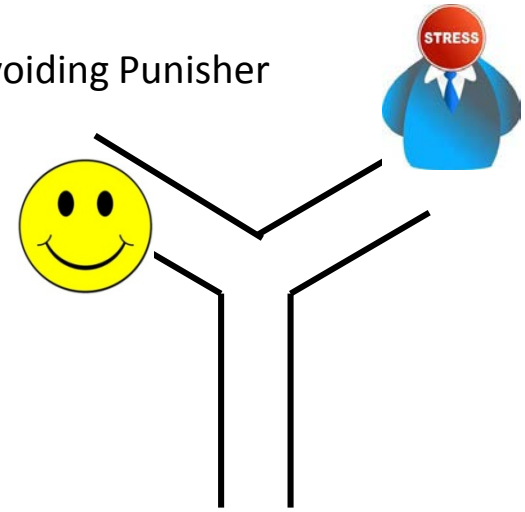
Emotional and cognitive stimulus processing:

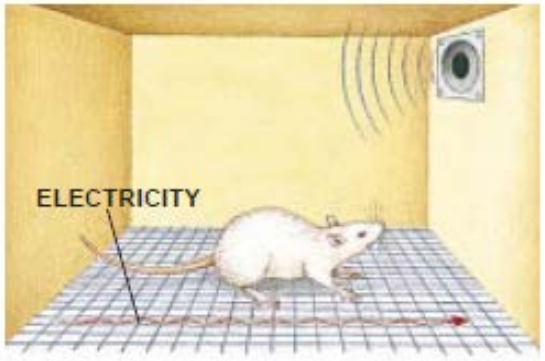
Aversive stimuli, fear and the amygdala

- Amygdala anatomy
- Fear learning
- Long-term potentiation / synaptic plasticity in amygdala synapses
- Emotional centre for behavioural and physiological responses to fear
- Neurotransmitters modulating amygdala function
- Neuropeptides modulating amygdala function
- Amygdala important for processing aversive and rewarding stimuli and also whether or not these stimuli were expected

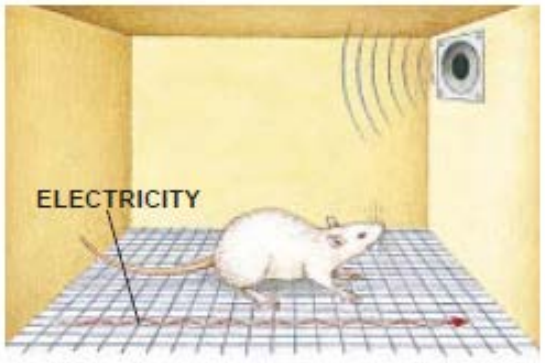
Individuals respond to and learn efficiently about environmental factors

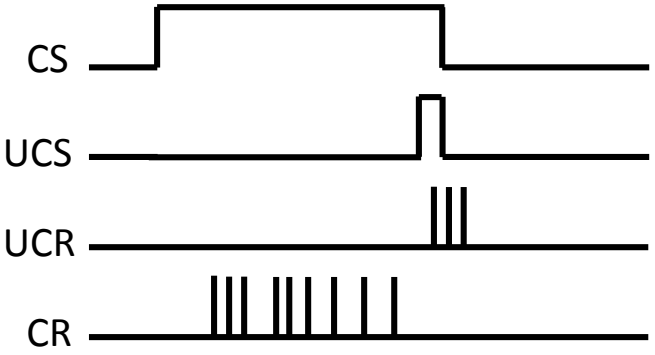
Escaping/Avoiding Punisher

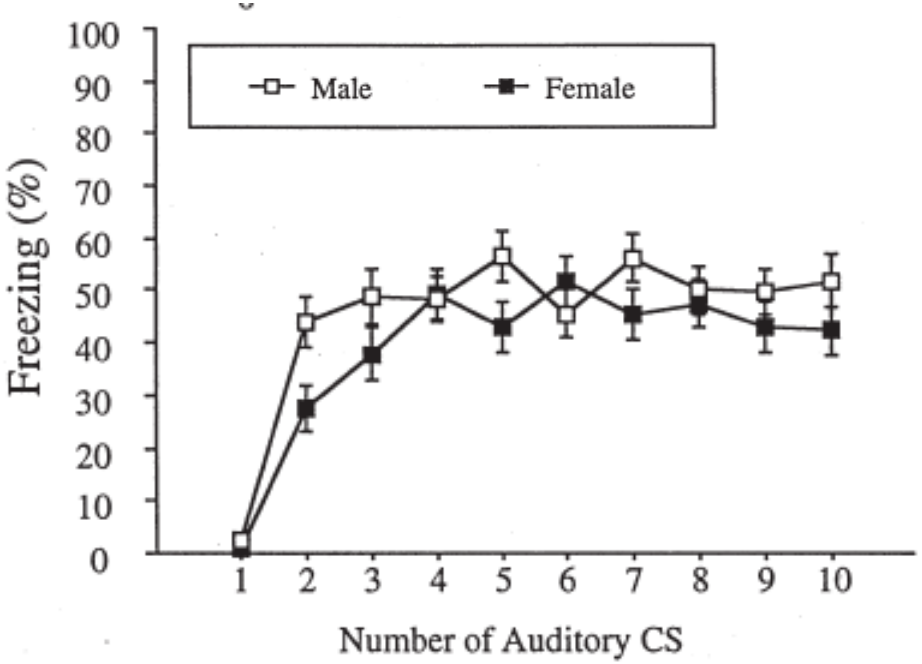


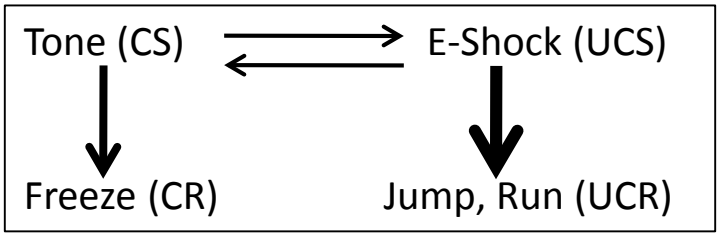


Classical conditioning or stimulus-stimulus conditioning: the learning curve for conditioned fear-freezing





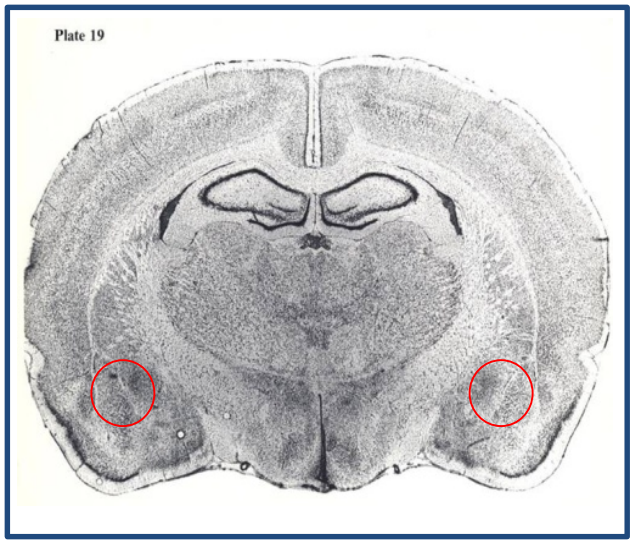




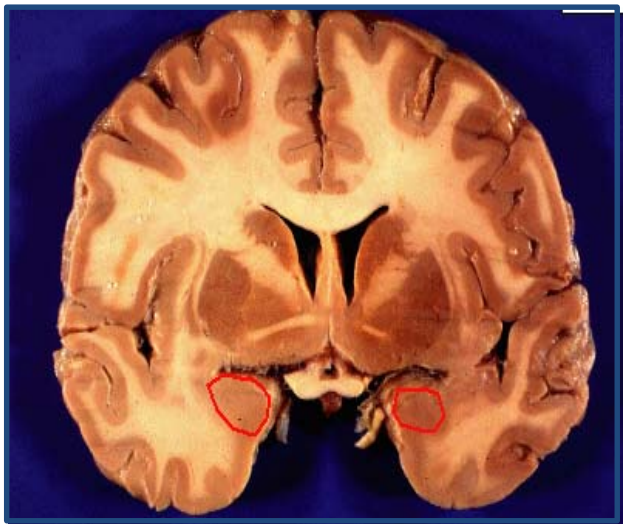
freeze: remove probability that a cat e.g. would see mouse, so just stay still

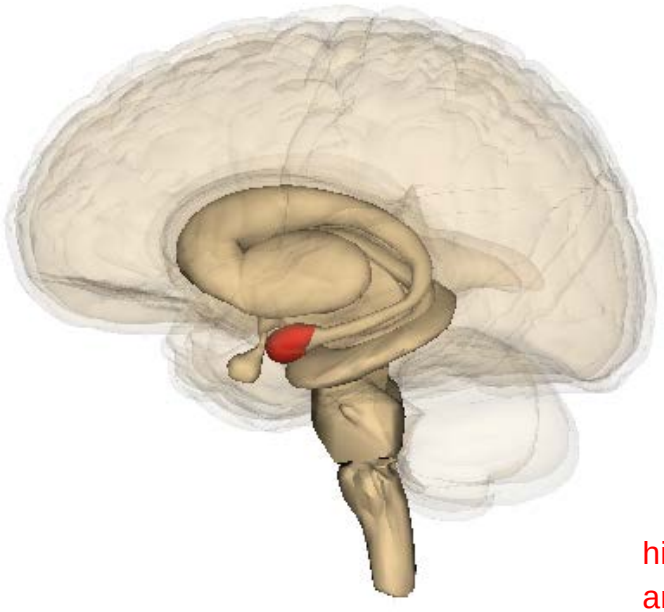
The comparative anatomy of the amygdala

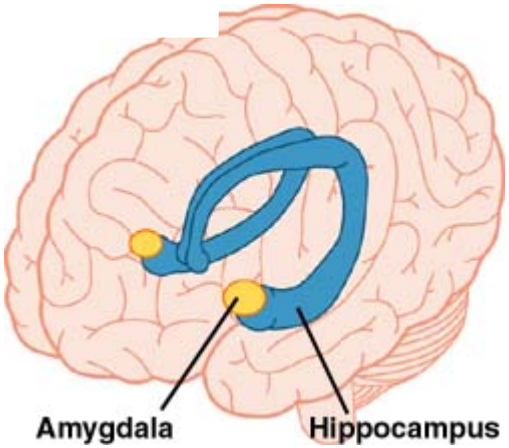
Rat



Human







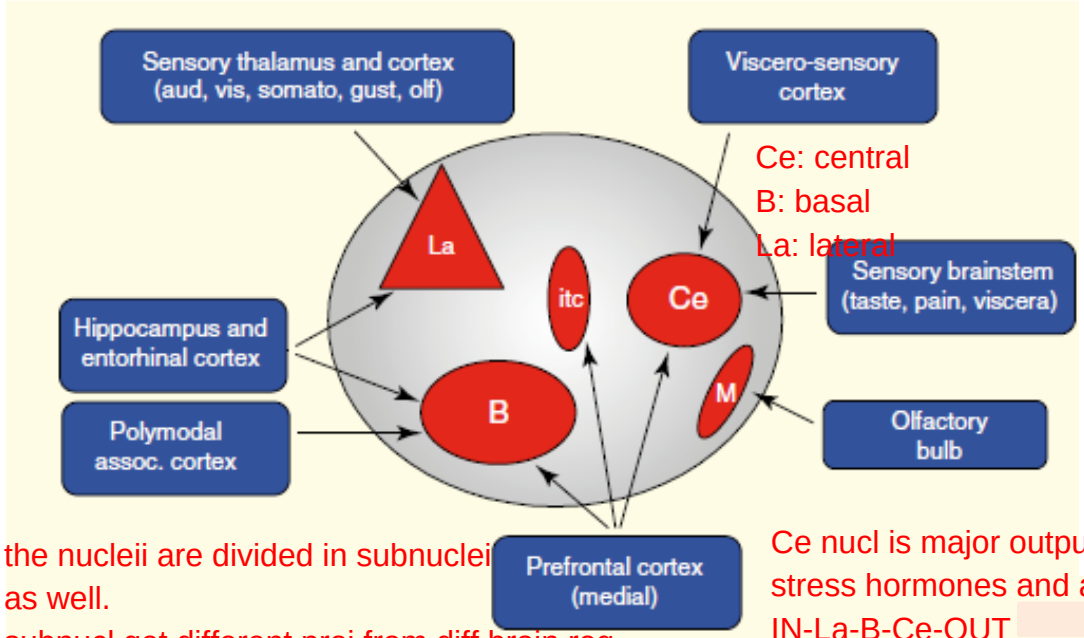
What is to be done? *What is it?*

hippo: what is it? proj info to cortex AND hippo

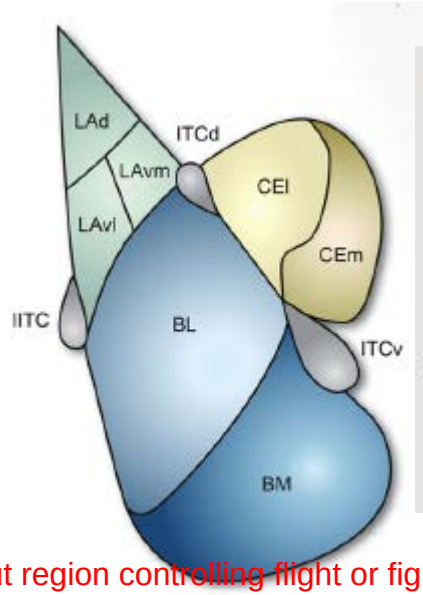
amyg: ok. what is to be done now. amyg has to make an emotional response to stim

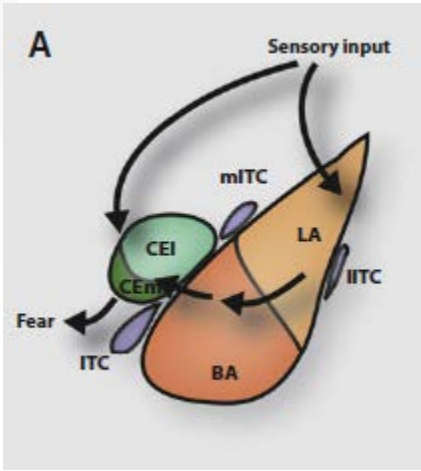
important three nuclei in ymag: lateral nucl basal nucl, central nucl

Inputs to and information flow between specific amygdala nuclei



Ce: central
B: basal
La: lateral

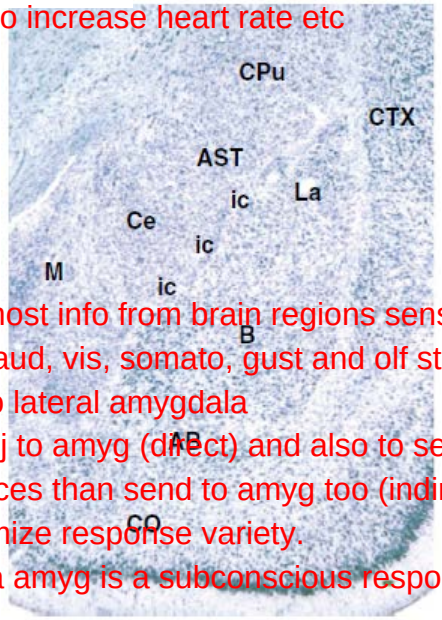


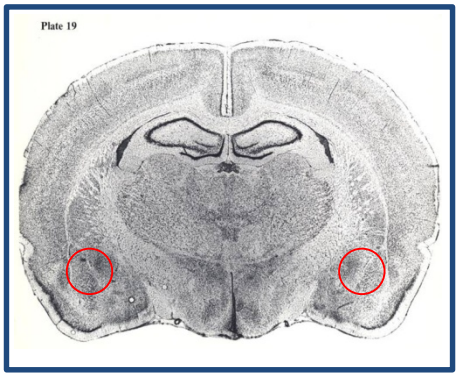


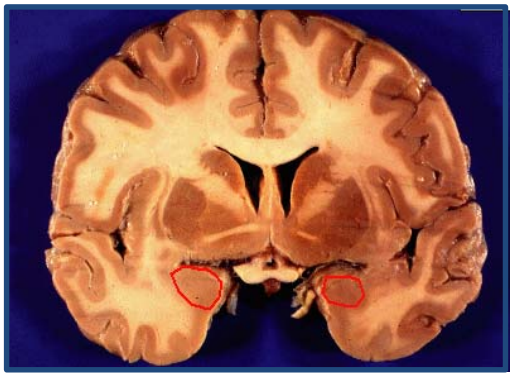
the nucleii are divided in subnuclei as well.
subnucl get different proj from diff brain reg
terefore they are anatomically seperated

Ce nucl is major output region controlling flight or fight beha, to hypthoamalus for stress hormones and autonomous system to increase heart rate etc
IN-La-B-Ce-OUT

La, Lateral nucleus; B or BL, Basolateral nucleus; M or BM, Medial or Basomedial nucleus; Ce, Central nucleus; Cel, lateral Central nucleus; Cem, medial Central nucleus; AB, Accessory basal nucleus; CO, Cortical nucleus; itc, Intercalated cells; CTX, Cortex ; AST, Amygdalo-striatal transition area; Cpu, Caudate putamen







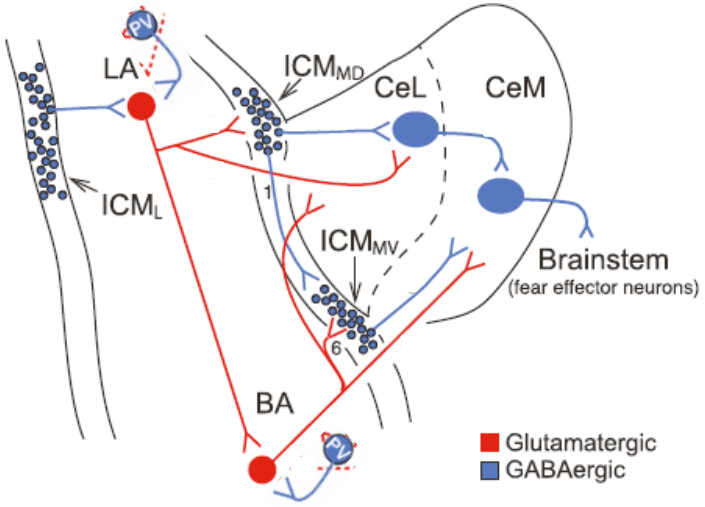
lateral nucel gets most info from brain regions sensing different info, gets aud, vis, somato, gust and olf stim. all senses send info to lateral amygdala
thamalus direct proj to amyg (direct) and also to sens cortices. sens cortices than send to amyg too (indirect)
two inputs to maximize response variety.
sens thamalus to la amyg is a subconscious response often

LeDoux (2007) Curr Biol 17: R868
Lee et al. (2013) Frontiers Neural Circuits 7: 129

Intrinsic Connectivity of the Amygdala

amygdala is made up of the same types of cells like the cortex which are GABA neurons, glutamate neurons, interneurons

some neurons express certain proteins like PV or somatostatin, what defines them further

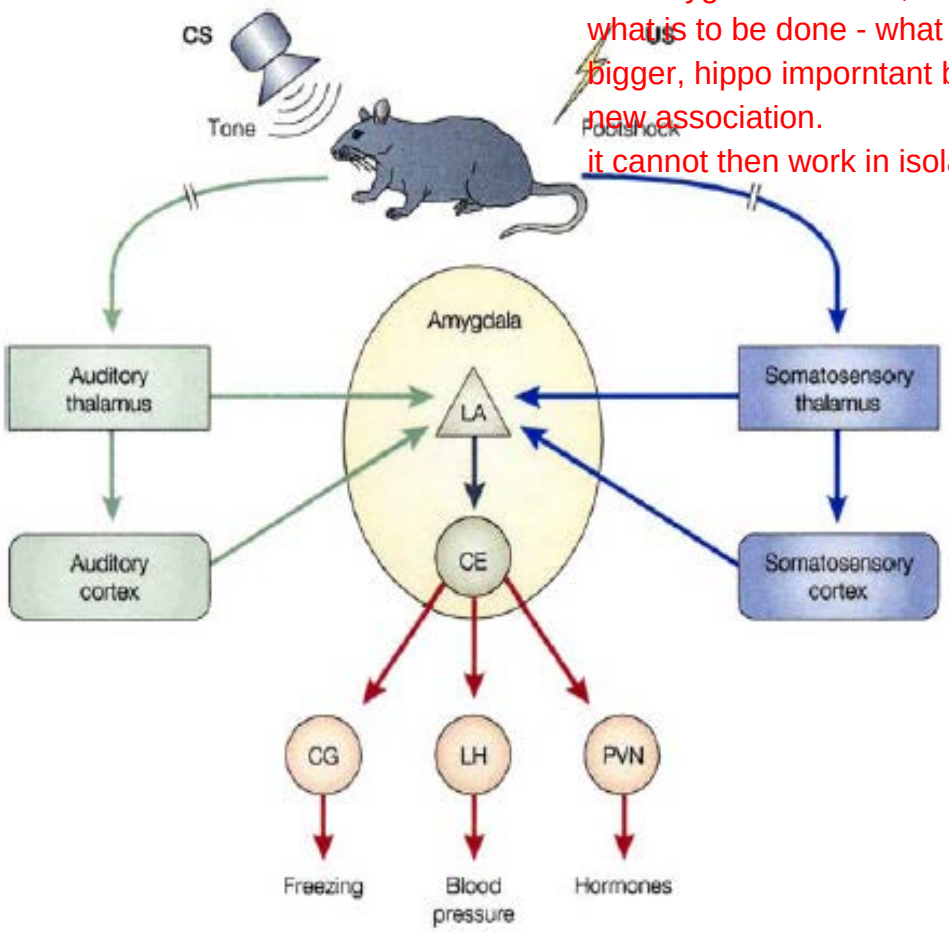


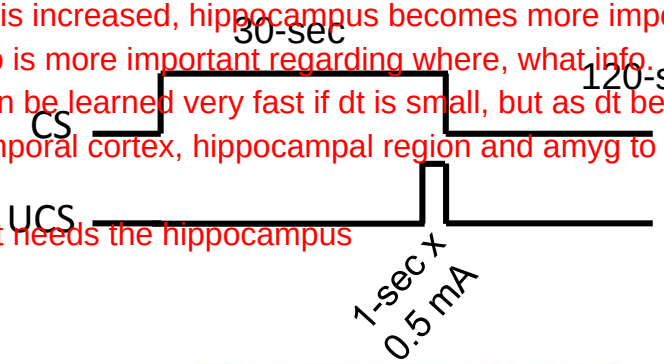
Duvarci & Pare (2014) Neuron 82: 966

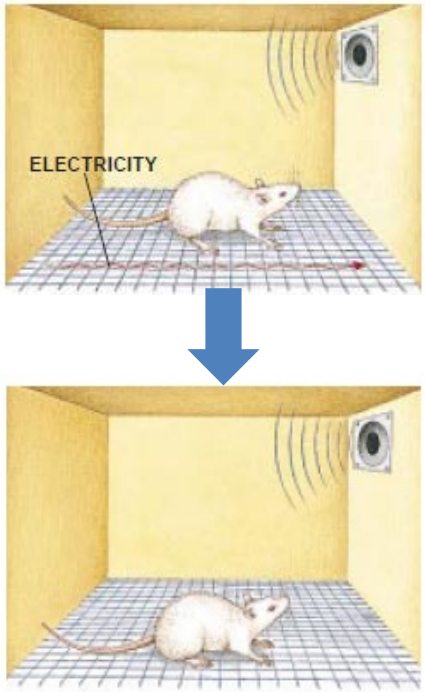
Neural pathways underlying fear conditioning – measured as freezing

Convergence of CS and UCS sensory neuron inputs at the lateral amygdala

as the interval btw CS and UCS is increased, hippocampus becomes more imporntant. the amyg still involved, but hippo is more important regarding where, what info. what is to be done - what is it can be learned very fast if dt is small, but as dt becomes bigger, hippo imporntant btw temporal cortex, hippocampal region and amyg to learn a new association.
it cannot then work in isolation, it needs the hippocampus





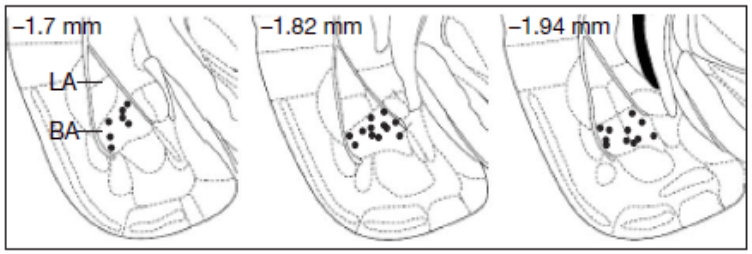


inputs to amygdala via these sens thamalus are senosry and there is no learning if they are lesioned

Phelps & LeDoux (2005) Neuron 48: 175

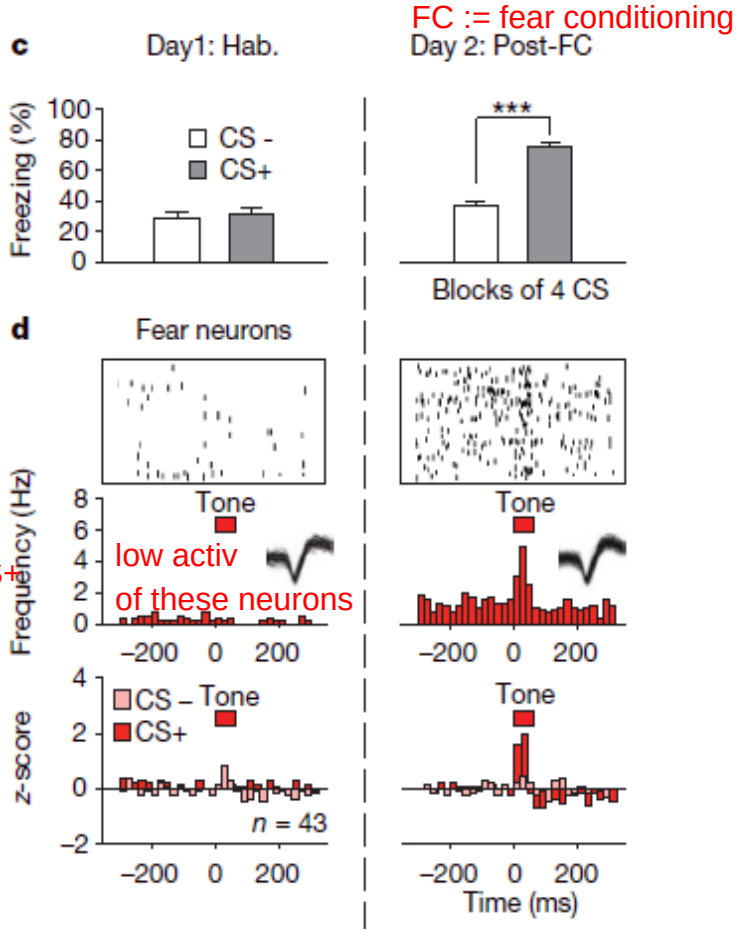
Electrophysiological evidence for CS-Fear neurons in mouse amygdala

LA, Lateral nucleus
BA, Basal nucleus



tone is neutral CS+

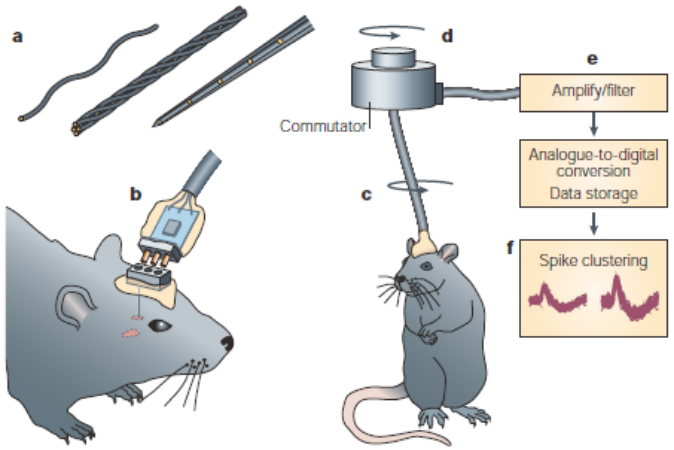
FC := fear conditioning

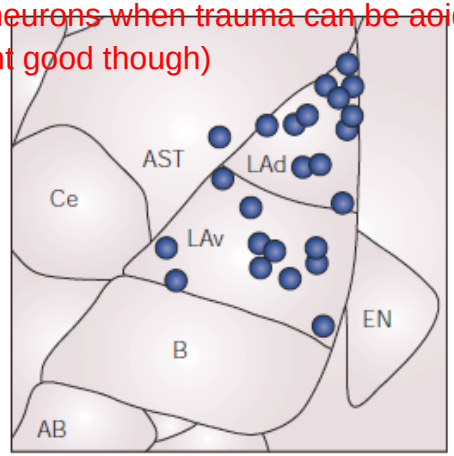


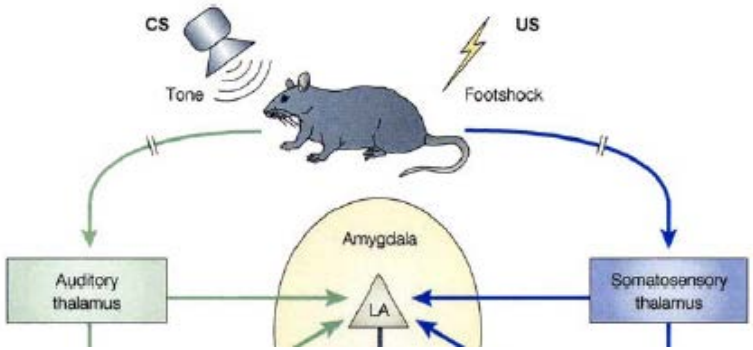
Herry et al. (2008) Nature 454: 600

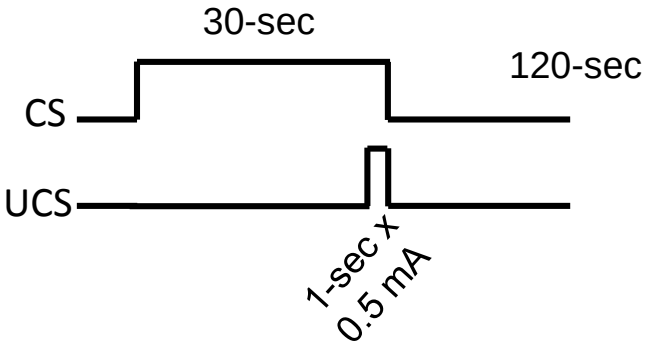
Tone-evoked spike firing in lateral amygdala neurons is increased by conditioning

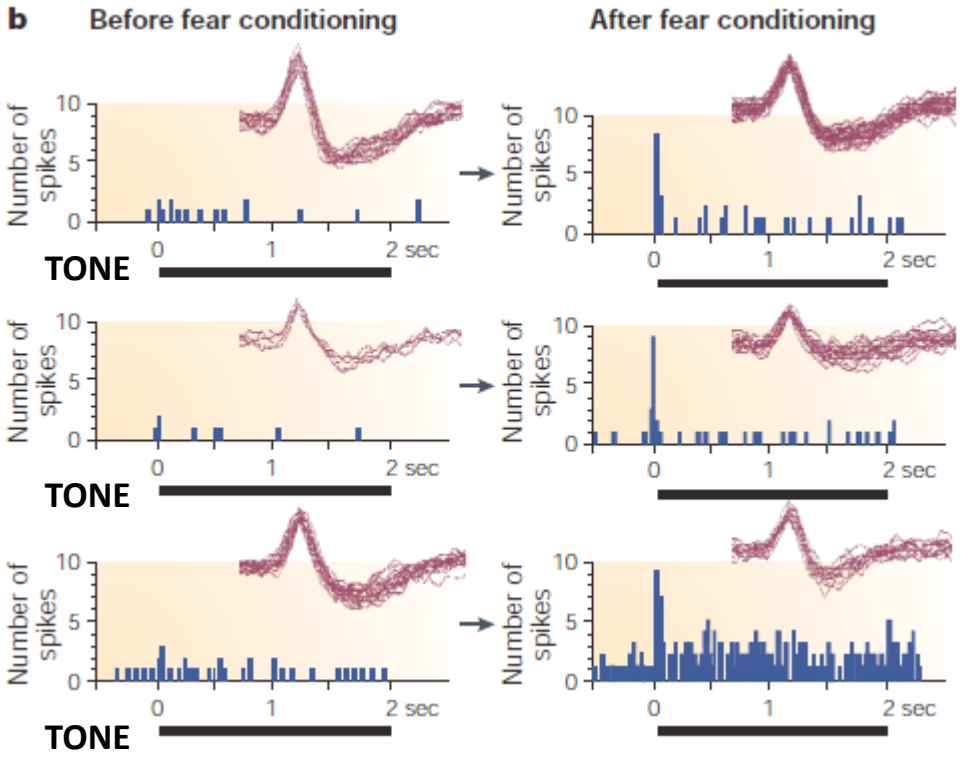
less activity in amyg neurons when trauma can be aoided in childhood (totally carefree childhood isnt good though)





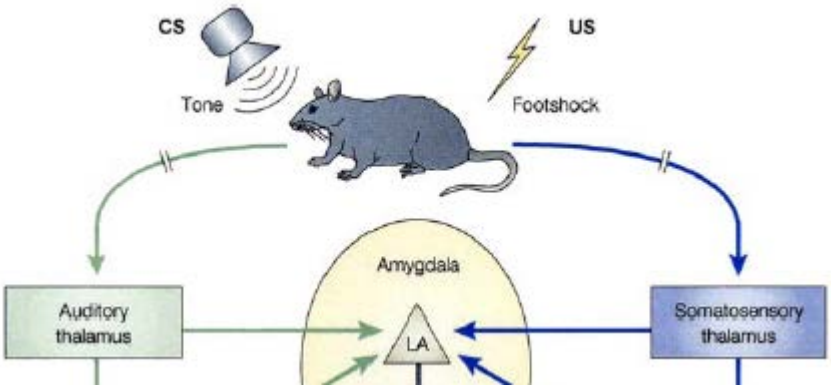


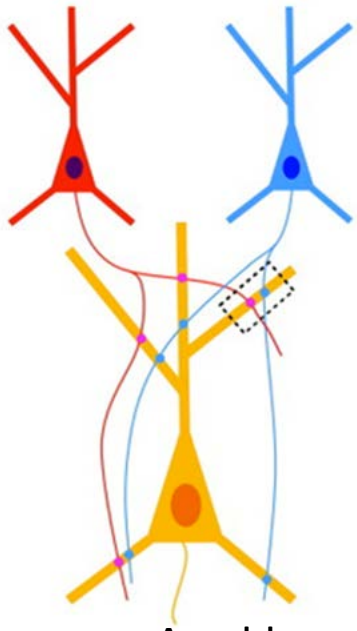




Maren & Quirk (2004) Nature Rev Neuroscience 5: 844

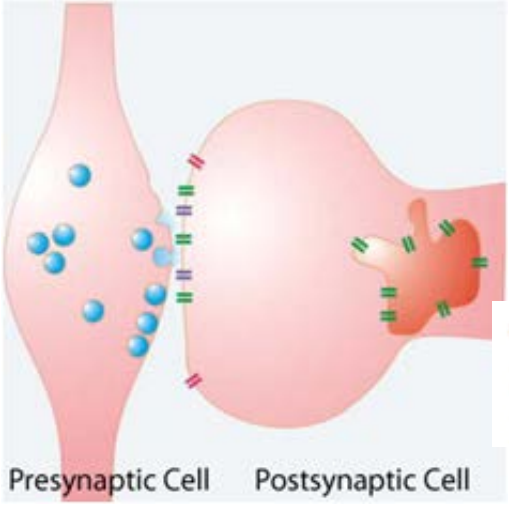
Simultaneous firing of weak auditory and strong somatosensory presynaptic neurons increases the synaptic strength of the auditory neuron
Long-term potentiation (LTP) / Synaptic plasticity



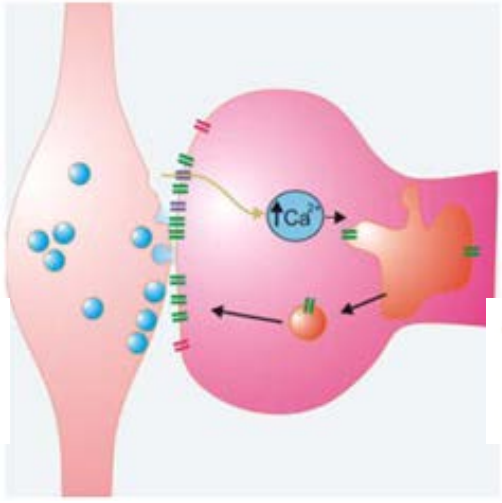


LTP is ratio on two diff neurons of their rela of glut(?)

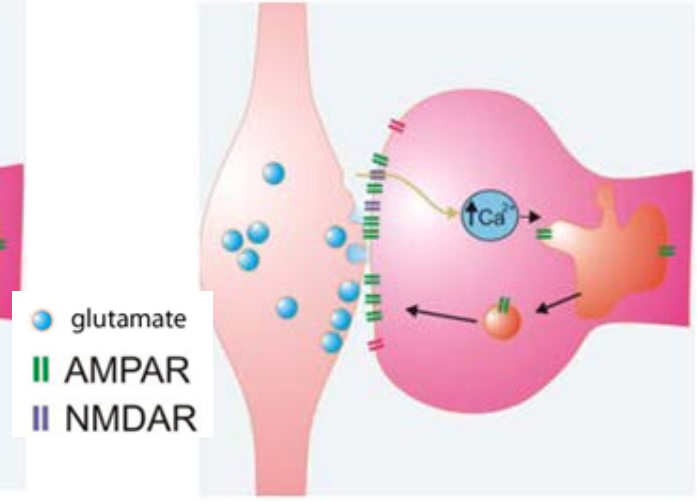
Auditory neuron –Amygdala neuron
Before fear conditioning



Somatosensory neuron – Amygdala neuron
Before and After fear conditioning



Auditory neuron – Amygdala neuron
After fear conditioning

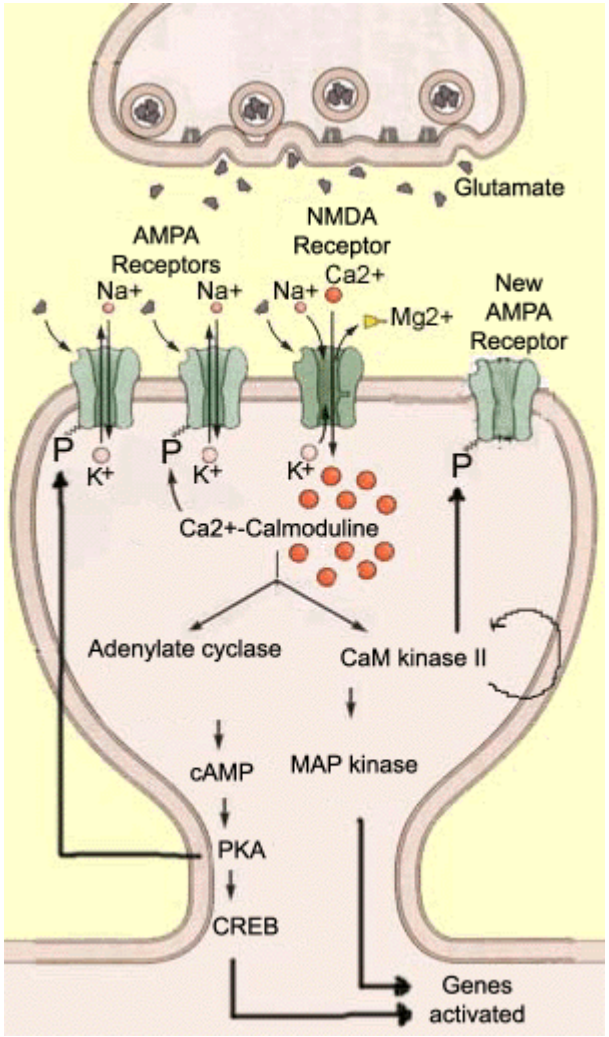


NMDA Receptor: N-methyl-D-aspartate
AMPA Receptor: Amino-hydroxy-methyl-isoxazole-propionic acid

Long-term potentiation (LTP) / Synaptic plasticity: Molecular mechanisms

A lot of the understanding of these mechanisms has come from fear conditioning studies

here we should have pavlovian conditioning in mind



Johansen et al (2011) Cell 147: 509

- NMDA and AMPA receptors are permeable to sodium (Na^+) and potassium (K^+) ions.
- The pore of NMDA receptor channel is blocked by magnesium (Mg^{2+}) ions, which can only be released when the postsynaptic cell is sufficiently depolarized (i.e. the amount of positive charges inside the cell increases).
- NMDA receptors are permeable to Ca^{2+} ions in addition to Na^+ and K^+ ions

- Glutamate is released from the presynaptic terminal and binds to NMDA and AMPA receptors.
- Na^+ and K^+ ions only pass through AMPA receptors because of the Mg^{2+} block in the NMDA receptor channel.
- In the region including the CS and UCS synapses, the postsynaptic cell membrane depolarizes as the Na^+ and K^+ ions enter the cell via AMPA receptors. When it is sufficiently depolarized, the NMDA Mg^{2+} block is lost. Na^+, K^+, and Ca^{2+} now enter the channels.

- Calcium acts as a second messenger, activating several intracellular signaling cascades:

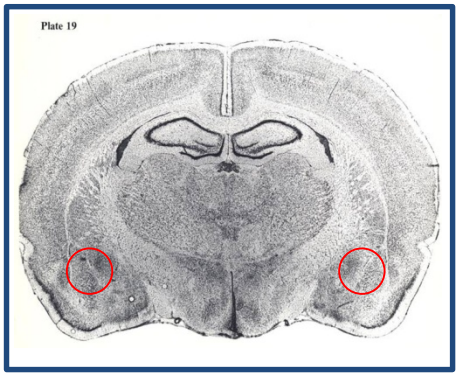
1. Phosphorylates (adds a phosphate to) AMPA receptors, thus facilitating the conductance of AMPA receptors (allowing more ions to enter).
2. Recruits additional AMPA receptors to the postsynaptic membrane, thereby creating a larger postsynaptic dendritic spine with an enhanced synaptic strength.

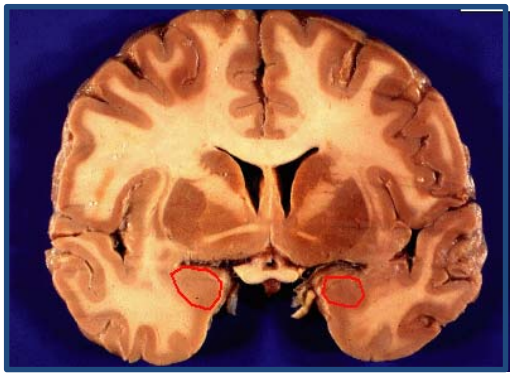
- A strengthened synapse will respond faster to a presynaptic glutamate release, opening a greater number of AMPA receptor channels, which allows NMDA receptors to open sooner and calcium to activate its cascades soon, so that the neural connection will be activated even more rapidly.

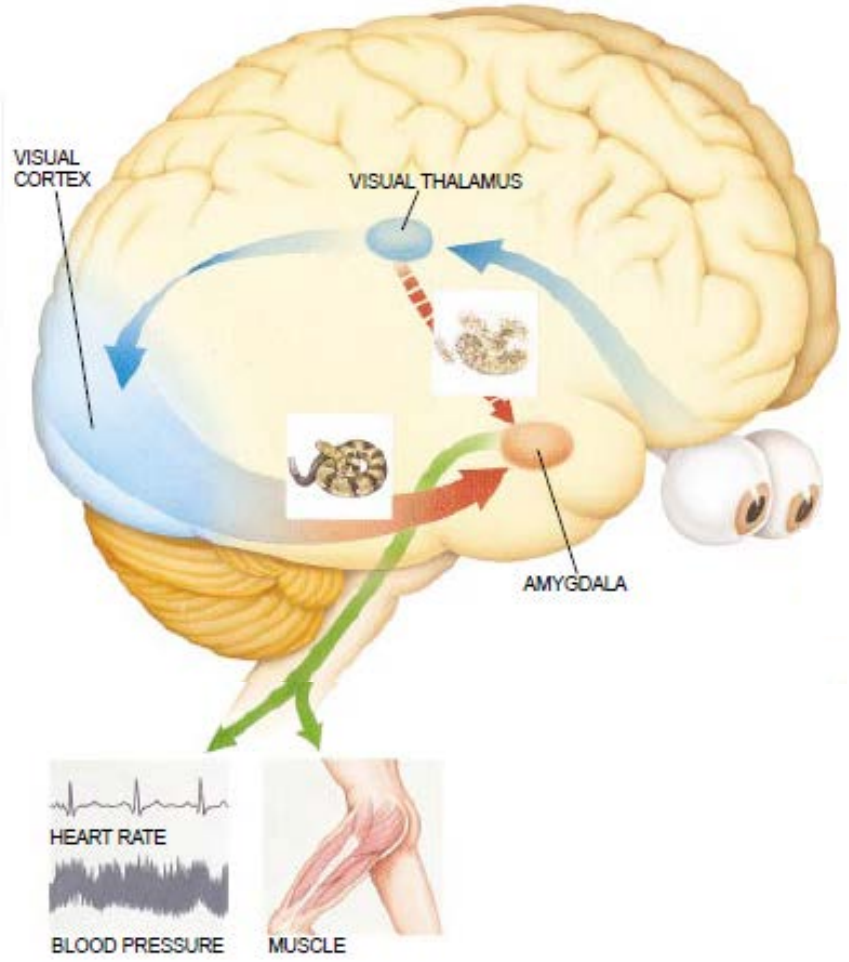
Universal features of emotions to aversive stimuli

- The amygdala is the centre of a survival circuit that perceives and responds to threat -

circuit to be completed: 200ms

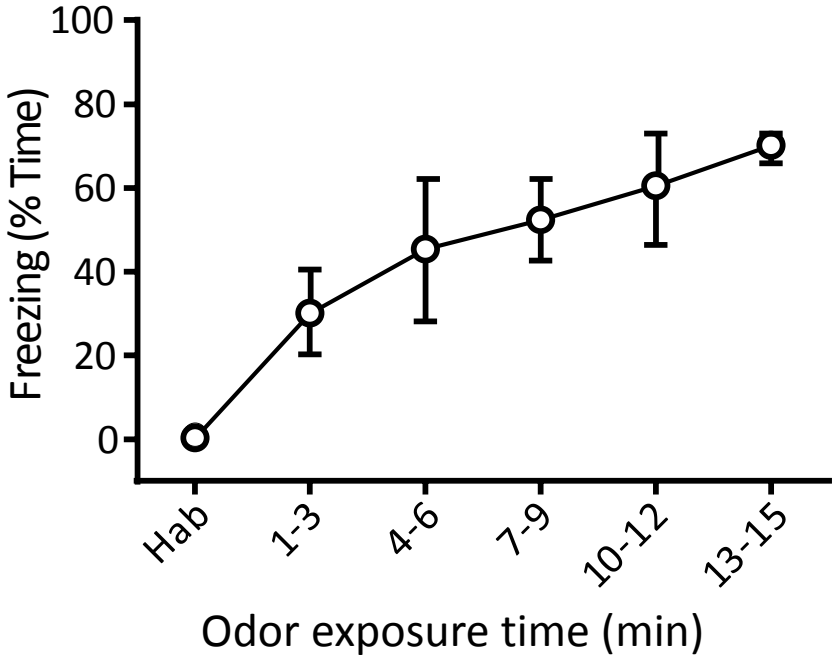


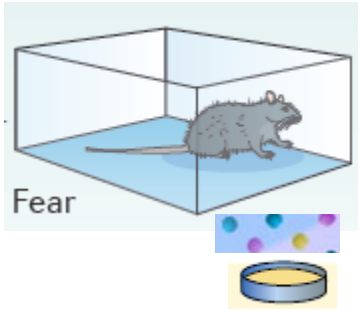


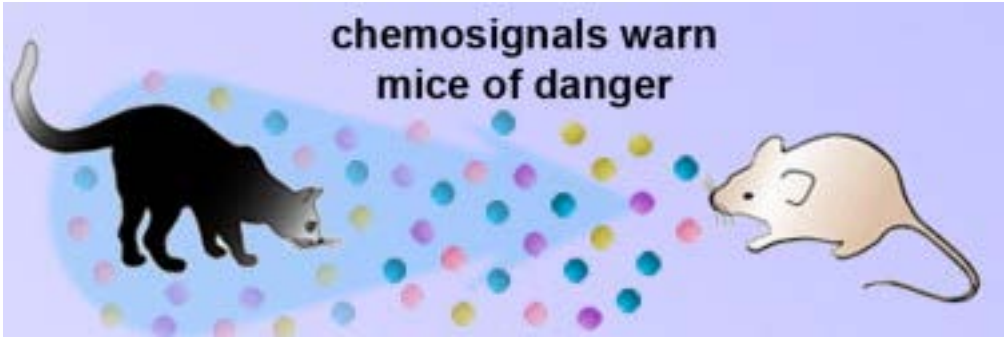


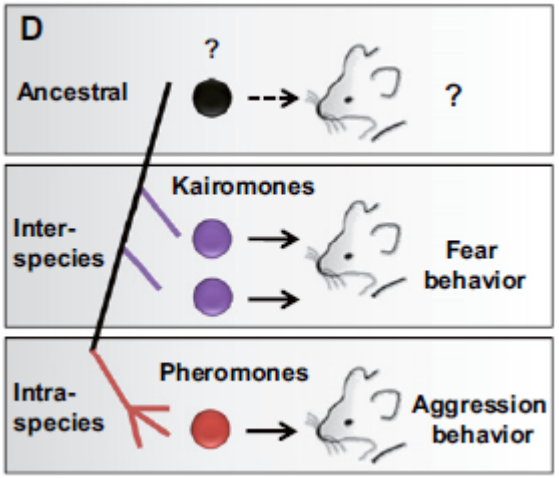
Rodent freezing to unconditioned aversive stimuli is amygdala-mediated

rodents developed receptors for cat kairomones (interspecies pheromones) so that they can learn fear and avoid cats



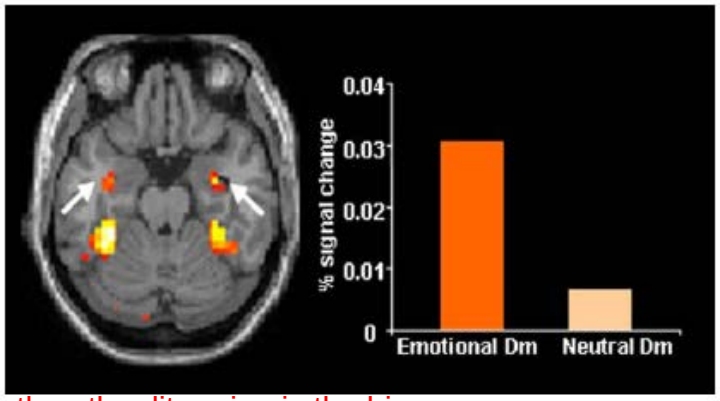






Human Amygdala: increased neural (MRI) activity in response to unconditioned aversive stimuli

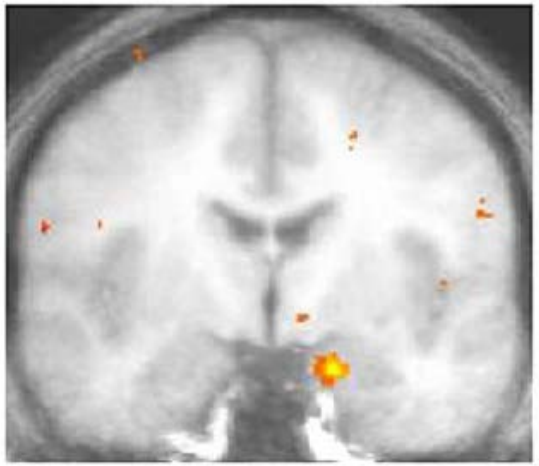
International
Affective Picture System



the other lit region is the hippocampus

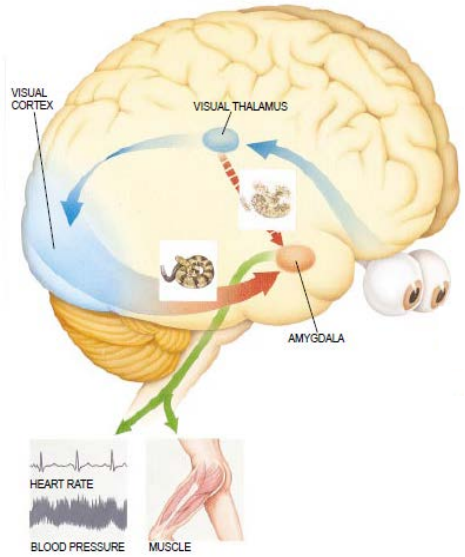
in this exp, 17ms was not enough for conscious awareness, but amyg response occurred anyway. it resposnded to somethwing we did not even have in mind

Human (conspecific)
Social stimuli



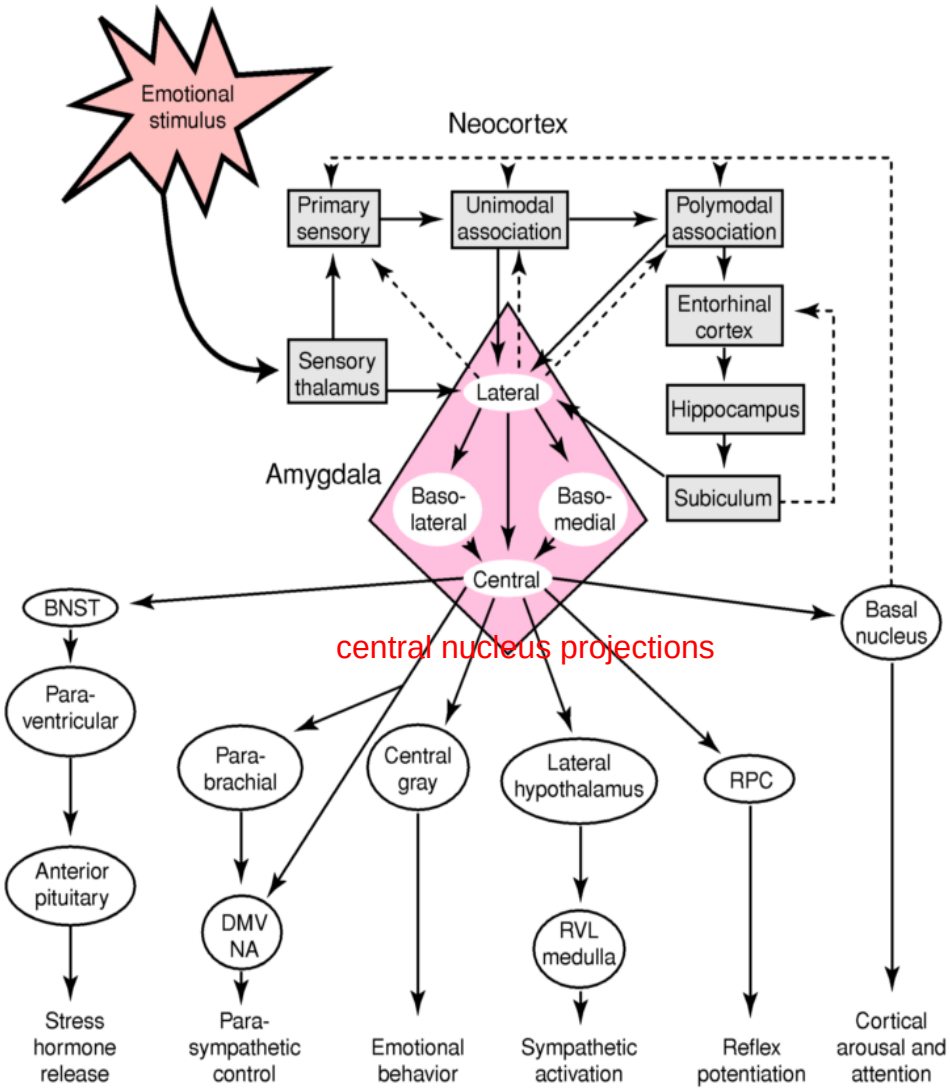
Phelps & LeDoux (2005) Neuron 48: 175

The amygdala: at the interface of emotional-cognitive input and emotional output



BNST := bed nucleus of stria terminalis
region closely associated with amyg
projects to hyptothamalus

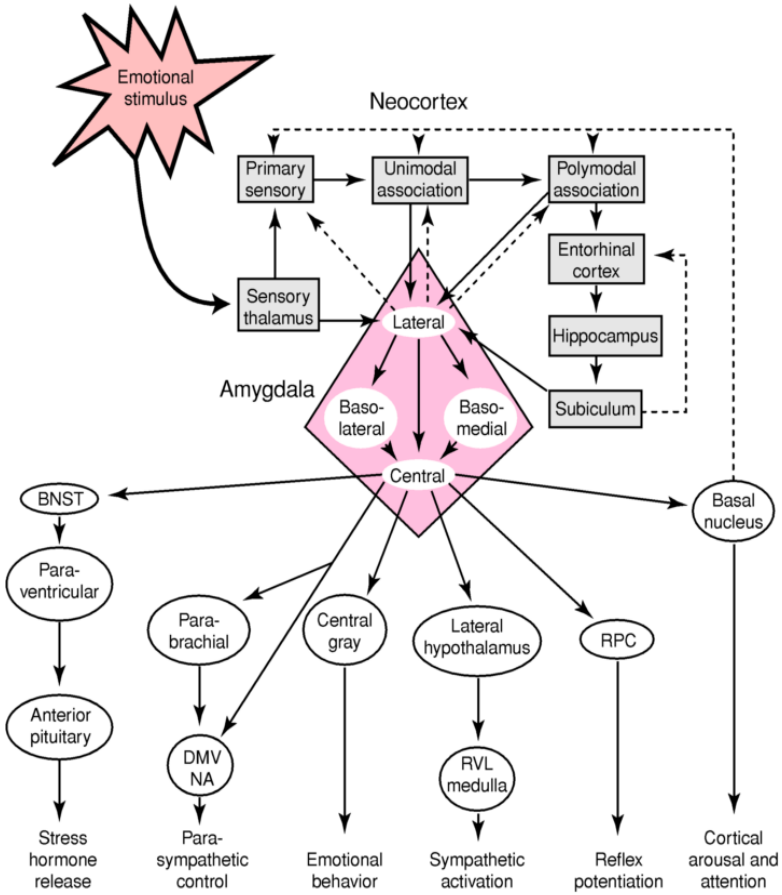
in paraventricular, CRH is produced

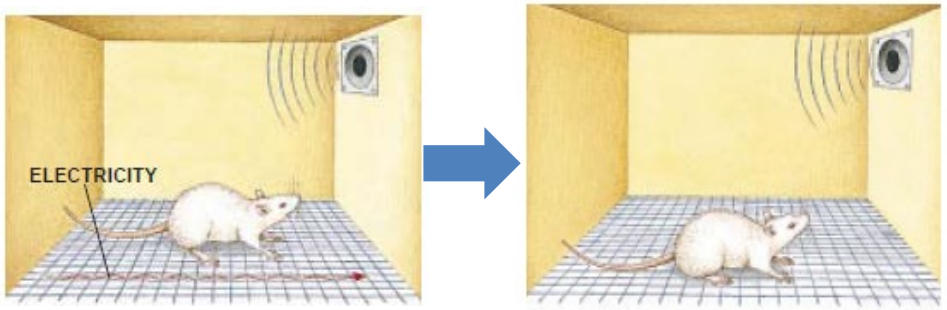


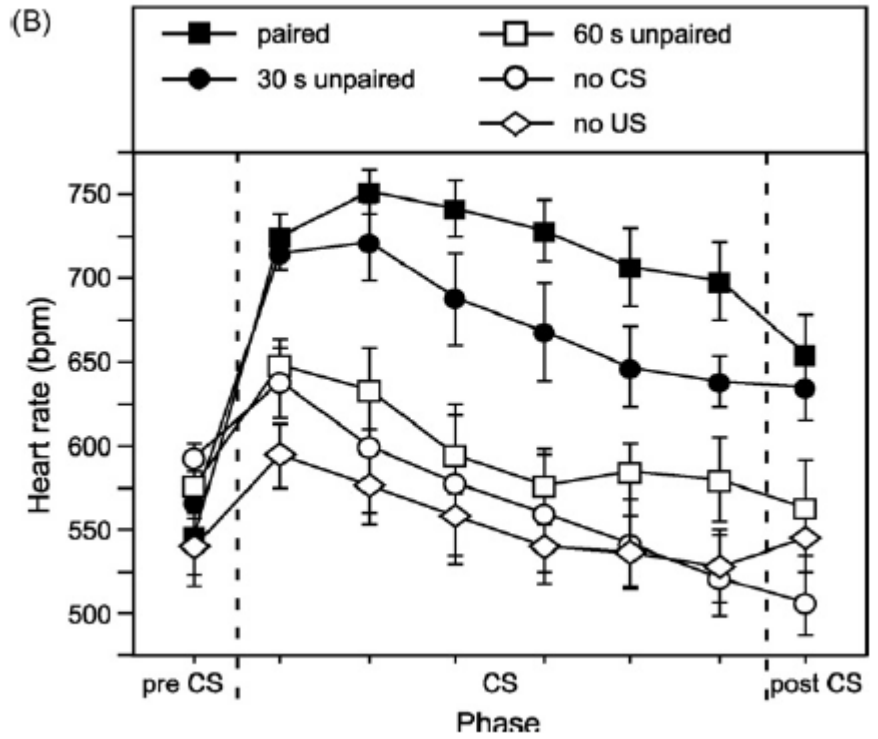
central nucleus projections

emotional learning and beha can be measured using these ouputs (one can use several outputs)

Amygdala integration of behavioural and autonomic fear responses: CS-US fear conditioning of heart rate (Tachycardia)



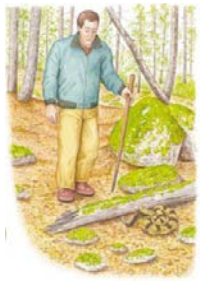


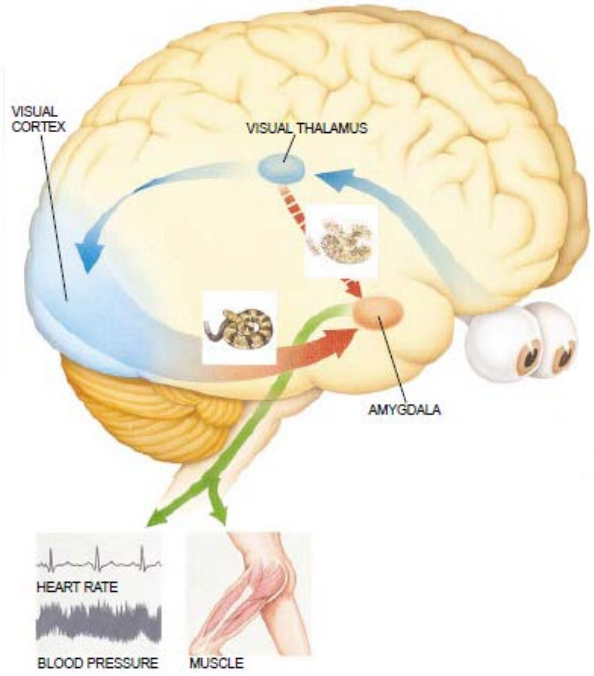


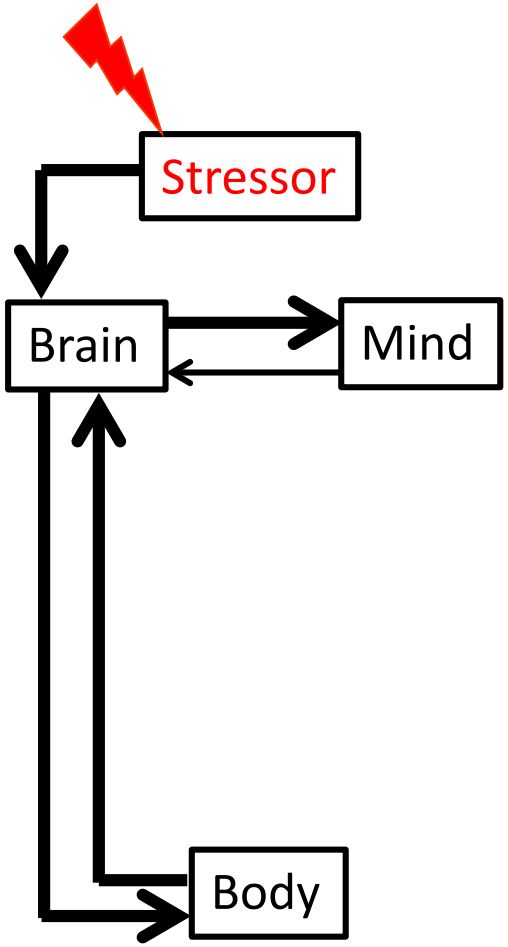
Stiedl et al (2009) Neurosci Biobehavioral Reviews 33: 181

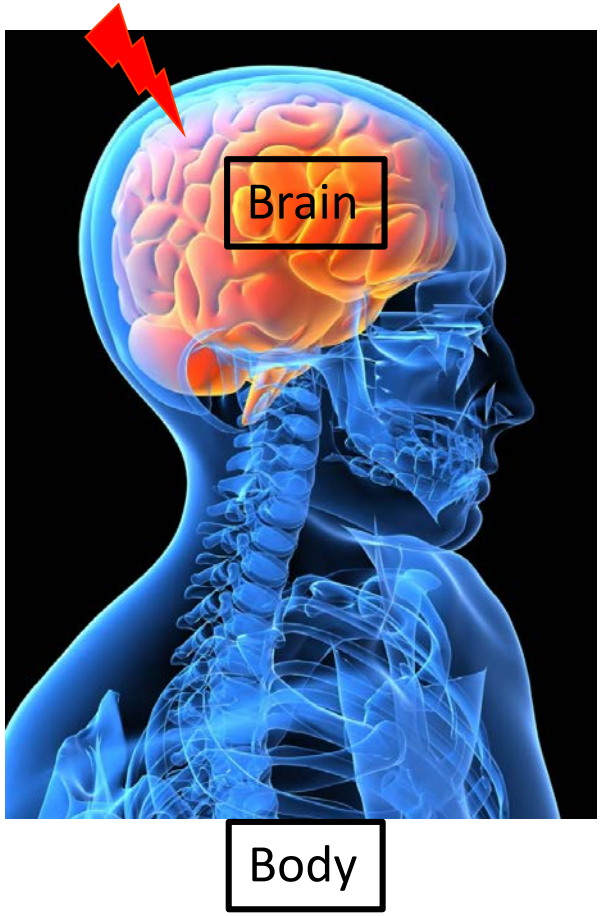
Universal features of emotions to threatening stimuli

- The amygdala stimulates changes in brain, and brain in body, that feed back to brain -

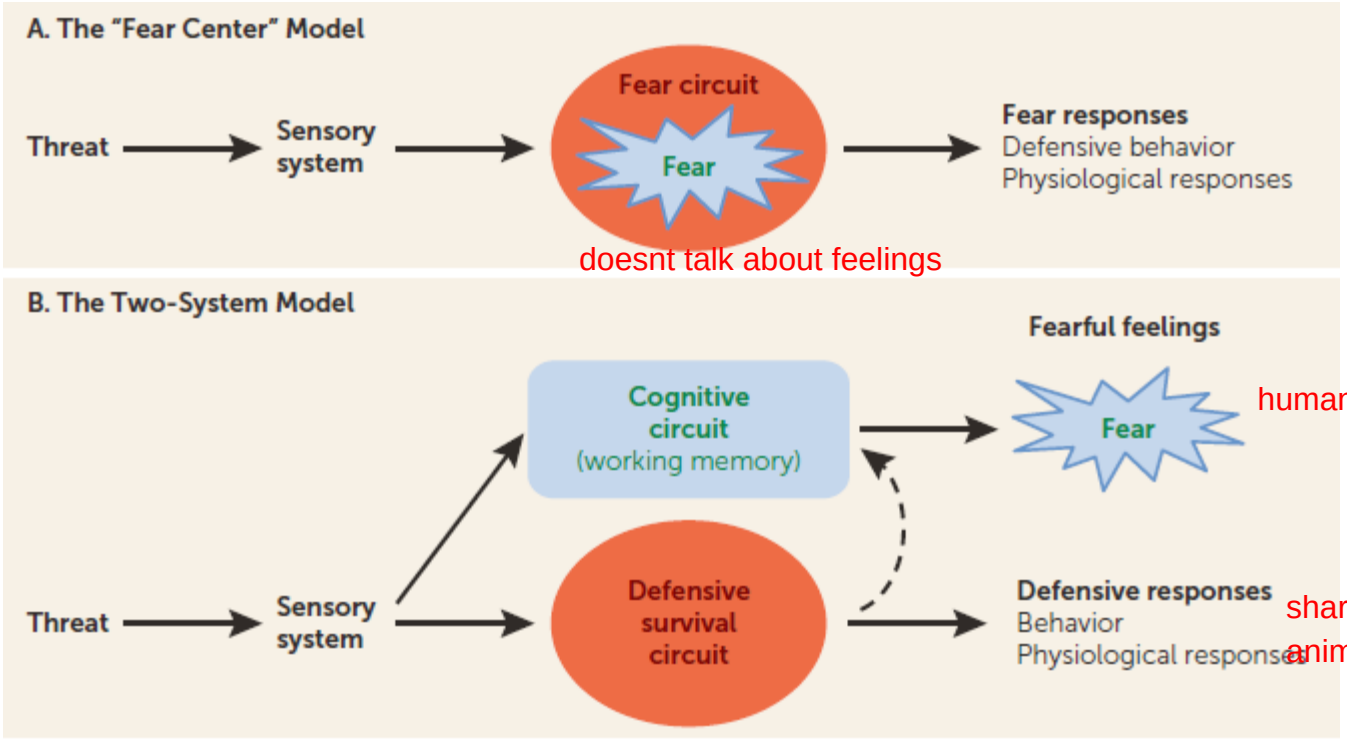








Fear: Traditional “Fear Centre” view versus “Two-System” view



doesnt talk about feelings

human system

shared amongst all animals

fear center model: fear circuit

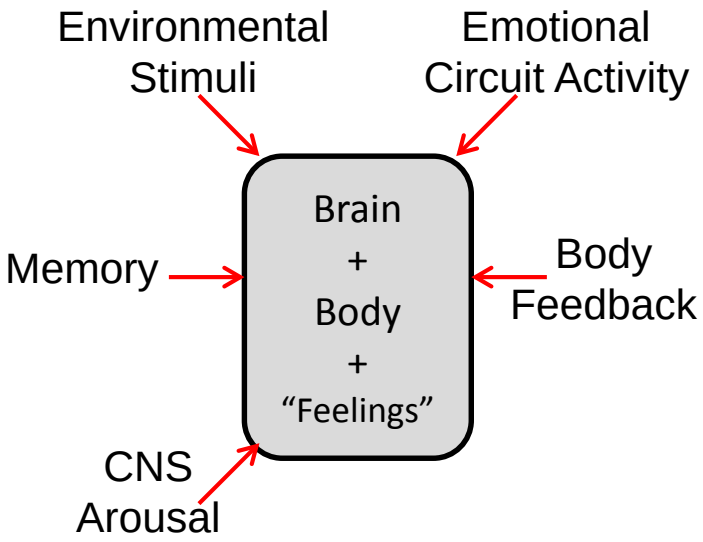
two system model: cognitive circuit ("feelings" - cognition; cortex allows complex processing - humans) + defensive survival circuit (this one shared in all animals)

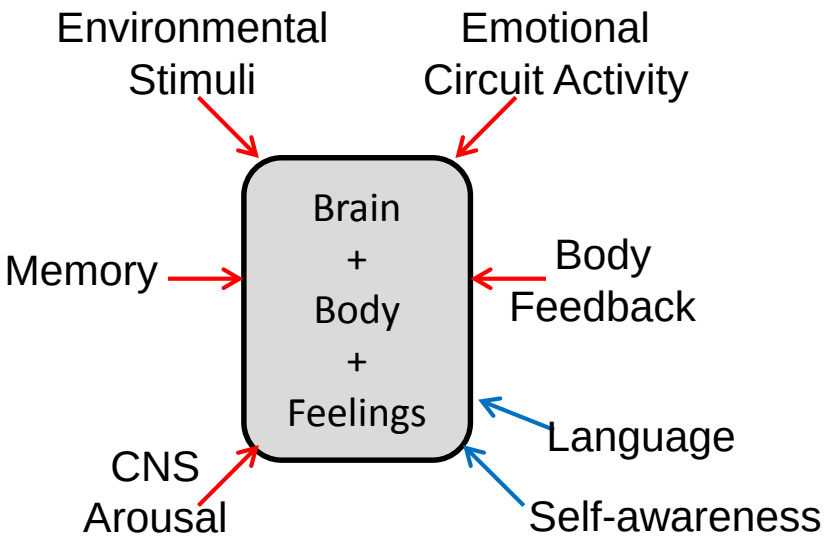
cognitive circuit can say: I am in a state of fear

LeDoux & Pine (2016) Am J Psychiatry 173: 1083

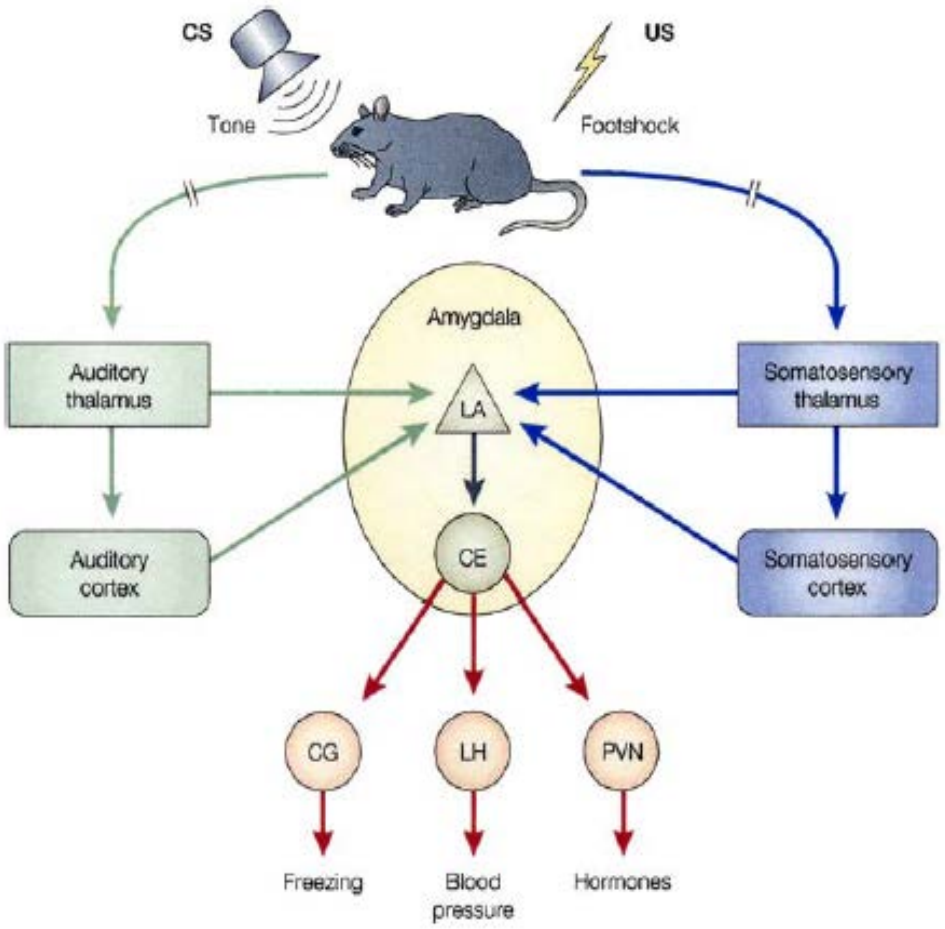
Summary of Universal and Human-unique features of emotions

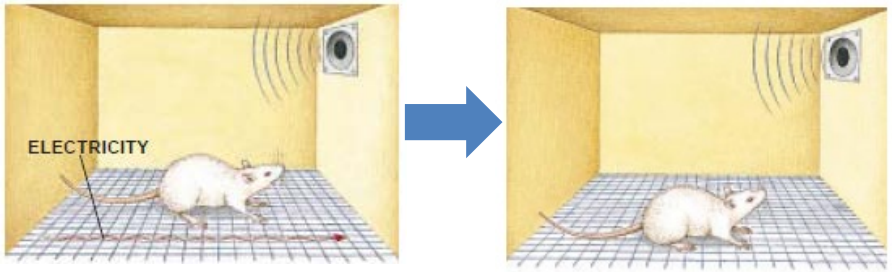
- Much is universal, and what is universal is essential to that which is human -

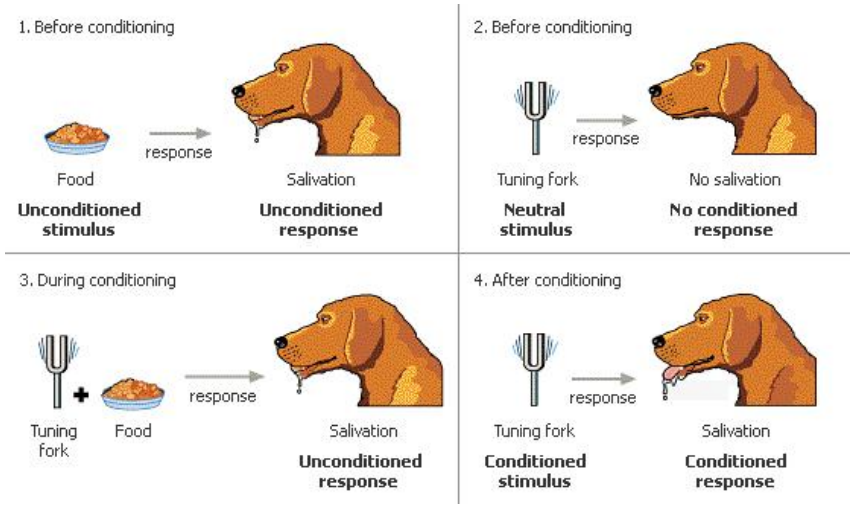




The amygdala: a major neural area for CS-UCS conditioning of aversion and reward



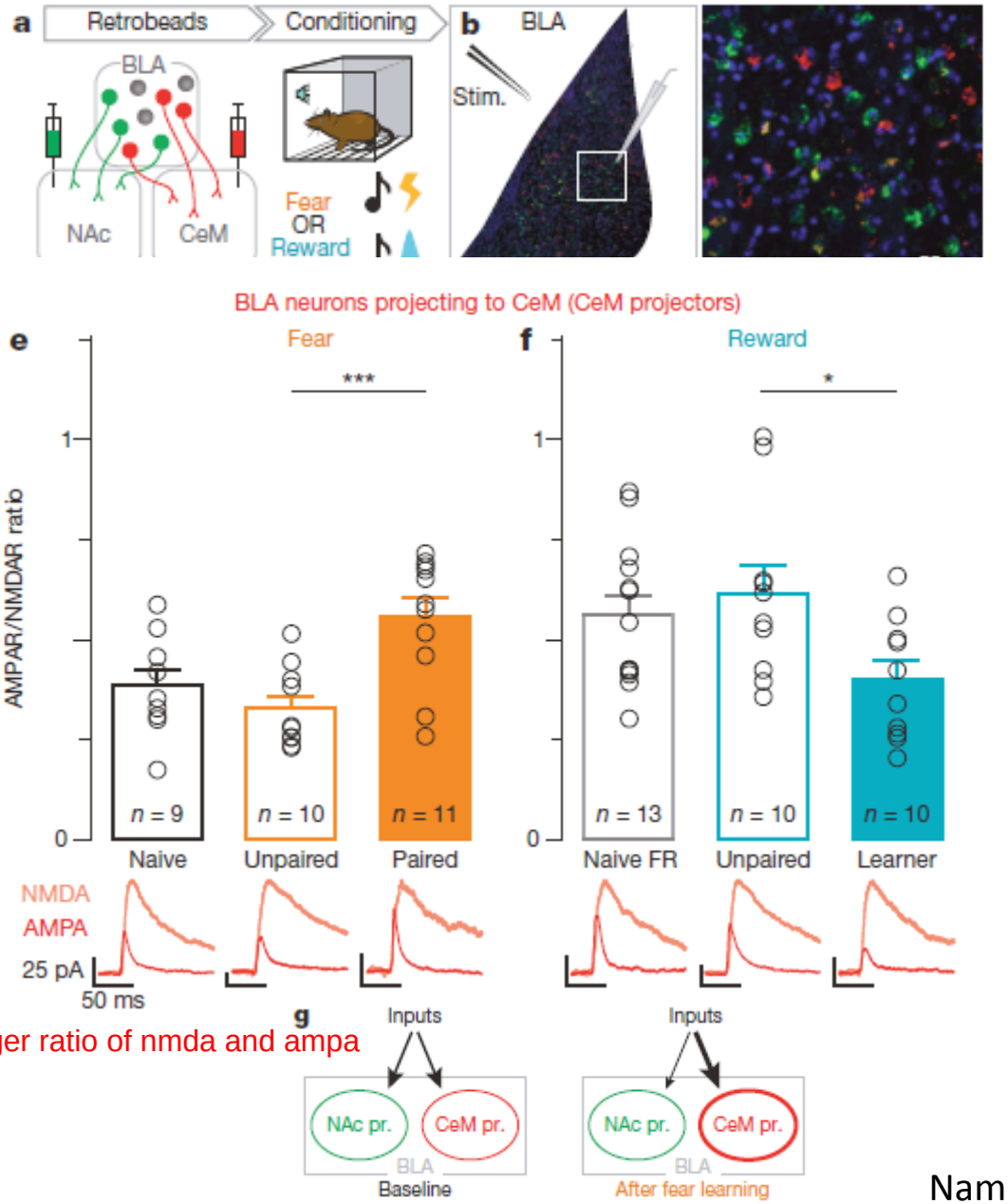




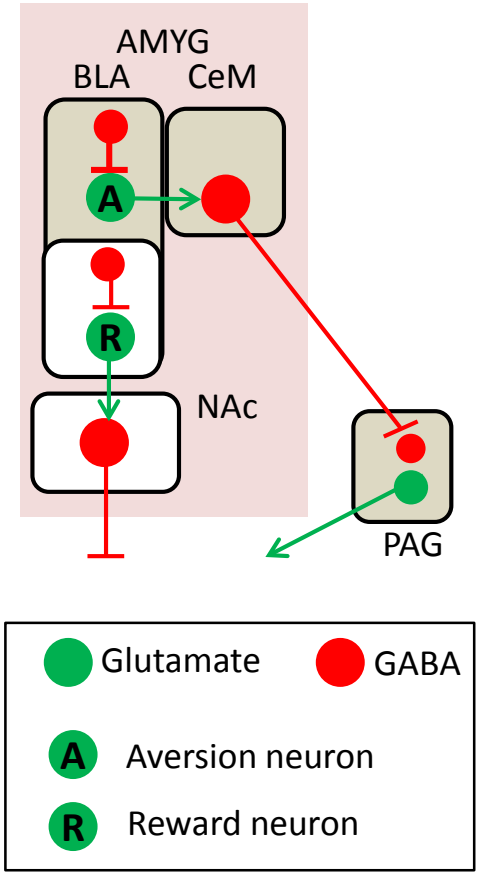
Phelps & LeDoux (2005) Neuron 48: 175

Aversion processing in the basolateral Amygdala: BLA output to the central Amygdala

Whole-cell patch-clamp recording
Excitatory post-synaptic current (EPSC)



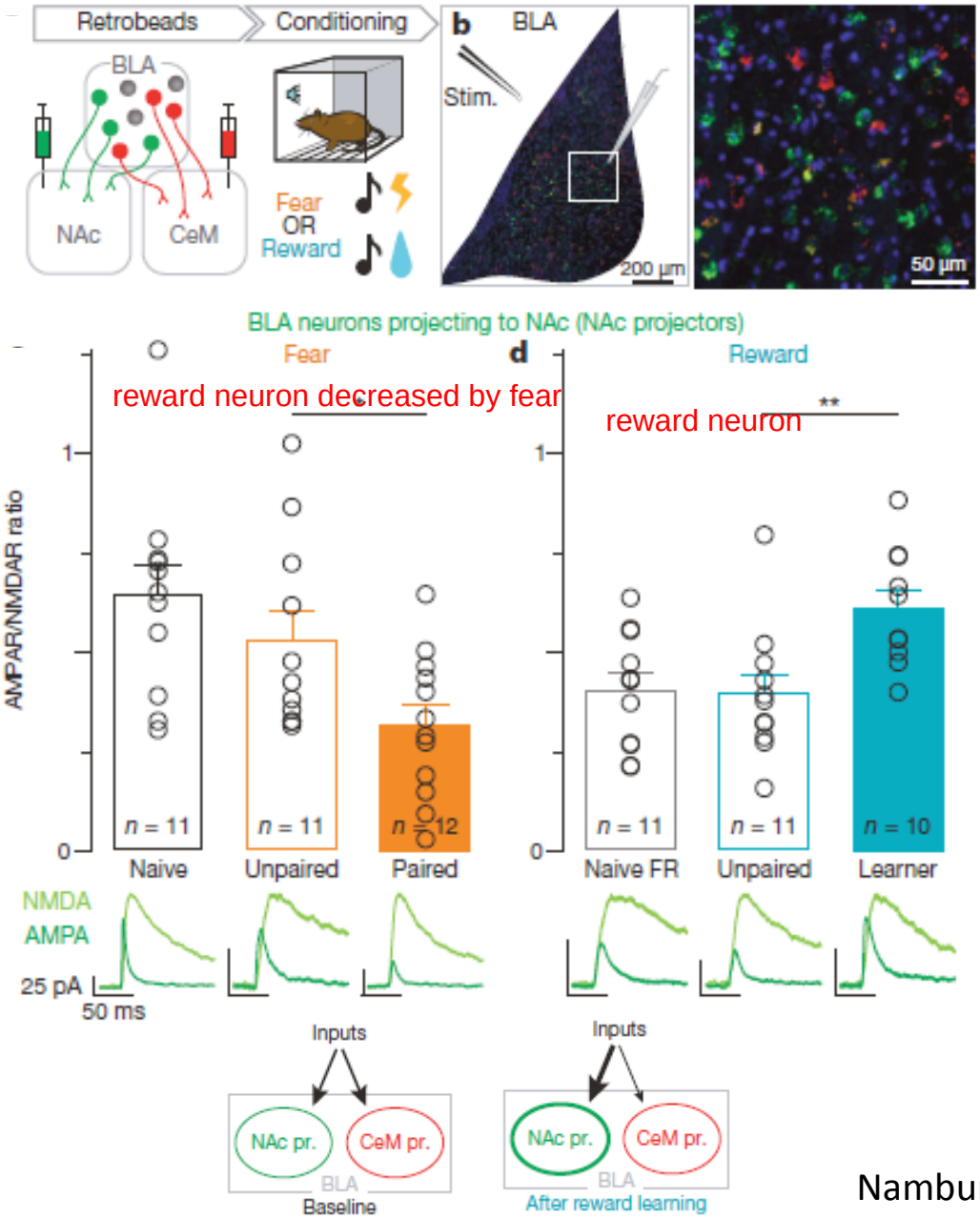
hihger ratio of nmda and ampa

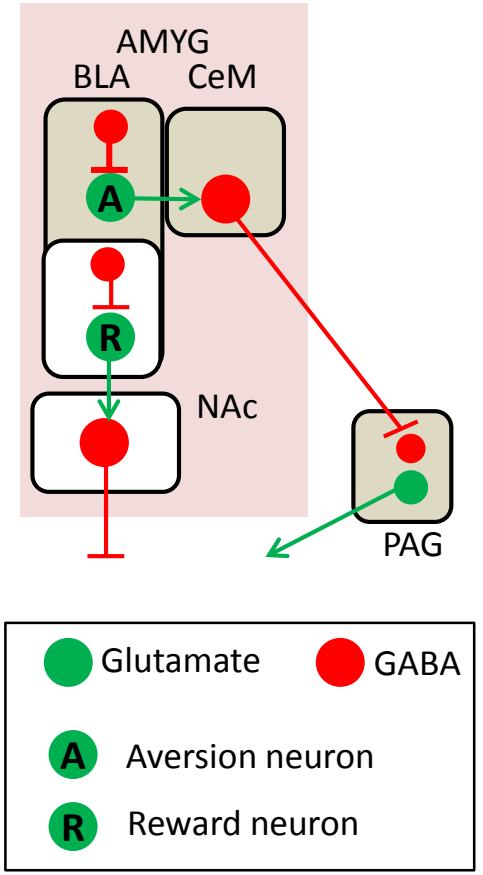


Namburi et al. (2015) Nature 520: 675

Reward processing in the basolateral Amygdala: BLA output to the Nucleus accumbens

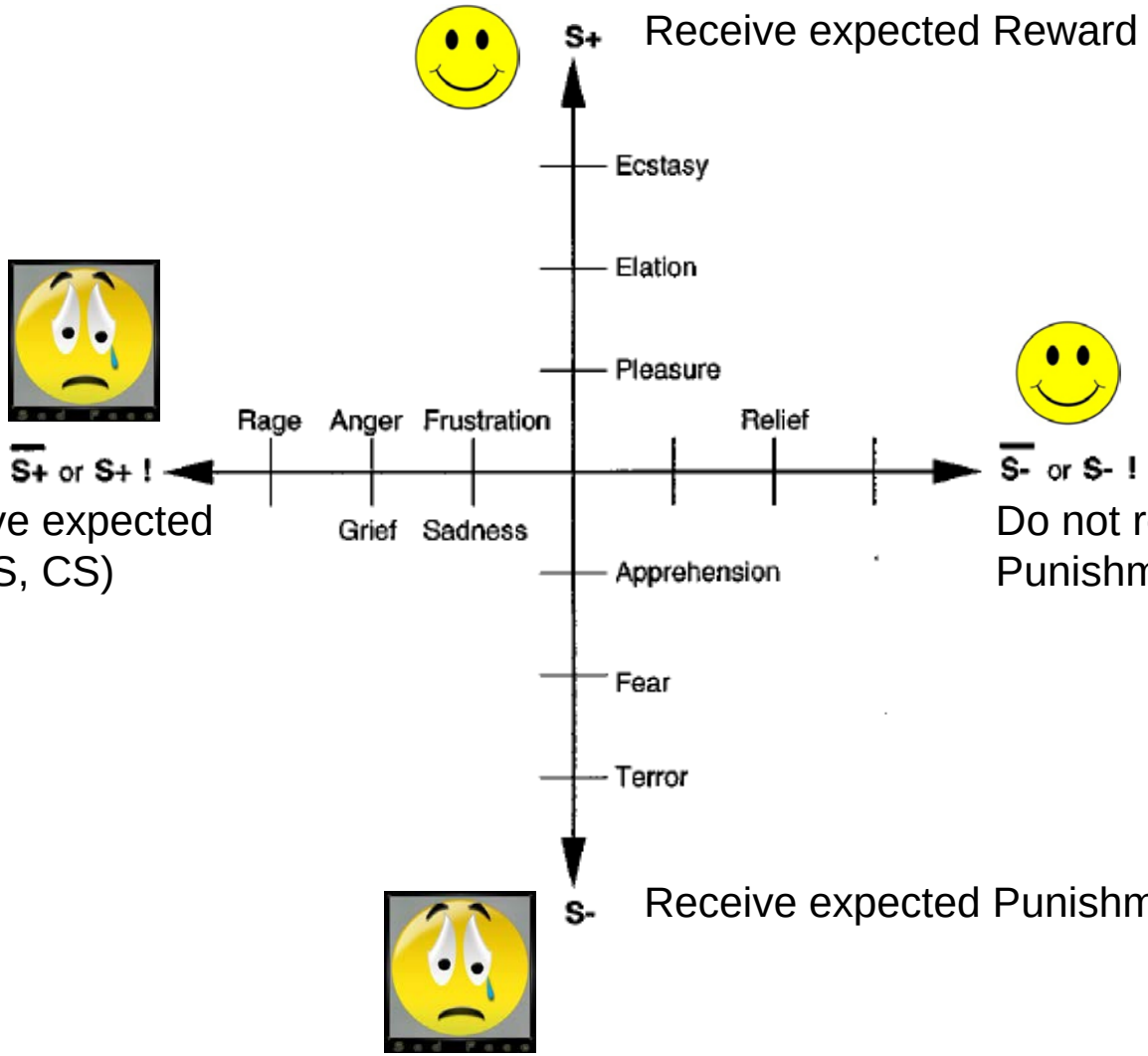
Whole-cell patch-clamp recording
Excitatory post-synaptic current (EPSC)





Namburi et al. (2015) Nature 520: 675

Emotions: caused by (1) unconditioned stimuli, (2) classical conditioned stimuli, and (3) the expected relationship between behaviour and the UCS or CS (Outcome)



Do not receive expected Reward (UCS, CS)

Do not receive expected Punishment (UCS, CS)

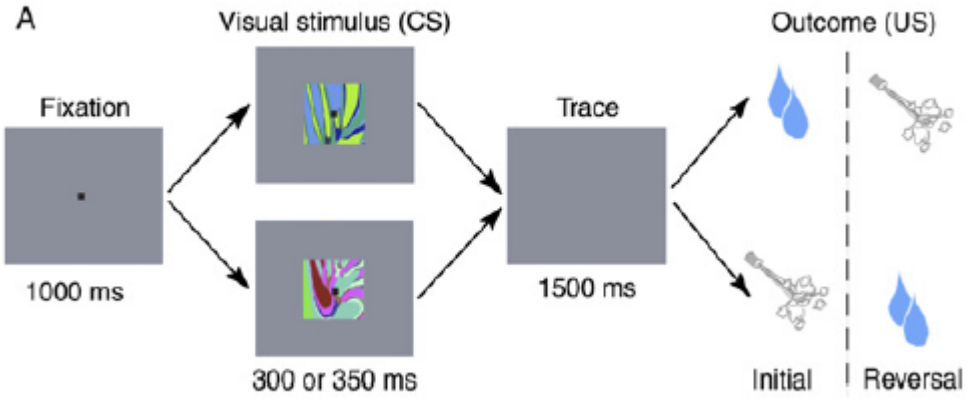
Amygdala neuron responses to expected and unexpected reward and punishment

UCS+ = Juice

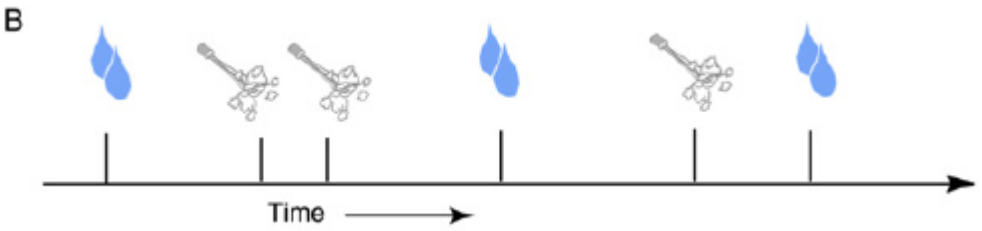
UCS- = Air puff

air puff is punishing stim - animals dont like it

CS-UCS task
UCS expected

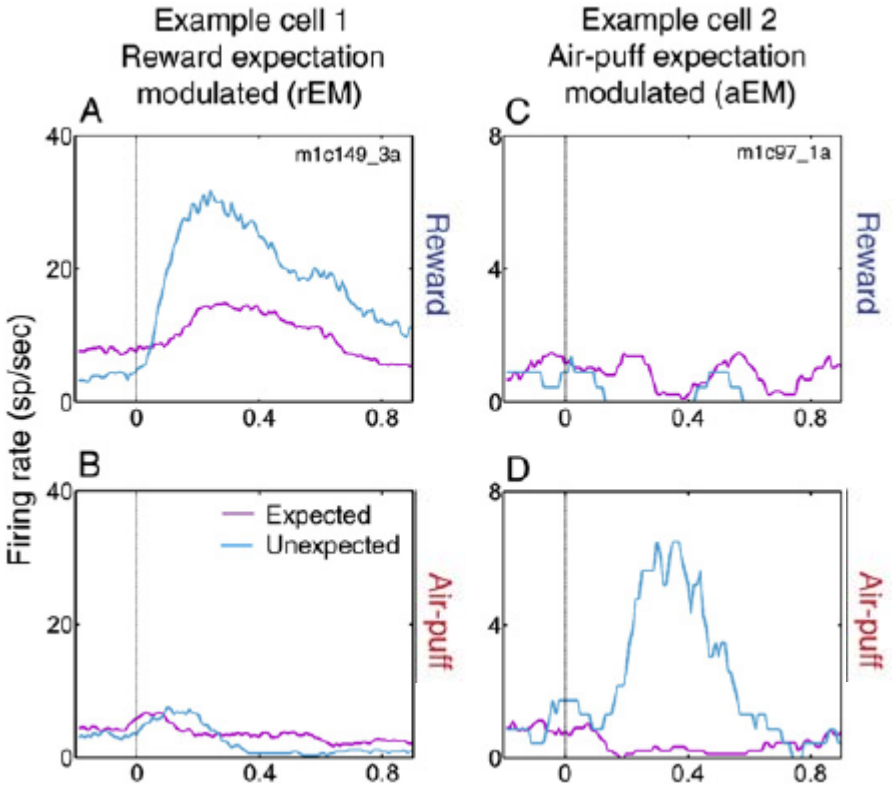


Random UCS task
UCS Unexpected



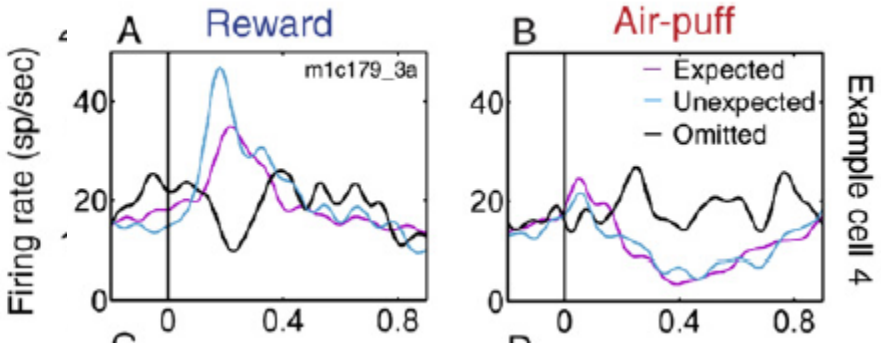
Belova et al. (2007) Neuron 55: 970

Amygdala neuron responses to expected and unexpected reward and punishment



Amygdala cell exhibiting stronger response to juice (A), but not to air puff (B), when UCS unexpected

Amygdala cell exhibiting stronger response to air puff (D), but not to juice (C), when UCS unexpected

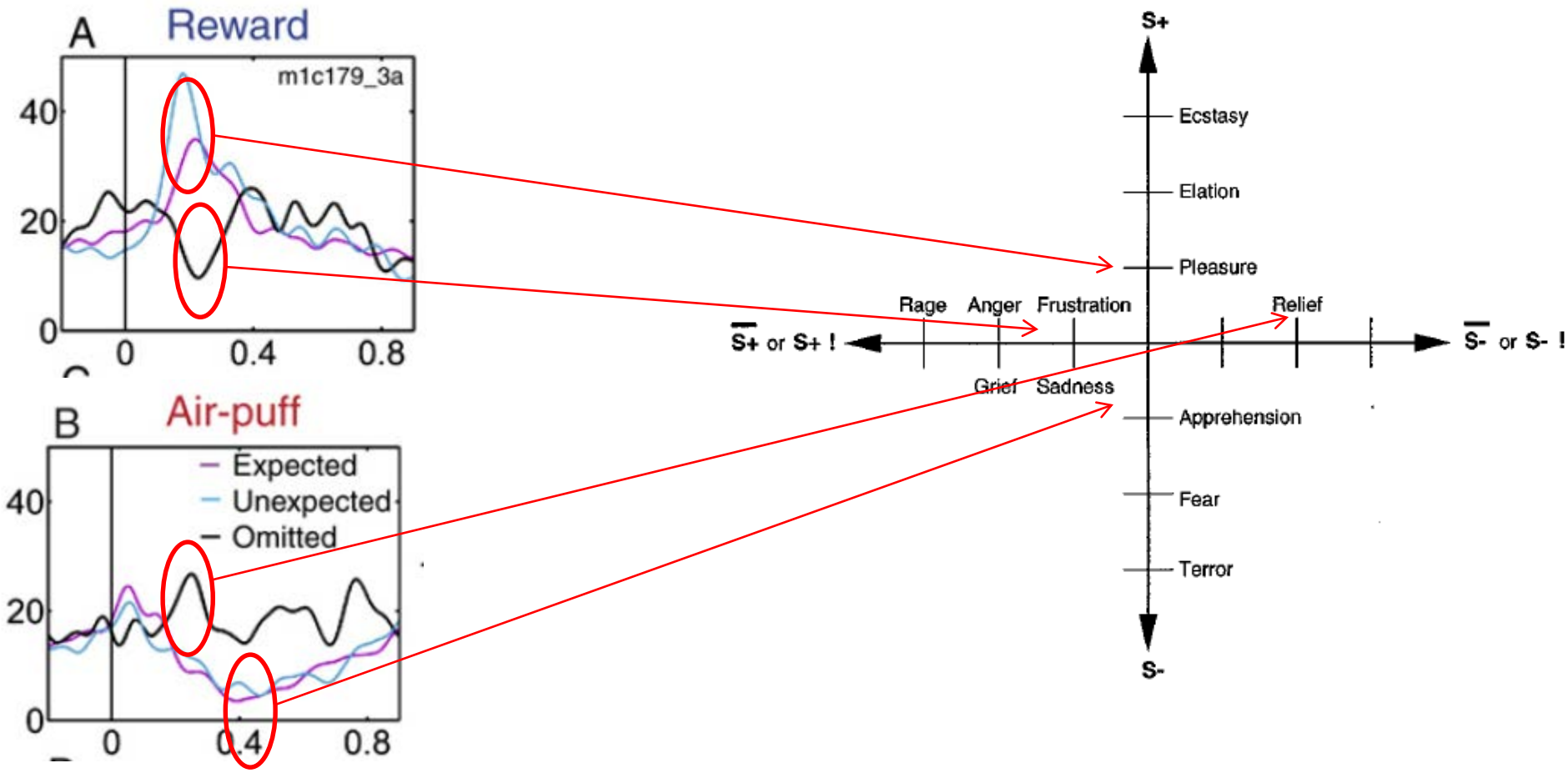


Amygdala cell exhibiting increased response to unexpected juice (A) and decreased response to expected+omitted juice (A); and decreased response to airpuff (B) and increased response to expected+omitted air puff (B)

Belova et al. (2007) Neuron 55: 970

Amygdala neuron responses to expected and unexpected reward and punishment

there is a neuron type in amyg for a spec response



Aversive stimuli, fear and the amygdala

- Aversive stimuli can be unconditioned or conditioned
- The amygdala is the emotional centre of the CNS
- The amygdala is composed of several nuclei e.g. Lateral, Basal, Central
- The amygdala (lateral nucleus) is responsible for fear conditioning (freezing)
- Neurons in the lateral amygdala fire more to the tone after conditioning than before conditioning
- The increased firing to the tone-CS is due to long-term potentiation / synaptic plasticity in presynaptic-to-postsynaptic glutamate neurons
- In addition to behavioural responses to aversive stimuli, the amygdala also controls physiological responses e.g. Heart rate, sweating, HPA axis
- Several neurotransmitters modulate activity of amygdala neurons e.g. Corticotropin releasing factor
- Several neuropeptides modulate activity of amygdala neurons e.g. Vasopressin, Oxytocin
- Amygdala neurons respond to aversion AND reward, and also to whether a stimulus is expected or unexpected. That is, all 4 types of emotional response are encoded by amygdala neurons