Inhibition – Erasure or suppression?

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Overview

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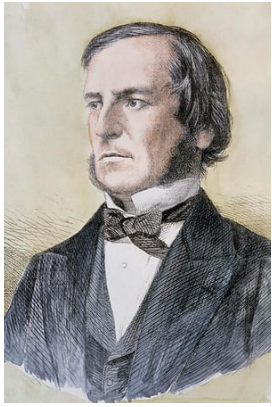
- Inhibition at the level of neurons and canonical circuits
- Inhibition in neural networks
- Behavioral inhibition
- Psychological inhibition
- Conclusion: the 4 faces of inhibition

Erasure or suppression?

Overarching question:

Does inhibition lead to **erasure** of an activity pattern / a behavior / a memory trace or to its temporary **suppression** that may be followed by a rebound – the „return of the repressed“?

$\neg(x \wedge \neg x)$



George
Boole

Georg Wilhelm Friedrich
Hegel

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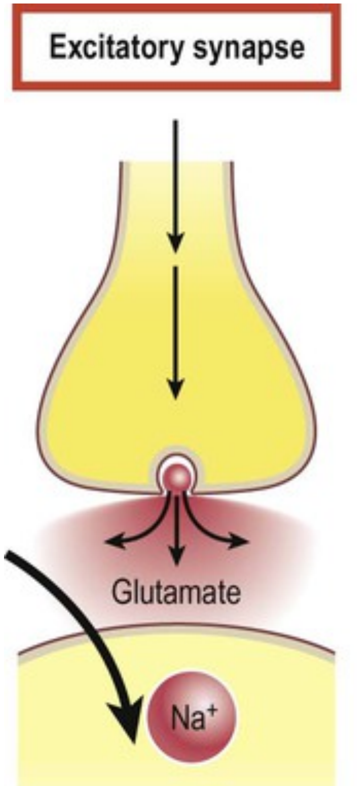
Inhibition at the level of neurons



Glutamate release

→ [Na^+] channels open

→ [Na^+] influx

→ Depolarisation:
action potential more likely

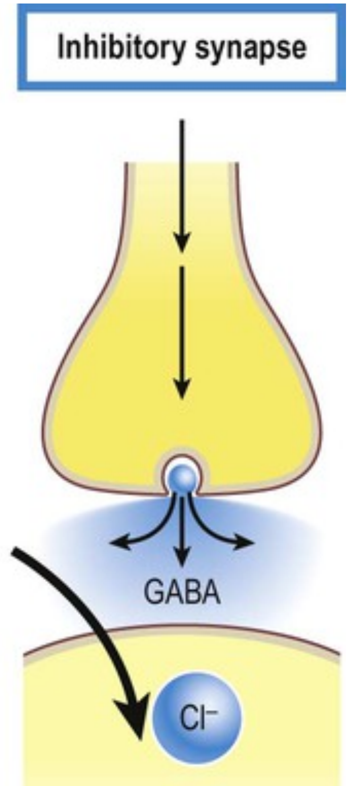
GABA release

→ [Cl^-] channels open

→ [Cl^-] influx

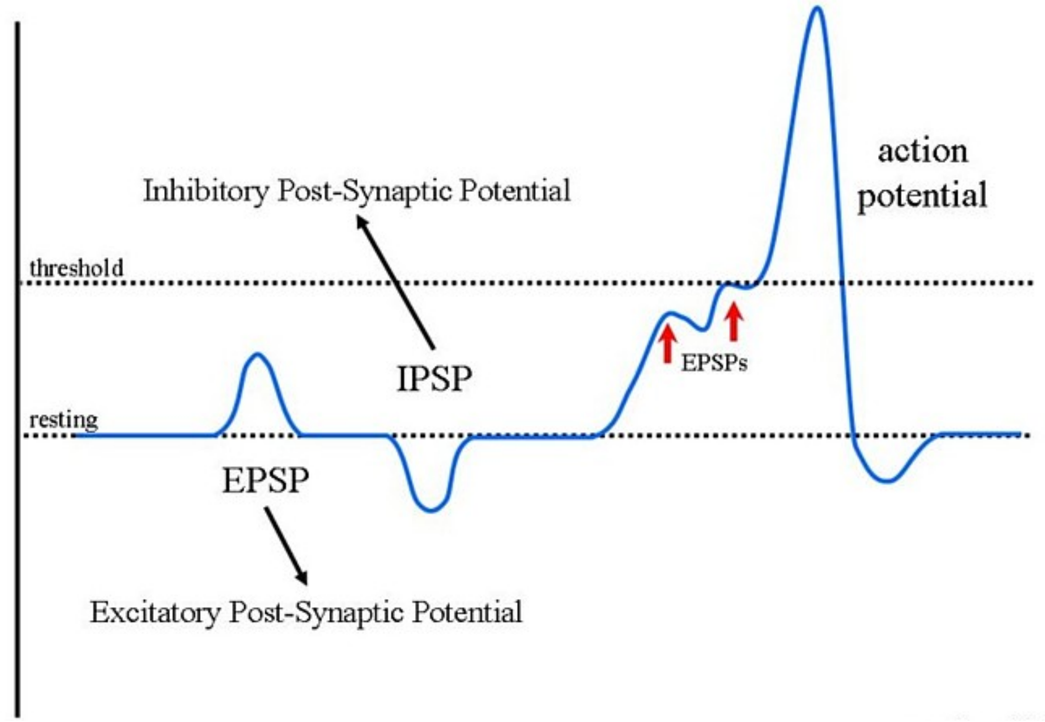
→ Hyperpolarisation:
action potential less likely

GABA effects: enhanced e.g. by benzodiazepines



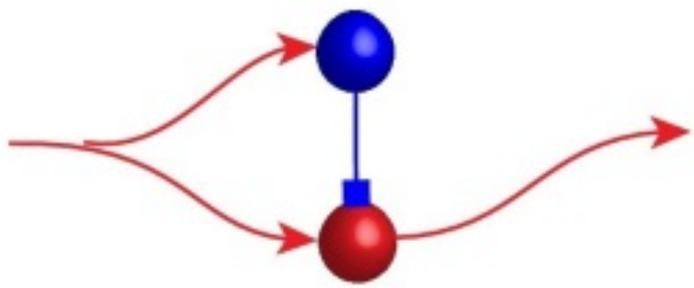
- Pyramidal cell: excitatory (e.g. glutamatergic)
- Interneuron: usually inhibitory (e.g. GABAergic)

Inhibition at the level of neurons

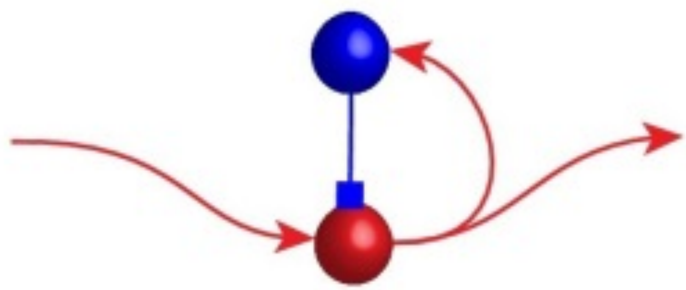


Summation of EPSPs and IPSPs determines cellular excitation

Feedforward and feedback inhibition



Feedforward inhibition
Input $\uparrow$
$\rightarrow$ Activation of pyramidal cell and interneuron
$\rightarrow$ Output $\leftrightarrow$

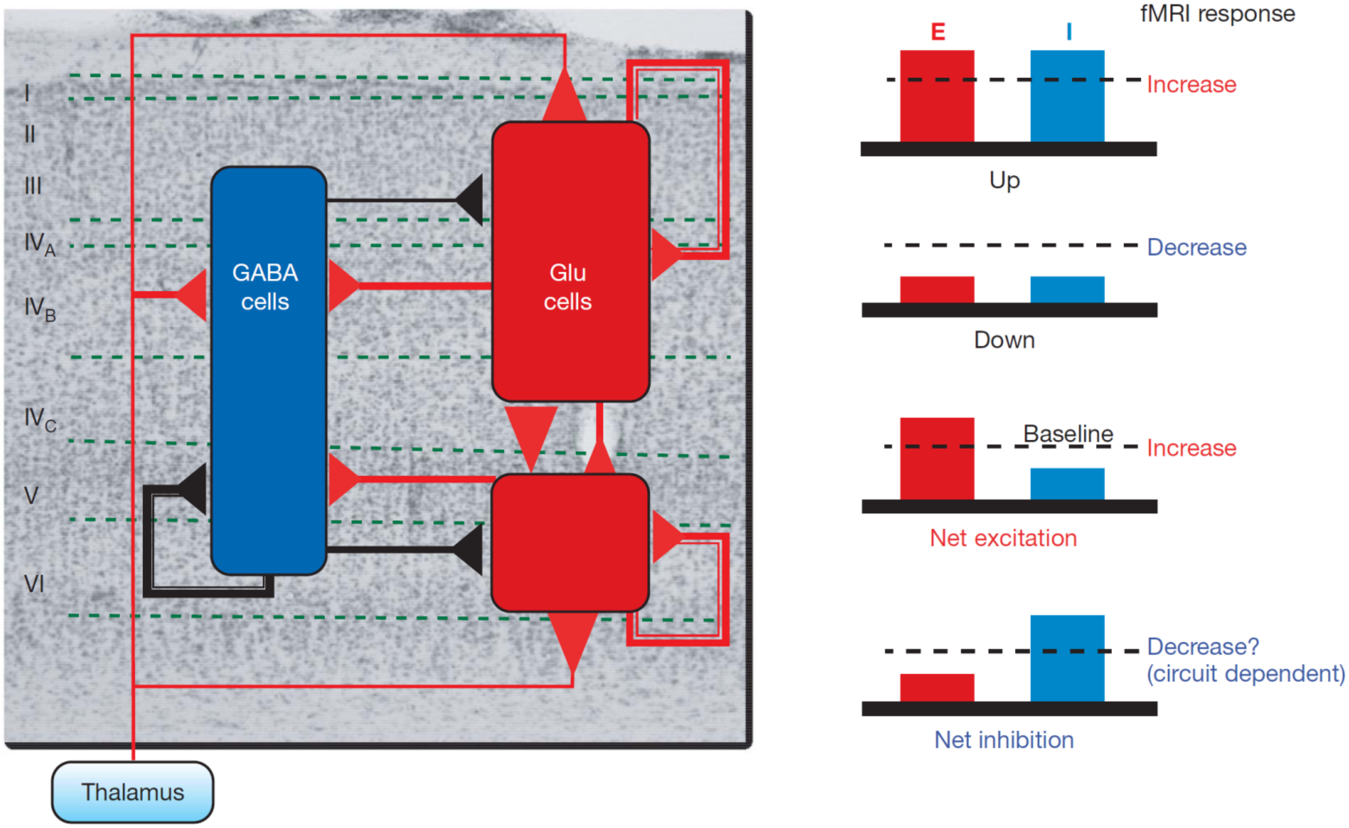


Feedback inhibition
Input $\uparrow$
$\rightarrow$ Activation of pyramidal cell
$\rightarrow$ Activation of interneuron
$\rightarrow$ Output $\leftrightarrow$

Inhibition can serve to counterbalance excitation (homeostasis)

Braganza and Beck, TINS 2018

Feedforward and feedback inhibition



- Excitation / Inhibition balance determines circuit output
- fMRI may reflect overall activity independent of net excitation/inhibition

Logothetis, Nature 2008

Interim summary

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- Inhibition at the cellular level depends on GABAergic interneurons that can effectively counterbalance excitation
- Both net levels of excitation and overall amount of excitation and inhibition may be relevant

- **In addition to net levels of excitation/inhibition, temporal structure of activity may be relevant → oscillations**

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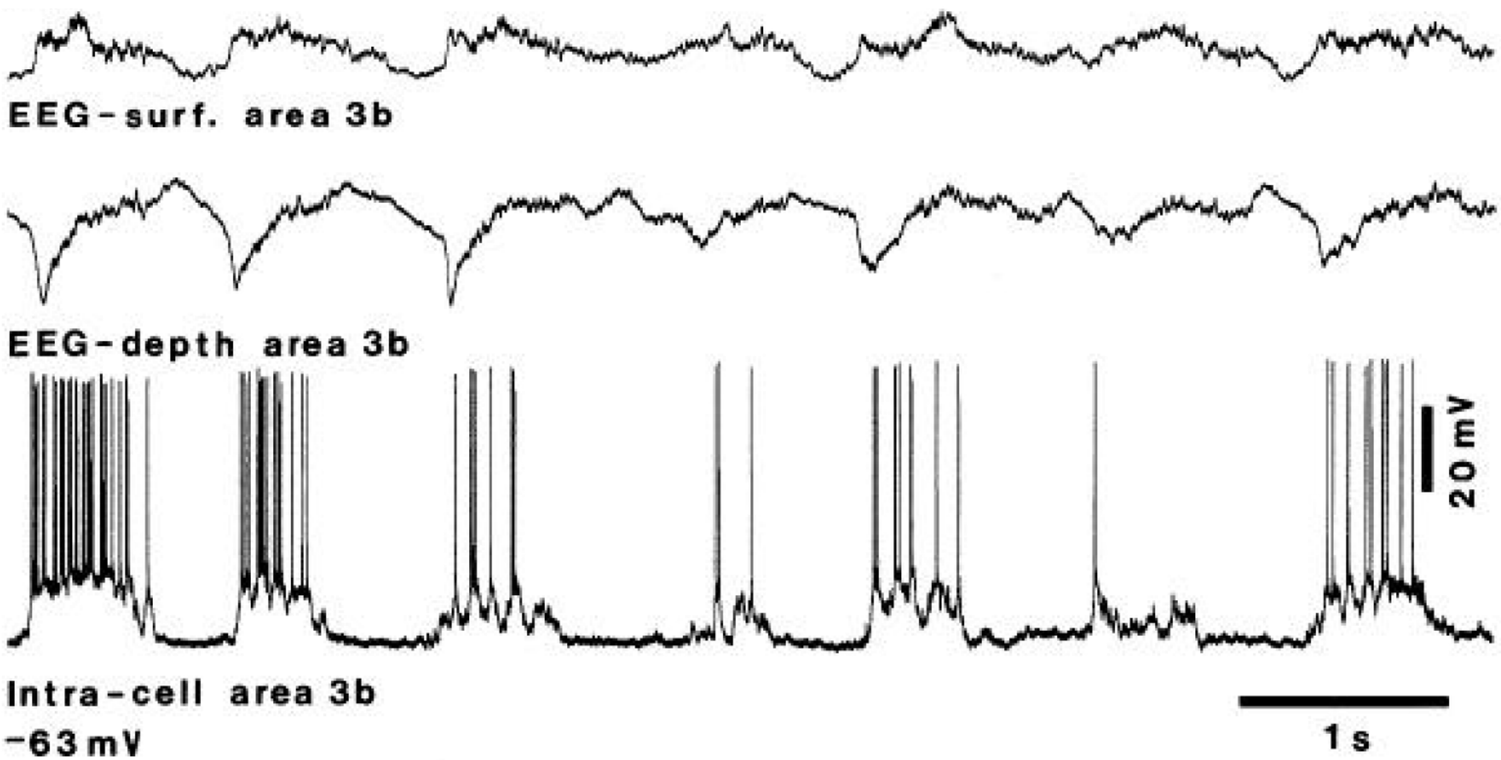
Oscillations: Basics

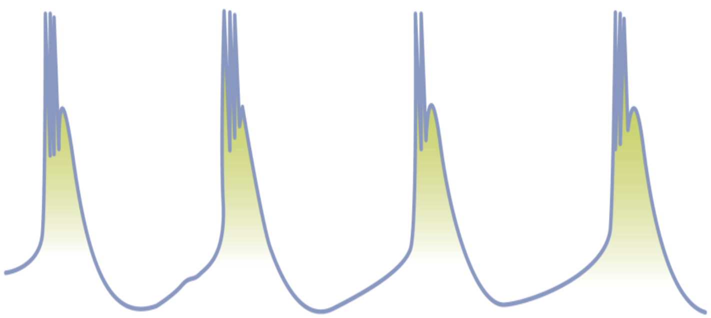
EEG oscillations reflect excitability within a networks of neurons



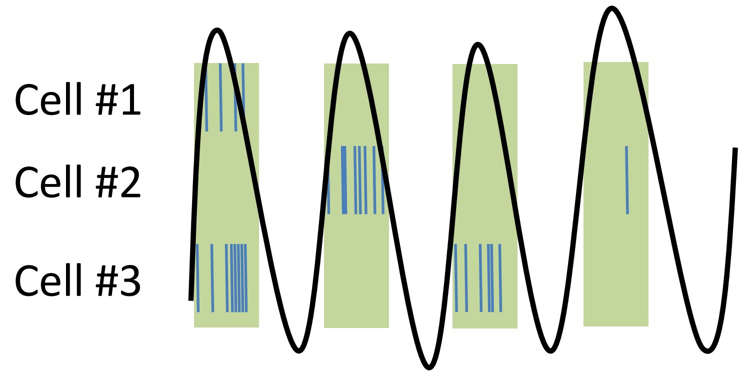
Contreras and Steriade, J Neurosci 1995

Oscillations: Mechanisms

Oscillations may be due to single pacemaker cells or reflect an „emergent“ network phenomenon



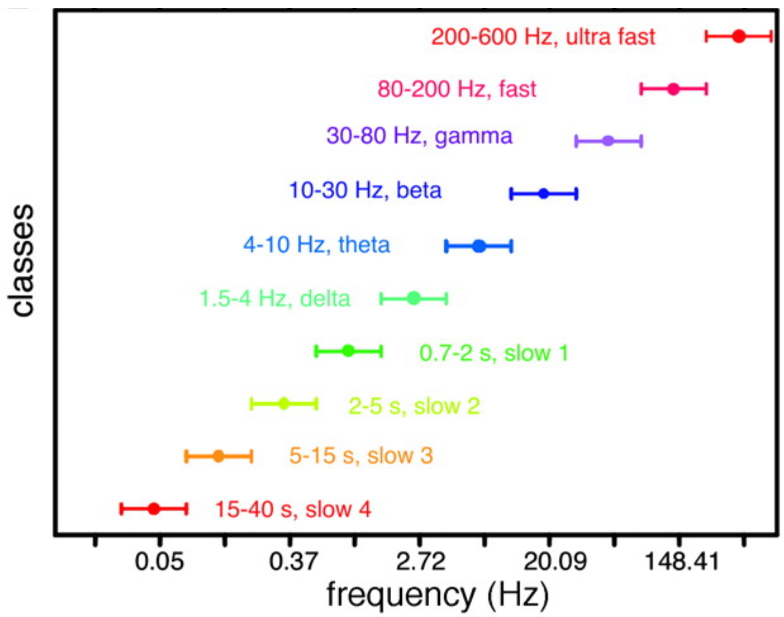
Oscillations in a single cell



EEG oscillations as a pure network phenomenon

Crunelli et al., Nat Rev Neurosci 2018

Oscillations: Frequency bands

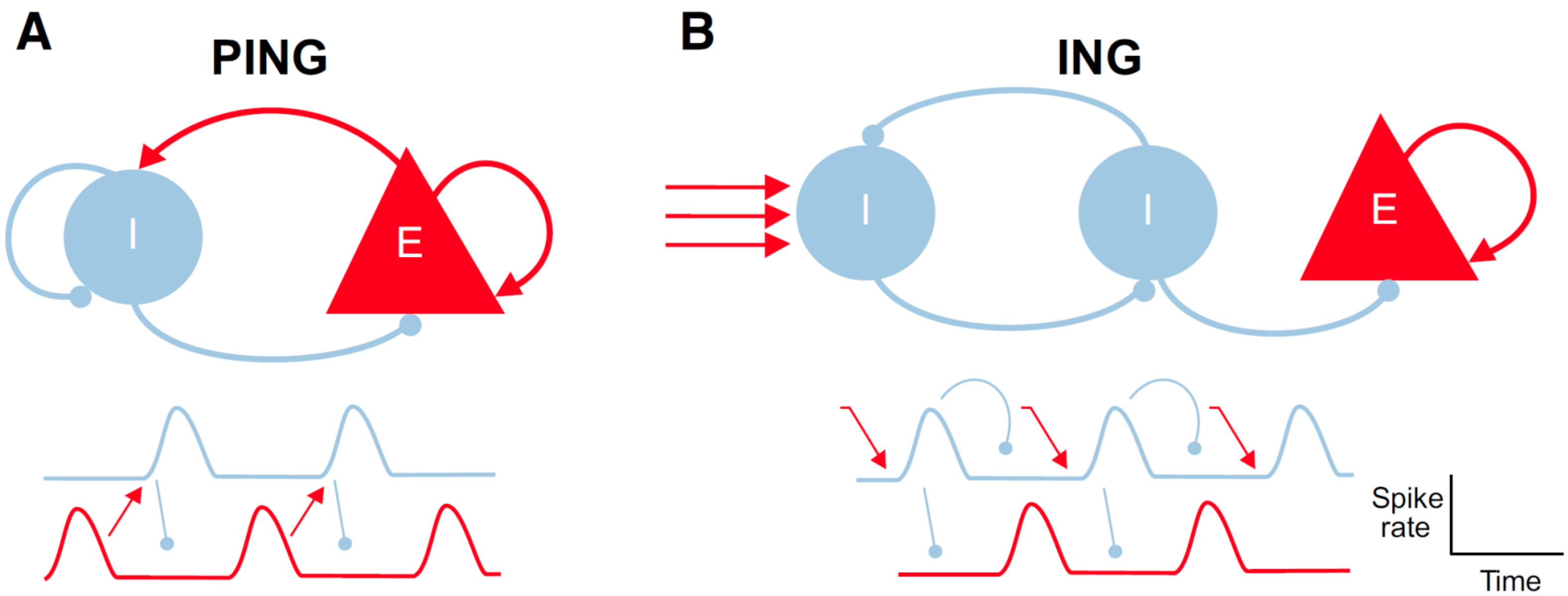


- EEG oscillations occur at various different frequencies
- Relationship to specific cognitive functions?
- All oscillations apart from very slow ones require inhibition to maintain rhythmicity (important for various diseases)

Buzsaki and Draguhn, Science 2004

Oscillations and inhibition

Oscillations in small pyramidal cell – interneuron circuits



Pyramidal cell –
interneuron gamma

Interneuron gamma

Oscillation frequency depends on cellular and synaptic time constants

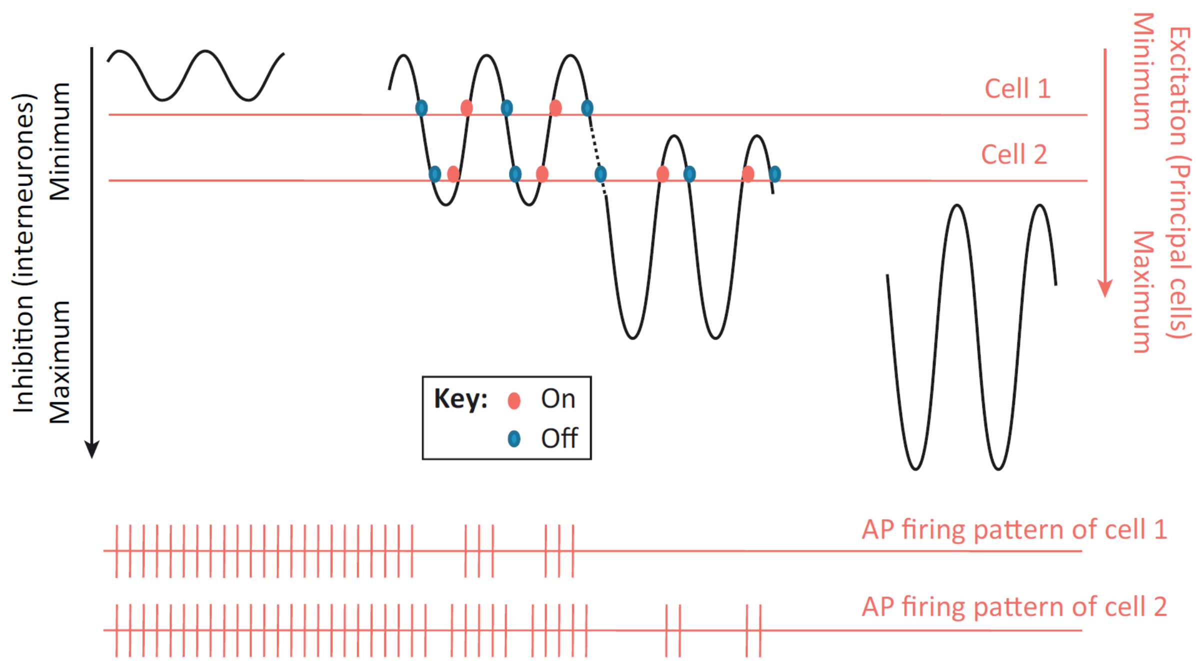
Bosman et al., Eur J Neurosci 2014

Oscillations: Alpha and inhibition

Alpha oscillations reflect functional inhibition of an area

„Berger effect“: alpha oscillations in visual cortex with closed eyes

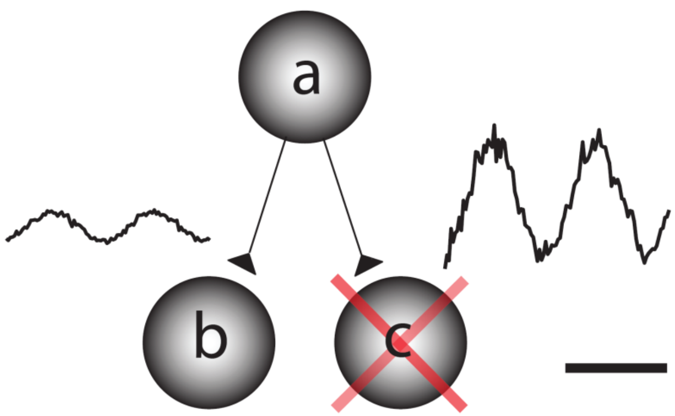
Case 1: Alpha in task-irrelevant networks: no AP modulation	**Case 2:** Alpha in task-relevant networks: AP modulation by inhibition-timing	**Case 3:** Alpha in task-irrelevant/competing networks: inhibition



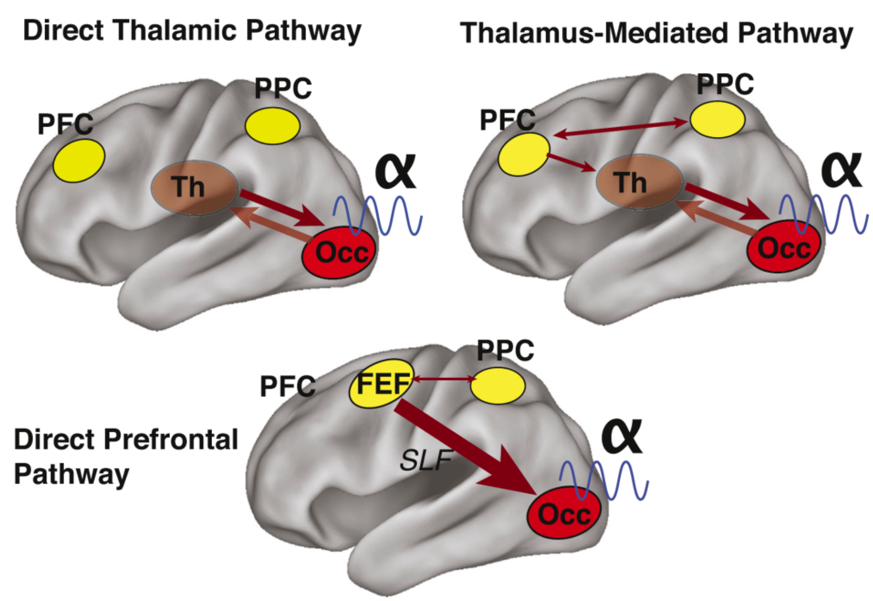
Katz et al., TiNS 2015

Oscillations: Alpha and inhibition

Alpha-related inhibition can be controlled by the prefrontal cortex



„Gating by Inhibition“
hypothesis



Direct or indirect prefrontal control
of alpha oscillations

Jensen and Mazaheri, Front Hum Neurosci 2010; Lenartowicz et al., Biol Psychiatry 2018

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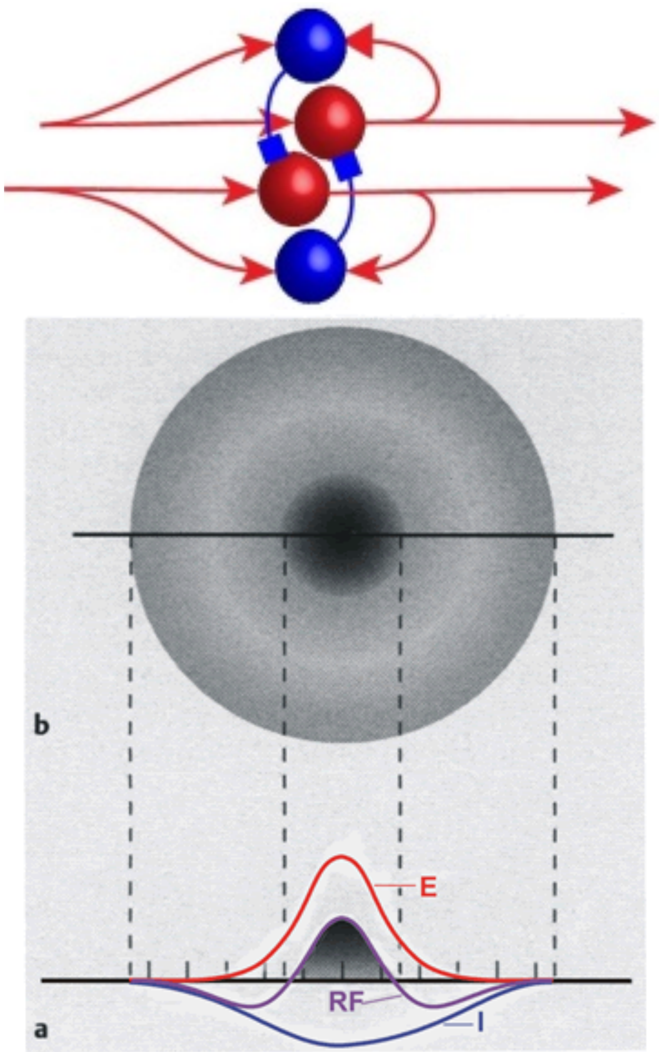
Local inhibition and attention



Lateral inhibition

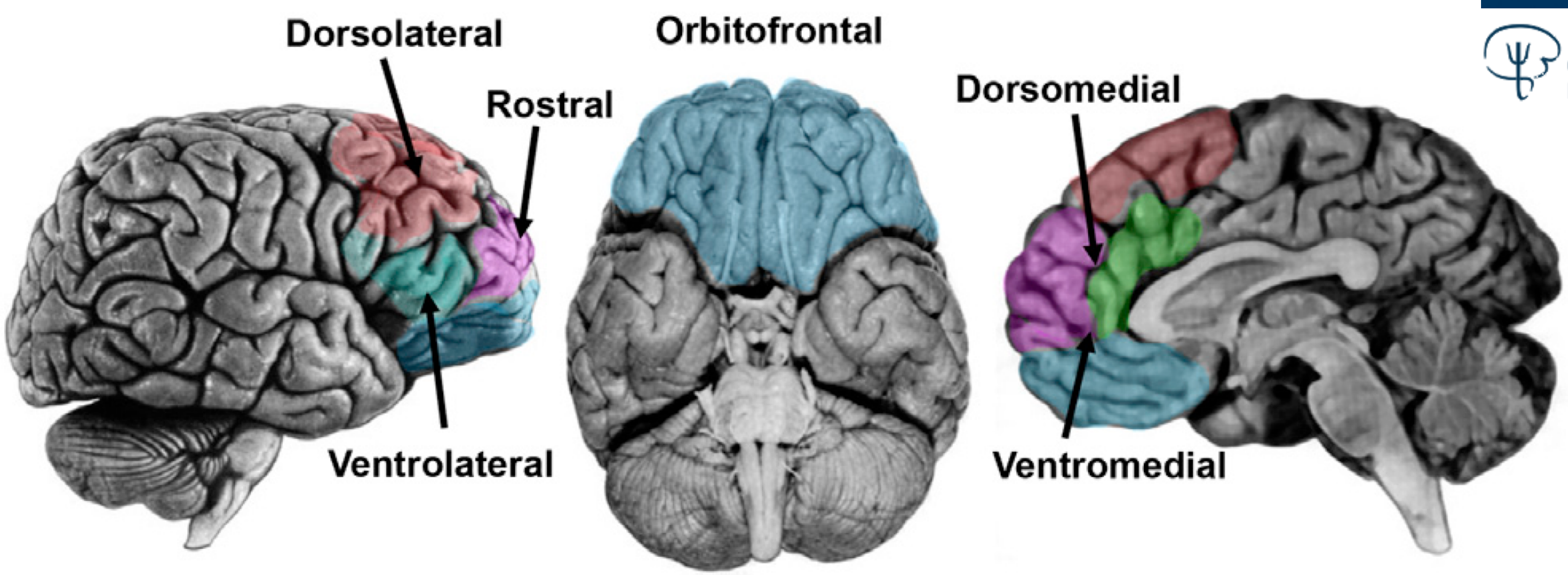
→ All pyramidal cells activated
→ Each cell inhibits its neighbours
→ Only the most active cells survive: „winner-takes-all“

- Mechanism for stimulus-driven (bottom-up) attention
- Can lead to sharpening of stimulus representations

Attention can also be voluntarily controlled (top-down)

Braganza and Beck, TINS 2018

The prefrontal cortex: overview

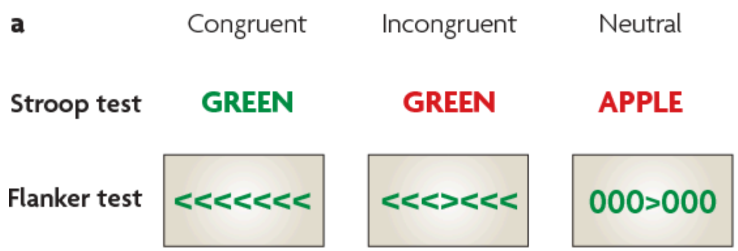


Functions: Executive control, selective attention…

→ inhibition of irrelevant/distracting/interfering…
- …stimuli (selective attention)
- …cognitive processes (task-directed attention)
- …emotions (emotion suppression, reappraisal)
- …responses (motor control)

Szczepanski and Knight, Neuron 2014

The prefrontal cortex and inhibition



Stroop task

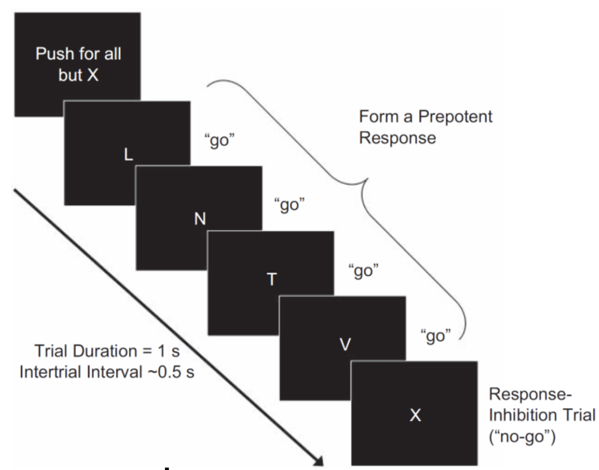
- Conflict of 2 response tendencies (respond to color / word meaning)
- Inhibition of automatic response (reading word meaning)

Flanker task

- Inhibition of surrounding stimuli

Go/No-Go task

- Response inhibition



Costs of inhibition: reaction times ↑, accuracy ↓

Mansouri et al., Nat Rev Neurosci 2009

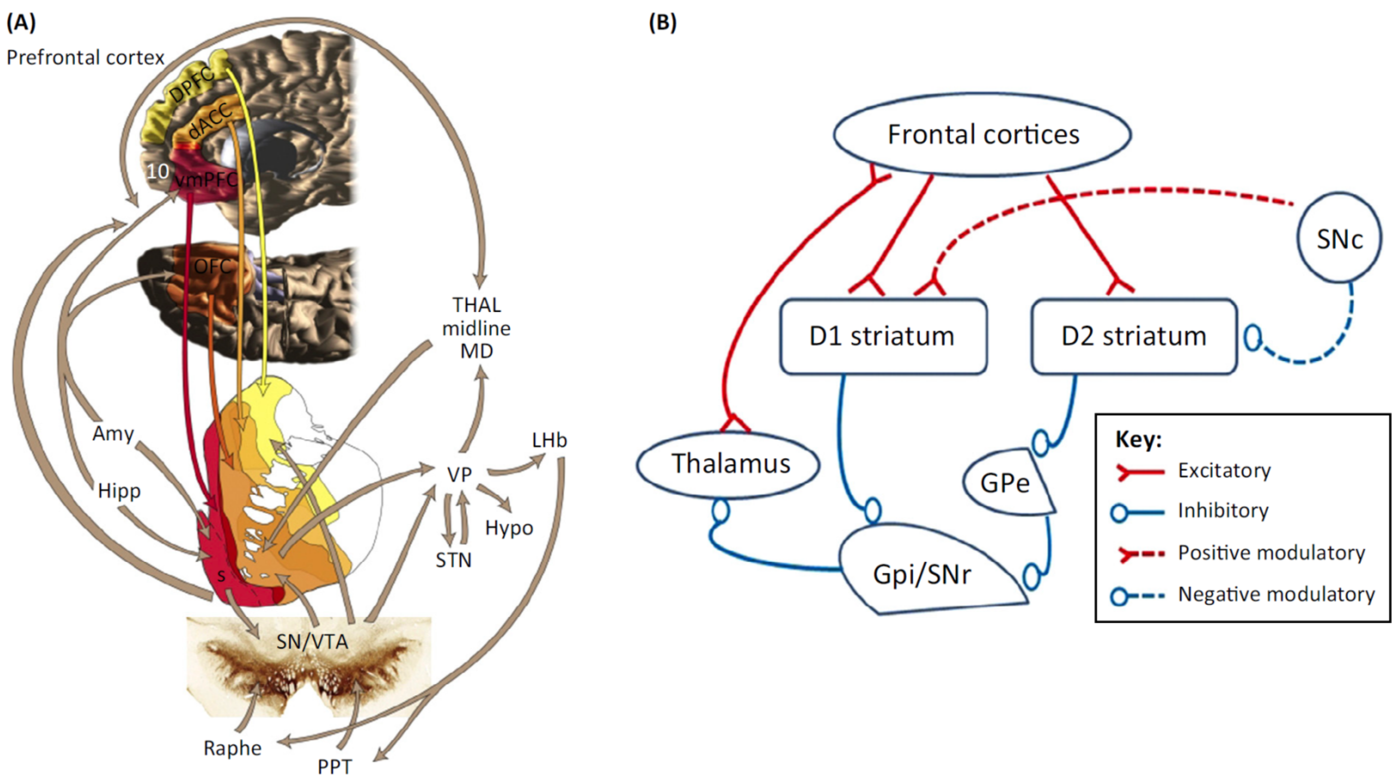
Thought suppression

„Don‘t think of a white bear!“

- Suppression period is followed by intrusive thoughts of the suppressed content: paradoxical rebound phenomena
- Postsuppression rebound depends on various factors and may be circumvented

Wenzlaff and Wegner, Annu Rev Psychol 2000; Wegner, Am Psychol 2011

Inhibition of reward



- Controlling impulsive behavior and delaying rewards can be unpleasant and difficult (secondary process thinking)
- Neural basis: prefrontal cortex inhibits reward processing
- Addiction: prefrontal hypoactivity → reduced inhibition

Tang et al., TICS 2015

Rewarding inhibition

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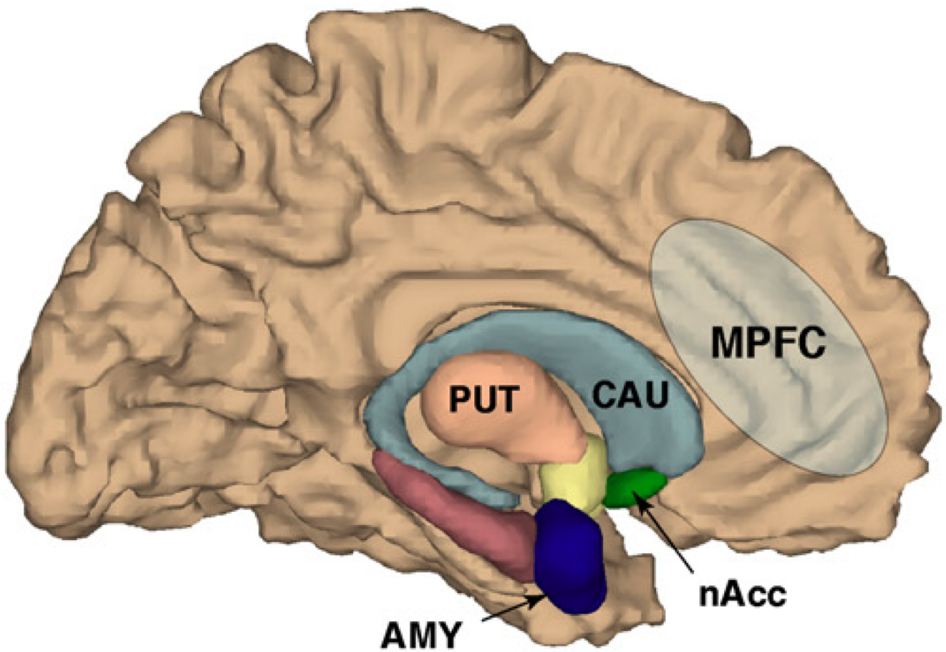

Choice opportunity

↑ Reward experience (↑ striatum)

↑ Increased self relevance (↑ MPFC)

Choice (threat context)

↑ Cognitive control of emotion (↑ MPFC)

↓ Negative affect (↓ AMY)

Cognitive control during choice allows for perceived **self-efficacy**, **autonomy**, and **self-determination**

→ Inhibitory control can be intrinsically rewarding!

→ **„Paradoxical“ relationship between inhibition and reward**

Leotti et al., TICS 2010

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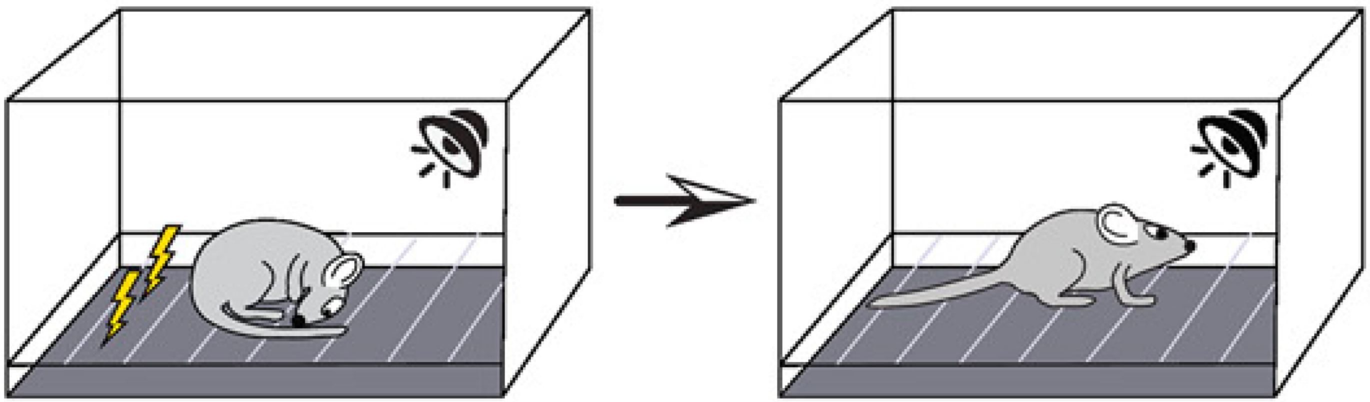
Extinction learning: basics

Proposed mechanism of action for exposure therapy



Conditioning Extinction

Rescorla-Wagner model for conditioning and extinction

$$\Delta V(t) = k(V_{max} - V(t))$$

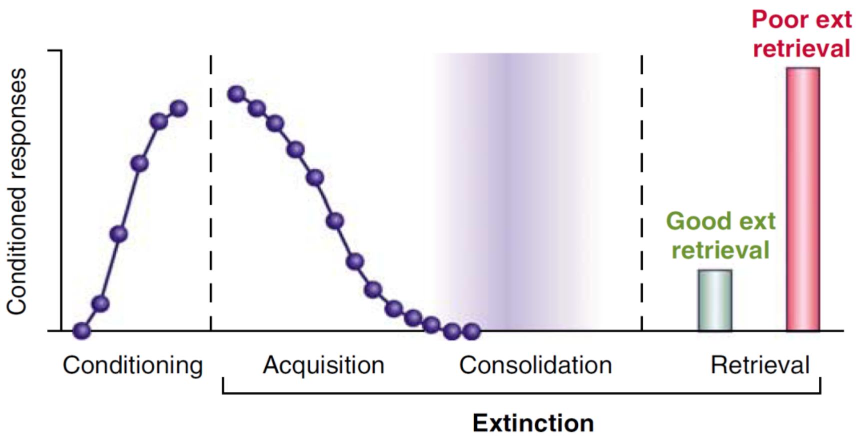
- $\Delta V(t)$: Change in associative strength (reward value) of a stimulus at time *t*
- k: learning rate
- V_{max}: maximal possible associative strength of a stimulus
- $V(t)$: current associative strength

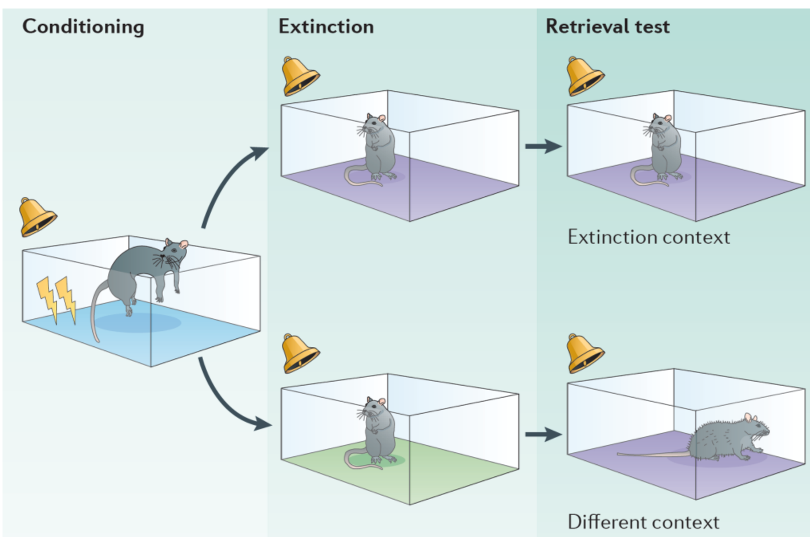
Rescorla-Wagner model assumes that extinction is „unlearning“

Li et al., PLOS Comput Biol 2016

Extinction as novel learning

Extinction is not just unlearning but involves novel learning



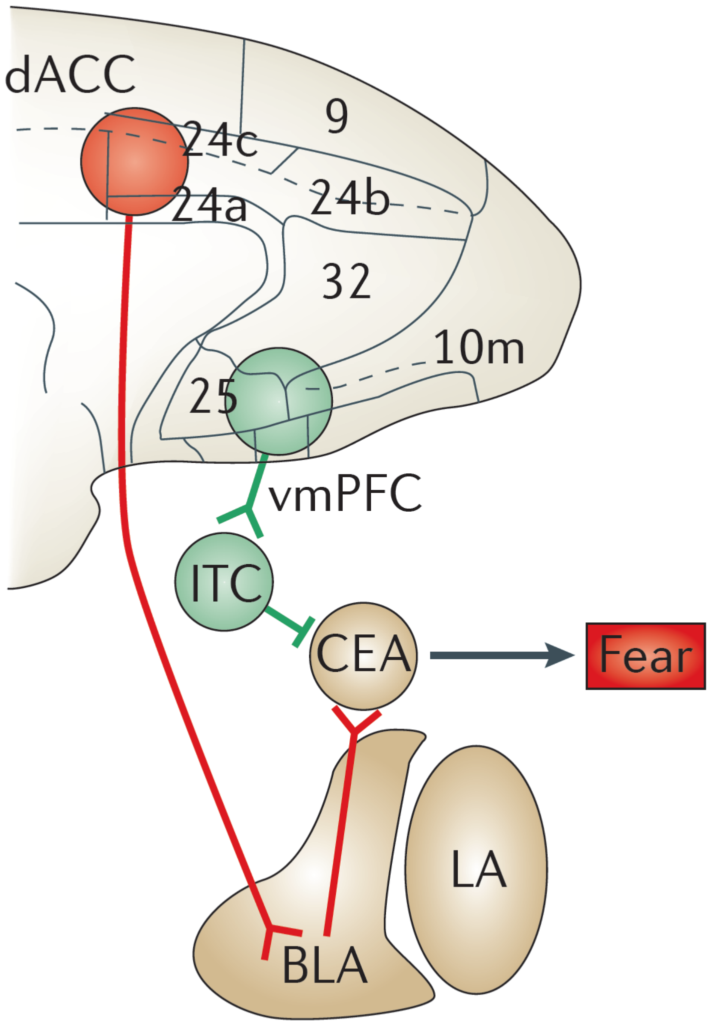


Conditioned responses can reoccur after extinction

- **Spontaneous recovery**
- **Renewal:** in particular in ABA/ABC paradigms (strong context dependence of extinction)
- **Reinstatement:** triggered by reoccurence of US

Quirk and Mueller, Neuropsychopharmacology 2008; Maren et al., Nat Rev Neurosci 2013

Extinction learning: neural basis



Acquisition

- Fear response: basolateral and central amygdala (BLA, CEA)
- Maintainance of fear: dorsal anterior cingulate cortex (dACC)

Extinction

- Ventromedial prefrontal cortex (vmPFC) activates GABAergic intercalated cells (ITC) in the amygdala

→ inhibition of fear response

Extinction learning as a translational research paradigm: similar processes in rodents and humans

Quirk and Mueller, Neuropsychopharmacology 2008; Maren et al., Nat Rev Neurosci 2013

Self-related inhibition of fear: the ventromedial prefrontal cortex

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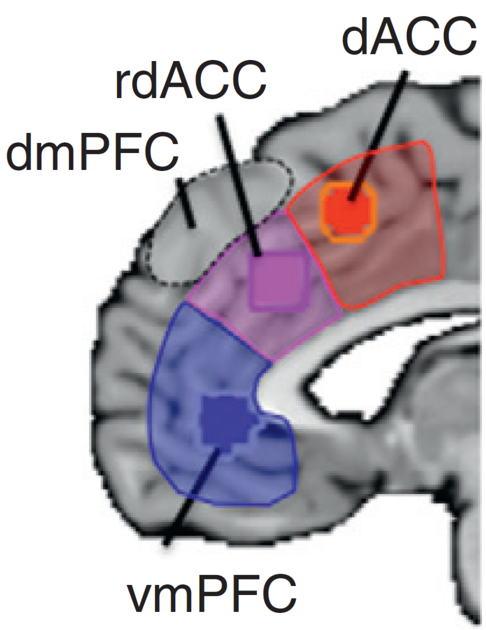

1. Inhibition of amygdala-dependent fear response: **safety signal**
2. Representation of **schemas/concepts** following memory consolidation
3. Part of cortical midline structures: **self-related processing**
4. Termination zone of mesolimbic dopamine system: representation of reward / “seeking“ / appetitive behavior / libidinous cathexis, i.e. supporting **valuable object relations**

- Impairment in depression and PTSD

→ the vmPFC *„is critical when affective responses are shaped by conceptual information about specific outcomes”*

→ **Representation of protective self-objects that are crucial for healthy object relations**

Roy et al., TICS 2012

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- Inhibition **at a behavioral level** depends on the prefrontal cortex
- Behavioral and reward inhibition can have paradoxical effects
- Inhibition **at the psychological level** substantially transforms learning
- Ventromedial prefrontal cortex seems to be crucial for self-related transformation of experiences during inhibition (self-objects)

Conclusion: the 4 faces of inhibition

- **The efficacy of inhibition:** fundamental homeostatic mechanism to counteract excitation
- **The costs of inhibition:** binding resources, increasing reaction times, reducing task performance – may lead to rebound phenomena
- **The benefits of inhibition:** free choice, autonomy, and development of a stable self
- **The transformative nature of inhibition:** rhythmic structure in neural activity, context dependence of extinction learning

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