Learning and Memory:
Chapters 24 & 25, parts of 18 (amygdala)

1. **To review fundamental themes of learning and memory (2 forms of memory, HM, phases of memory, molecular mechanisms, and memory enhancement)**
2. **To review standard models of learning and memory (e.g. fear conditioning, water maze, CREB knockout mice, etc.**
3. **To mention pathologies and treatments of learning and memory (post-traumatic stress disorder, brain injury, phobias)**

Learning and memory

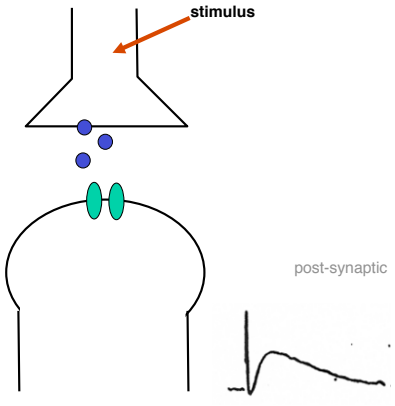
The six things everyone should know about learning and memory.

1. Plasticity is mediated by changes in synaptic connections that alter transmission in response to the learned stimulus

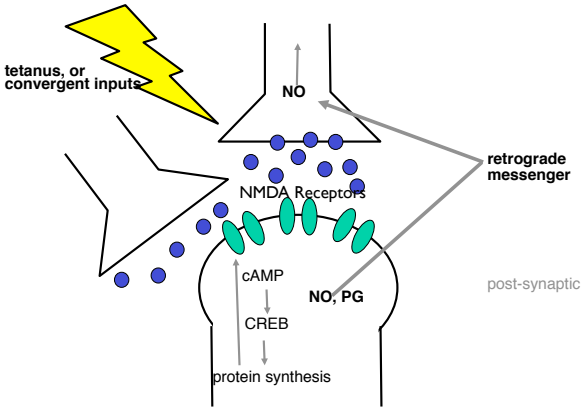
Long-term potentiation & retrograde messengers are an example of a Hebbian synapse:

coincident activity in pre- and post-synaptic neuron strengthens the connection between the two neurons.

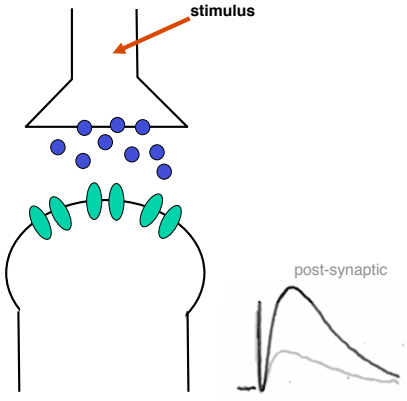
pre LTP Synapse



Mechanism of LTP



post LTP = Stronger Synapse



Mechanisms of Long-Term Potentiation

Increase in presynaptic transmitter release, postsynaptic receptors or signaling, or structural changes (more synapses, sprouting of spines)

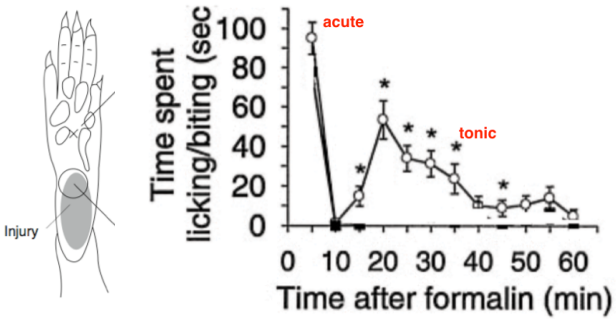
Mediated by some specific transmitters:
e.g., Glu at NMDA receptors, Nitric oxide

2 Phases: short-term (minutes) and long-term (days)

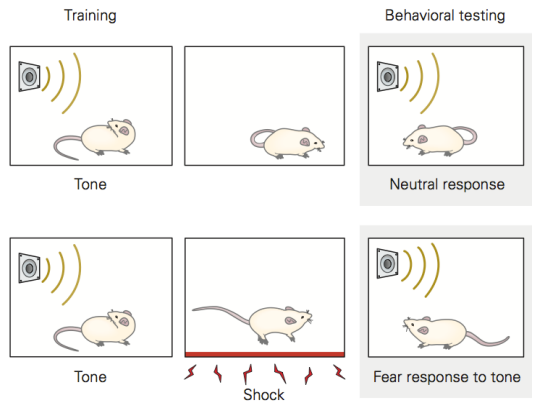
Short-term mediated by second-messengers and kinases (e.g. cAMP and protein kinase A)

Long-term mediated by gene expression induced by transcription factors (e.g. CREB (cAMP response element binding protein))

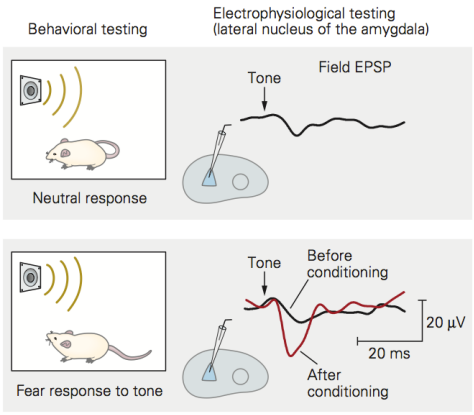
Formalin paw-licking test
Acute and tonic phases



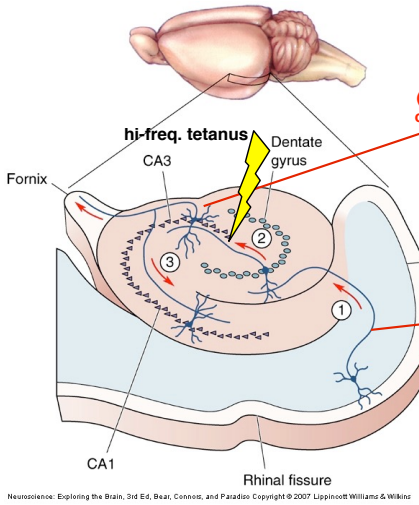
Fear Conditioning and Long-Term Potentiation



Fear Conditioning and Long-Term Potentiation

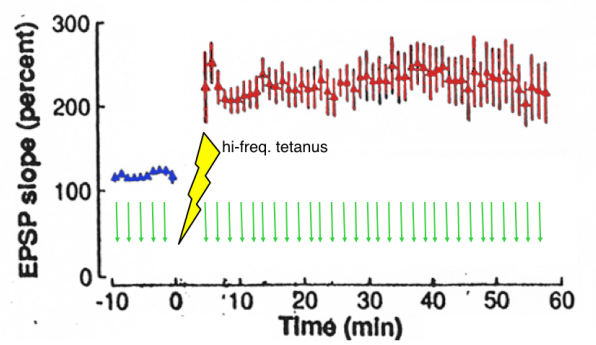


Synaptic Changes in a hippocampal slice

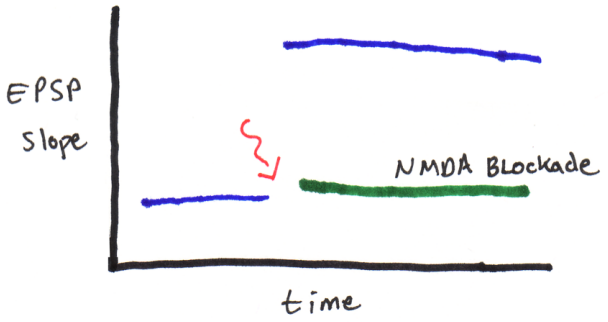


HC has good architecture for studying synaptic plasticity:
cell bodies in CA1-3 layer. dendrites and input axons form array in accessible space without cell bodies.

Long-Term Potentiation (LTP)

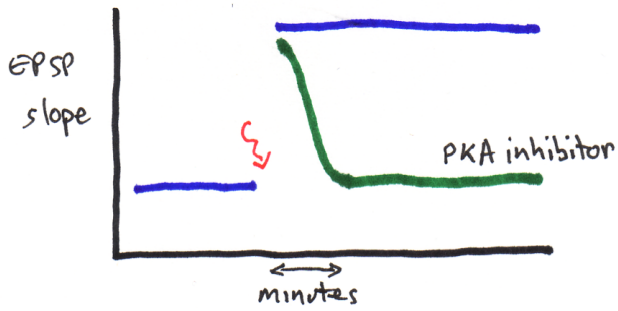


Probing Plasticity using LTP:
Role of NMDA neurotransmission



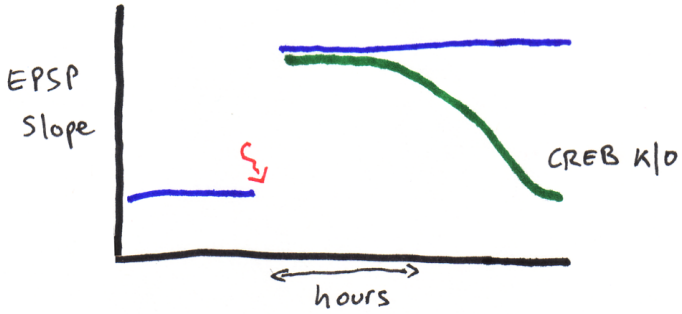
NMDA glutamate receptors are required for LTP

Probing Plasticity using LTP:
Role of Intracellular Signaling Cascades



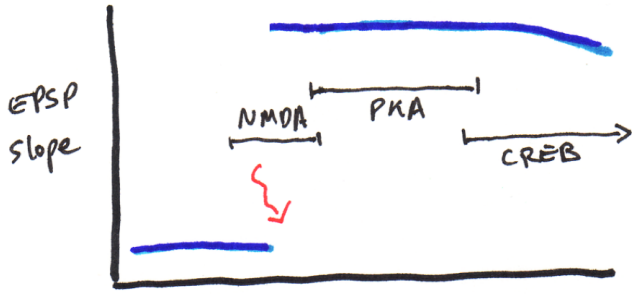
After a seconds or minutes, second messenger systems like cAMP->PKA are required for LTP

Probing Plasticity using LTP:
Transcription Factors & Gene Expression



no need for protein synthesis for ~6h.
After 6h, gene expression controlled by transcription factors like CREB is critical.

Probing Plasticity using LTP:
Assembling the Time Line

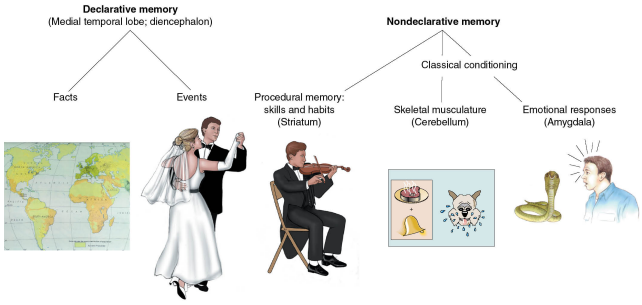


PreRx
boosting NMDA levels
might boost memory

Short-term Rx
maintaining high PKA
might boost memory

No Long-Term Rx
available
to boost gene exp.

2. There are two categories of learning



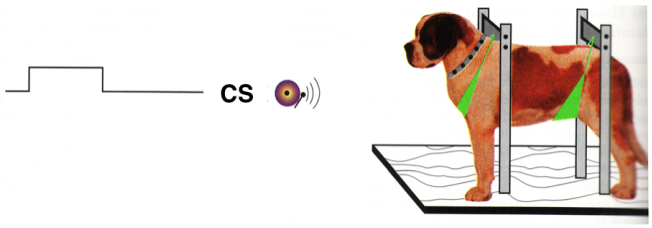
Implicit/Non-declarative

Implicit/Non-declarative
cerebellum, brainstem, amygdala

Associative learning
e.g. classical conditioning:
- **Pavlov's dogs**
- **Eye-blink conditioning**
- **Fear Conditioning via amygdala**

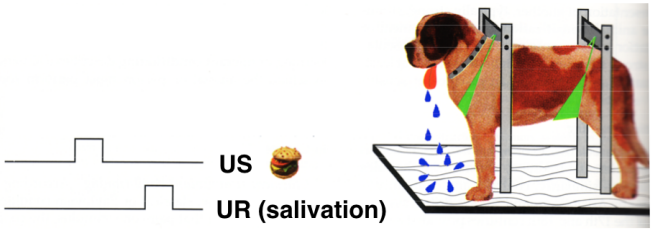
Motor-learning (skills and habits)
e.g riding a bike

Pavlovian Conditioning



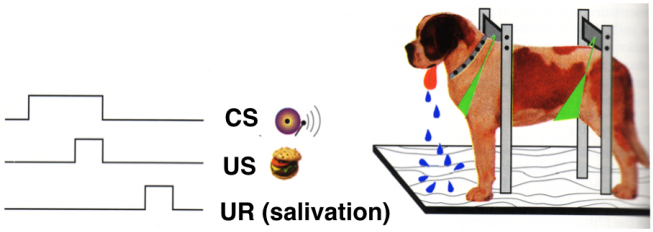
CS = conditioned stimulus

Pavlovian Conditioning



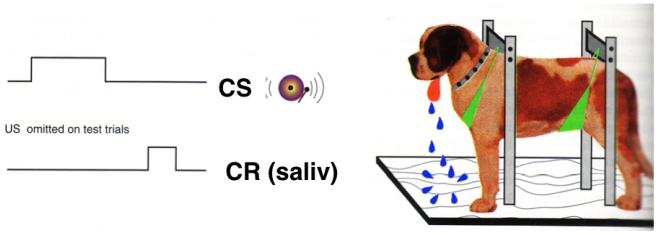
US = unconditioned stimulus
UR = unconditioned response

Pavlovian Conditioning



CS = conditioned stimulus
US = unconditioned stimulus
UR = unconditioned response

Pavlovian Conditioning



CS = conditioned stimulus
CR = conditioned response

Eye-Blink Conditioning

US = Air puff to eye

UR = blink reflex

CS = tone

CR = blink to tone

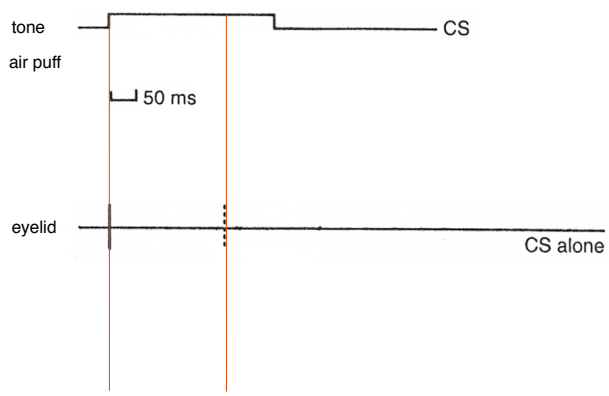
Illustrates:

Easy to perform in humans

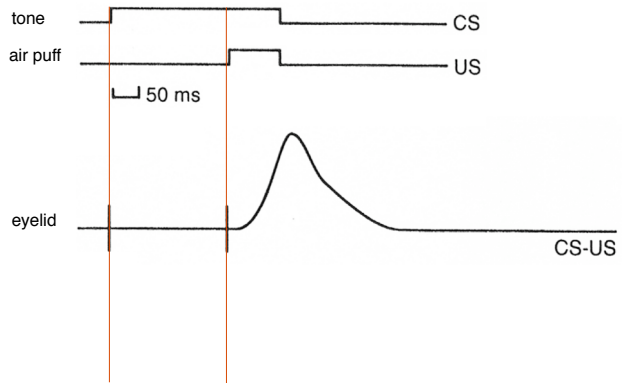
Development of conditioned response to blink

Meditated by Cerebellum and brainstem (I.e. cortex is not required)

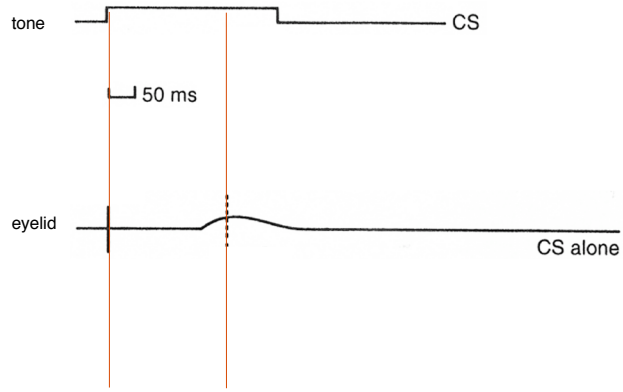
Eye-Blink Conditioning: Trial 1



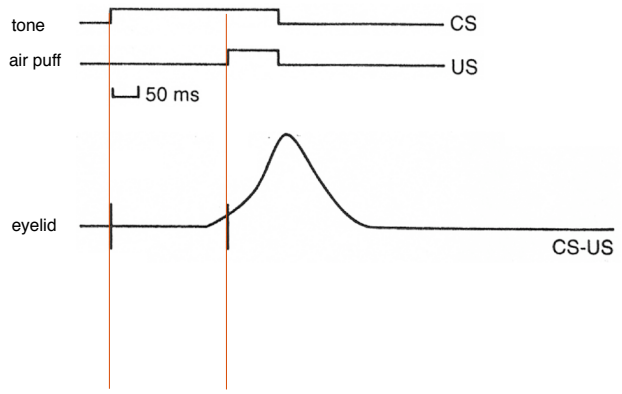
Eye-Blink Conditioning: Trial 1



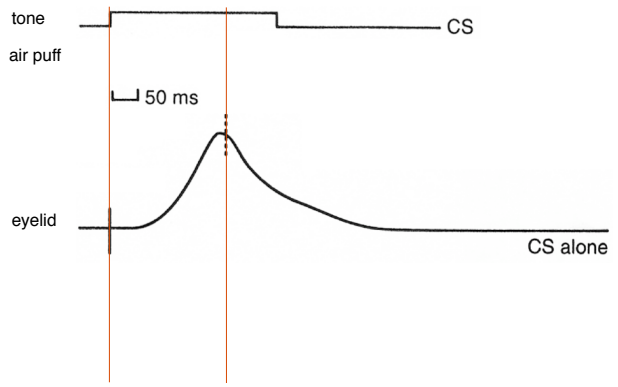
Eye-Blink Conditioning: Trial 30



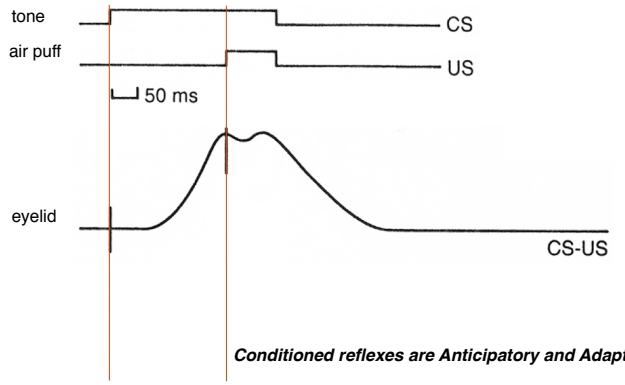
Eye-Blink Conditioning: Trial 30



Eye-Blink Conditioning: Trial 100+

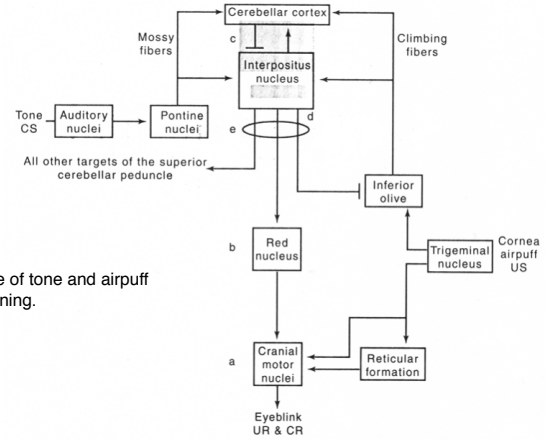


Eye-Blink Conditioning: Trial 100+



Conditioned reflexes are Anticipatory and Adaptive

Eye-Blink Conditioning: Neural Circuit



Convergence of tone and airpuff is site of learning.

Fear Conditioning

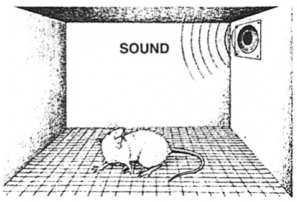
CS = tone
US = shock
CR = freezing, stress response (heart rate, sweat)

Model of post-traumatic stress disorder, anxiety, and phobias

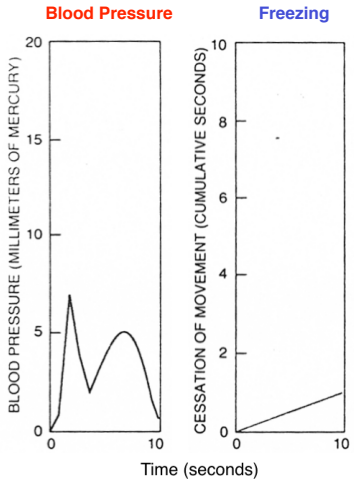
Requires amygdala with thalamic and cortical inputs

Illustrates limbic conditioning with learned emotional, behavioral, and physiological responses

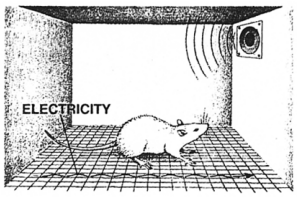
Fear Conditioning



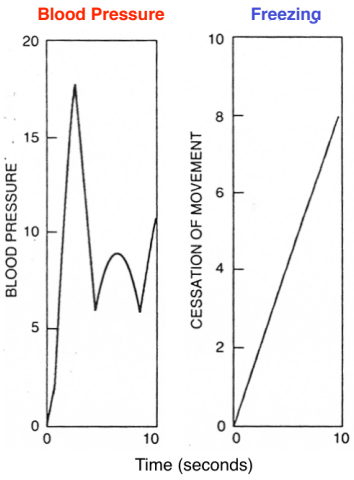
CS



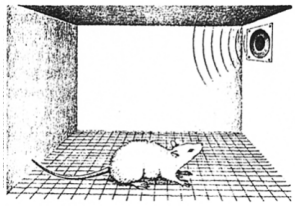
Fear Conditioning



CS + US



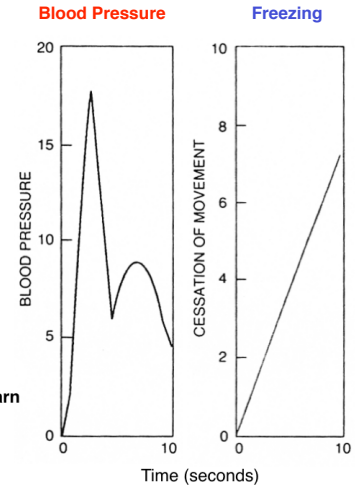
Fear Conditioning



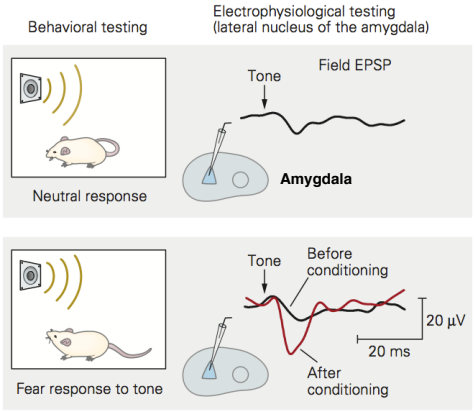
CS

mediated by amygdala

(rats with amygdala lesion do not learn association)

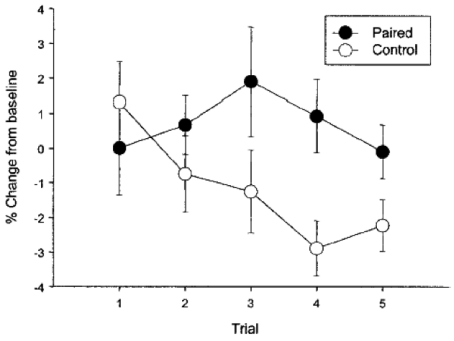


Fear Conditioning and Long-Term Potentiation



Fear Conditioning in Humans

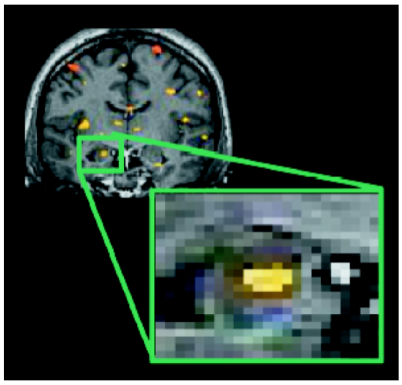
Galvanic skin response to red light



Cheng 2003

CS = flashing red light
US = shock to tibial nerve

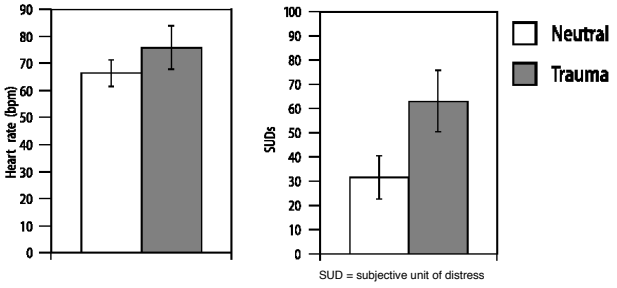
Activation of Amygdala in Conditioned Fear



Cheng 2003

PTSD as Fear Conditioning in Humans

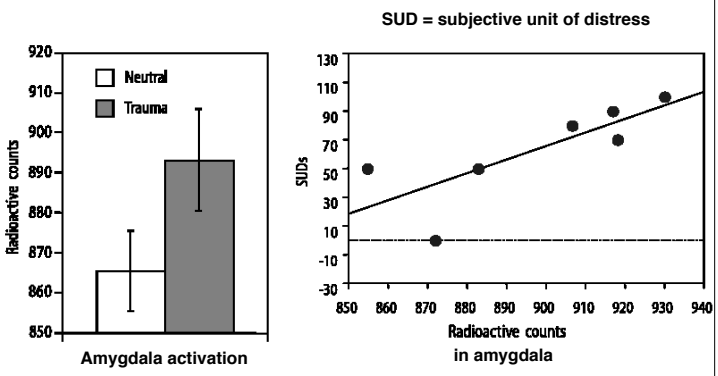
The traumatic war stimulation included combat related sounds (e. g., machine gun fire, explosions, helicopter sounds) and the neutral stimulation consisted of simple 1000 Hz tones.



Data from the Panic Anxiety Scale revealed that 6 of the 7 patients had a full-blown panic attack in the scanner during traumatic stimulation (vs 2/7 during neutral stimulation)

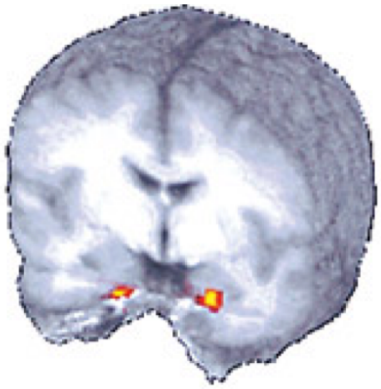
Pissiota 02

PET Activation of Amygdala = Distress



(PET = positron emission tomography, here localizing radioactive glucose utilization within brain)

Amygdala as "Fear Center" in Humans



Enhanced amygdala activation to disapproving or angry faces in Generalized Social Phobia patients

Stein 2002

Reversal of Conditioned Responses

Forgetting
decay of memory (synapses?) with the passage of time leads to attenuated response

Problem: fear conditioning is not readily forgotten.

Extinction
Reversal of learning by repeated, unpaired presentation of conditioned stimulus

(e.g. repeatedly play tone without shock, or expose phobic to object of fear)

3. The case of HM

Surgical ablation of the entorhinal cortex, amygdala, and most of the hippocampus to treat epileptic seizures

HM has only working or very short-term declarative memory, but has ability for motor learning.

Retains memory of events prior to surgery.

Illustrates localization of memory formation, and separation of recent and distant memories.

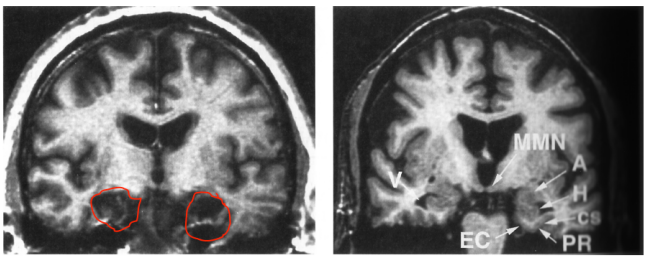
Lead to development of declarative memory models in animals.

The case of HM

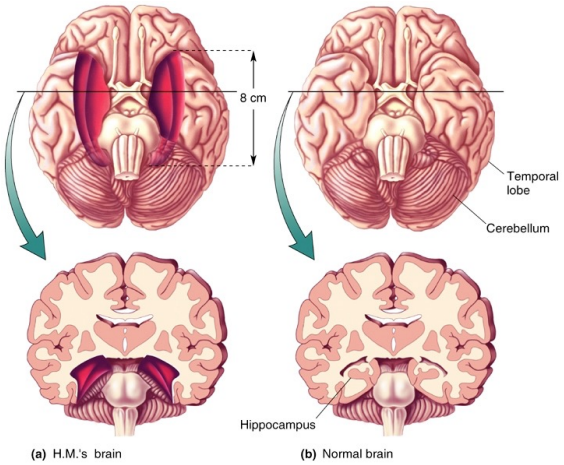
This 27-year-old motor winder, a high school graduate, had had minor seizures since the age of 10 and major seizures since the age of 16. Despite heavy and varied anticonvulsant medication, the major attacks had increased in frequency and severity through the years until the patient was quite unable to work. The etiology of this patient's attacks is not clear. He was knocked down by a bicycle at the age of 9 and was unconscious for 5 min afterward, sustaining a laceration of the left supraorbital region. Later radiological studies, however, including two pneumoencephalograms, have been completely normal, and the physical examination has always been negative. Electroencephalographic studies have consistently failed to show any localized epileptogenic area.

The case of HM

On September 1, 1953, bilateral medial temporal-lobe resection was carried out, extending posteriorly for a distance of 8 cm from the midpoints of the tips of the temporal lobes, with the temporal horns constituting the lateral edges of resection.



but these are less incapacitating than before.



The case of HM

A *psychological examination* was performed on April 26, 1955. The memory defect was immediately apparent. The patient gave the date as March 1953, and his age as 27. Just before coming into the examining room, he had been talking to Dr. Karl Pribram, yet he had no recollection of this at all and denied that anyone had spoken to him. In conversation, he reverted constantly to boyhood events and seemed scarcely to realize that he had had an operation.

In summary, this patient appears to have a complete loss of memory for events subsequent to bilateral medial temporal lobe resection 19 months before, together with a partial retrograde amnesia for the 3 years leading up to his operation, but early memories are seemingly normal and there is no impairment of personality or general intelligence.

Significance of H.M.

Demonstrated that declarative memory is distinct from associative memory
H.M. can still learn non-declarative motor tasks, like reverse mirror tracing

Demonstrated that declarative memory has a discrete neurological substrate.
Hippocampus is required for memory acquisition and short-term storage; after several hours, memory is transferred to cortical locations.
Hippocampal deficits or trauma -> memory deficits
Increased memory or spatial learning -> increased hippocampal growth

Suggested that animal models could be used to explore neurological basis for declarative memory.
after hippocampal lesions, rats do poorly at swim test, monkeys poorly at delayed match to sample task.

Declarative Memory:

places, events, and things

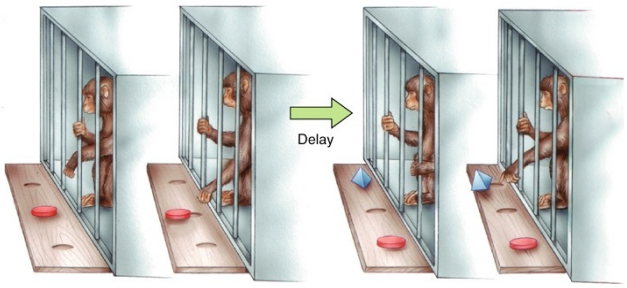
cortex, hippocampus

How to test in animals?

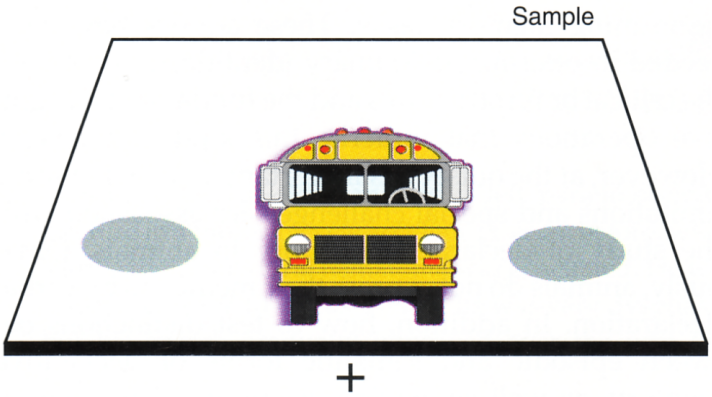
Delayed Non-Match to Sample
visual memory test in primates

Water-Maze
spatial test in rodents

Delayed Non-Match-To-Sample



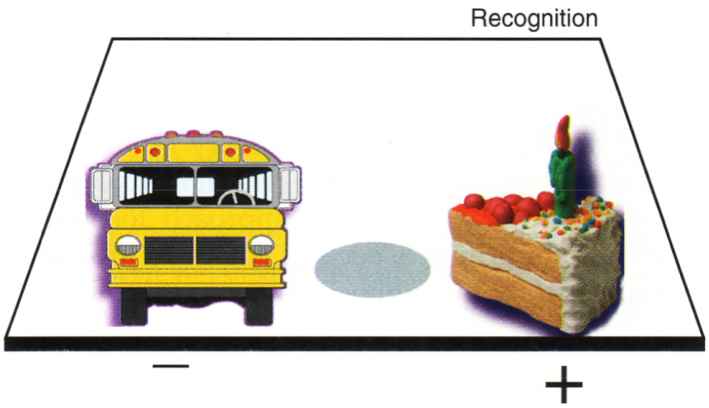
Delayed Non-Match-To-Sample

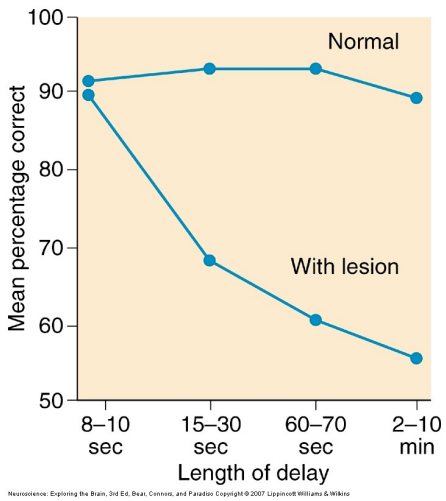


Delayed Non-Match-To-Sample

….Delay….

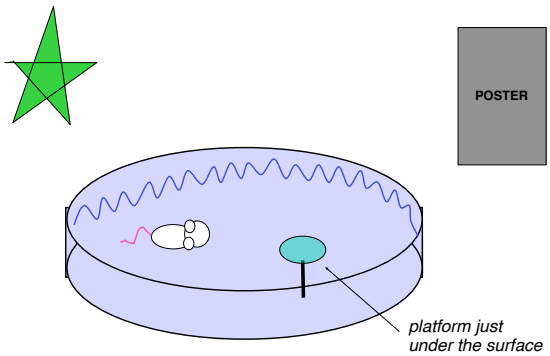
Delayed Non-Match-To-Sample





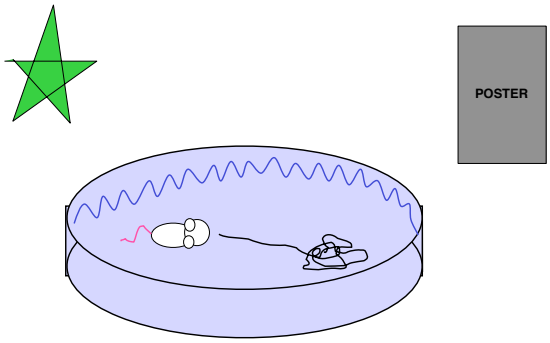
Water-Maze test of spatial memory

Over several trials, rat learns the location of submerged platform relative to "landmarks" hanging on the wall.

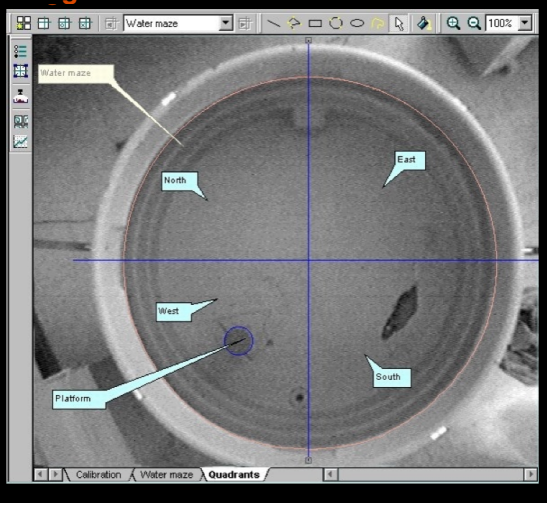


Water-Maze recall of spatial memory

Platform is removed; Rat demonstrates memory for the location by swimming in the correct vicinity.



Video image of water maze

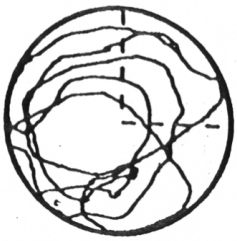


Water-Maze for Drug testing

Vehicle Rx

Control swims in vicinity of (removed) platform

NMDA Antagonist

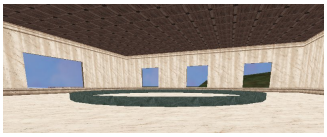


When trained under NMDA blockade, no memory of platform.

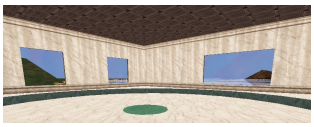
Also apply to enhancers, pathologies, or brain lesion studies, etc.

“Water Maze” testing in humans

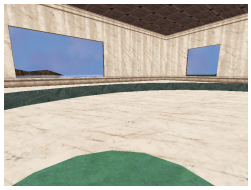
Virtual water maze requires combinations of distal and proximal cues for navigation (not just single cues or landmarks)

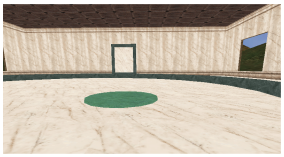


Views showing visible platform and outside scenery



Views of the arena, room and visible platform

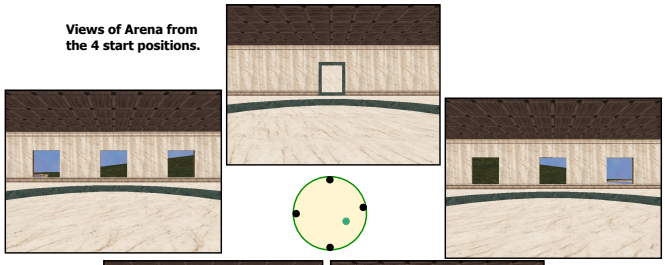




Views of Arena

Trials start from 4 different positions.

Views of Arena from the 4 start positions.

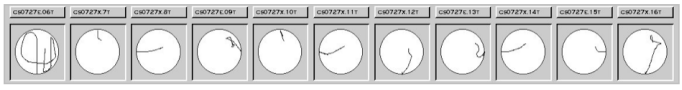


Visible platform

Invisible platform

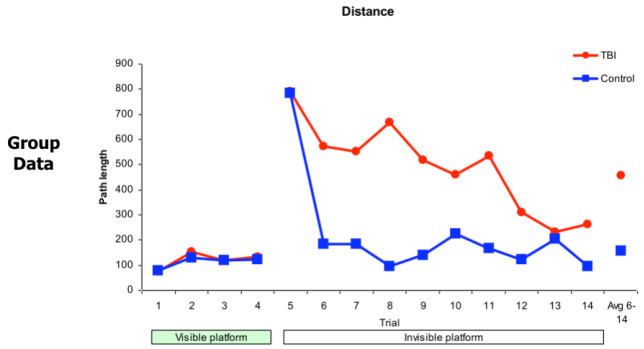
Sample Data

Participant with no injury quickly learns to find the invisible platform



Participant with brain injury takes longer to learn to find the platform

Traumatic Brain Injury Patients take more trials to find platform



4. There are (at least) 3 phases of memory time

i. Working memory (a few seconds?)

lasts while the memory is being acquired or used in a task. Probably relies on continuing neural activity and synaptic transmission

(e.g. your cerebellum calculating the trajectory of a basketball shot, or your hippocampus remembering a phone number)

4. There are (at least) 3 phases of memory time

ii. Short-term memory (seconds to hours)

transient memory that does not require protein synthesis.

Probably relies on modifications of receptors (e.g. by phosphorylation) or upregulation of second messengers (e.g. more cAMP, more G-protein activation) at existing synapses.

4. There are (at least) 3 phases of memory time

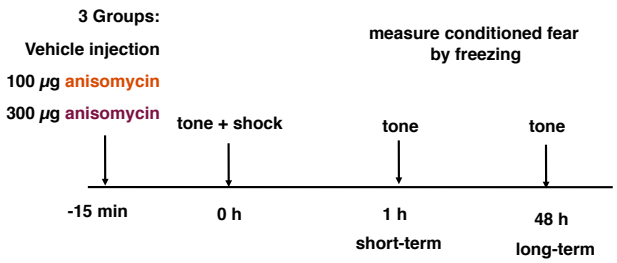
iii. Long-term memory (days to years)
requires protein synthesis (expression of genes) to make new proteins to make new semi-permanent connections in the neural network.

The transistion from short-term to long-term memory is called consolidation of the memory.

If the learning is sufficiently strong, the short-term mechanisms (e.g. elevated second messengers) may induce protein synthesis and hence consolidation.

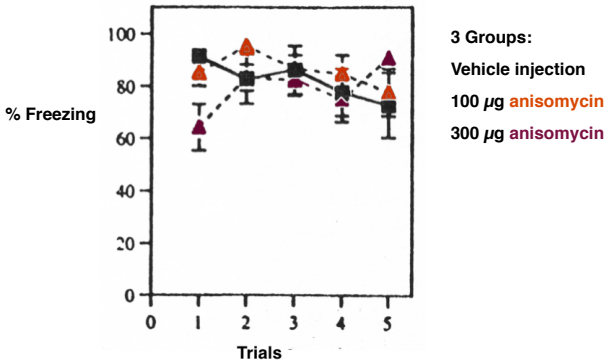
Consolidation requires protein synthesis

anisomycin blocks synthesis of new proteins



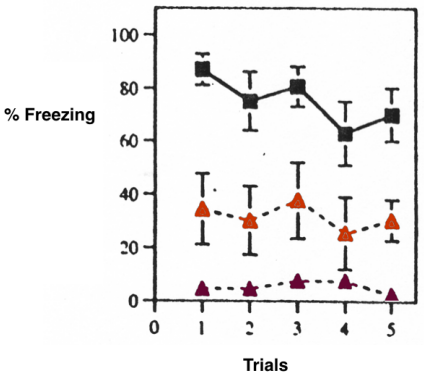
Consolidation requires protein synthesis

Short-Term Memory Test of Fear Conditioning at 1 hour



Consolidation requires protein synthesis

Long-Term Memory Test of Fear Conditioning at 6-48 hours



3 Groups:

Vehicle injection

100 μg anisomycin

300 μg anisomycin

5. Some of the molecular mechanisms underlying learning are common to all animals (from snails to fruit flies to mice).

Learning event

-> cAMP

-> CREB activation (cAMP-response element binding protein)

-> gene promoters that have CRE in promoter (up to ~4,000 genes in human genome)

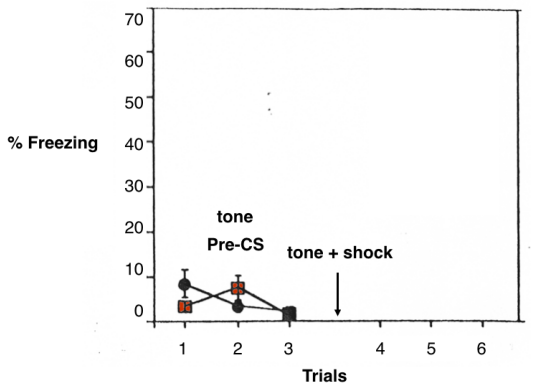
-> gene expression

-> new proteins

-> new synaptic connections.

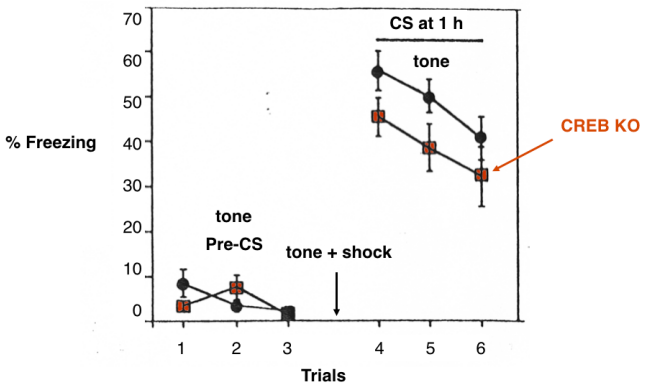
Fear Conditioning in CREB Knockout mice

Short-Term Memory Test of Fear Conditioning at 1 hour



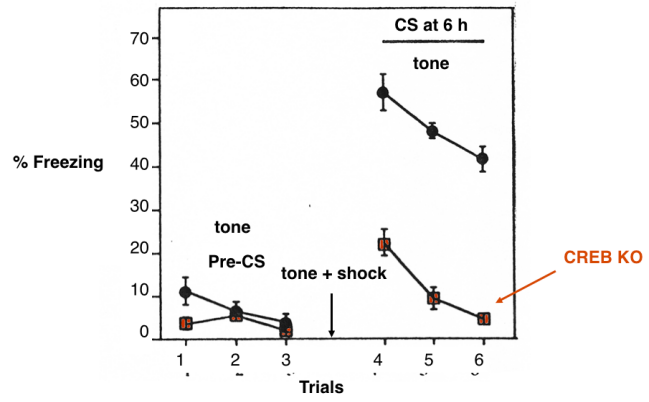
Fear Conditioning in CREB Knockout mice

Short-Term Memory Test of Fear Conditioning at **1 hour**



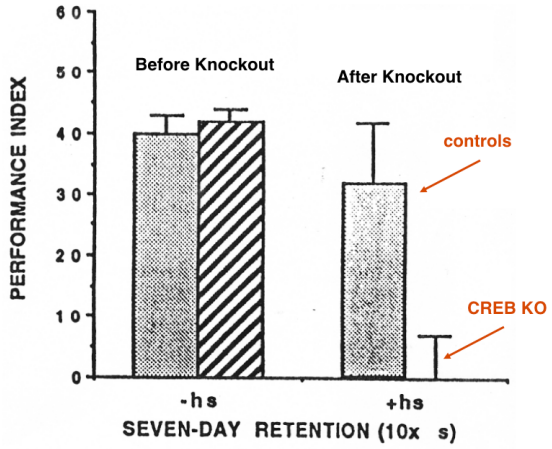
Fear Conditioning in CREB Knockout mice

Long Term Memory Test of Fear Conditioning at **6 hour**



Fear Conditioning in CREB Knockout flies

flies trained to avoid odor paired with shock



6. Cognitive Enhancers are on their way

- Cholinergic drugs to ameliorate Alzheimers
- AMPAkines boost glutamate transmission
- Screening for CREB enhancers

  (e.g. phosphodiesterase blocker -> more cAMP)
- D-cycloserine (DCS) to boost NMDA neurotransmission

Use of D-cycloserine (DCS) to boost NMDA dependent learning

Old-fashioned tuberculosis drug = safe

Binds to d-serine/glycine site of NMDA receptor and potentiaties actions of glutamate

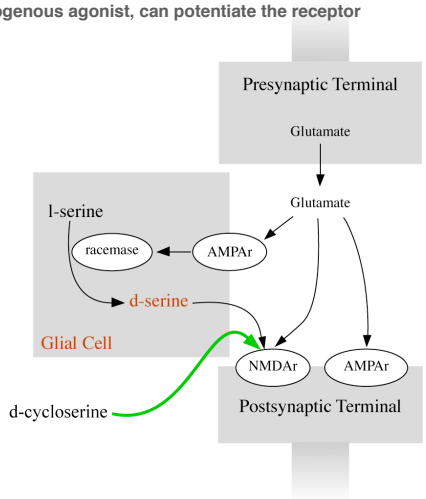
(e.g. like a benzodiazepine boosts GABA at GABA-A receptor)

Enhances cognition in Alzheimers, schizophrenia

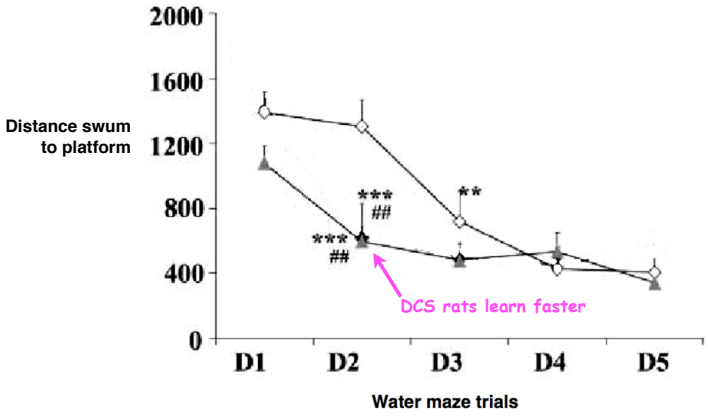
Exciting new data supporting enhancement of learning, including extinction of phobias

D-Serine is required for NMDA Receptor activity

DCS, an exogenous agonist, can potentiate the receptor



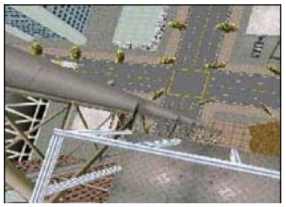
DCS enhances water maze learning in rats



DCS enhances extinction of phobias

1. **Extinction is a form of learning that overrides earlier associations.**
2. **DCS treatment accelerates extinction of fear conditioning in rats.**
3. **Desensitization is a standard extinction therapy for phobias.**
4. **Using virtual reality elevator, Davis et al. at Emory accelerated extinction of acrophobia.**
5. **DCS before therapy improved panic both in elevator, and in self-report of bridges, buildings, etc. for 6 months.**
6. **DCS + 2 therapy sessions = 8 therapy sessions w/o drug.** ***(n.b. no need for long-term drug rx)***

Virtual reality elevator:



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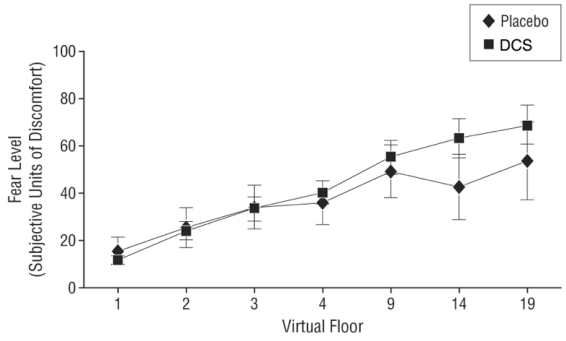
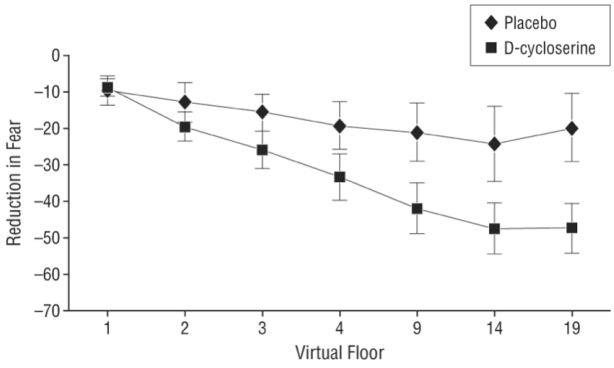
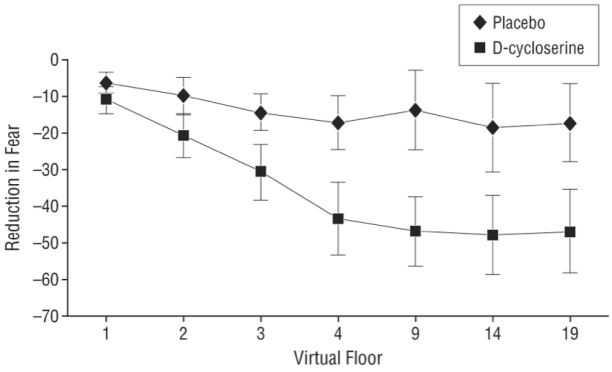
Level of Fear in the Virtual Elevator during Treatment



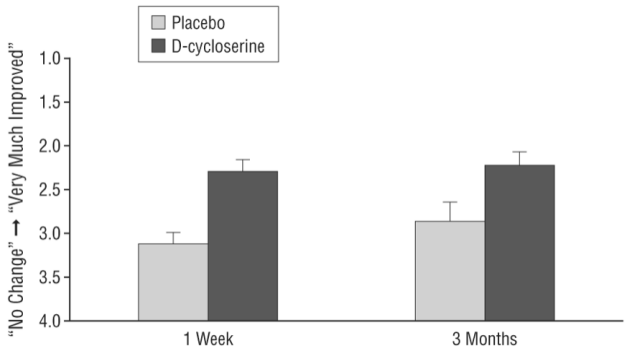
Reduction in Fear: One Week after Last Exposure Sessions



Reduction in Fear:
3 months after Last Exposure Session

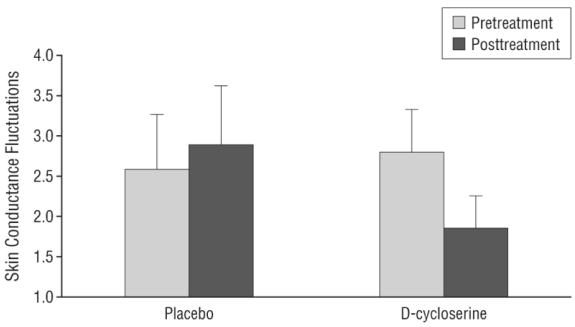


Reduction in Fear:
Patients report greater improvement in acrophobia



Physiological measures of anxiety within the virtual environment.

Skin conductance fluctuations = measure of perspiration = measure of sympathetic activity



D-cycloserine during exposure therapy showed significant decreases in posttreatment fluctuations (paired t-test, $P<0.05$). Placebo treated showed no improvement; $P>0.05$)

Learning and Memory Summary

Two forms of memory:

Implicit/Non-declarative
Model: motor learning, Pavlovian eyeblink and fear conditioning.
Pathology: Enhanced in phobias, posttraumatic stress disorder

Declarative
Model: delayed non-match to sample, and water maze learning.
Pathology: deficient in forebrain injury, HM, Alzheimers, etc.

Specific mechanisms common to many brain regions and species
NMDA receptors, 2nd messengers-> short-term memory
CREB & protein synthesis -> long-term memory

NMDA receptors are targets for cognitive enhancers
Blockade/enhancement of consolidation is next target