The neuromodulation of cognition

Andrew Reid

DONDERS INSTITUTE

Radboud University Radboudumc

Overview

I. The optimization of action

- An abstract example - simulated annealing
- A somewhat more concrete example - foraging

II. Some biology

- The noradrenergic system
- Physiology of the locus coeruleus - tonic vs. phasic modes
- The classic model - arousal

III. Some cognitive neuroscience

- Decision making
- Working memory
- Short- and long-term utility
- Adaptation & novelty
- Reinforcement learning

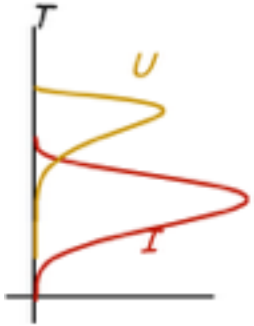
Overview

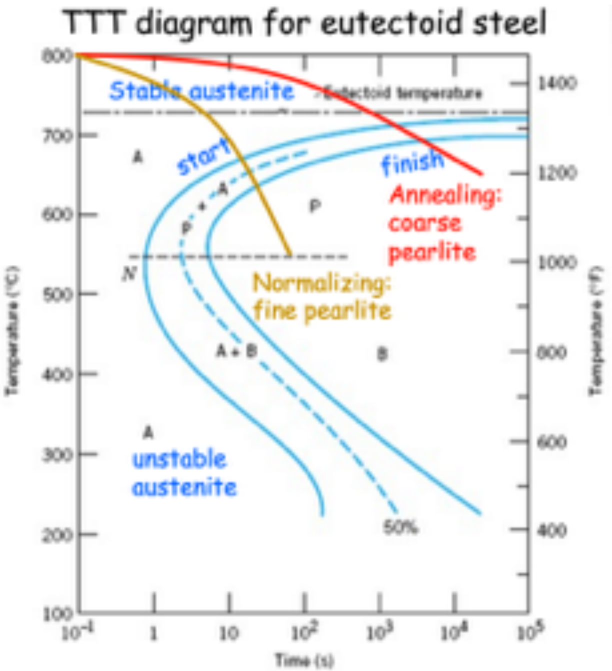
IV. Research ideas

- Role in reinforcement learning model?
- Modelling clinical disorders
- Pharmacological interventions

I. The optimization of action

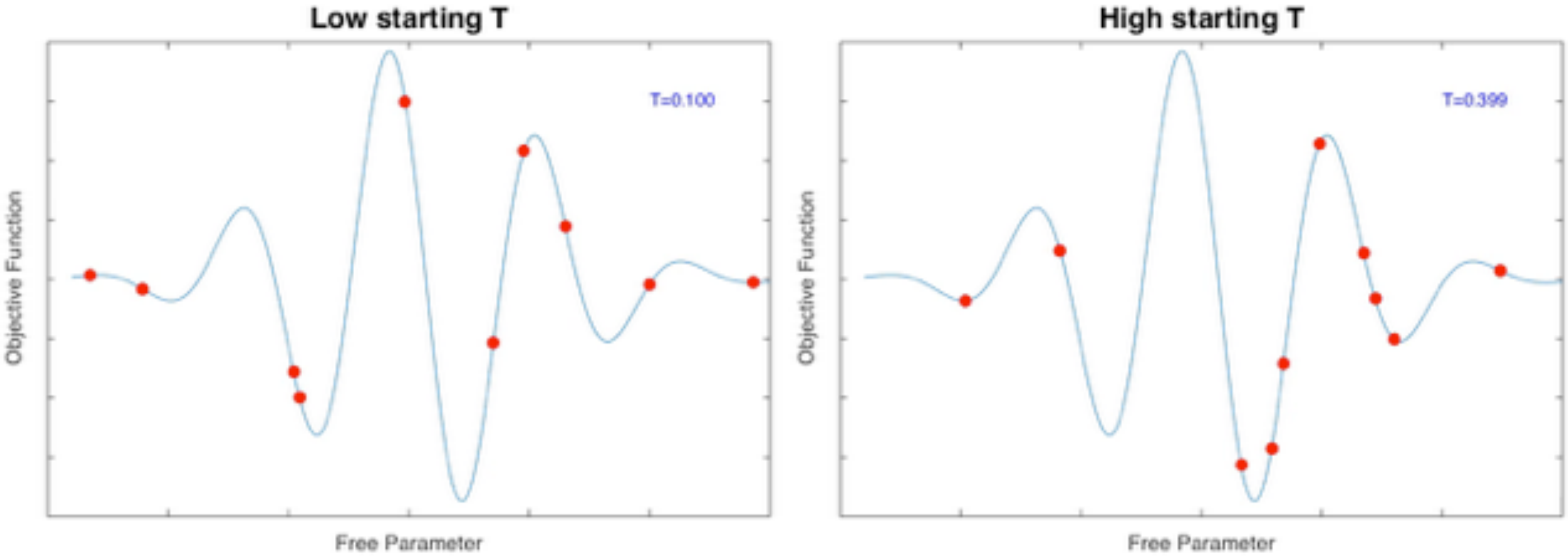
A thought exercise - **annealing**





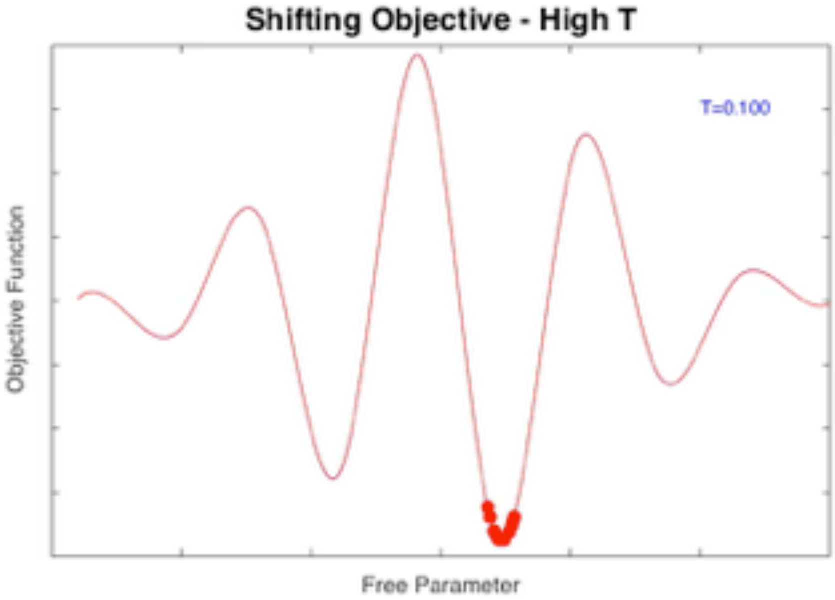
I. The optimization of action

A thought exercise - **simulated** annealing (**stationary** environment)



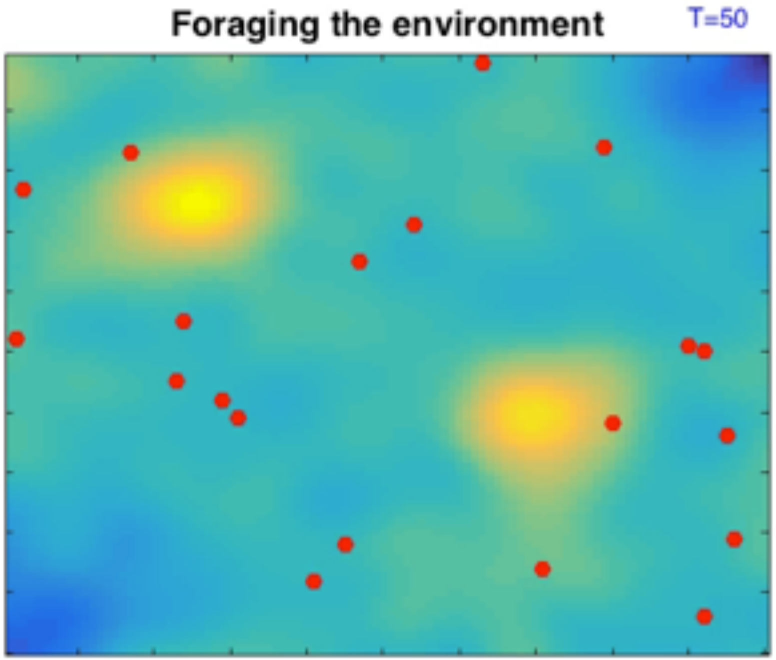
I. The optimization of action

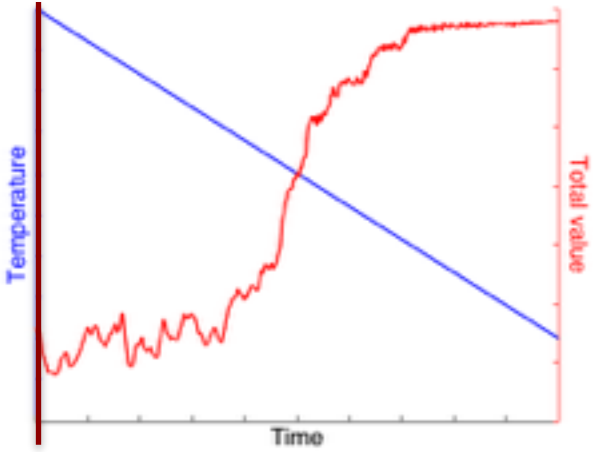
A thought exercise - **simulated** annealing (**changing** environment)



I. The optimization of action

Something a bit more concrete - foraging behaviour





I. The optimization of action

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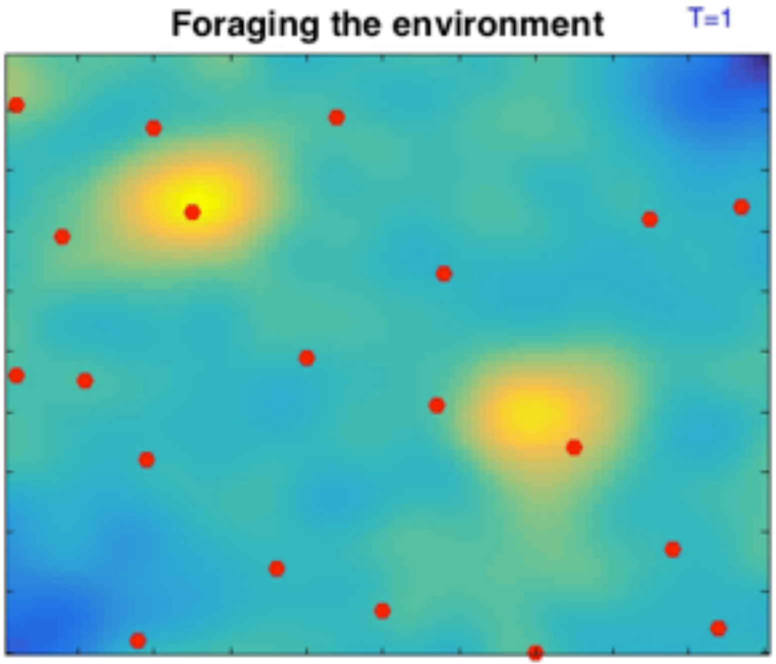
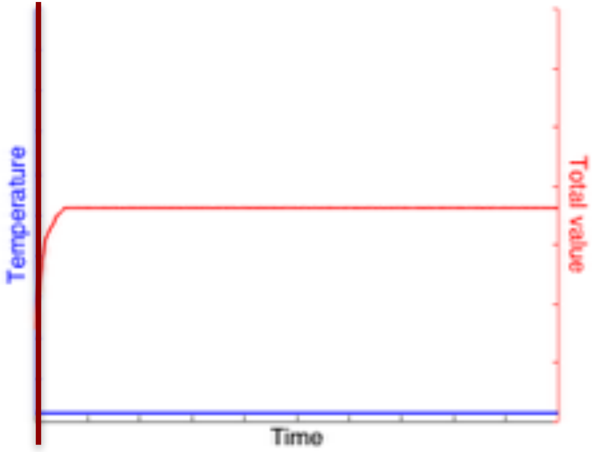
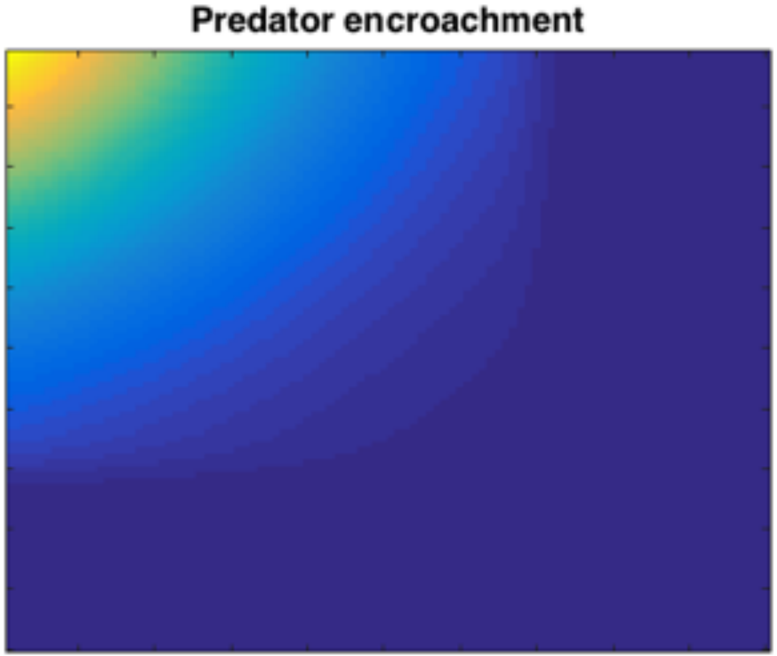
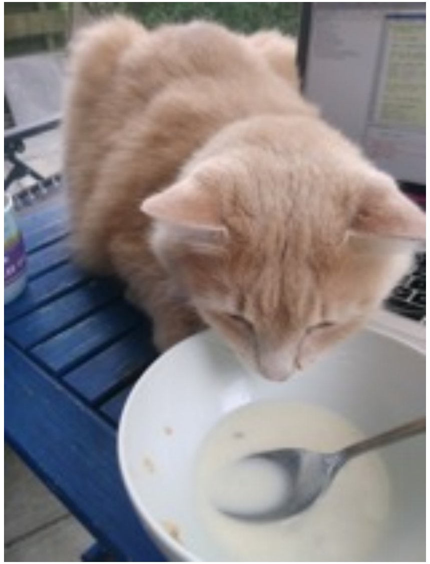




I. The optimization of action

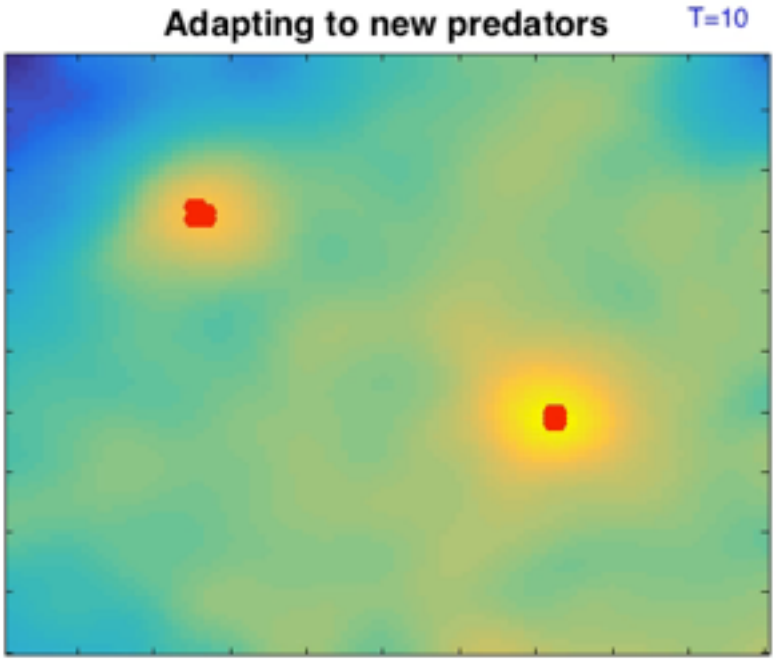
Something a bit more concrete - **adaptive** behaviour

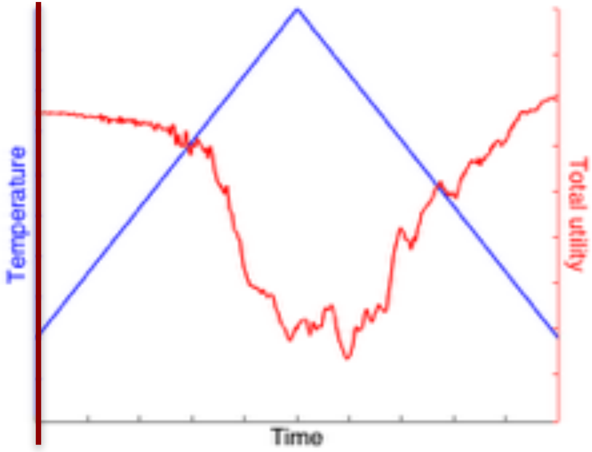




I. The optimization of action

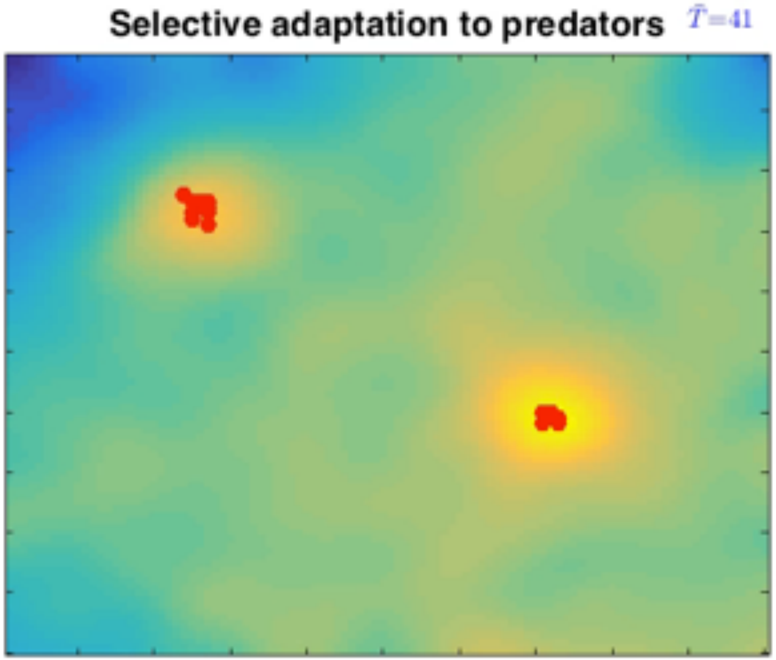
Something a bit more concrete - **adaptive** behaviour

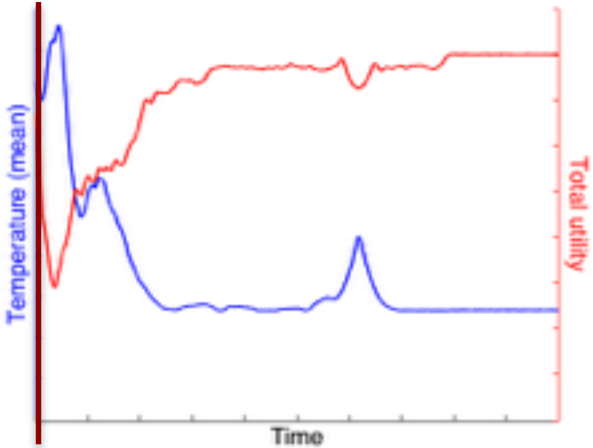




I. The optimization of action

Something a bit more concrete - **adaptive** behaviour





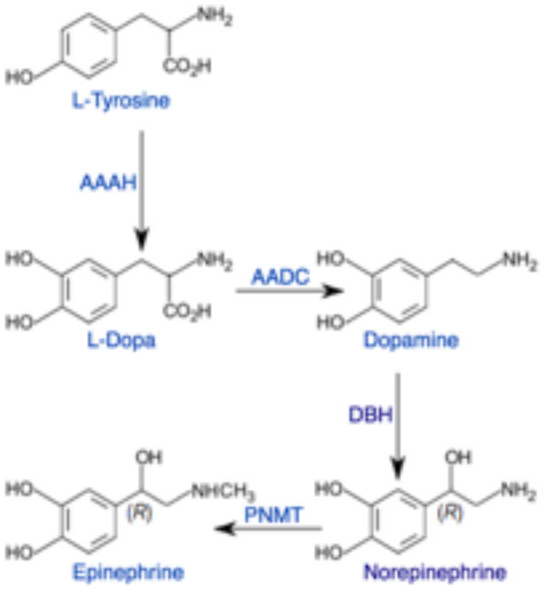
Why are we talking about gazelles and lions!?

- Annealing is an apt metaphor for **all** adaptive behaviour
- Optimization is an evolutionary necessity; it consists of:
  - Making **decisions** based on the relative utility of actions
  - **Exploring** unknown territory (high temperature state)
  - **Exploiting** known resources (low temperature state)
  - **Adapting** to changing environments (selective regulation of temperature)
- *Hypothesis*: optimization in mammals is accomplished largely through **neuromodulators** (particularly catecholamines)
  - **Dopamine**: evaluation of reward prediction errors (Dr. den Ouden) - this constitutes the **valuation** signal
  - **Norepinephrine**: evaluation of salience; including novelty, utility, and volatility (this lecture) - this constitutes the **temperature** signal

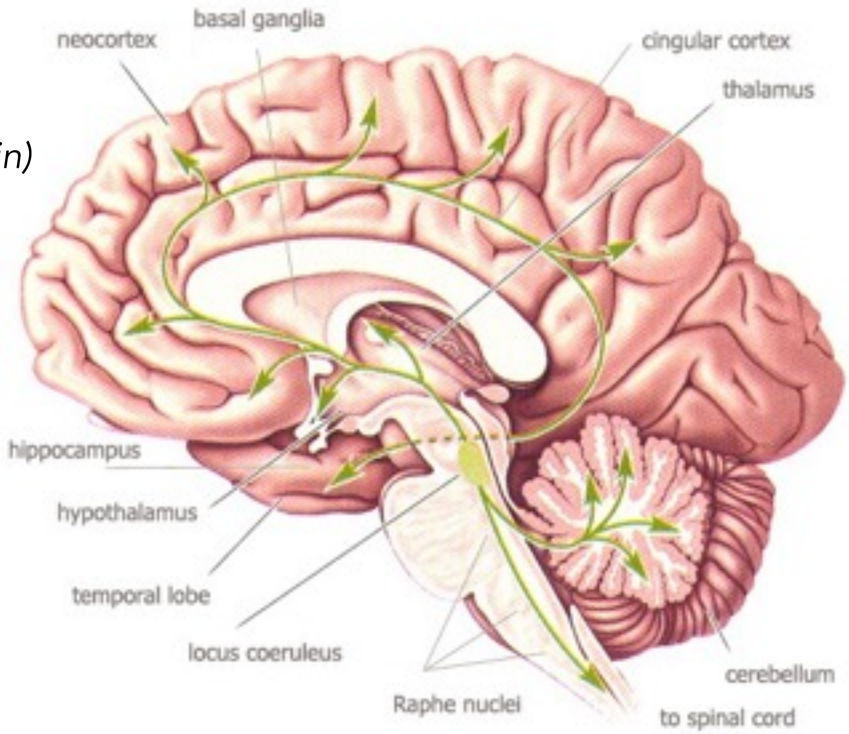
II. Some biology

The **noradrenergic system**

Norepinephrine (NE; Greek) = Noradrenaline (Latin)



Catecholamine synthesis chain



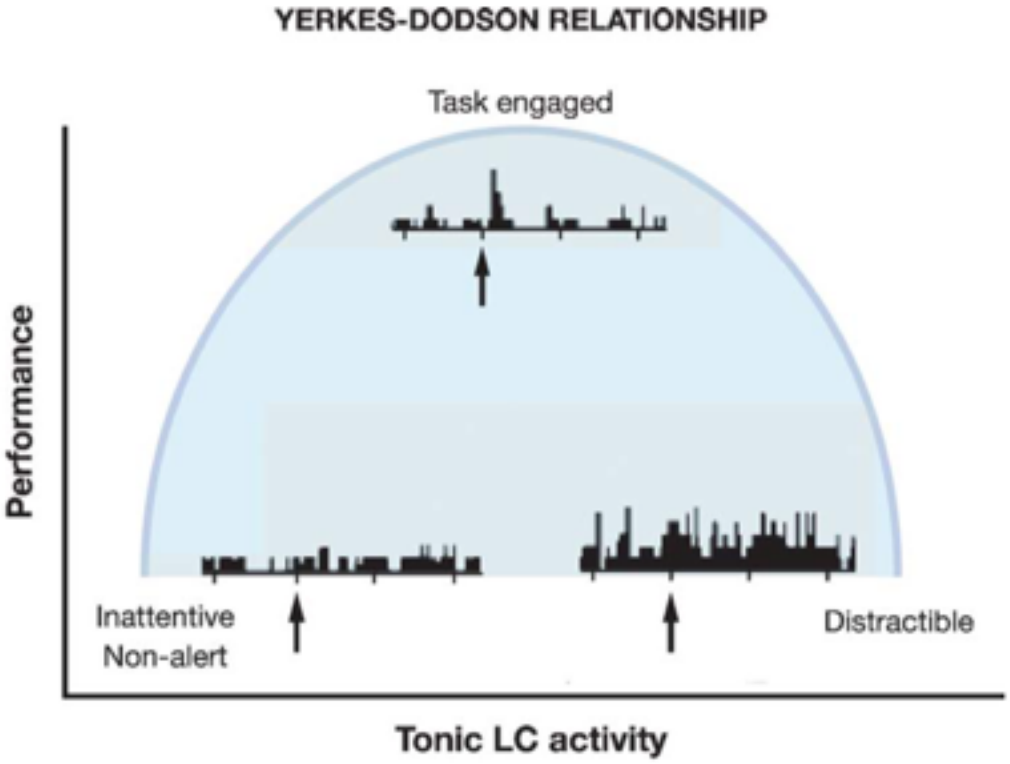
*The vast majority of NE producing cells are localized in the **locus coeruleus (LC)***

II. Some biology

Physiology

Two modes of firing:

- **Tonic:** baseline mean firing rates of LC neurons
- **Phasic:** transient, synchronized, robust firing of LC neurons



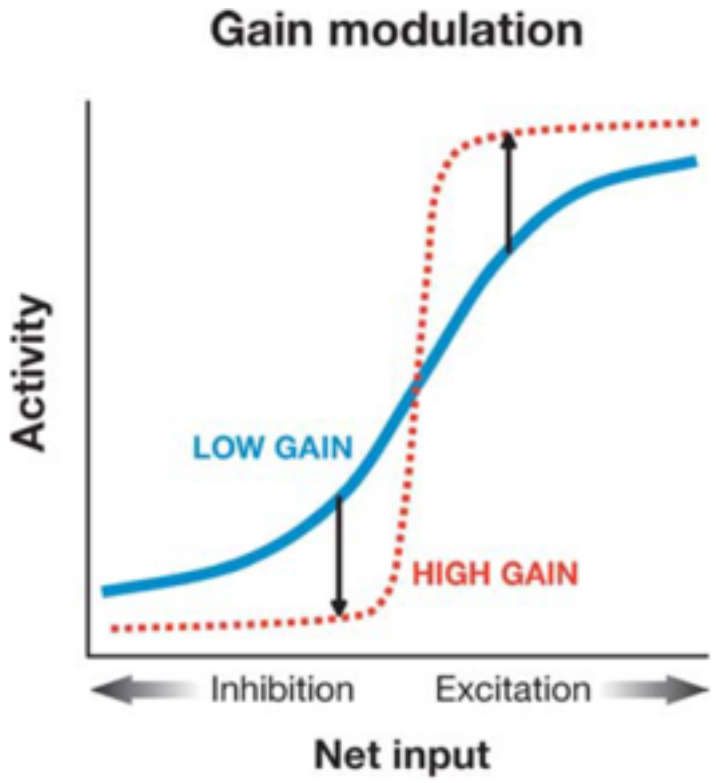
Aston-Jones & Cohen, *Annu Rev Neurosci*, 2005

II. Some biology

Physiology

Two modes of firing:

- **Tonic:** baseline mean firing rates of LC neurons
- **Phasic:** transient, synchronized, robust firing of LC neurons
- LC firing has the effect of **gain modulation**

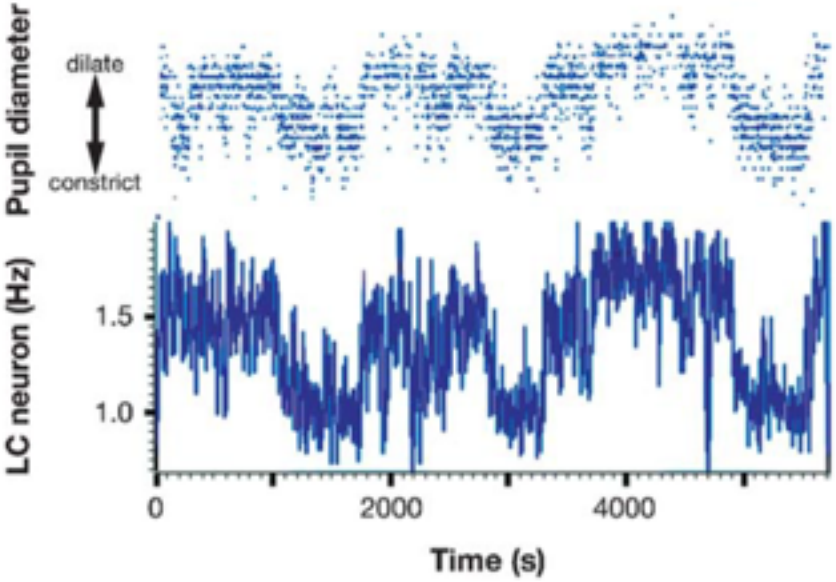


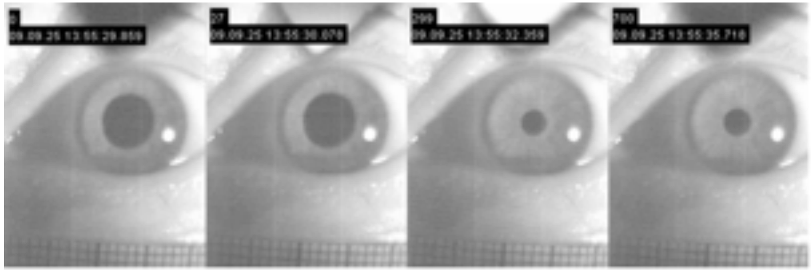
Aston-Jones & Cohen, *Annu Rev Neurosci*, 2005

II. Some biology

LC activity is next to impossible to directly measure in humans

- However, it is closely related to **pupil dilation**, which can be used as a **proxy** measure
- **Pupillometry** can be used to estimate both tonic (baseline) and phasic (transient) firing





Aston-Jones & Cohen, *Annu Rev Neurosci*, 2005
Gilzenrat et al., *Cogn Affect Behav Neurosci*, 2010

II. Some biology

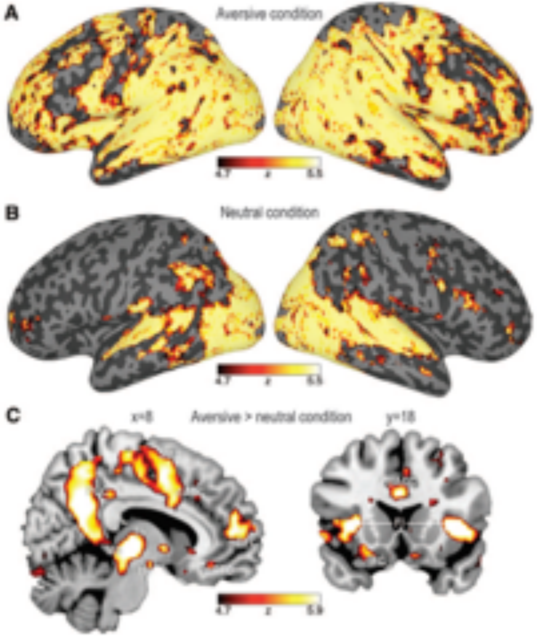
The classic role of NE and (peripheral) epinephrine is **arousal** and **stress**

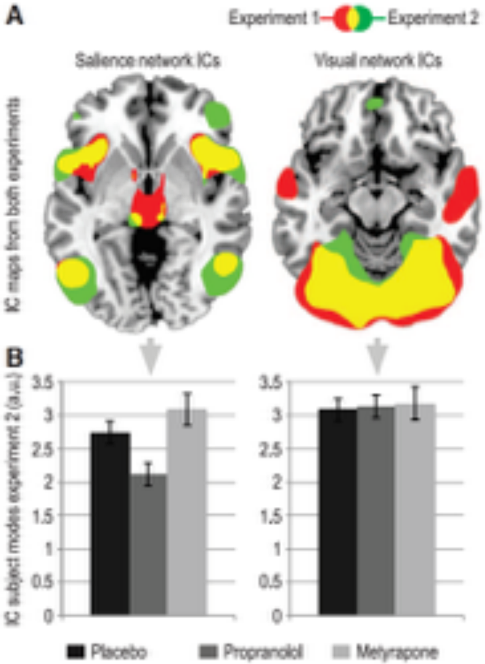
- Dense reciprocal connectivity of LC with the amygdala (fear response)
- Strong connectivity of LC with hypothalamus — and thus pituitary and adrenal glands (via the **HPA axis**), resulting in rapid release of peripheral epinephrine ("adrenaline rush")

II. Some biology

Aversive video viewing results in robust BOLD activation of the **salience network**

- This is **NE-dependent** (blocked by propranolol)





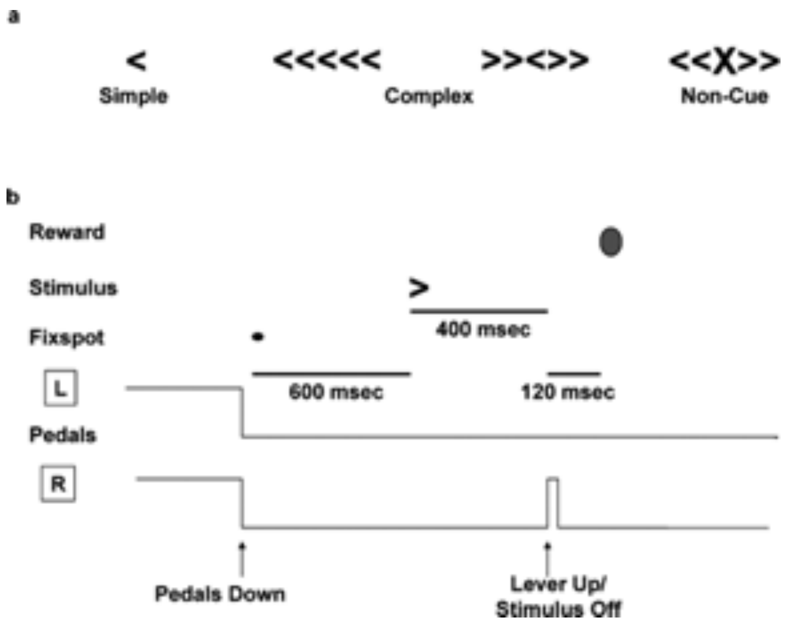
Hermans et al., *Science*, 2011

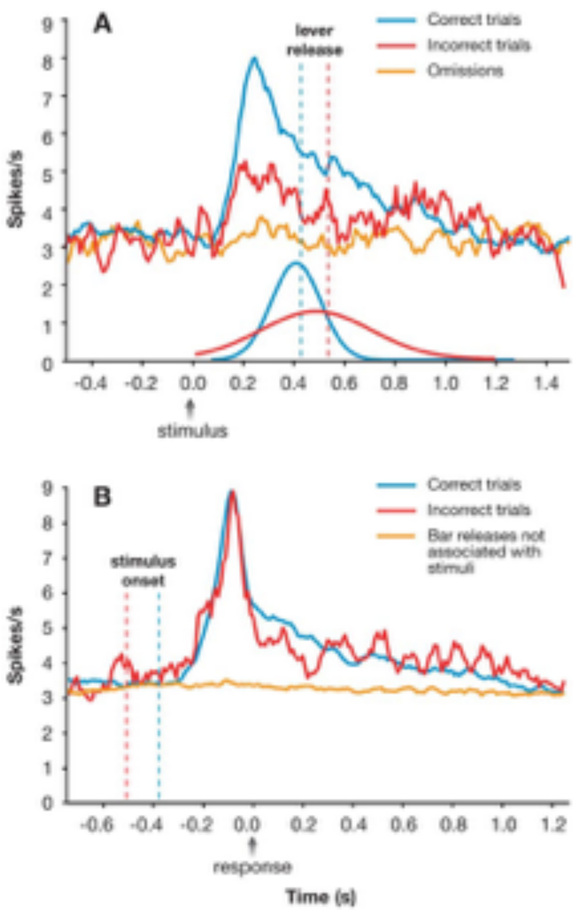
II. Summary

- Norephinephrine is synthesized directly from **dopamine**; this biochemical similarity reinforces the idea that they are functionally closely related
- Most NE neurons are located in the **locus coeruleus (LC)**, which has **diffuse connectivity** both in descending (brainstem, spinal cord) and ascending (neocortex, thalamus, amygdala, hippocampus, cerebellum) directions
- LC firing has **tonic** and **phasic** modes; these have an inverted-U relationship. *Hypotheses*: the tonic mode is more closely related to **exploration**; the phasic mode is more closely related to **exploitation**
- Robust NE release is associated with **arousal** and the **stress response**; in human fMRI, this preferentially activates the **salience network**

III. Some cognitive neuroscience

Decision making — (monkey) two-alternative forced choice task

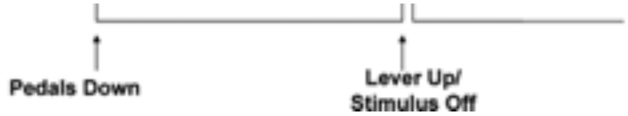




Aston-Jones & Cohen, *Annu Rev Neurosci*, 2005
Clayton et al., J Neurosci, 2004

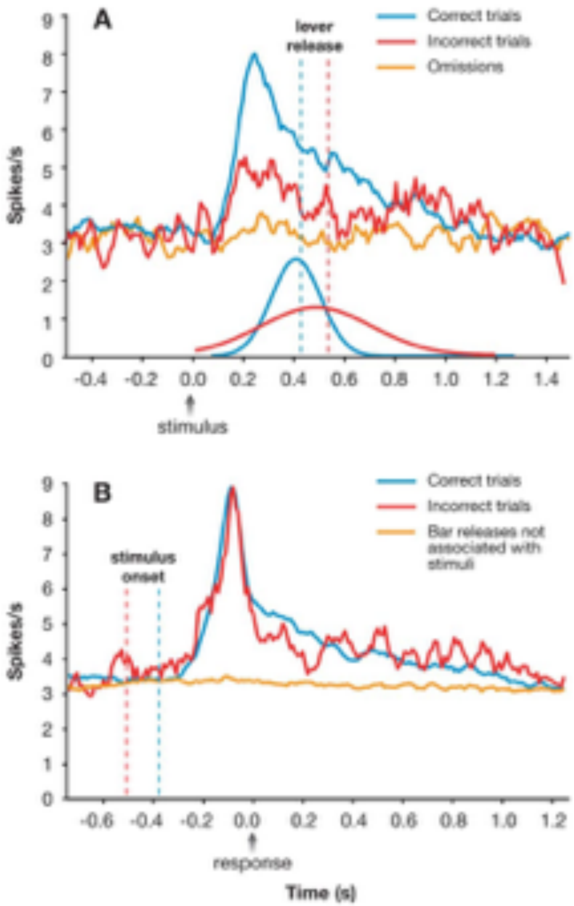
III. Some cognitive neuroscience

Decision making — (monkey) two-alternative forced choice task



Synchronous (phasic) LC firing

- Time-locked to **stimulus** (cue) for correct, but **not** incorrect trials
- Time-locked to **response** (lever release) for **both** correct and incorrect trials
- Suggests LC phasic response **executes** a decision (which has already been made by higher-level areas such as OFC and ACC)



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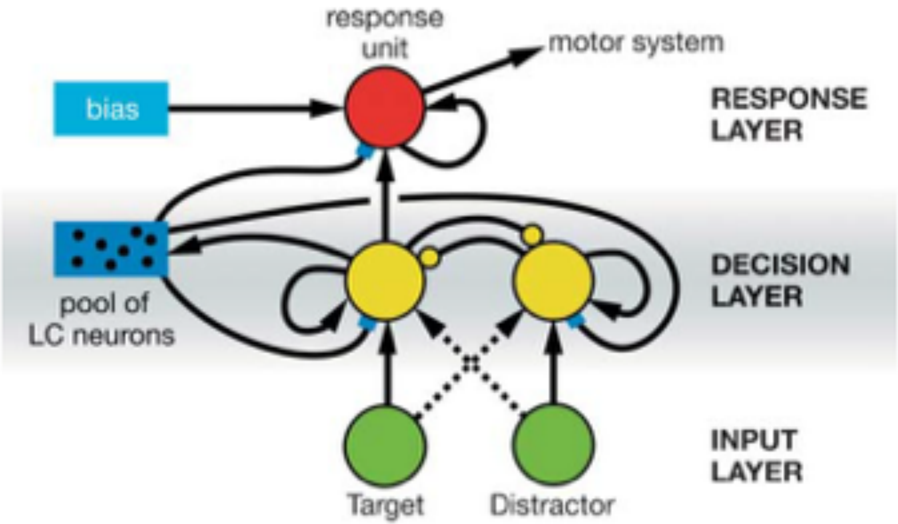
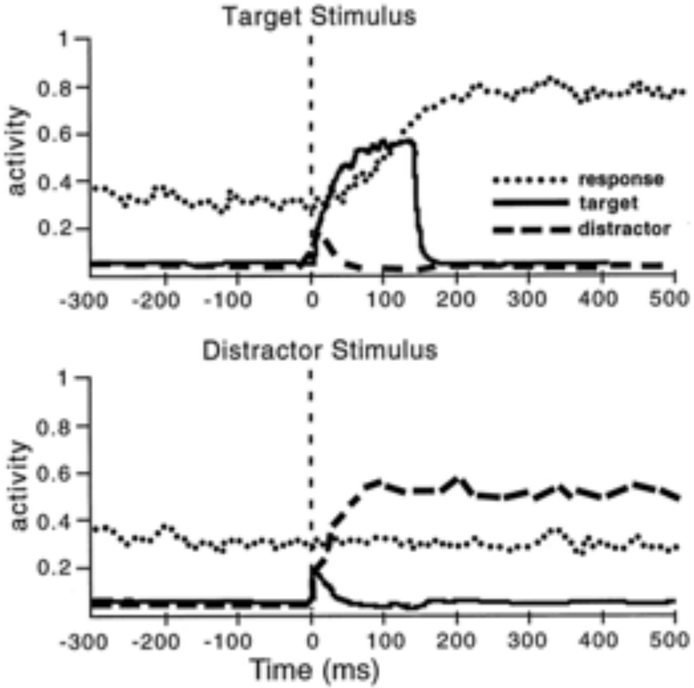
Clayton et al., J Neurosci, 2004

III. Some cognitive neuroscience

Decision making — mutual inhibition model

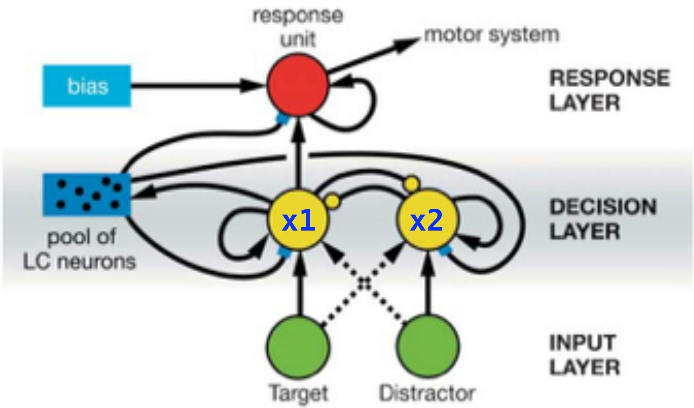




Usher et al., *Science*, 1999

III. Some cognitive neuroscience

Decision making — mutual inhibition model



Target:

$$dx_1 = [-\gamma x_1 - f(\beta x_2) + f(\mu_1)]dt + f(\sigma)dW_1$$

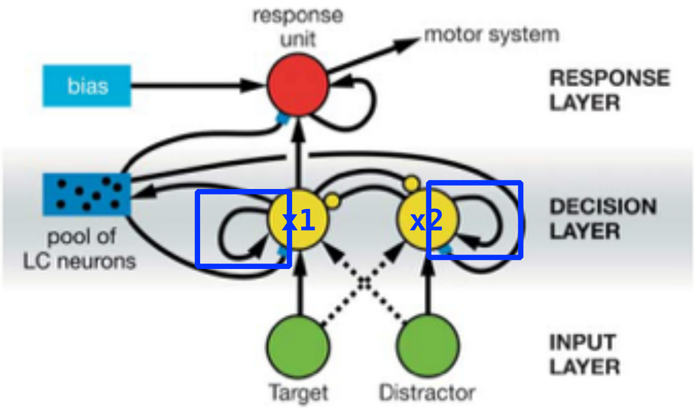
Distractor:

$$dx_2 = [-\gamma x_2 - f(\beta x_1) + f(\mu_2)]dt + f(\sigma)dW_2$$

Usher et al., *Science*, 1999
Holmes & Cohen, *Topics Cog Sci*, 2014

III. Some cognitive neuroscience

Decision making — mutual inhibition model



Firing rate decays with rate γ

$$dx_1 = [\boxed{-\gamma x_1} - f(\beta x_2) + f(\mu_1)]dt + f(\sigma)dW_1$$

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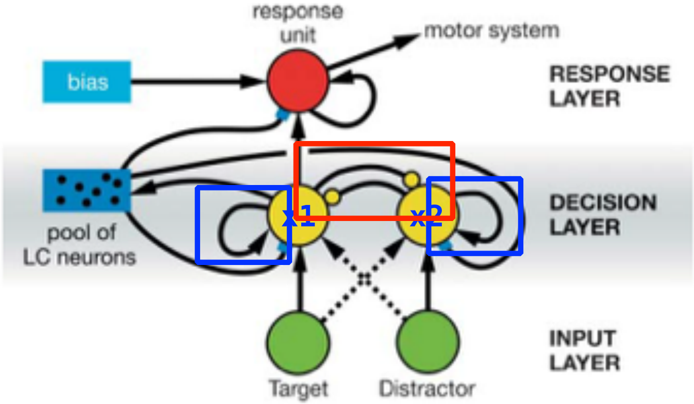
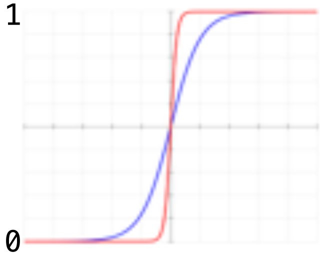
Usher et al., *Science*, 1999
Holmes & Cohen, *Topics Cog Sci*, 2014

III. Some cognitive neuroscience

Decision making — mutual inhibition model



$$f(x) = \frac{1}{1+\exp[-g(x-b)]}$$



f(•) is a sigmoid function

Firing rate decays with rate γ

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Lateral inhibition with weight β

Usher et al., *Science*, 1999
Holmes & Cohen, *Topics Cog Sci*, 2014

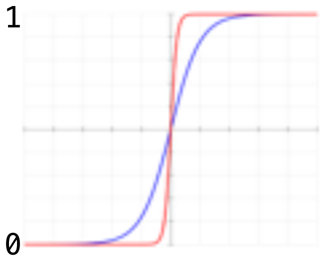
III. Some cognitive neuroscience

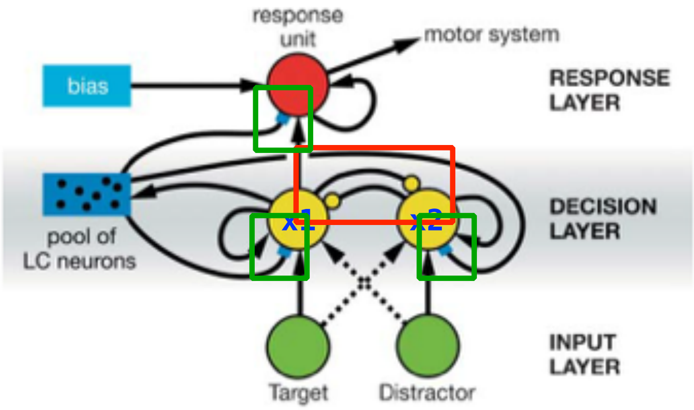
Decision making — mutual inhibition model

g is the gain

$$f(x) = \frac{1}{1 + \exp[\boxed{-g(x-b)}]}$$

f(•) is a sigmoid function





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III. Some cognitive neuroscience

Decision making — mutual inhibition model

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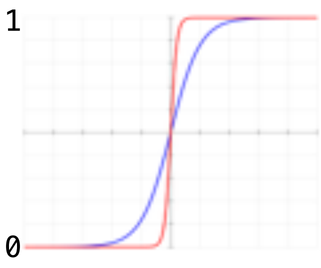

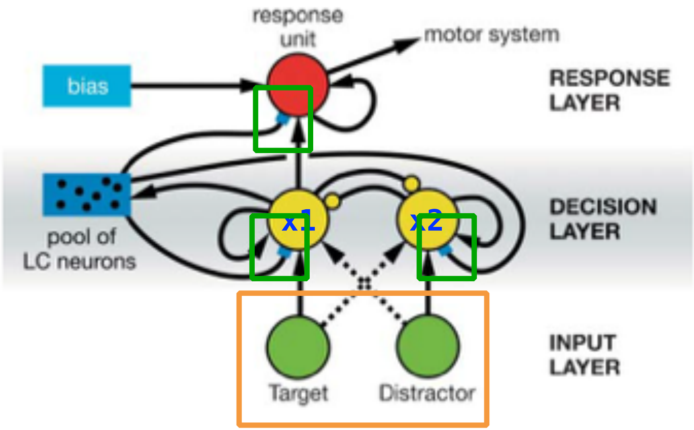

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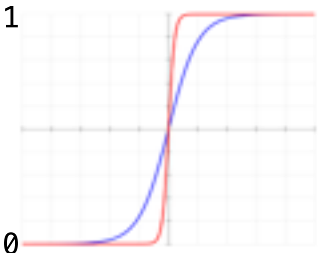
Mean input μ

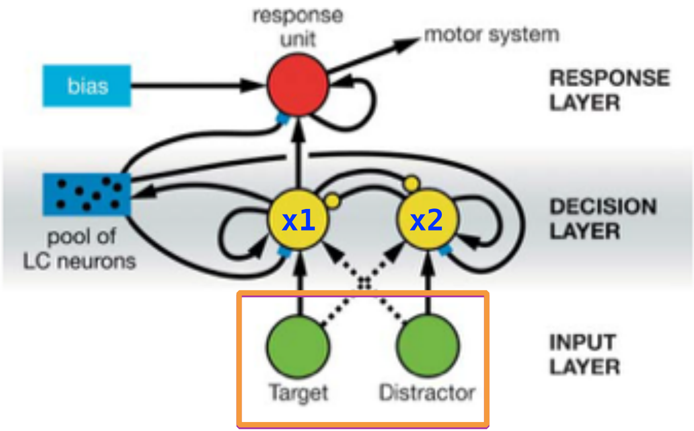
Usher et al., *Science*, 1999
Holmes & Cohen, *Topics Cog Sci*, 2014

III. Some cognitive neuroscience

Decision making — mutual inhibition model

$$f(x) = \frac{1}{1 + \exp[-g(x-b)]}$$





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Mean input μ

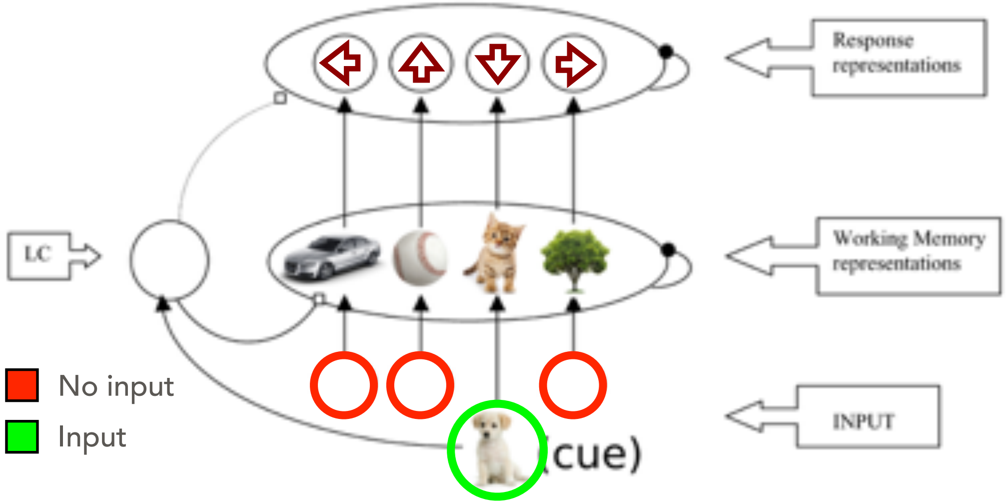
Input noise with magnitude σ

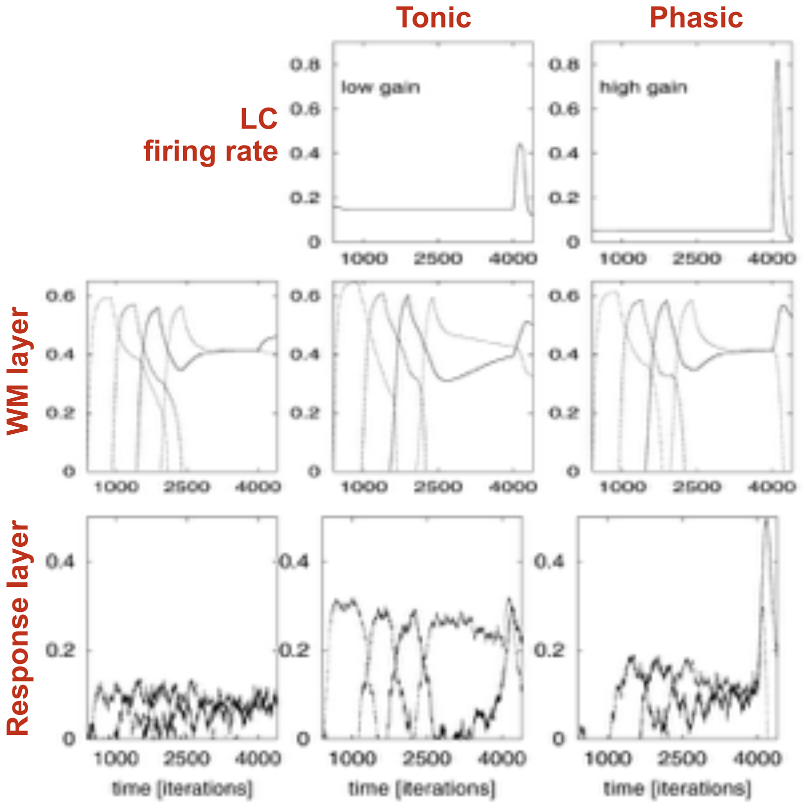
Usher et al., *Science*, 1999
Holmes & Cohen, *Topics Cog Sci*, 2014

III. Some cognitive neuroscience

Working memory — semantic cued recall

- Similar to mutual inhibition model, multiple units
- WM units have **recurrence** - sustained activity



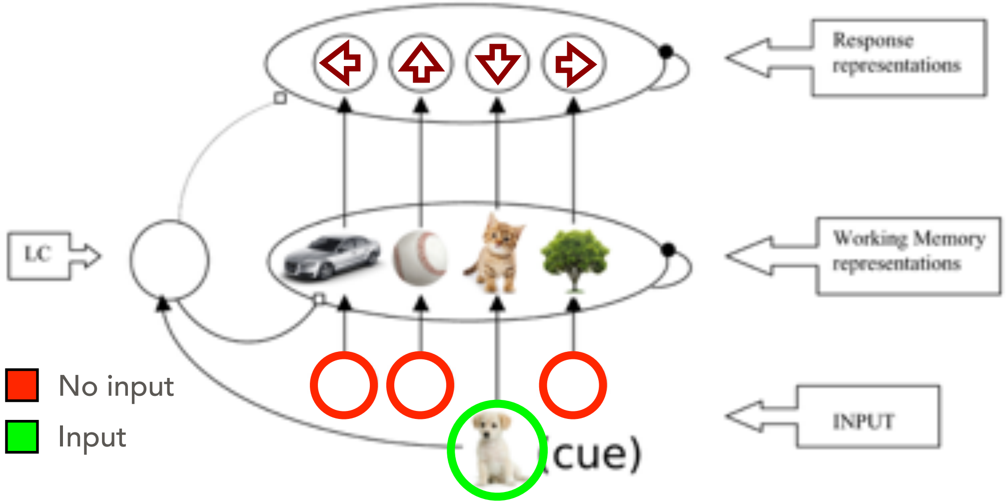


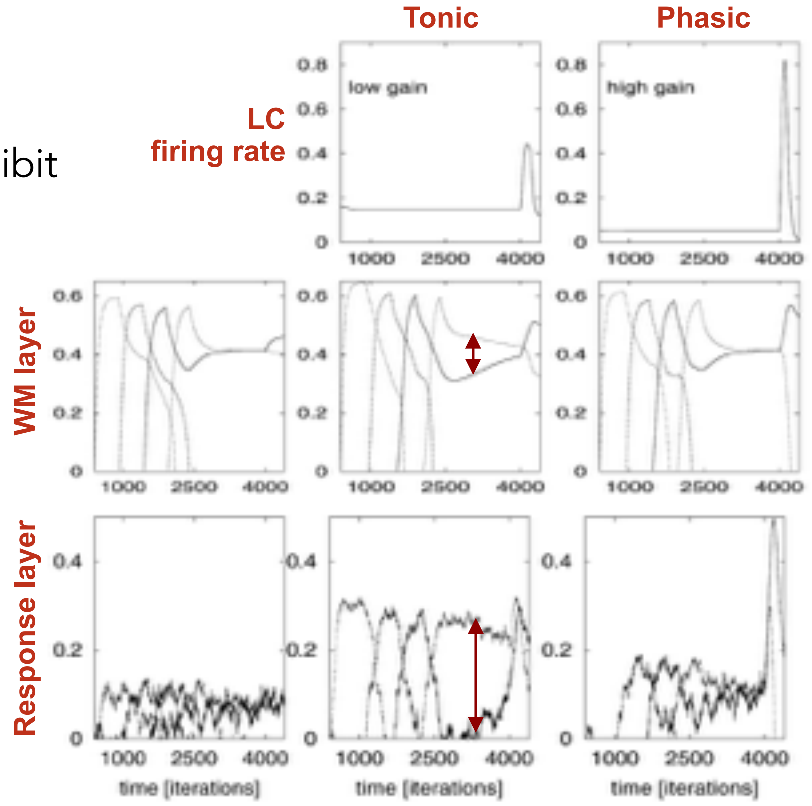
Usher & Davelaar, *Neural Networks*, 2002

III. Some cognitive neuroscience

Working memory — semantic cued recall

- LC neuromodulation can facilitate (phasic) or inhibit (tonic) task performance





Usher & Davelaar, *Neural Networks*, 2002

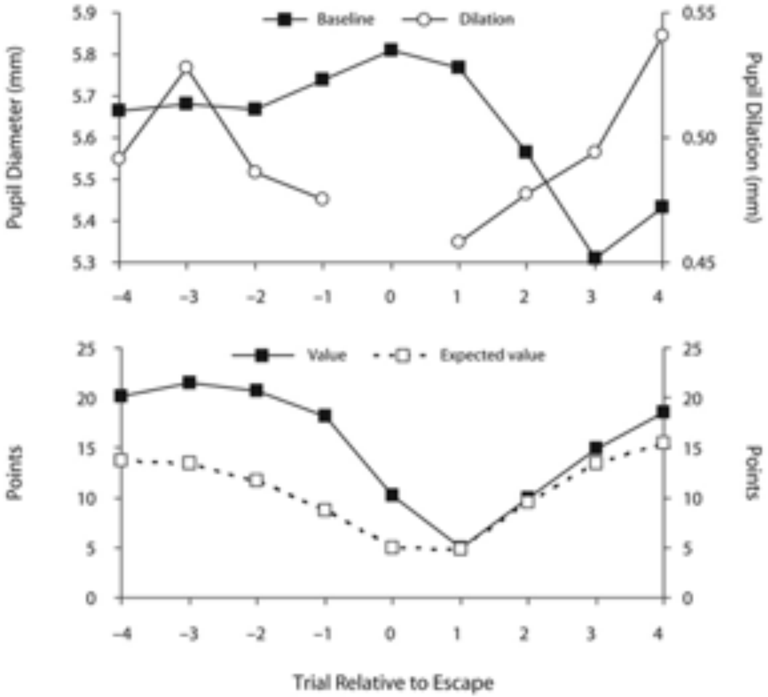

12
11
1
10
2
TIME
KORTE PAUZE?

III. Some cognitive neuroscience

Utility — (human) auditory discrimination task

Pitch discrimination task

- Increasing difficulty with increasing reward
- Utility ∝ reward - difficulty
- "Escape" option where subject can choose to restart at low difficulty/reward
- Tonic (baseline) NE appears to increase as **short-term** utility decreases
- Phasic NE (dilation) appears to decrease as expected **long-term** utility decreases

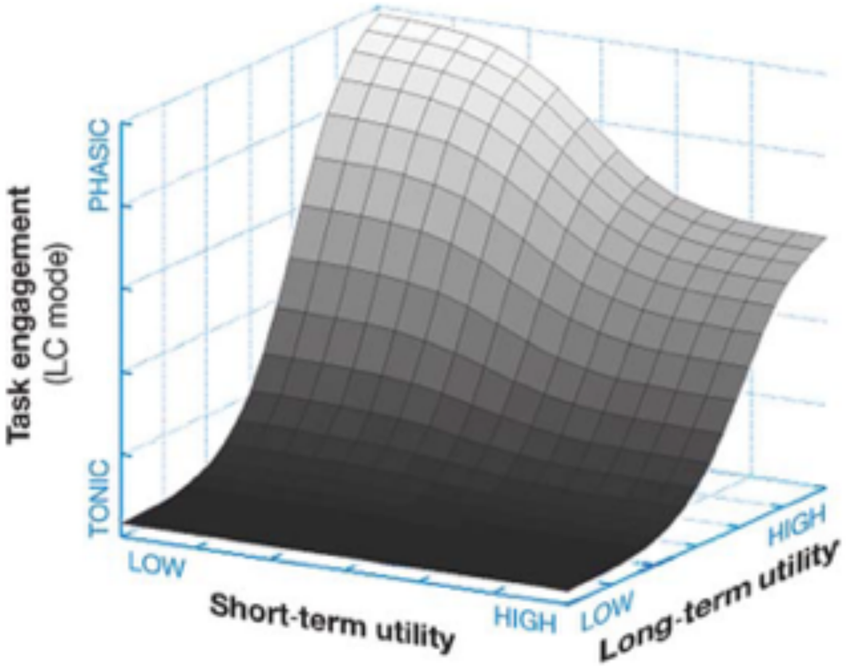


Gilzenrat et al., *Cogn Affect Behav Neurosci*, 2010

III. Some cognitive neuroscience

Utility — theoretical relationships

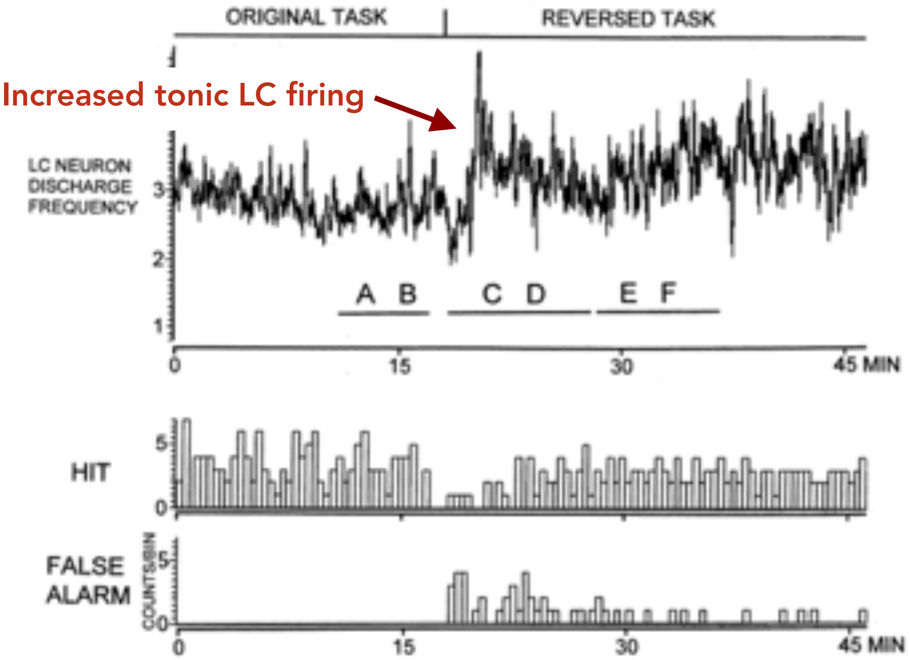
- While long-term (expected) utility is high, poor short-term utility (e.g., performance errors) is compensated by larger **phasic** NE on subsequent trials
- If expected long-term utility decreases (e.g., with the observation of repeatedly poor outcomes), so will the phasic response; the LC will shift towards a **tonic** firing mode

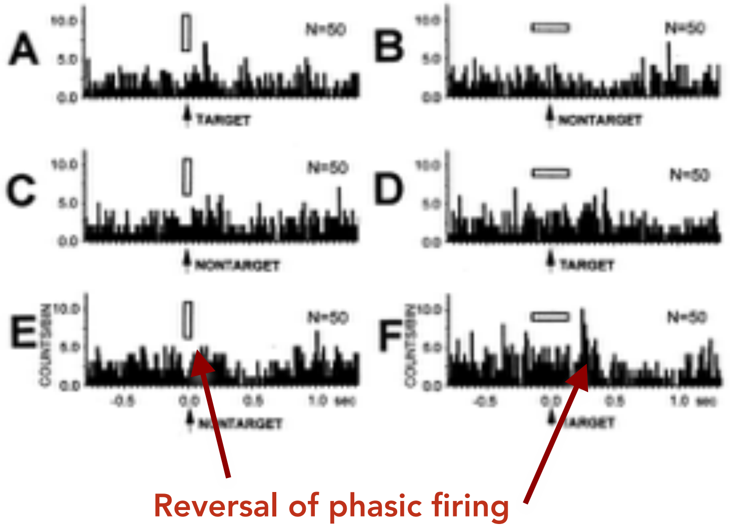


Aston-Jones & Cohen, *Annu Rev Neurosci*, 2005

III. Some cognitive neuroscience

Adaptation — (monkey) two-alternative forced choice with cue reversal



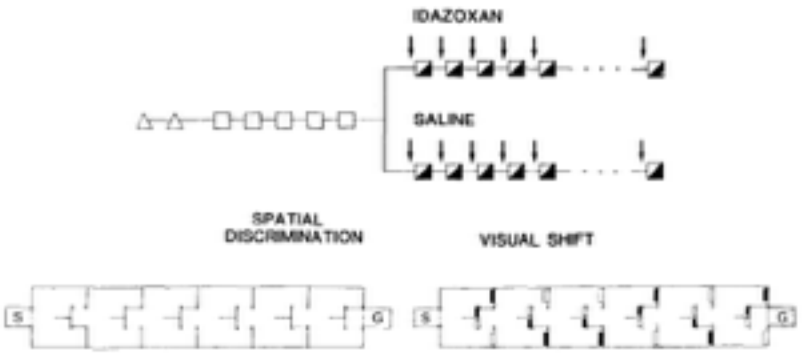


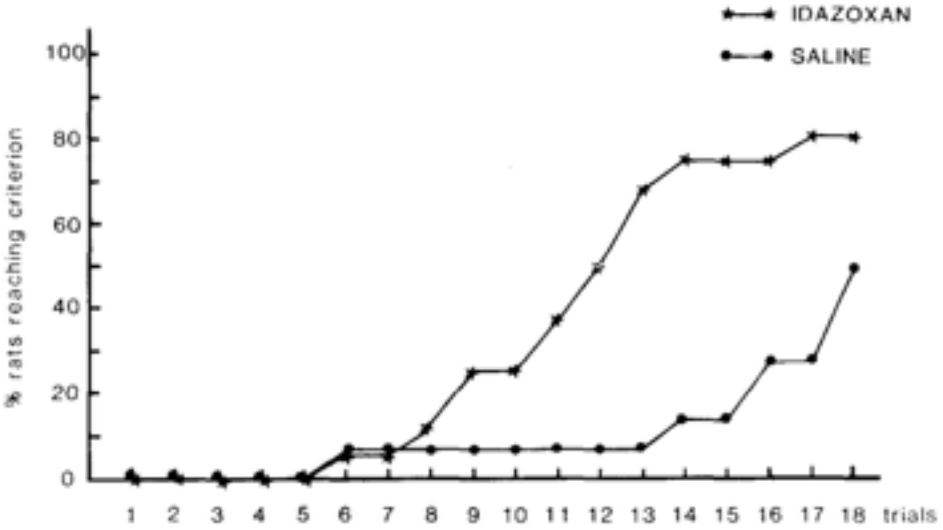
Aston-Jones et al., *Neuroscience*, 1997

III. Some cognitive neuroscience

Adaptation — (rat) sequential decision task with cue change

Idazoxan: boosts tonic NE*





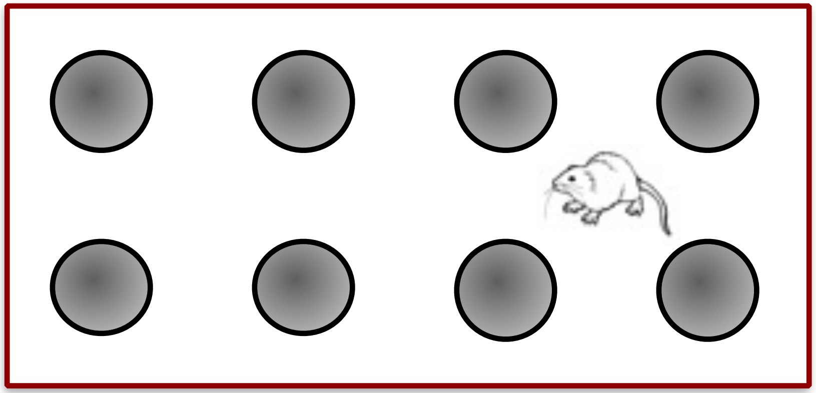
* Not super selective; likely also has effects on DA and 5-HT

Devauges & Sara, *Behav Brain Res*, 1990

III. Some cognitive neuroscience

Novelty — (rat) novel hole-board exploration

- Rats were placed in a "hole-board" apparatus
- Day 1/2: holes contained no objects

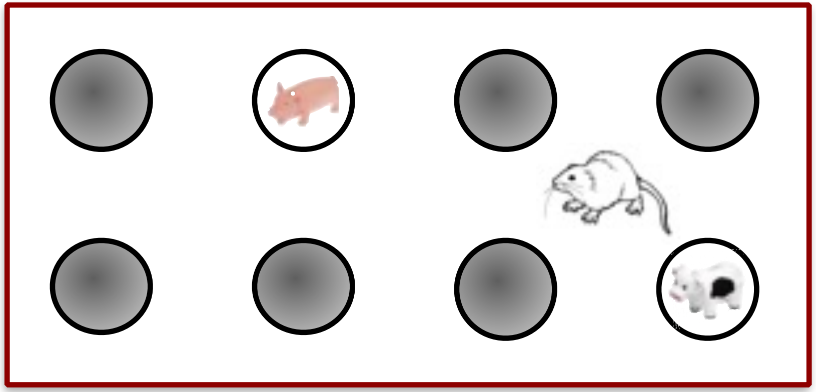


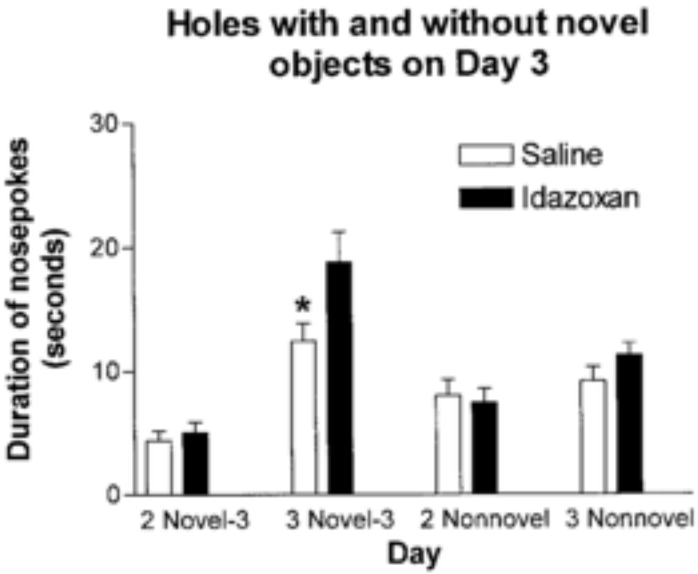
Mansour et al., *Behav Neurosci*, 2002

III. Some cognitive neuroscience

Novelty — (rat) novel hole-board exploration

- Rats were placed in a "hole-board" apparatus
- Day 1/2: holes contained no objects
- Day 3: some holes contained (novel) objects



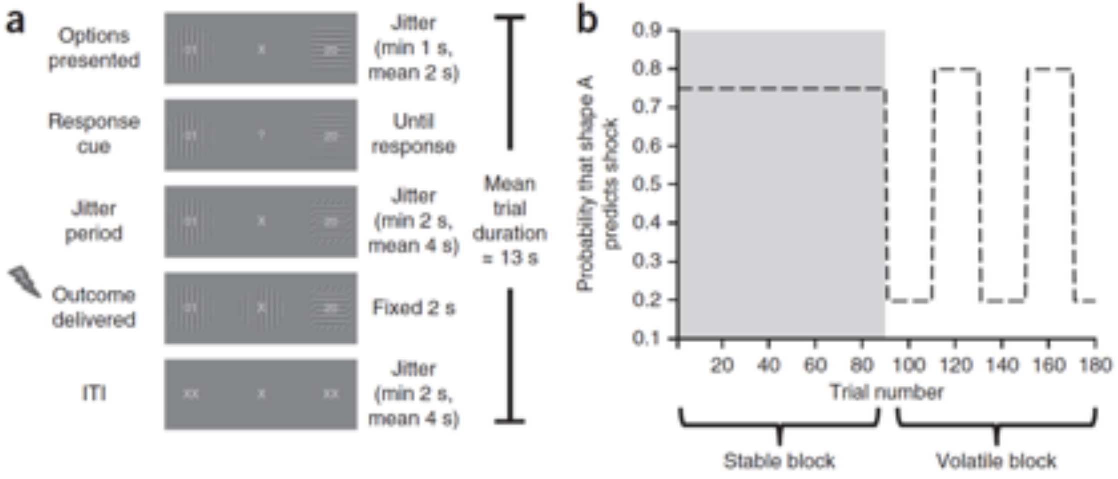


Mansour et al., *Behav Neurosci*, 2002

III. Some cognitive neuroscience

Reinforcement learning — volatility

- Stable block (stable statistics over 90 trials)
- Volatility block (changing statistics every 20 trials)



Browning et al, *Nat Neuro*, 2015

III. Some cognitive neuroscience

Reinforcement learning — volatility

- Responses fit to **Rescorla-Wagner** learning rule:

$$r_{(i+1)} = r_{(i)} + \alpha\varepsilon_{(i)}$$

- *r*(*i*+1) is the expected next reward (or punishment!)
- *r*(*i*) is the expected current reward
- α is the **learning rate** (likely a NE signal)
- ε(*i*) is the **prediction error** (likely a DA signal)

Browning et al, *Nat Neuro*, 2015

III. Some cognitive neuroscience

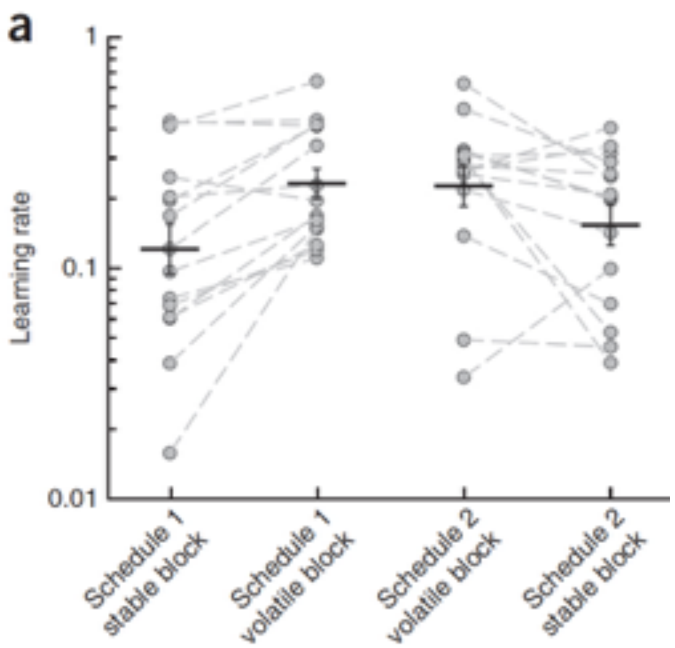
Reinforcement learning — volatility

- Responses fit to **Rescorla-Wagner** learning rule:

$$r_{(i+1)} = r_{(i)} + \alpha\varepsilon_{(i)}$$

- *r*(*i*+1) is the expected outcome probability at *t*=*i*+1
- *r*(*i*) is the expected outcome probability at *t*=*i*
- α is the **learning rate** (likely a NE signal)
- ε(*i*) is the **prediction error** (likely a DA signal)

- Learning rate α was generally **increased** for the volatile block

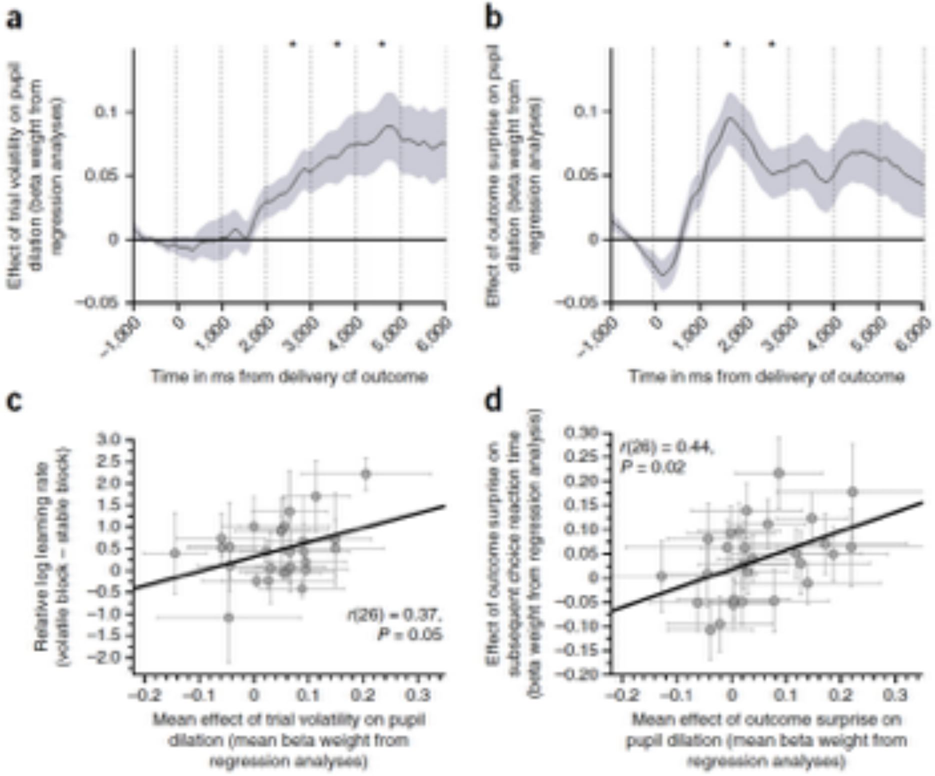


Browning et al, *Nat Neuro*, 2015

III. Some cognitive neuroscience

Reinforcement learning — volatility

- **Increased phasic** pupil response for higher volatility & surprise
- Phasic pupil response related to the **learning rate**
- Phasic pupil response related to **surprise** reaction time
- **Decreased tonic** response

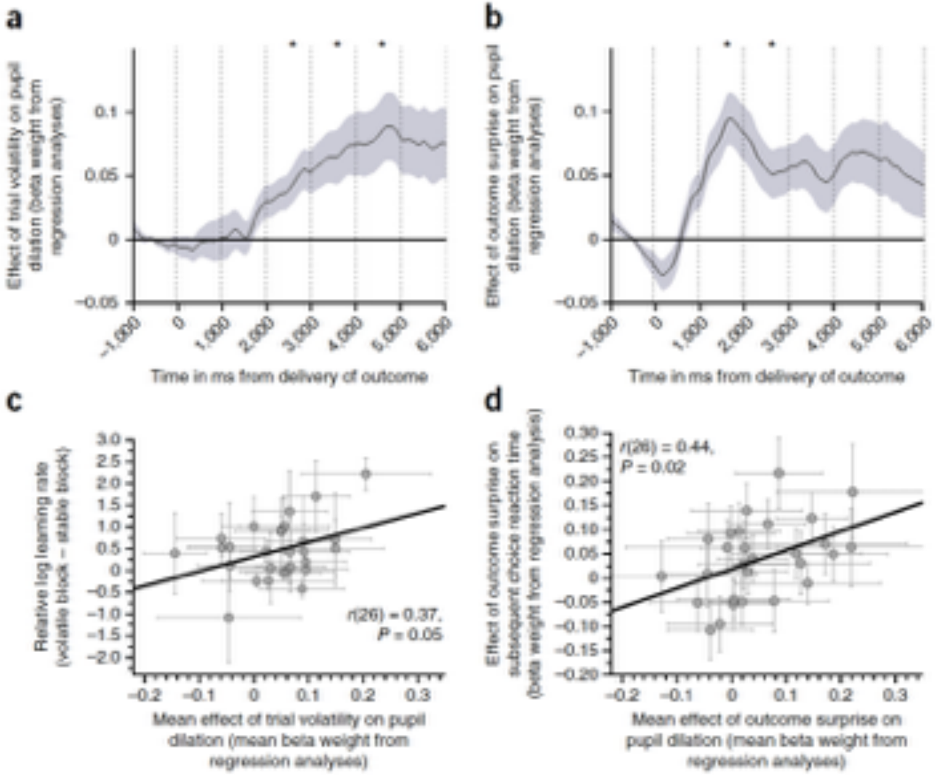


Browning et al, *Nat Neuro*, 2015

III. Some cognitive neuroscience

Reinforcement learning — volatility

- Increased phasic pupil response for higher volatility & surprise
- Phasic pupil response related to the learning rate
- Phasic pupil response related to surprise reaction time
- Decreased tonic response
- **Wait, what!?!**



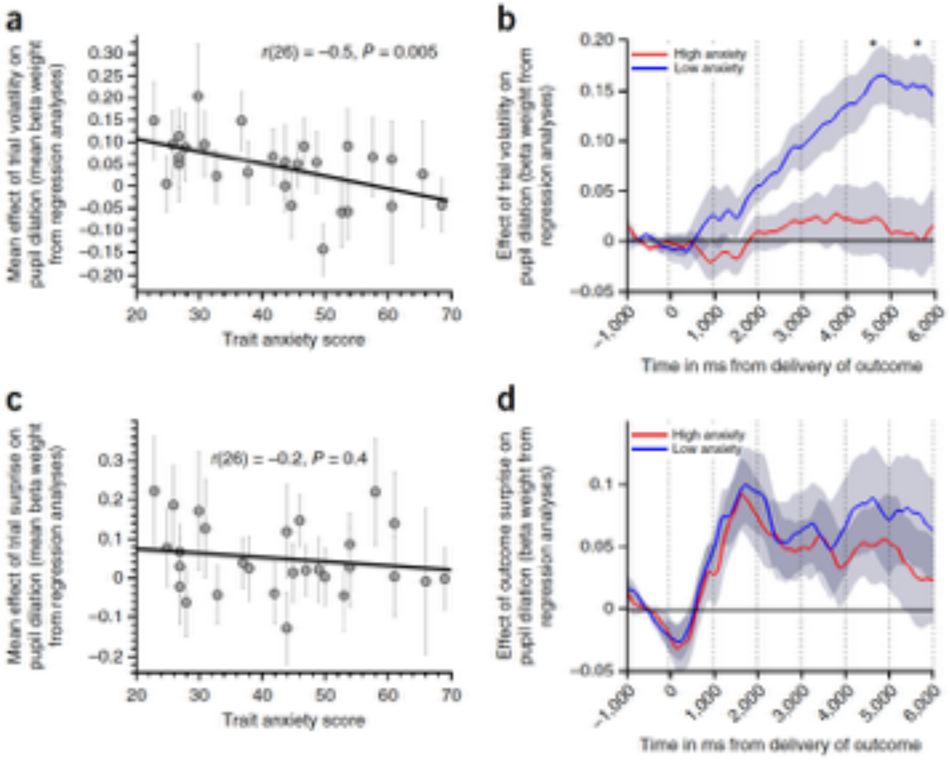
Browning et al, *Nat Neuro*, 2015

III. Some cognitive neuroscience

Reinforcement learning — volatility

- Individuals with high **trait anxiety** do not show this relationship between phasic pupil response and volatility
- Higher anxiety predicts lower effect
- Effect still there for surprise

- Suggests **heritable** differences in individual NE responses to volatility

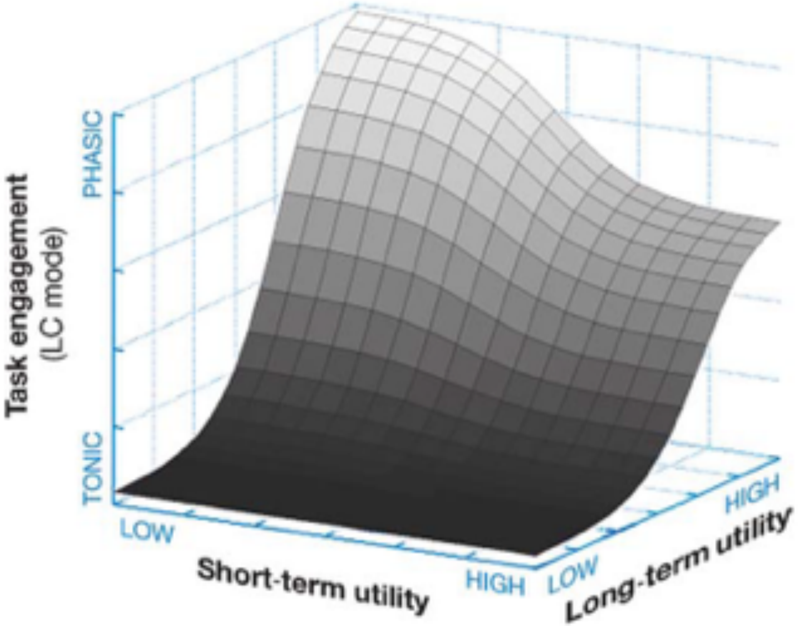


Browning et al, *Nat Neuro*, 2015

III. Some cognitive neuroscience

Reinforcement learning — volatility

Q: *Why don't we see increased tonic pupil diameter in the volatile condition?*



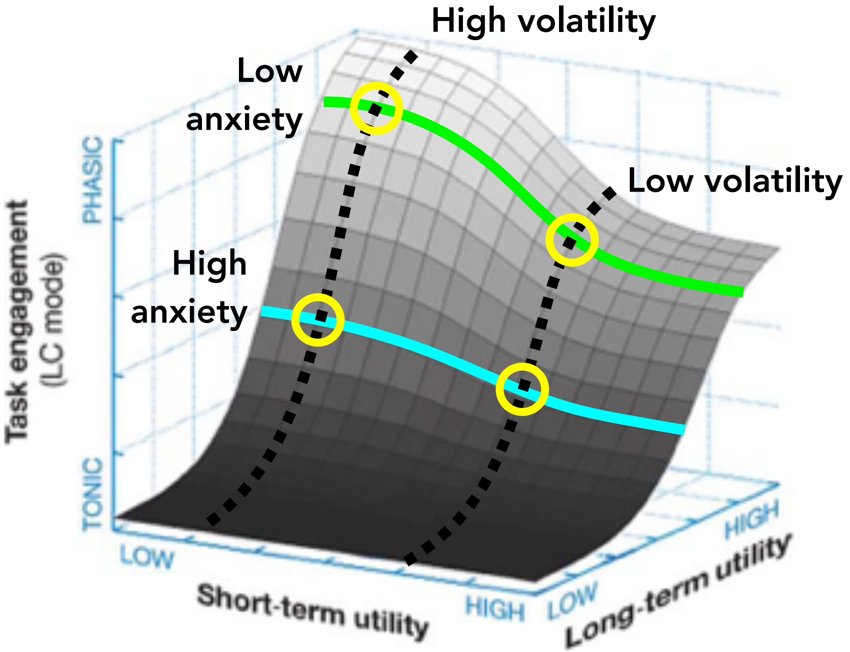
Browning et al, *Nat Neuro*, 2015

III. Some cognitive neuroscience

Reinforcement learning — volatility

Q: *Why don't we see increased tonic pupil diameter in the volatile condition?*

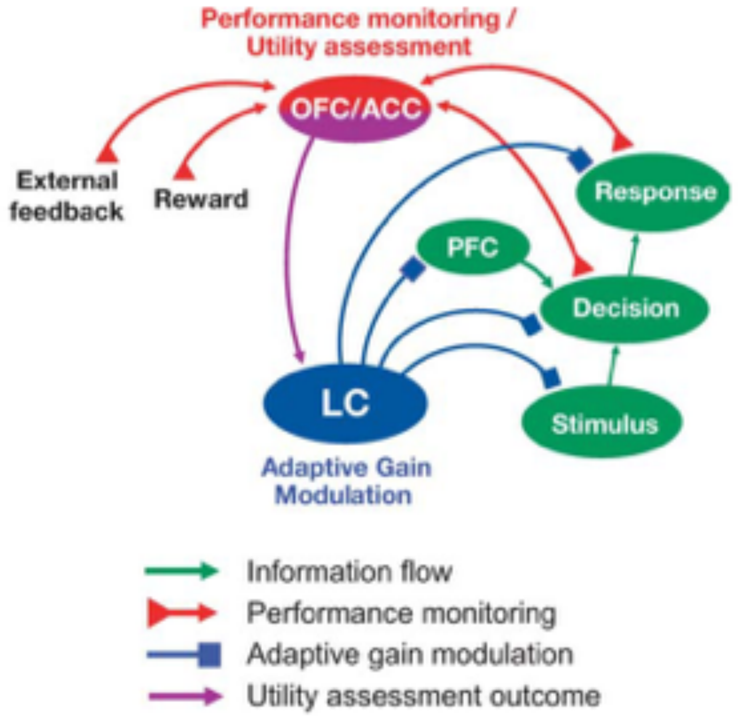
- **Aversive** learning, rather than reward?
- Decreased **short-term** utility, intact **long-term** utility?
- This could explain lack of significant phasic effect for high anxiety group (anxiety may translate to a more pessimistic long-term outlook)

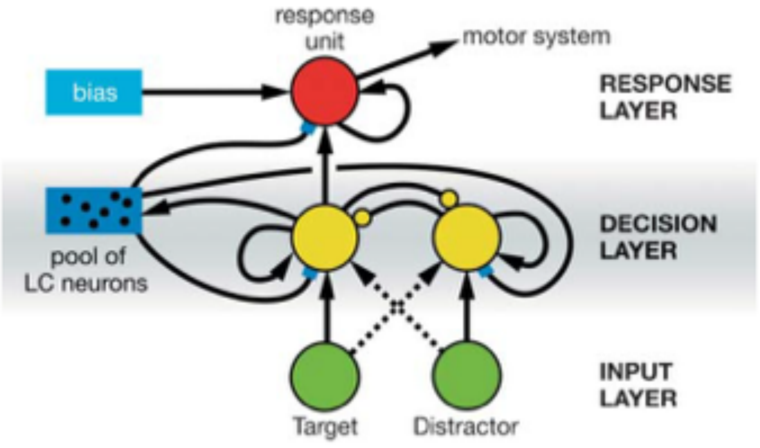


Browning et al, *Nat Neuro*, 2015

III. Some cognitive neuroscience

A systems-level model of NE function — adaptive gain theory





Aston-Jones & Cohen, *Annu Rev Neurosci*, 2005

III. Summary

- In two-alternative forced choice **decision making** (monkeys), phasic LC firing is more tightly coupled to the response rather than the cue
- Phasic firing is thus likely an "**execute**" signal, based on performance monitoring by higher-level areas (such as ACC and OFC)
- This can be modelled as a **mutual inhibition model**, wherein two competing neural representations are biased by the global LC signal
- This model can be extended to simulate **working memory** tasks
- Phasic LC firing may represent decreases in **short-term utility**, while tonic firing represents decreases in **long-term utility**
- Tonic NE response is also likely important for **adaptation** to changing task contingencies, and **exploration** of novel environmental stimuli

III. Summary

- Finally, in a reinforcement learning framework, the phasic NE response appears to be important for gauging outcome **volatility** (i.e., by increasing transient pupil dilation)
- This result can be explained by considering the differential effects of short- and long-term utility

IV. Some research ideas

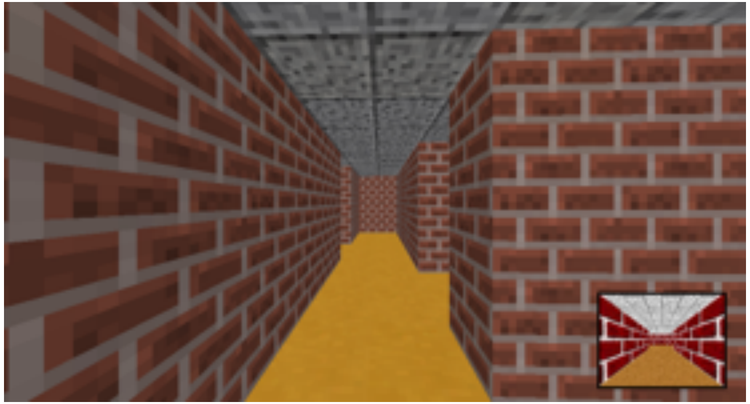
Role in reinforcement learning?

- Include tonic/phasic NE signals as variables in **learning model**
- **Paradigms**?
  - Challenging tasks, feedback (positive/negative/punishment), event-related
  - Examples: Learning the rules of a game, exploring a novel environment, encountering social scenarios, dealing with volatility
- **Measurements**?
  - Pupil diameter, behavioural outcomes, neuroimaging
- **Analysis**?
  - Do reinforcement learning model parameters predict measurements?
  - *What are our hypotheses?*

IV. Some research ideas

Role in reinforcement learning?

- *Example (idea)*: navigating a 3D maze, with hidden rewards/threats, using eye tracking
- Hypotheses?
  - High starting **baseline pupil diameter**, decreasing with experience
  - Low **phasic pupil dilation** at decision points, increasing with experience
  - **Learning rate α** over time corresponds to baseline diameter
  - **Errors ε** correspond to phasic dilation



IV. Some research ideas

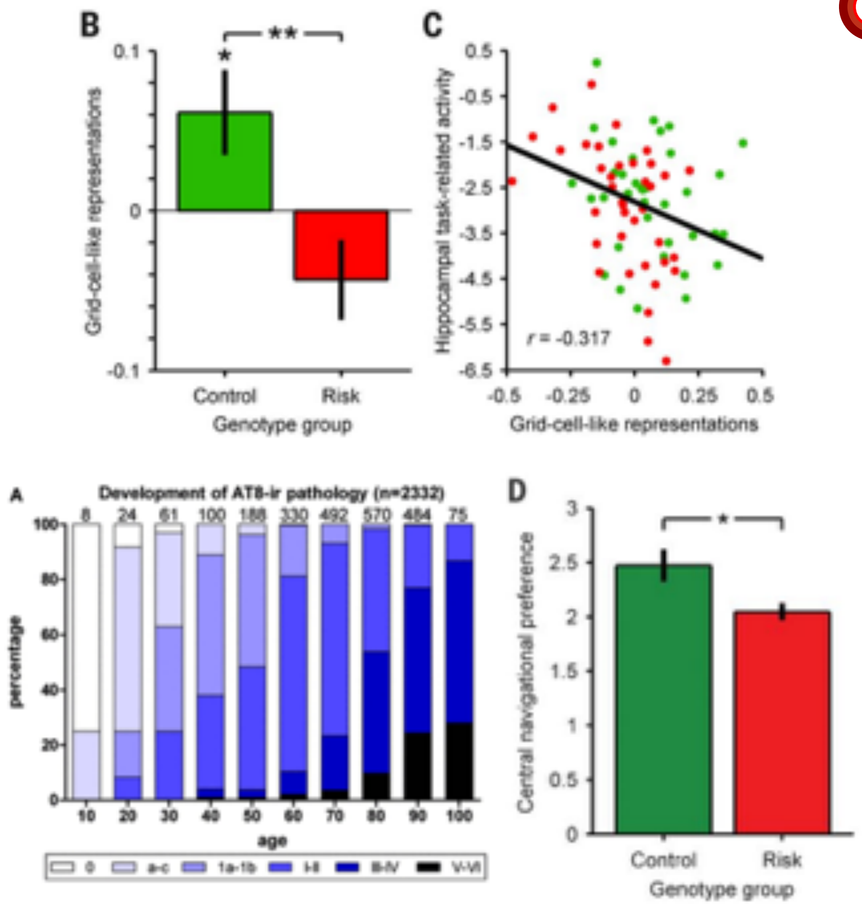
Modelling clinical disorders

- LC/NE implicated in (for example): post-traumatic stress disorder (PTSD), anxiety disorders, attention deficit and hyperactivity disorder (ADHD), Alzheimer's disease
- How does the presence of these disorders (or genetic risk factors) alter cognitive performance (e.g., utility assessment, adaptation, exploration, decision making, working memory)? How is this related to LC function?
- **Measurements**?
  - Disease severity, behavioural performance, pupillometry, neuroimaging
- **Analysis**?
  - Can model parameters predict disease outcomes?
- We saw an example with Browning et al. (anxiety, volatility & pupil diameter)

IV. Some research ideas

Modelling clinical disorders

- *Example*: Alzheimer's disease
- Early, highly prevalent LC-localized AD pathology
- Entorhinal cortex (fMRI) and navigational differences in young adults with AD risk mutations (APOE-ε4)
- Can we find similar differences in NE-related behaviour or LC function (such as pupillometry)?



Kunz et al., *Science*, 2015
Braak et al., *J Neuropathol Exp Neurol*, 2011

IV. Some research ideas

Pharmacological interventions

- How does **selective pharmacological manipulation** of NE receptors affect behavioural performance?
- There are two sub-types and five sub-subtypes of NE receptor (α1,2 and β1,2,3)
- Many agonists and antagonists exist; some prominent ones:
  - Isoproterenol (β1,2 agonist) - main effect, increases NE response
  - Propranolol (β1,2 antagonist) - main effect, reduces NE response
  - Clonidine (α2 agonist) - main effect, *reduces* NE response
  - Idazoxan (α2 antagonist) - main effect, *increases* NE response

IV. Some research ideas

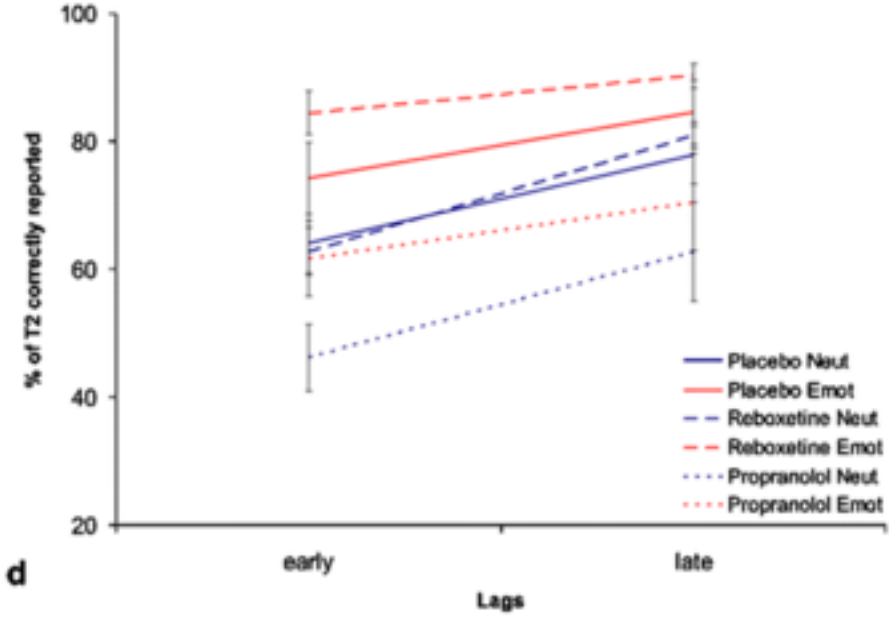
Pharmacological interventions

- Some complications…
  - Most pharmacological agents also have **peripheral** effects and other debilitating **side effects**
  - Some **contradictory** effects; e.g., propranolol reduces β receptor binding, but increases α binding by inhibiting NE reuptake. Likewise, clonidine can both inhibit and enhance NE release due to differential receptor effects
  - **Non-specificity**; e.g., changes to NE pharmacology will have effects on other neurotransmitter systems, especially other neuromodulators such as dopamine and 5-HT; e.g., propranolol is also a likely antagonist of 5-HT receptors, idazoxan is an agonist of DA and 5-HT receptors

IV. Some research ideas

Pharmacological interventions

- *Example 1*: attentional blink
- Propranolol (β1,2 antagonist)
- Reboxetine (NE reuptake inhibitor)
- T2: neutral or emotional

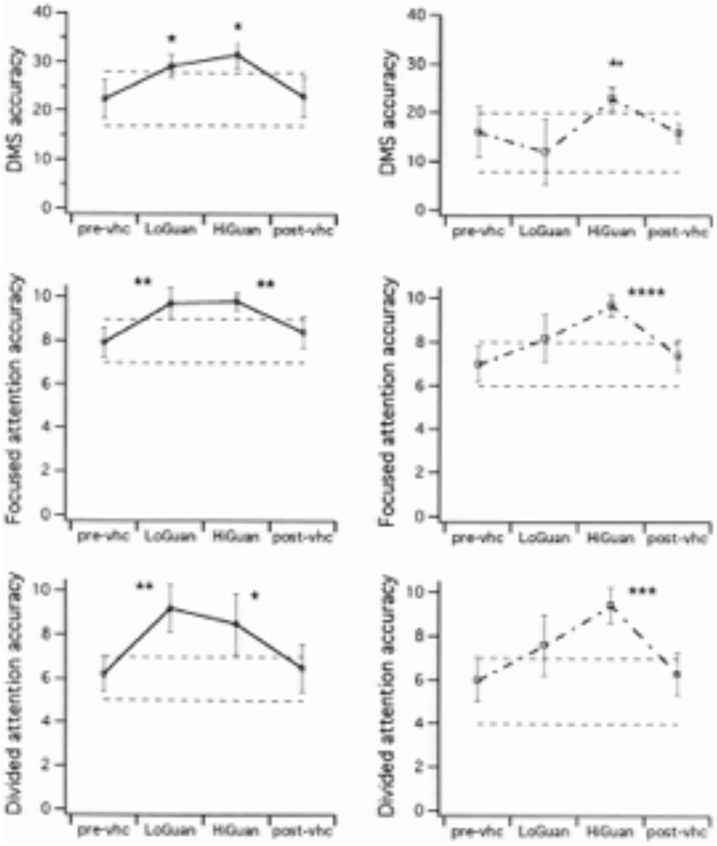


De Martino et al., *Psychopharm*, 2008

IV. Some research ideas

Pharmacological interventions

- *Example 2*: aging macaque monkeys
- Guanfacine administration (α2 agonist)
- **Enhanced attention** and **reduced distractibility**
- DMS = delayed match to sample (working memory task)



O'Neill et al, *Life Sci*, 2000

Wrapping up

- **Optimization** is a universal requirement of adaptive organisms
- In higher order mammals (like us), neuromodulators such as NE are essential for this optimization; in particular, for determining an adaptive balance between **exploratory** and **exploitative** states
- NE has **tonic** and **phasic** firing modes, which have an inverted-U relationship
  - Phasic states correspond to higher attention and better cognitive performance; ideal for a **stationary** environment
  - Tonic states correspond to more vigilance and false alarms; ideal for a **changing** environment

Wrapping up

- In the two-alternative forced choice task, phasic LC firing is more tightly time-locked to the animal's **response**, and likely implements an **execute** signal
- Decision making and working memory tasks can be modelled as a **mutual inhibition network**, with a phasic LC burst acting to bias the competing neural representations towards the current network state
- LC signals may represent both **short-term** and **long-term utility** assessments, boosting subsequent phasic responses for short-term decreases in utility, but shifting towards the tonic mode when long-term utility flags for a given behaviour
- For rats, when task contingencies are **reversed**, LC firing shifts towards tonic mode; while pharmacological boosting of tonic NE enhances both **adaptation** and **exploration** of novel items in familiar environments

Wrapping up

- On the other hand, when task **volatility** is introduced in an aversive paradigm (electrical shock), humans show increased phasic LC firing (measured by transient pupil dilation), rather than a change in tonic response — suggesting a short-term utility assessment
- Future studies might utilize **reinforcement learning** models, **clinical** models, and/or **pharmacological interventions** to better understand the specific role of NE signals in adaptive behaviour

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