



University of  
Zurich<sup>UZH</sup>

# Decomposing salience

Philippe Tobler

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# Aspects of motivated behavior



Direction  
Approach/Avoidance  
Value



Intensity  
Attention  
Salience

# Aberrant salience in psychiatry

1. Variation of a concept from addiction research: incentive/motivational salience (Berridge & Robinson, 1998), building on motivational psychology
2. Originally developed to capture psychosis (Kapur, 2003): dysregulated stimulus-independent dopamine release; not etiological but pathophysiological
3. Salience assignment to irrelevant internal and external stimuli
4. Specification of two aspects of dopamine theory of schizophrenia – psychosis and antipsychotic action

# Antipsychotics and aberrant salience

1. All antipsychotics have some dopamine action
2. They reduce humans' tendency to be distressed by salient percepts/associations and act on them
3. They reduce animals' attempts to avoid a shock-predicting tone and their willingness to work for reward-predictive cues
4. Accordingly, aberrant salience was proposed to have a dopaminergic basis

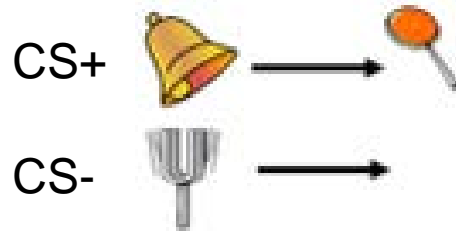
# Decomposing salience

1. Test effect of one antipsychotic on human incentive/motivational salience (behavior only)
2. Define motivational salience and test alternative definitions in the human brain
3. Operationalize stimulus generalization as one form of salience attribution to non-relevant cues and test effects of antipsychotic

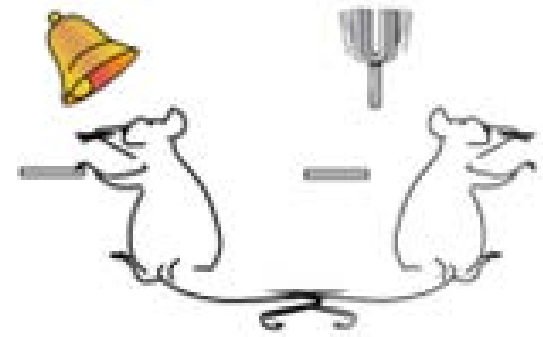
# Testing incentive/motivational salience: Pavlovian to instrumental transfer (PIT)



Instrumental



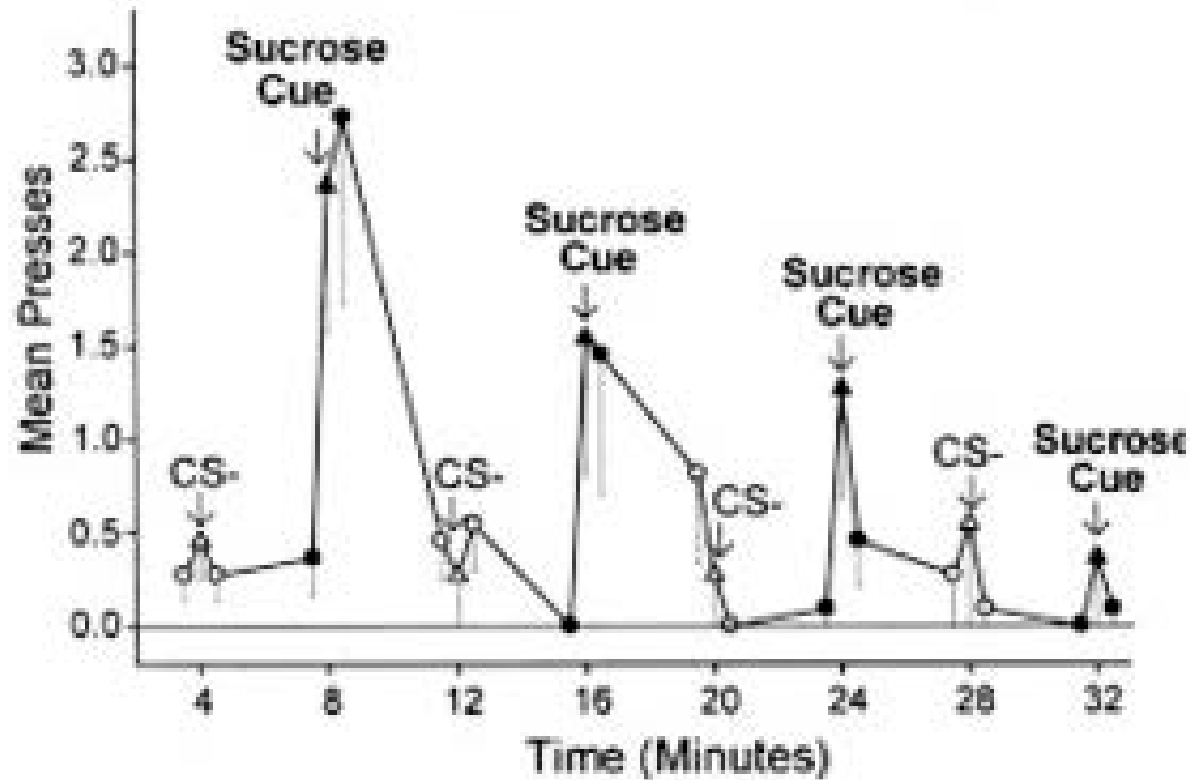
Pavlovian



Transfer test

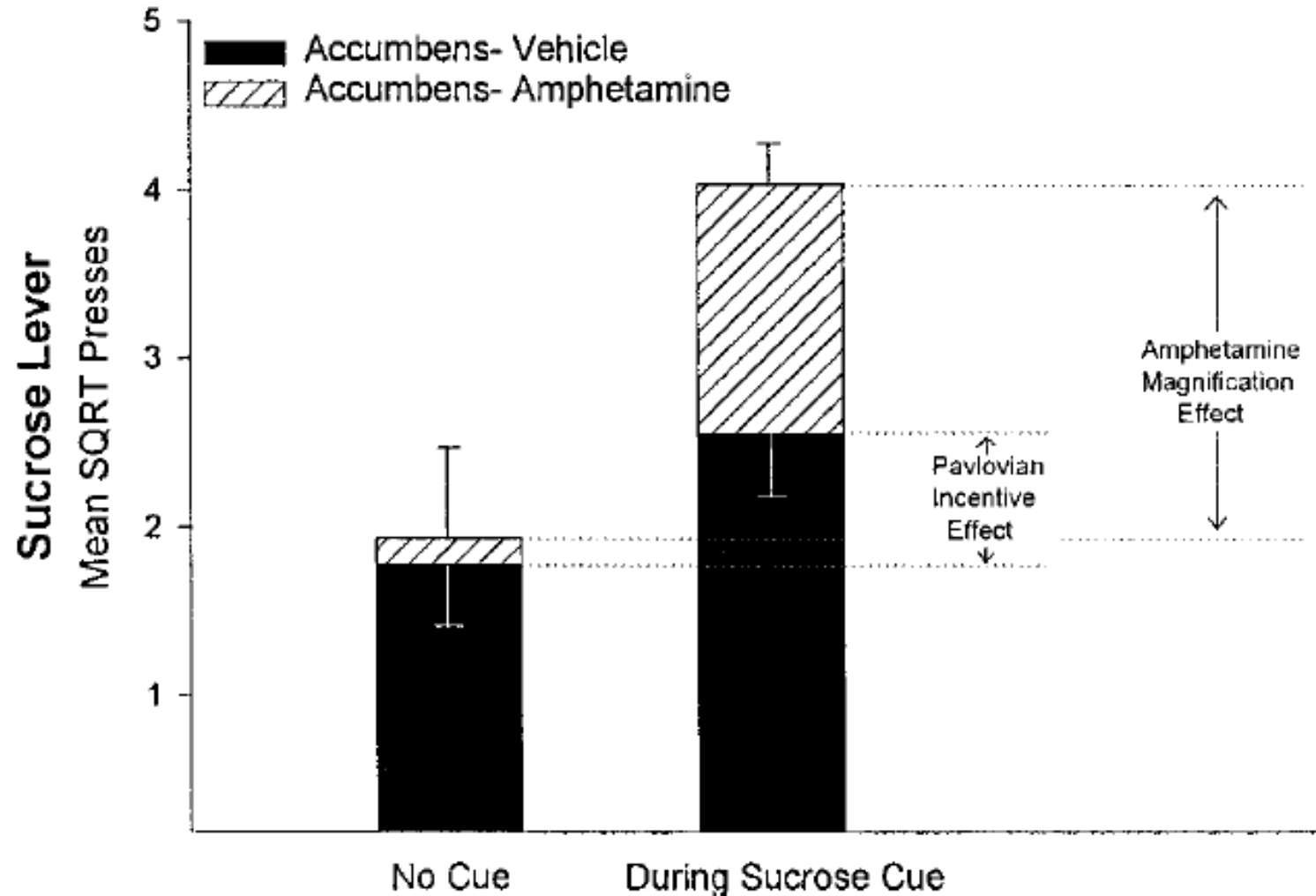
Transfer test occurs in extinction (no rewards)

# PIT measured by increased lever pressing for reward cues in presence of CS+



The increase occurs for the 30s-sucrose cues (CS+) but not for control cues (CS-)

# Amphetamine in the nucleus accumbens enhances PIT



Thus, dopamine may underpin motivational salience



*Does dopamine D2/D3-receptor blockade with amisulpride reduce Pavlovian instrumental transfer in humans?*

# Animal physiology vs. human pharmacology

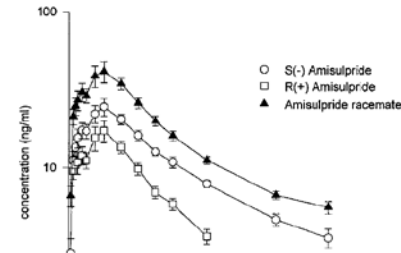
2 ms



Phasic effects

Computational and transmission  
functions of dopamine

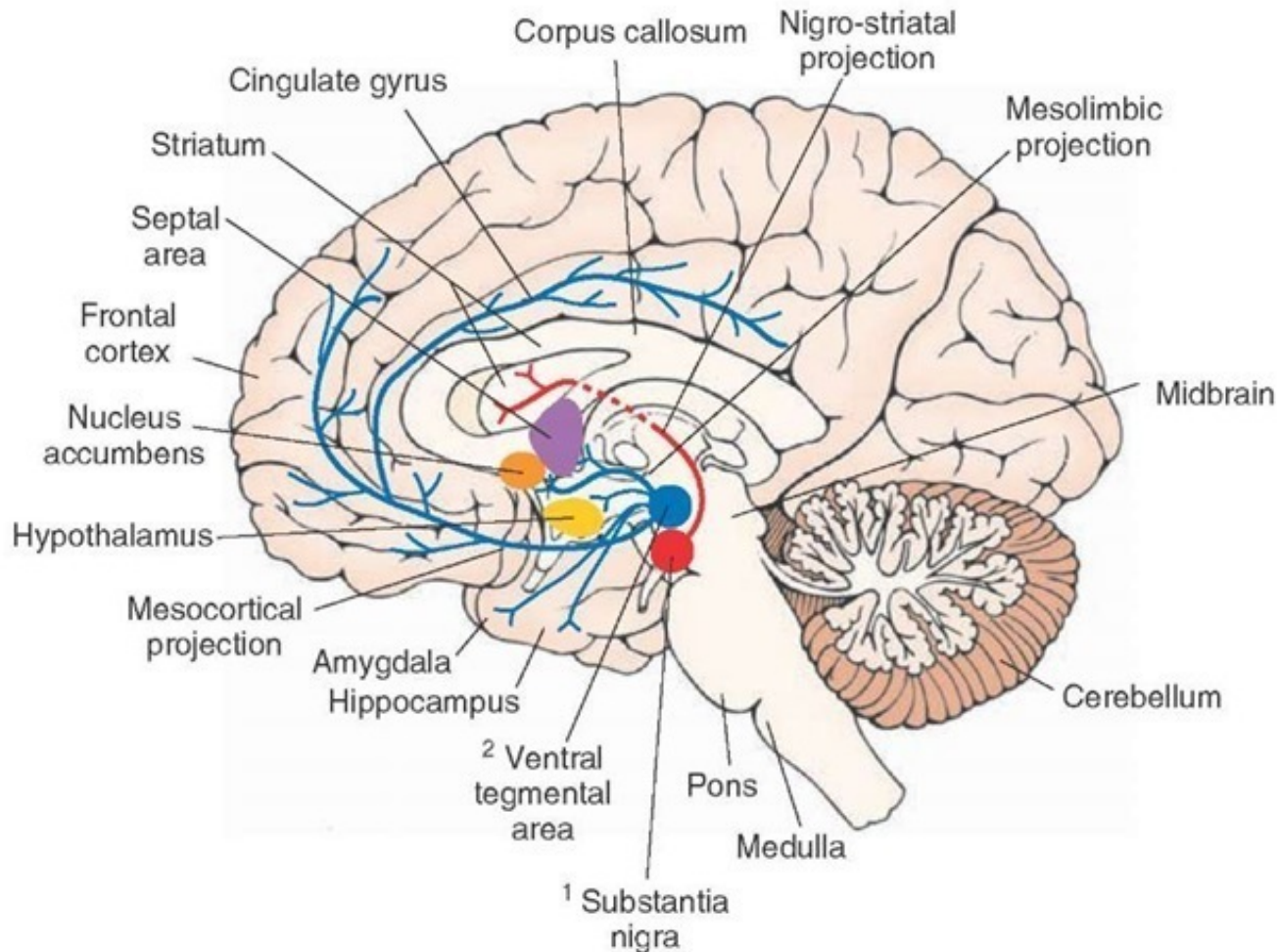
24 hrs



Tonic effects  
(amisulpride has first  
peak in plasma  
concentration after 1 hr,  
half life of about 12 hrs)

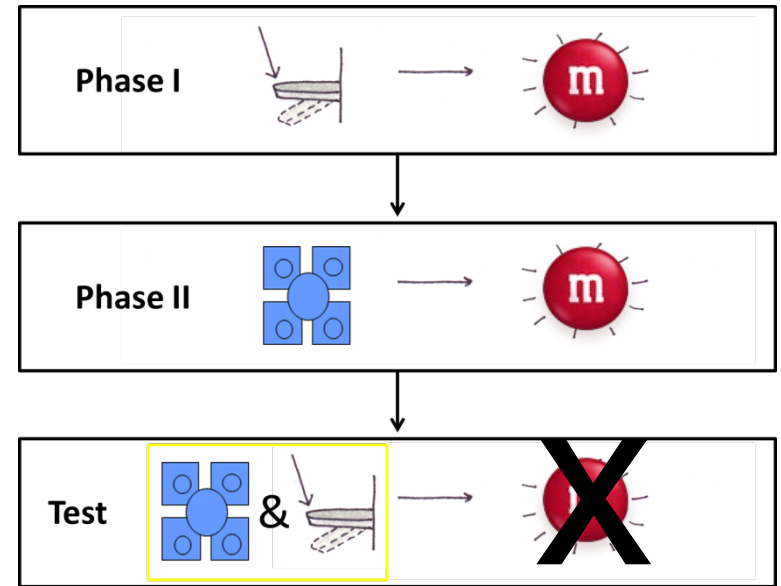
Enabling functions of  
dopamine (e.g. motor  
effects in striatum)

# Widespread projections of dopamine neurons



Enabling effects may be depend on function of target region

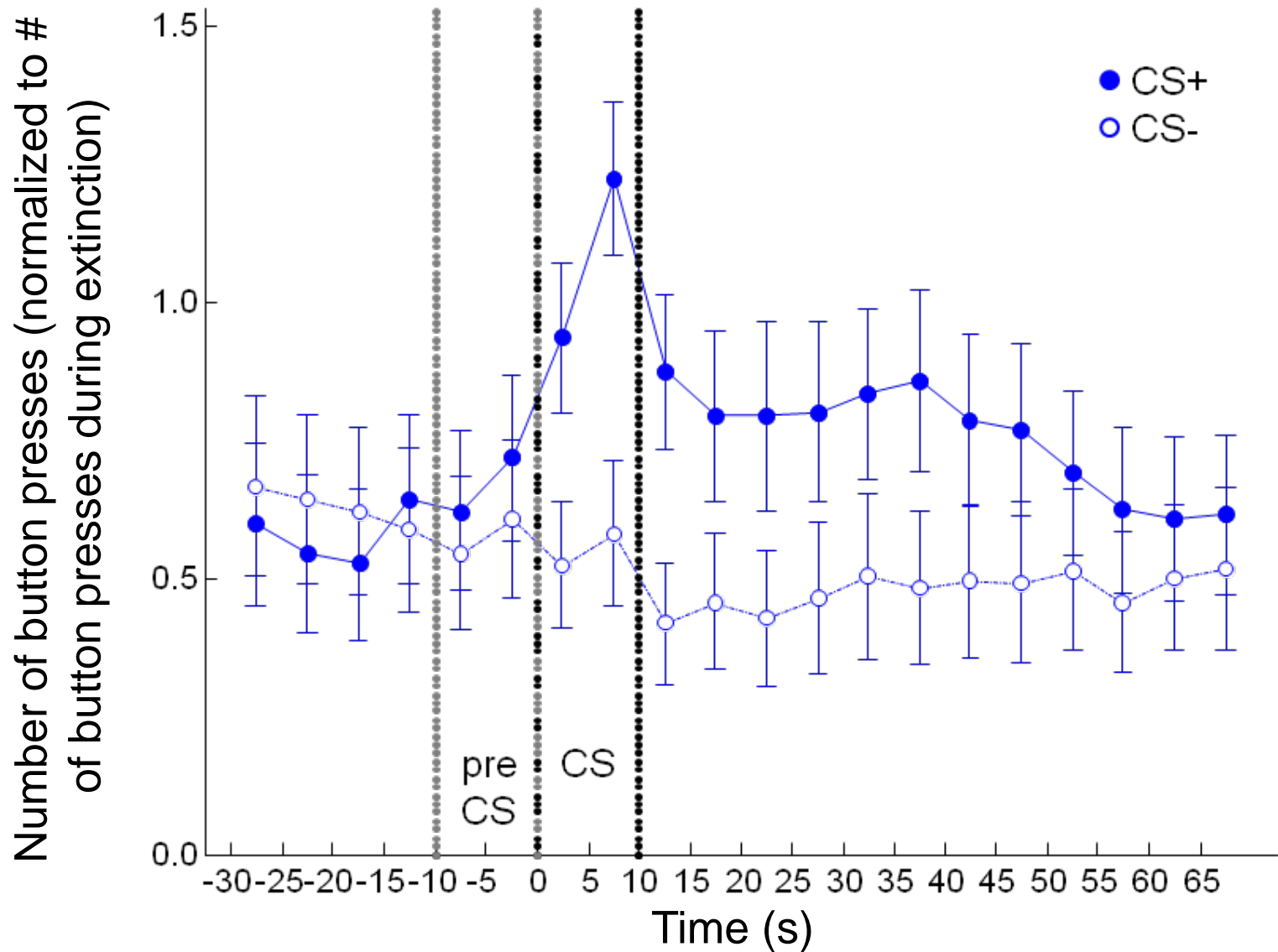
# Human PIT task



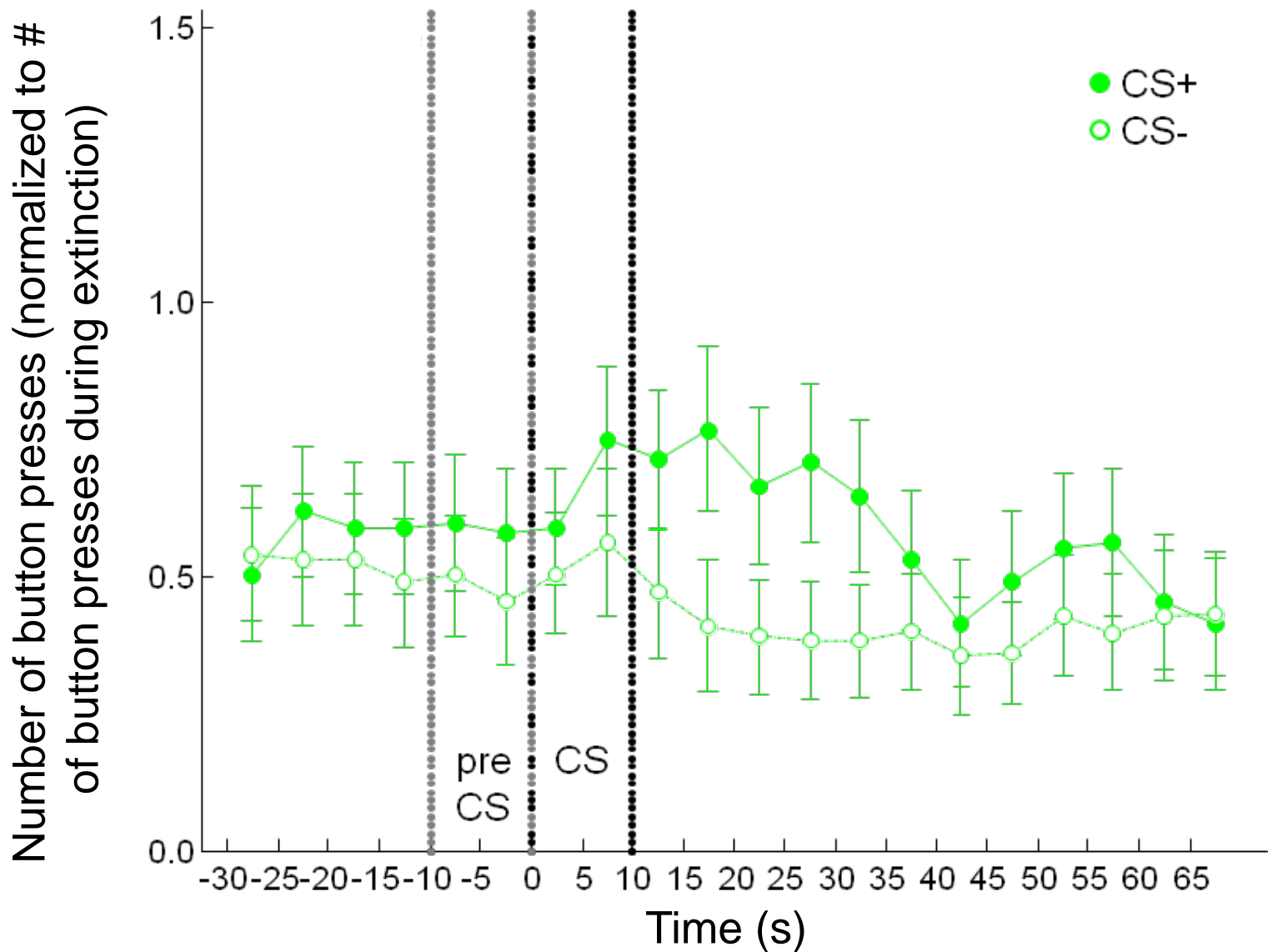
# Motivational aspects of reward: Pavlovian-instrumental transfer

Instrumental phase	Button pressing (VR 10 schedule) for chocolate
Pavlovian phase	CS+ (10s; chocolate) CS – (10s; no chocolate)
Transfer phase	Present CSs in extinction, and after extinction of instrumental responding

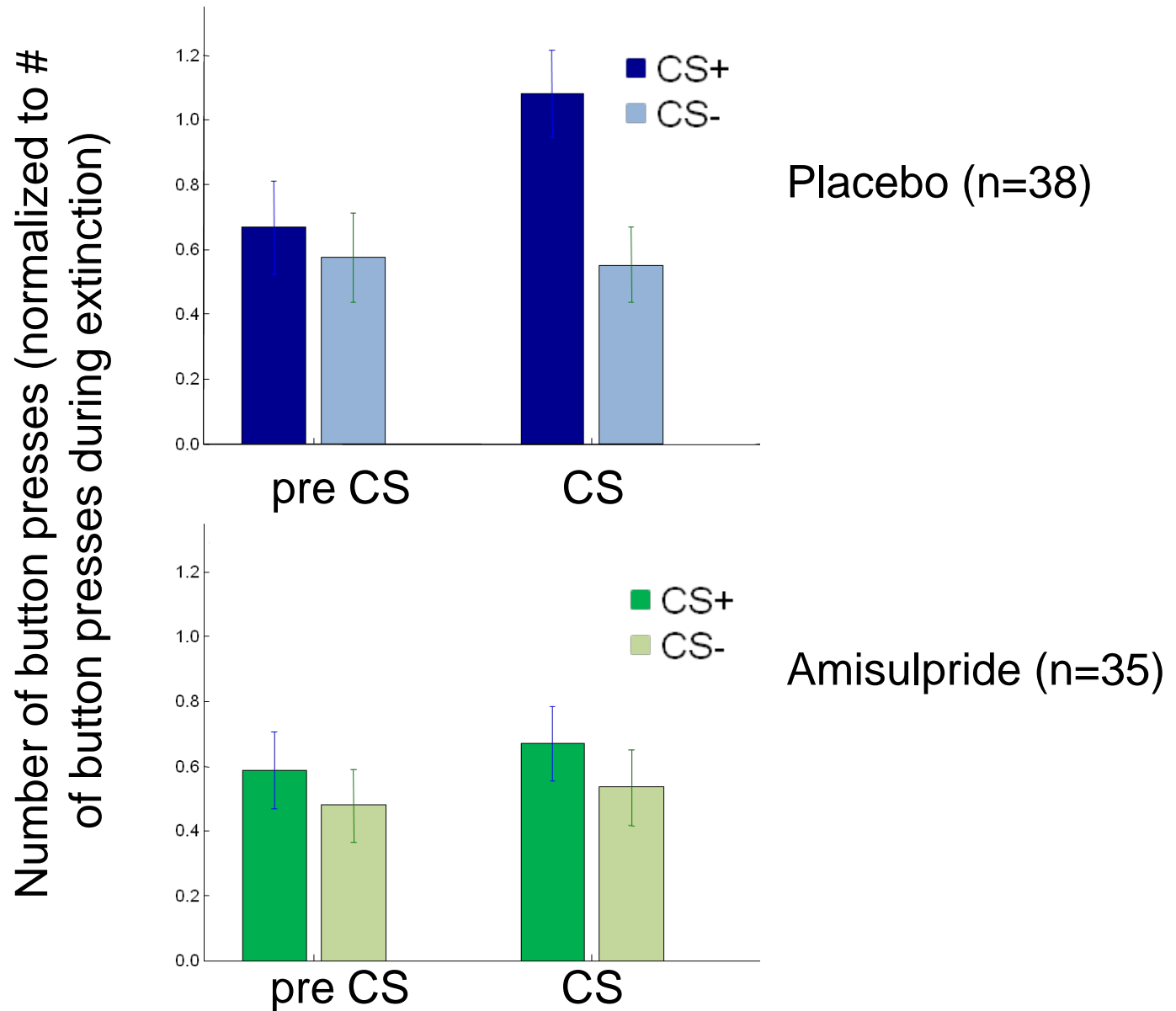
# Pavlovian-instrumental transfer (PIT): Placebo



# Amisulpride reduces PIT



# Amisulpride reduces PIT





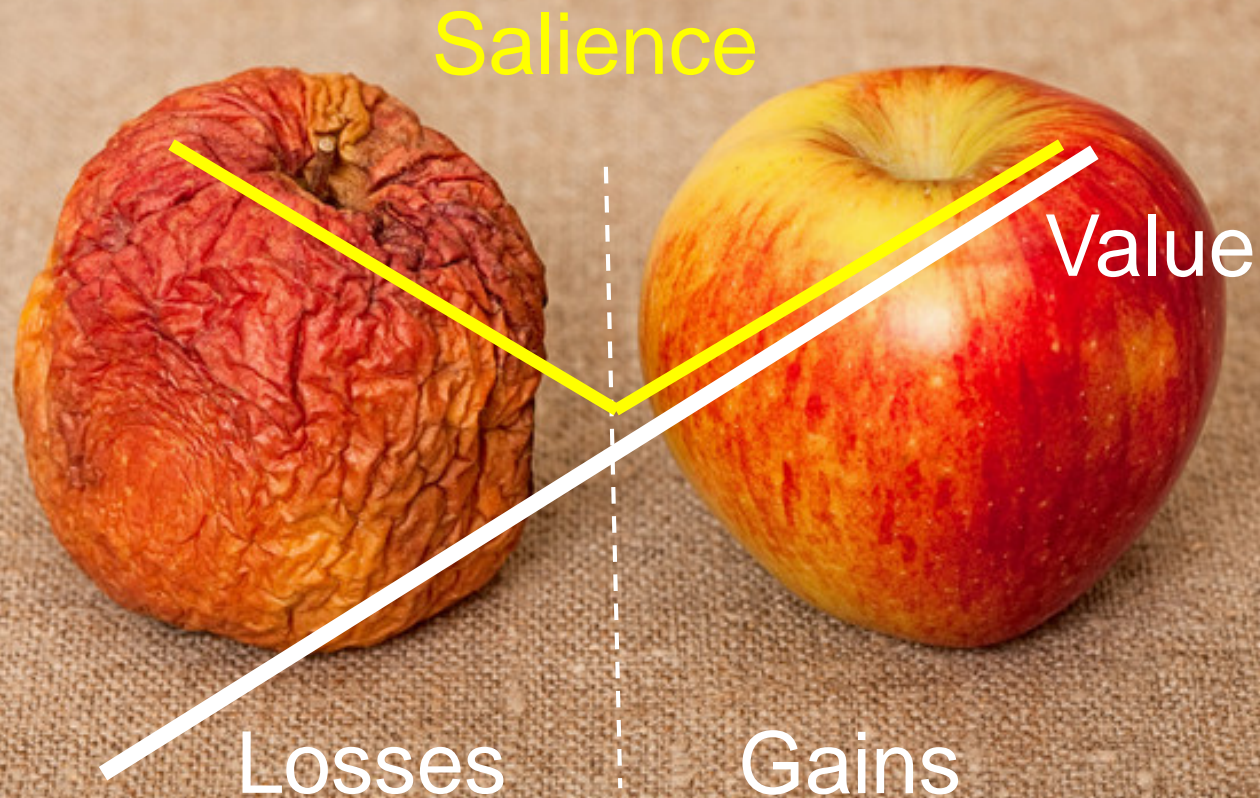
# Decomposing salience

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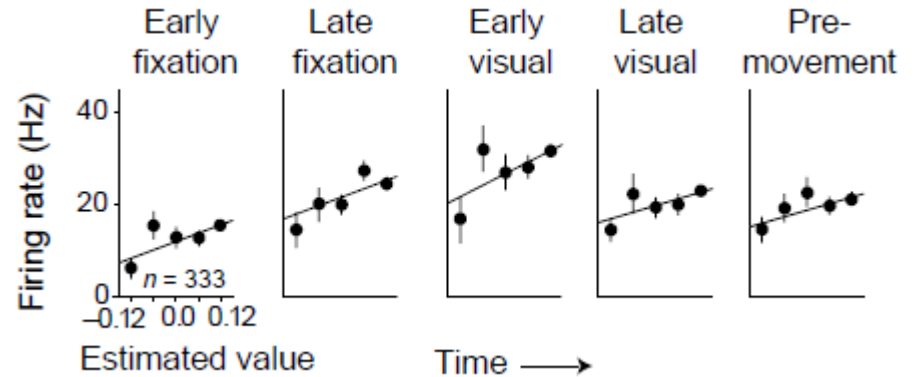
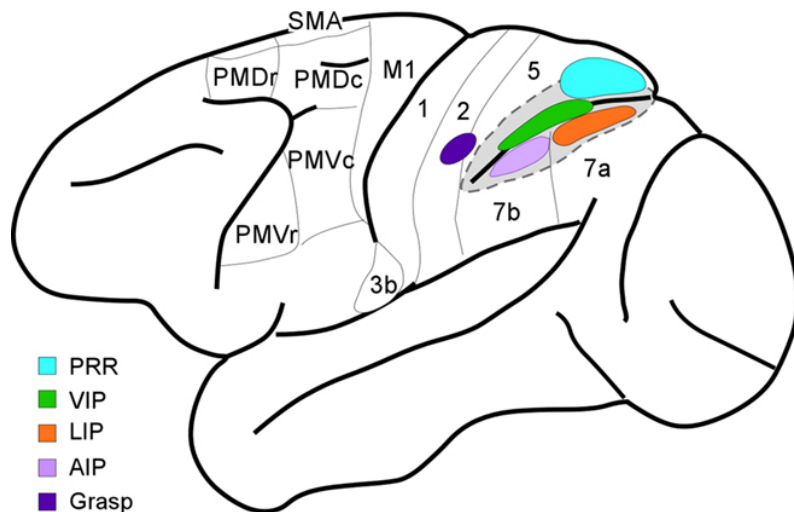
# How to define salience?

1. Relative to context – in vision e.g. brightness, colour, contrast, movement, orientation -> topographic map (detection salience)
2. Relative to internal state/goals of organism (identification/motivational salience)
  1. Expectation
    1. Size of signed prediction error (outcome – prediction)
    2. Size of unsigned prediction error (abs (outcome – prediction))
    3. Novelty
  2. Goals
    1. Absolute magnitude/value (size of reward, punishment)

# Quantifying motivational salience as absolute value

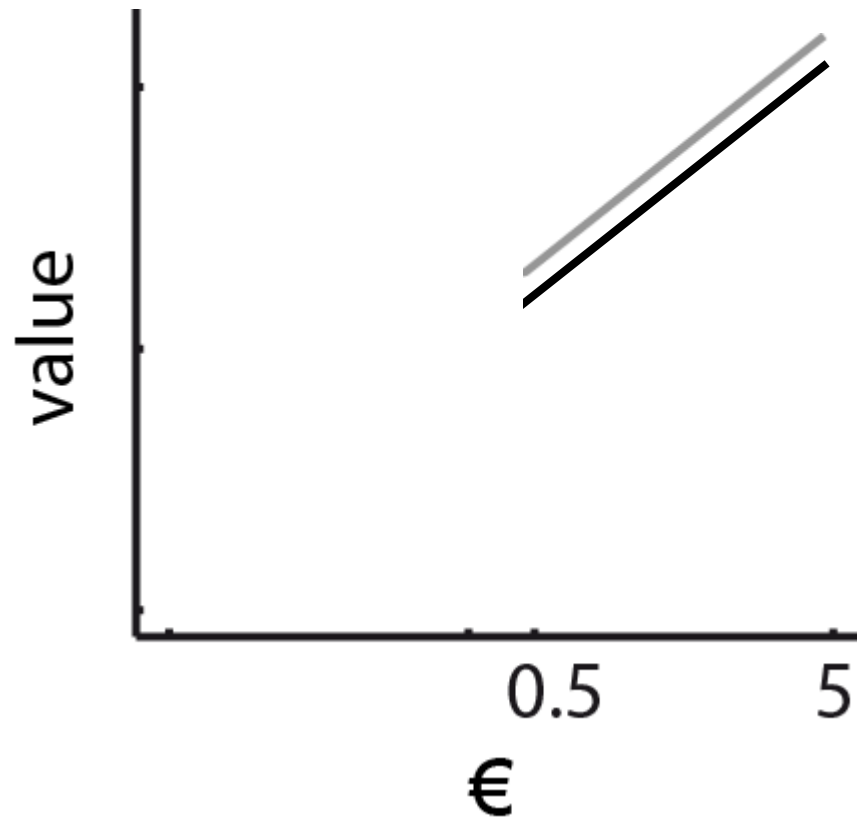


# Dissociating value and salience

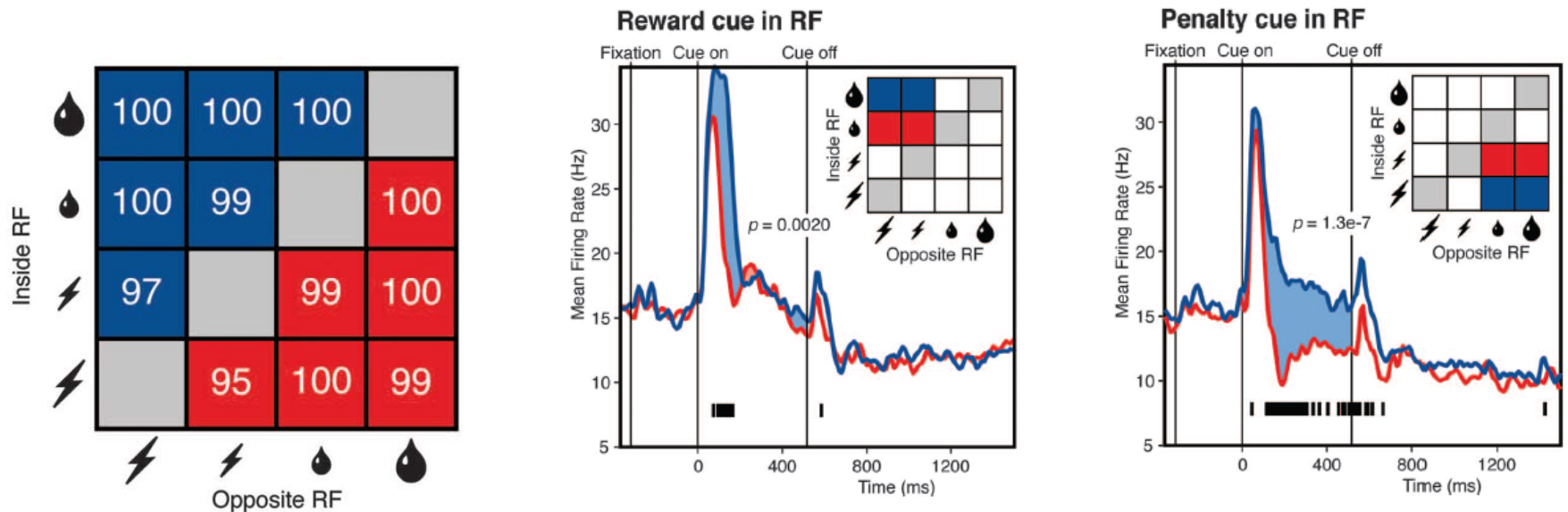


Neurons in lateral intraparietal sulcus show increasing activation with value

# Value or salience?



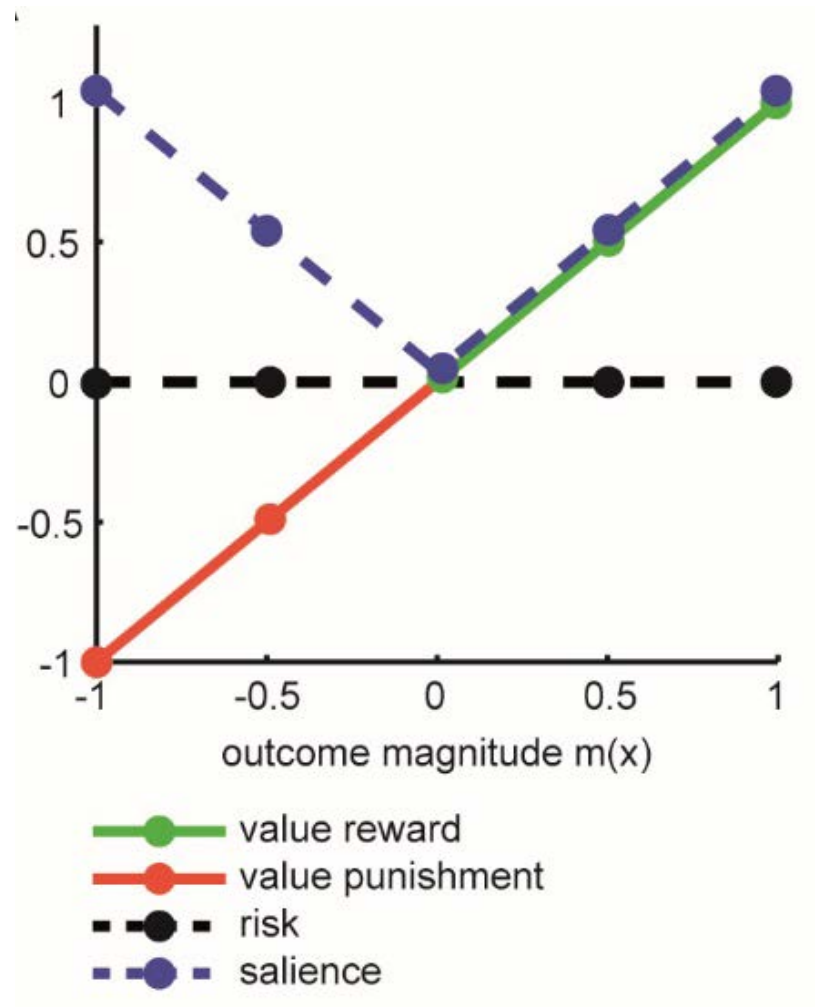
# Value or salience in parietal cortex?



Neurons in lateral intraparietal sulcus are more activated by more appetitive **and** more aversive stimuli

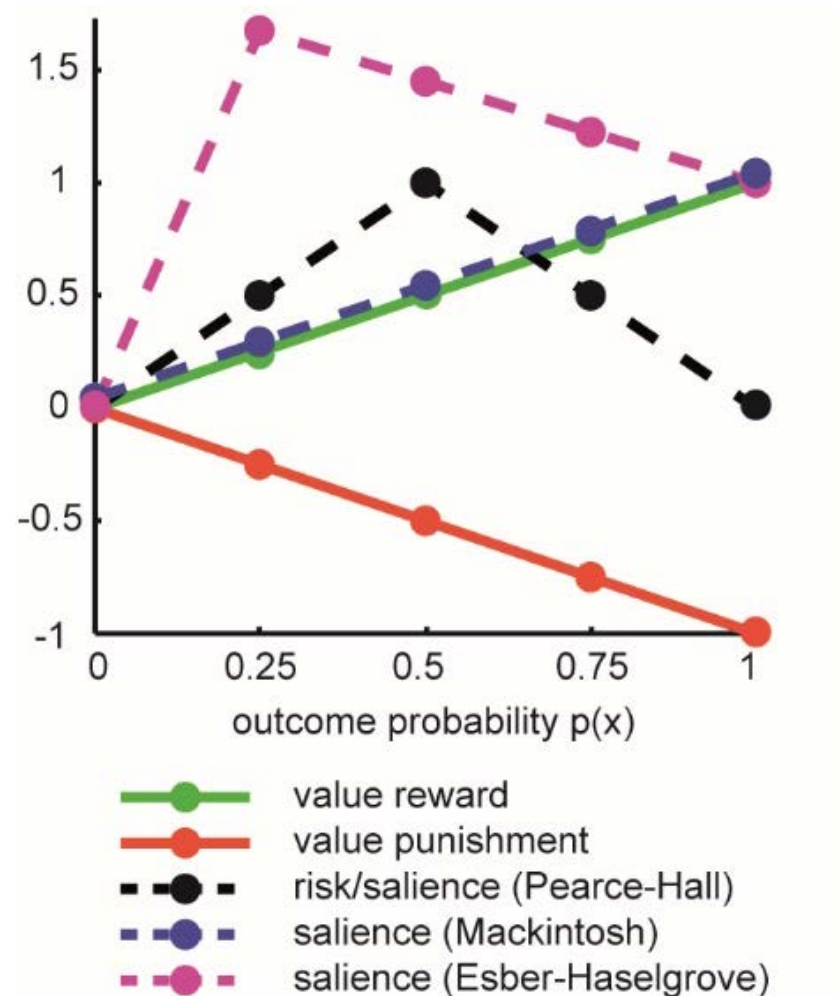
Thus, in order to dissociate value and salience, one needs to study both types of outcomes

# Quantifying motivational salience based on magnitude (absolute value)



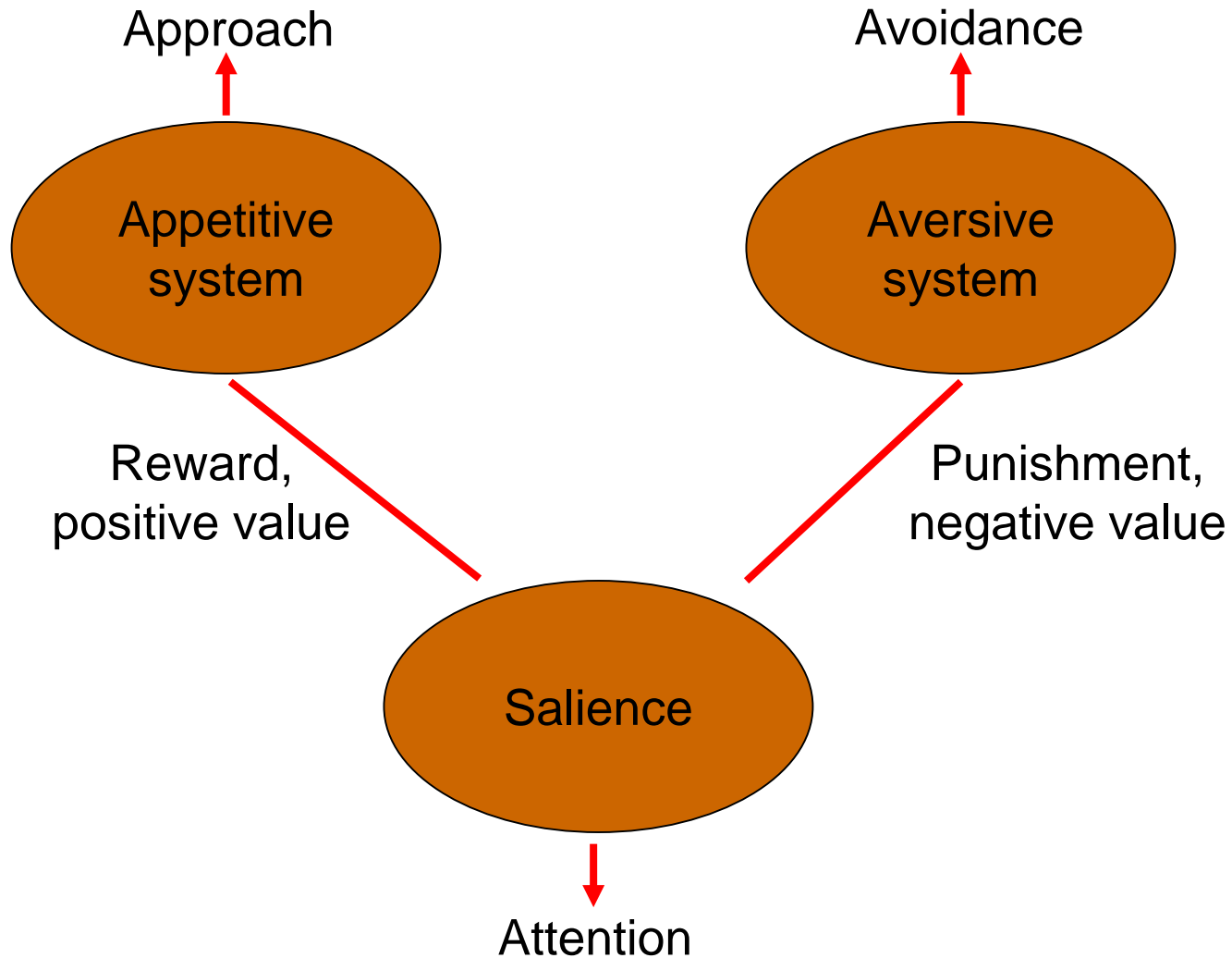


# Quantifying motivational salience based on probability (reliability of prediction)

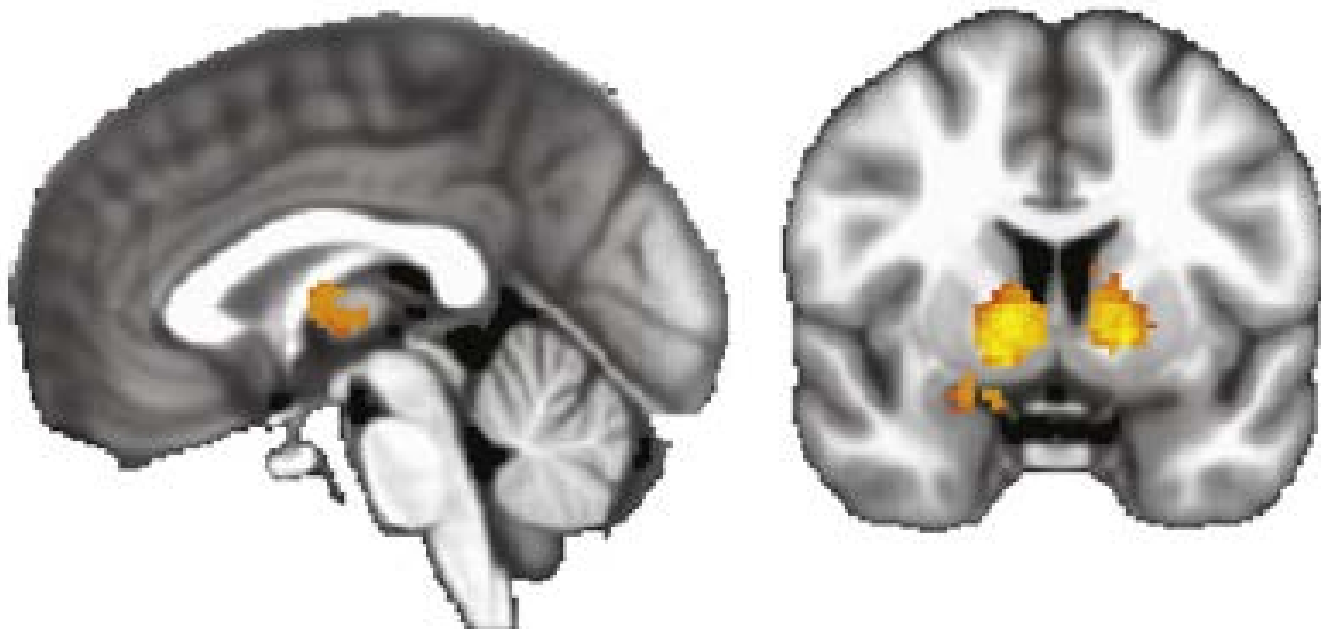




# Value versus motivational salience

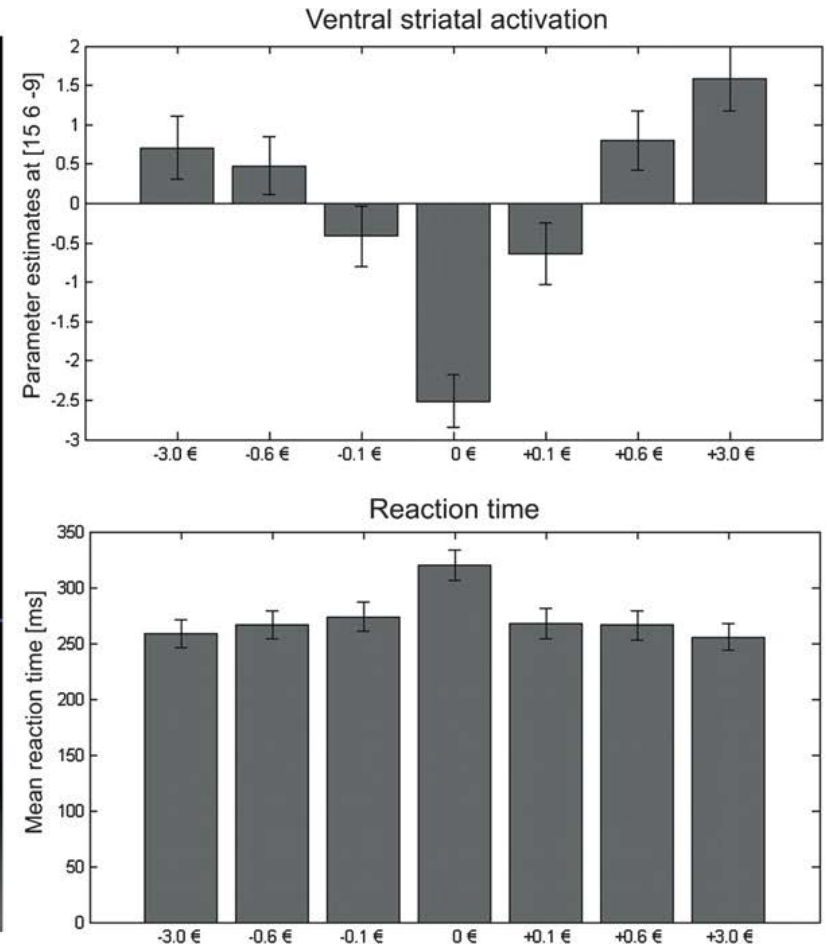
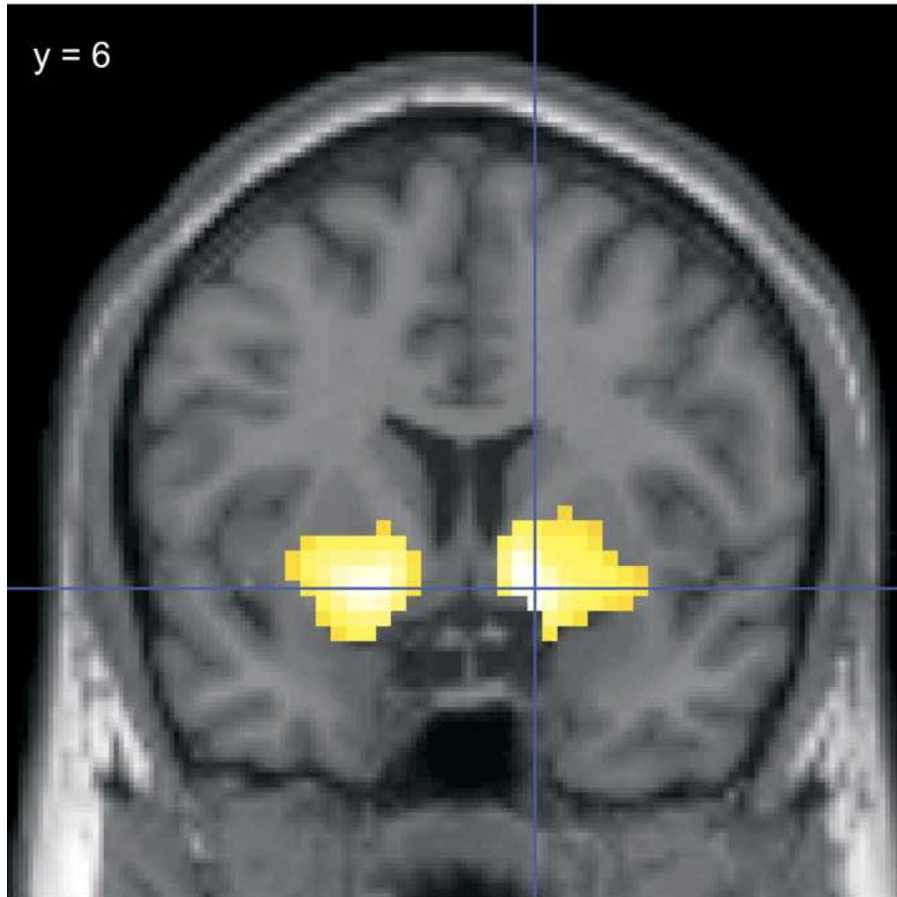


# Salience responses in the striatum?



Common activation increases (conjunction) for larger gains  
and larger losses suggests salience coding

# Not all activations that look like salience necessarily are salience; e.g. MID task



Higher activation during anticipation of larger amounts of monetary gain/loss avoidance

# Defining motivational salience: two variants of absolute value



$a_1$        $a_2$



$b_1$        $b_2$

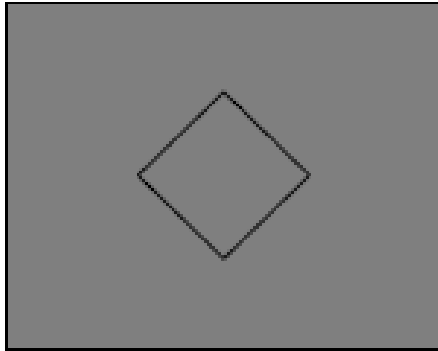


Elemental salience ( $|a_i| + |b_i|$ )

Global salience ( $|a_i + b_i|$ )

# Dissociating acquired value and motivational salience

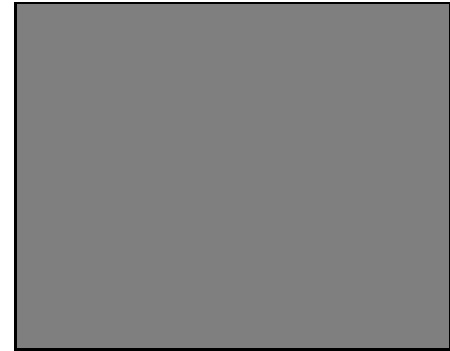
Training (100% reinforced)



cue 3 s



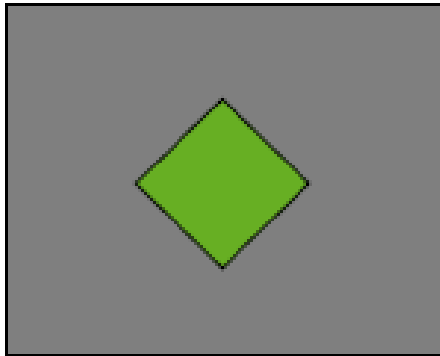
outcome 1 s



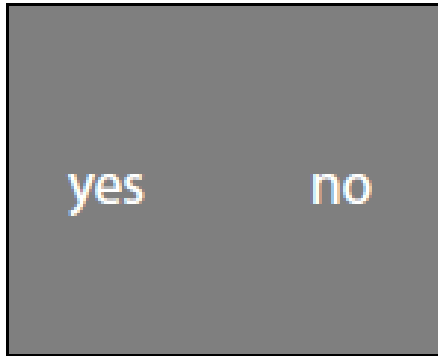
variable ITI

# Compound cues used inside scanner (choice)

Value-based choice



cue 3 s

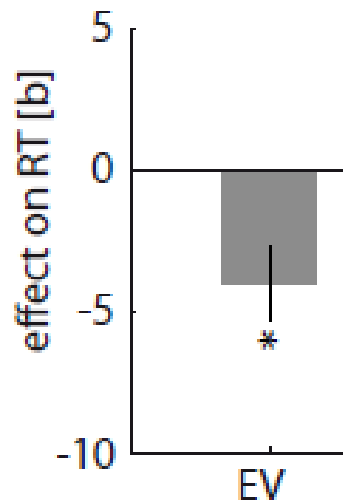
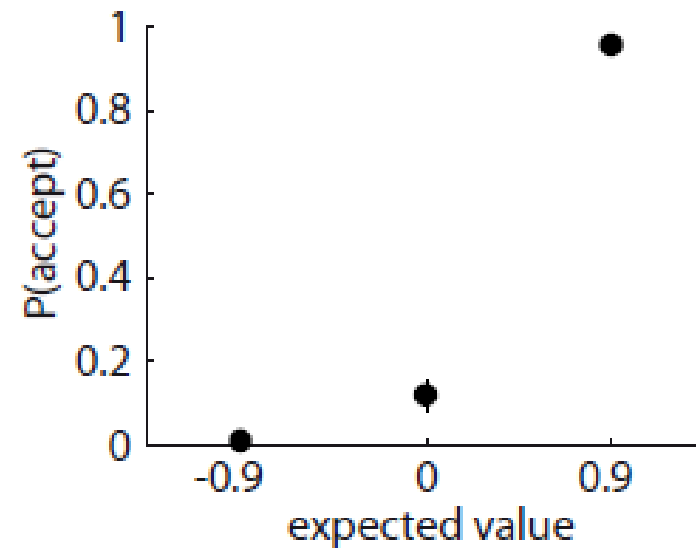
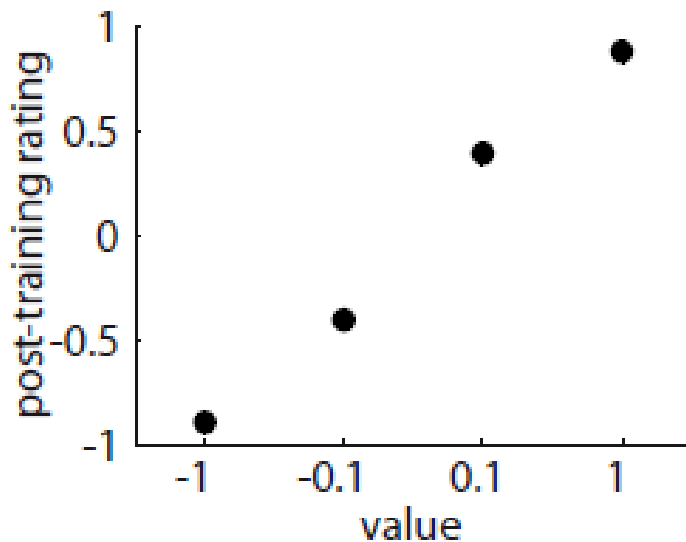


response 1 s



variable ITI

# Distinct behavioral effects of value and salience



Value impacts choice and response time (RT),  
elemental salience impacts RT (compound trials) Kahnt & Tobler, 2013

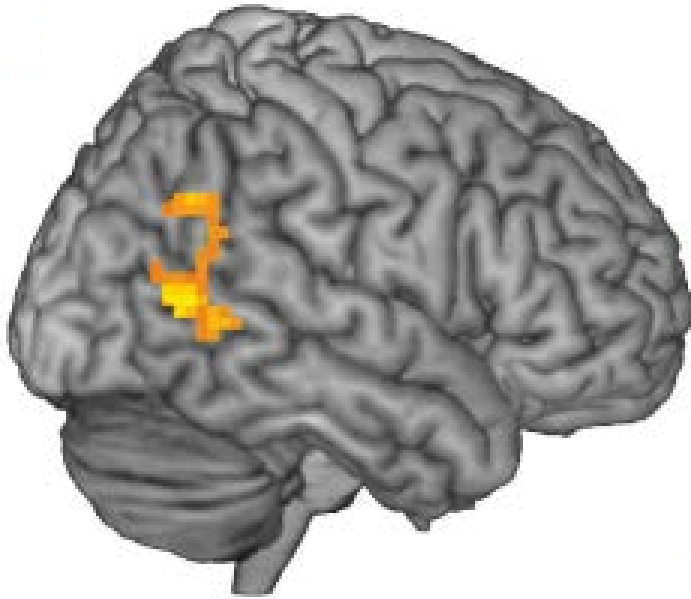
# Striatal value responses in both compound and single conditions



Compound offers:  
value responses

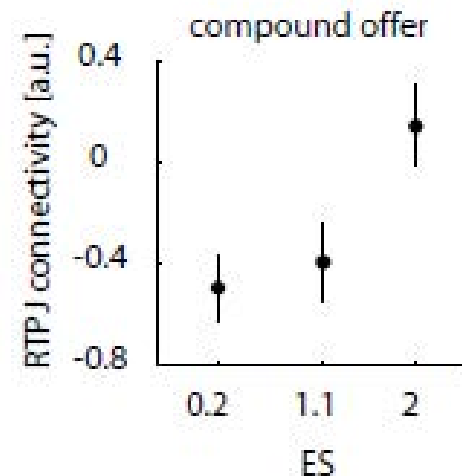
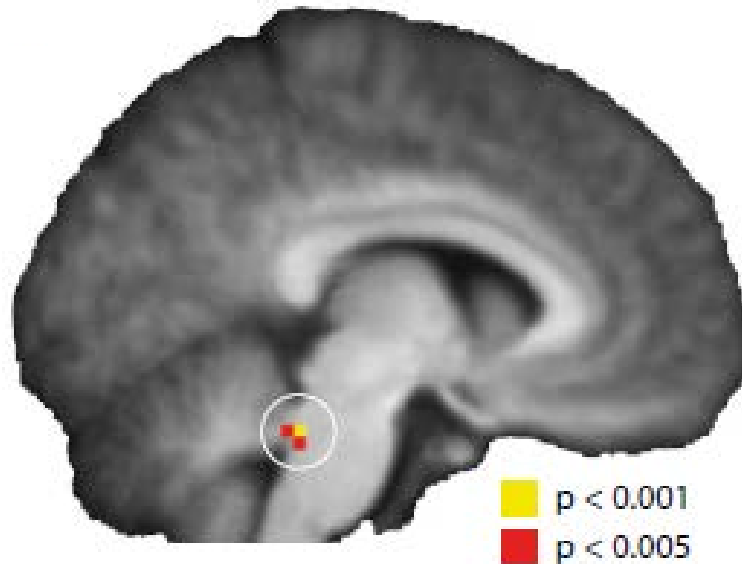
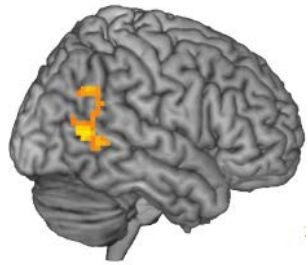


# Temporo-parietal responses scale with elemental salience and correlate with its impact on RT



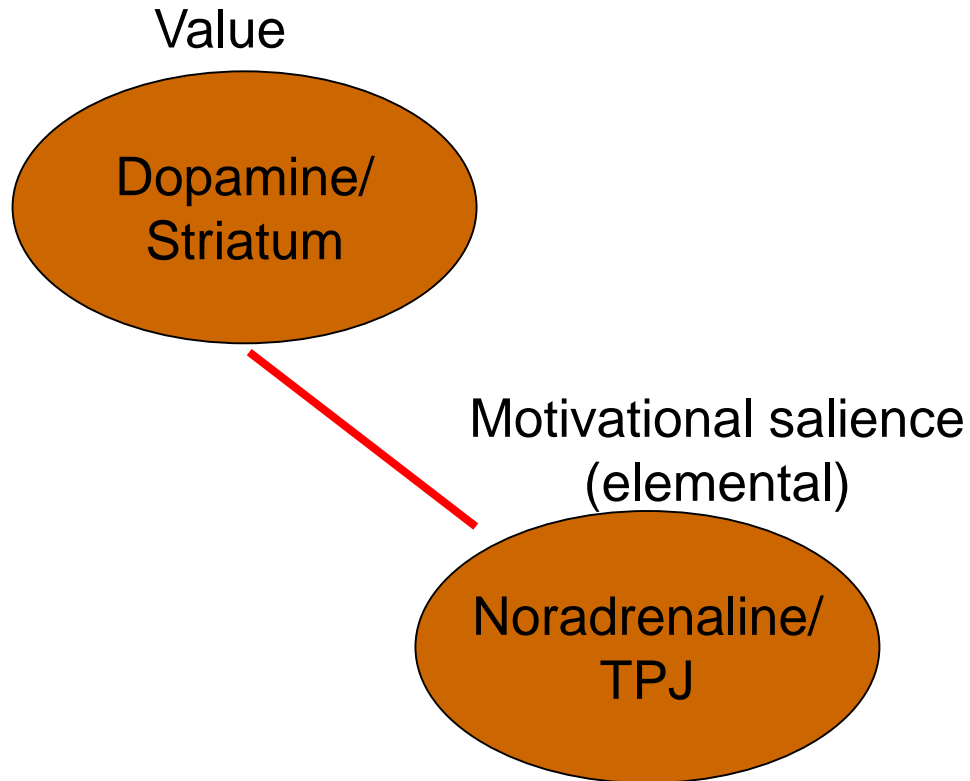
Taken together, there is a double dissociation between acquired value (striatum, not temporo-parietal region) and acquired salience (temporo-parietal region, not striatum)

# Regulation of elemental salience by locus coeruleus (noradrenaline)?



During high levels of elemental salience, the temporo-parietal region and the locus coeruleus are more tightly coupled than during low levels of elemental salience (also in single offers)

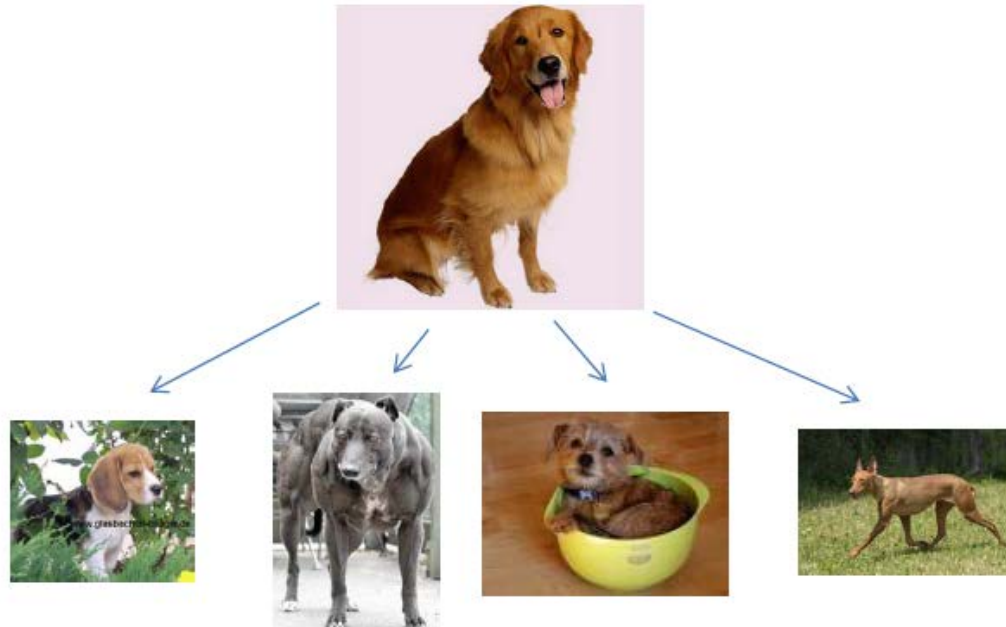
# Intermediate summary



# Decomposing salience

1. Test effect of one antipsychotic on human incentive/motivational salience (behavior only)
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# Similarity-based generalization

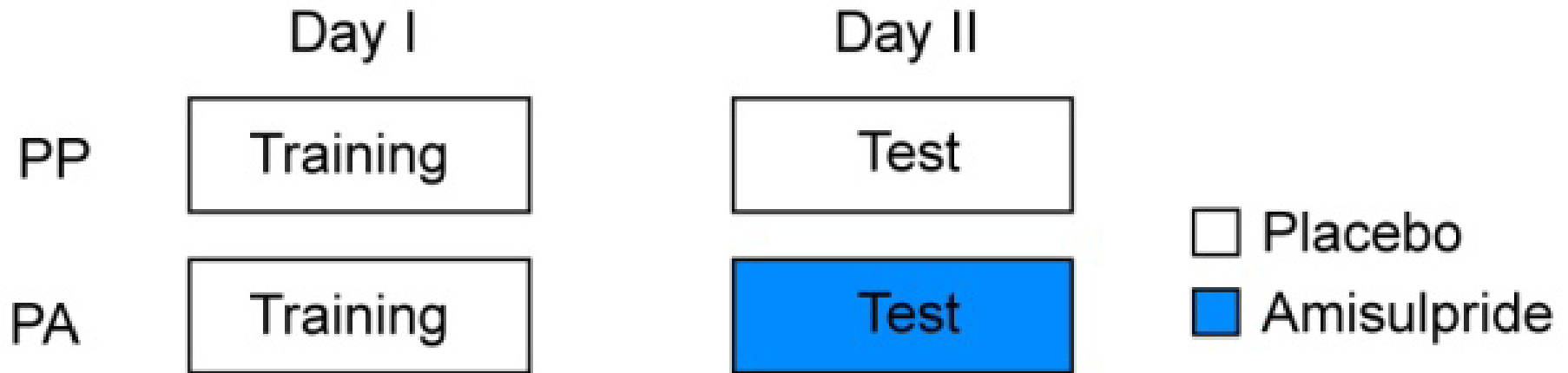


Conditioned responses generalise to other CSs (dogs), as function of similarity with original CS, even in absence of experience with these novel CSs; adaptive preparation of behavior to novel stimuli

# (Aberrant) salience and generalization

1. Dopamine neurons show generalization
2. Under the aberrant salience hypothesis, patients with schizophrenia can be thought to overgeneralize and at least some evidence supports this (see also the salience attribution test of Roiser et al., 2009, 2010)
3. In animals, antipsychotics reduce similarity-based generalization

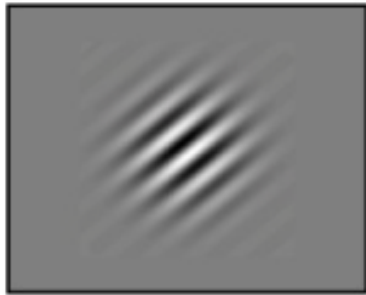
# Role of dopamine in stimulus generalization



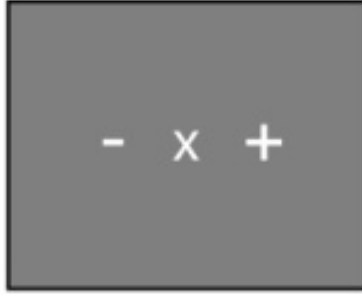
Training and test were separated by one day

# Training (day I) and test (day II)

Discrimination training (CS+ 50% reinforced)



cue 0.6 s



response 1.5 s



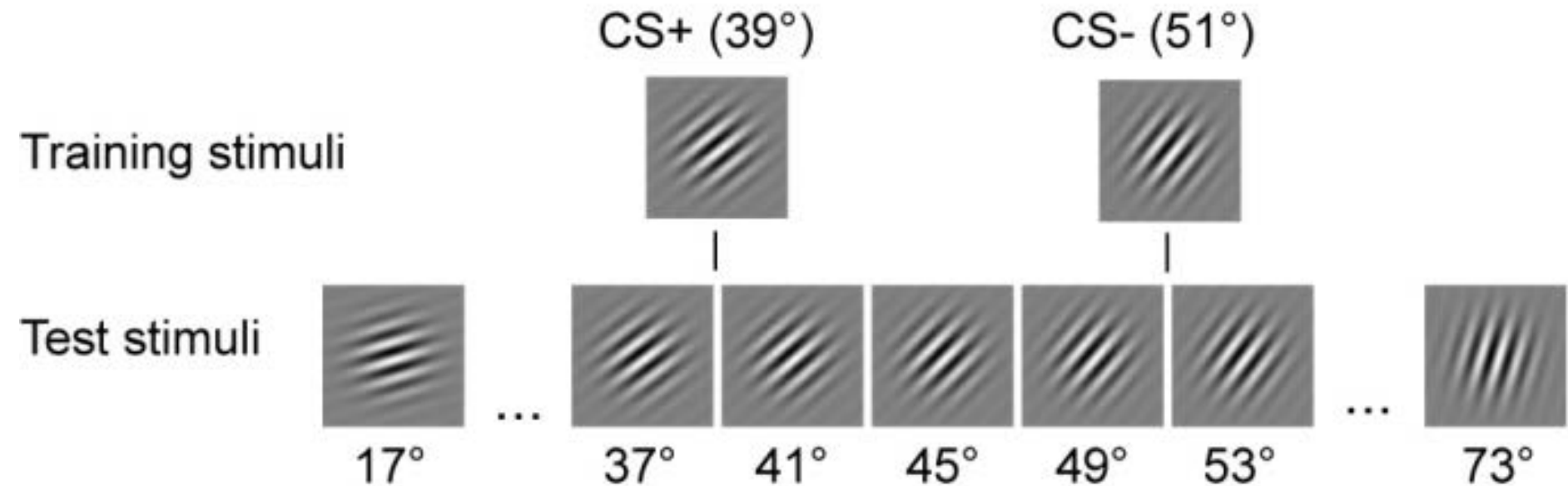
outcome 1 s



variable ITI

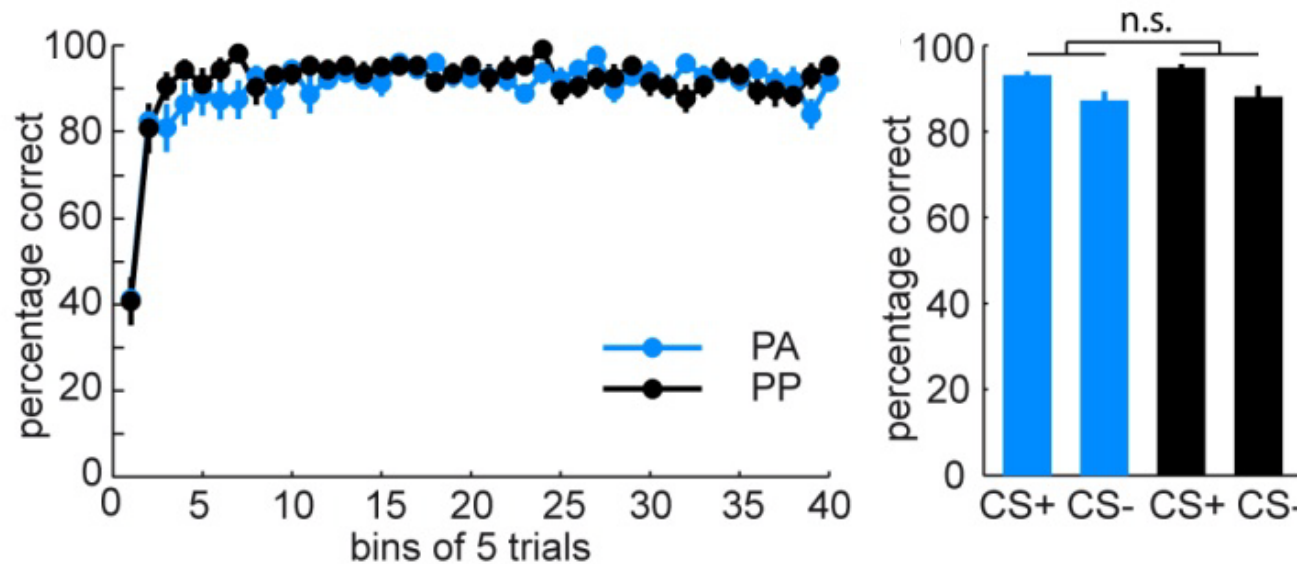


# Training (day I) and test (day II)



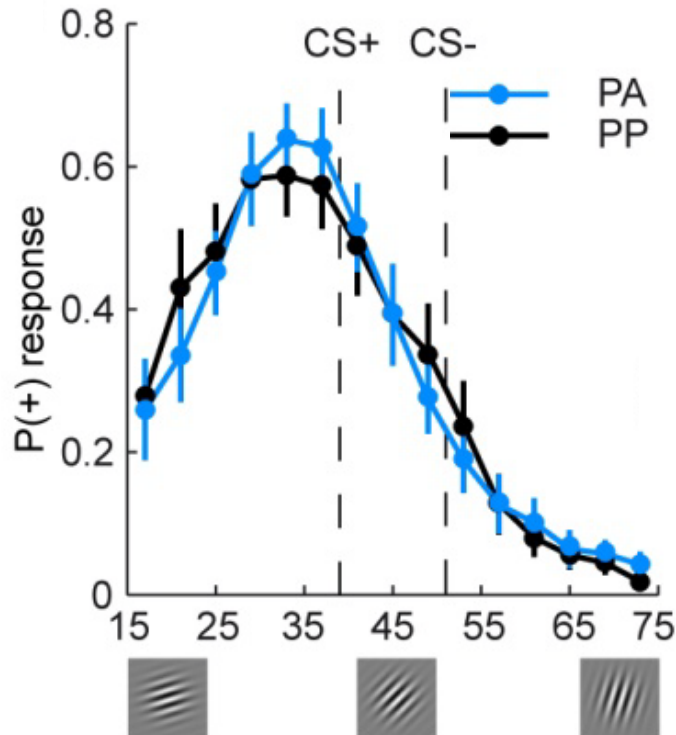
Training orientations are counterbalanced across subjects.  
CS+ and CS- are not shown during test

# Training proceeds similarly in both groups



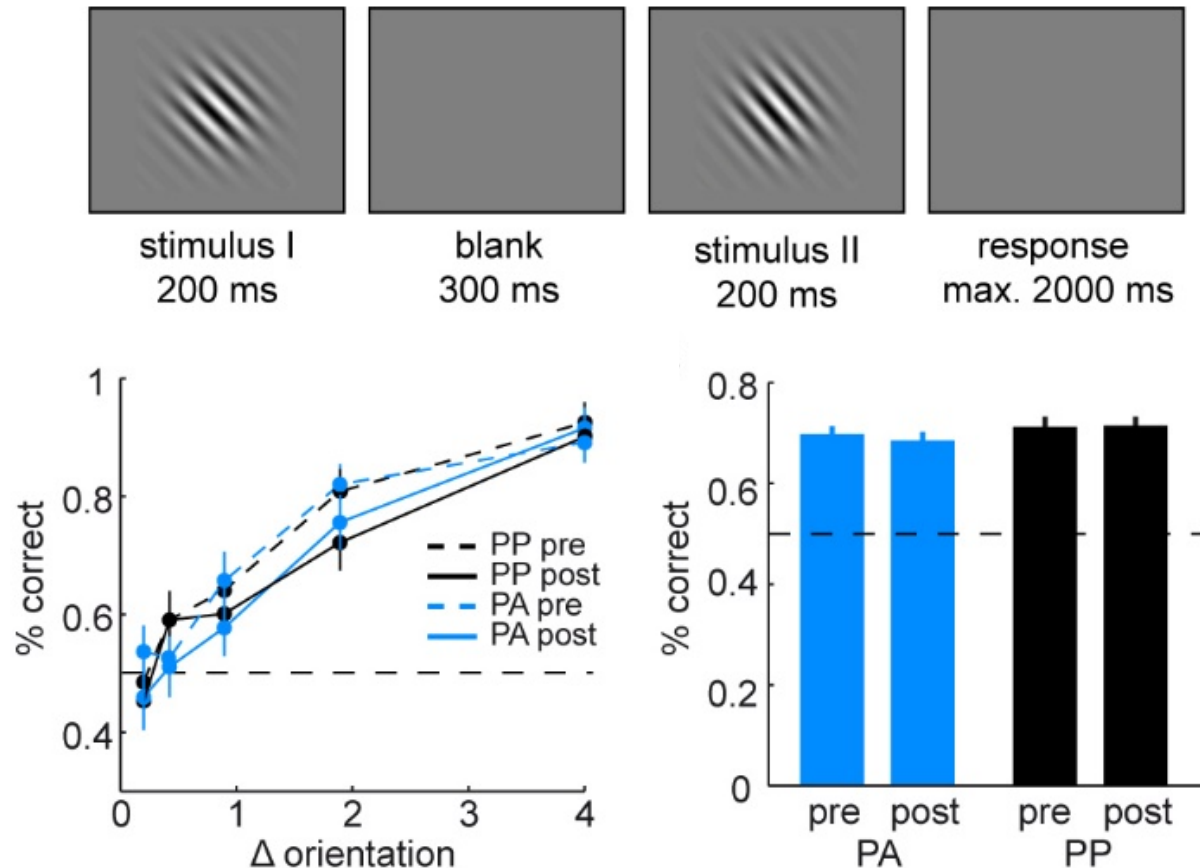
Performance reaches asymptote within the first 50 trials in both groups

At test, amisulpride group generalizes less widely than placebo group ( $\Delta$  kurtosis)



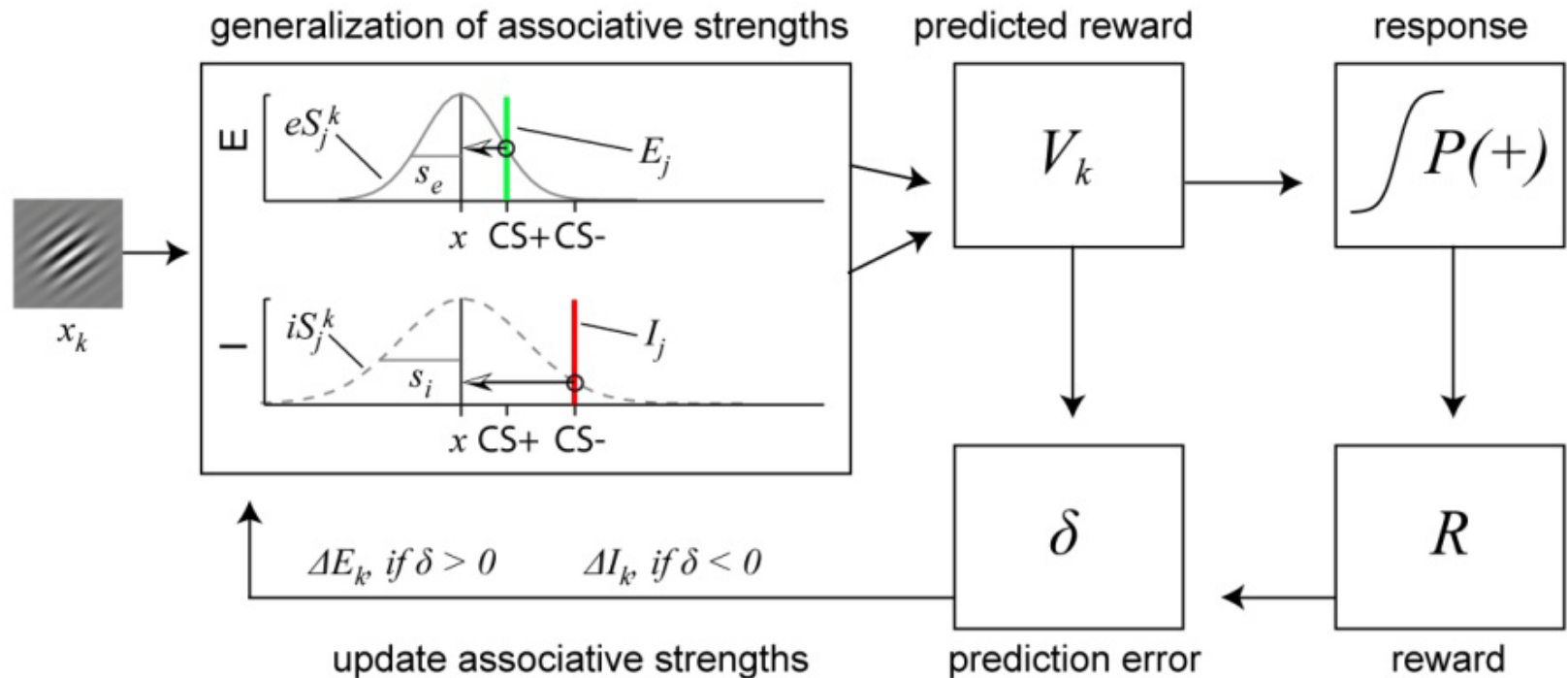
Both groups show peak-shifts (stronger responding for orientations away from CS-). Peak shifts may result from the summation of excitatory and inhibitory gradients around the CS+ and CS-

# Unchanged orientation discrimination performance between groups



To explain the narrower generalization, amisulpride should have improved discrimination compared to placebo

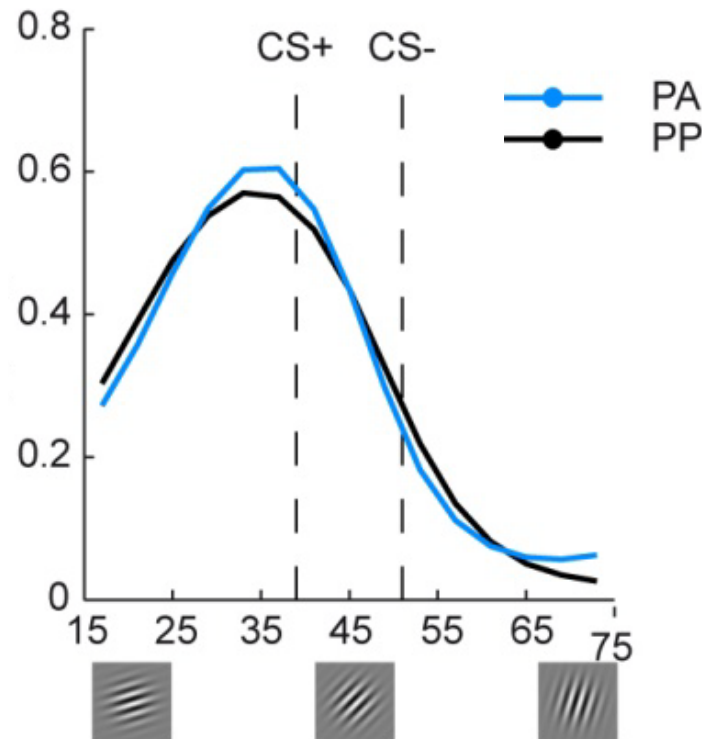
# A model of stimulus generalization (based on Pearce, 1987)



Inhibitory and excitatory associations change with learning.

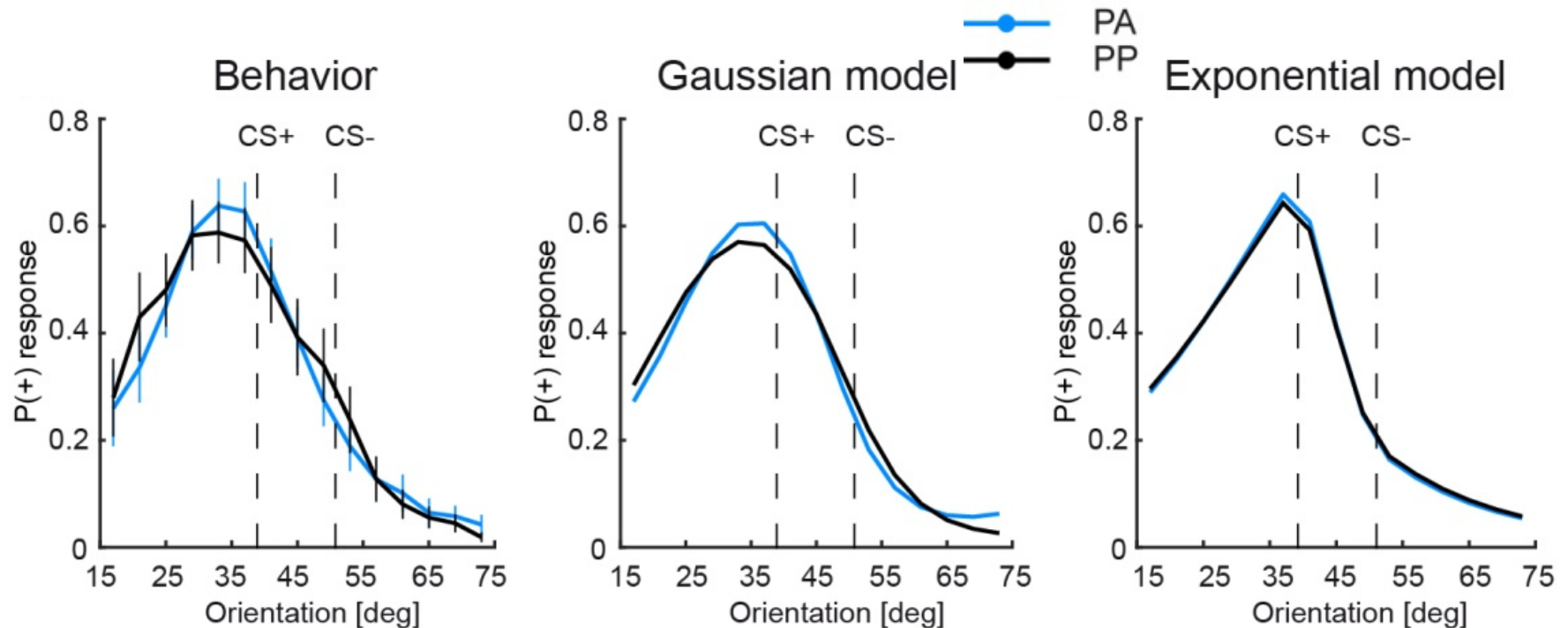
Associations of stimuli that are similar to the currently presented stimulus have a stronger contribution than the associations of dissimilar stimuli

# The model captures the reduced generalization in the amisulpride group



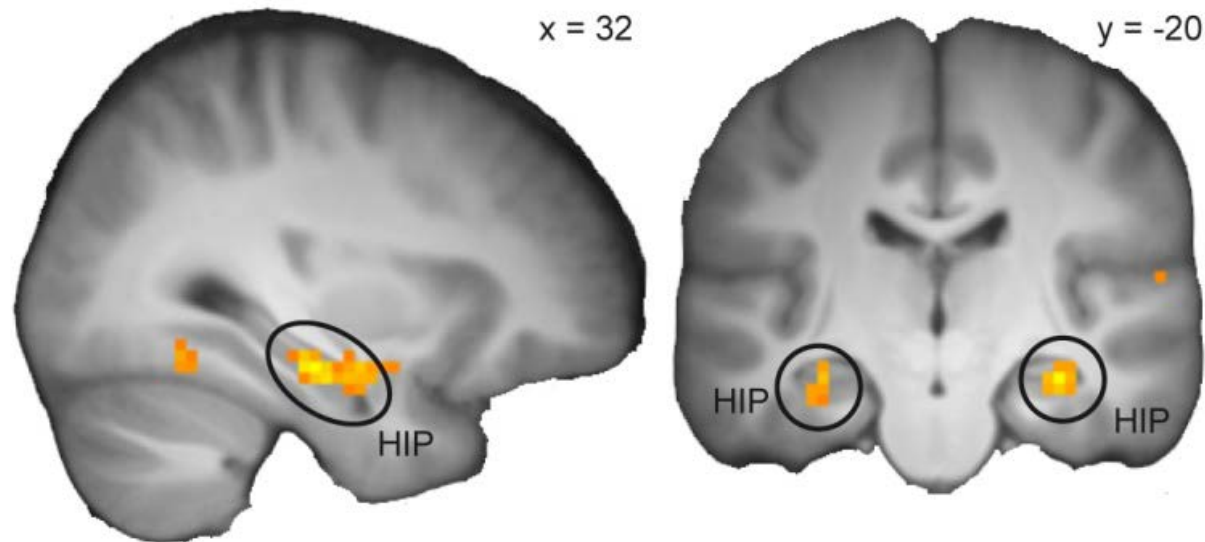
The width of both excitatory and inhibitory generalization coefficients was smaller in the amisulpride group compared to the placebo group

# The model captures behavior better than alternative models



A model with a Gaussian similarity function fits both groups better than a model with an exponential similarity function

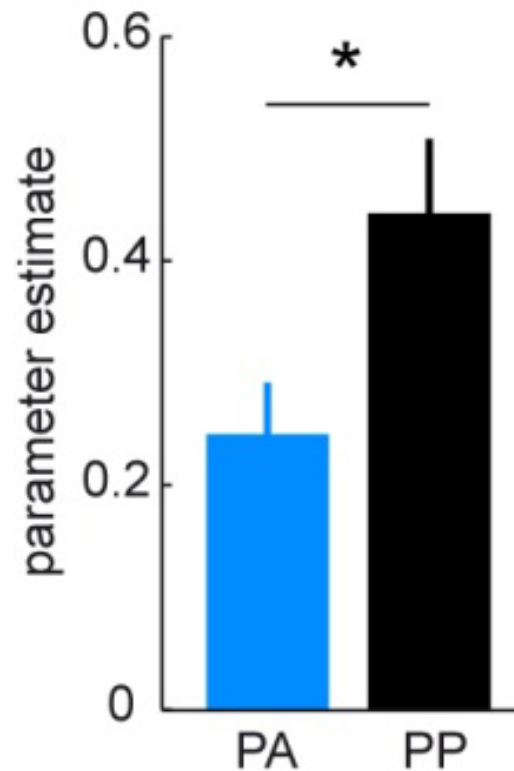
# Similarity-based prediction errors in hippocampus during generalization



Across both groups, activity in the hippocampus is significantly correlated with model-derived prediction errors during generalization test

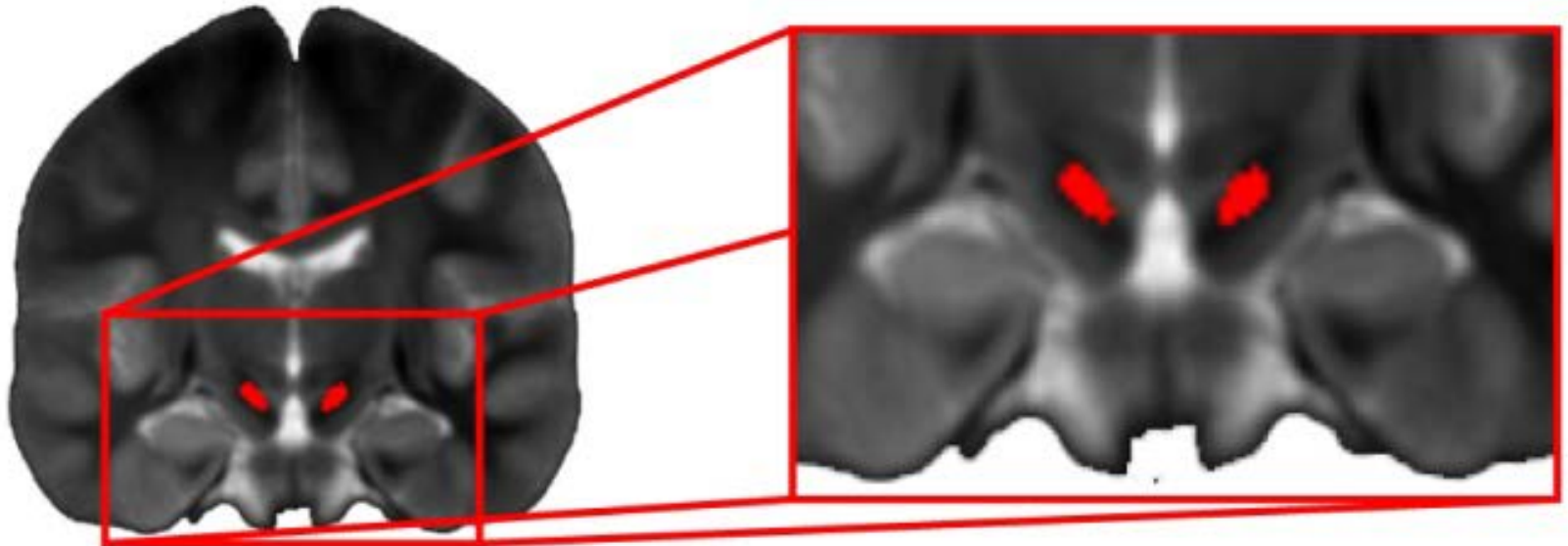


# Reduction of hippocampal prediction error signaling in amisulpride group



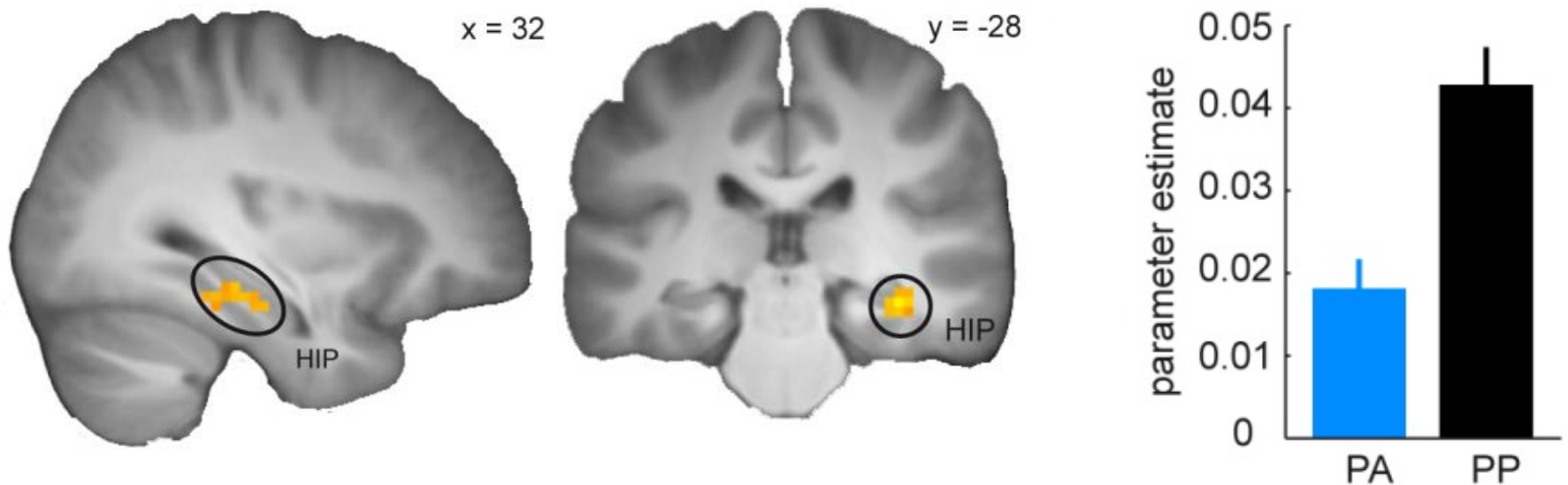
Parallel with reduction of behavioral generalization width in amisulpride group

# Functional connectivity between midbrain and hippocampus...



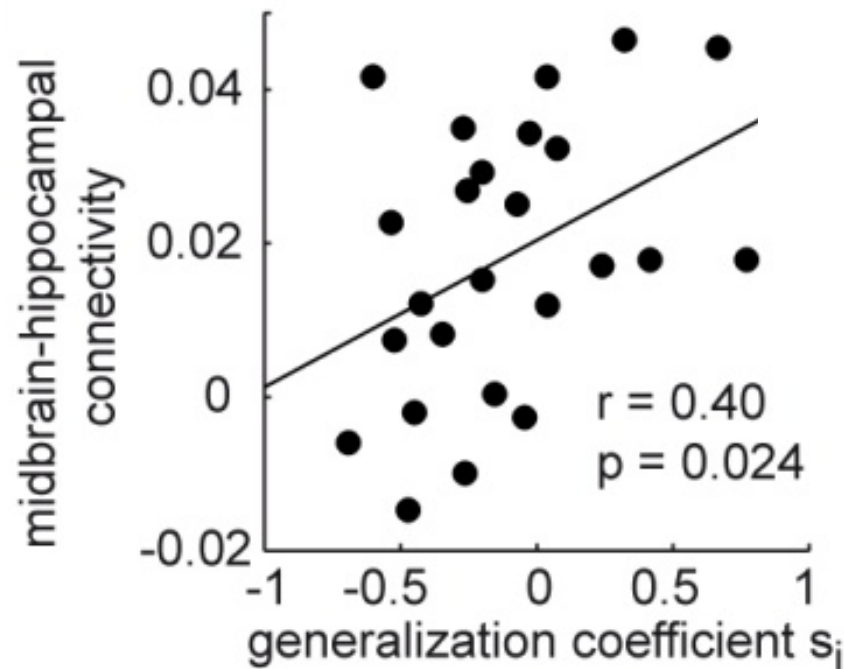
Seed region in the midbrain

# Functional connectivity between midbrain and hippocampus is reduced under amisulpride



Midbrain connectivity is also reduced in the striatum under amisulpride compared to placebo

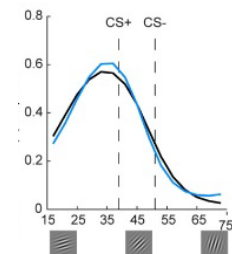
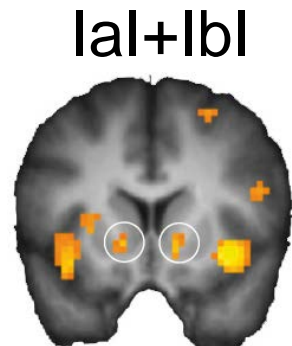
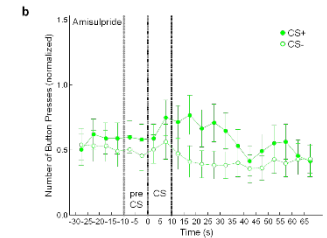
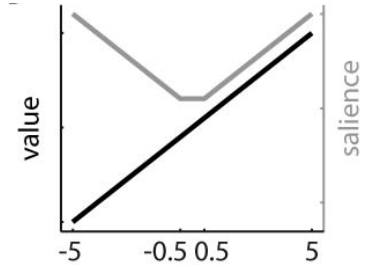
Under amisulpride, midbrain-hippocampus connectivity correlates particularly with the width of the inhibitory generalization gradient



No significant relation for excitatory generalization gradient and for midbrain-striatum connectivity

# Summary

1. Salience is in need of definition but can be studied with appropriate tasks
2. Dopamine D2/D3 receptor blockade attenuates PIT (motivational salience)
3. Elemental salience captures behavioral and neural effects better than global salience and is represented in the striatum
4. Dopamine D2/D3 receptor blockade attenuates hippocampus-mediated reward generalization



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