Learning & Memory (Ch.17) IV

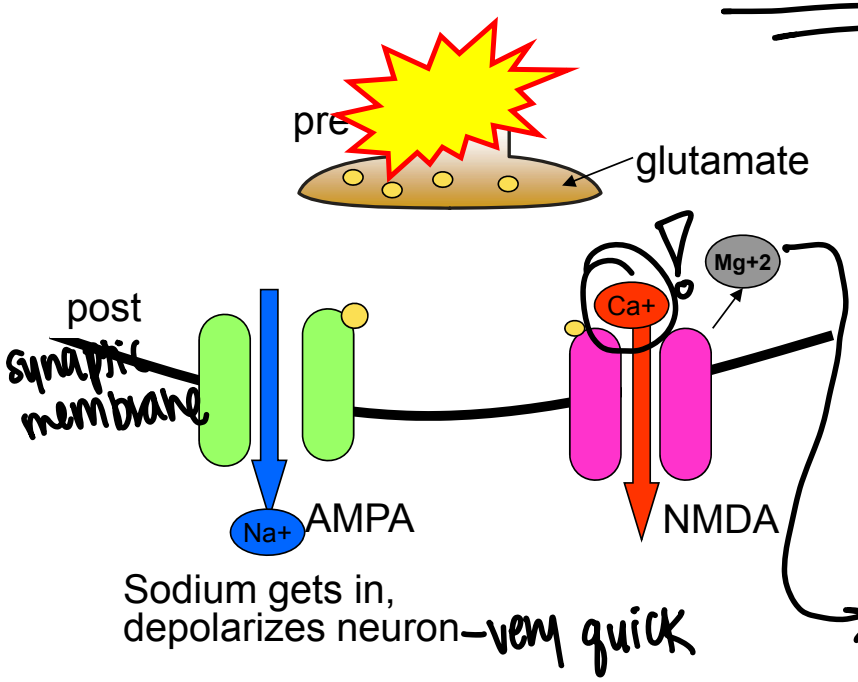
- Synaptic Plasticity
  - **Long term potentiation**: A cellular model for long term memory- mechanisms
- The Prefrontal Cortex
  - Anatomy
  - Working Memory
  - Behavioural Flexibility
  - Planning
- Relevant parts of the textbook: Ch 18, pgs 622-632
- Section on “Consciousness and Executive Function”
  - Subsection “*A flexible anterior system plans and monitors our behavior*”
- For next day- Start reading Chapter 16, Schizophrenia section

he will re-explain this on Thursday ♡ thanks stan :-)

Glutamate Mechanisms of LTP

- LTP can occur anywhere in the brain where there are **glutamate synapses**
  - Hippocampus, Cortex, Amygdala, Striatum etc
- Two main types of ionotropic glutamate receptors: activation

brain doesn't release these :o
NT ?
a bit confused about this para >.<



AMPA and NMDA receptors

- Both allow Na+ to pass thru and depolarize neuron

Only NMDA receptor allows Ca2+ to get into neuron

- If neuron is hyperpolarized, NMDA receptor blocked by Mg2+ ions cannot be activated by glutamate
  PLUG RECEPTOR!!!
- AMPA receptors are not blocked; can always be activated by glutamate

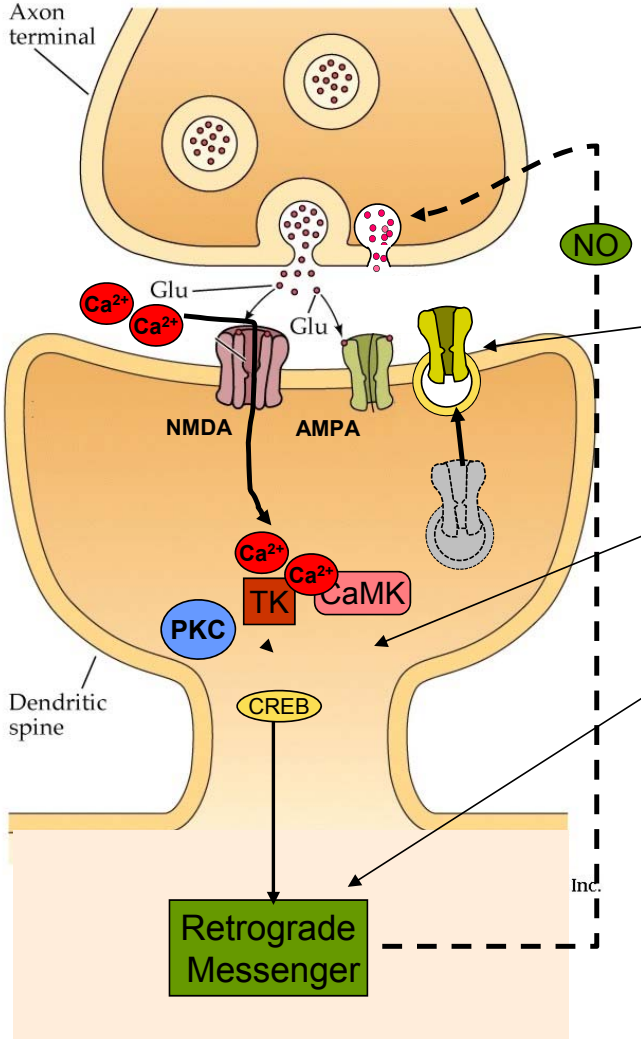
gets thrown off if neuron is excited

NMDA blocked by magnesium → once activated NMDA (Ca enters cells) gets crazyyyyyyyy: night to remember

- If AMPA receptors depolarize neuron enough, Mg2+ block of NMDA receptor is removed (**voltage dependent Mg2+ block**)
- Glutamate can now activate NMDA receptor, allows Ca2+ to get into cell

stop

Cellular Mechanisms of LTP (I)



- Once Ca2+ enter cell, it activates multiple enzyme pathways (**kinases = phosphorylate other proteins)**
- Ca2+ activates **Ca**lcium-Cal**m**odulin which in turn activates other kinases
- CaM Kinase hits latent AMPA receptor (floating inside cell) and inserts in membrane = more receptors

- **P**rotein **K**inase **C** and **T**yrosine **K**inase can activate CREB = short term and long term effects
- CREB can lead to formation of retrograde messenger (molecule that goes from postsynaptic neuron to presynaptic terminal (e.g., Nitric Oxide)
  - These messengers promote more transmitter release
- ↑ synaptic strength by both pre and postsynaptic mechanisms

incr. receptors incr. synaptic strength

feedback to presynaptic terminal

Calcium → CaM Kinase → AMPA receptor → more receptors → stronger synapse

blocking calcium blocks both

blocking NMDA or protein synthesis = block formation of LTP

long term potentiation

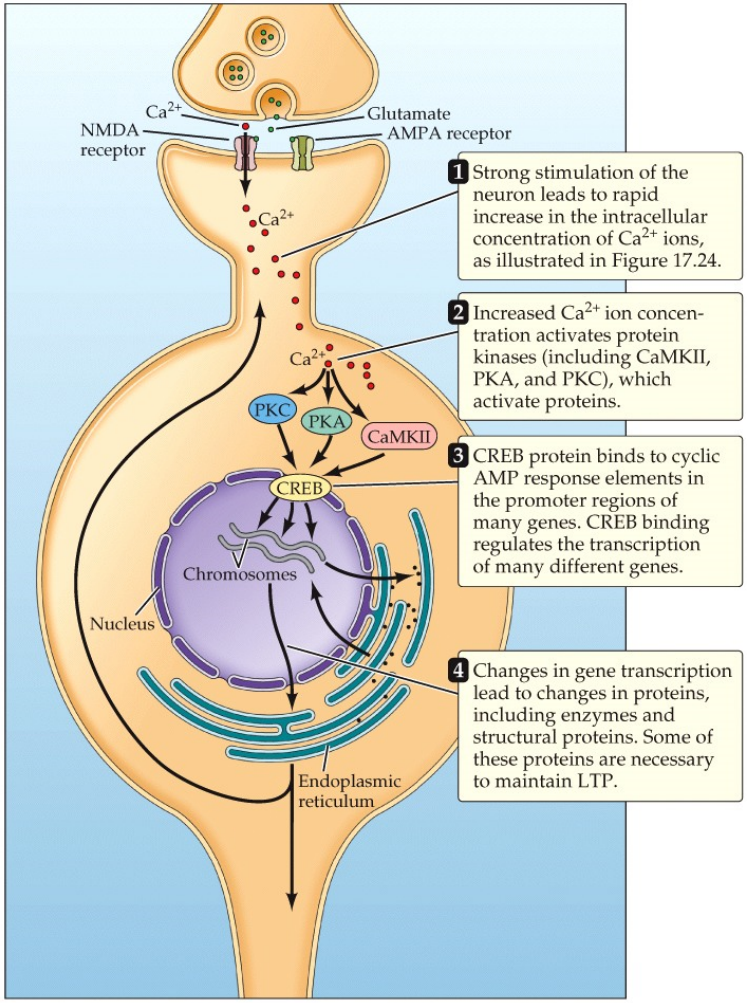
Cellular Mechanisms of LTP (II)

- LTP comes in two phases:
- **1st phase:** ↑ in receptors/glutamate release occur quickly (<1 hr)
  - ➢ These changes blocked by NMDA antagonists
- **2nd phase:** CREB activates **protein synthesis**, that causes longer lasting changes (>3 Hrs)
  - — Dendrite shape and size, more ion channels, more dendrites, etc
  - — These changes are processed for hours after initial memory was encoded
  - ➢ These latter of LTP phases also blocked by **protein synthesis inhibitors**

eg. antibiotics

- **Both phases blocked by prevention of Ca2+ entry into the cell**
  - Ca2+ entry is localized, so only certain synapses/ dendrites on a neuron will change synaptic strength

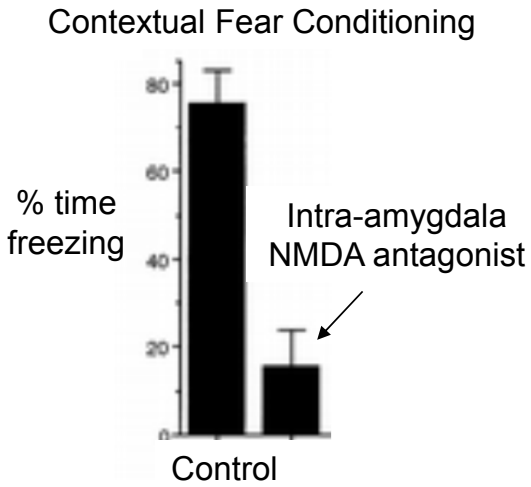
CREB goes to nucleus, tells it to change synaptic strength, induces protein synth. → more permanent changes



without protein synthesis; no consolidation or permanent changes

LTP as a mechanism for memory? (I)

- **Pharmacological studies:** drugs that block LTP formation also disrupt learning
  - ➢ Block NMDA receptors during learning in:
  - – hippocampus = disrupt spatial learning
  - – amygdala = disrupt fear conditioning
  - – striatum = disrupt instrumental learning
- Treatments immediately *after* training **do not disrupt** memory formation



block NMDA in hipp DURING EVENT: disrupt spatial learning
block NMDA in amyg. DURING EVENT: disrupt fear conditioning

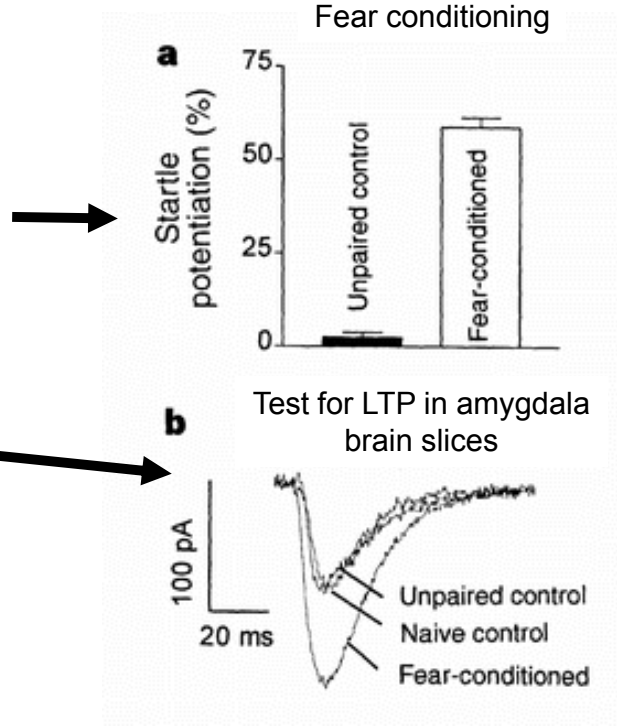
- Blocking protein synthesis also disrupts different forms of learning
  - – Treatments immediately ***after*** training **DO *disrupt*** memory formation
  - – Longer term changes in neurons occur for some time after initial learning

tone now has greater influence over amyg activity bc learned that it predicts shock

LTP as a mechanism for memory? (II)

light training: either no reliable relationship between light and shock or paired light and shock only paired light & shock → light fear response

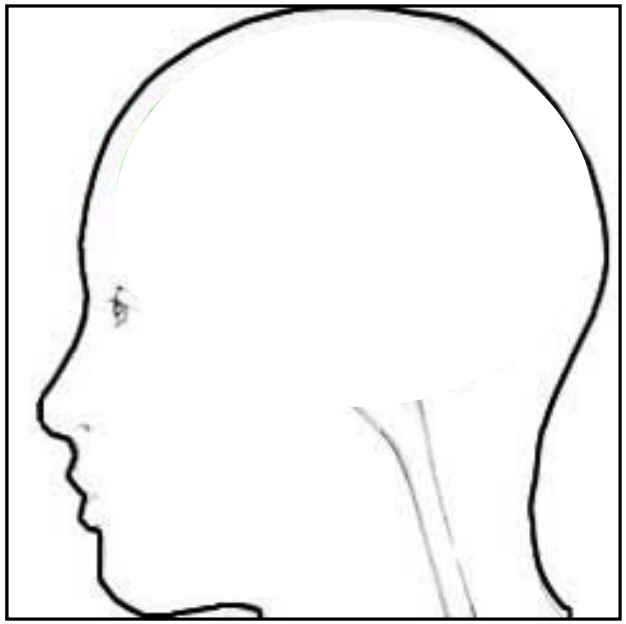
- **Behavioural Electrophysiology:** changes in neural activity resembling LTP that occur after learning
  - Lateral amygdala and fear conditioning: neurons fire more in response to CS+ after learning **(see Lecture 17(1), slide 8)**
  - *in vitro*: train one group rats on fear conditioning task, other groups no treatment (naïve), or the tone is not predictive of shock (unpaired)
    - Remove brains 24 hrs later: only rats that were trained on task show ↑ in synaptic strength **selectively** amygdala pathways
    - Rats that received tones and shocks but were unpaired did not show potentiation



learned/conditioned → synaptic stronger amyg. pathway

Prefrontal Cortical Function

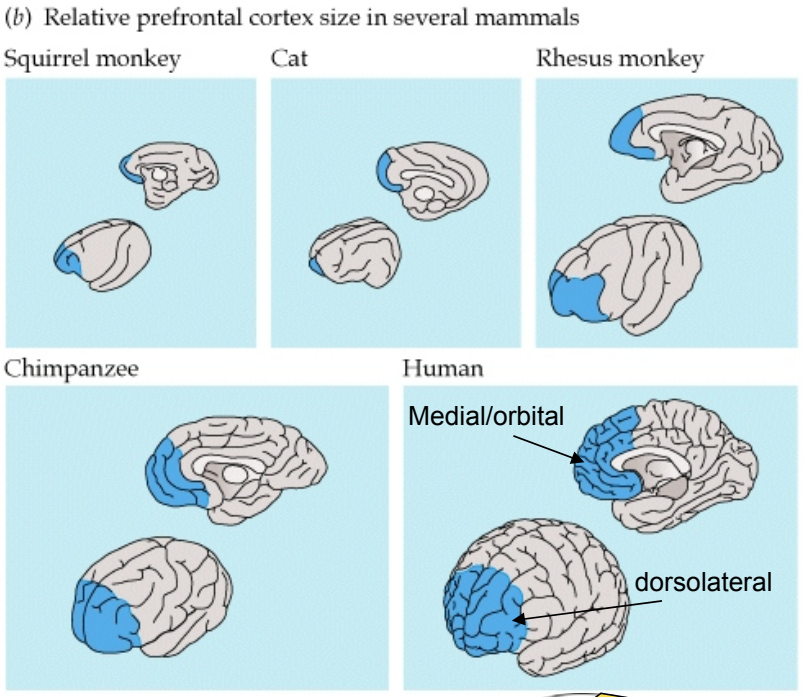
- ***"Thinking is done by the cells of the brain behind the forehead...The cells of the rest of the brain may know how to feel and see and hear, and how to make the body move, and may have wonderful things stored in memory, but if the forehead cells do not know how to think, the mind cannot make use of such memories.***
- ***We say that such a person is a fool, even though he has great knowledge.***
  - » ***Overton, 1897***



Prefrontal Cortex: Comparative Anatomy

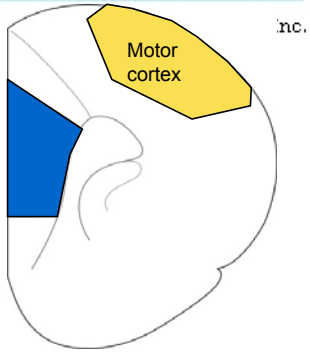
- Moving up evolutionary scale, relative % size of PFC increases: largest in humans
- Medial and Orbital regions = emotion regulation
- **Dorsolateral Regions** in Primates = working memory, flexibility, planning
- PFC functions develop late in humans (~2-3 years)

PFC allows humans to do complex (emotional and logical) processing



- The **medial PFC** in the rat is shares some of the functions of the dorsolateral PFC in primates/ humans

Medial PFC in rat= dorsolateral PFC in primates



squirrel monkey

Prefrontal Cortex and Working Memory (I)

- The PFC regulates a number of "**executive functions**" – a sort of "command and control" function; can be viewed as a "conductor" of various cognitive skills.
  - Aids in selecting and successfully monitoring behaviors that facilitate the attainment of chosen goals

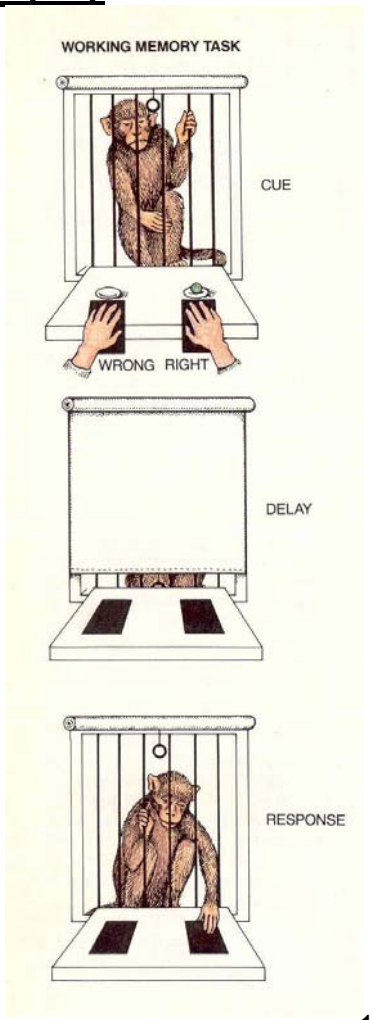
- Working memory = short term **manipulation** and retrieval of **trial unique information**
  - Use info temporarily, manipulate it, then discard it
  - Info is encoded in one form, but used to guide behaviour in another form
  - e.g.: remembering a sequence of digits: recalling digits forward = short-term memory
  - **BUT** - recalling sequence ***backwards*** = **working** memory

working memory ≠ short term memory

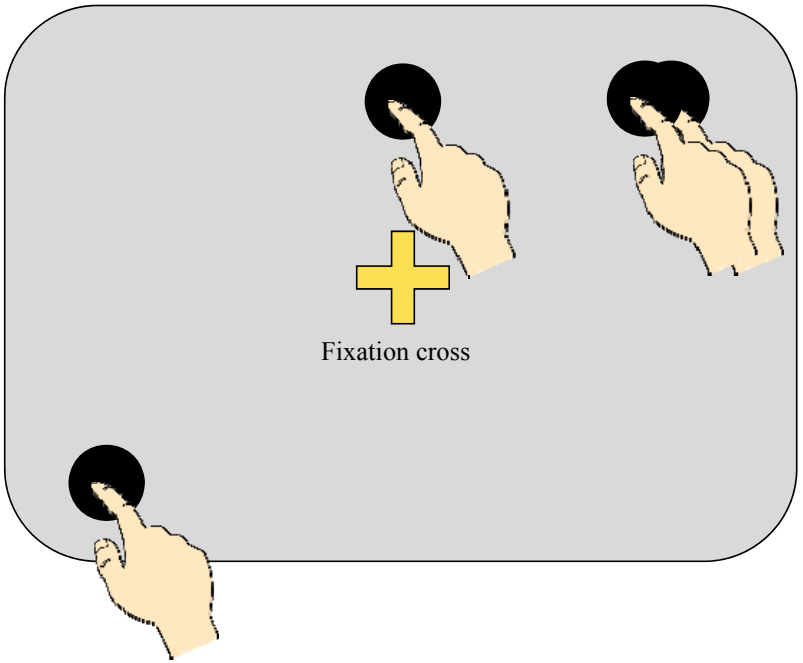
recall = short term
manipulating = working

Prefrontal Cortex and Working Memory (II)

- "Delayed response"- Classic PFC task that can be used across species
  - Animal acquires information, holds it over a delay and then uses it to guide a response
  - During "response" phase, animal must figure out where food may be based on what it saw
- Humans and primates: dorsolateral PFC lesions impairs, even at shortest delay
- Rats: medial PFC lesions impairs delayed response



Delayed Response Tasks and Working Memory



Sample

Delay

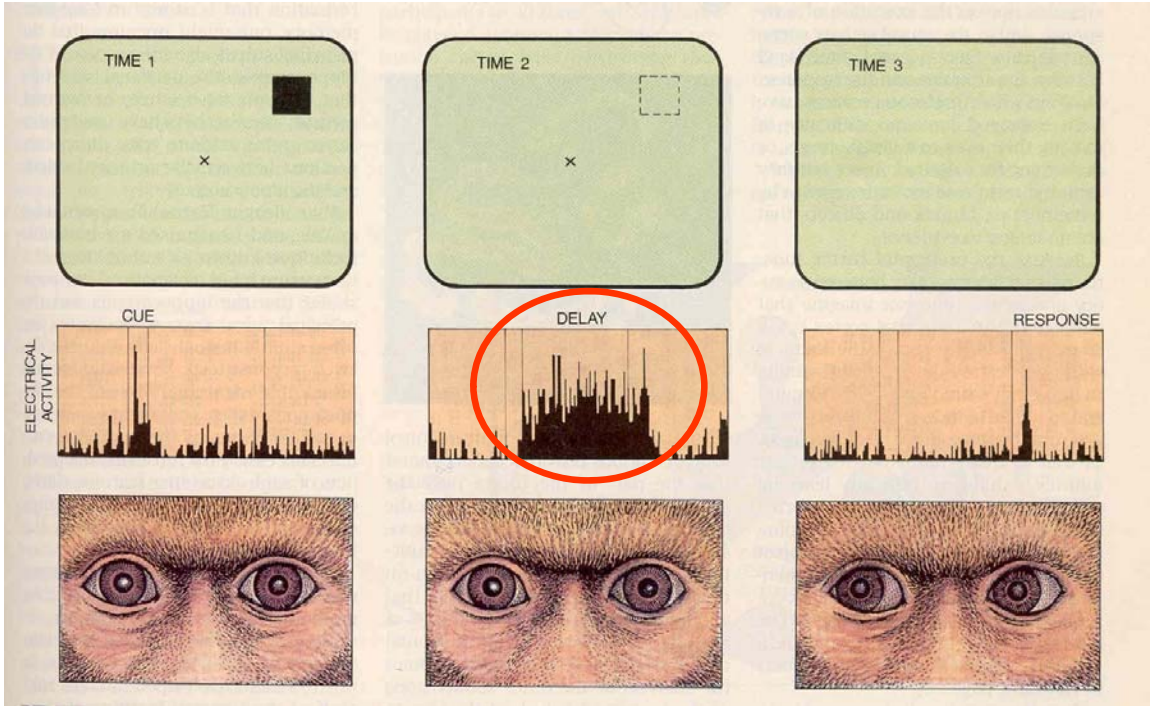
Response

object/"fixation point" shown on screen, subject has to point to where it was

- Trials are given in rapid succession with short inter-trial intervals: on each trial, subject needs to distinguish the information to remember on THAT trial vs previous ones
- This task taps into component processes of working memory that involve storage and manipulation of short-term information

one trial = no PFC involvement
rapid succession trials = need to focus on most recent instance, PFC

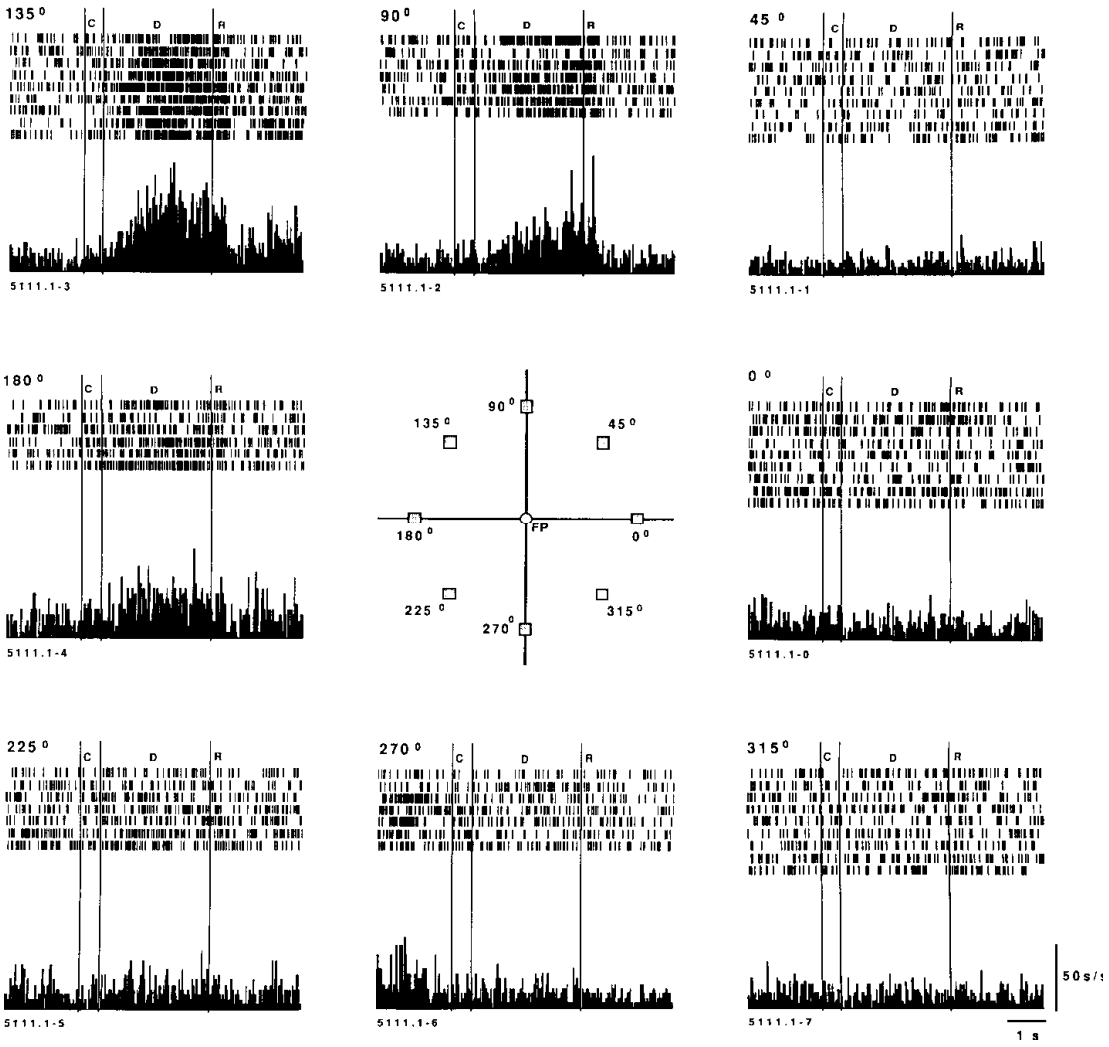
PFC neural activity and delayed response



•Record from PFC neurons: different neurons fire at different parts of task
•This activity is resistant to distracters (unlike similar activity in other brain regions)

• Delayed period activity **predicts accuracy** of response
-Reduced delay activity = animal makes an error

delay neurons activity holds info: more activity → more accurate response



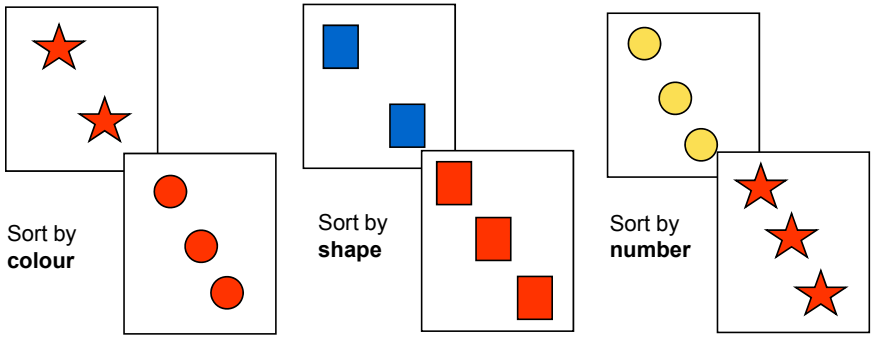
sort of like place cells

- Multiple PFC neurons may "encode" different bits of information
- One theory is that activity of different groups of PFC cells "holds" information online that aids in manipulating information to guide behavior

diff cells hold diff info simultaneously → allows manipulation

SUMMARY: PFC lesion prolongs time to extinction

Prefrontal Cortex and Behavioural Flexibility (I)



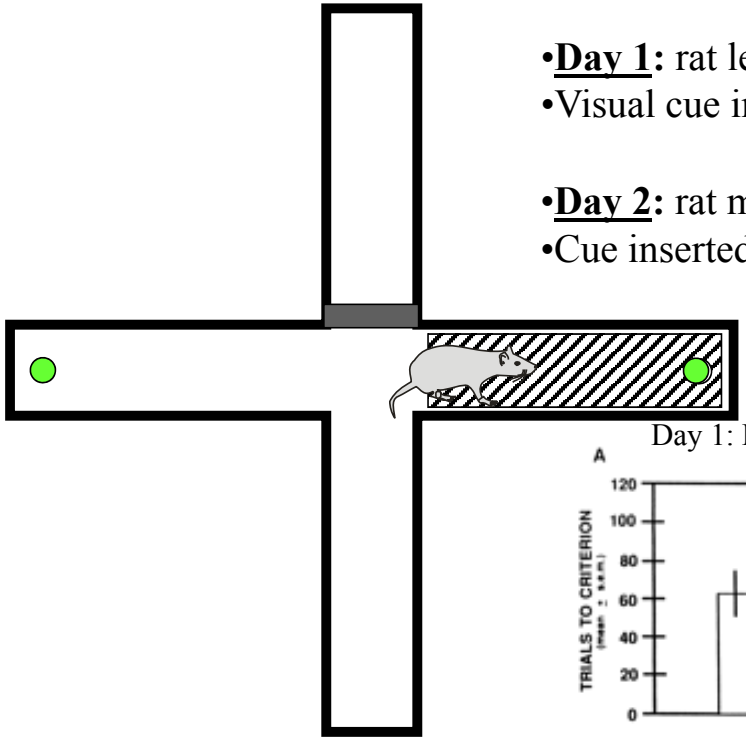
➢ **Wisconsin Card Sorting Task**: Test behavioural flexibility (ability to change strategies)

- Subjects must first sort cards by one stimulus dimension (e.g., number of items on cards)
- Then task switches, patients have to ignore old strategy and switch to new one (eg. shape)
  - Patients not told what they must do, are only given positive or negative feedback from experimenter (ie: “yes, that is right”, “no that is wrong”)
- Patients with damage to dorsolateral PFC can learn first discrimination
- ***However*** they cannot switch strategies, keep sorting cards by first stimulus dimension (keep sorting by number) = **perseveration**

even when they say they know it’s wrong

SUMMARY: PFC lesion prolongs time to extinction

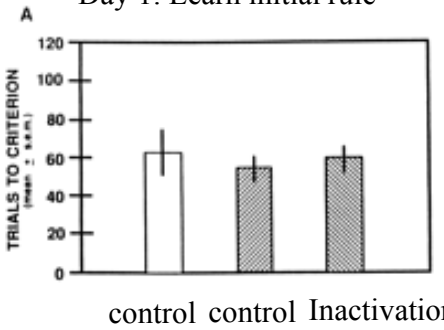
Prefrontal Cortex and Behavioural Flexibility (II)



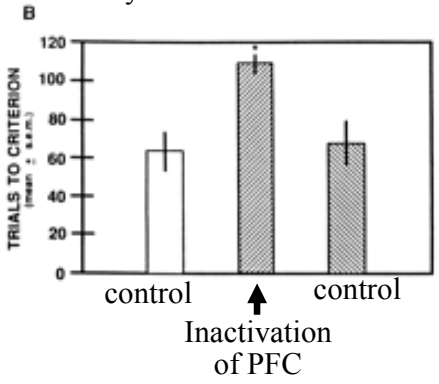
•**Day 1:** rat learns ***Response Rule*** (ie: always turn left)
•Visual cue inserted in either left or right arm on each trial; rat must ignore cue

•**Day 2:** rat must now approach ***Visual Cue***
•Cue inserted in either left or right arm; rat must stop using old rule, engage new one

Day 1: Learn initial rule



Day 2: shift to the new rule



•Reversible inactivations of PFC: infuse local anesthetic into PFC; lasts for ~ 1 hr

•**Inactivate PFC during initial learning: no effect** (PFC not involved in learning simple rules)

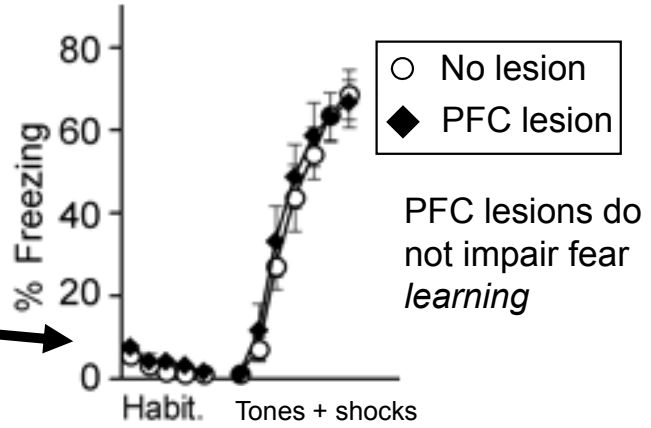
•**Inactivate PFC during the shift: MAJOR impairment** (PFC selectively involved in switching strategies)

SUMMARY: PFC lesion prolongs time to extinction

Prefrontal Cortex and Extinction Learning

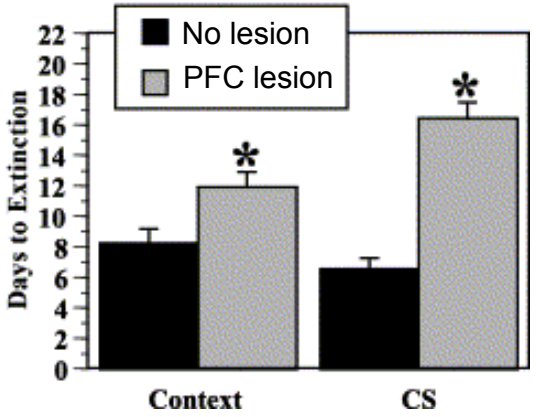
- Give tone and shock pairings = rats freeze to tone
- KEEP giving tones with no shock = rats eventually stop freezing (**extinction**)
  - Extinction is not "forgetting" ; it is a form of new learning (e.g: the tone is not bad anymore) that suppresses the old response
  - Fear memory doesn't fade away, it is actively suppressed
- PFC damage in rats **does not disrupt learning of fear conditioning to cues or context**
- However, rats with PFC damage take **longer to extinguish** fear response during extinction
- PFC is connected with the amygdala, and PFC inputs can inhibit neural activity in the amygdala

Acquisition of Fear Conditioning



PFC lesions do not impair fear *learning*

Extinction of Fear Conditioning



Prefrontal Cortex and Planning (I)

- PFC keeps track of/helps plan sequences of action (**Temporal Organization of Behaviour)**
  - e.g: cooking a meal: you have to remember all the ingredients and actions, and put them together in a set sequence
  - Patients with PFC damage can remember all the ingredients, but cannot carry out various steps in proper sequence

➢ PFC lesions = patient remembers particular items (long term memory intact) but cannot order them correctly

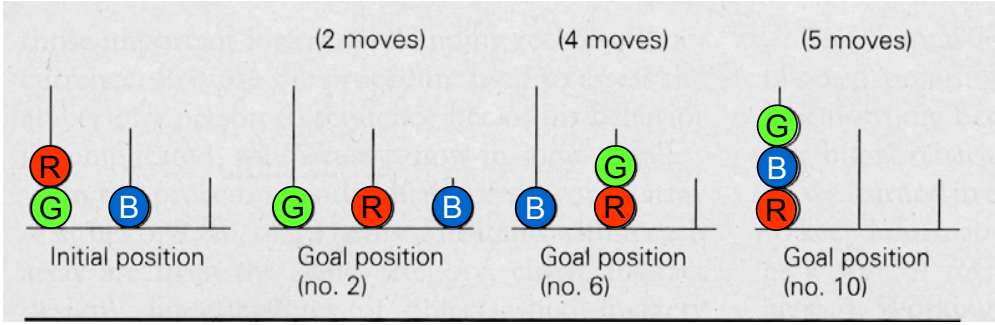
- PFC damage impairs recalling the temporal order of events in memory
  - Ask patient "Which movie did you see most recently, Pulp Fiction or Anchorman"
  - They can remember seeing both movies, but cannot remember where in time they saw them

PFC lesions —> can't chronologically organize memories

Prefrontal Cortex and Planning (II)

➢ **Tower of London task:**

- Assesses planning of movement sequences
- "Move the balls from the start position to this final position in as few moves as possible."



- PFC patients need many more moves to reach goal position; often, they don't reach goal at all

➢ **Dinner Party Problem":** subjects given "real-world" planning task

- •Given 6 errands to run (e.g.: buy loaf of bread, etc)
- •Also told to get answers to 4 questions (e.g.; price of tomatoes).
- •Explicitly told **not** to enter shops unnecessarily finish as quick as possible

- PFC damaged patients very inefficient: broke rules (entered unnecessary shops) and failed on many tasks
- All patients remembered and understood rules and attempted to comply
- NOT a memory deficit, but a deficit in integrating memory to form plan of action