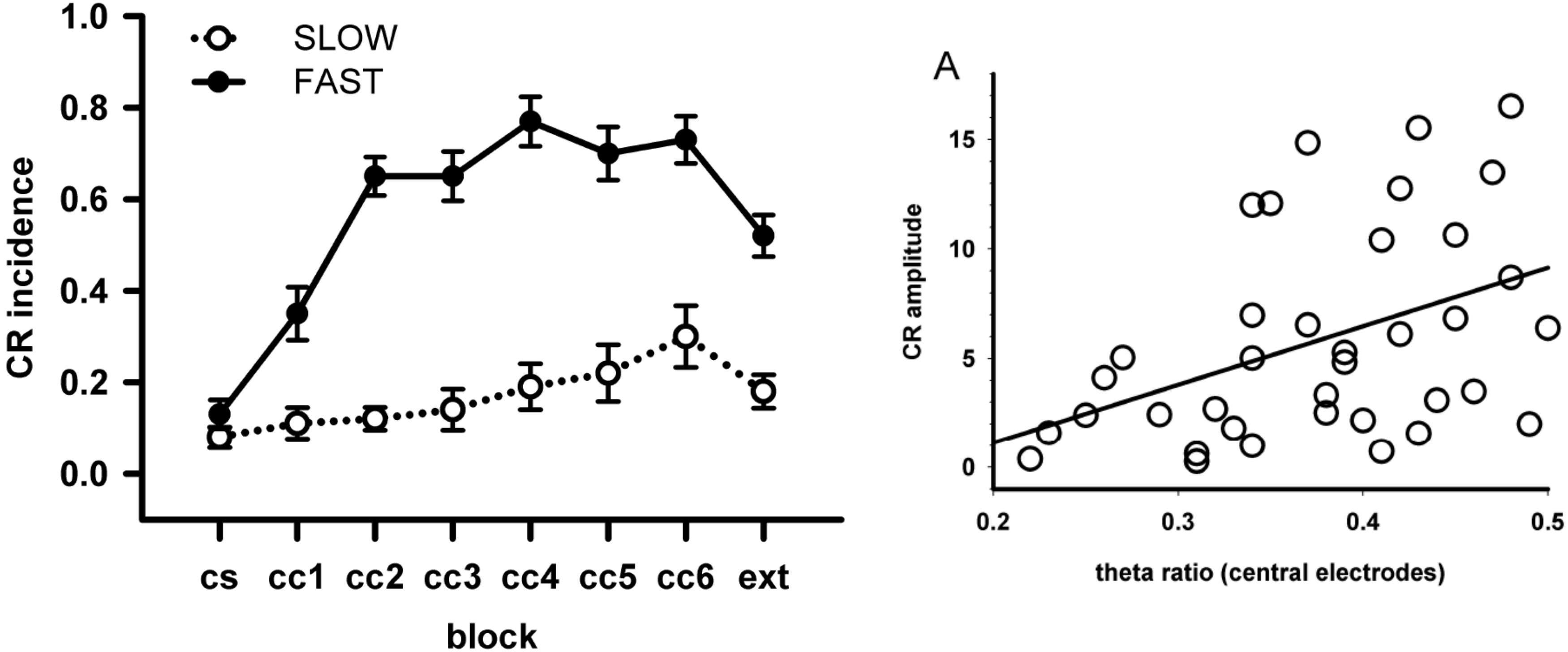
The presence of theta in spontaneous hippocampal oscillation predicts learning



Theta oscillation and learning rate

- Spontaneous theta before any training predicts learning (Berry & Thompson, 1978, *Science*)
- Increasing/decreasing the relative amount of theta facilitates/retards learning (Berry & Thompson, 1979, *Science*; Salvatierra & Berry, 1989, *Behavioral Neuroscience*)
- Administering the training trial during high/low theta ratio facilitates/ retards learning (Seager et al., 2002, *PNAS*)
- In trace eyeblink conditioning spontaneous theta predicts the onset of learning but not the asymptotic learning (Nokia et al., 2009, Behavioral Neuroscience)
- There is theta oscillation also in the cerebellum, and it can be phase locked with hippocampal theta (Wikgren et al. 2010 Neuroscience)
- At the onset of learning the CS evoked stronger theta response in the hippocampus (Nokia et al., 2010 J Neurosci)

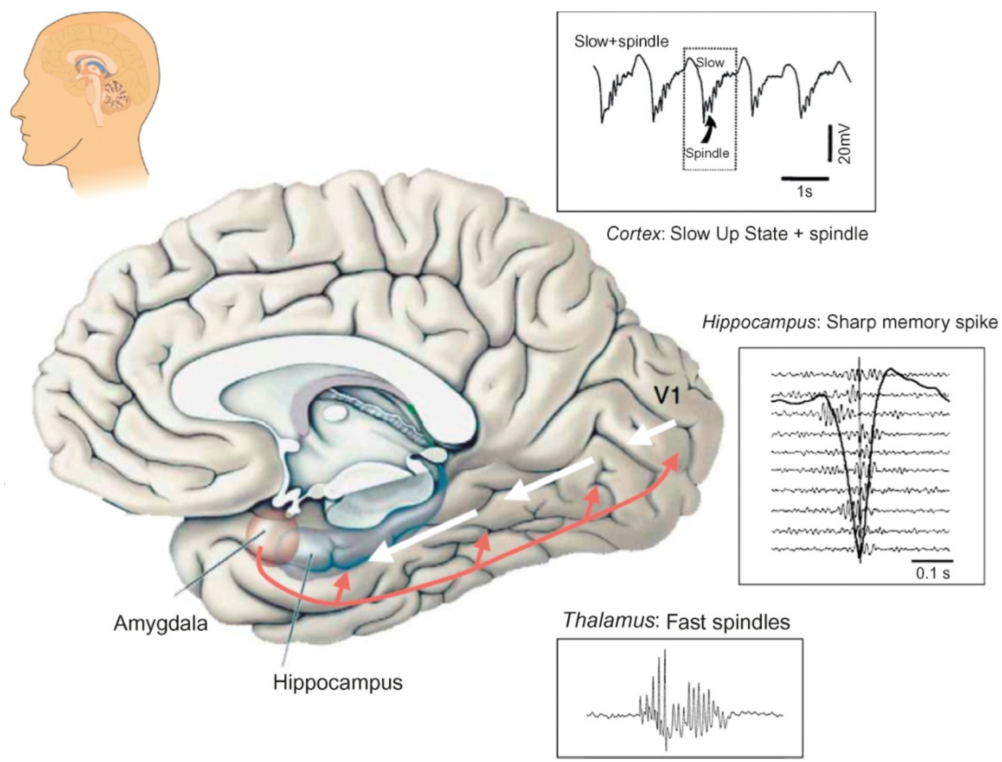
Amount of stimulus-evoked hippocampal theta = a measure of how much the animal pays attention to the stimulus?



The relative amount of spontaneous theta in human scalp EEG also predicts learning in human eyeblink conditioning. (Pyykönen et al. 2008)

Sharp-wave ripples

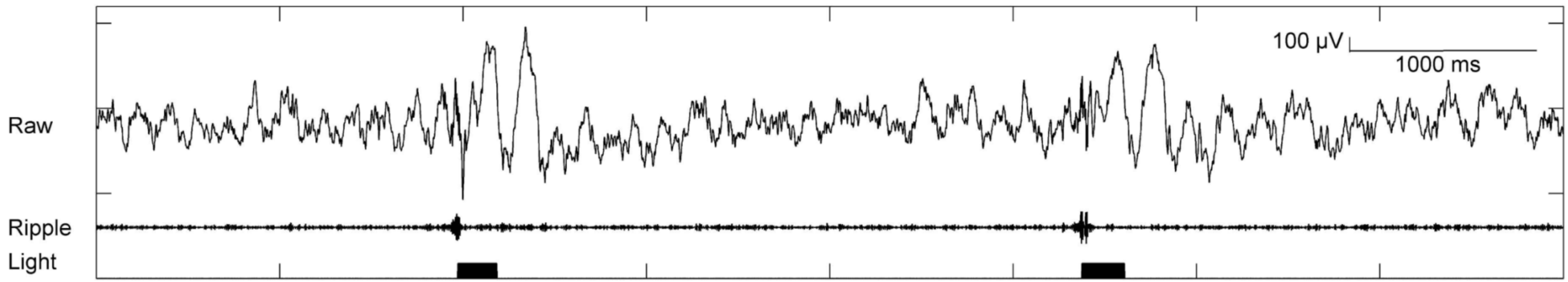
- The putative mechanism of consolidation of hippocampus-dependent memories
- A massive amount of research suggests that there is a correlation between the amount of ripples in sleep and memory performance in tasks that were completed before sleep
- Until 2009 only one study (Girardeau et al., 2009) showed a causal relationship between post-training ripples and consolidation. Girardeau et al trained rats with a spatial task and gave ripple-contingent electrical stimulation to the hippocampus during sleep after training. Learning was significantly retarded by this interference



Marshall et al (2006) conducted a study where the participant was trained with word-pairs and procedural tasks after which he/she slept a night in the laboratory.

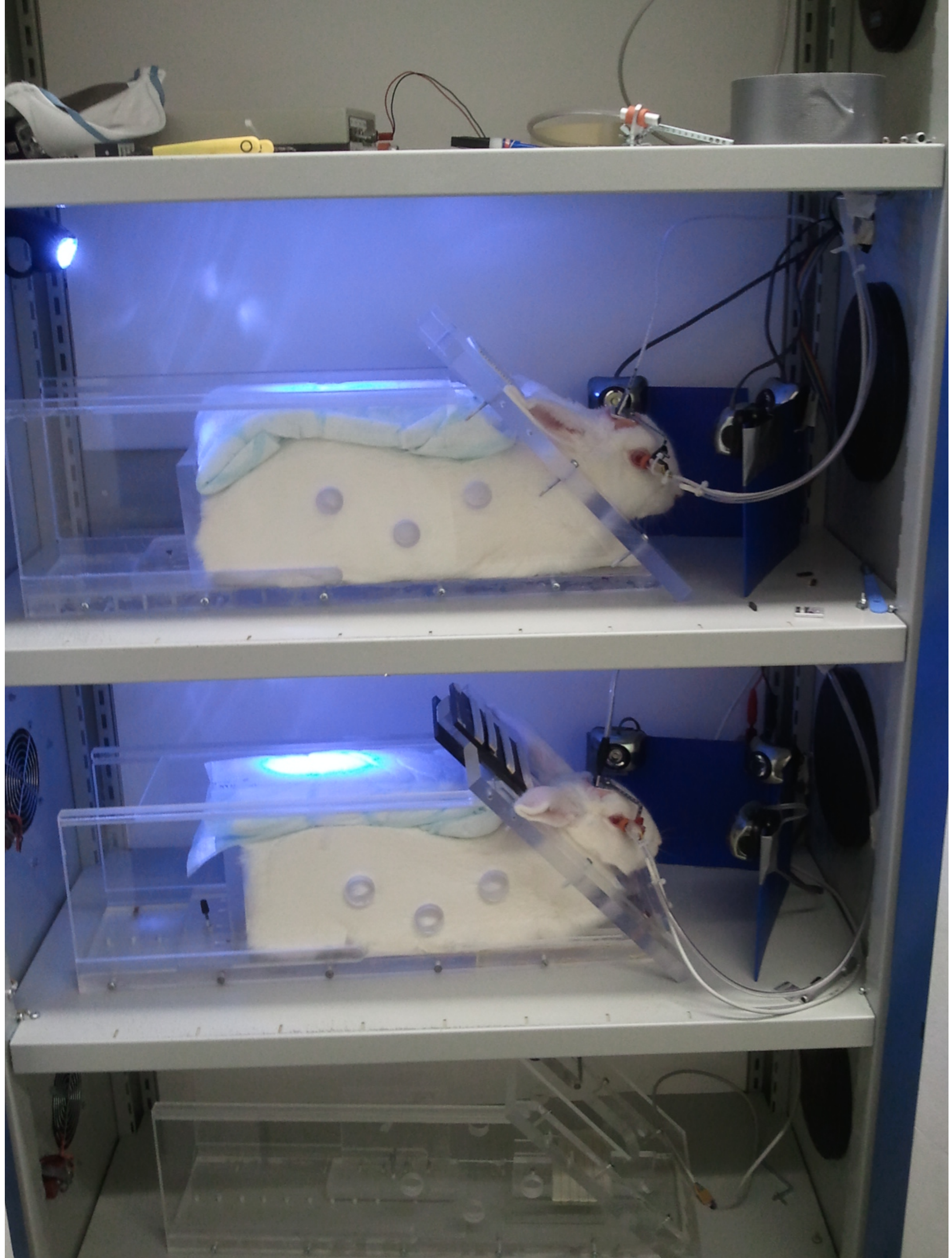
During slow wave sleep, slow oscillation was enhanced by slow transcranial electrical stimulation.

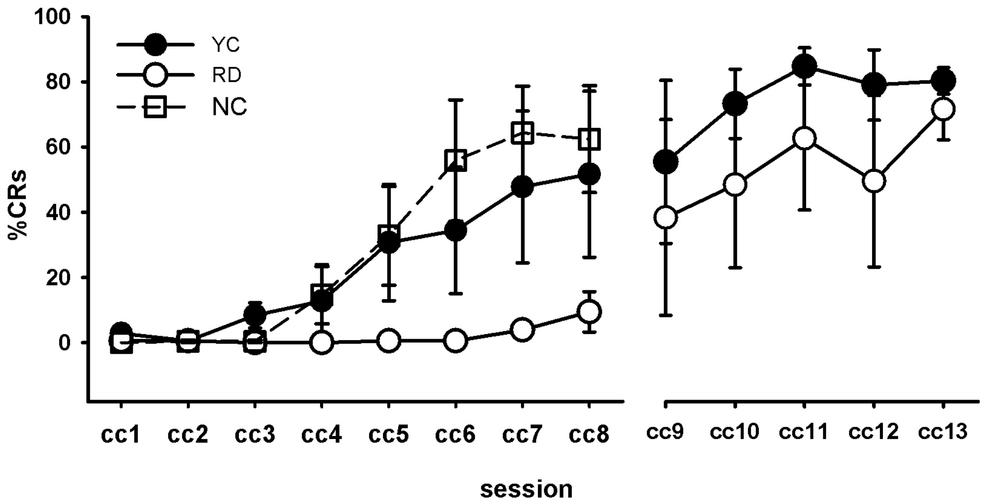
In the next day, the subjects were again tested for their memory. Treatment augmented performance in declarative (explicit, requiring conscious processing) but not in procedural (implicit, not requiring conscious processing) tasks.



We asked whether learning could be interfered (or even prevented?) by giving rabbits interfering natural stimulation every time there was a ripple event in the hippocampus during inter-trial intervals in eyeblink conditioning session.

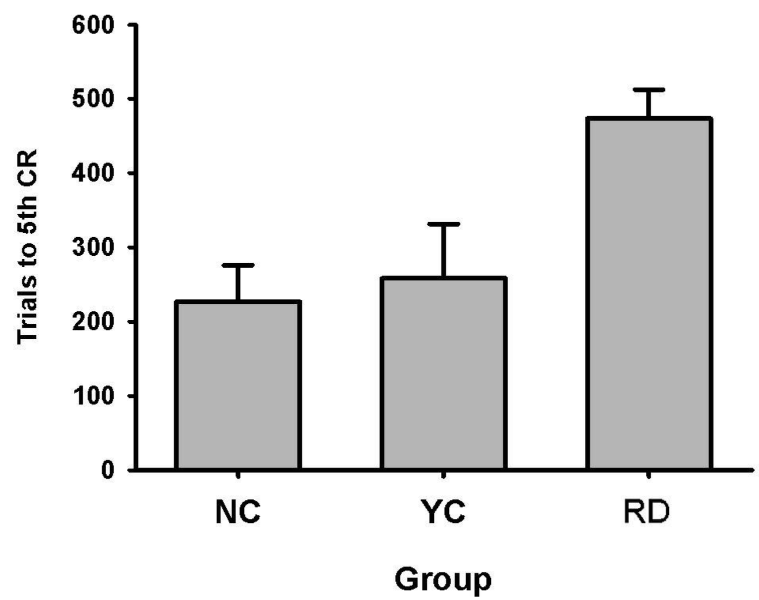
The animals were trained in pairs. The other received a bright LED flash every time there was a ripple. The control animal received the same LED flash at the same time but irrespective of its oscillatory state.





Ripple-contingent LED flash significantly retarded (or almost prevented) learning.

It seems that something necessary for learning occurs when there is a ripple event right after the presentation of learning-relevant material.



Interim summary

- Theta oscillations probably reflect the ”read-state”, when the animal is paying attention to something specific in its surroundings
- Ripples occur in a state where the animal ”relaxes”. During that state, memories are ”written” to the brain.

Thanks for your hippocampal theta oscillation!