Introduction to Neuroscience:
Systems neuroscience

Integrating

The prefrontal cortex

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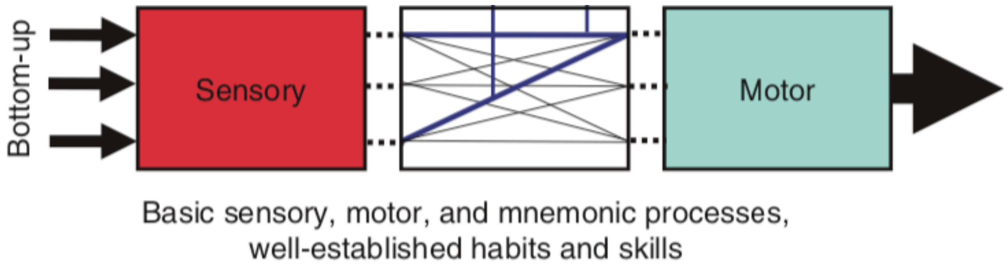
What does the prefrontal cortex do?

Executive functions:

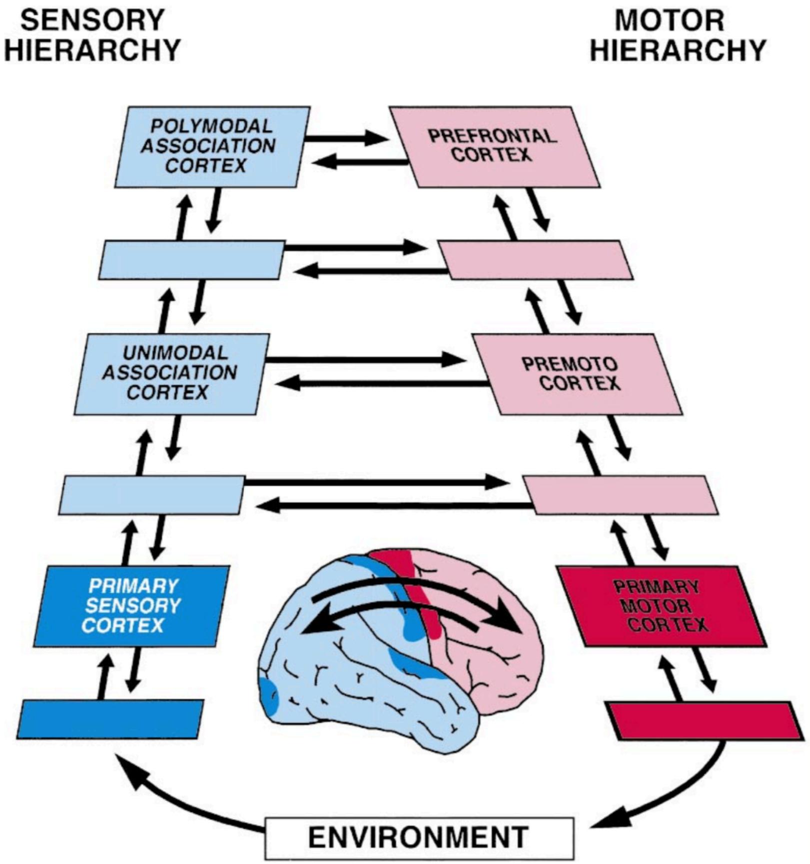
Cognitive, or executive, control refers to the ability to coordinate thought and action and direct it toward obtaining goals.

It is needed to overcome local considerations, plan and orchestrate complex sequences of behavior, and prioritize goals and subgoals. Simply stated, you do not need executive control to grab a beer, but you will need it to finish college.



Miller and Wallis, 2010

The cortical stages of the perception-action cycle



Fuster, 2000

John Fulton

Egas Moniz

The lobotomists

- London 1935, Second International Congress of Neurology: John Fulton and Carlyle Jacobsen present work on prefrontal lesions in chimps, which reduced “tantrums” and made them “happier”.

Fulton Muniz ?

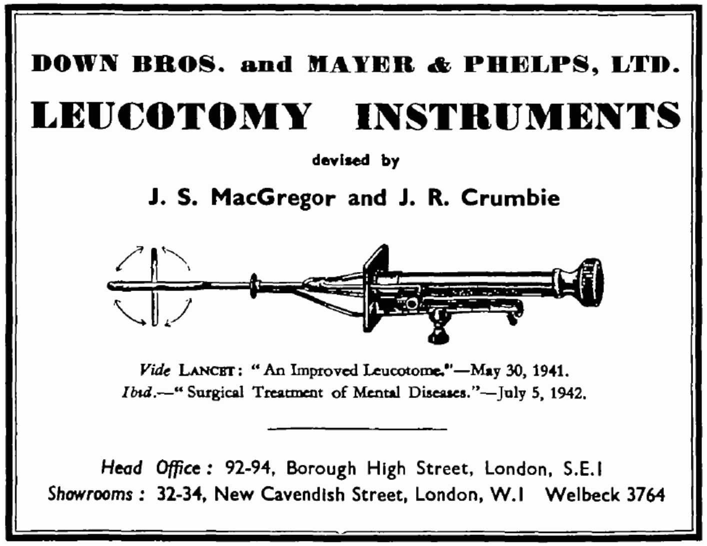
- Egas Muniz asks Fulton if such surgery can be performed on psychiatric patients. Fulton rejects the idea.

Boettcher, L. B., & Menacho, S. T. (2017). **https://doi.org/10.3171/2017.6.FOCUS17249**

The lobotomists

Egas Moniz

- November 1935: Moniz performs "frontal leucotomy" on several psychiatric patients in Lisbon.
- The goal of the operation was "to remove some of the long fibres that connected the frontal lobes to other major brain centres"



- The mode of action: ethanol injection into the white matter tracts under the prefrontal cortex
- Later patients were treated with a "leucotome", making circular lesions of white matter fibers.
- 1949 - Moniz receives the Nobel Prize for Physiology and Medicine for the development of leucotomy.

Boettcher, L. B., & Menacho, S. T. (2017). **https://doi.org/10.3171/2017.6.FOCUS17249**

The lobotomists

Egas Moniz

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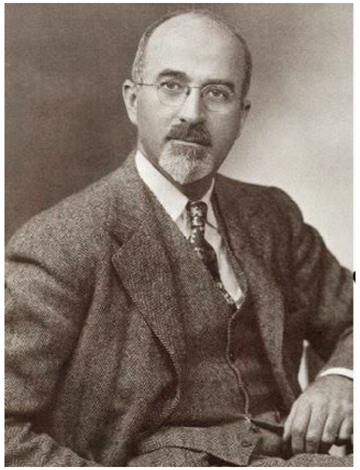
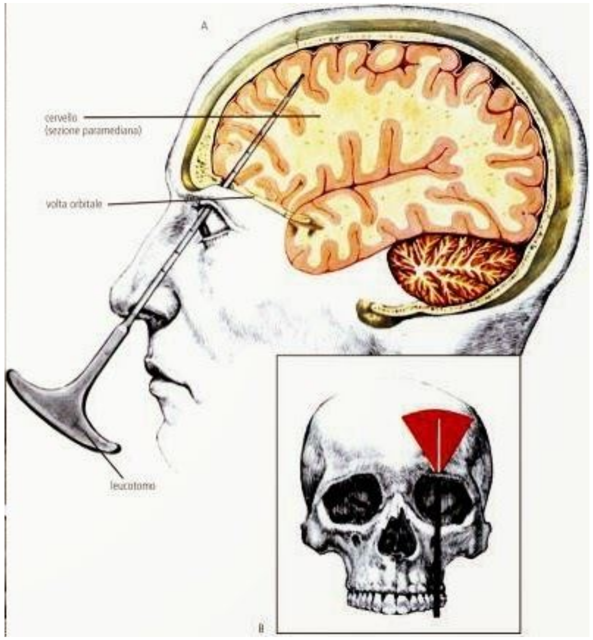
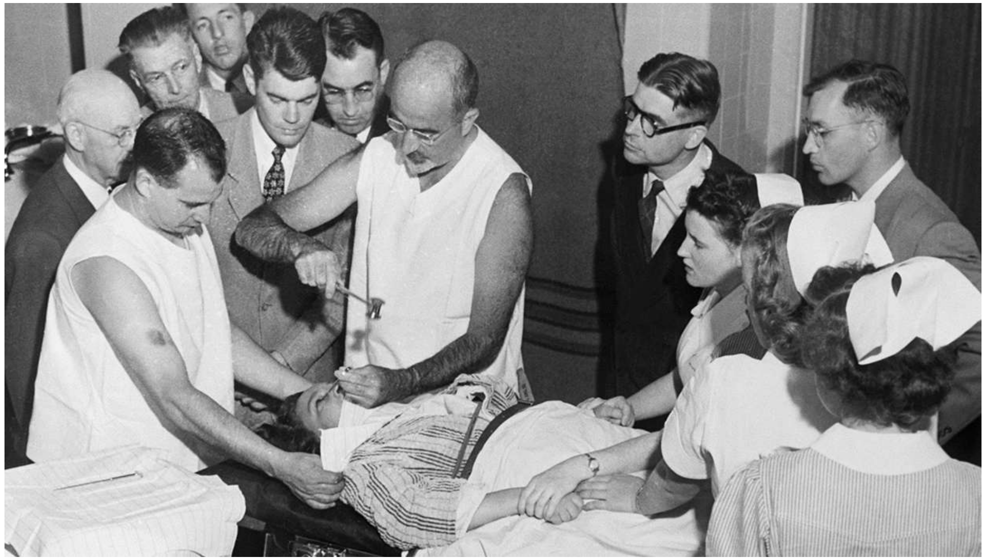


Walter Freeman II

- Walter Freeman, an American neurologist, adopts Moniz's procedure and develops a more rapid method for lobotomy
- The major advance: can be performed as an "office procedure" without complex surgical equipment.



Transorbital **lobotomy**



Egas Moniz

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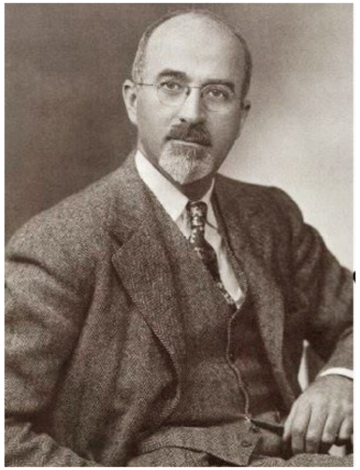


Walter Freeman II

The lobotomists

- Approx. 40,000 psychiatric patients were lobotomized by Freeman and his colleagues in the US from 1946 to the 1970s.
- Criticism of the procedure mounted, mainly regarding the efficacy and the lack of consistent long-term follow-up on patients.
- A majority of lobotomies was performed on women and minorities (up to 70% in some cases). In Japan - mostly done on children with behavior “problems”.
- Very minimal follow-up on patients after their discharge -> poor scientific evidence for the efficacy of the procedure and its side effects.
- Calls to revoke Moniz’s Nobel Prize were rejected by the Nobel committee.

Further reading: “The Lobotomist” by Jack El-Hai

Experiments of chance: what have we learned from accidental lesions?

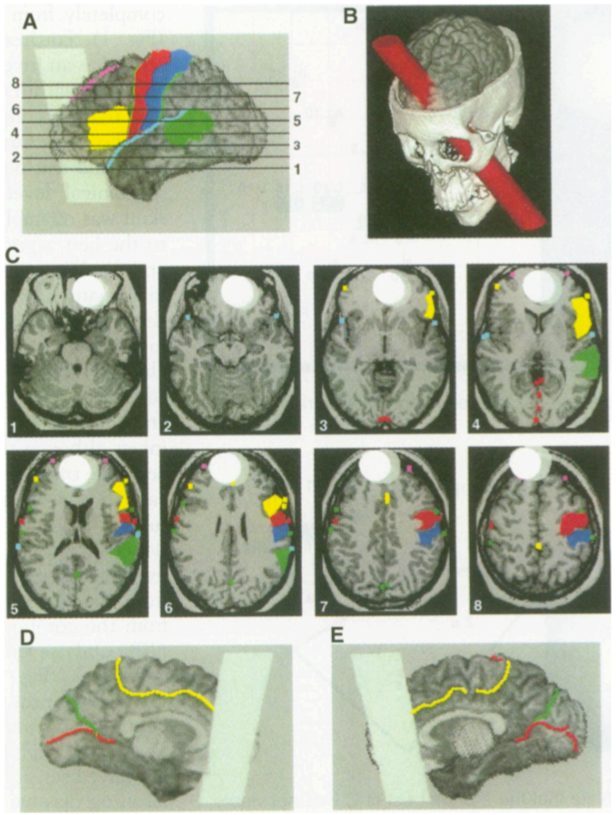
Phineas P. Gage (1823–1860)

“The equilibrium or balance, so to speak, between his intellectual faculties and animal propensities, seems to have been destroyed. He is fitful, irreverent, indulging at times in the grossest profanity (which was not previously his custom), manifesting but little deference for his fellows, impatient of restraint or advice when it conflicts with his desires….”

John Harlow, "Recovery from the Passage of an Iron Bar through the Head”, 1868

Experiments of chance: what have we learned from accidental lesions?

Fig. 5. Normal brain fitted with the five possible rods. The best rod is highlighted in solid white [except for (**B**), where it is shown in red]. The areas spared by the iron are highlighted in color: Broca, yellow; motor, red; somatosensory, green; Wernicke, blue. (**A**) Lateral view of the brain. Numbered black lines correspond to levels of the brain section shown in (**C**). (**D** and **E**) Medical view of left and right hemispheres, respectively, with the rod shown in white.



Mapping the connectivity damage to Gage's brain:

- Only 4% of the cortex was directly injured by the metal rod.
- ~11% of left frontal lobe WM was damaged.
- Broca's area was spared, along with motor, somatosensory and Wernicke's area.
- The rod went through the **ventromedial area** of both hemispheres and exited dorsomedially.
- Pattern consistent with several modern cases, which showed similar behavioral changes ("Their ability to make rational decisions in personal and social matters is invariably compromised and so is their processing of emotion. On the contrary, their ability to tackle the logic of an abstract problem, to perform calculations, and to call up appropriate knowledge and attend to it remains intact.")

Damasio et al., Science 1994

Experiments of chance: what have we learned from accidental lesions?

PFC damage leads to very little overt impairment, but can be devastating.

- Executive functions: alertness, set, task switching, rule learning, working memory
- Decision making, value and rule learning deficits

Cognitive

- Depression
- Euphoria

Emotional

- Hyper / Hypokinesia, perseverance in old behavioral patterns

Motor / arousal

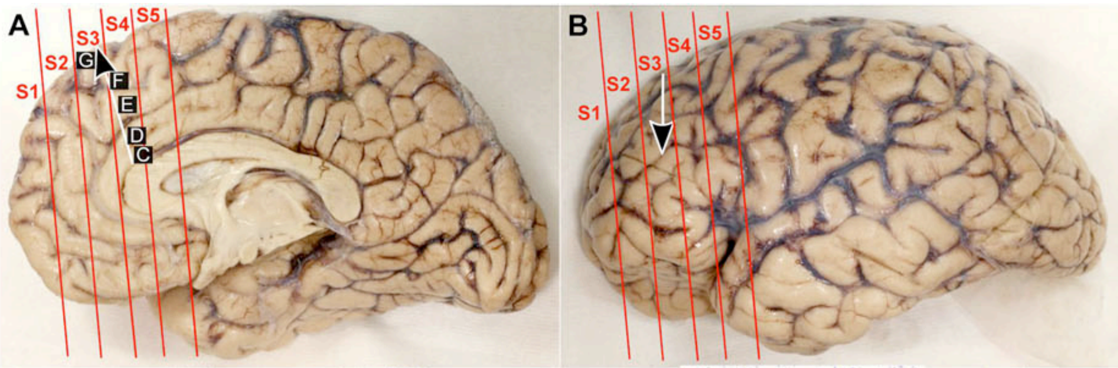
- Social deficits - social anxiety, theory of mind, social motivation

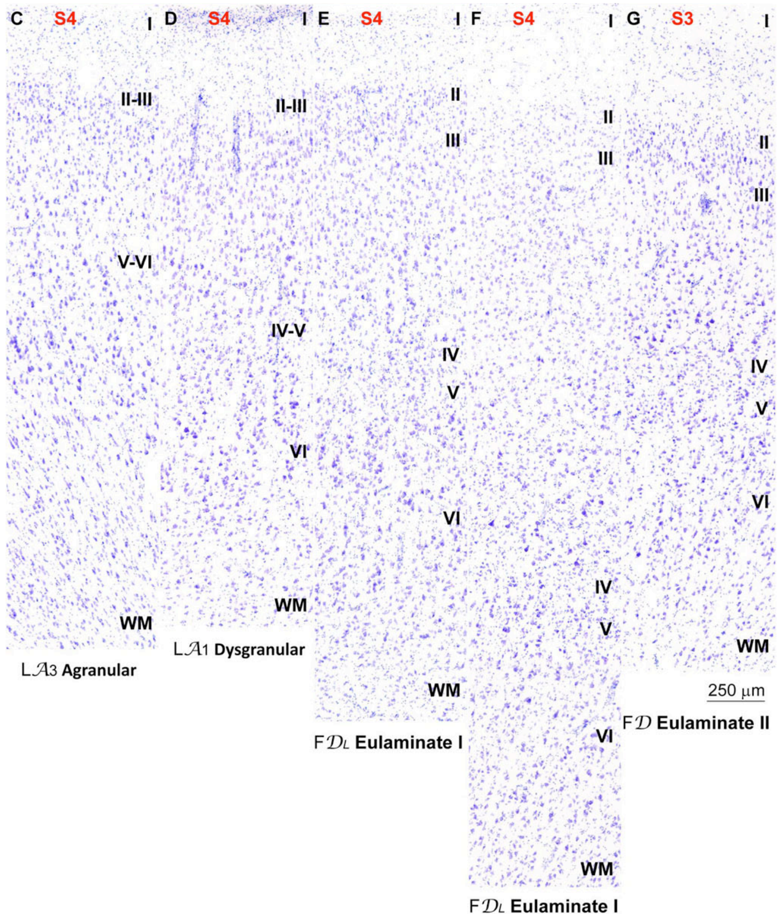
Social

"The Prefrontal Cortex", Joaquim Fuster (4th ed.) Ch. 5

Anatomy of the prefrontal cortex

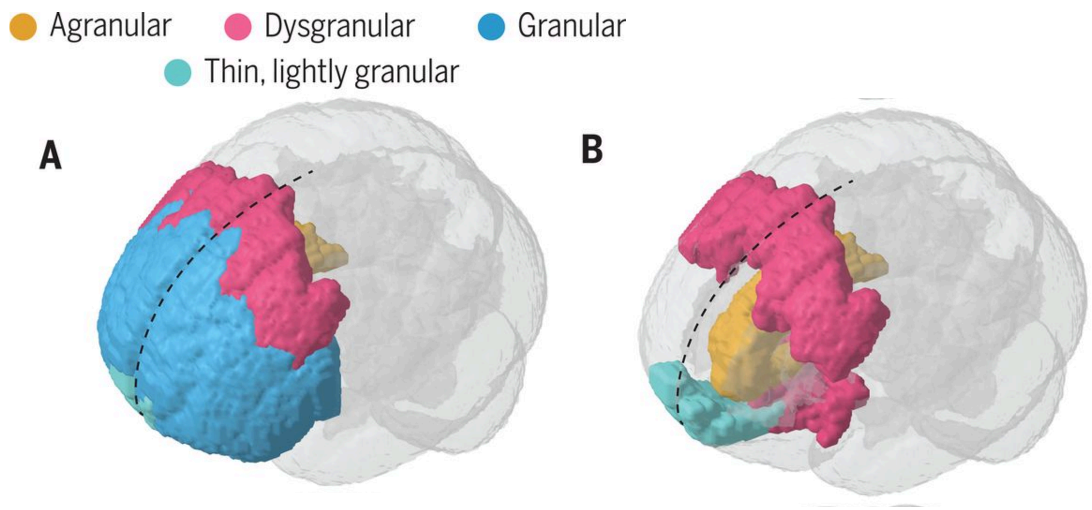
Brodmann (1909): the prefrontal cortex in primates is defined as the **frontal granular region** (anatomical/ cytoarchitectonic definition).





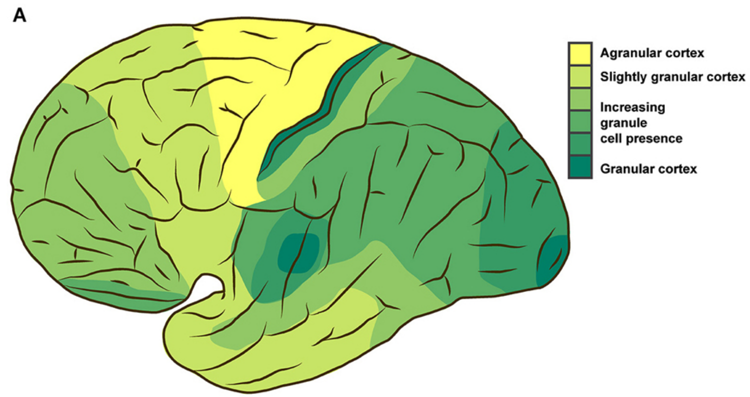
Garcia-Cabezas et al., Front. Neuroanat., 07 December 2020

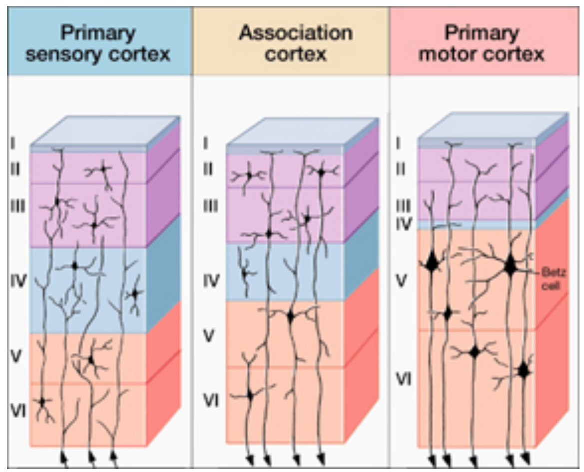
Cytoarchitectonics of the PFC



Human prefrontal cortex

Granular cortex: contains layer 4 with large “granule cells” that receive direct thalamic input; agranular cortex has no layer 4; dysgranular - less pronounced L4.





Granular Dysgranular Agranular

Carlén, Science 358, 478–482 (2017)

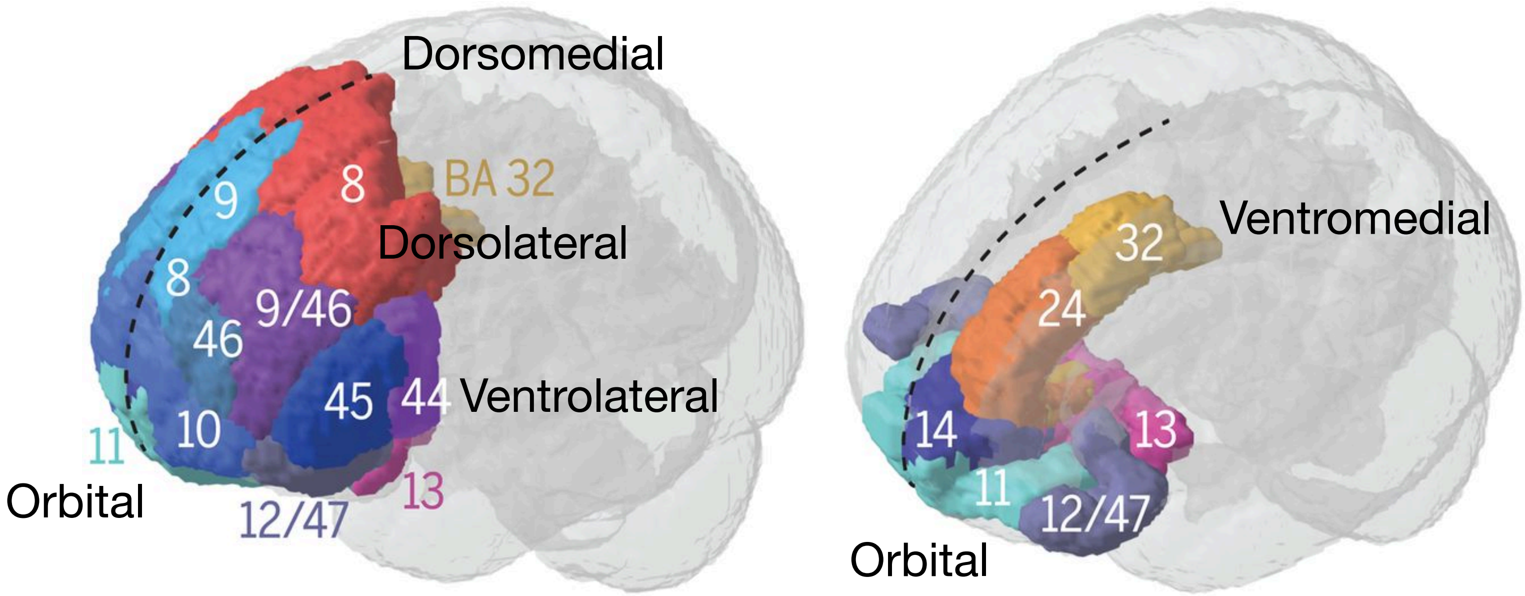
Beul & Hilgetag, Front. Neuroanat., 2015

Anatomy of the prefrontal cortex

Brodmann (1909): the prefrontal cortex in primates is defined as the frontal granular region (anatomical/ cytoarchitectonic definition).

Dorsolateral granular PFC - unique to primates;

Dorsomedial, ventromedial and orbital (dysgranular and agranular) exist in all mammals to some extent.

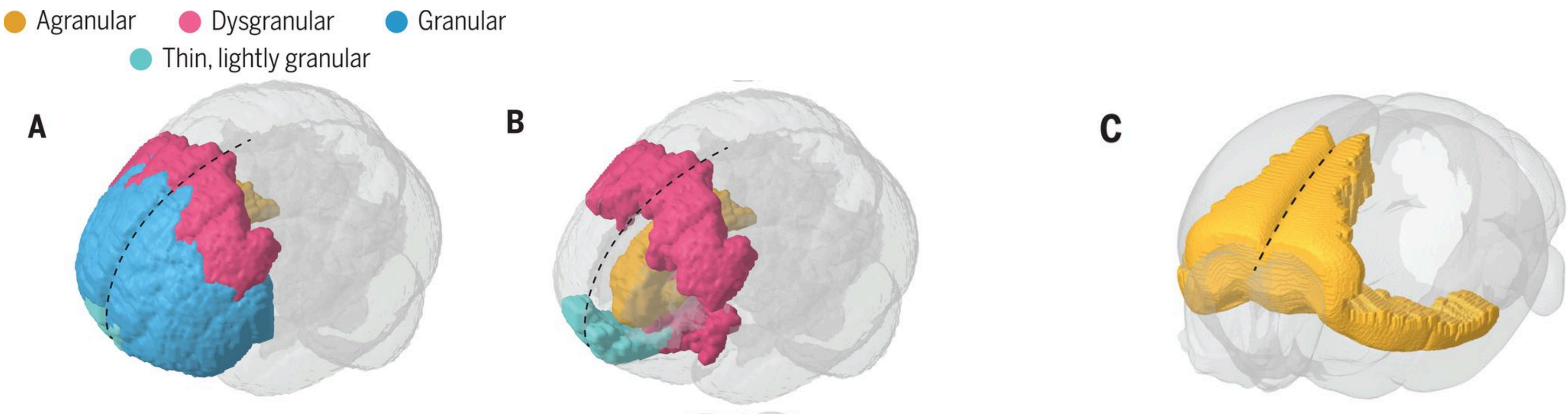


Carlén, Science 358, 478–482 (2017)

Problem: the “PFC” in many animals is mostly agranular

Does this mean that rodents and carnivores have no PFC?

Rose and Woolsey (1948): the prefrontal cortex should be defined as the termination field of the mediodorsal thalamus (***hodological*** definition)



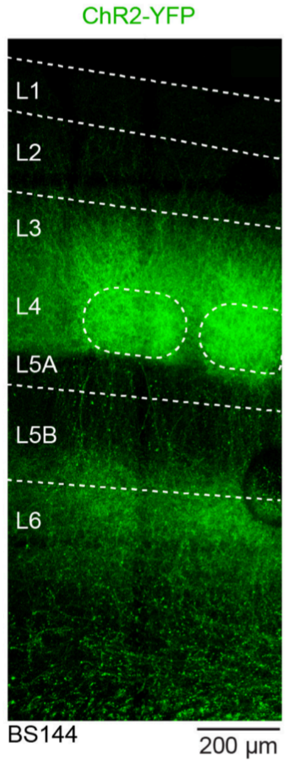
Human prefrontal cortex

Mouse prefrontal cortex

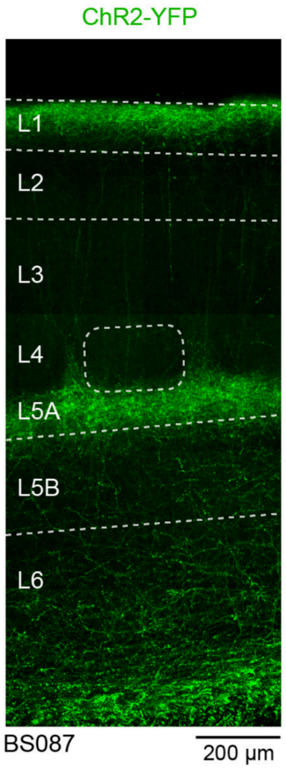
Carlén, Science 358, 478–482 (2017)

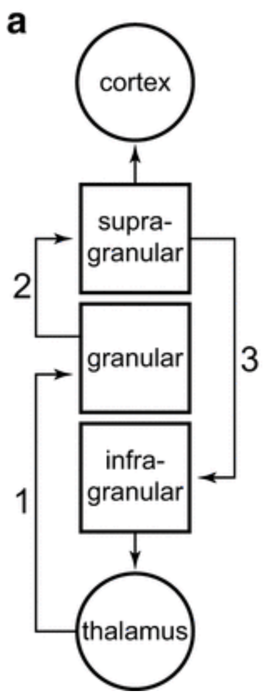
Thalamic input to agranular cortex arrives at L1, L3

VPM-S1



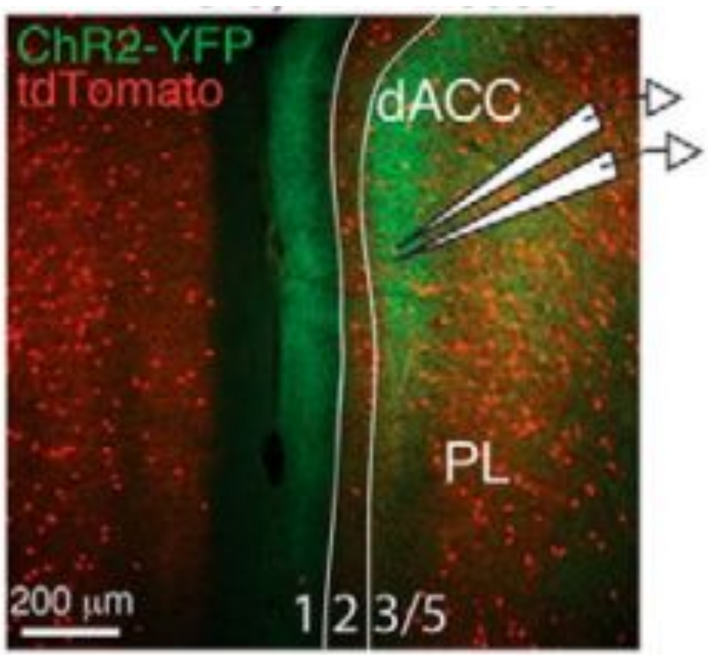
POM-S1





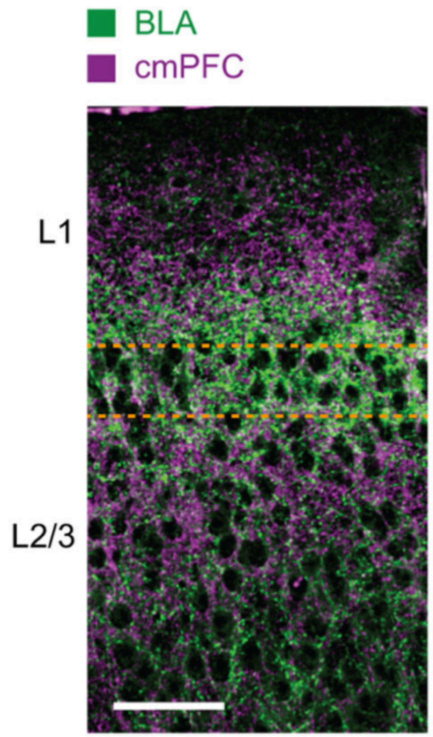
Sermet et al. eLife 2019

MD - mPFC projections



Delevich et al., JN 2015

Other inputs

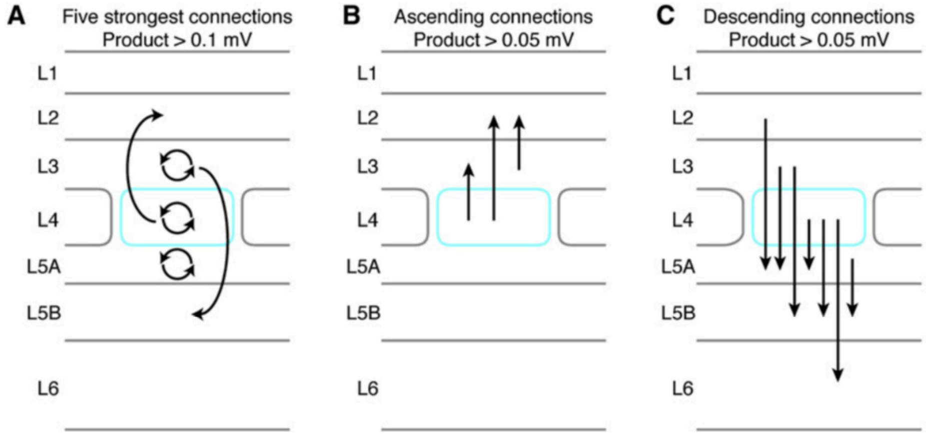


Little & Carter 2012

A canonical microcircuit for agranular cortex?

The canonical microcircuit in (granular) S1:

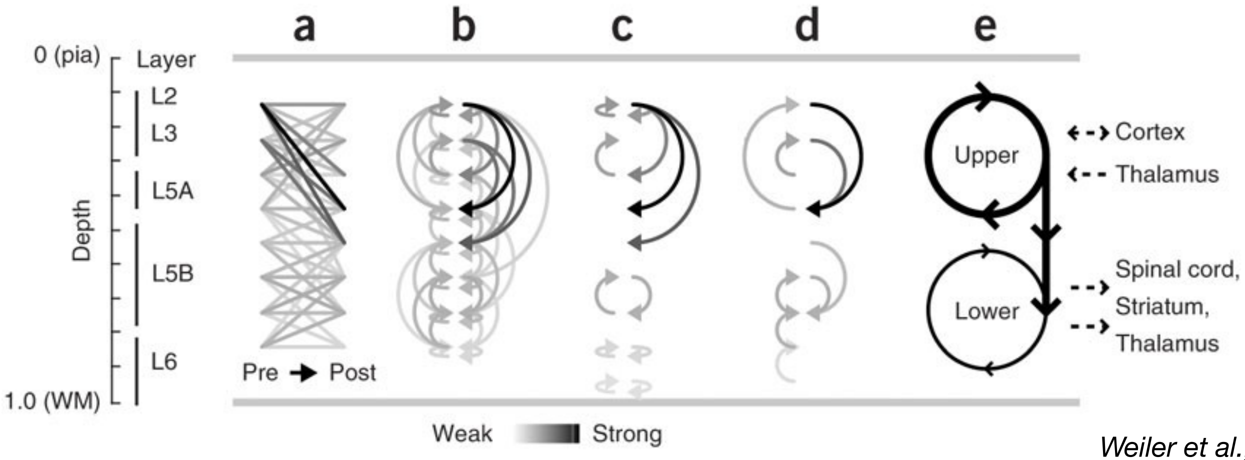
Strong recurrence in L4, ascending inputs L4->L2/3, descending from L2/3->L5A



Lefort et al., Neuron 2009

Organization of connectivity in (agranular) M1:

Strong recurrence in L2/3, ascending from L5A->L2 (might replace L4-L2/3)



Weiler et al., Nat Neuro 2008

The **medial** prefrontal cortex is conserved across mammalian species

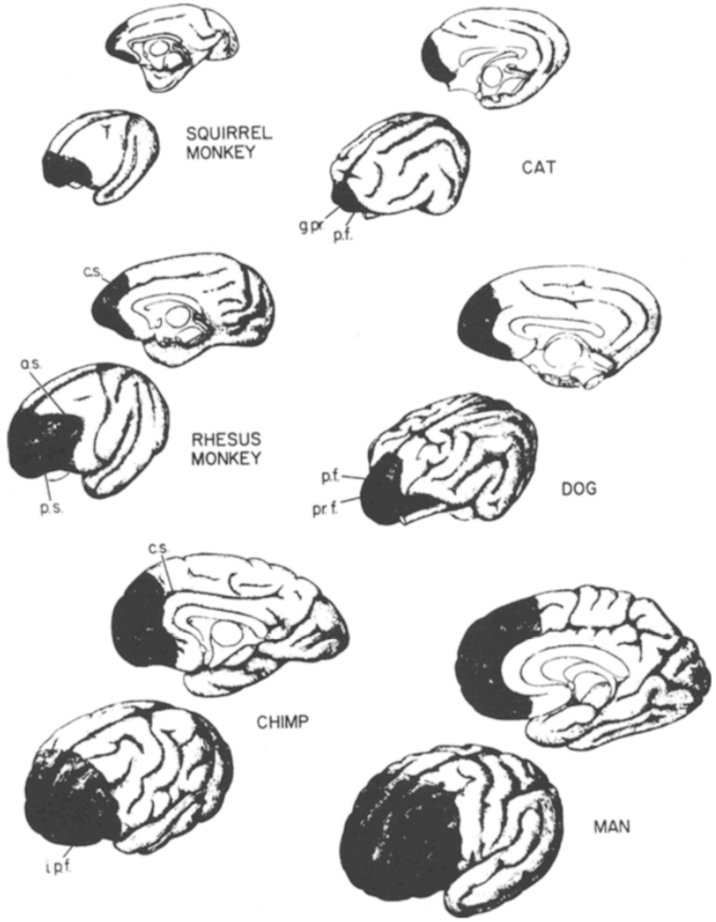
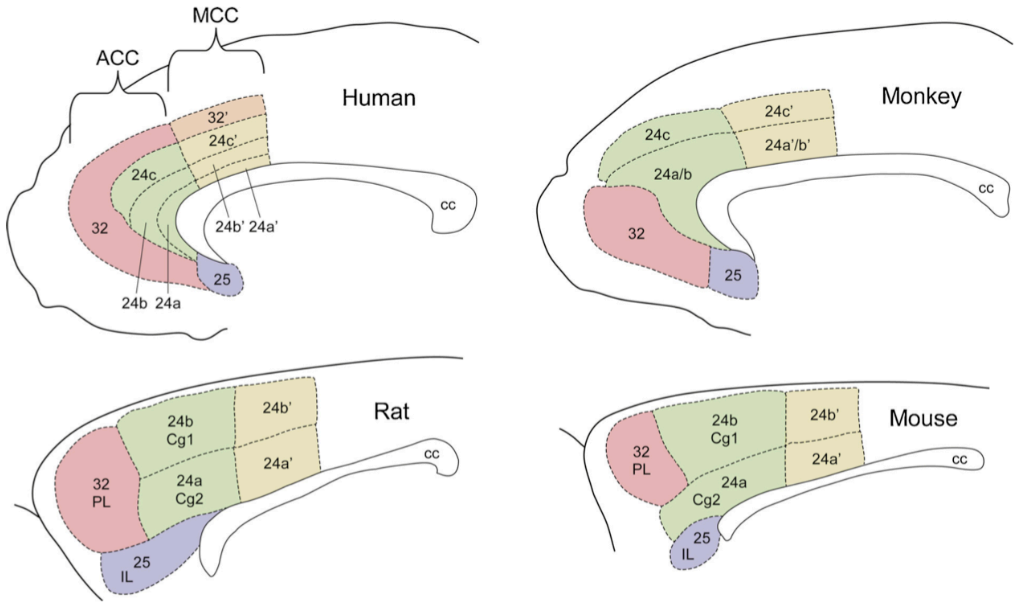


Figure 1. The prefrontal cortex (dark shading) in six animal species.



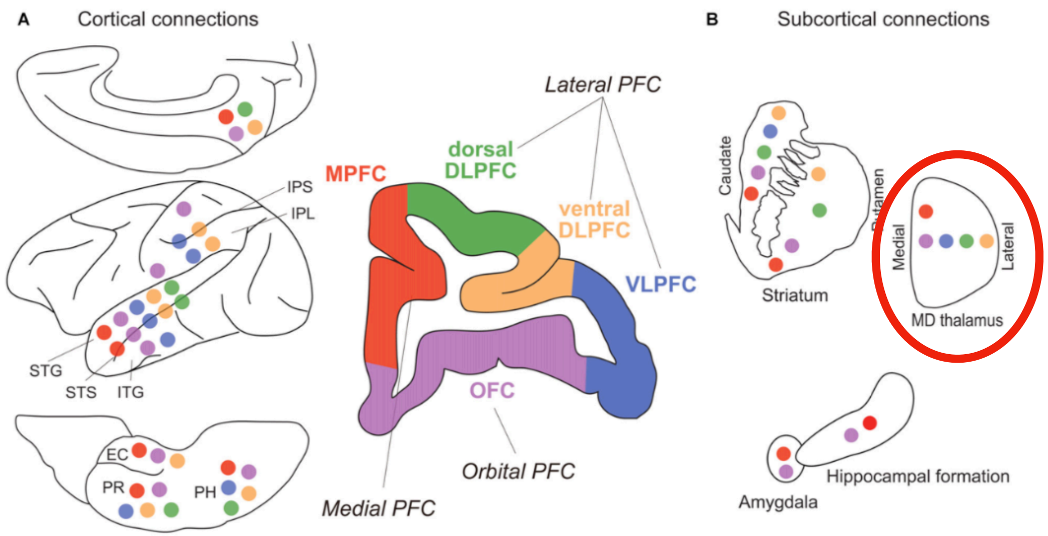
"The orbital and medial prefrontal areas are especially well connected with the medial and anterior nuclei of the thalamus, the prepiriform cortex, the hippocampus, the amygdala, and the hypothalamus.

The cortex of the dorsolateral prefrontal convexity is profusely connected with other frontal areas homolaterally and-through the corpus callosum-contralaterally, with the hippocampus, and with the temporal and parietal cortex." (Fuster, 2000)

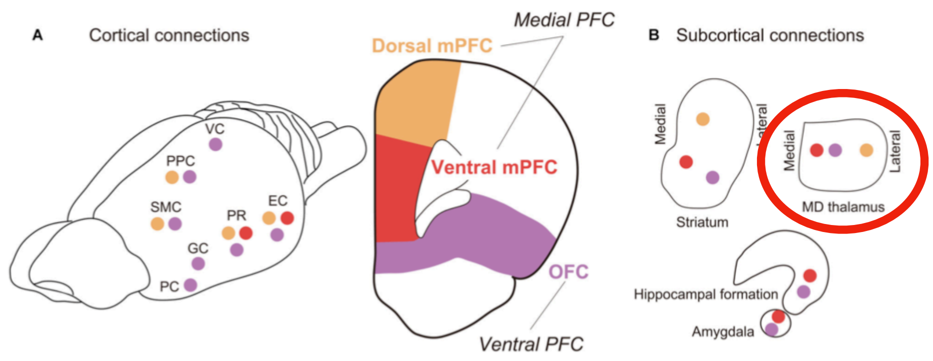
Fuster, Psychobiology 2000

Burgos-Robles et al., 2019

Long-range connectivity of the PFC



Monkey PFC connectivity



Rodent PFC connectivity

Connectivity with MD is conserved across mammals;

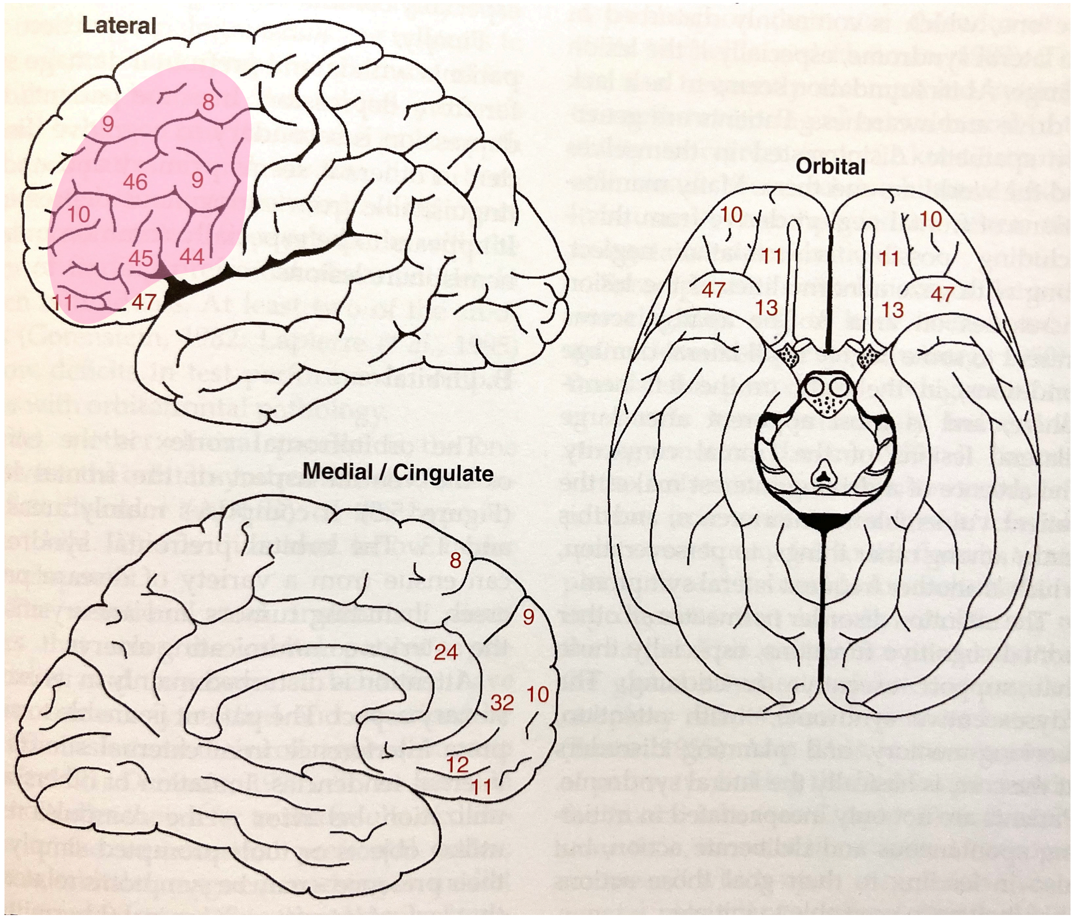
Some prefrontal connections are unique to granular DLPFC/VLPFC in primates, but are replaced by other PFC regions in rodents;

Medial PFC regions connect heavily with the hippocampus and amygdala in all mammals.

Tsutui et al., Front. Sys. Neurosci 2016

Subregion specificity of prefrontal syndromes

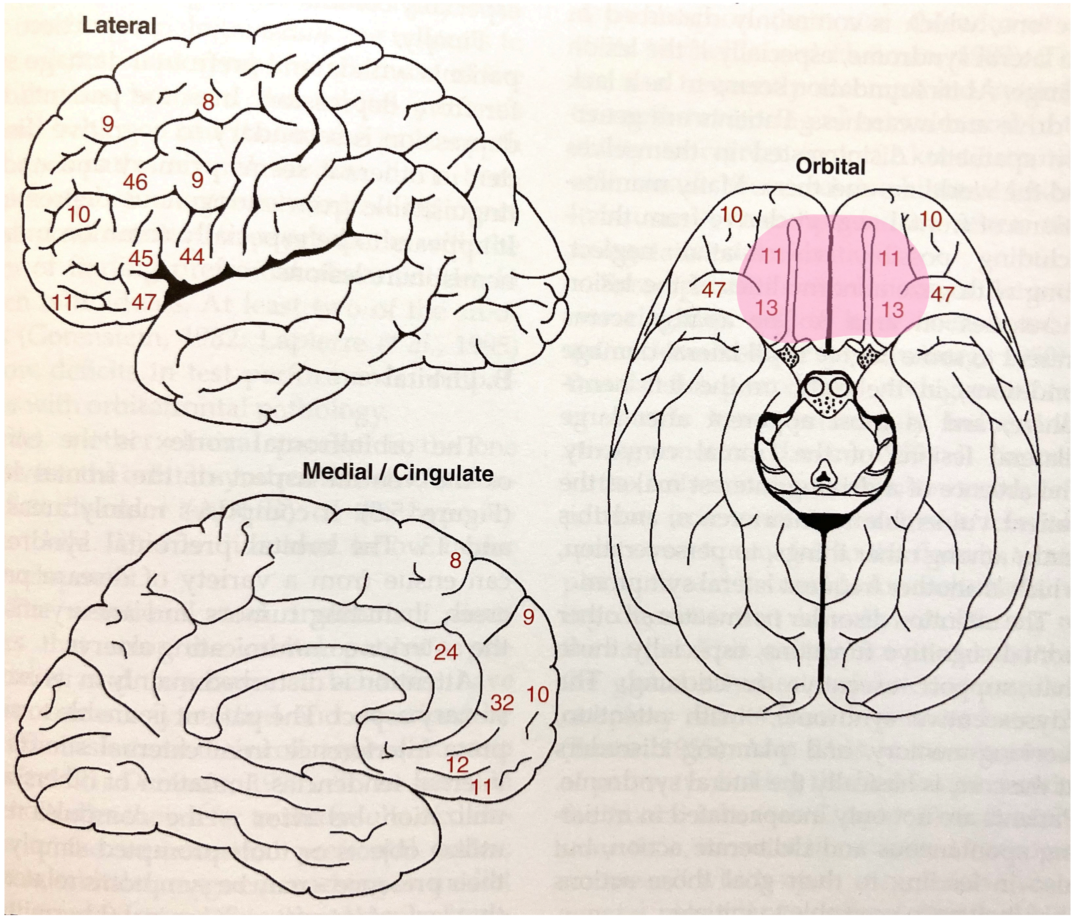
- Lateral prefrontal lesions (areas 8, 9, 10, 46):
  - Attention disorder (**selective/inclusive**, exclusive);
  - Apathy (“frontal neglect”);
  - Perseveration;
  - Working memory and planning deficits
  - Spoken language disorders (mainly left hemisphere).
  - Depression



“The Prefrontal Cortex”, Joaquim Fuster (4th ed.) Ch. 5

Subregion specificity of prefrontal syndromes

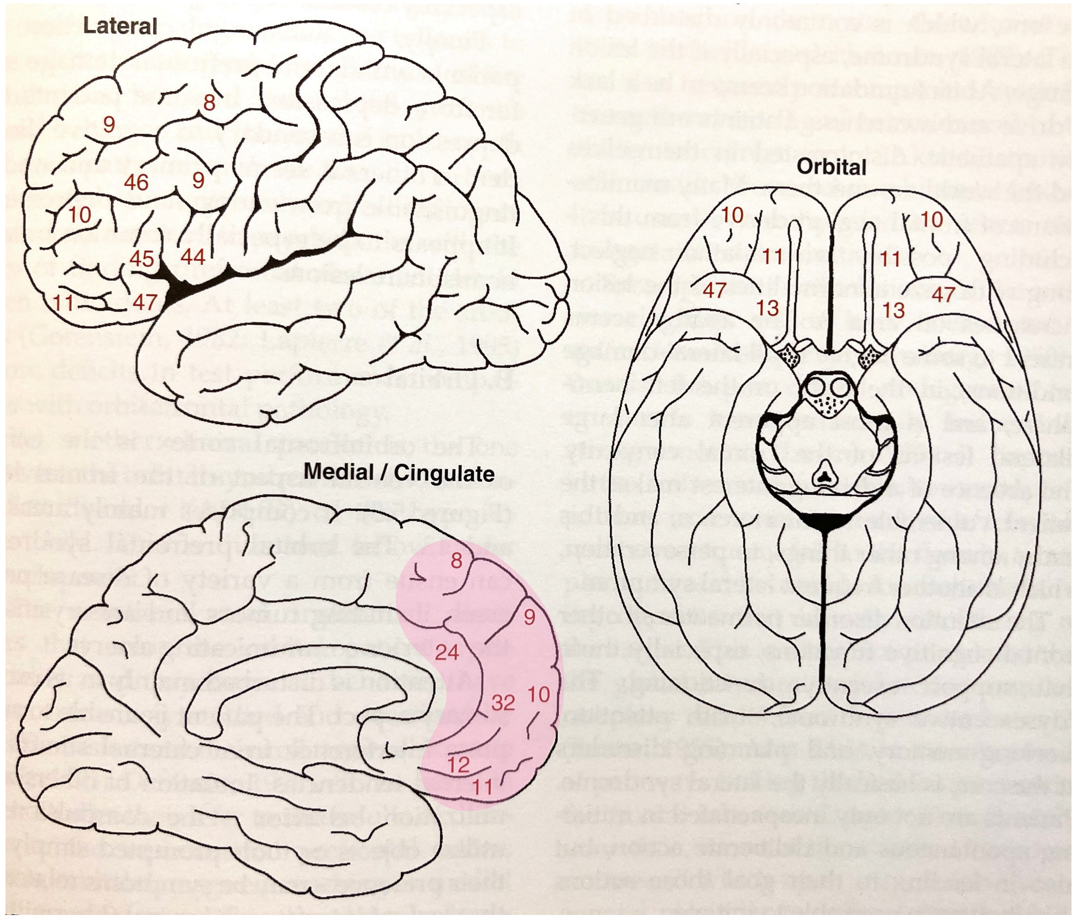
- Orbital lesions (areas 11,13):
  - Attention deficit (mainly **exclusive**)
  - Hypermotility
  - Impulsivity and compulsivity
  - Perseveration, bad decision making
  - Disinhibition, disrupted moral judgement
  - Sociopathy
  - Disinhibition of instinctual behaviors



"The Prefrontal Cortex", Joaquim Fuster (4th ed.) Ch. 5

Subregion specificity of prefrontal syndromes

- Medial lesions (areas 8-10, 12, 24, 32):
  - Action initiation difficulties
  - Cataplexy (loss of whole-body muscle tone during intense emotion)
  - Apathy - most prevalent disorder
  - Social deficits: theory of mind impairments, aggression

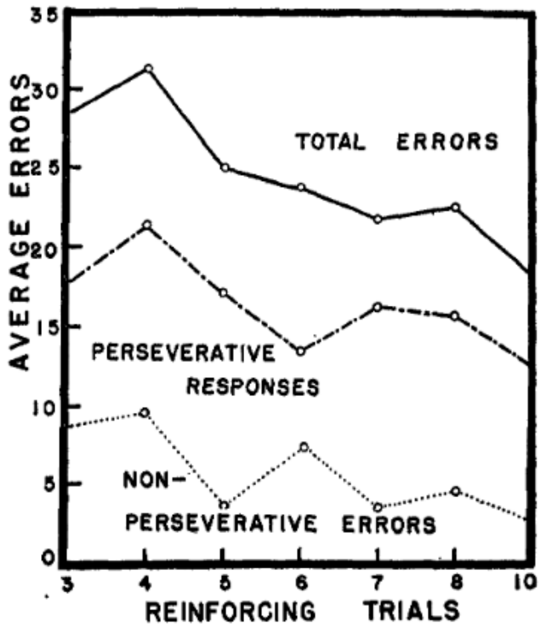


"The Prefrontal Cortex", Joaquim Fuster (4th ed.) Ch. 5

Identifying prefrontal dysfunction

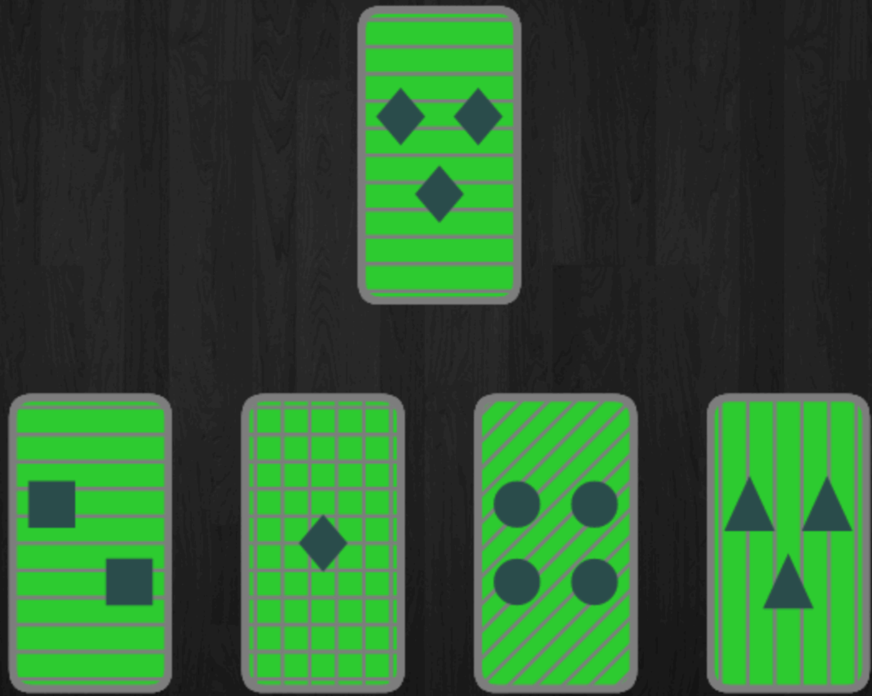
- Executive function tasks are particularly difficult for people with lateral prefrontal damage

WCST experiment: **https://www.psytoolkit.org/experiment-library/experiment_wcst.html**



Grant and Berg, Journal of Experimental Psychology, 38, 404-411 (1948)

The Wisconsin Card Sorting Task



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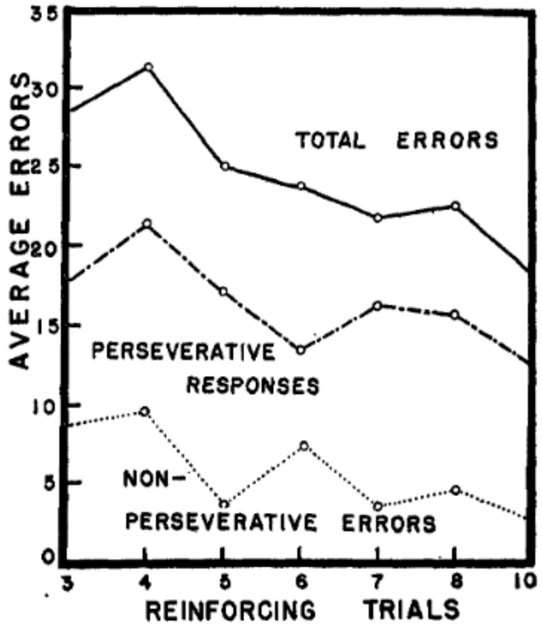


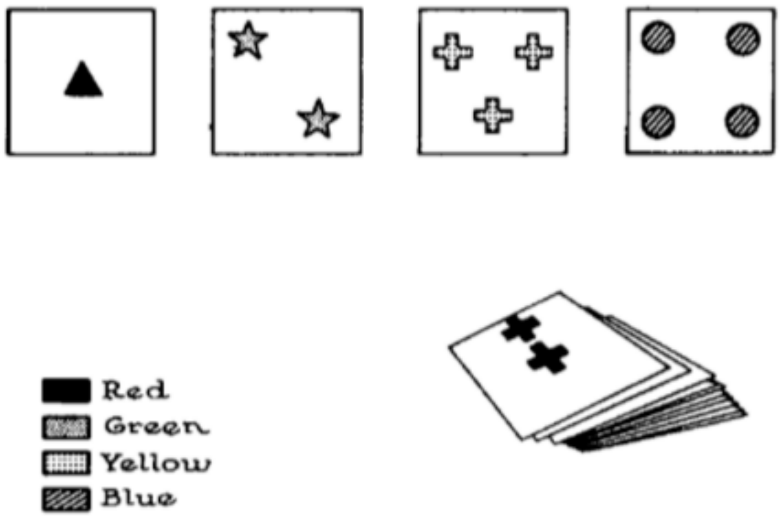


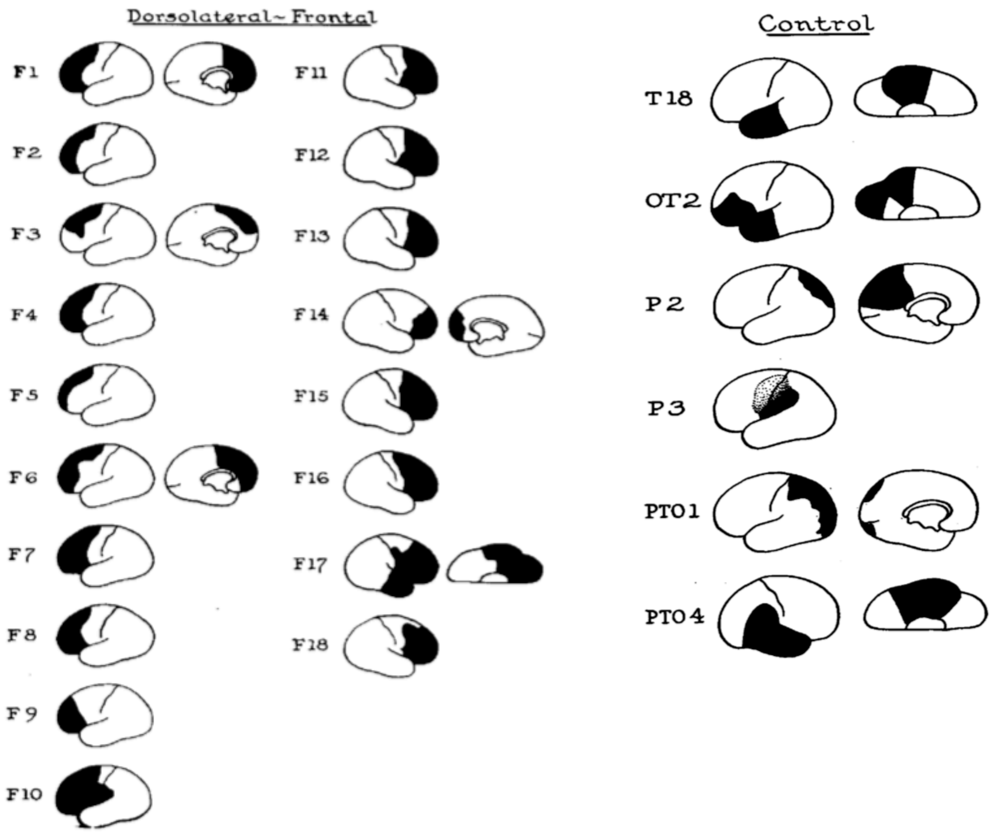
Fig 1.—Wisconsin Card Sorting Test, showing the material as presented to the subject.

Grant and Berg, Journal of Experimental Psychology, 38, 404-411 (1948)

Brenda Milner, JAMA 1963

Identifying prefrontal dysfunction

- Executive function tasks are particularly difficult for people with prefrontal damage



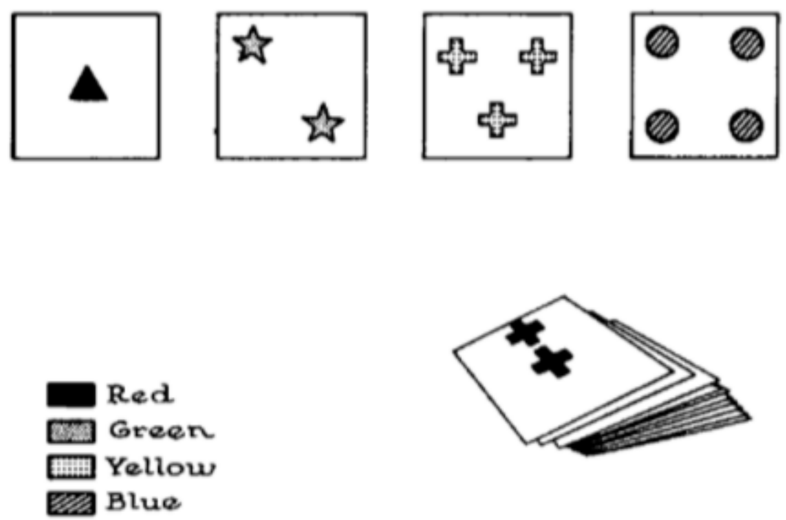


Fig 1.—Wisconsin Card Sorting Test, showing the material as presented to the subject.

Brenda Milner, JAMA 1963

Identifying prefrontal dysfunction

- Executive function tasks are particularly difficult for people with prefrontal damage

Table 3.—*Card Sorting Data for Group 1: Pre-Post Comparisons*

Locus of Excision	No. Cases	Total Errors: Preop. (Mean)	Total Errors: Postop. (Mean)	Categories Achieved, Max 6: Preop. (Mean)	Categories Achieved, Max 6: Postop. (Mean)
Dorsolateral frontal	18	54.9	73.2	3.3	1.4
Control					
Temporal	33	39.5	30.2	4.3	4.6
Parietal	8	36.8	30.1	4.9	5.1
Parietotemporo-occipital	5	46.2	37.6	4.8	3.8
Orbitofrontal + temporal	7	24.7	27.6	5.3	4.9
Total control	53	37.7	30.6	4.6	4.7

"The impairment shown by patients after frontal lobectomy reveals itself as a strong perseverative tendency. In extreme cases, a patient may sort all 128 cards to one preferred category (for example, form), despite the experimenter repeatedly telling him that his responses are wrong."

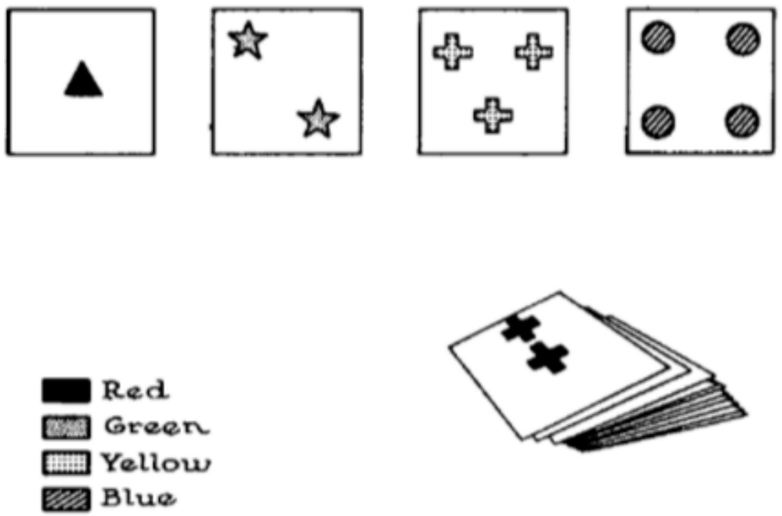


Fig 1.—Wisconsin Card Sorting Test, showing the material as presented to the subject.

Brenda Milner, JAMA 1963

Behavioral/cognitive functions of the PFC

Working memory: the ability to remember and manipulate information over a brief period (in the order of seconds).

Definitions:

Limited capacity: originally proposed as 7 items; recent studies suggest a limit of 4 items.

Associated with increased PFC activity: PFC activity increases with increased working memory load (fMRI and ephys evidence).

Individual differences in WM capacity are associated with variation in several important abilities, including control of attention, non-verbal reasoning ability and academic performance.

Working memory ≠ Reference memory

But what distinguishes working memory from short-term memory?

Is it more about the rate of forgetting than a unique acquisition mechanism?

WM experiment: **http://try.cognitionlab.com/demo/demo_types/sternberg/shell.html**

Memory Search

In this task, you must memorize a set of digits.

This memory set is then followed by a probe
which was or was not in the previously shown set of digits.

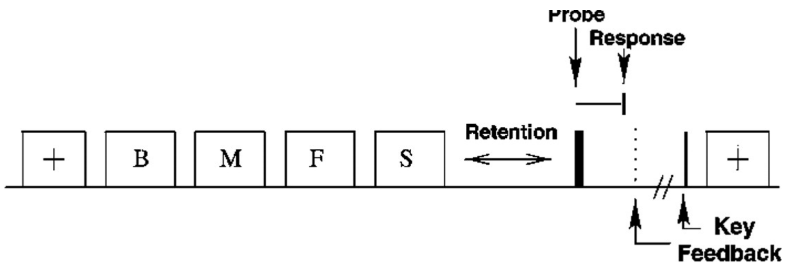
Press a key to continue reading instructions ...

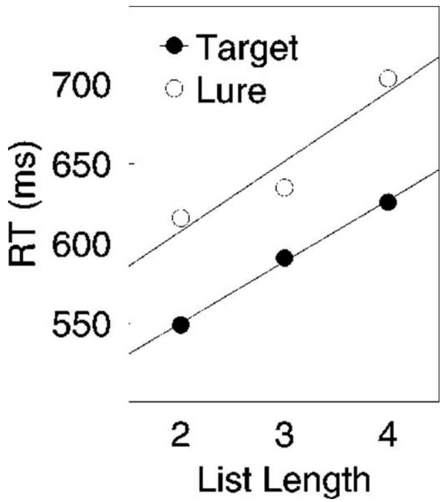
No
[X]

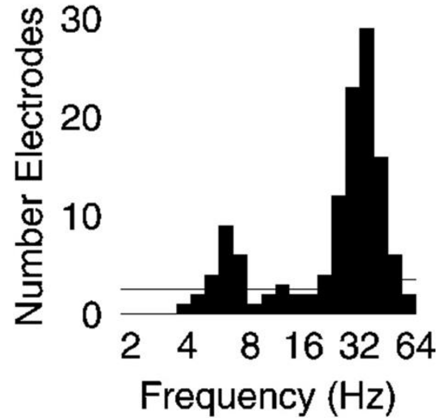
Yes
[M]

Reaction time and gamma oscillations during WM

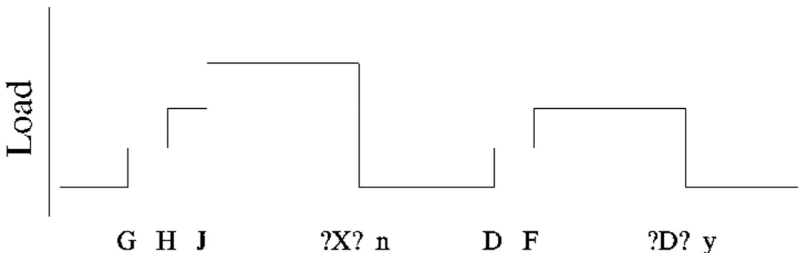
Subjects: two hospitalized epilepsy patients implanted with intracranial electrode arrays for monitoring seizure activity.

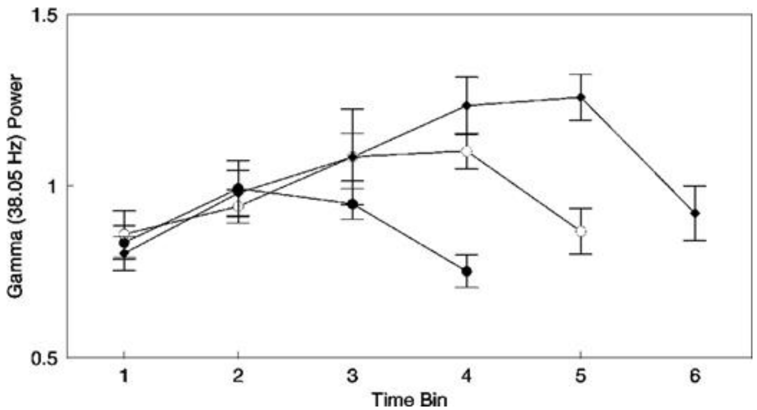






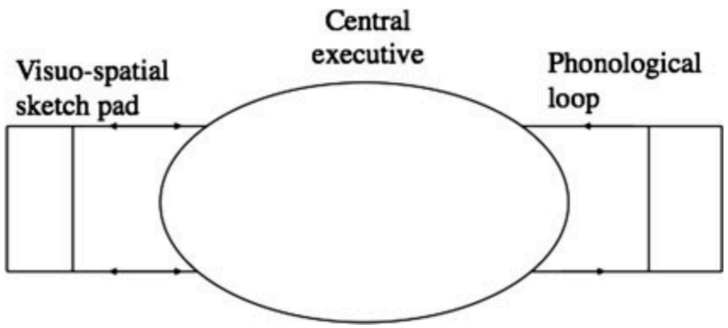
High WM load
Low WM load





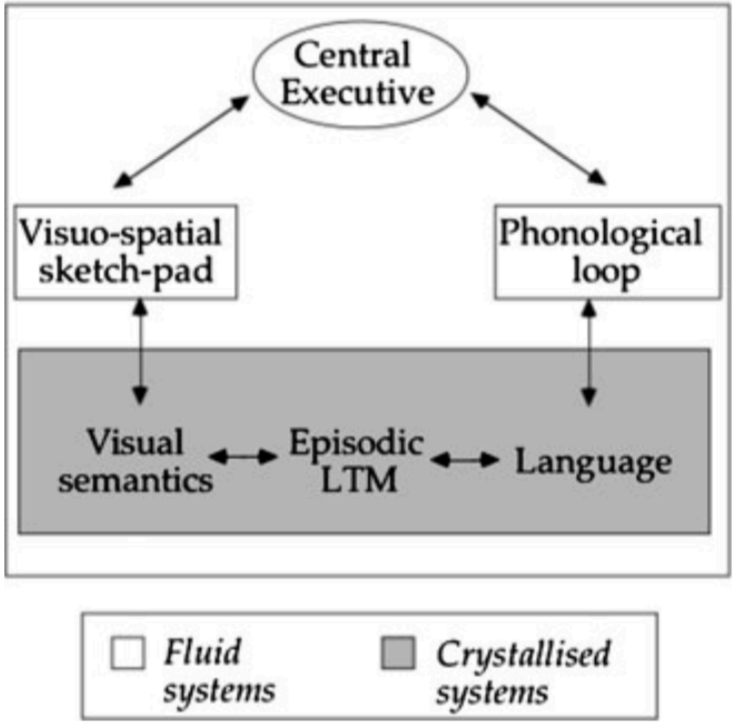
Howard et al., 2003

Definition and putative mechanism of WM in humans:



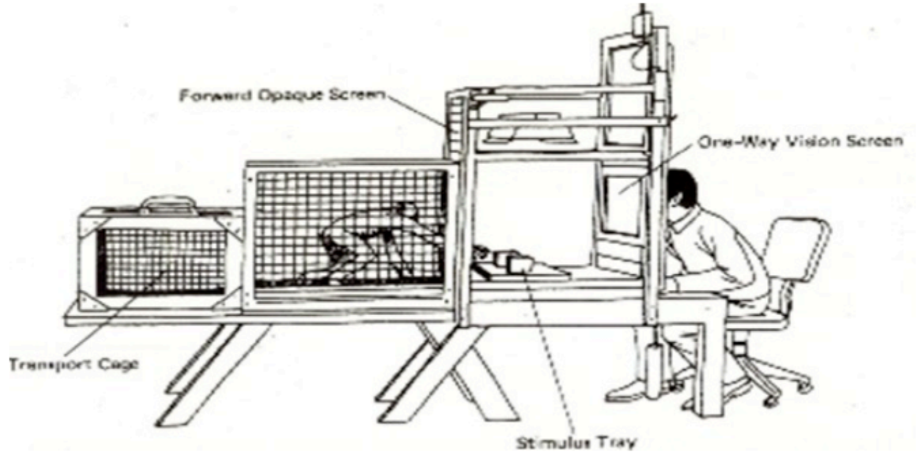
Working memory as a basis for long-term memory (WM —> LTM)

Language habits as a template for WM performance (“contramponist” vs “loddenapish”)



Baddeley A. Working memory. Science 1992;255:556–9.

Prefrontal cortex is required for working memory



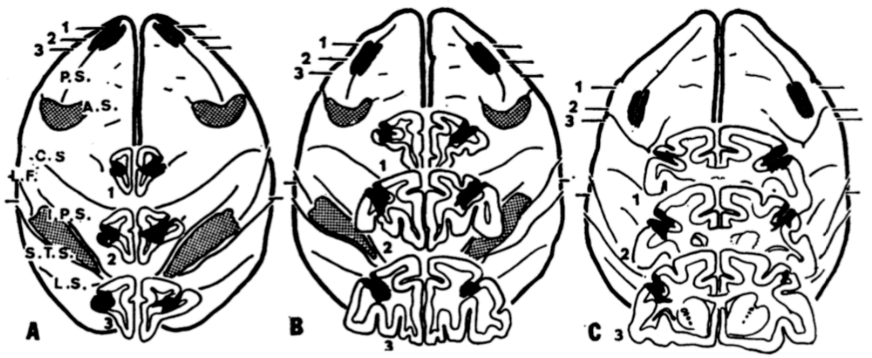
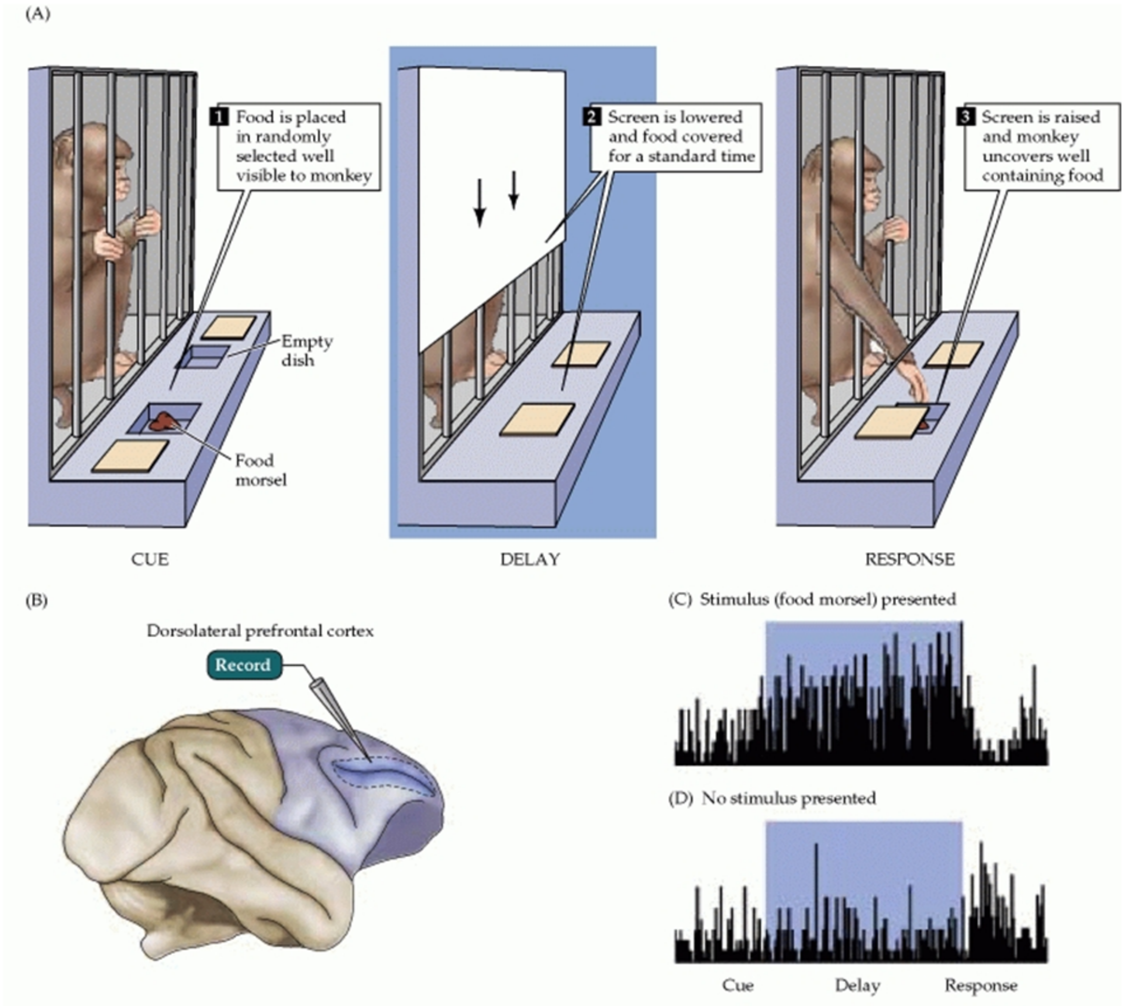


Table 1. Mean number of trials and errors to relearn 5-second spatial delayed-alternation. Midprincipalis (MP), periarcuate (PA), inferior parietal (IP), anterior principalis (AP), unoperated control (UC), posterior principalis (PP). For all groups, $N = 3$ except operation III MP where $N = 2$.

Group	Trials	Errors
	*Operation (retention) I**	
MP	1000	408
PA	343	61
IP	30	8
UC	83	16
	Operation (retention) II†	
PA	260	76
IP	227	45
UC	57	9
	Operation (retention) III‡	
MP	1000	359
AP	243	44
PP	570	131

* The difference in trials and errors between MP and other groups is significant (Mann-Whitney U test). † The difference between PA and UC is significant ($P = .05$; Mann-Whitney U test). ‡ The difference between MP and others is significant ($P < .05$; Mann-Whitney U test).

Neural correlates of working memory

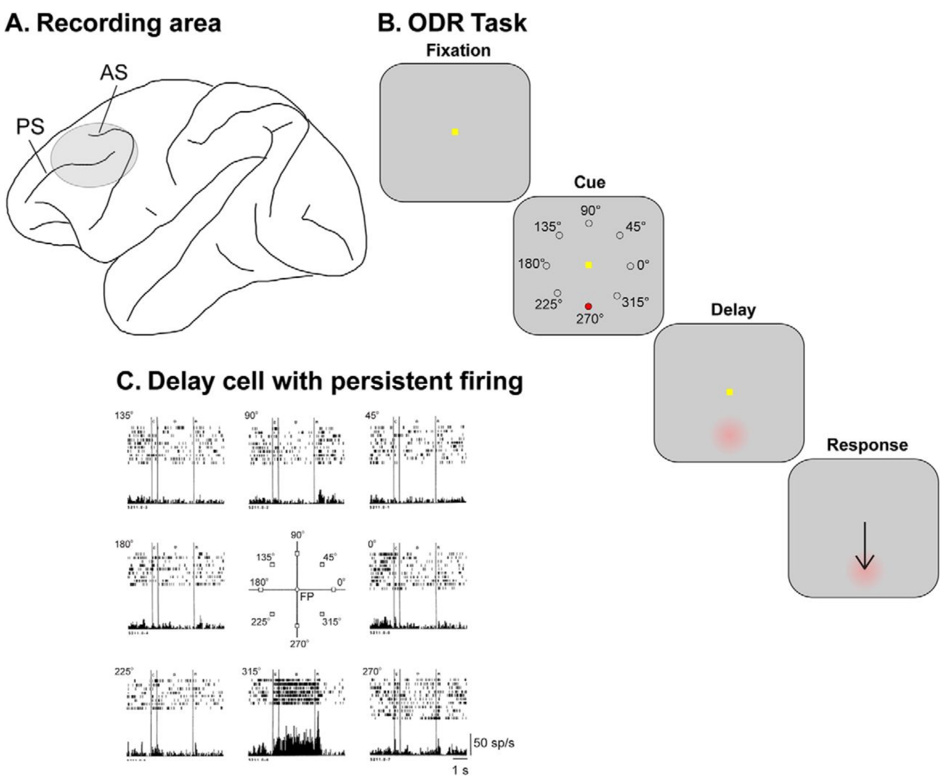


Fuster and Alexander, Science 1971

Neural correlates of working memory

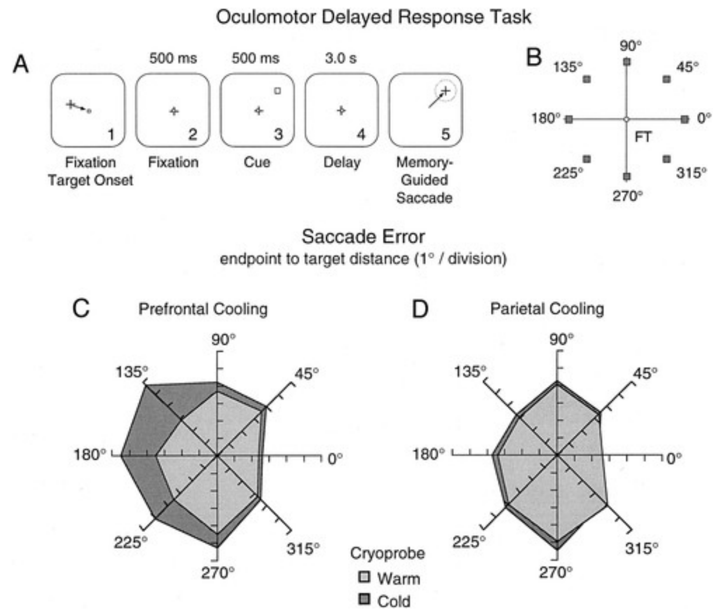
The oculomotor delayed-response (ODR) task:

~30% of DLPFC neurons around the principal sulcus (PS) show delay-period persistent firing activity after presentation of a cue and before making a motor response.



Funahashi et al., 1989

Cooling the PFC impairs WM performance:



Chafee and Goldman-Rakic, 2000

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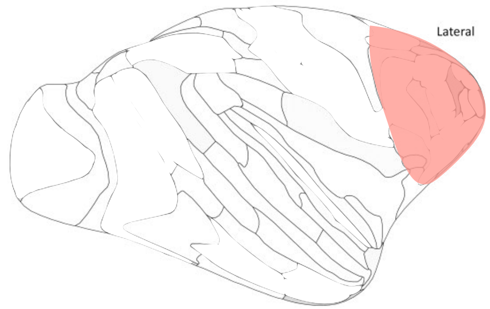
Where else in the brain can you find delay-period activity?



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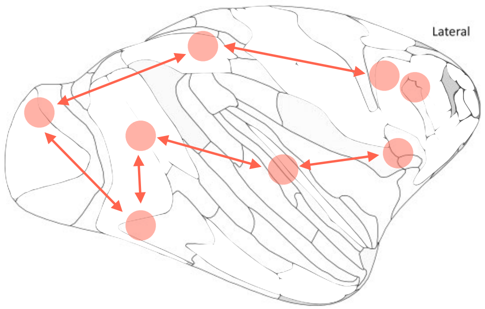
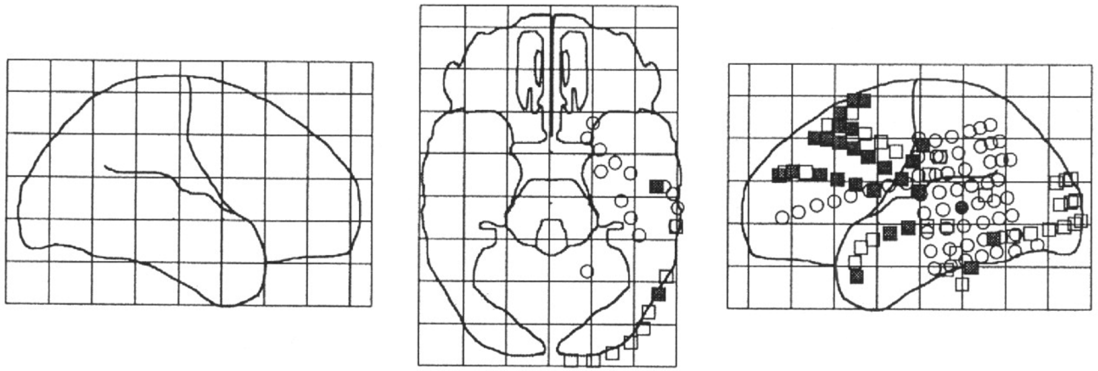
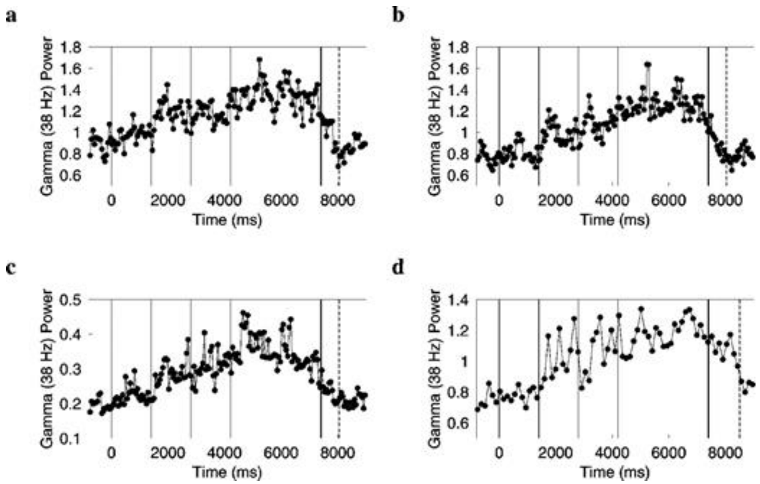


Gamma Oscillations (in PFC, parietal and temporal cortex) during performance of the Sternberg task in two human subjects:





Howard et al., 2003

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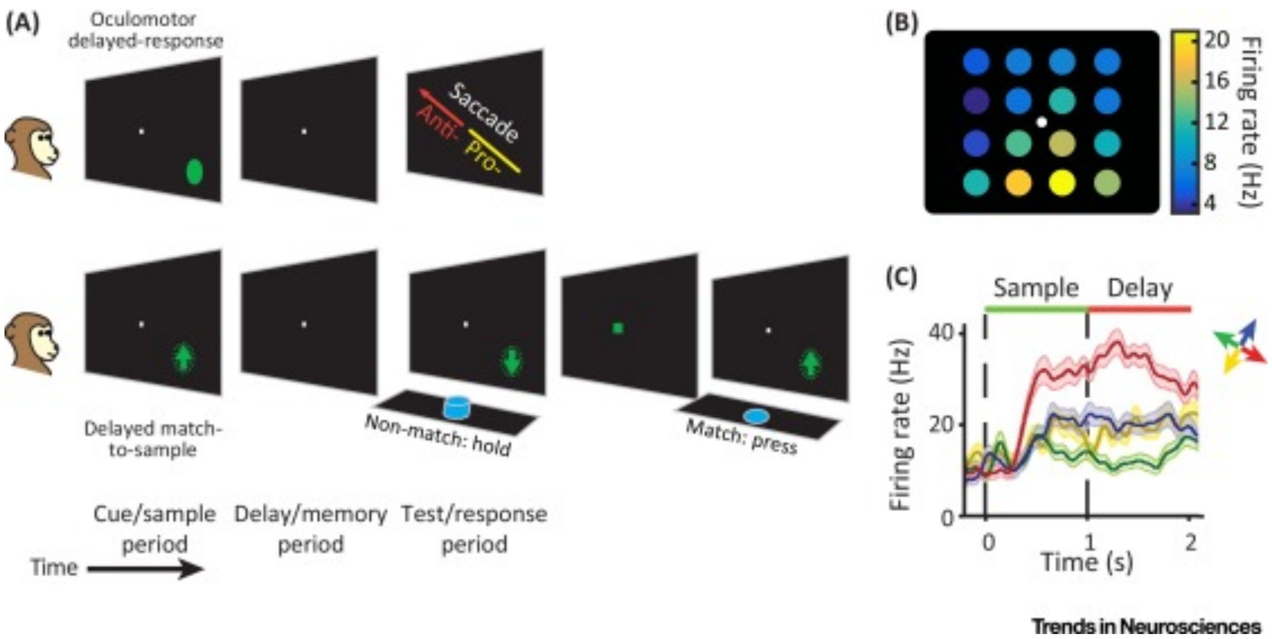
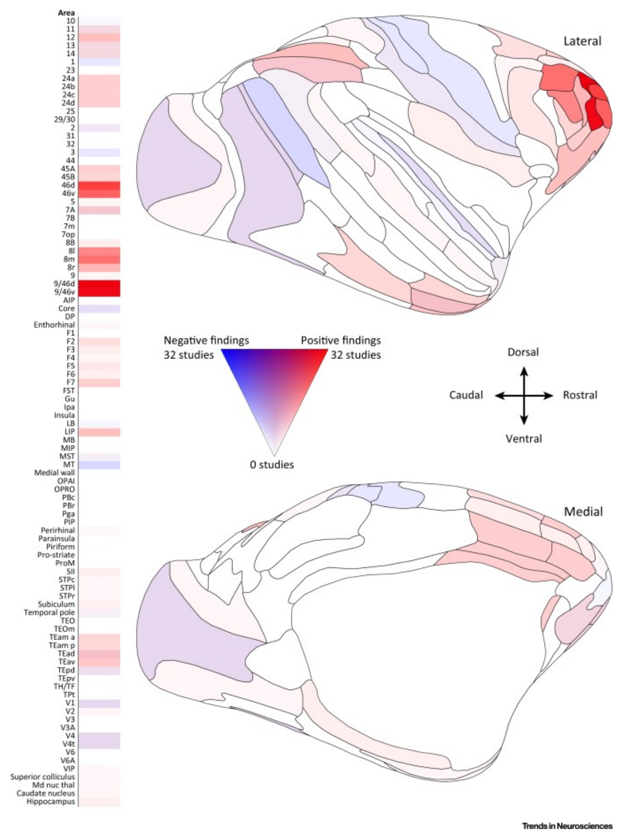


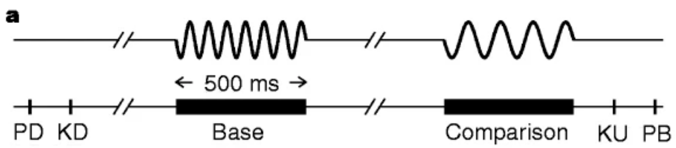


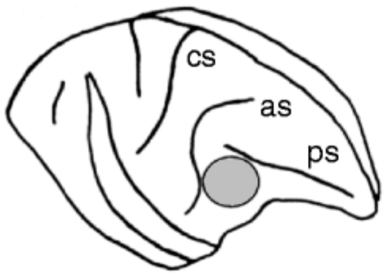
Leavitt et al., Trends Neurosci 2017

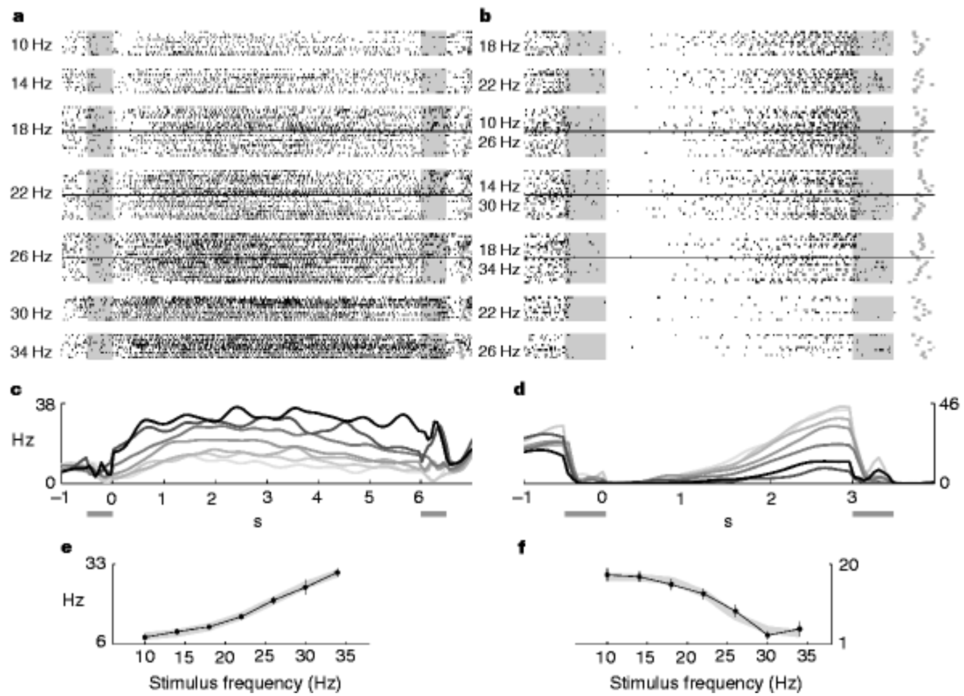
Neural correlates of working memory

The vibrotactile comparison task (Ranulfo Romo):

Monkey has to compare two vibrational stimuli applied to the finger, and make a choice (press right / press left) based on which one was higher frequency.







Romo et al., Nature 1999

What are the mechanisms of WM-related persistent activity?

- Cell-intrinsic mechanism: unique properties of prefrontal neurons that allow sustained firing
- Network mechanisms:
  - Local circuit dynamics
  - Cross-regional dynamics (cortico-cortical, thalamocortical)
- Synaptic mechanisms

** Persistent activity is *not* unique to WM. It is found in a variety of brain regions during behaviors (e.g. motor control) and is a general feature of neural circuit function. *(see Major and Tank 2004 for review)*

Kandel, Principles of Neural Science Ch. 67

What are the mechanisms of WM-related persistent activity?

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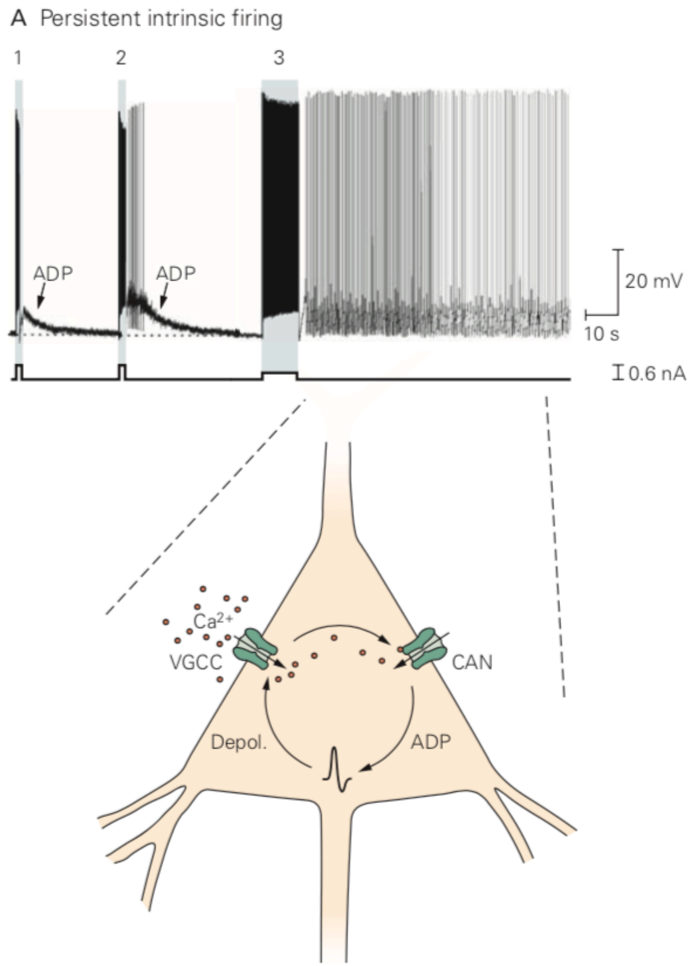

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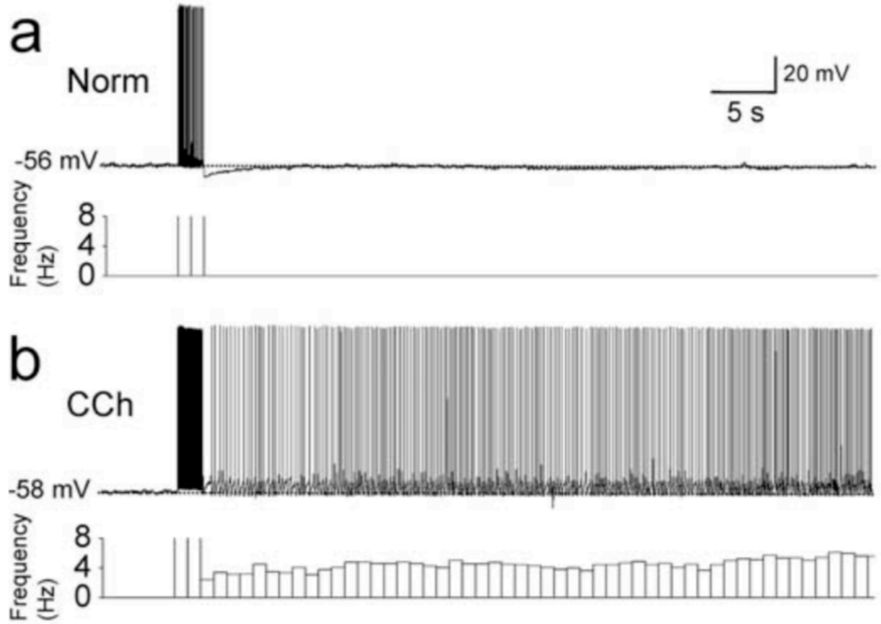
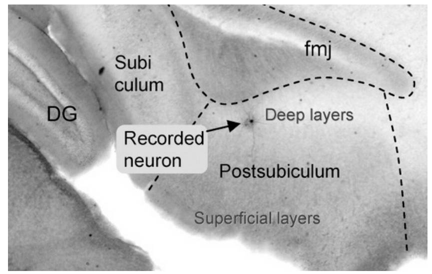


(entorhinal cortex postsubicular neurons)



Yoshida and Hasselmo, J Neurosci 2009

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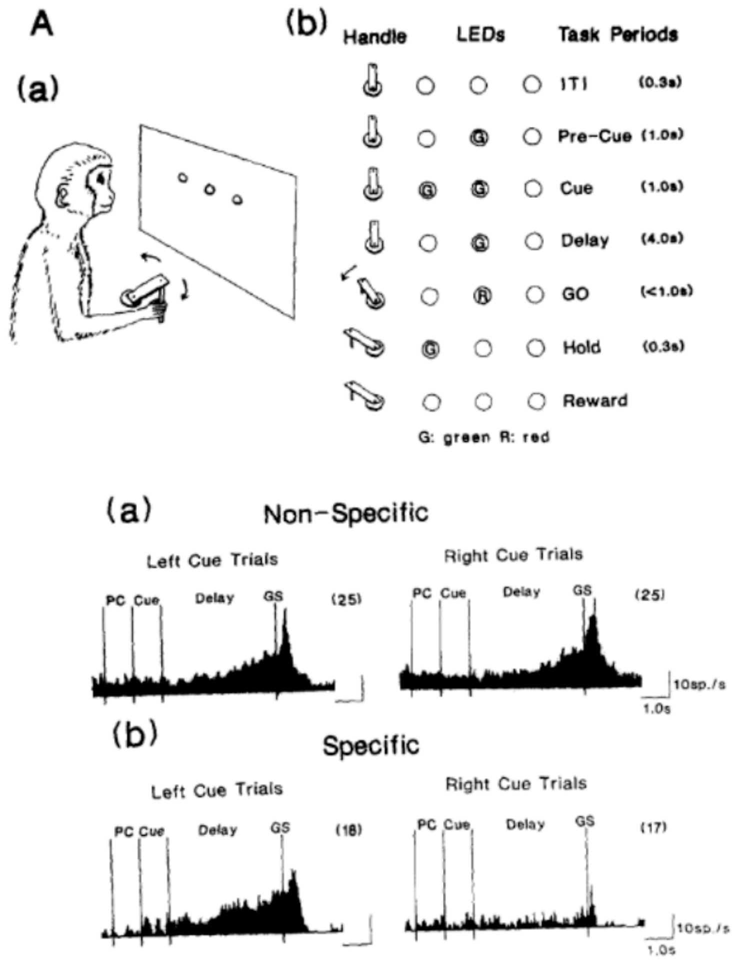

Sawaguchi, Matsumura, Kubota , Neurosci Res 1988

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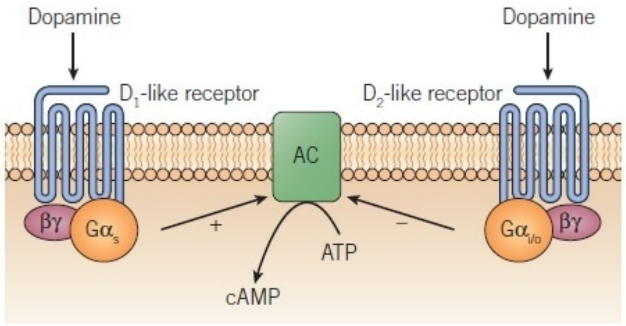
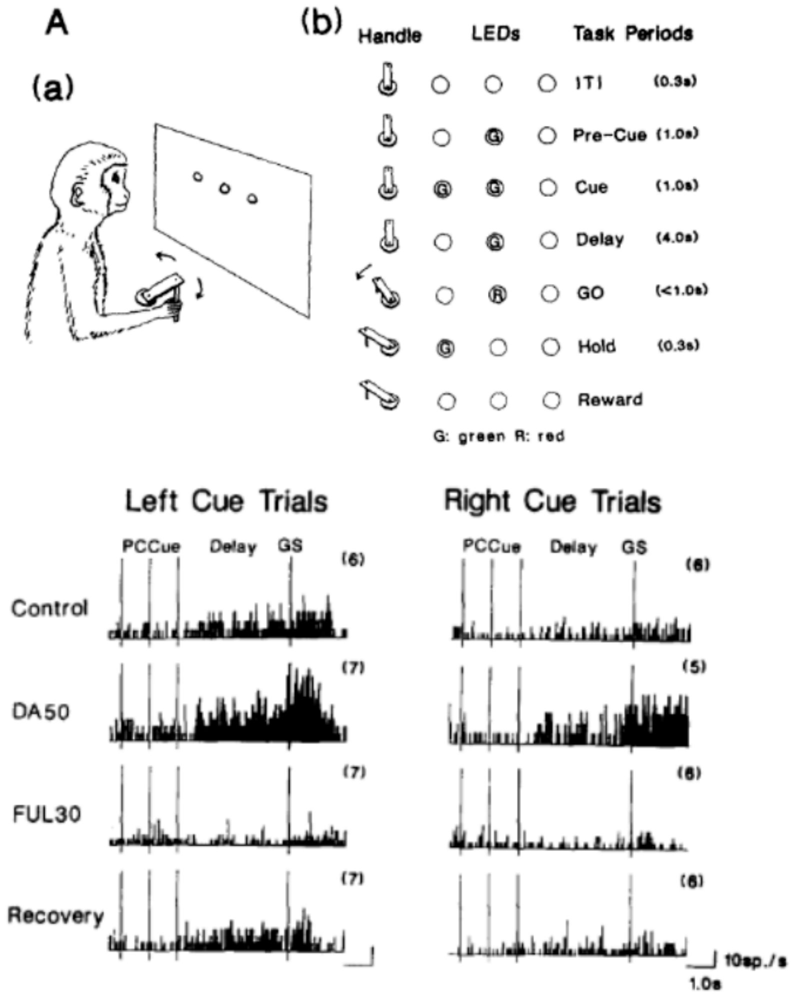


DA: Dopamine administration
Fluphenazine: D2 antagonist



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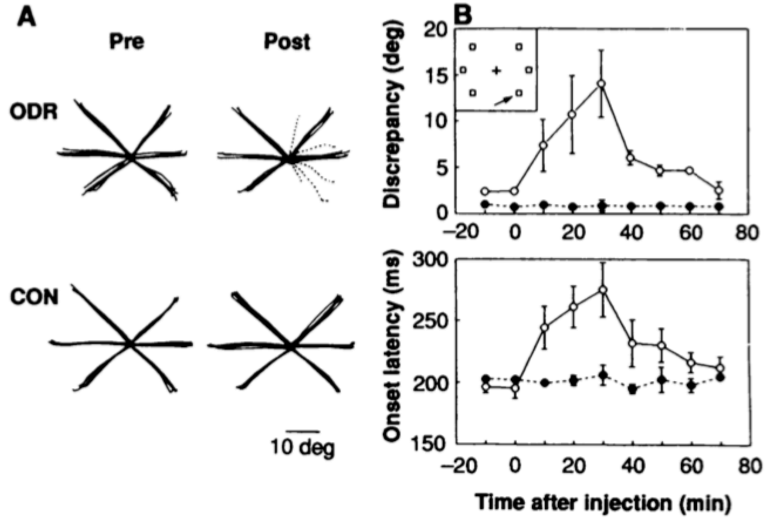
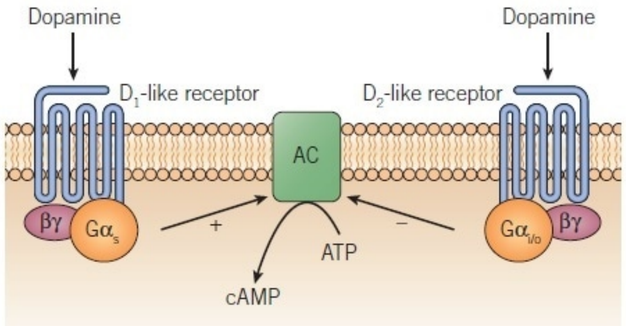
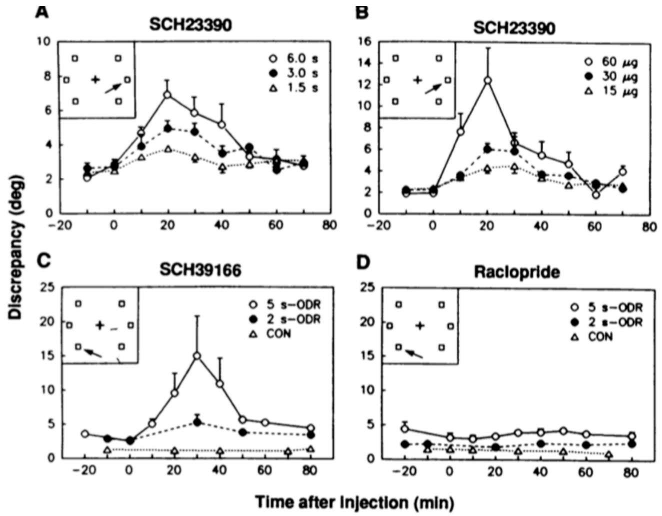




SCH23390: D1 antagonist



Sawaguchi and Goldman-Rakic, Science 1991

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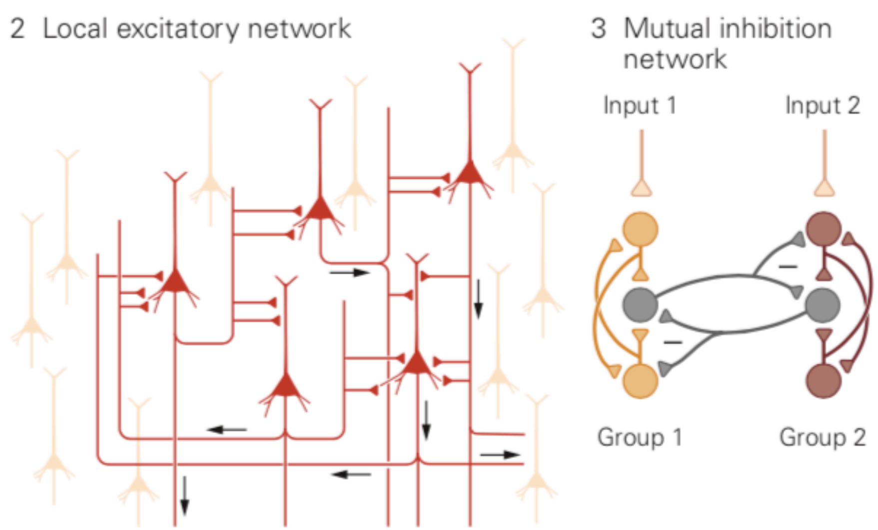

Kandel, Principles of Neural Science Ch. 67

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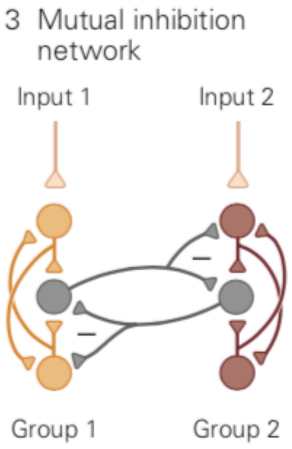
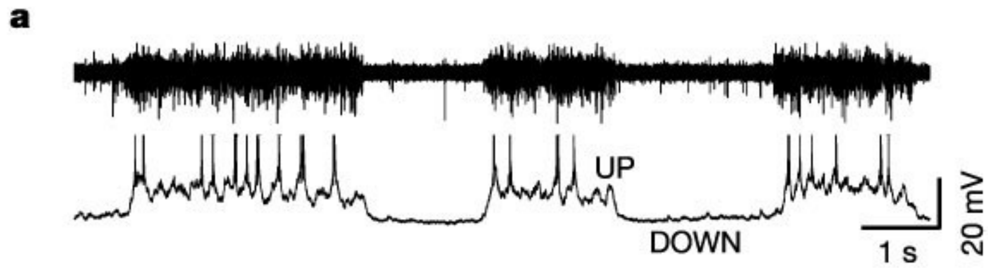
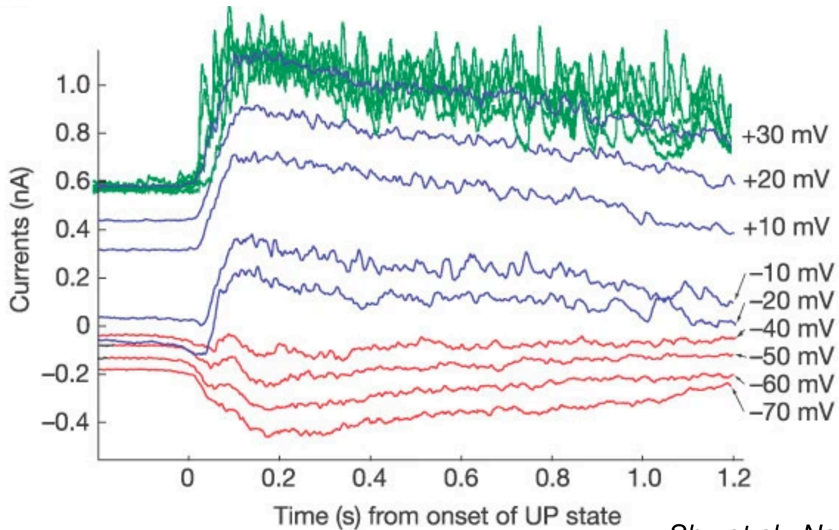


Ferret prefrontal cortical slices show intrinsic UP/DOWN state dynamics



Voltage-clamp recordings show that UP states involve balanced excitation/inhibition



Shu et al., Nature 2003

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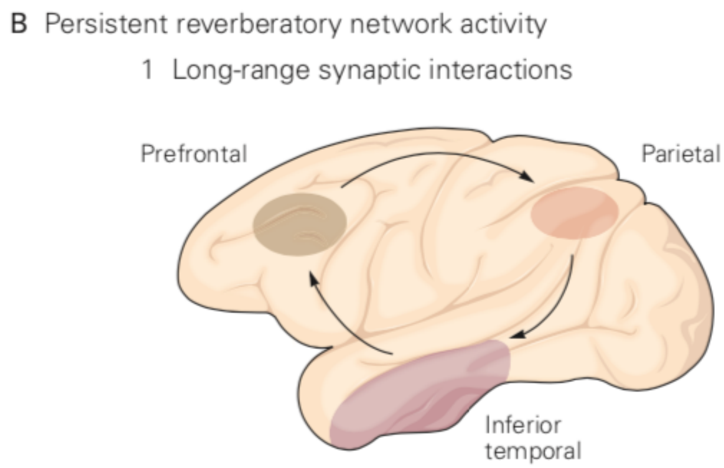

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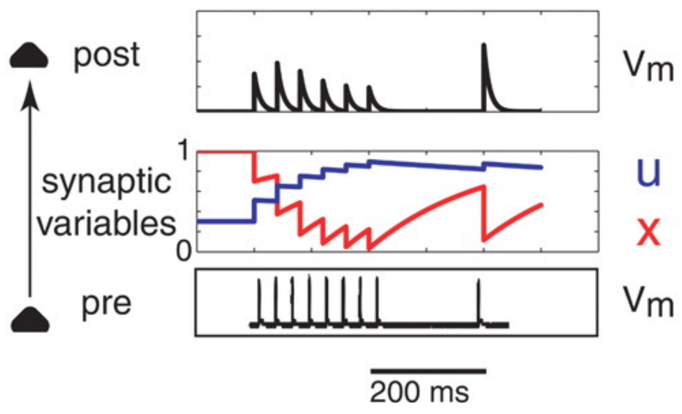
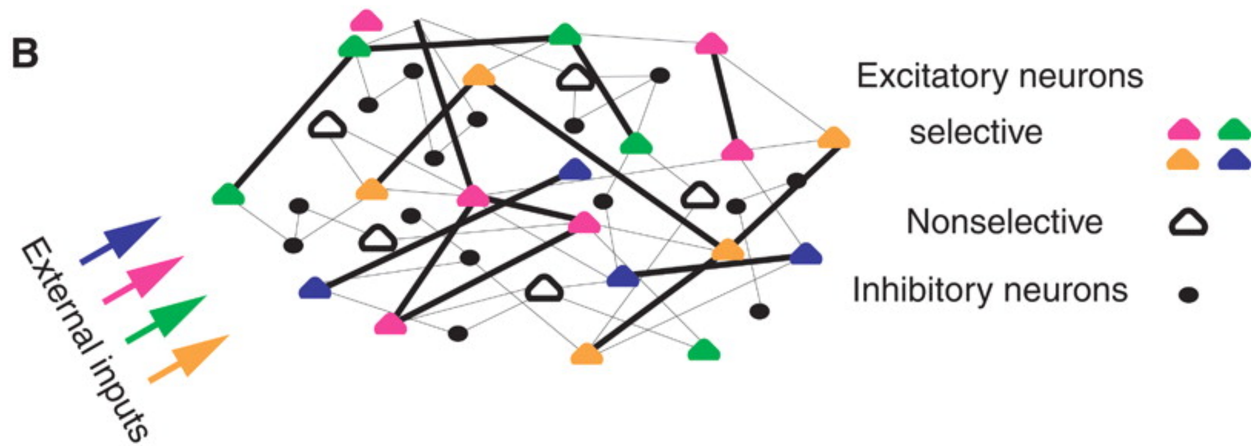
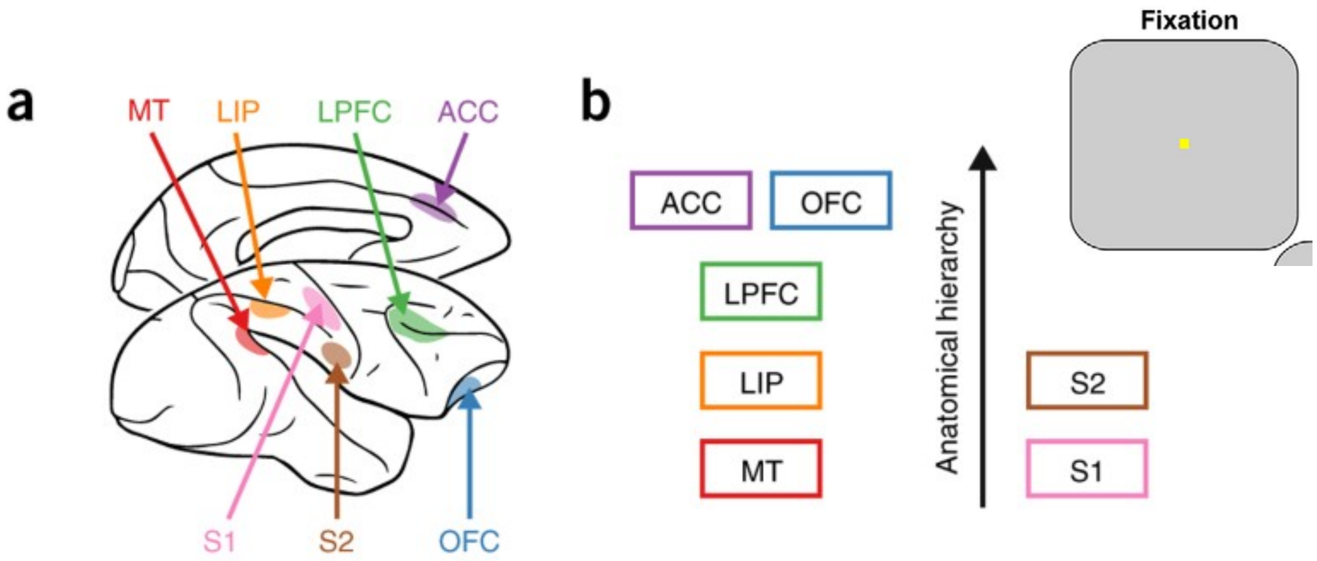


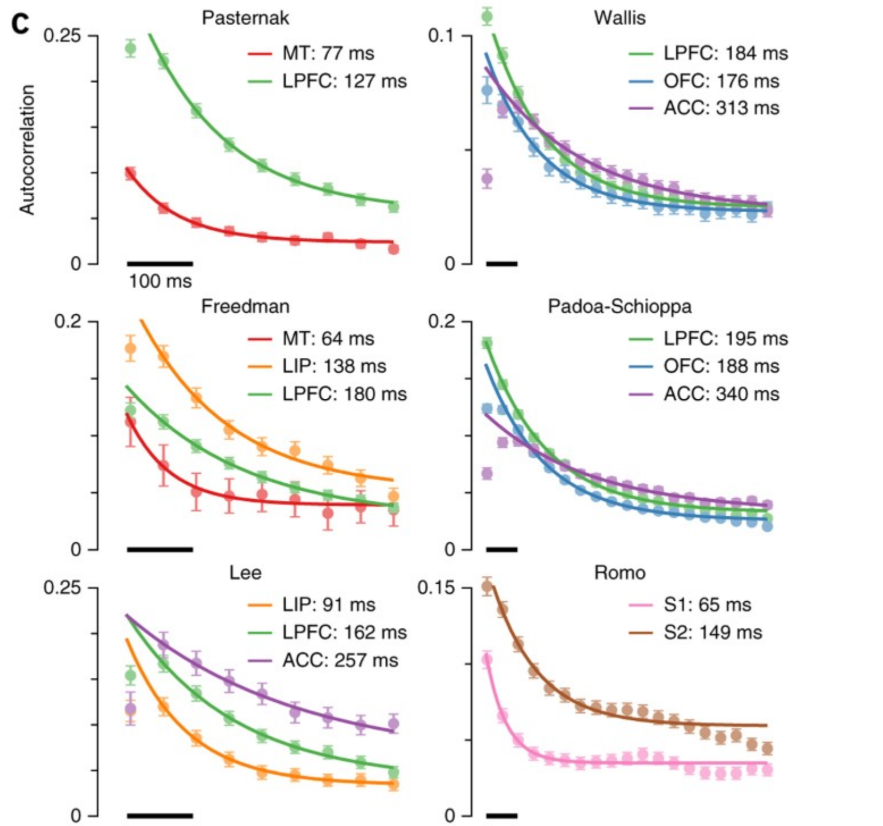


Mongillo, Barak, Tsodyks, Science 2008

Does the PFC have unique temporal properties that support WM?

- Recordings pooled from several labs across different anatomical locations along the sensory -> prefrontal hierarchy
- Measure autocorrelation decay in single-neuron spike trains
- Prefrontal regions show slower decay timecourse than sensory regions.





Murray et al., Nat Neuro 2014

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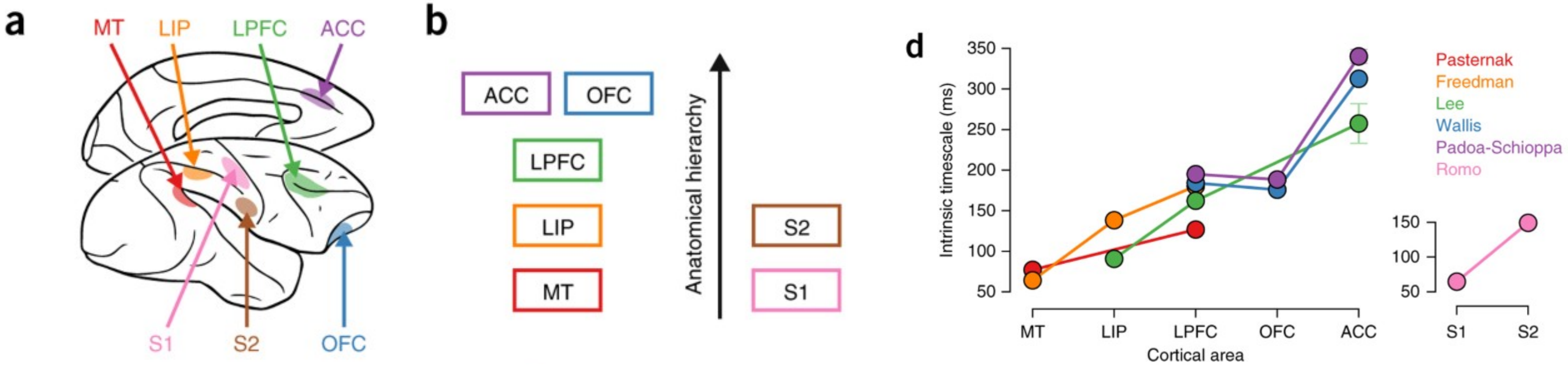
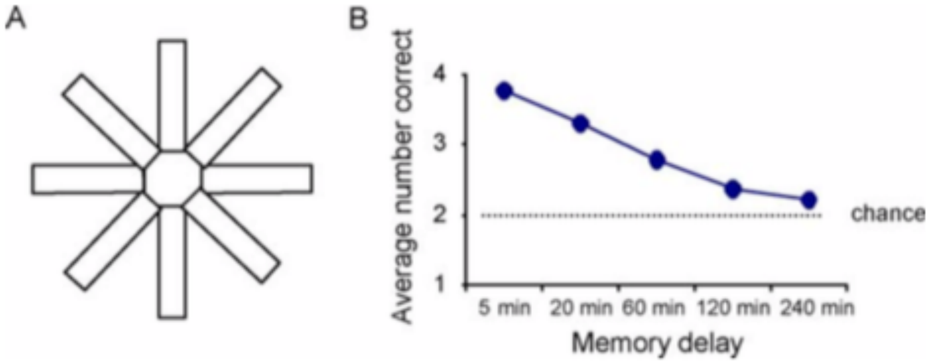


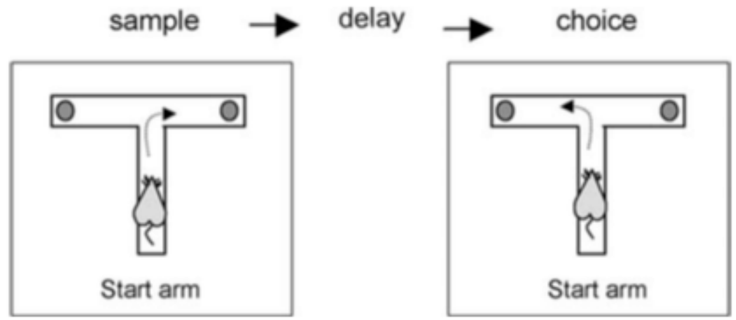
In search of circuit mechanisms: can rodents do working memory?

The 8-arm maze for rats (Olton et al., 1970):



Working memory: remove after 4 arm visits, check if animal returns to previously-visited arms

Delayed alternation on a T-maze (spontaneous/cued)



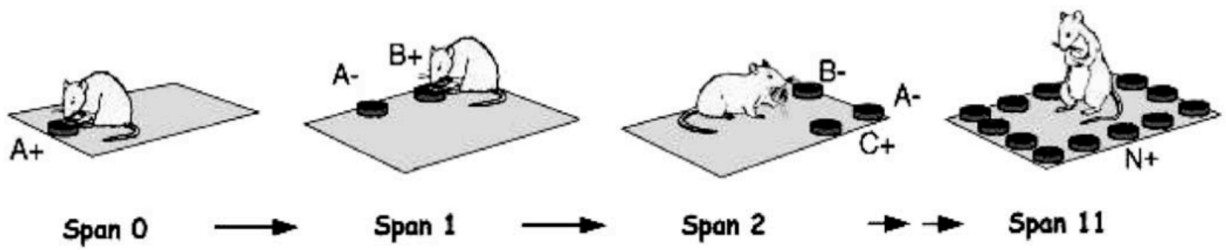
Spontaneous alternation: animal is removed after receiving reward on one side, has to alternate to receive the second reward.

Cued version: a light/sound/odor indicates correct side; animal is released after a delay.

Potential problem with spatial tasks: animals can “cheat” by “**postural cueing**”.

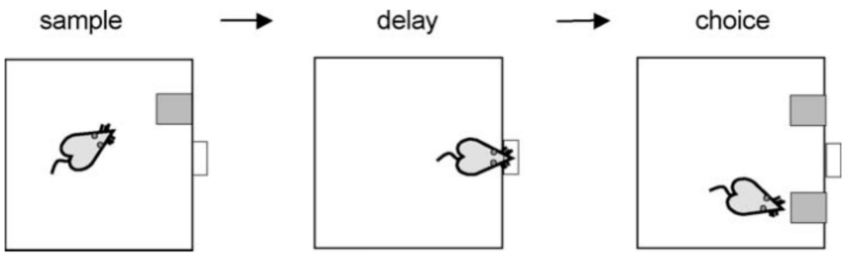
In search of circuit mechanisms: can rodents do working memory?

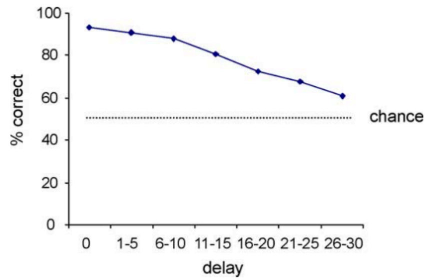
The odor span task:



Rats can remember up to 24 odors in this task

Operant delayed non-match to sample:

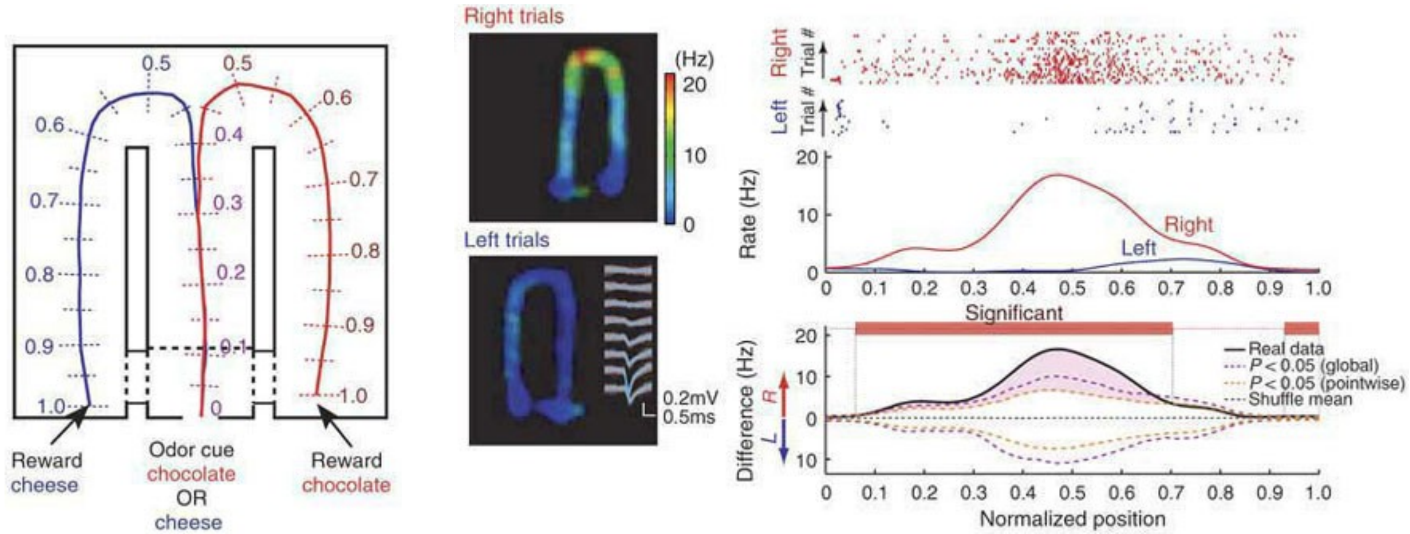


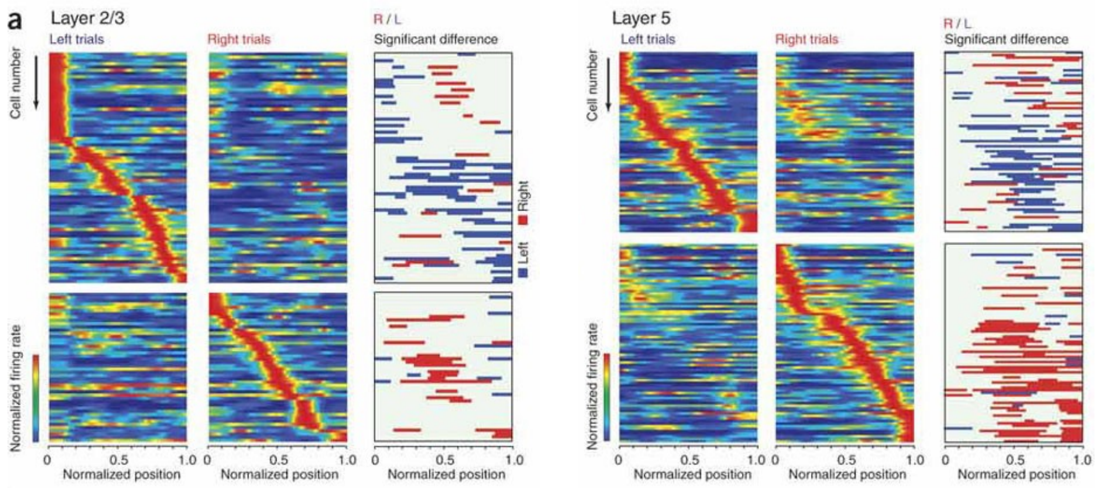


Automated, many trials, but might also suffer from "postural cueing"

Overall: delayed comparison tasks >>> delayed reaction tasks.

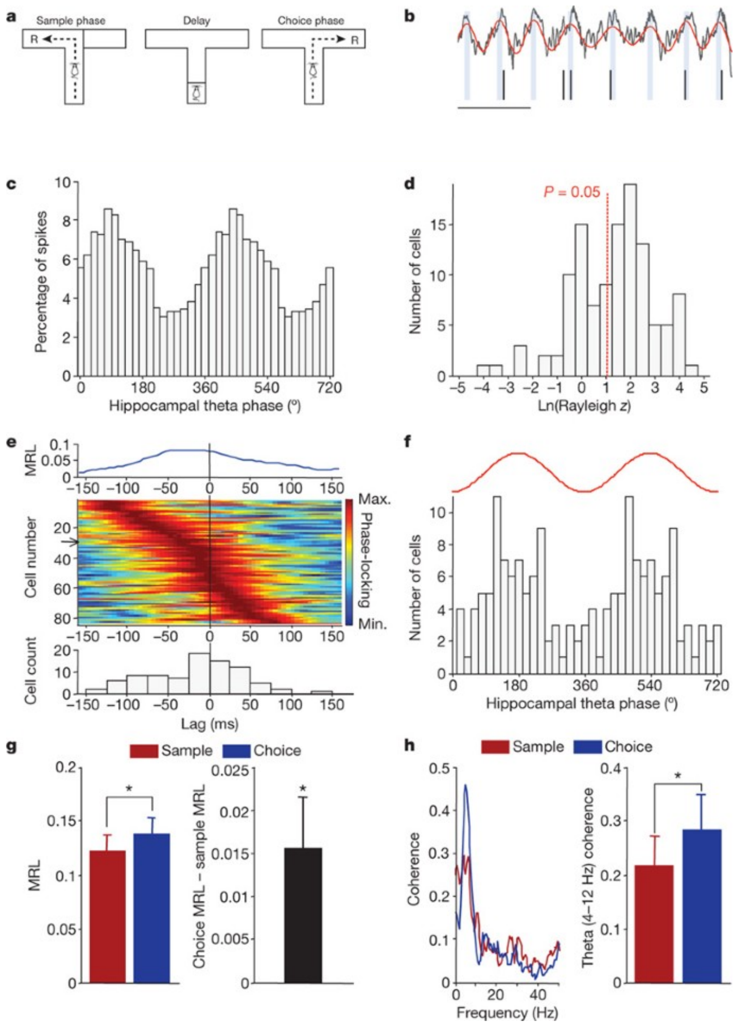
PFC neuronal activity during WM in rodents





Fujisawa et al., Nat Neurosci 2008

WM in rodents is associated with long-range synchrony



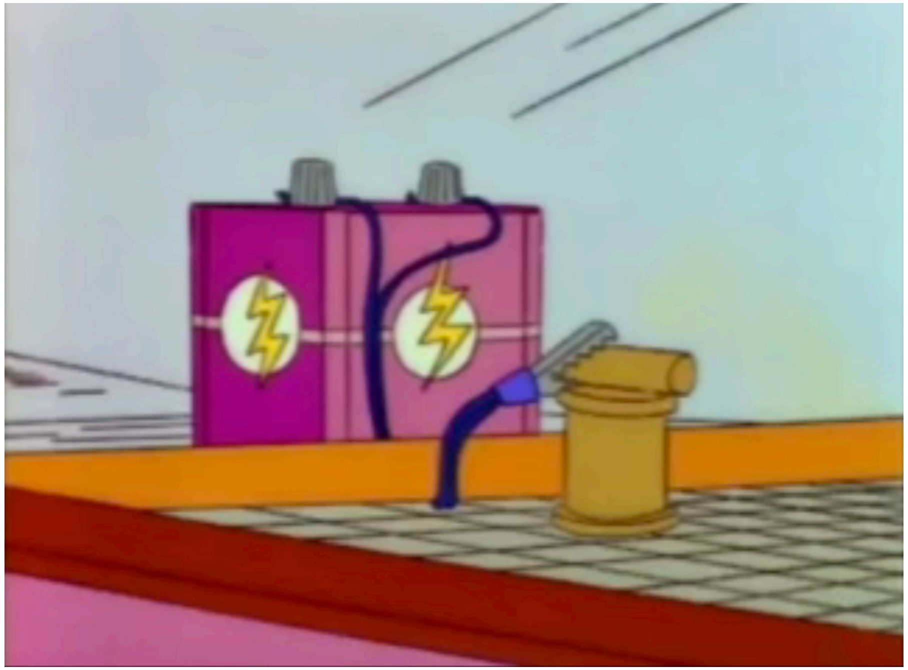
- Mice performing a T-maze task with a ***sample*** ("*forced-choice*") phase followed by a ***choice*** phase.
- Simultaneous mPFC single-unit + hippocampal LFP recording
- mPFC neurons show phase-locking to hippocampal theta oscillations
- Phase-locking is stronger during the "choice" phase of the task compared with the "sample" phase
- Also: mice with a schizophrenia associated mutation (Df16) show impaired phase-locking and impaired WM performance.

Sigurdsson et al., Nature 2011

Prefrontal cortex and working memory: summary

- Working memory performance is impaired by prefrontal lesions; particularly by lesions to the middle region of the principal sulcus
- Working memory tasks in primates: the delayed alternation task, the oculomotor delayed-response task (different flavors); the vibrotactile comparison task.
- Persistent activity in the PFC (and other regions) during WM tasks in monkeys
- Models of WM-related persistent activity including cellular, local-circuit and long-range interactions.
- A synaptic theory of WM permits retention of information in the circuit with minimal spiking (energy-efficient)
- Rodent WM tasks are mainly based on spatial alternation
- Ephys correlates: “tiling” of the delay period, hippocampal-prefrontal phase-locking, impairment in a mouse model of schizophrenia.

Prefrontal regulation of fear learning



Pavlovian fear conditioning: A previously safe stimulus (CS+) is paired with an aversive outcome (US).

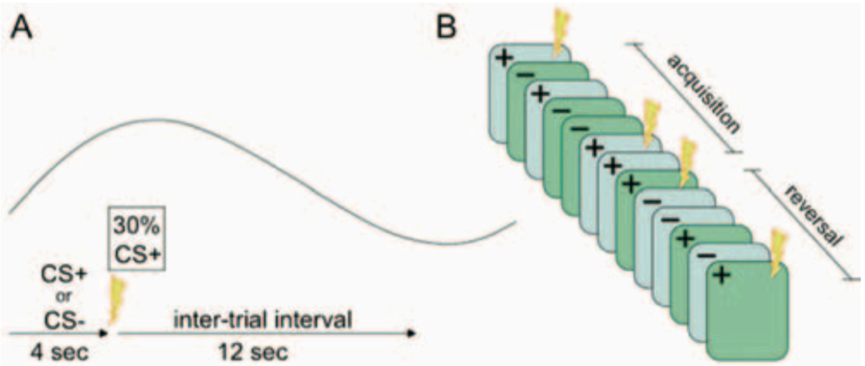
Prefrontal regulation of fear learning

Pavlovian fear conditioning: A previously safe stimulus (CS+) is paired with an aversive outcome (US).

The CS+ stimulus triggers a conditioned response

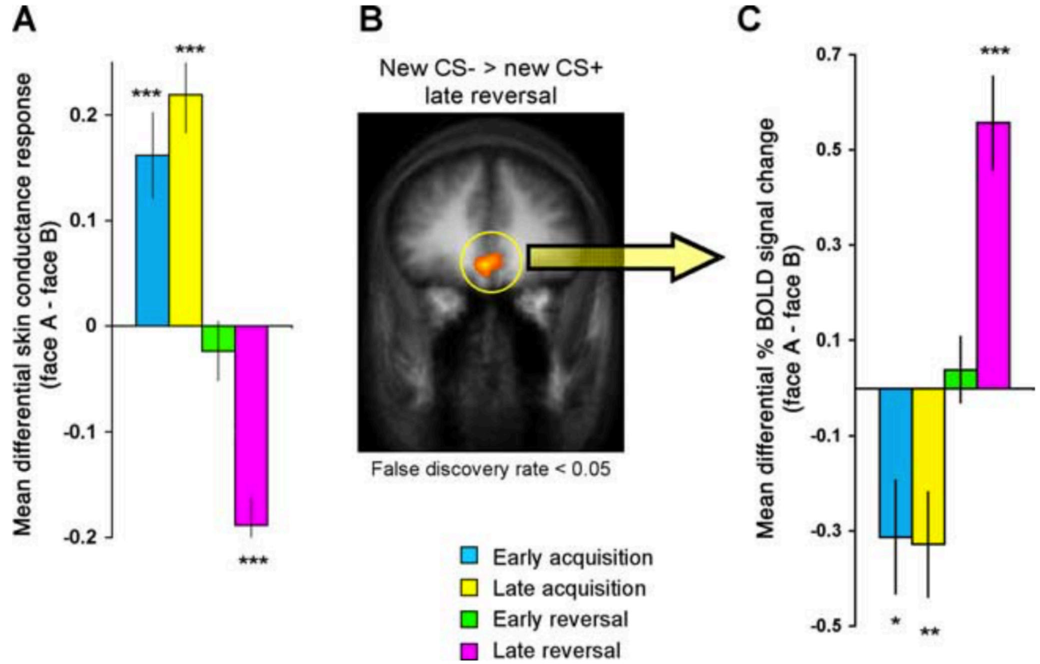
Extinction training: repeated presentation of the CS+ (cupcakes) without the US (electrical shock) triggers new learning that "overrides" the conditioned response.

Prefrontal regulation of fear learning



Aversive conditioning: Stimuli are paired with an electrical shock (in humans!) over several trials. Partial reinforcement. SCR measurements.

Reversal learning: The previously “safe” stimulus is now associated with electrical shock.

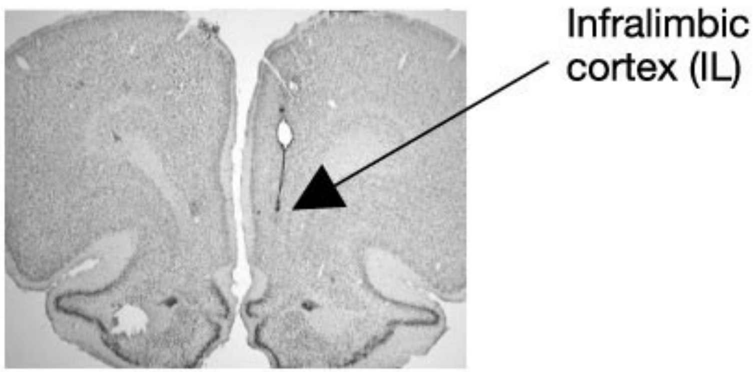


Skin conductance response (SCR) in response to CS (Face A) increases during conditioning, decreases during reversal.

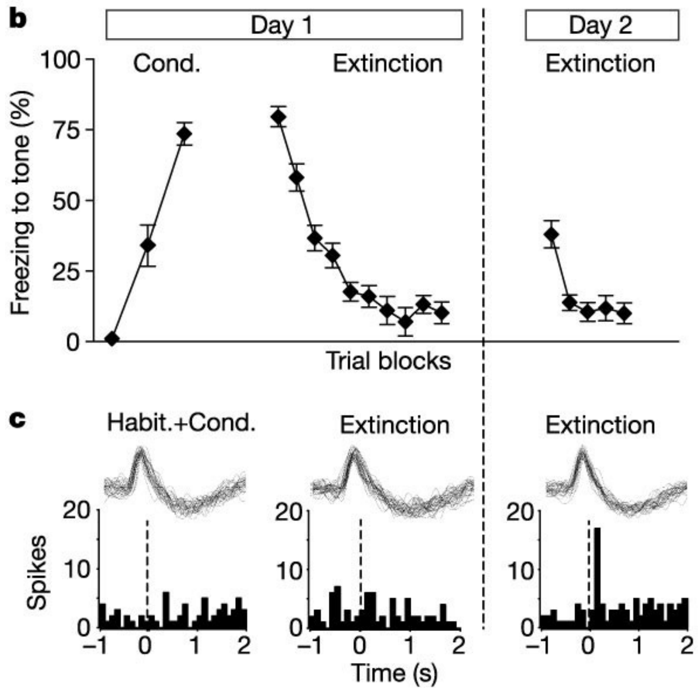
vmPFC (Brodmann’s Area 32/10): differential activity to CS decreases during conditioning, increases during extinction.

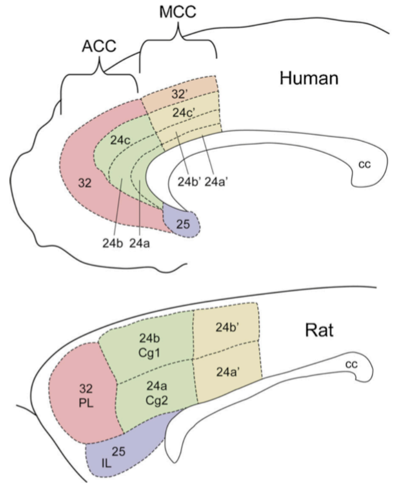
Schiller et al., 2008

Prefrontal regulation of fear learning



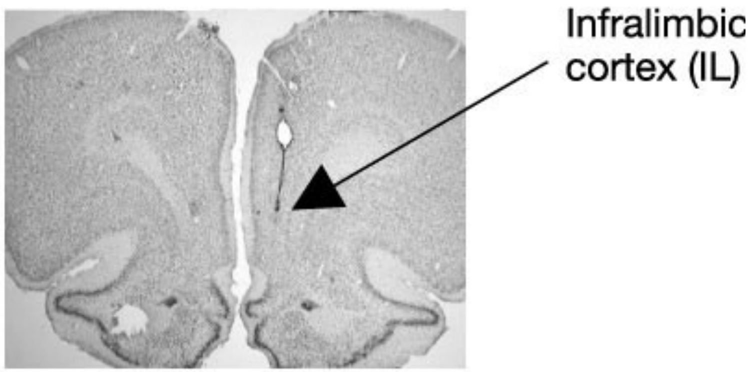
Infralimbic cortex (IL) neurons fire to the CS during extinction:



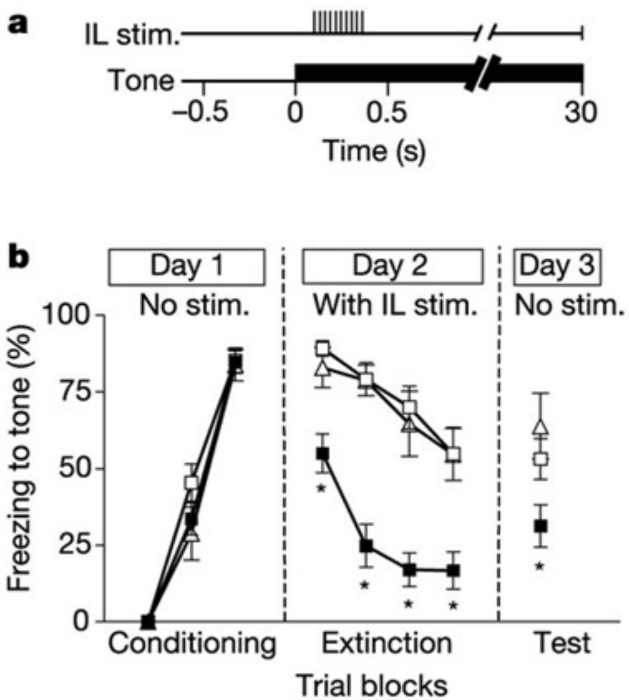


Milad & Quirk, Nature 2002

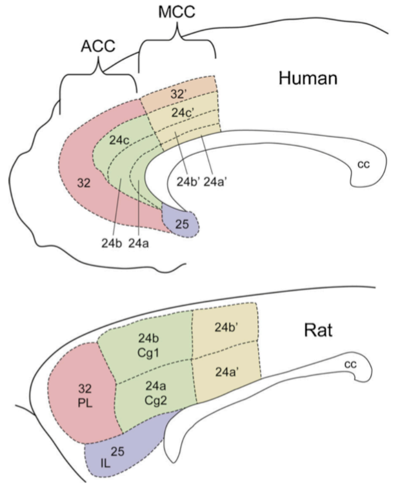
Prefrontal regulation of fear learning



Stimulation of the infralimbic cortex (IL) decreases freezing on Day 2:



unstimulated (open triangles), unpaired IL stimulated (open squares) and paired IL stimulated (filled squares)



Milad & Quirk, Nature 2002

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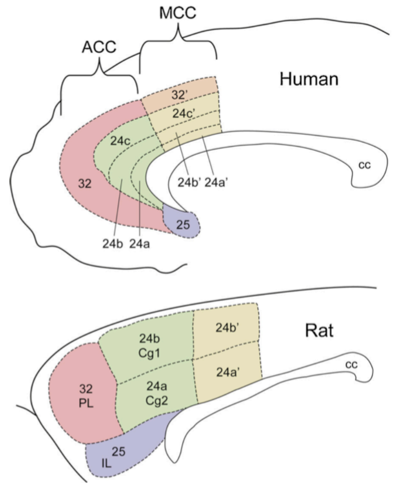
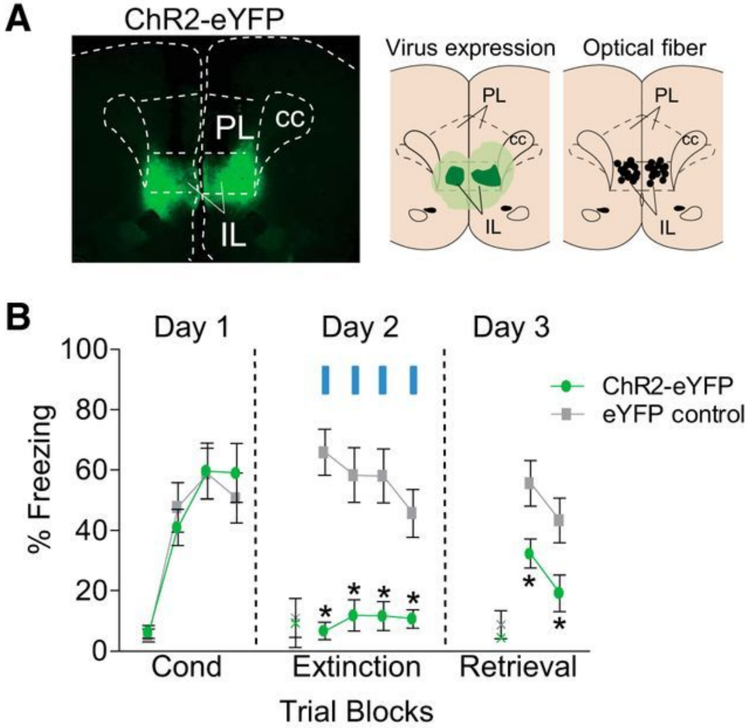
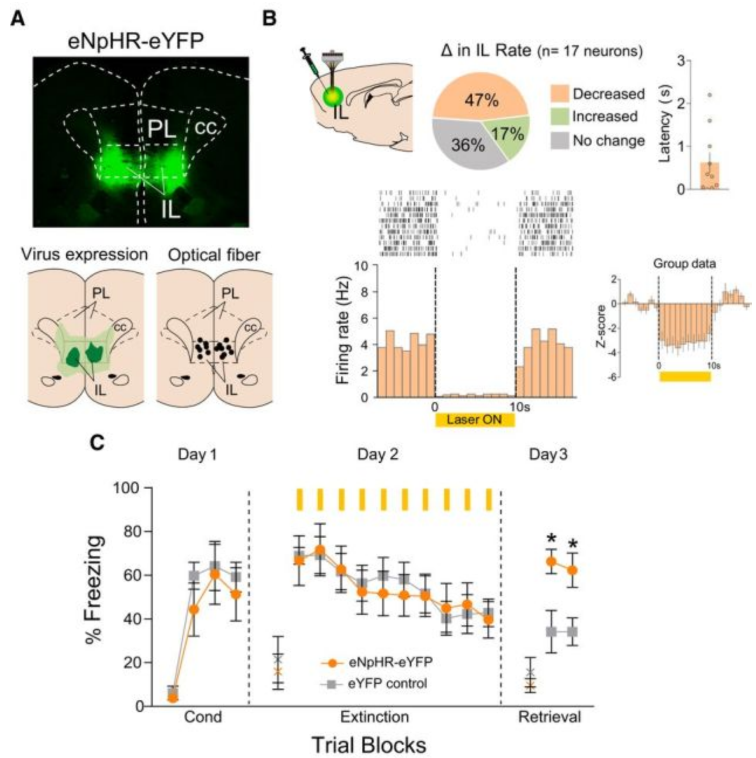


Optogenetic excitation of the infralimbic cortex (IL) decreases freezing:



Optogenetic inhibition of the infralimbic cortex (IL) impairs extinction learning:

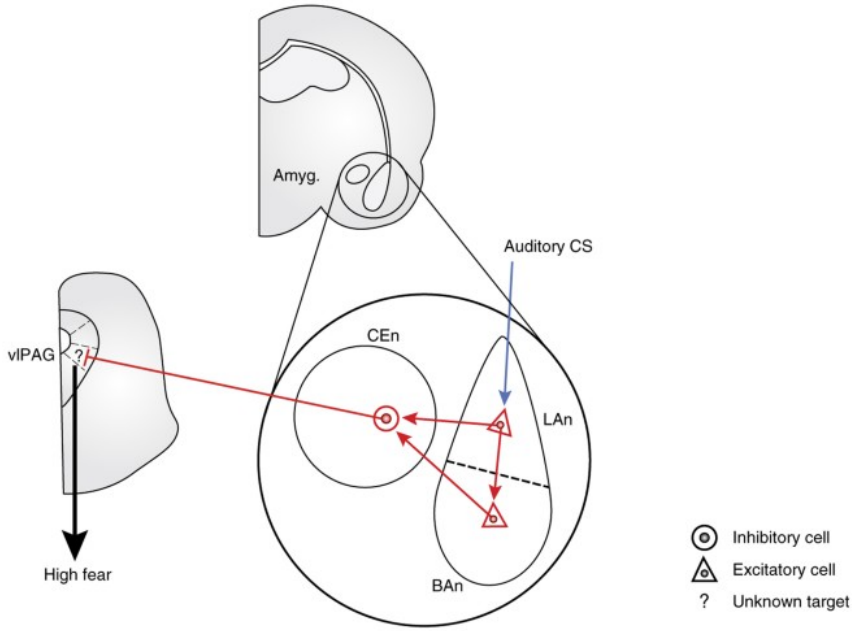


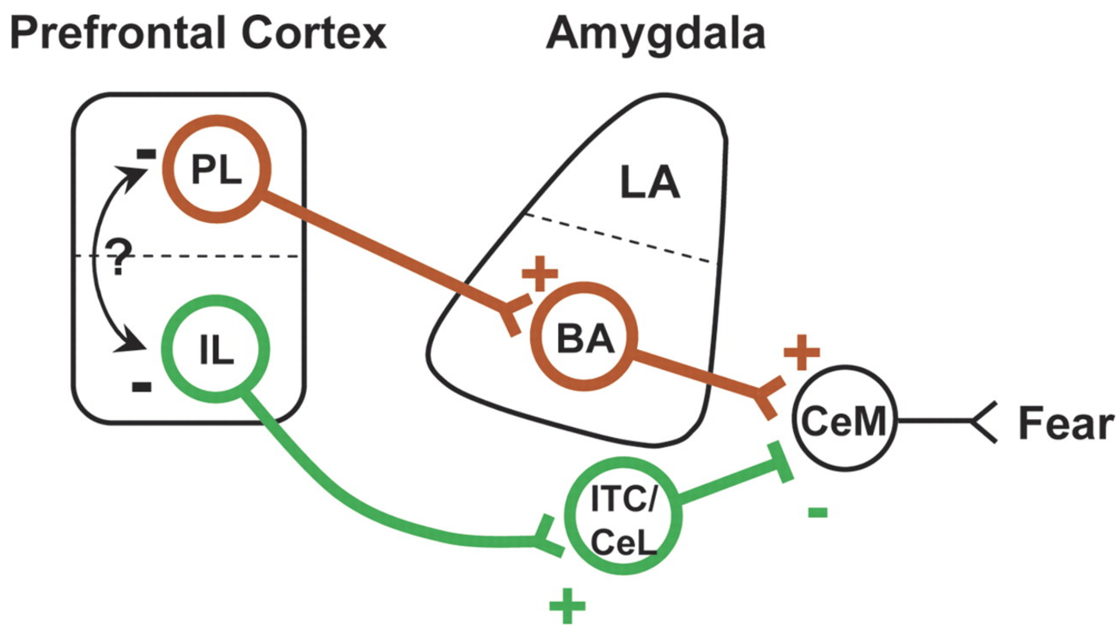
Do-Monte et al., J Neurosci 2015

Prefrontal regulation of fear learning

Circuit mechanism of extinction learning:

Auditory stimuli reach the BLA from cortex and thalamus; Excitatory BLA neurons project to PL and IL; PL projection to BLA is mostly excitatory; IL projection has strong feed-forward inhibitory component through the intercalated cells.

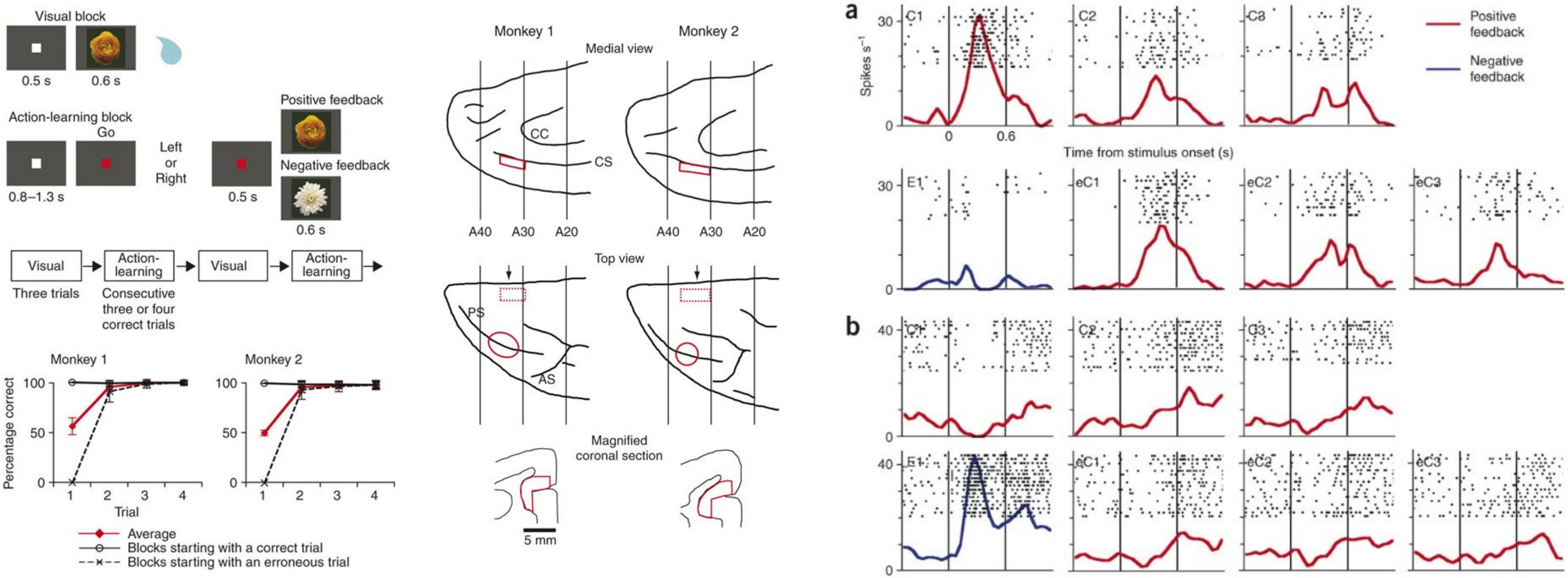




Johanssen and Herry., Nat Neurosci 2015

Representation of reward value and prediction error coding

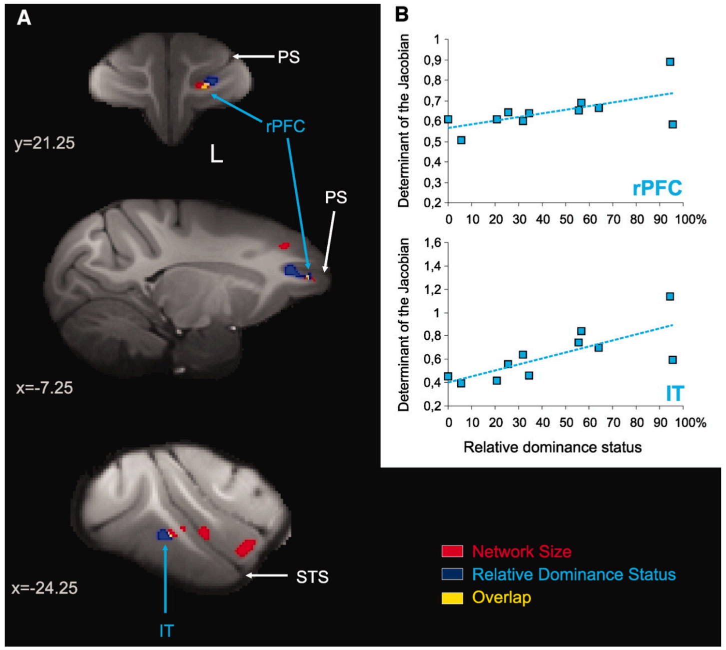
Prediction error coding in the ACC: Monkeys trained on a simple reward association task show activity in ACC that tracks the type of error performed.



Matsumoto et al., Nat Neuro 2007

The role of PFC in social behavior:

Prefrontal cortex volume in macaques is associated with social network size, and with social rank within the group.

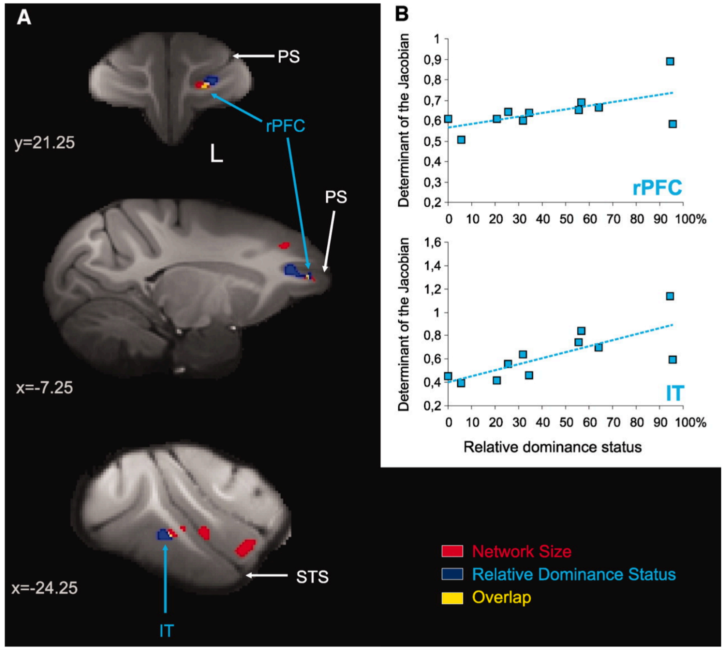


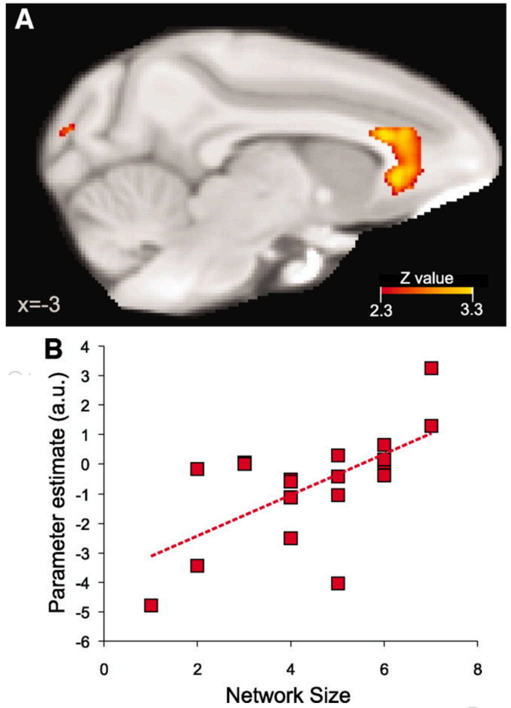
Sallet et al., 2011

The role of PFC in social behavior:

Prefrontal cortex volume in macaques is associated with social network size, and with social rank within the group.

Social network size correlated with increased BOLD signal correlations between rPFC and STS.

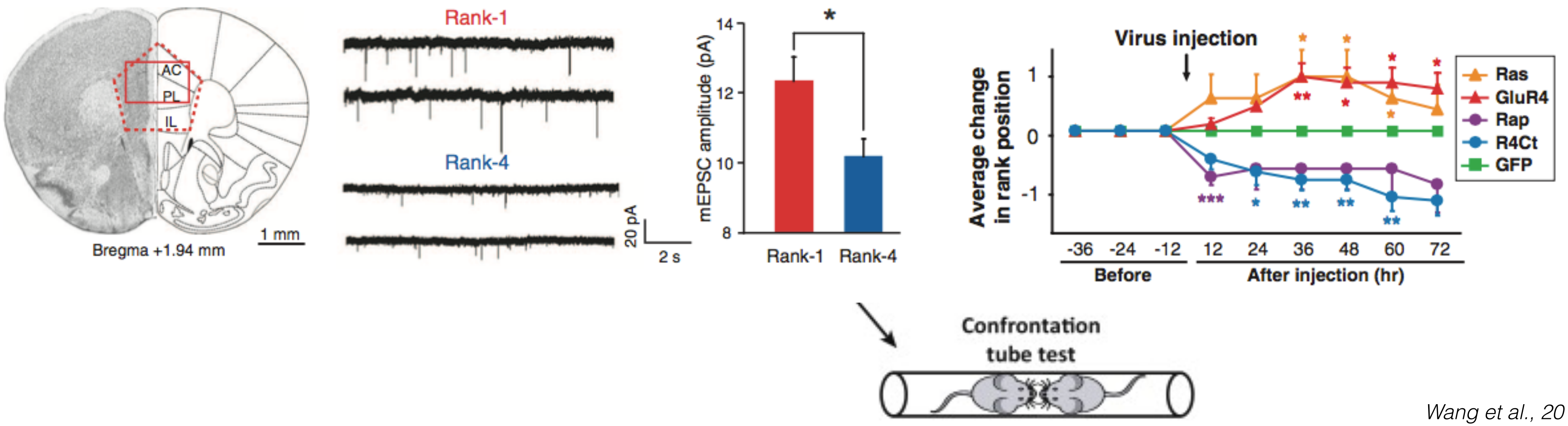




Sallet et al., 2011

The role of PFC in social behavior:

In mice, excitatory synaptic strength in the mPFC correlates with social rank
(Wang et al., 2011)

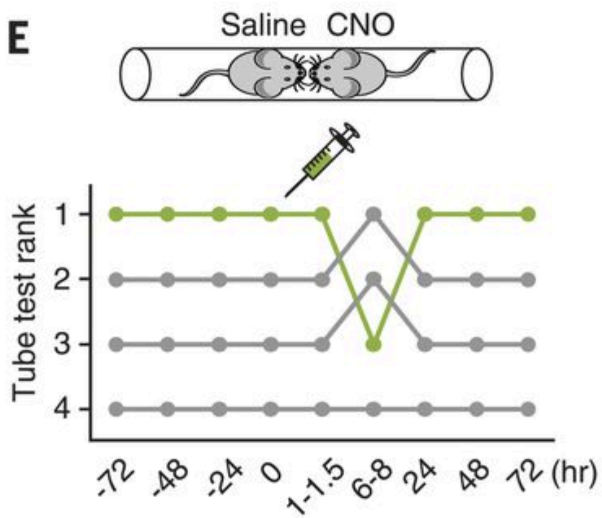


Wang et al., 2011

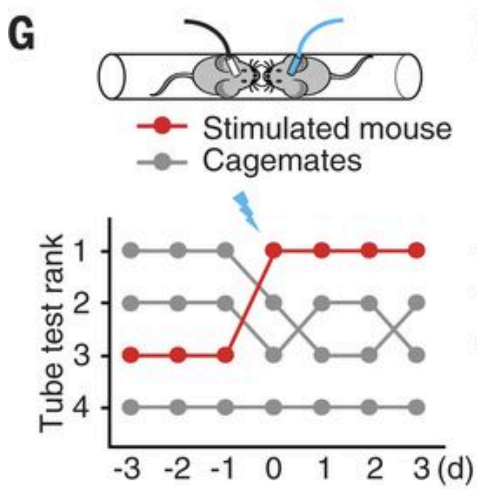
The role of PFC in social behavior:

Excitation or inhibition of dmPFC led to winning/losing in the tube test. Following repeated encounters, mice that consistently “won” showed increased synaptic strength in MD-PFC connections (Zhou et al., 2017)

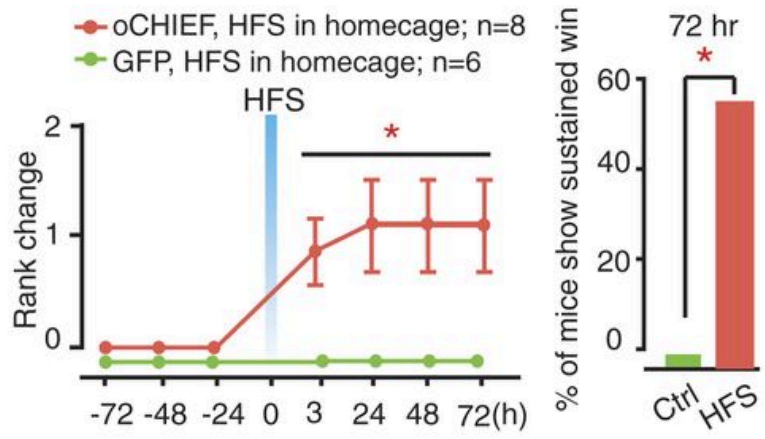
Chemogenetic inhibition:



Optogenetic excitation:



MD-PFC plasticity is sufficient:

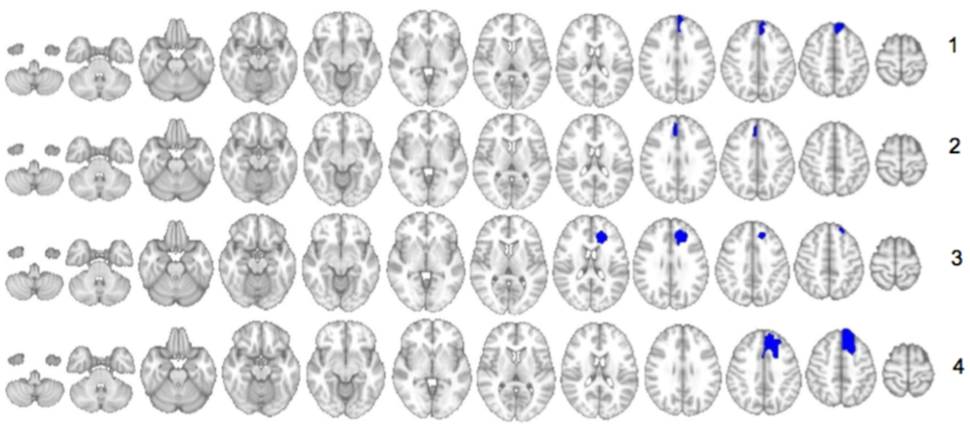


Zhou et al., Science 2017

The role of PFC in social behavior:

In human neurosurgical patients with ventromedial prefrontal lesions: deficits in emotion recognition (Jenkins et al., 2014; Rudebeck et al., 2007)

No social deficit in dmPFC or OFC lesioned patients.



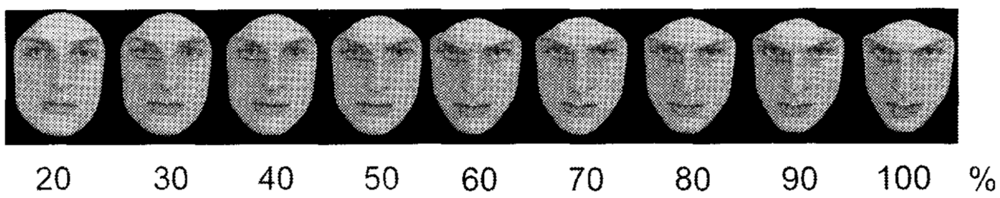
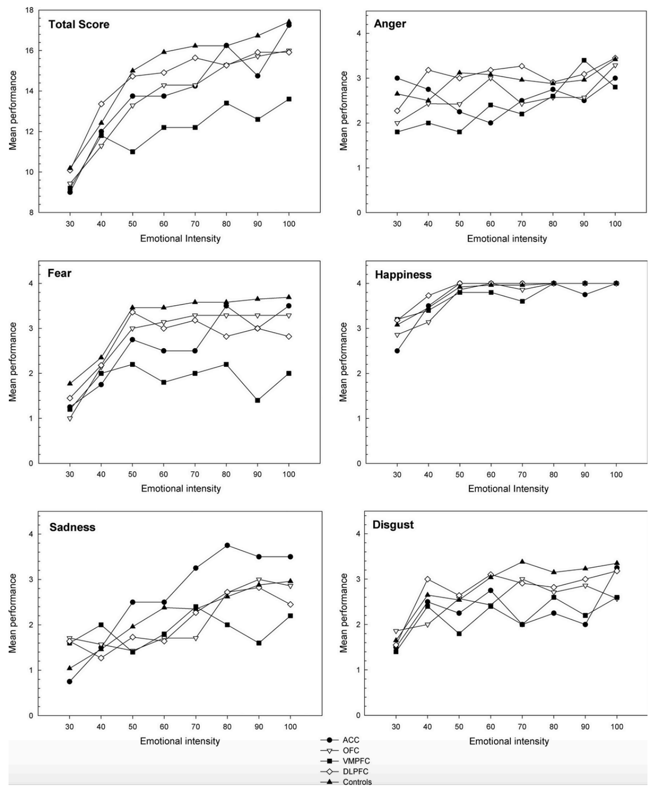


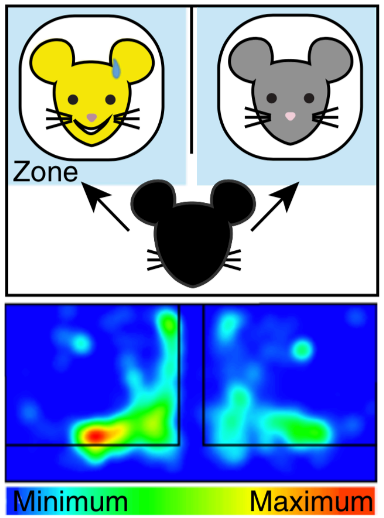
FIG. 1. Example of all nine morphing steps of facial emotion intensity for the emotion anger.



Jenkins et al, 2014

The role of PFC in social behavior:

Mice show preference toward “emotionally-altered” conspecifics (mice exposed to electrical shock, other acute stressors, liquid reward or social enrichment)

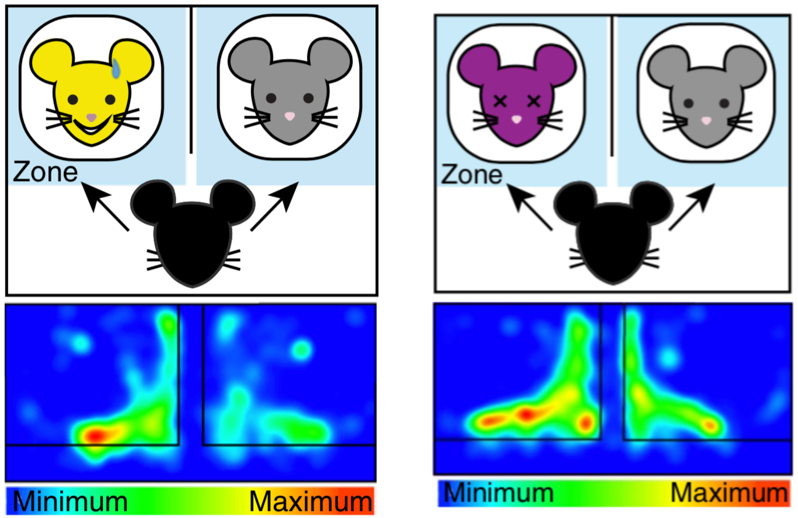


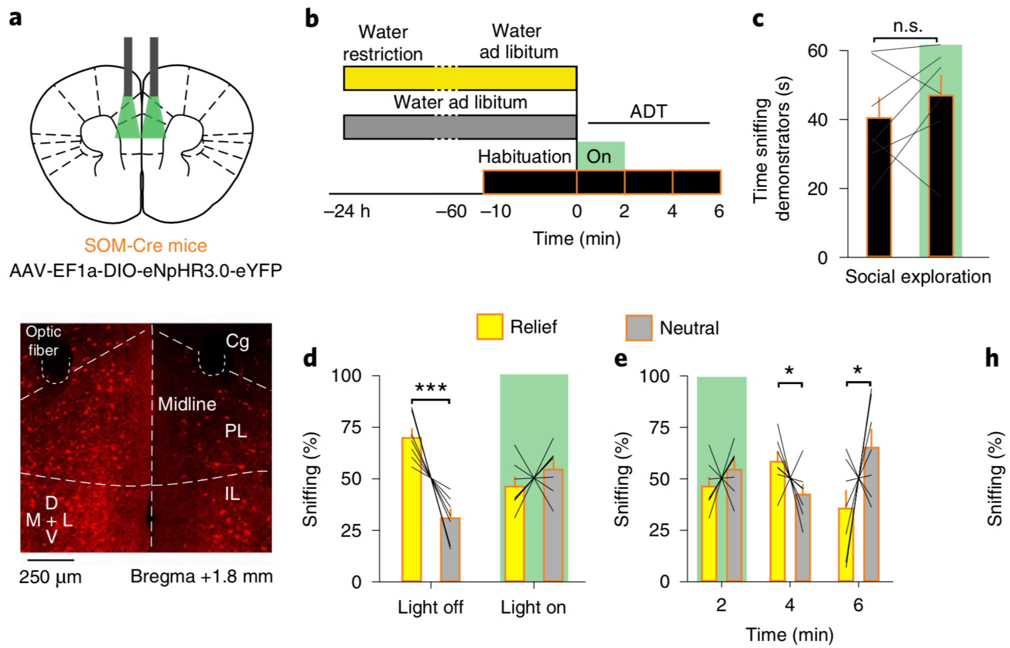
Scheggia et al., Nat Neuro 2019

The role of PFC in social behavior:

Mice show preference toward “emotionally-altered” conspecifics (mice exposed to electrical shock, other acute stressors, liquid reward or social enrichment)

Silencing of prefrontal somatostatin-expressing interneurons eliminates the preference toward an “emotionally-altered” conspecific.





Scheggia et al., Nat Neuro 2019

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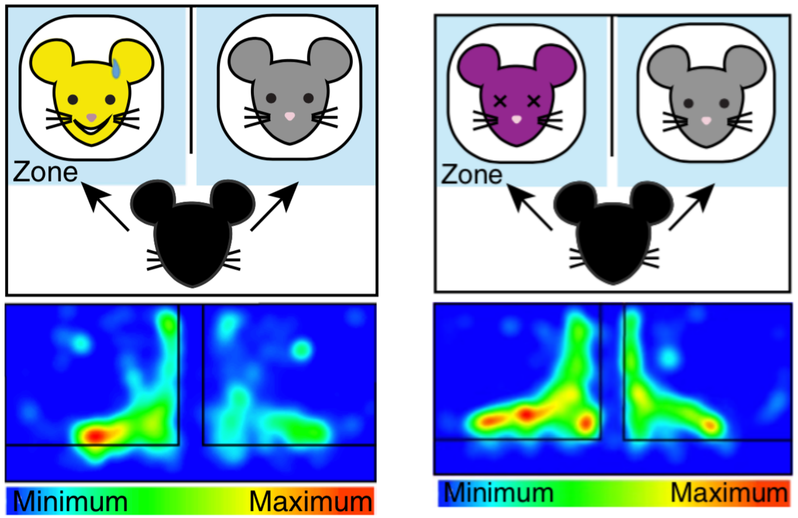
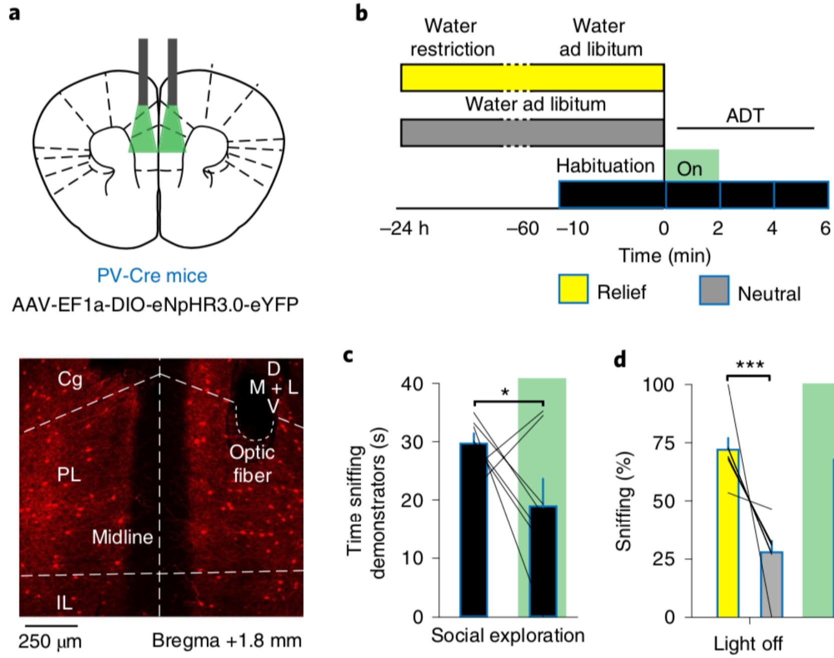
Silencing of prefrontal somatostatin-expressing interneurons eliminates the preference toward an “emotionally-altered” conspecific.

Silencing PV neurons had no effect on preference score, but changed overall sociability



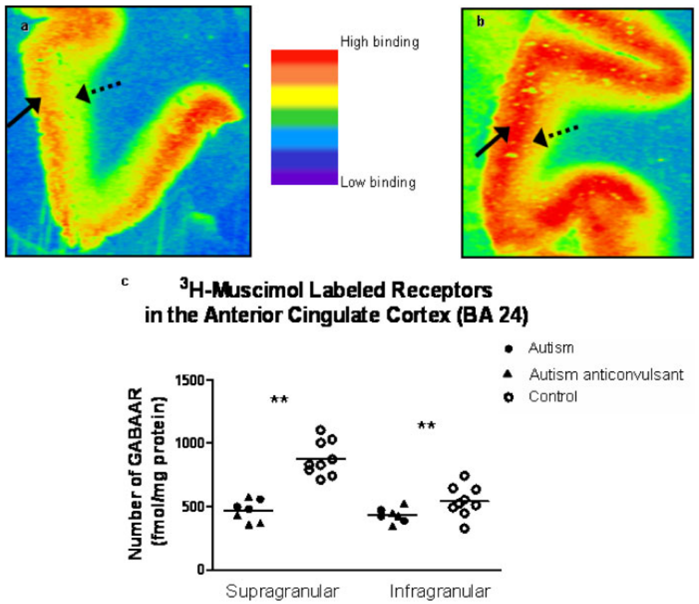


Scheggia et al., Nat Neuro 2019

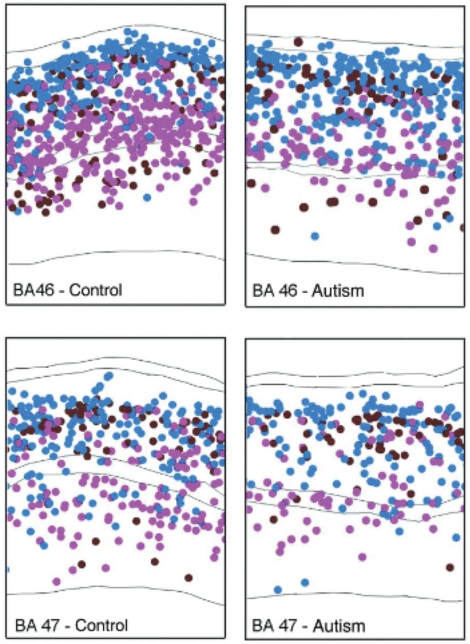
Autism-associated changes of GABAergic inhibition in the PFC

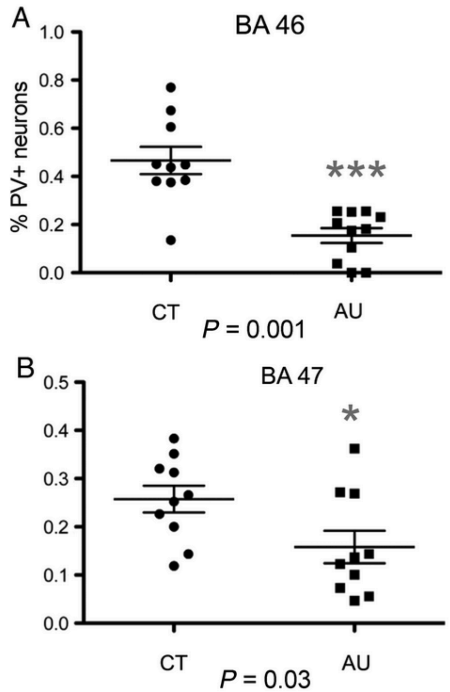
Decreased GABA receptor binding in the frontal cortex of humans with autism (Oblak et al., 2009)

Reduced interneuron density in prefrontal cortex of autism patients (Zikopoulous and Barbas, 2013, Hashemi et al., 2016)



Oblak et al., 2009

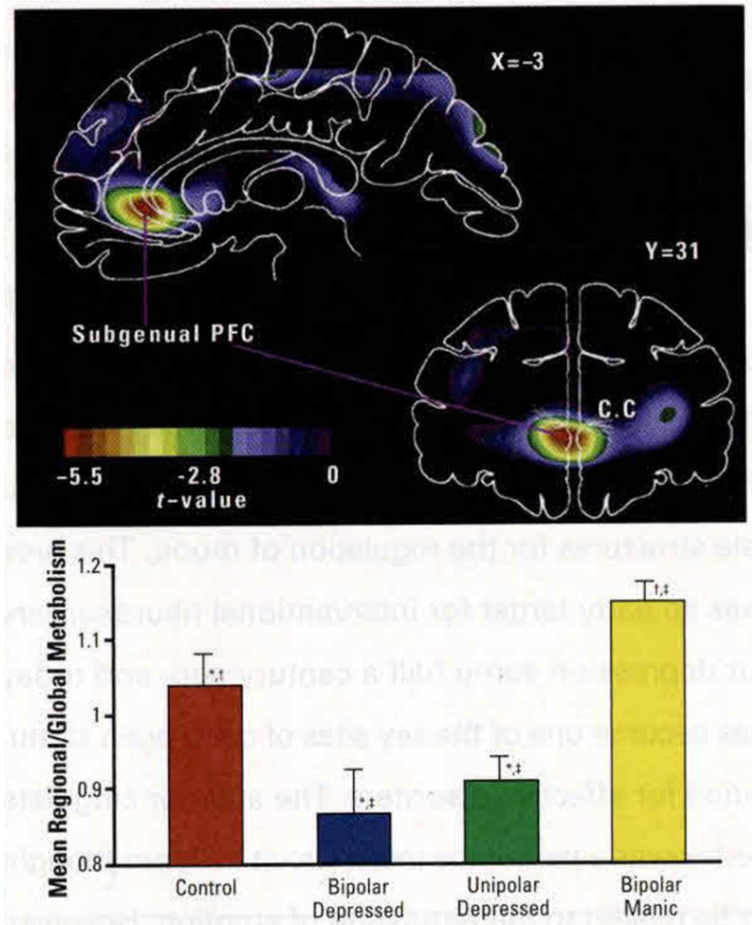




Hashemi et al., 2016

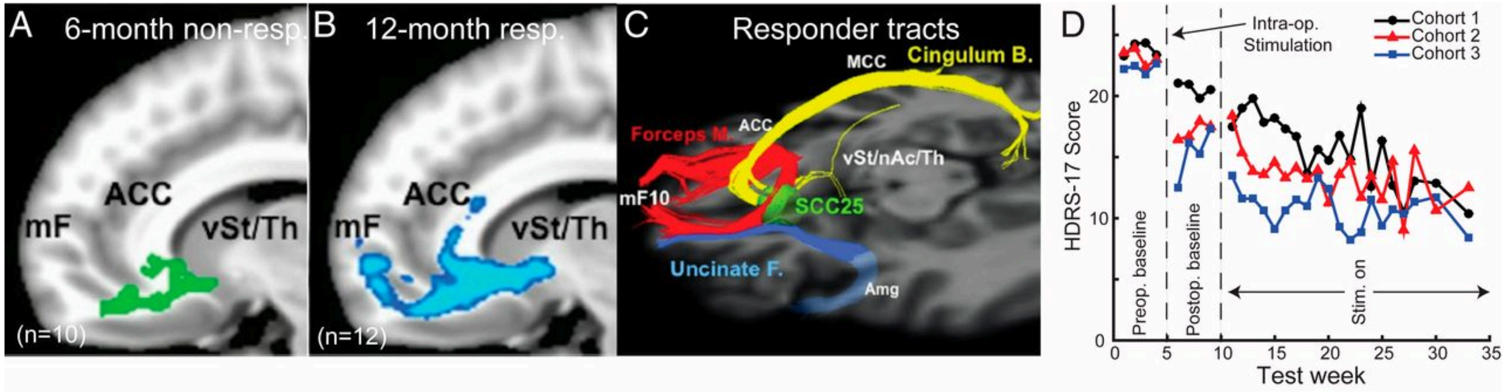
Dysfunction of PFC in psychiatric disorders

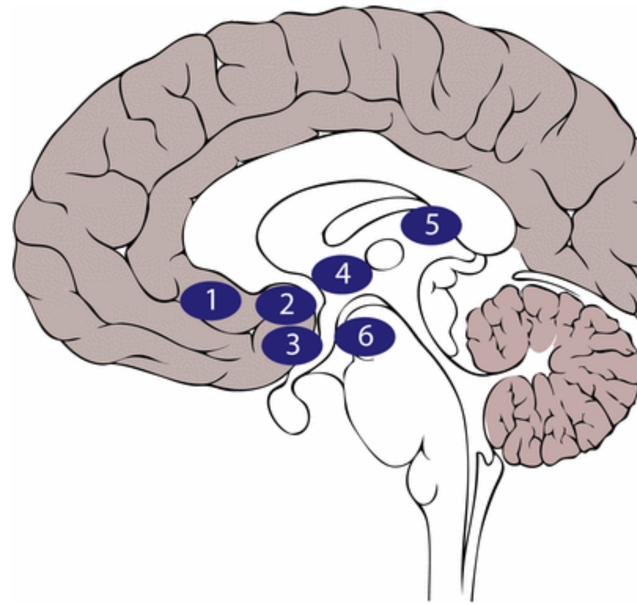
Reduced glucose metabolism was observed in the subgenual anterior cingulate area (BA 24/25) in patients suffering from major depression or bipolar disorder (during depressive stages)



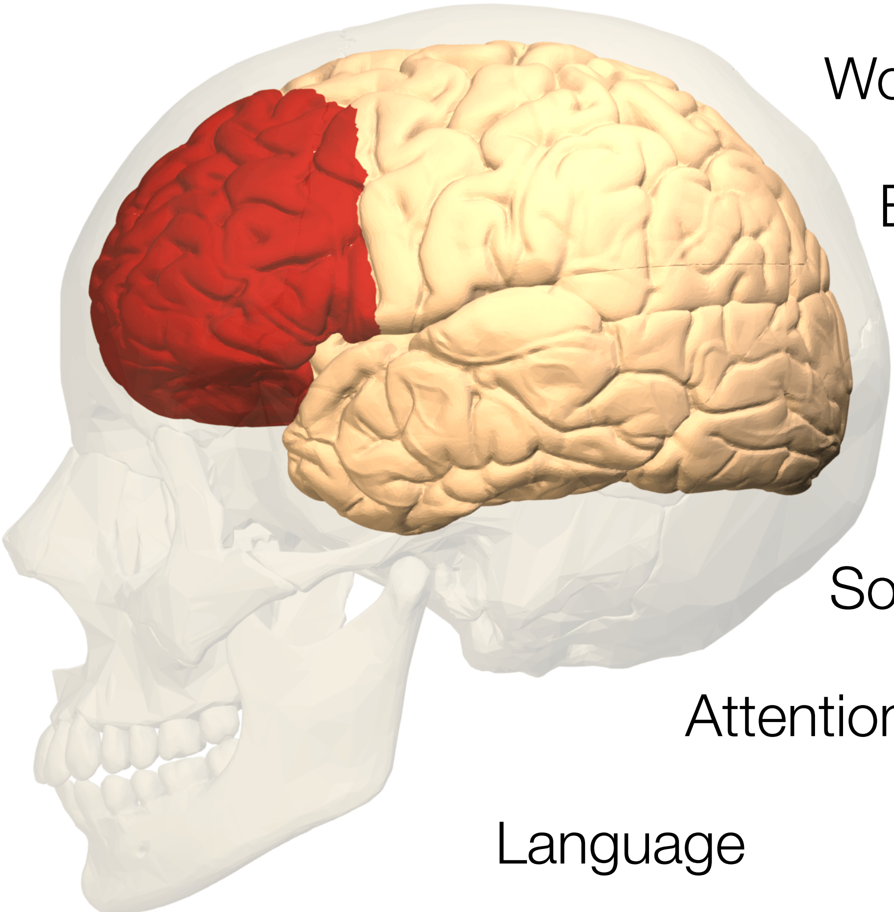
Drevets et al., Nature 1997

Deep-brain stimulation for major depression





Summary: the PFC is involved in multiple high-level cognitive/behavioral processes. Circuit mechanisms (outside of fear learning) are only partially elucidated.



Working Memory

Emotional regulation

Decision making

Value representation, prediction error

Social cognition

Attention

Language