Using computation to translate across species

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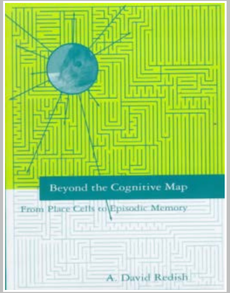
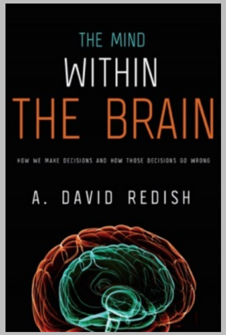
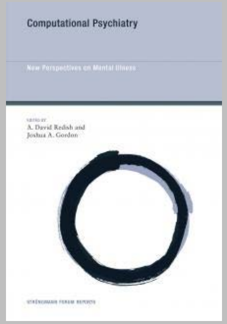




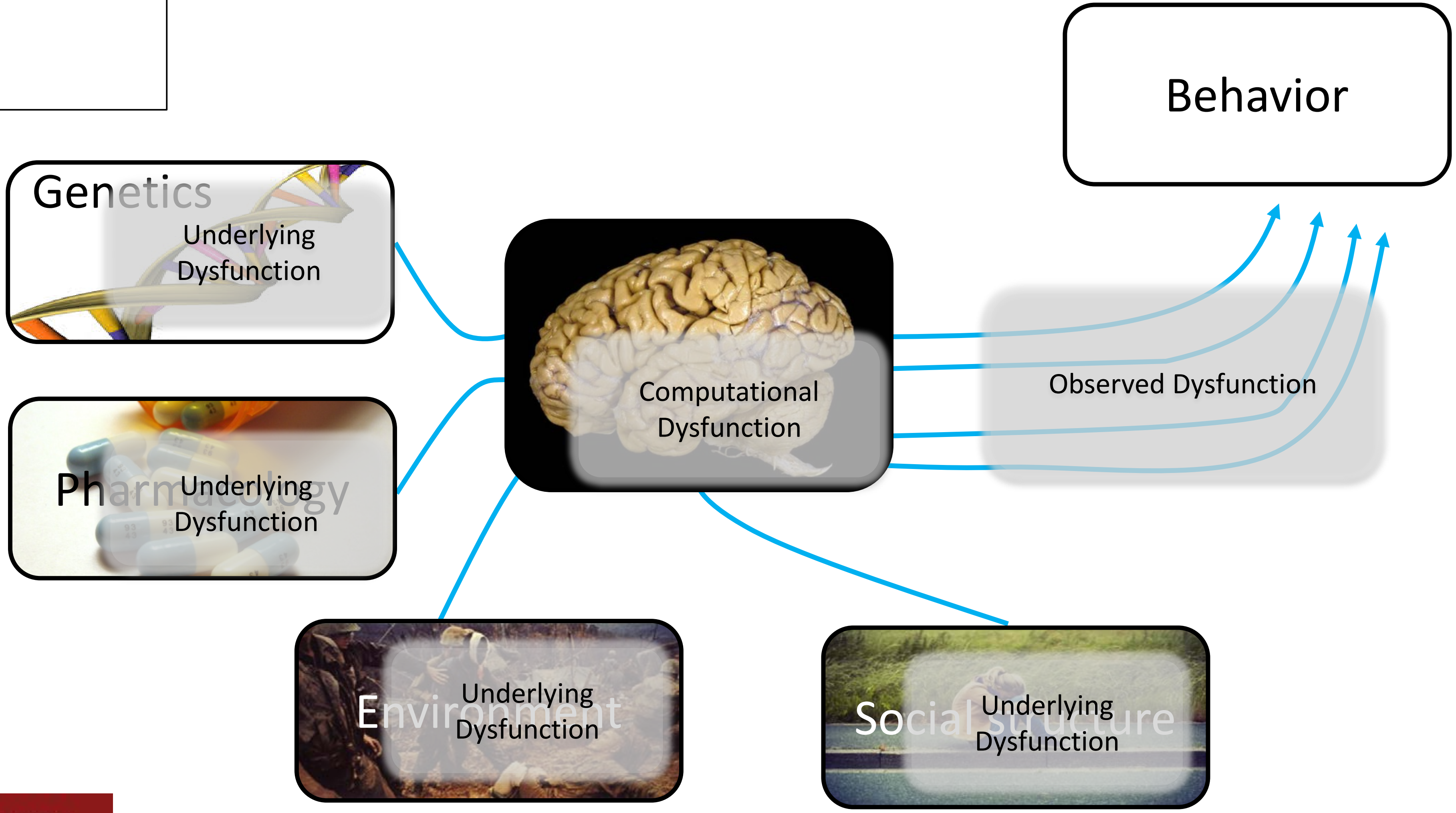


No conflicts of interest to declare.

Funded by
NIMH, NIDA.

Behavior depends on computation

This suggests
a new view
of psychiatry as
neurophysiological
computational
dysfunctions
in ***decision making***.

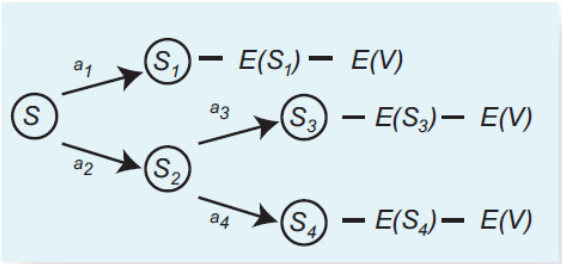


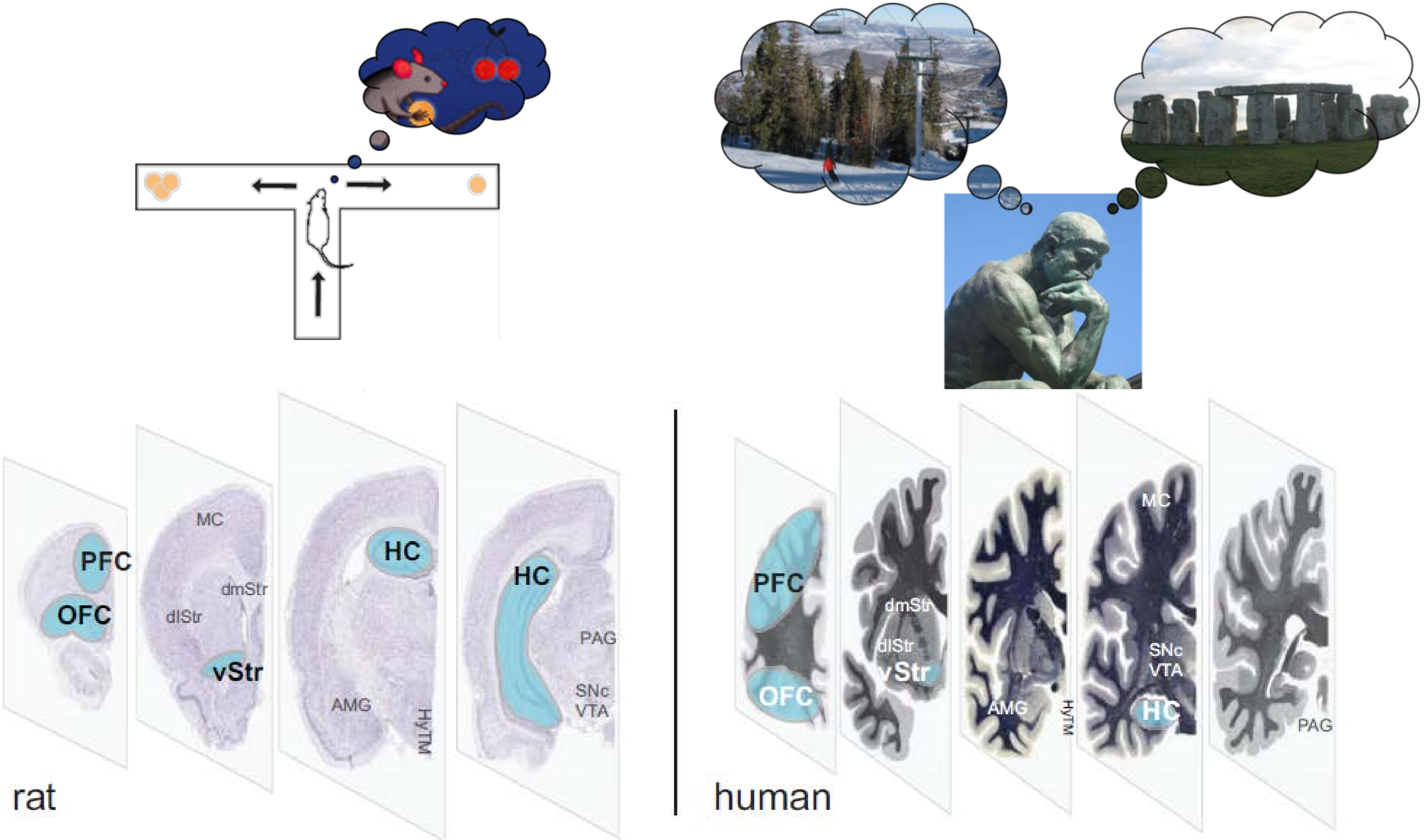
van der Meer, Kurth-Nelson, Redish (2012) *The Neuroscientist*

Redish (2016) *Nature Reviews Neuroscience*

Are the circuits the same?

Comparing circuits across species requires that both species are doing the same computations, not necessarily the same tasks.

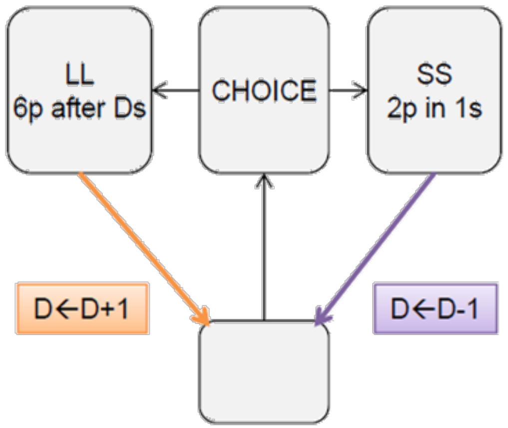


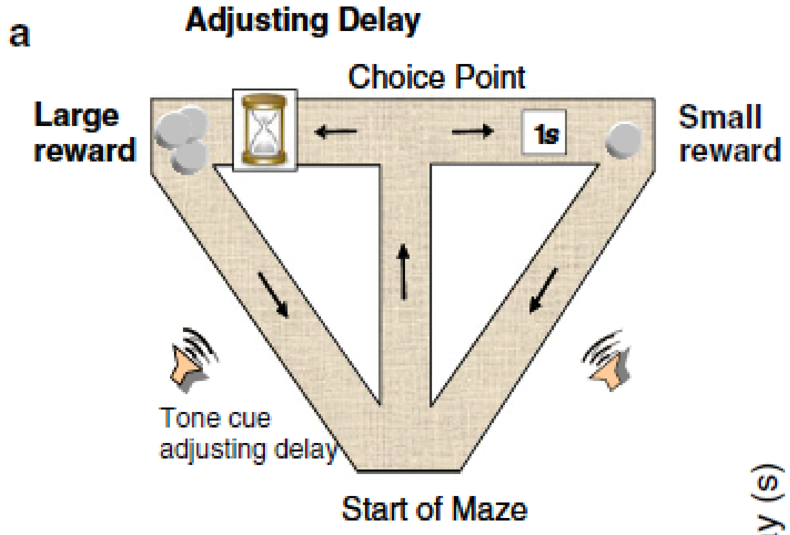


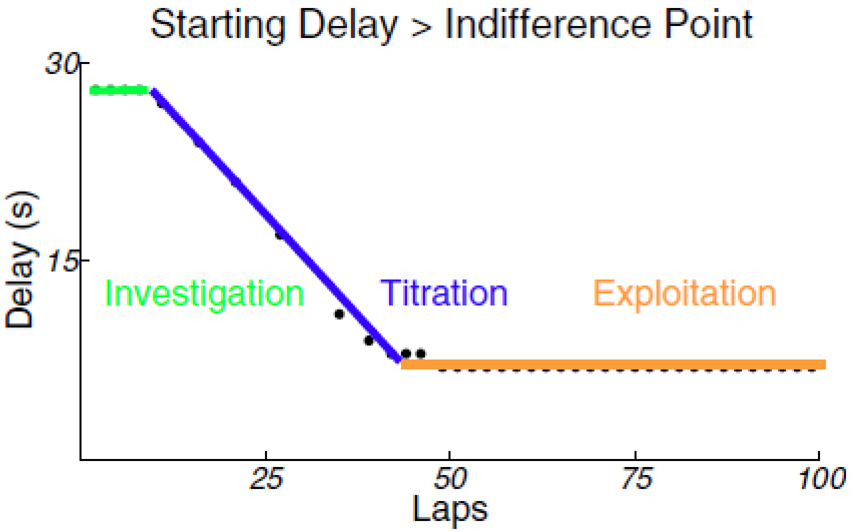
It helps to get the ethology right

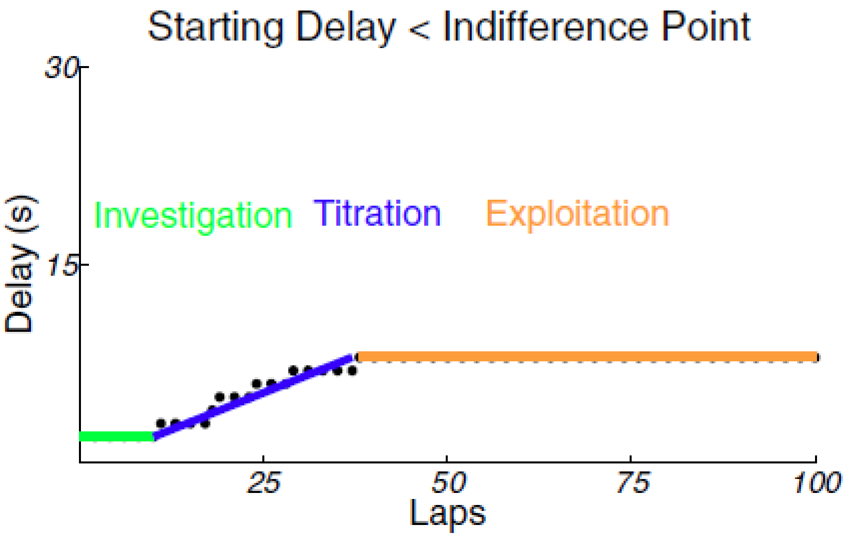
Rats on the Mazur adjusting delay discounting task are not locally differentiable from random.

Cardinal, Daw, Robbins, Everitt 2002 Neural Networks.









It helps to get the ethology right

This isn't just true for rats or mice. Human behavior depends on framing as well.

A vowel on one side implies an odd number on the other.

? B 7 ?

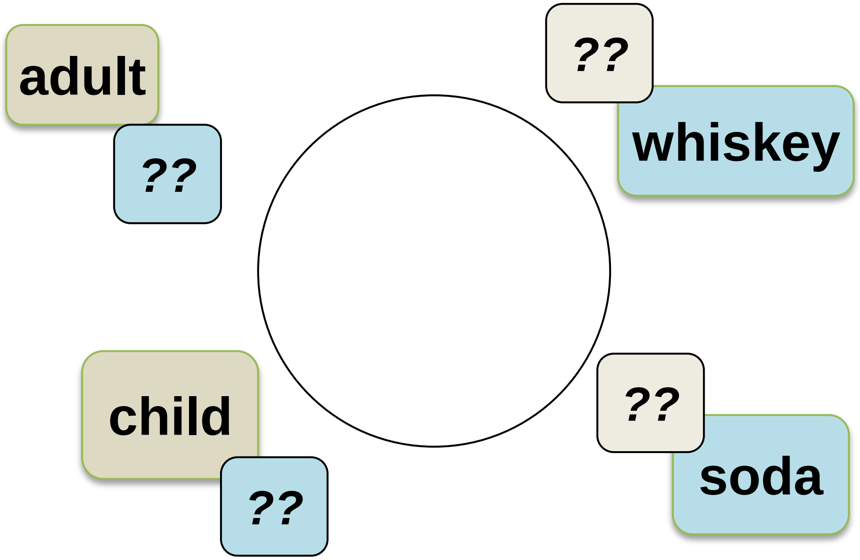
Which cards do you have to flip over to check this statement?

Wason and Johnson-Laird 1972

It helps to get the ethology right

This isn't just true for rats or mice. Human behavior depends on framing as well.

What do you have to do to check that no one underage is drinking alcohol?



Starting points…

- Computation is the key to cross-species translation

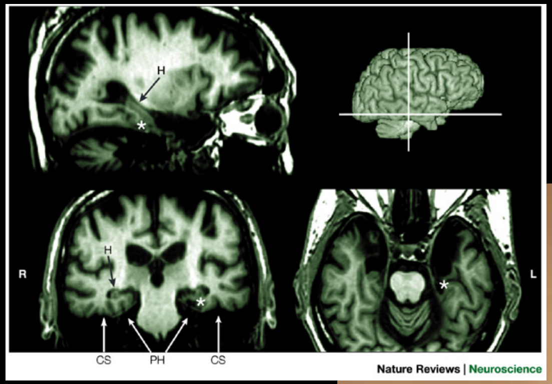
- Framing matters
  (it’s important to get the ethology right)

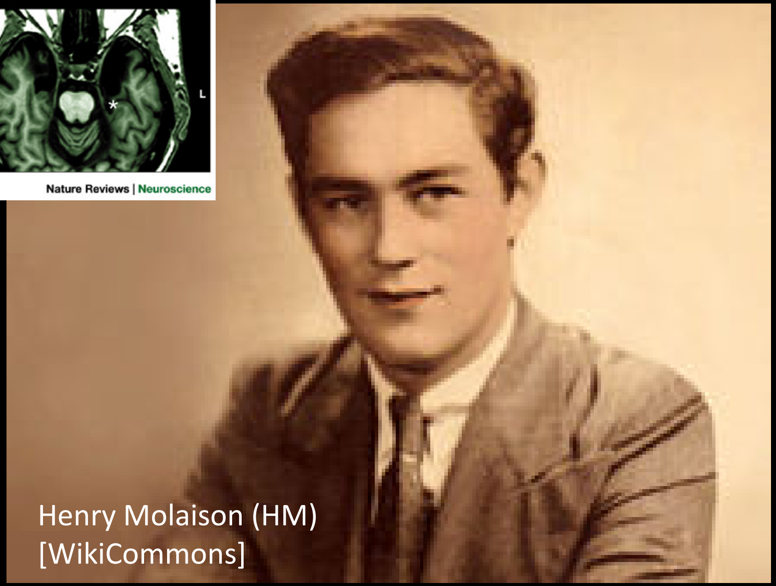
Two case studies

I Deliberation and Automation

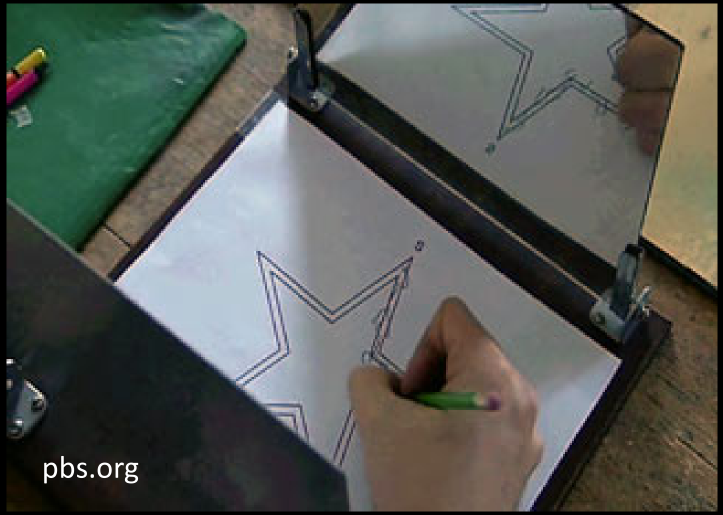
II Restaurant Row

I Deliberation and Automation





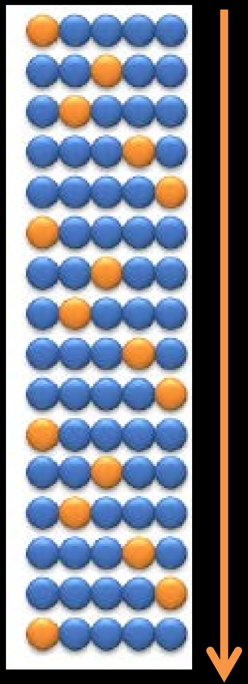
Henry Molaison (HM)
[WikiCommons]

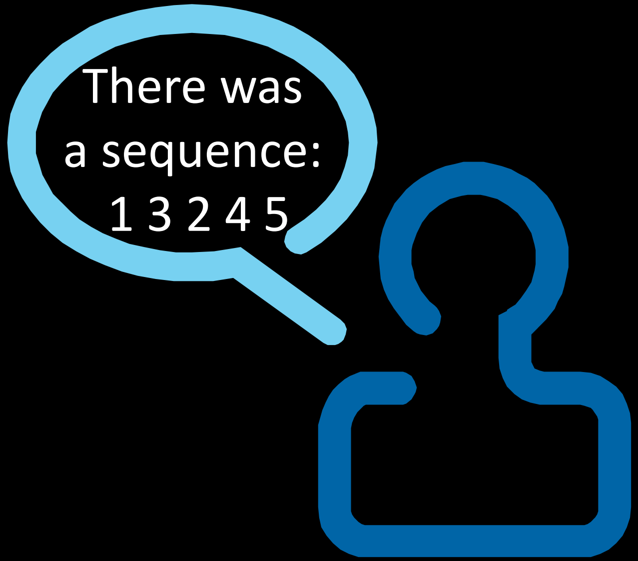


pbs.org

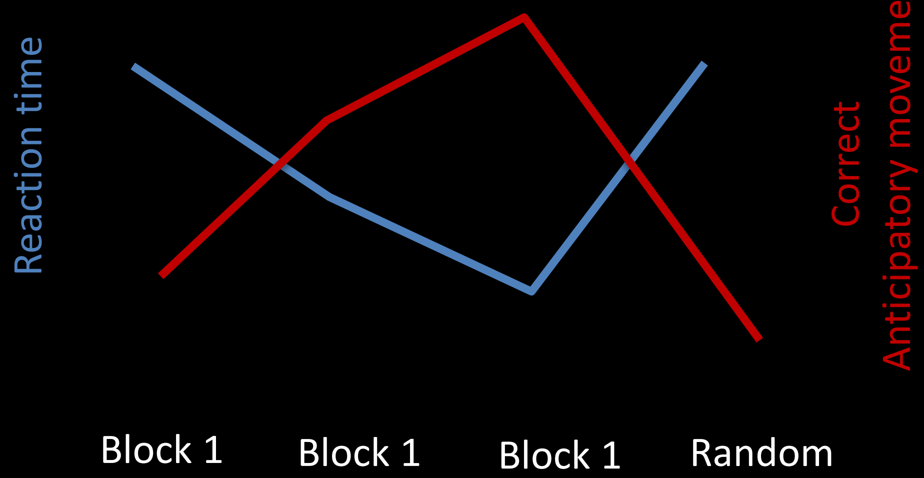
Serial reaction time task…

Sequence repeats over time

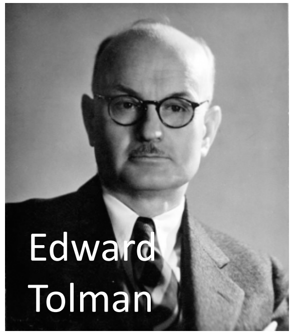




I Deliberation and Automation



We are not unitary decision-makers



Rats use cognitive maps to navigate.

(1932, 1948)

Rats learn stimulus-response action-chains.

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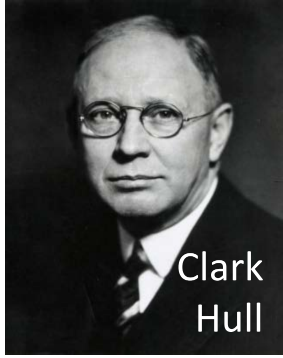
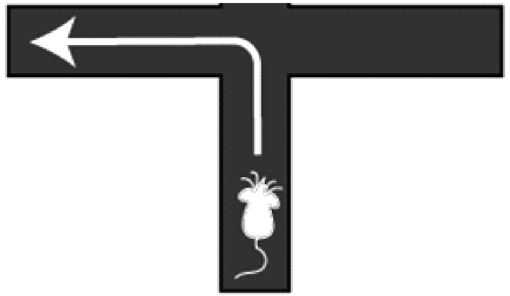
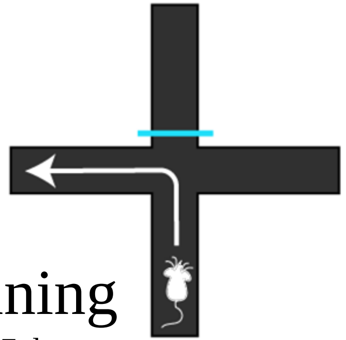
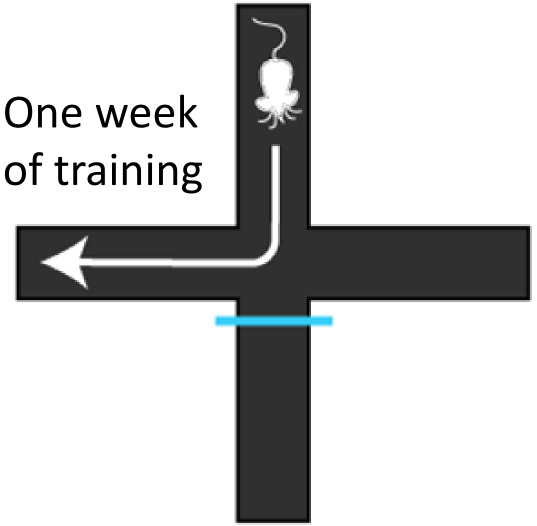




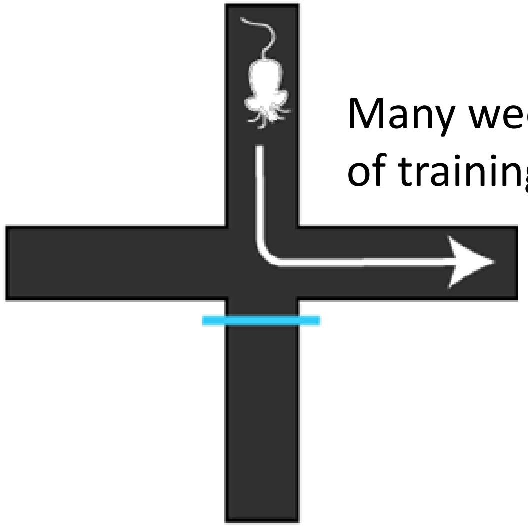


Training
4x/day, 7 days

One week of training



Many weeks of training



Place-strategy
(return to same location by taking a different action)

Dependent on hippocampal function

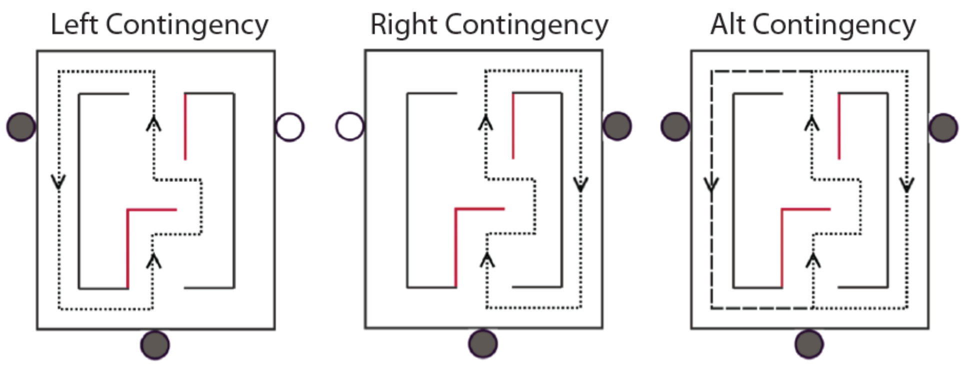
Response-strategy
(turn in same direction but reach a different goal)

Dependent on dorsolateral striatal function

Actual experiment from Packard & McGaugh 1992.

Matthijs van der Meer, Adam Johnson, Neil Schmitzer-Torbert, Redish (2010) *Neuron*

The left-right-alternate (LRA) task



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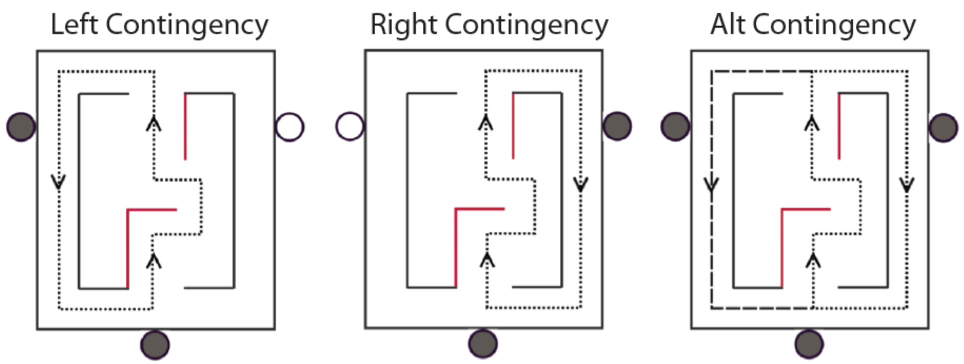

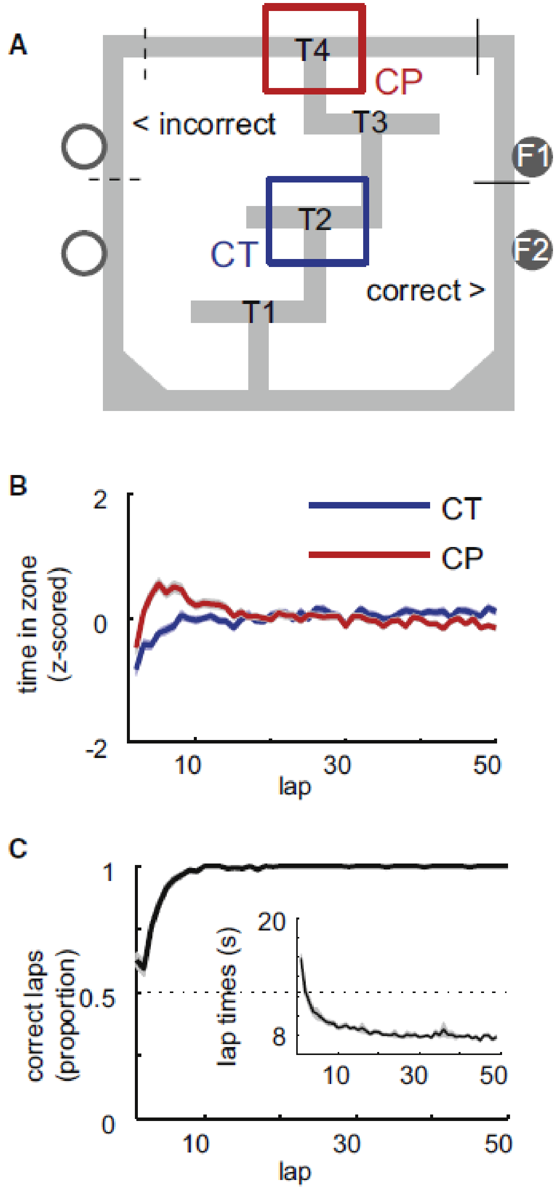

Version 1: *Strategy changes from day to day (2000-2010)*

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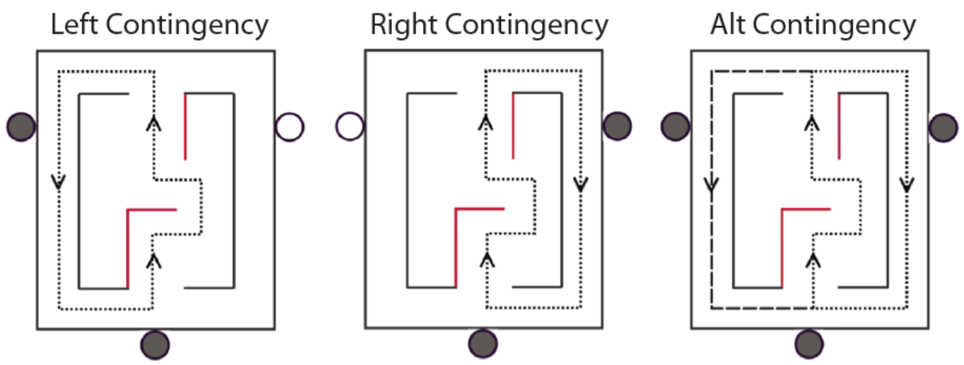
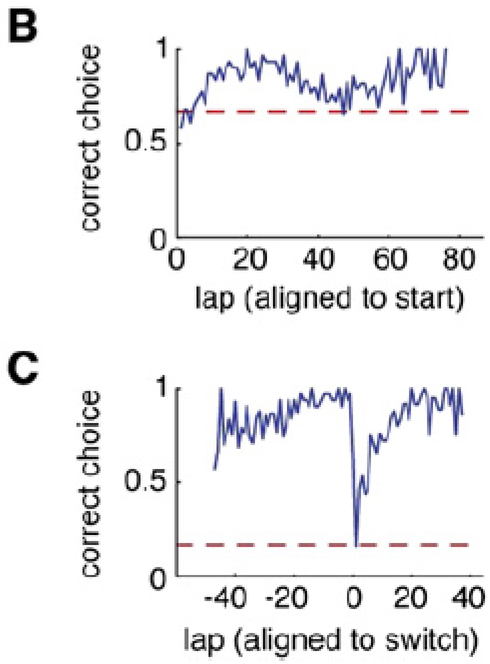


Version 1: *Strategy changes from day to day (2000-2010)*

Version 2: *One strategy change midway through a session on probe days (2010-2015)*



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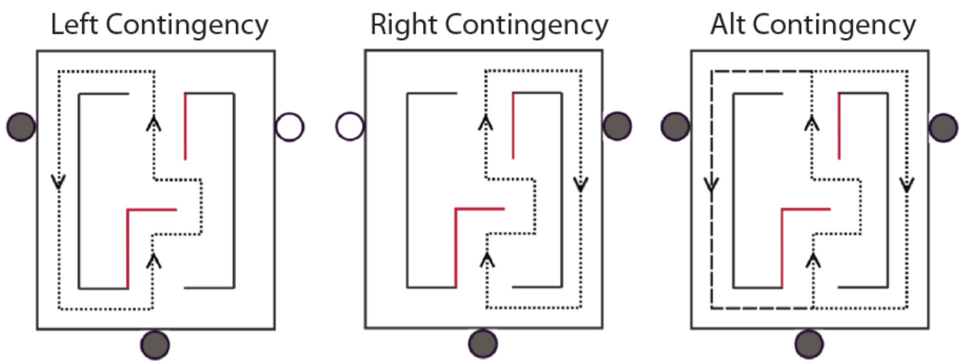
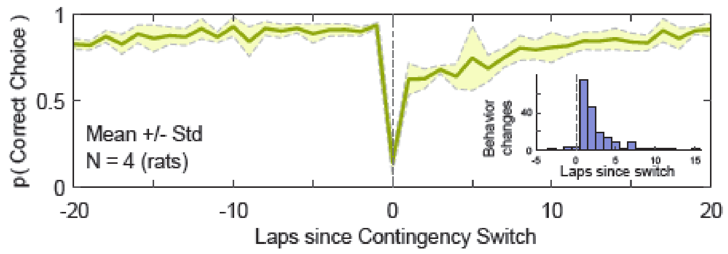


Version 1: *Strategy changes from day to day (2000-2010)*

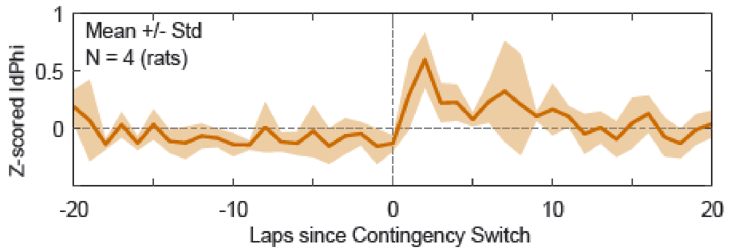
Version 2: *One strategy change midway through a session on probe days (2010-2016)*

Version 3: *Multiple strategy changes within each day (2017-present)*

Rat performance decreased after a contingency switch.



Vicarious trial and error, a behavioral marker of deliberation, increased after a contingency switch.

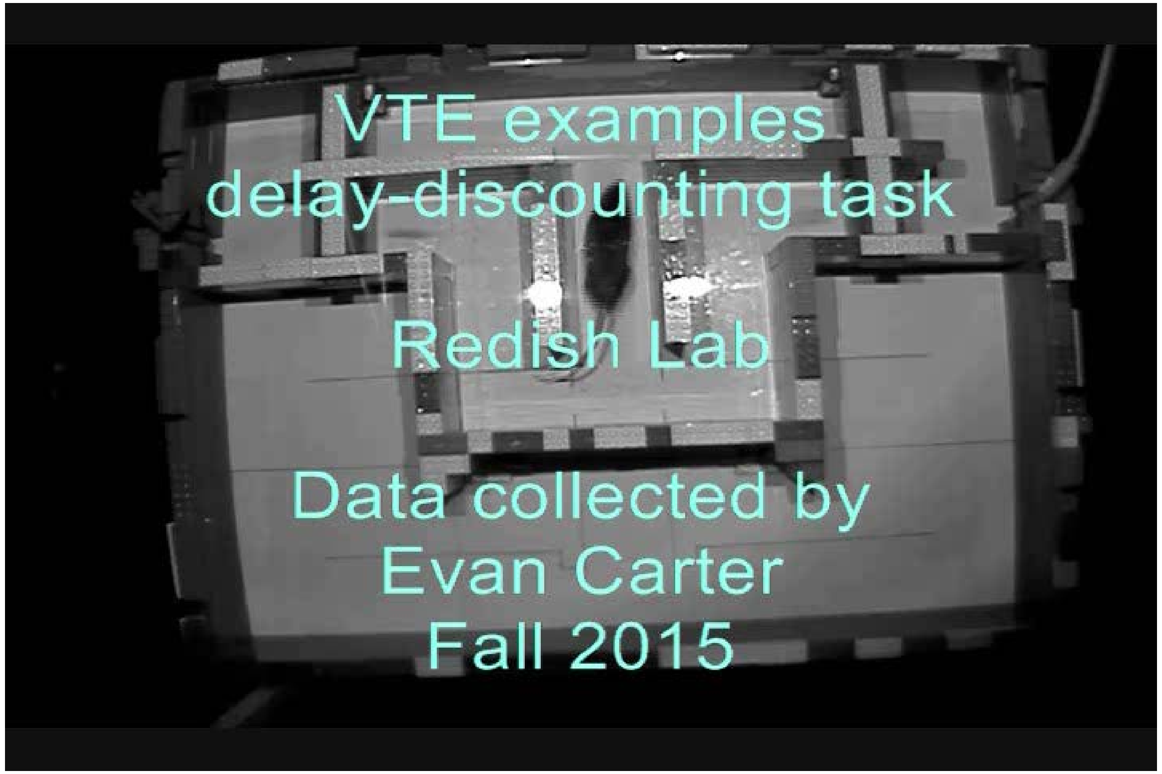


Result 1: VTE laps
A marker of deliberation

When rats come to choice-points, they sometimes pause and look back and forth.

(Meunzinger and Gentry 1931, Meunzinger 1938, Tolman 1938, 1939, 1946, 1948, ...)

Tolman suggested that this allows the animal to consider "future possibilities".



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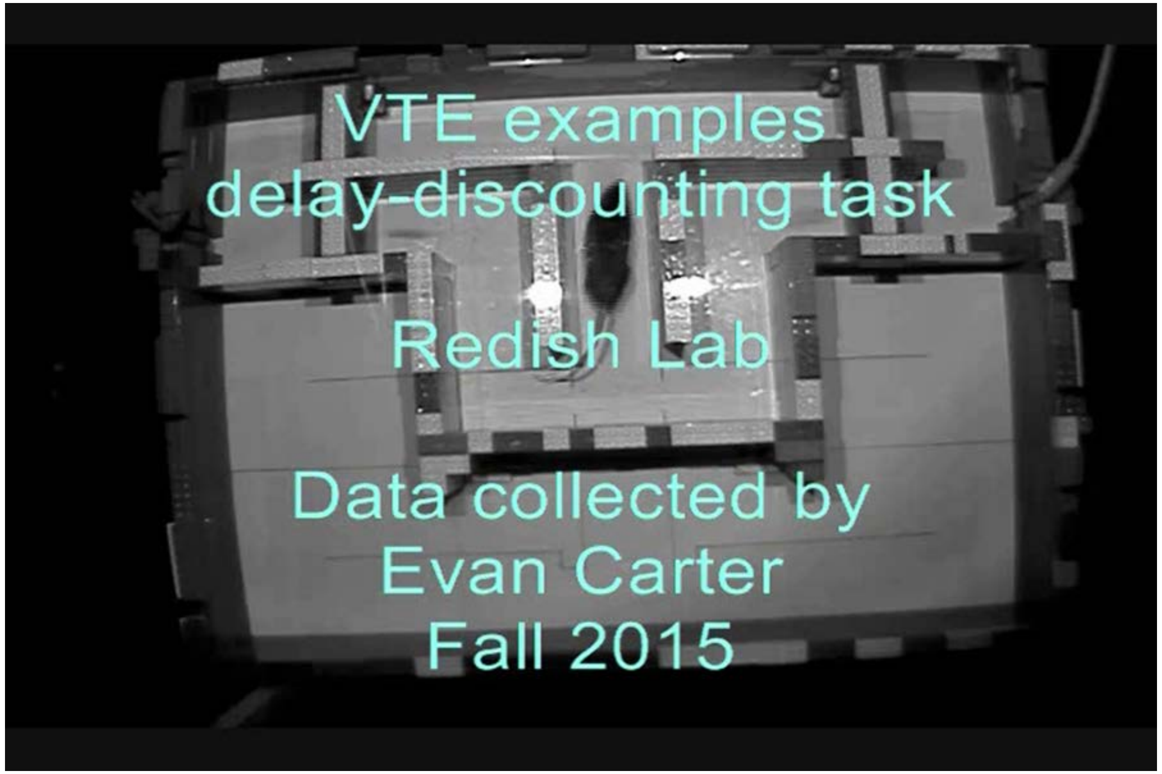

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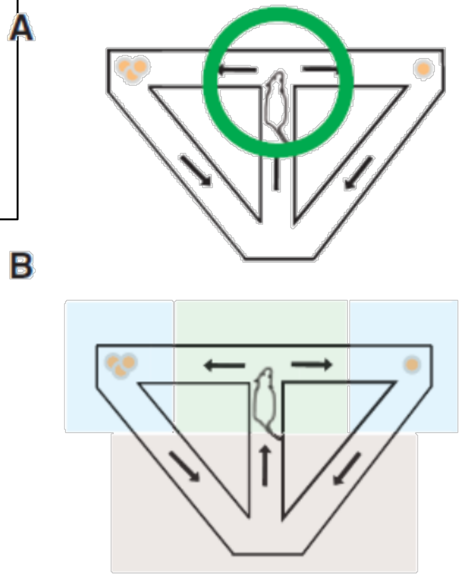
Adam Johnson, Redish (2007) J Neurosci
Anoopum Gupta, van der Meer, Touretzky, Redish (2012) Nat Nsci
Seiichiro Amemiya, Redish (2016) J Neurosci
Andy Papale, Zielinski, Frank, Jadhav, Redish (2016) Neuron



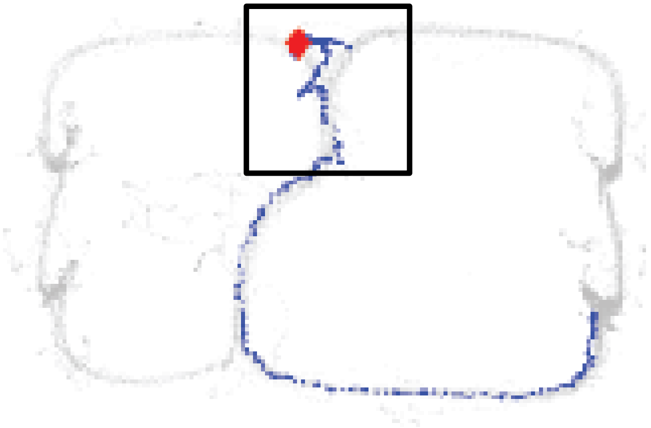
C

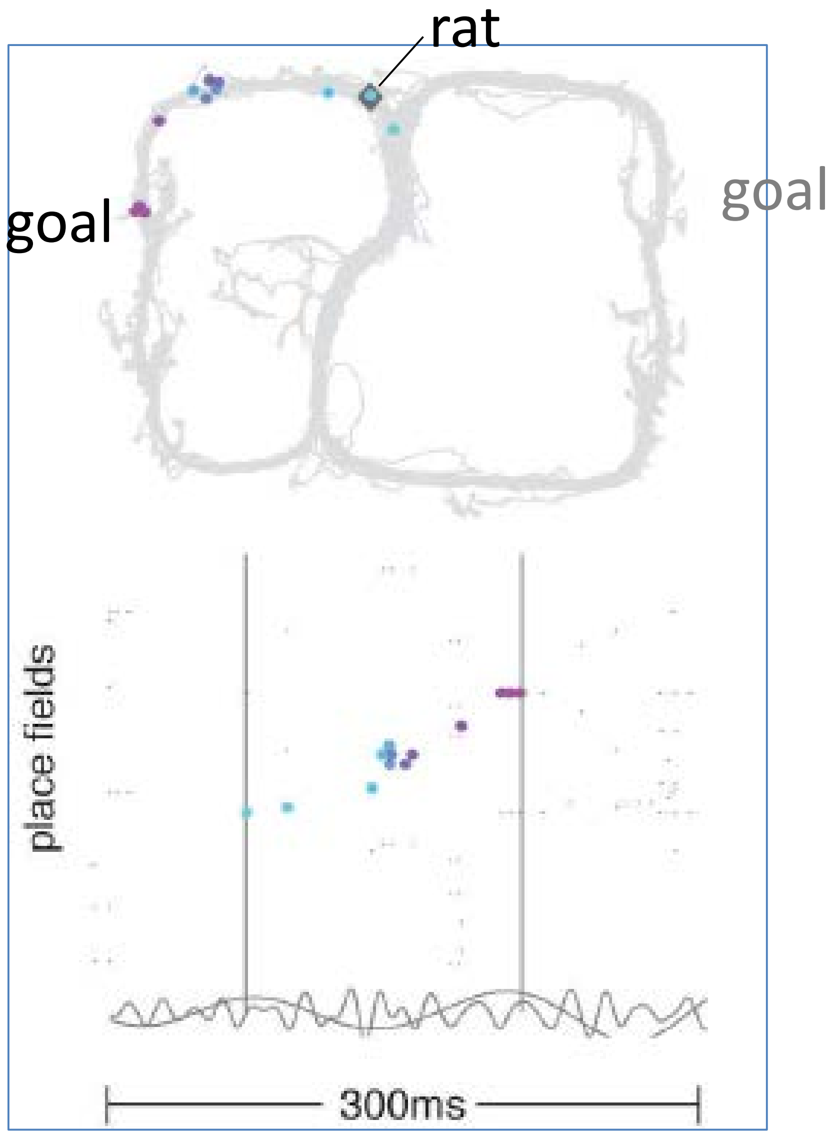
D

Hippocampal representations sweep ahead of the animal

Anoopum Gupta, van der Meer, Touretzky, Redish (2012) Nature Neurosci

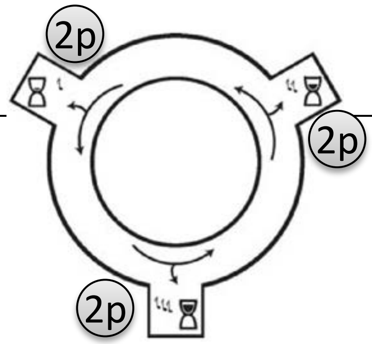
During vicarious trial and error (VTE) events, decoding reveals coherent sequences running ahead of the animal alternating between goals.

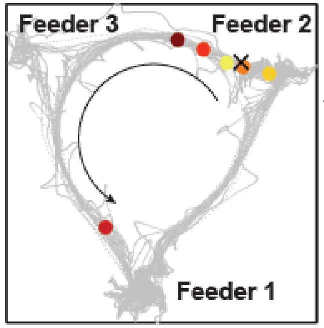


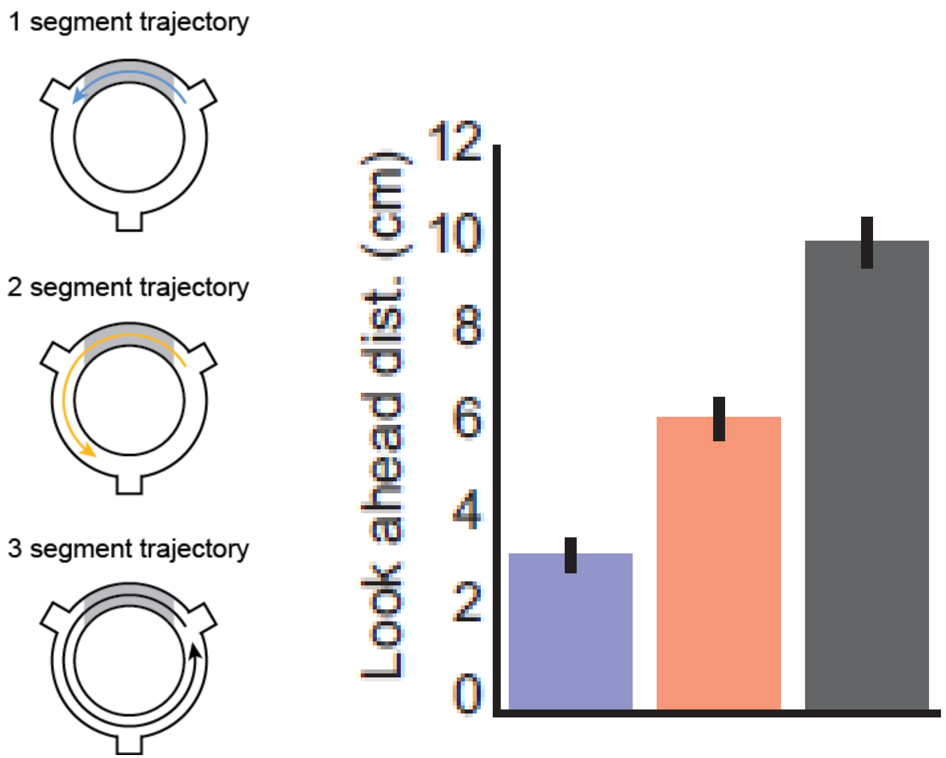


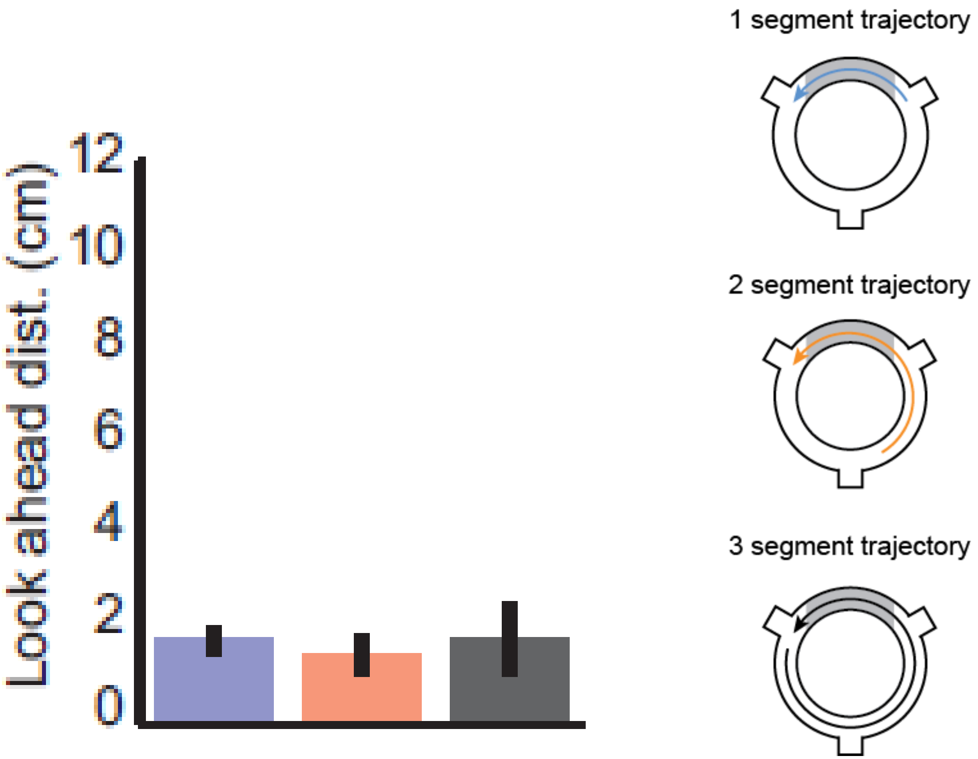
Hippocampal sequences go to the next goal

Andrew Wikenheiser, Redish (2015) Nature Neurosci

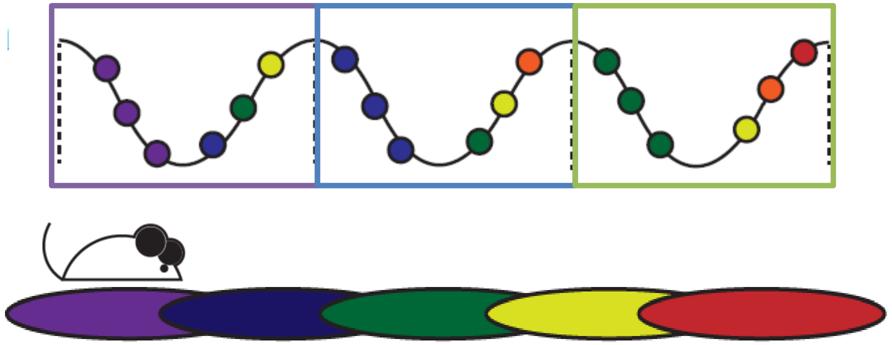




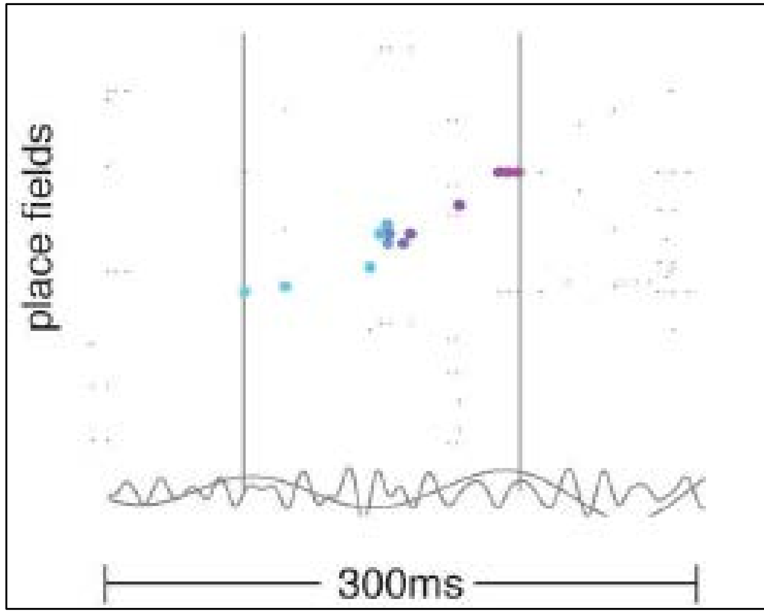




Theta sequences



Every theta cycle consists of a "you are there" component, followed by a "what's next" component.



Anoopum Gupta, et al (2012) Nature Neurosci

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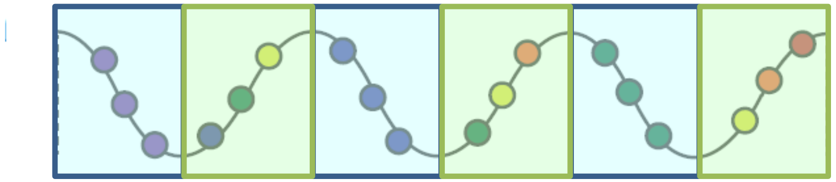

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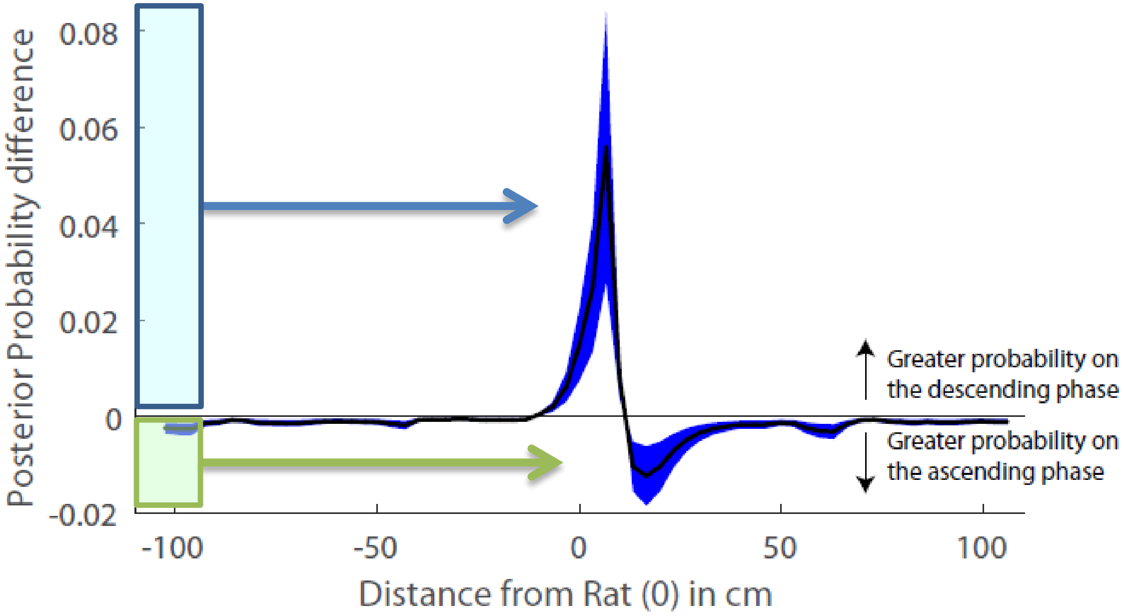

Brandy Schmidt, Anneke Duin, Redish (2019) J Neurophysiology

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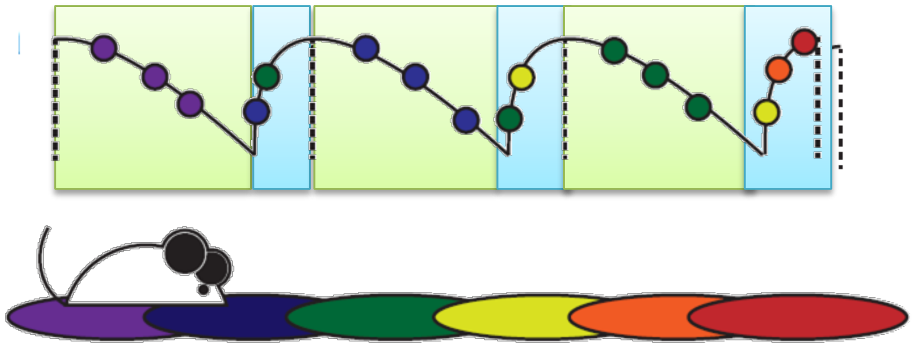

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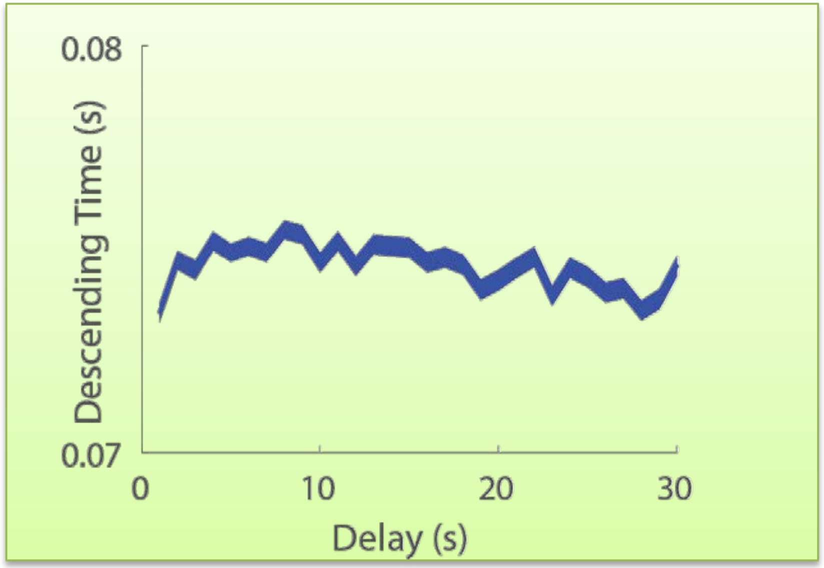
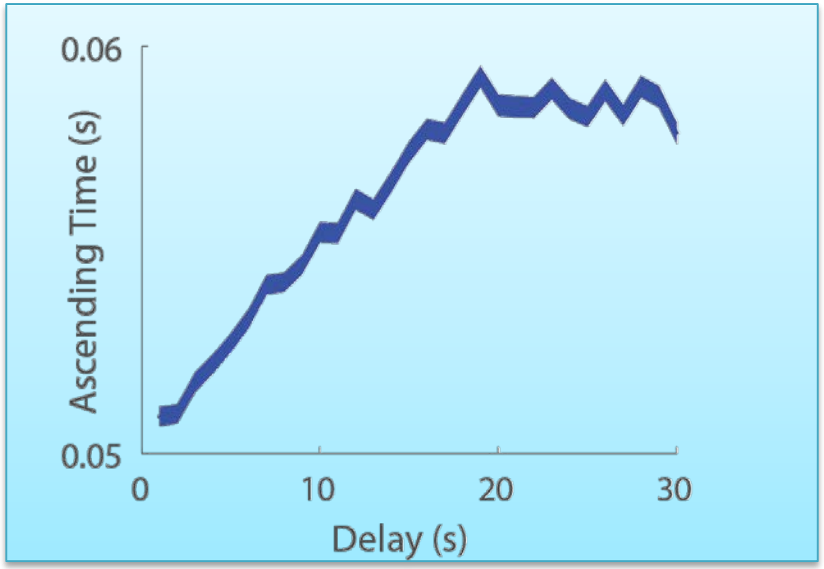
When faced with a delay to a goal, the second half (sweep portion) of the theta cycle lengthens.





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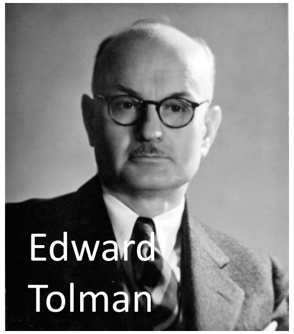

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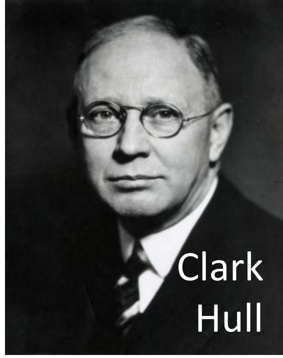

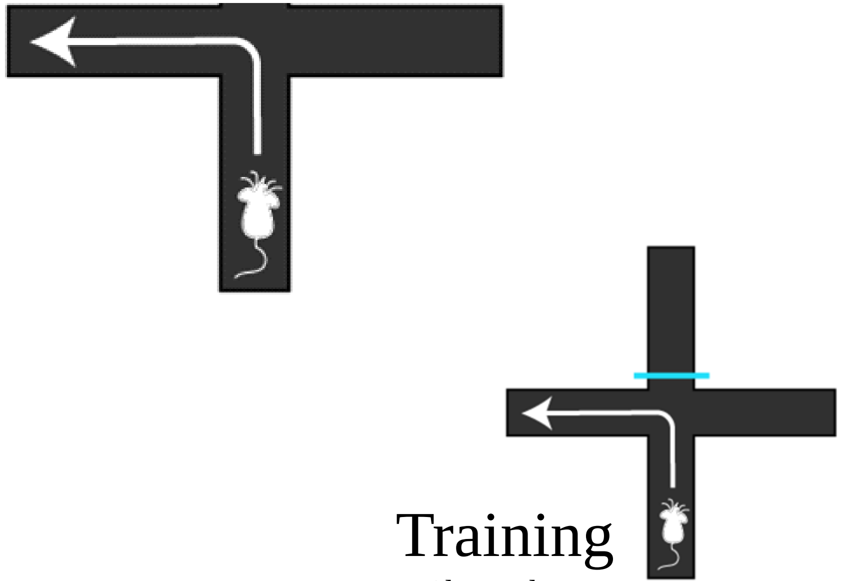

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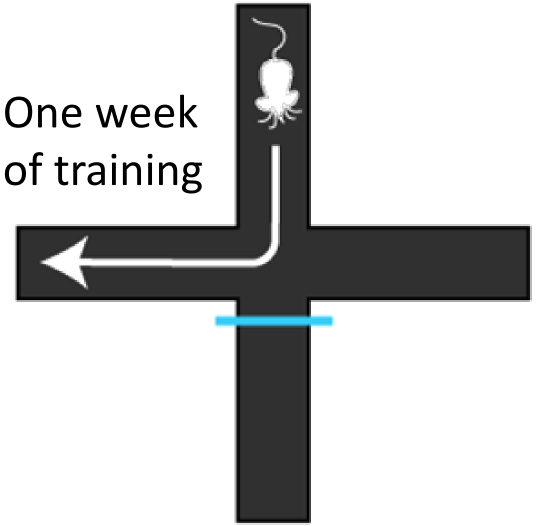
One week of training



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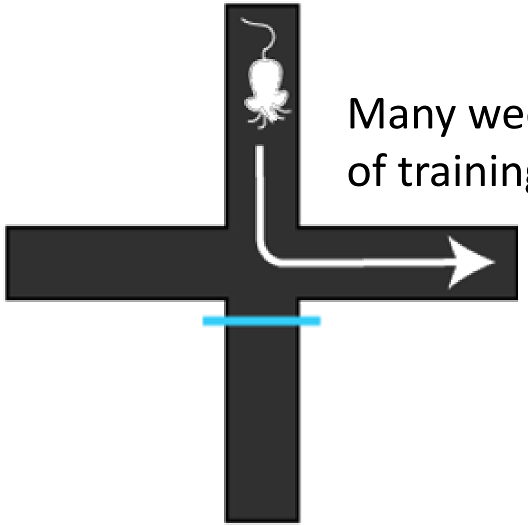

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Dependent on hippocampal function

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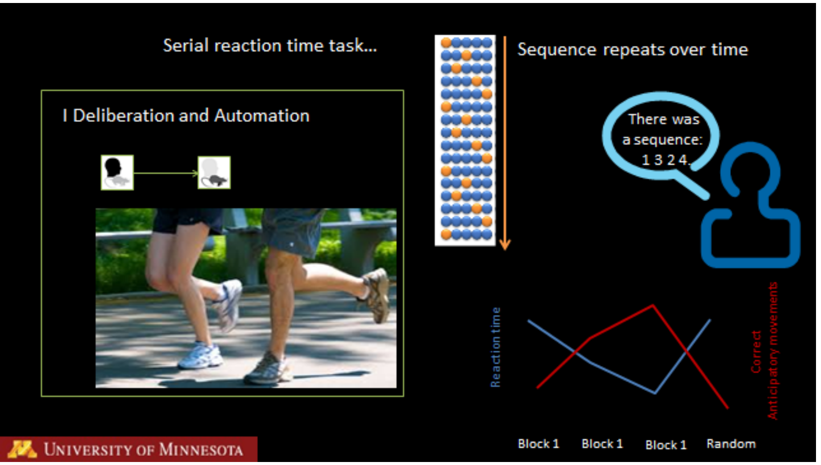
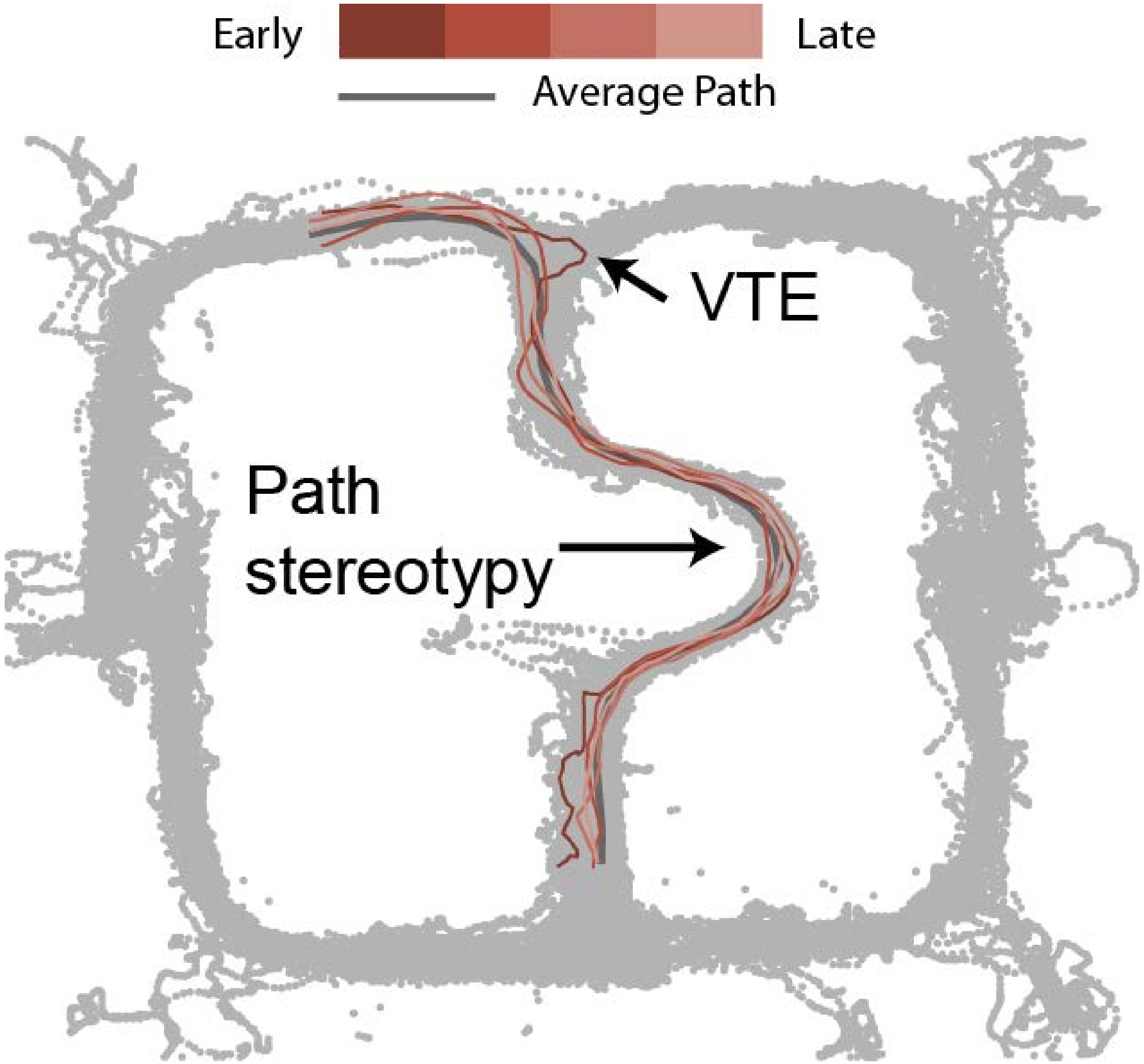
Dependent on dorsolateral striatal function

Actual experiment from Packard & McGaugh 1992.

Result 2: Rats develop automation (flow)





Neil Schmitzer-Torbert, Redish (2002) Arch Itals Biologie
Brendan Hasz, Redish (2018) *PhD Thesis; papers under review*

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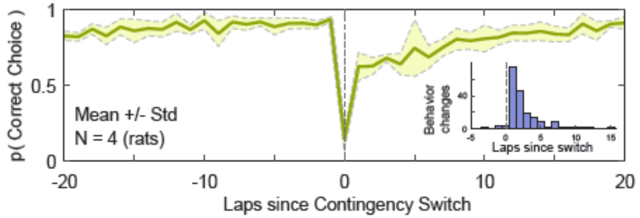
Rat performance decreased after a contingency switch.



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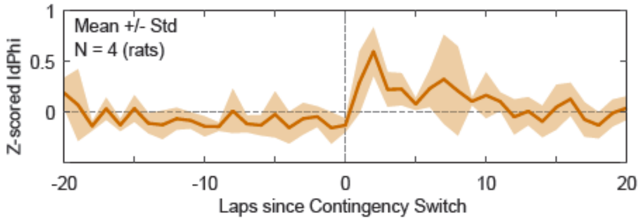

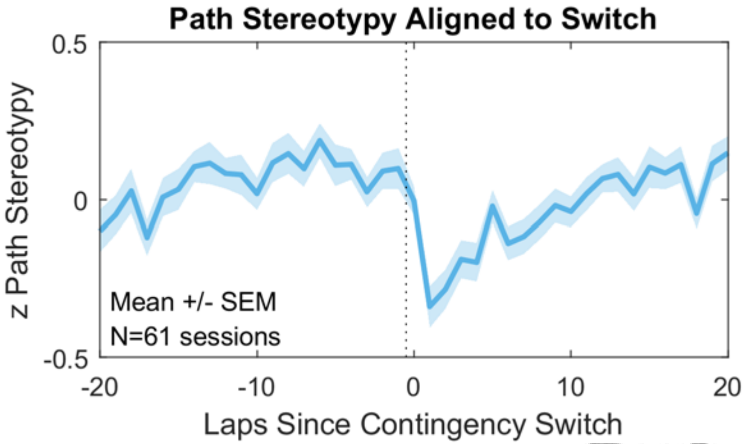

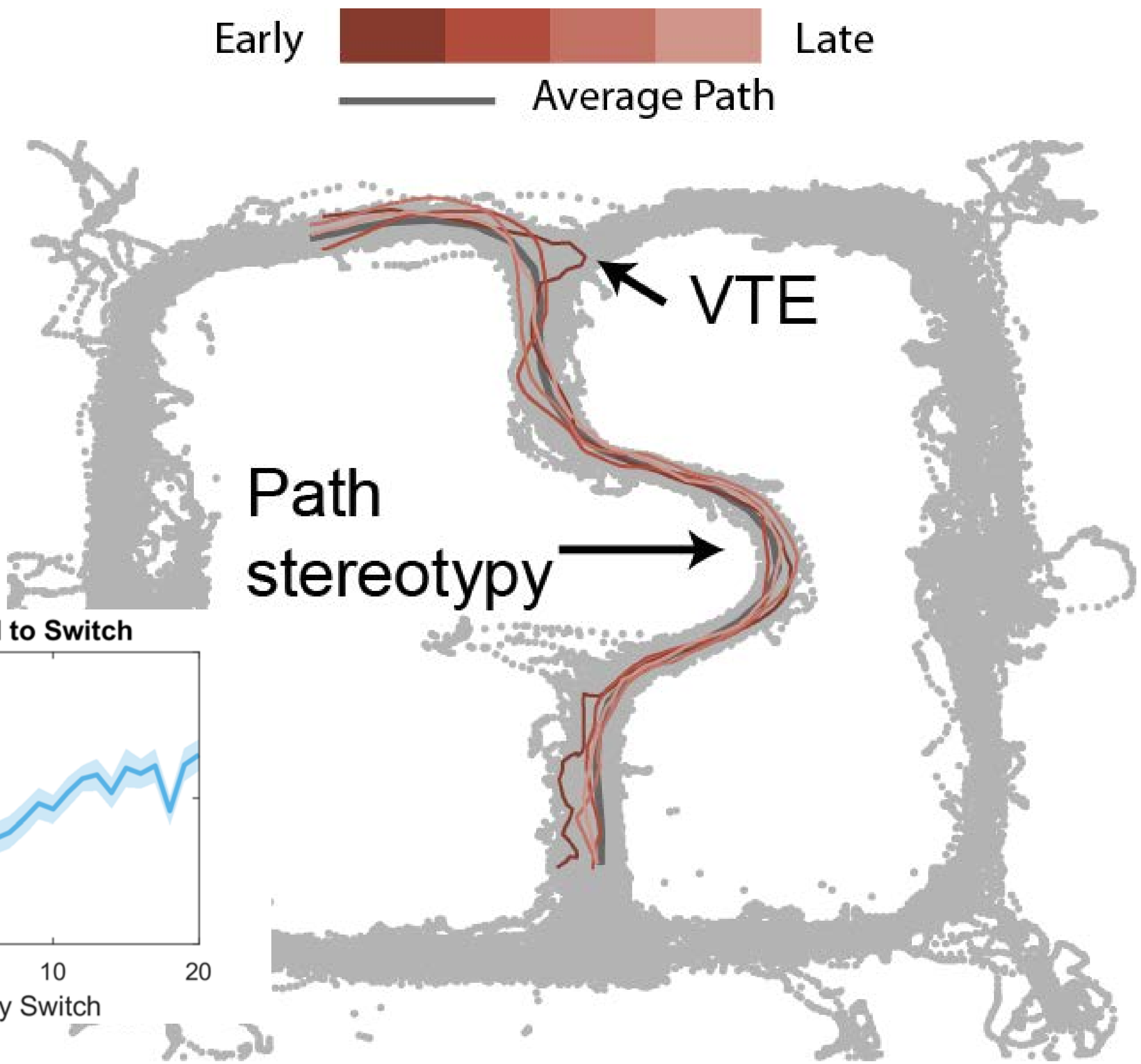

Procedural actions

Predictions:

1. We should see cells represent key situation parameters.
2. No sweeps to a goal
3. Represent the beginning of each action sequence

Neil Schmitzer-Torbert, Redish (2008) Neuroscience

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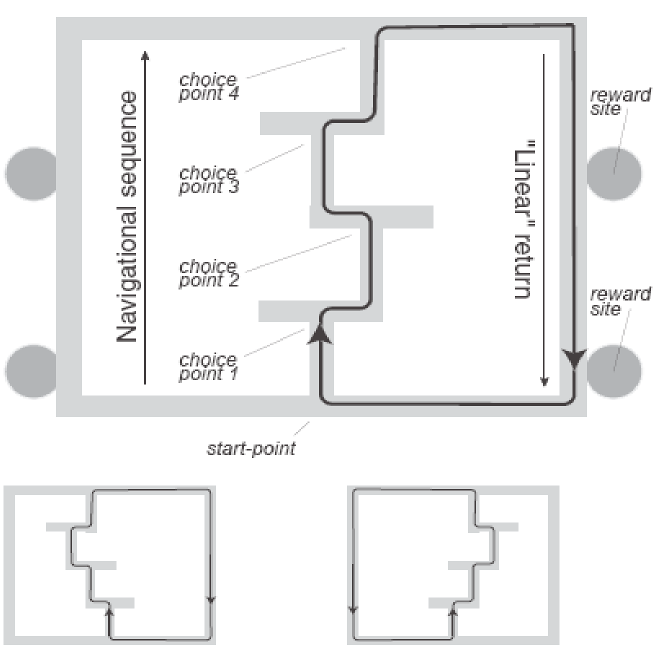
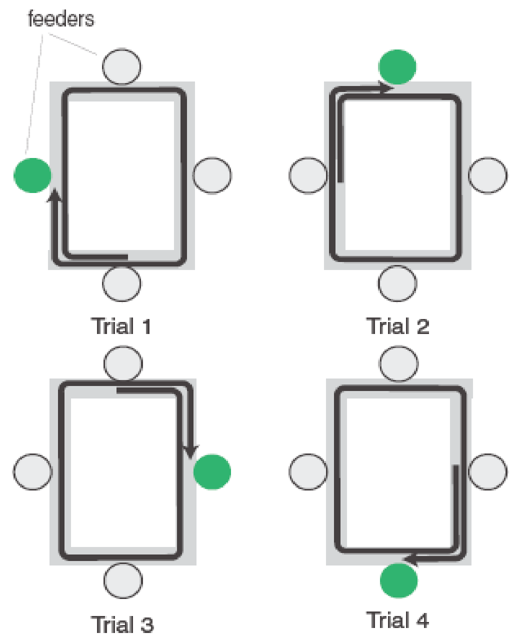
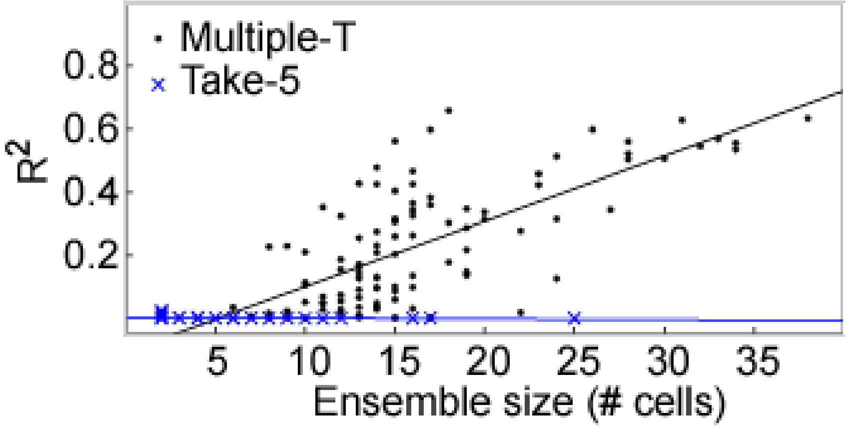
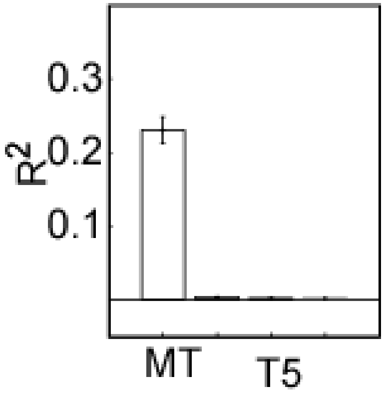


Take 5



Spatial reconstruction





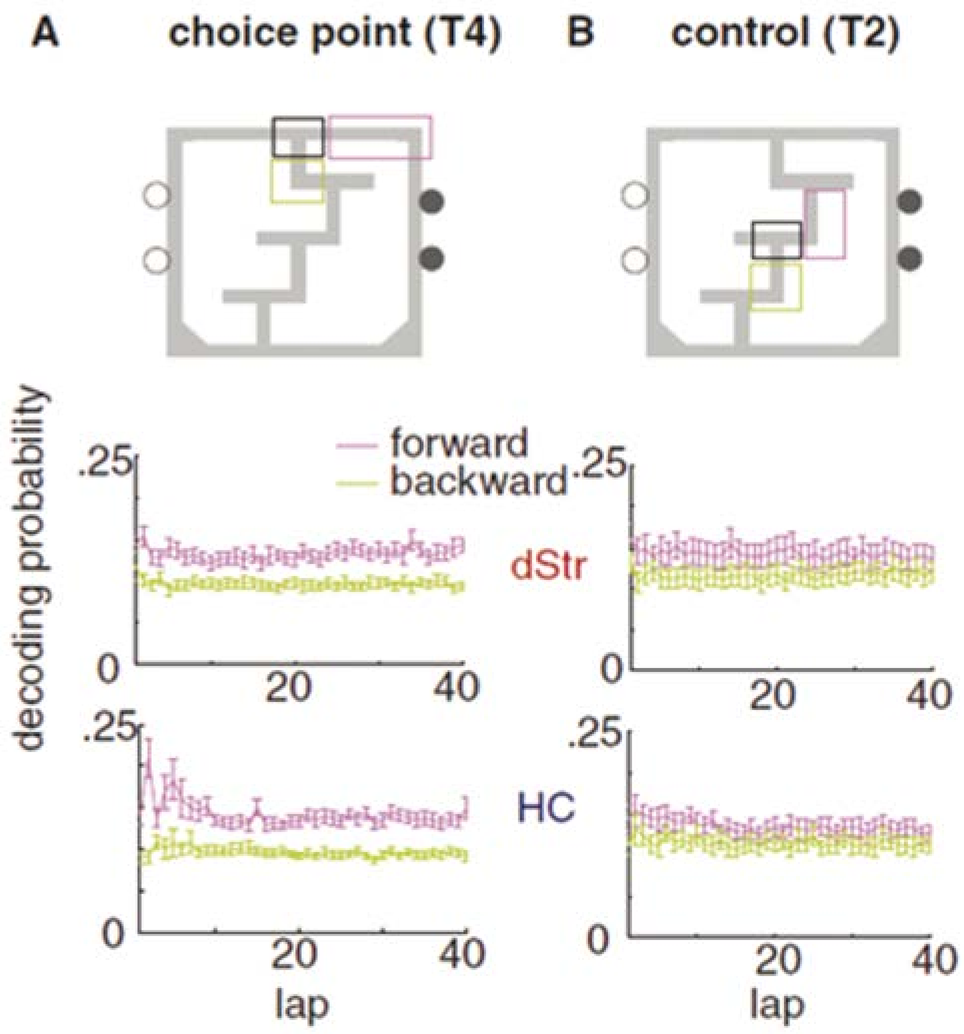
Procedural actions

Predictions:

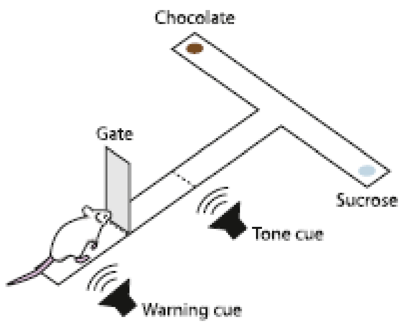
1. We should see cells represent key situation parameters.

2. No sweeps to a goal

3. Represent the beginning of each action sequence



Procedural actions



Smith & Graybiel 2013

Predictions:

1. We should see cells represent key situation parameters.
2. No sweeps to a goal
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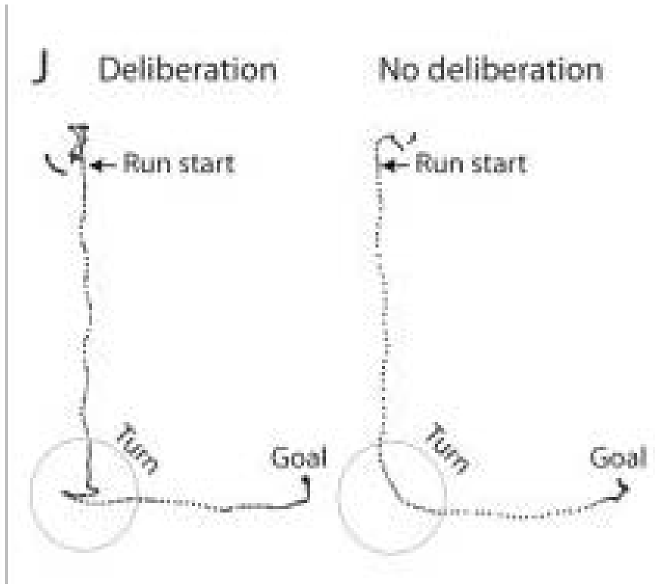

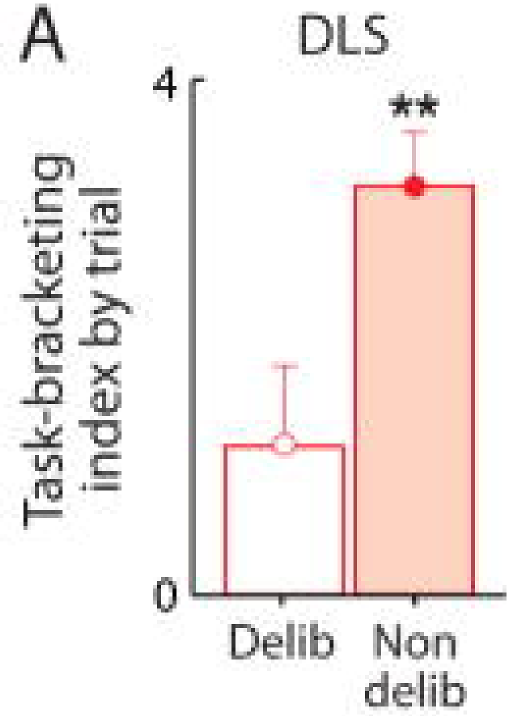

Procedural actions

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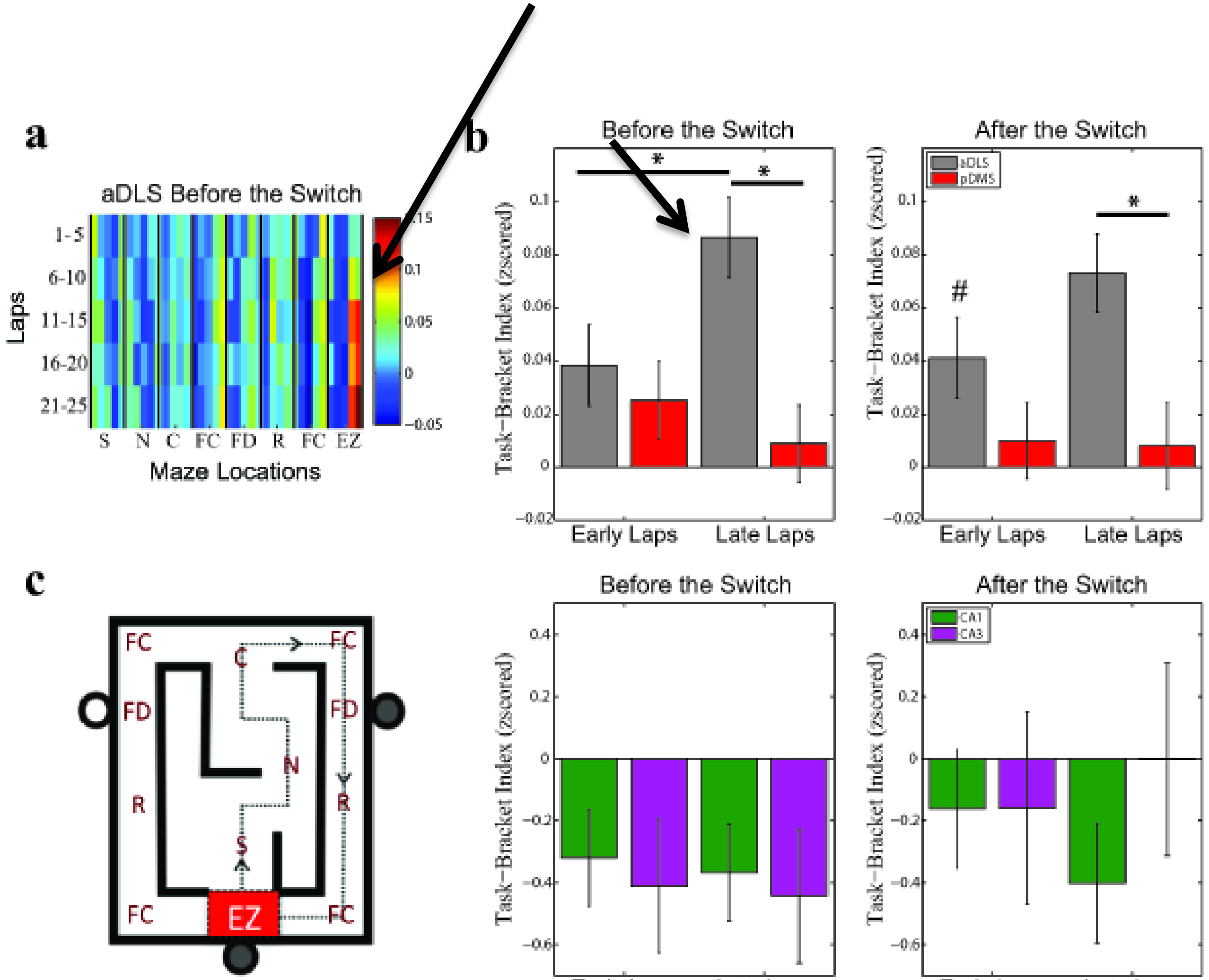


I Deliberation and Automation

Result 1: Rats deliberate over choices (prefrontal – hippocampal interactions; sweeps to the goal).

Result 2: Rats develop a flow as they automate their behavior (dorsolateral striatal interactions; task-initiation bursts).

Result 3: ventral striatum (and orbitofrontal cortex) represent reward during deliberation and value during automation.

Result 4: prelimbic cortex encodes strategy and reflects strategy changes

Two case studies

I Deliberation and Automation

II Restaurant Row

Two case studies

II Restaurant Row

Adam Steiner, Redish (2016) *Nature Neuroscience*
Brian Sweis, Mark Thomas, Redish (2018) *PLoS Biology*

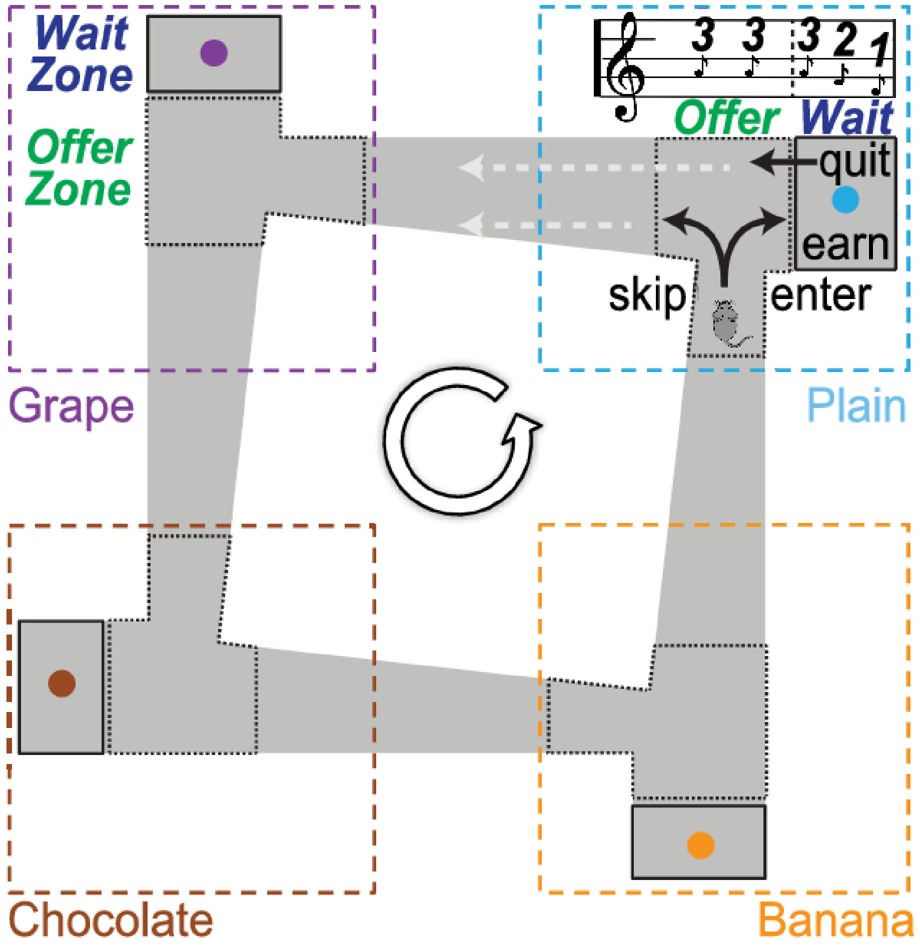
Restaurant Row

Rats run around a circular track for food reward.

On each encounter, they are offered reward only after a delay.

The delay is completely cued with an auditory tone that counts down. (pitch=delay)

Because they have a **limited time on the track**, waiting for one reward must be balanced against waiting for another.



Restaurant Row

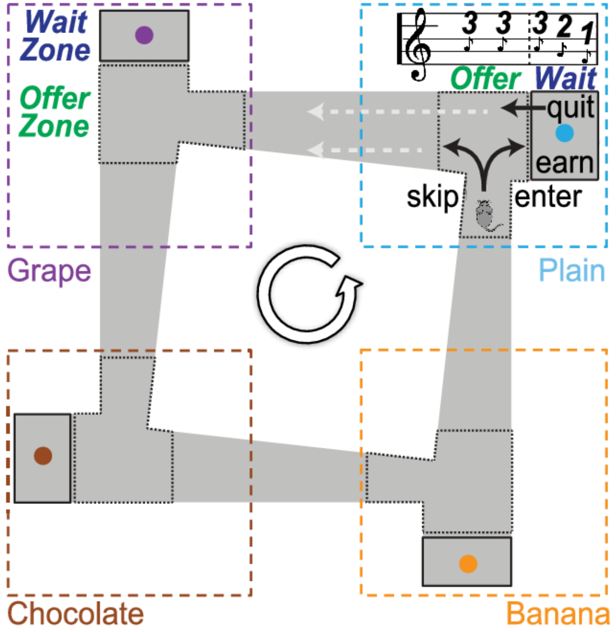
Restaurant Row

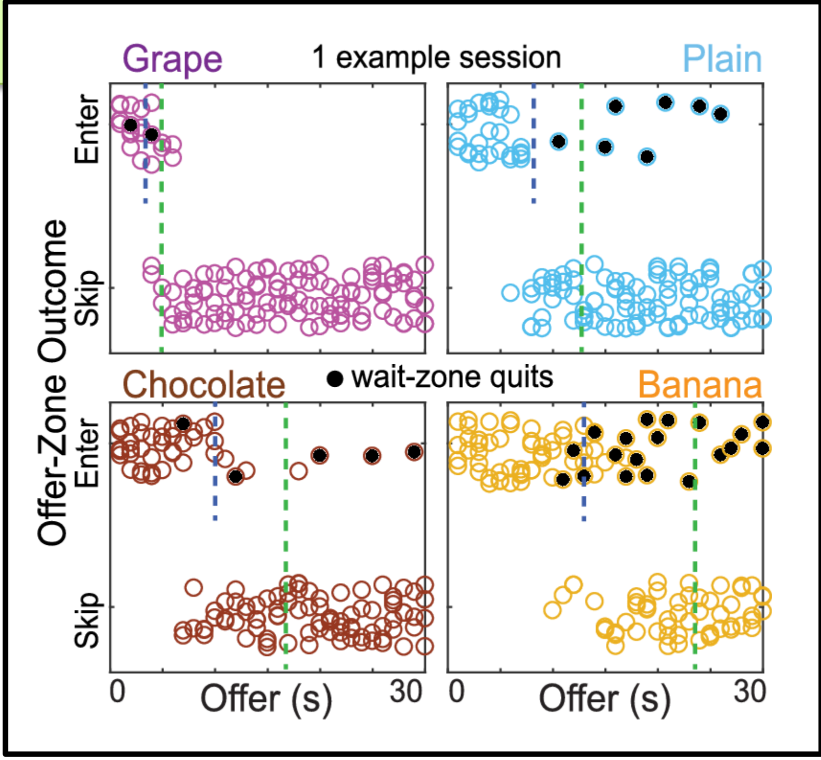
Adam Steiner, Redish (2016) *Nature Neuroscience*

Brian Sweis, Mark Thomas, Redish (2018) *PLoS Biology*

Because they have a limited time on the track, waiting for one reward must be balanced against waiting for another.

This means we can talk about ***good deals*** *and* ***bad deals***.





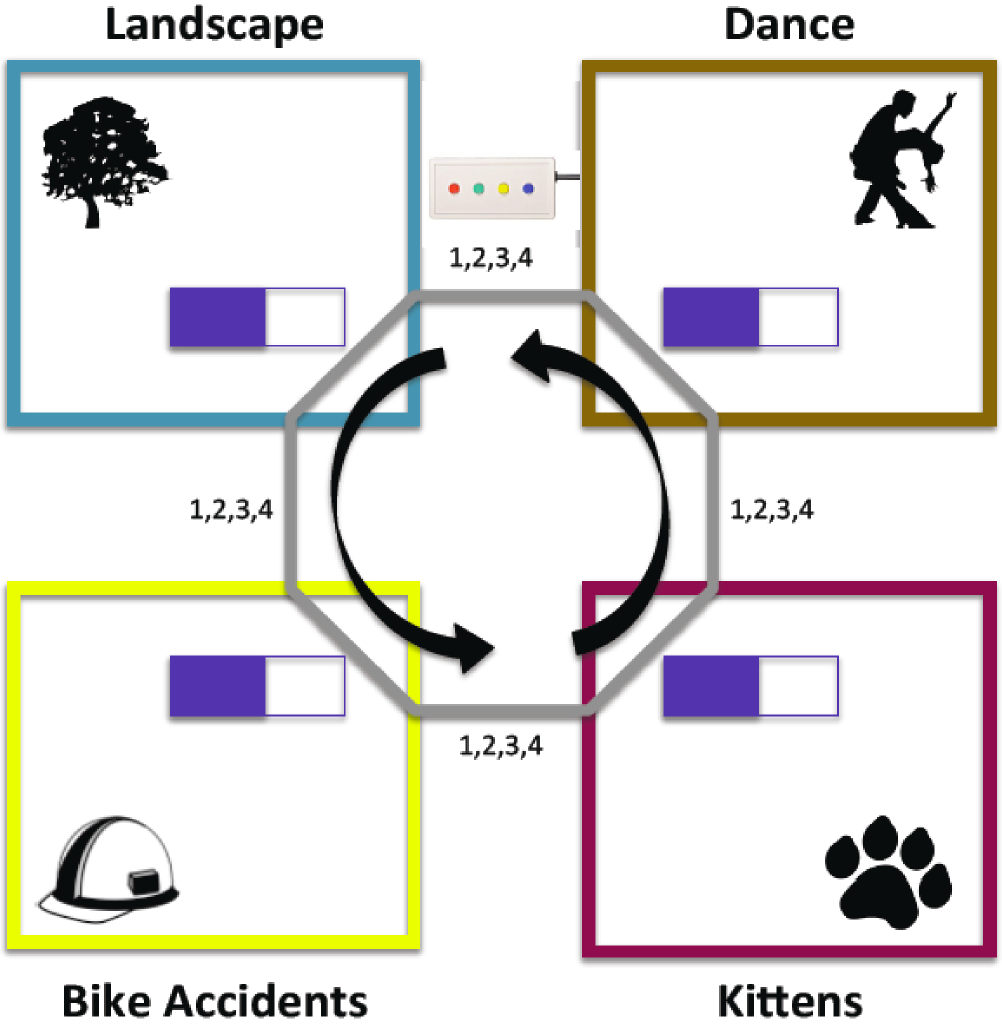
From rats and mice to humans

What do humans forage for?

Samantha Abram, Breton, Schmidt, Redish, MacDonald (2016) *CABN*

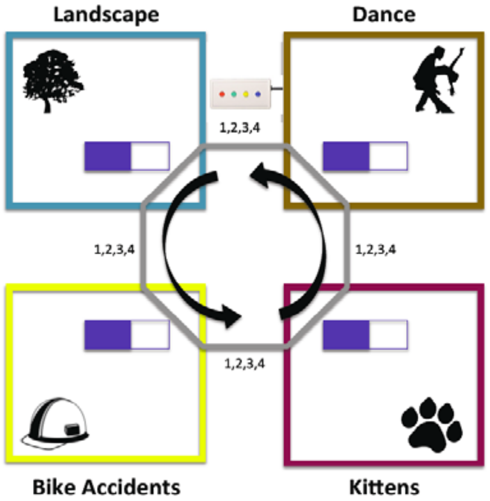
From rats and mice to humans

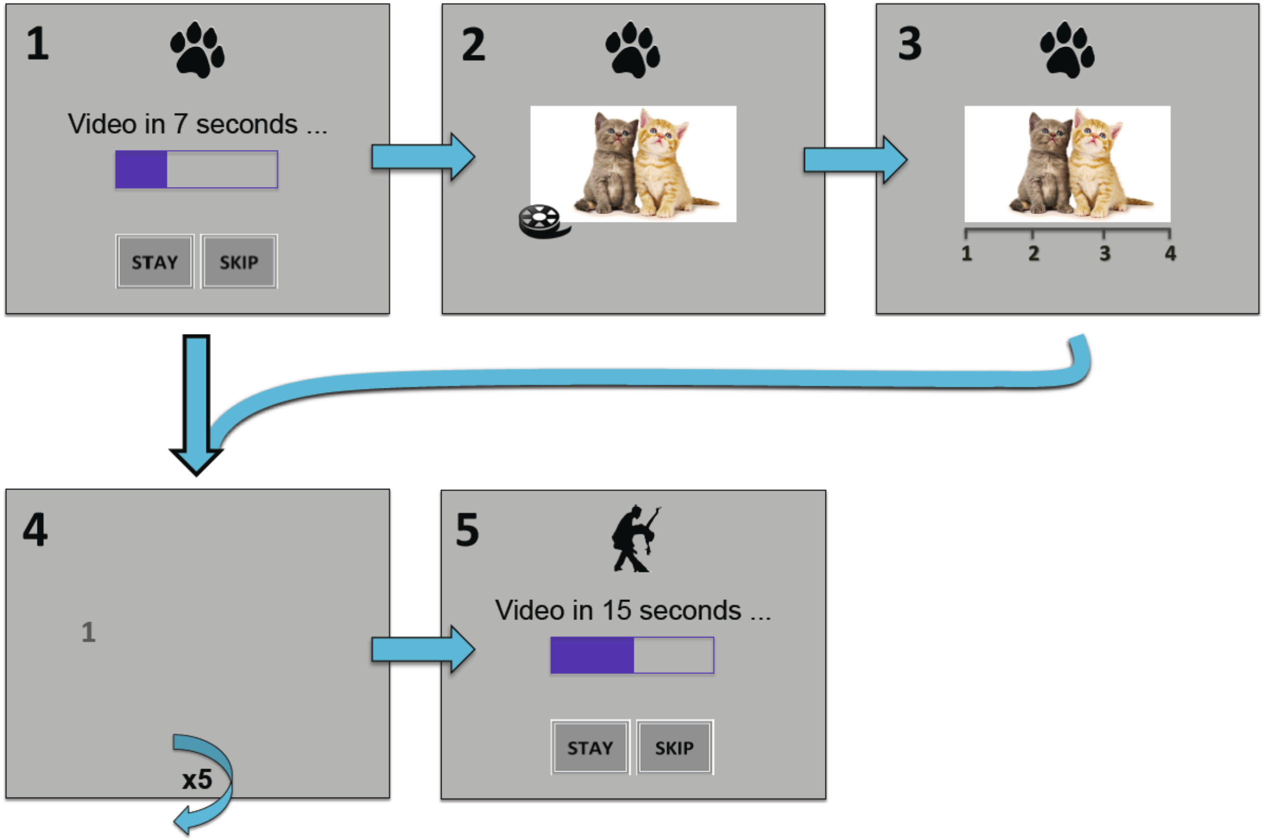
What do humans forage for?



From rats and mice to humans

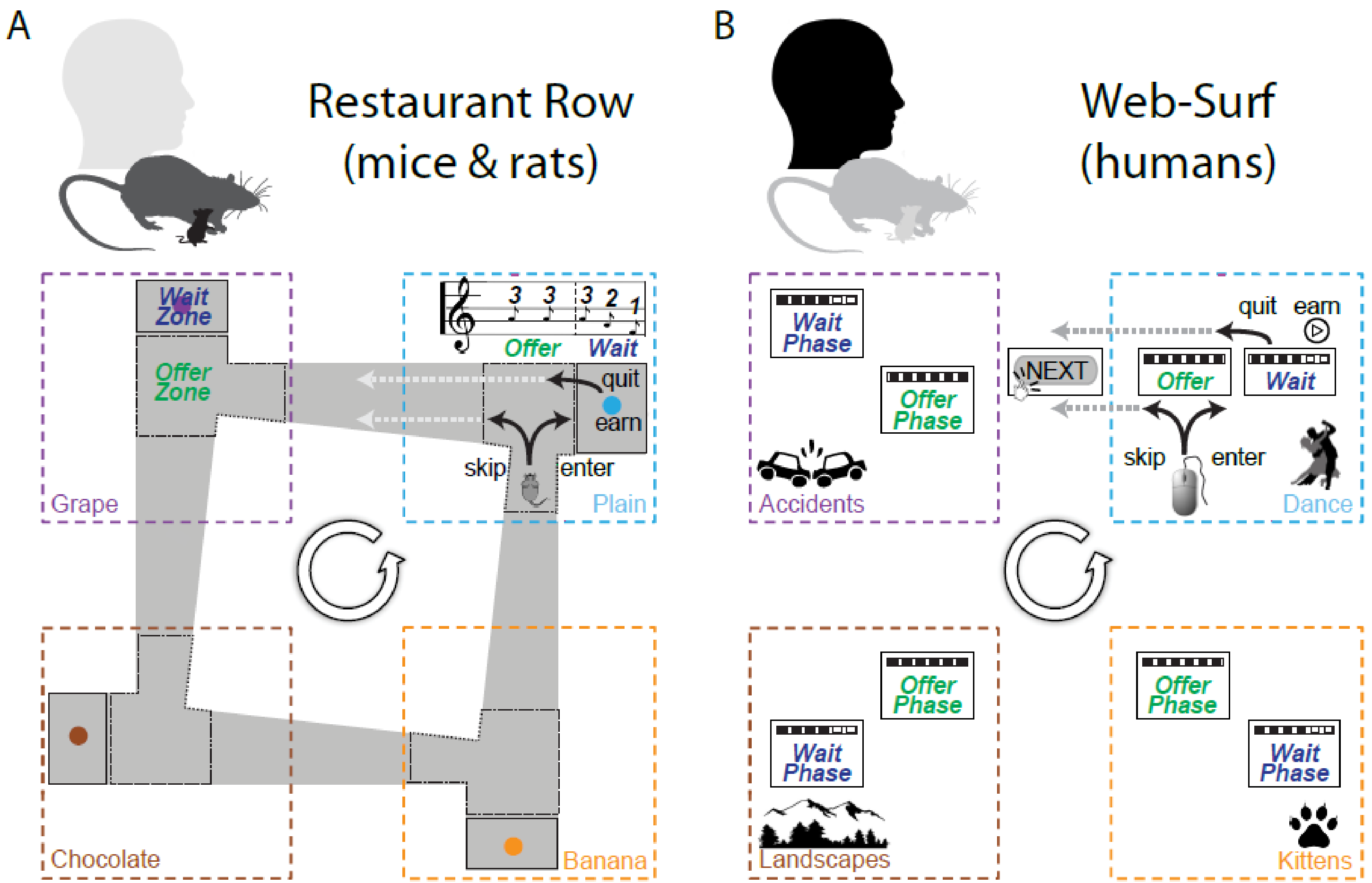
What do humans forage for?





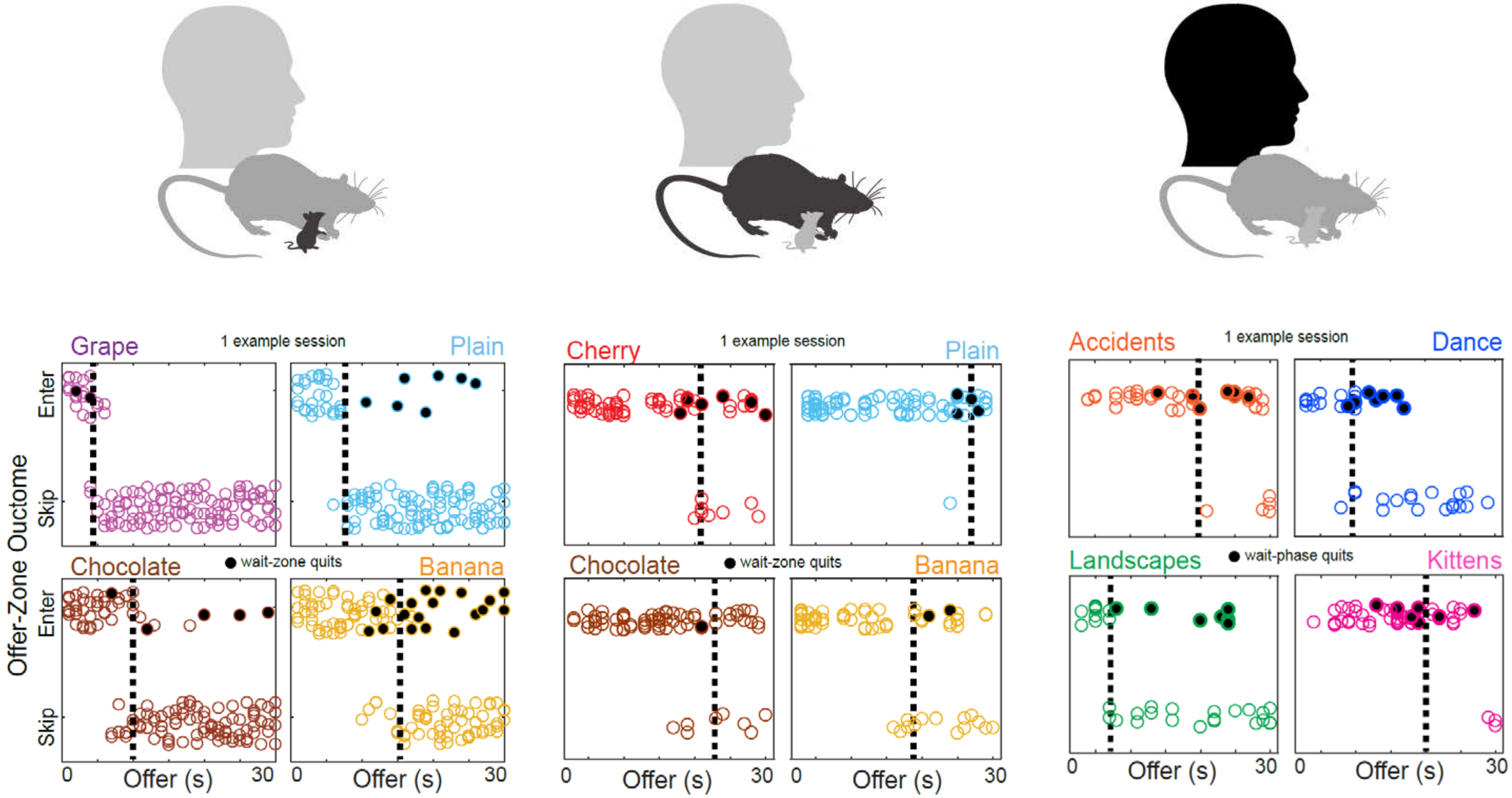
Brian Sweis, Samantha Abram, Brandy Schmidt, Kelsey Seeland, Angus MacDonald, Mark Thomas, Redish (2018) *Science*

Cross-species studies



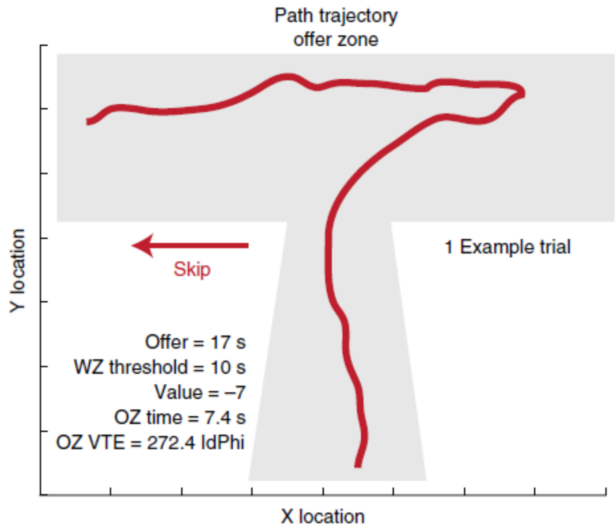
Brian Sweis, Samantha Abram, Brandy Schmidt, Kelsey Seeland, Angus MacDonald, Mark Thomas, Redish (2018) *Science*

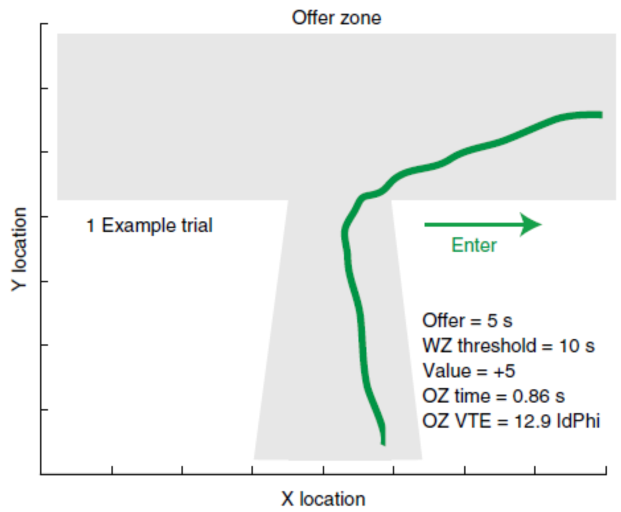
Cross-species studies



Rodents show different behaviors in the offer and wait zones

Brian Sweis, Samantha Abram, Brandy Schmidt, Kelsey Seeland, Angus MacDonald, Mark Thomas, Redish (2018) *Science*



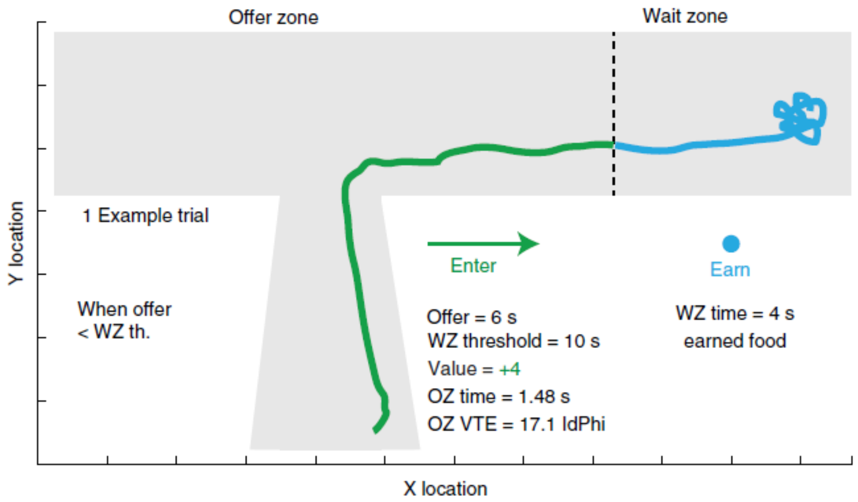


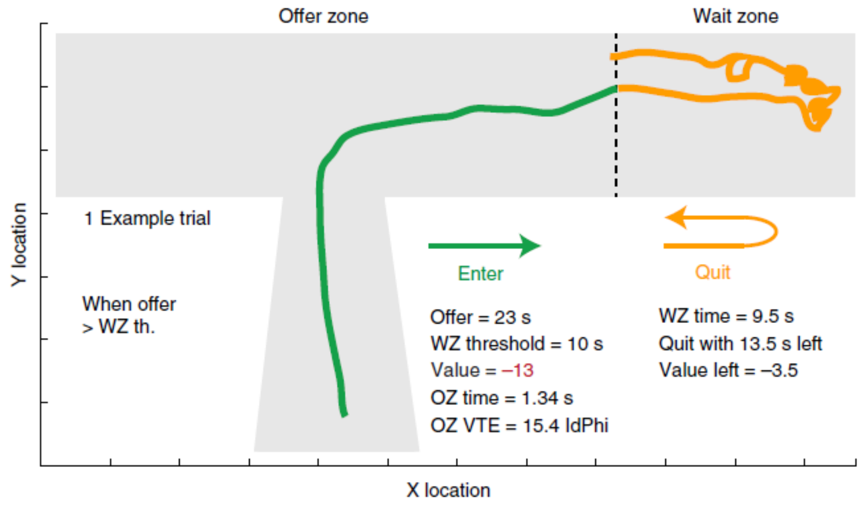
DELIBERATION

Rats and mice show **re-orientation behaviors** in the offer zone.

RE-EVALUATION

And **quit behaviors** in the wait zone.



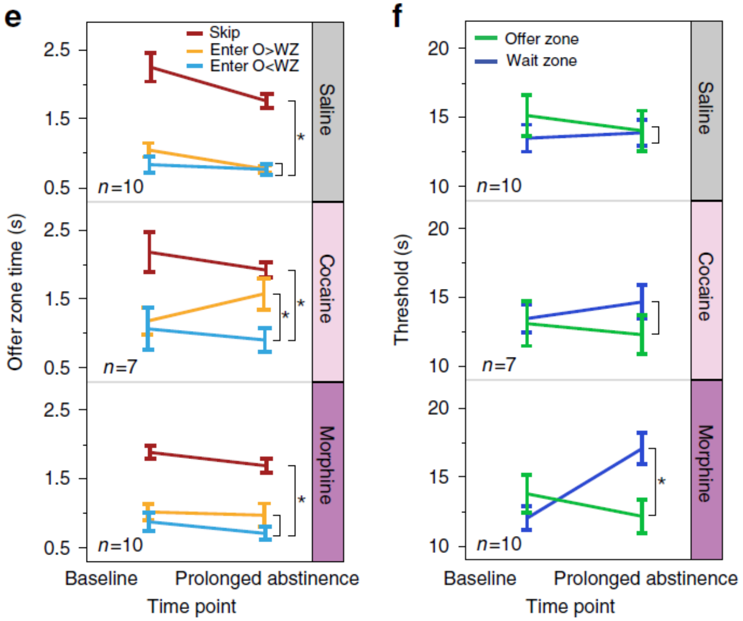


Manipulations separately affect the offer and wait zones

Cocaine affects offer zone decisions.

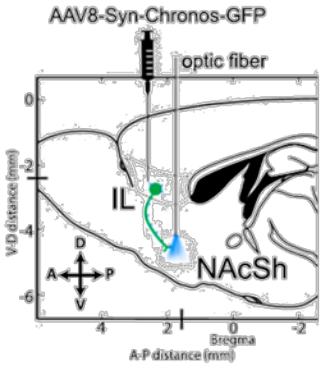
Morphine affects wait zone decisions.

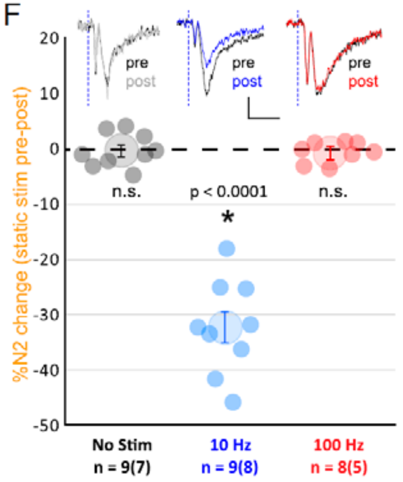
Brian Sweis, Redish, Thomas (2018) *Nature Communications*

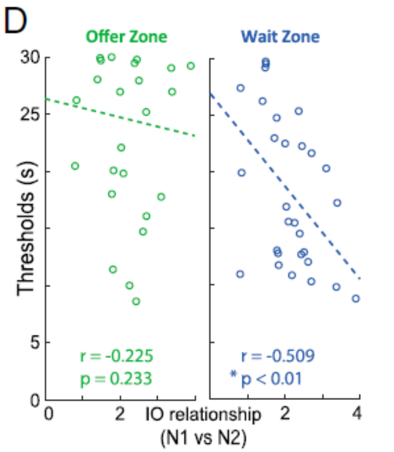


Optogenetic manipulations of infralimbic cortex to nucleus accumbens shell synaptic efficacy affects wait zone but not offer zone.

Brian Sweis, Larson, Redish, Thomas (2018) *PNAS*

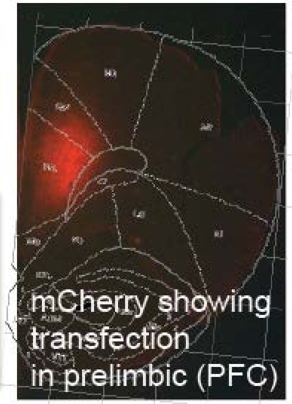


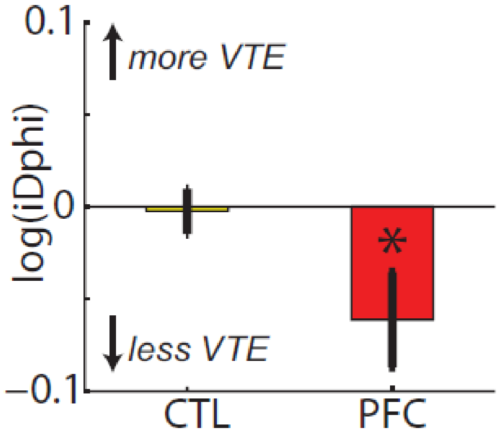




Brandy Schmidt, Duin, Redish (2019) *J Neurophysiology*

DREADD manipulations of prelimbic cortex affects offer zone but not wait zone.



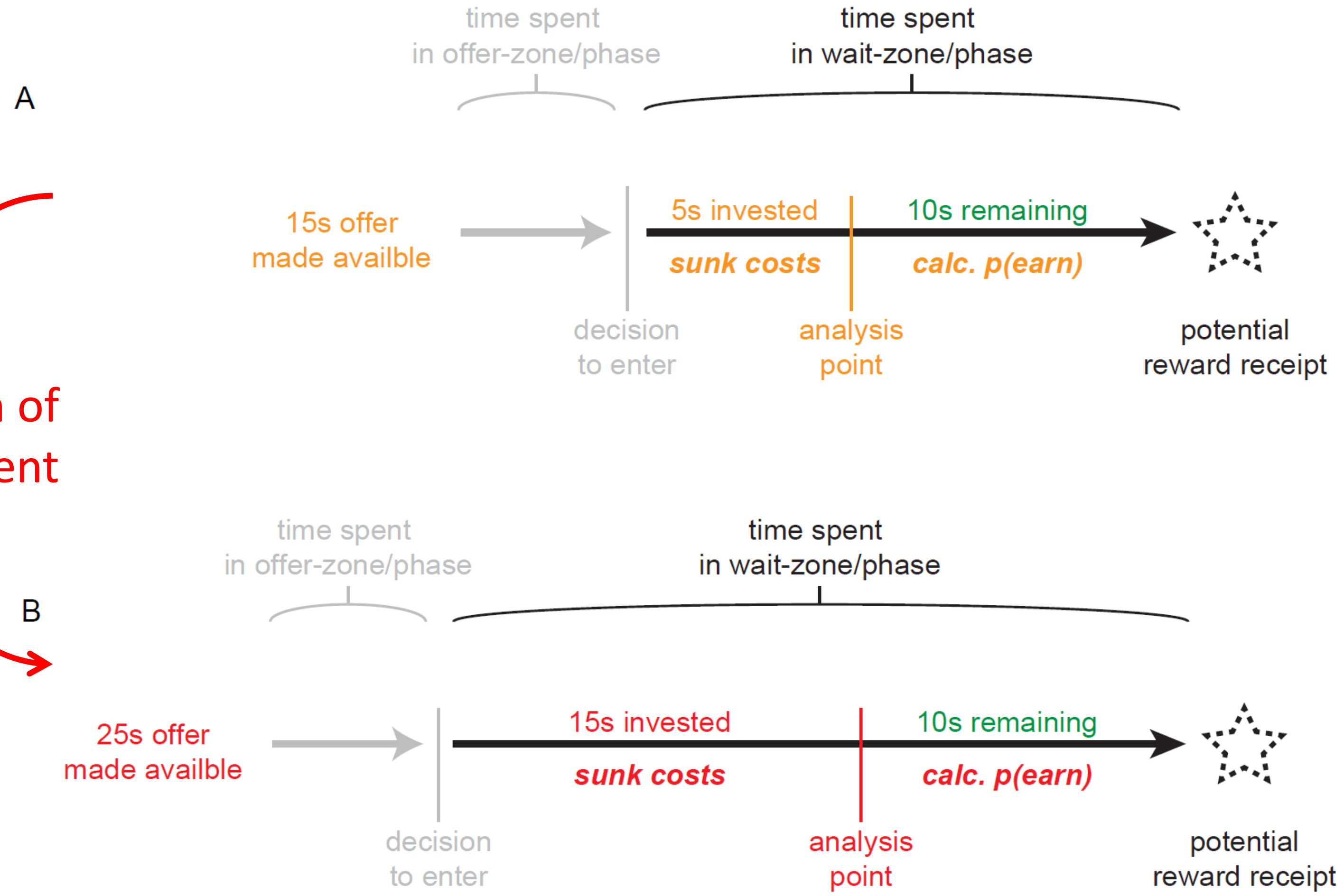


Brian Sweis, Samantha Abram, Brandy Schmidt, Kelsey Seeland, Angus MacDonald, Mark Thomas, Redish (2018) *Science*

The sunk cost fallacy

Sensitivity to sunk costs arises when decisions are made based on past expenses rather than future expectations.

Escalation of commitment



Brian Sweis, Samantha Abram, Brandy Schmidt, Kelsey Seeland,
Angus MacDonald, Mark Thomas, Redish (2018) *Science*

Sunk costs in the wait zone

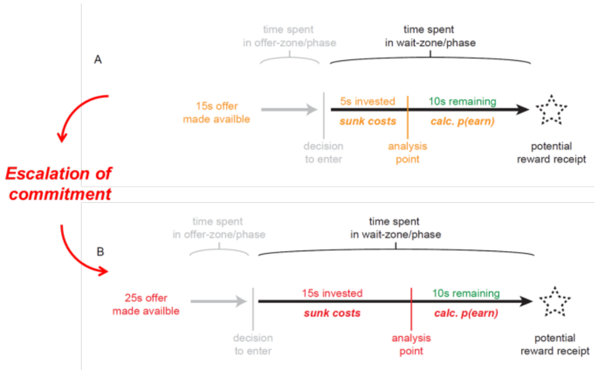
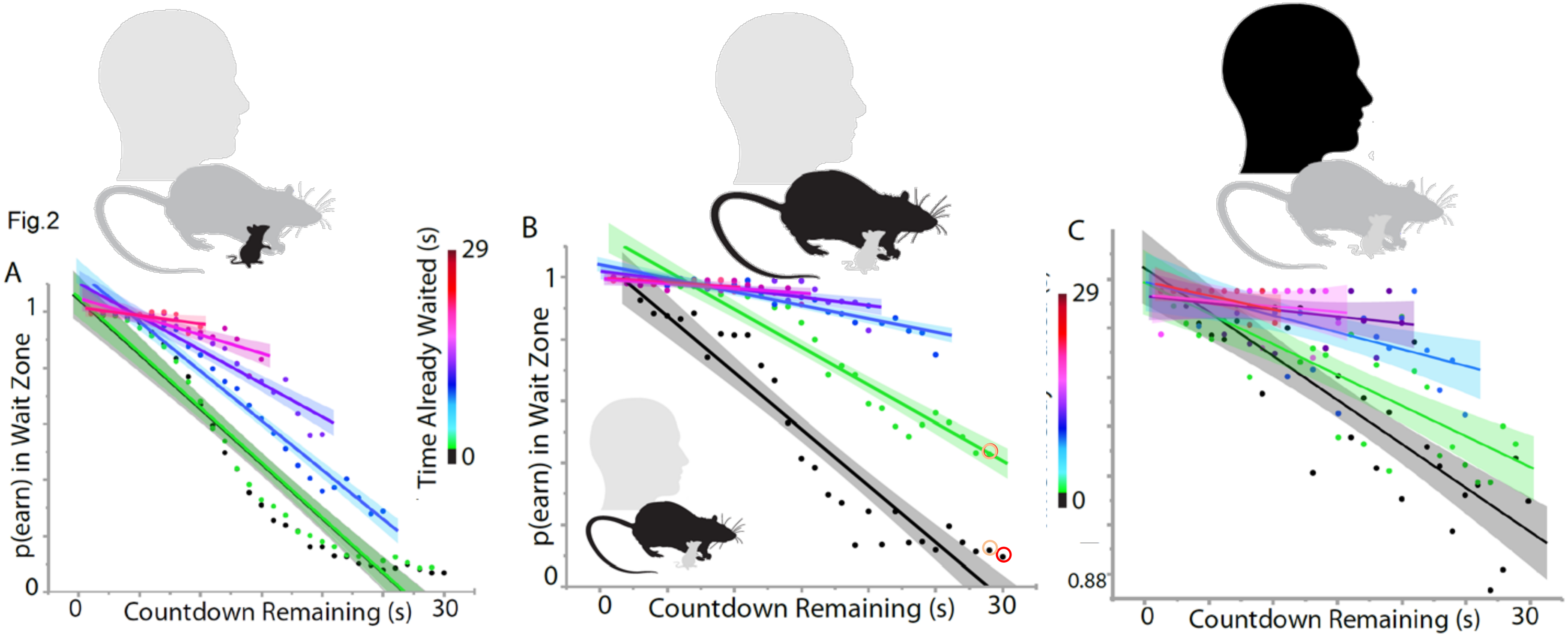


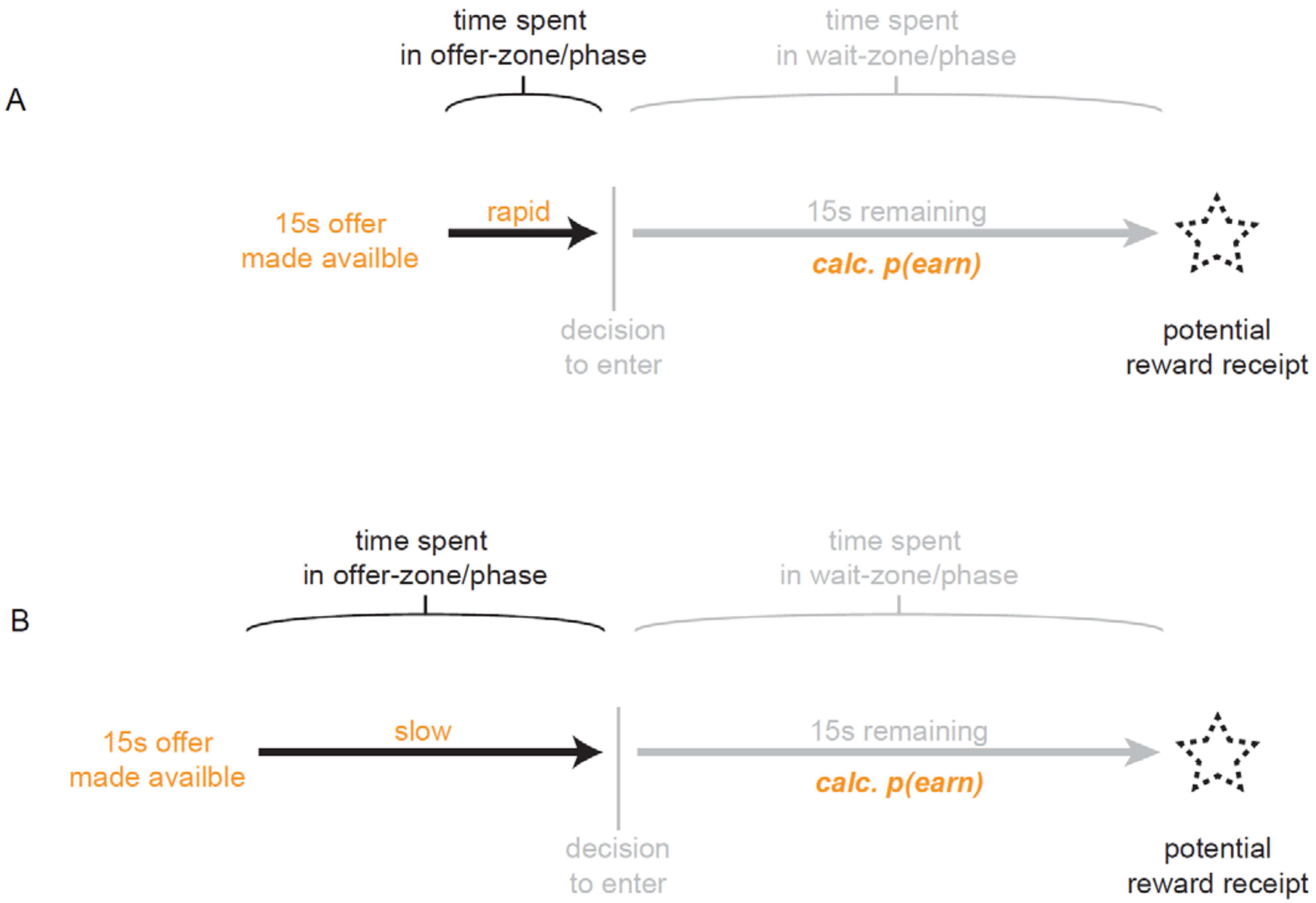
Fig.2



Sunk costs
in the offer zone?

Brian Sweis, Samantha Abram, Brandy Schmidt, Kelsey Seeland,
Angus MacDonald, Mark Thomas, Redish (2018) *Science*

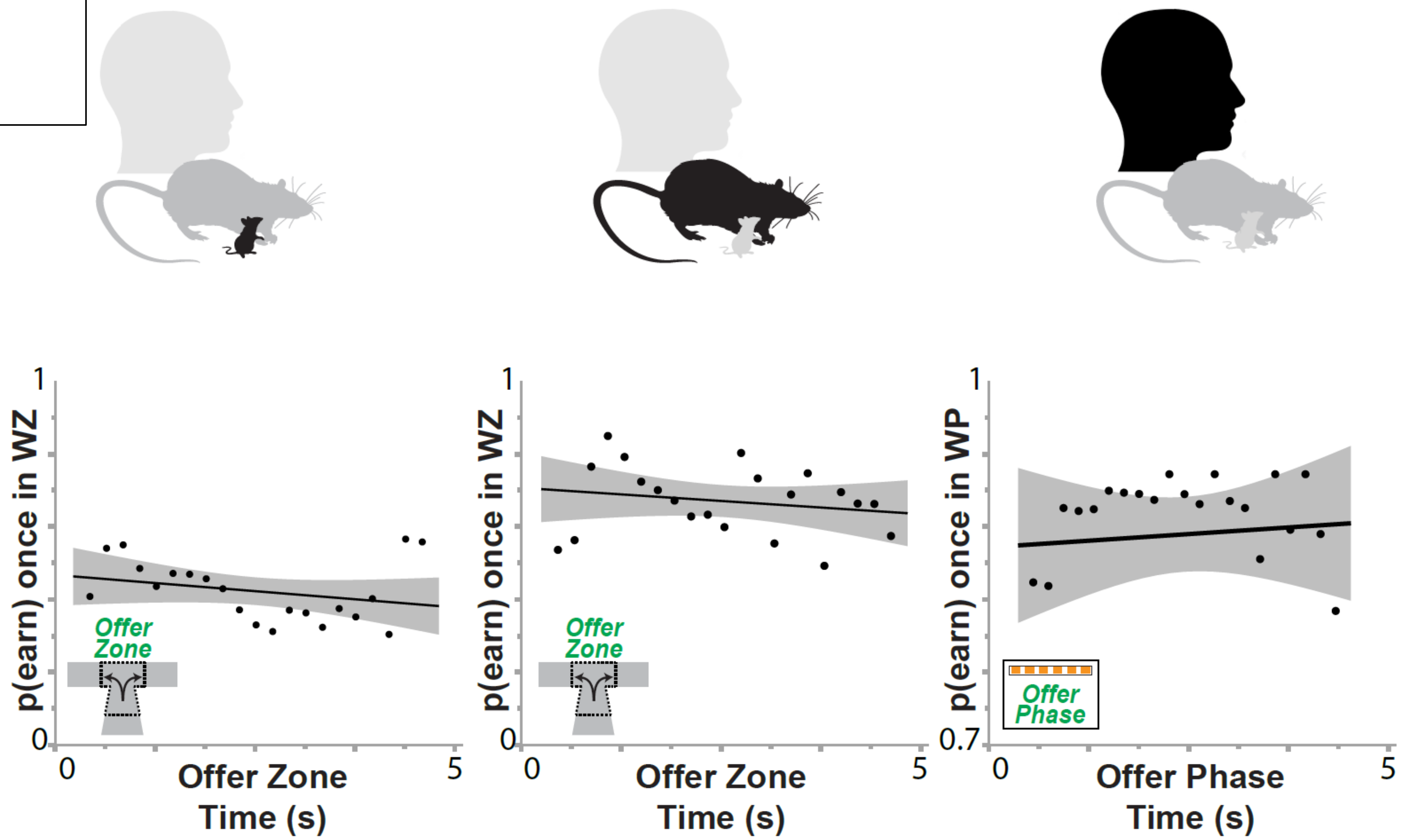
We can make the same measurement based on time spent in the offer zone.



Brian Sweis, Samantha Abram, Brandy Schmidt, Kelsey Seeland,
Angus MacDonald, Mark Thomas, Redish (2018) *Science*

No sunk costs in the offer zone

Sunk costs only start to accrue after **investment** in a choice.



Cross-species translation takes time

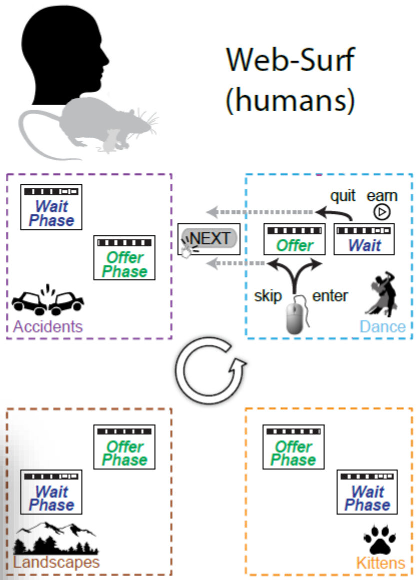
	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Cohort 5	Cohort 6
Date	Spring 2014	Spring 2014	Fall 2016	Spring 2017	Spring 2017	Fall 2017
Species	Rat	Human	Mouse	Rat	Human	Mouse
Breed	Brown-Norway	undergraduates	C57BL6J	Fisher Brown-Norway	undergraduates	C57BL6J
Sample Size & Sex	22 (M) & 0 (F)	4 (M) & 13 (F)	32 (M) & 0 (F)	4 (M) & 6 (F)	24 (M) & 41 (F)	32 (M) & 0 (F)
Age	8-12 months	19.63 years (mean)	13 weeks	6-10 months	20.23 years (mean)	13 weeks
Task Variant	wait zone only	wait phase only	offer zone + wait zone	offer zone + wait zone	offer phase + wait phase	offer zone + wait zone
Experimenters & Gender	1 (M) & 1 (F)	3 (M) & 5 (F)	2 (M) & 3 (F)	2 (M) & 2 (F)	0 (M) & 6 (F)	3 (M) & 3 (F)
Length of Training	20+ days	5 minutes	70+ days	20+ days	5 minutes	70+ days
Food Deprivation	>80% free weight	N / A	>80% free weight	>85% free weight	N / A	>90% free weight

Rebecca Kazinka, Angus MacDonald, Redish (work in progress)

Sunk costs – human replications

amazon mechanical turk

N = 280 (after Bot removal)



Rebecca Kazinka, Angus MacDonald, Redish (work in progress)

Sunk costs – human replications

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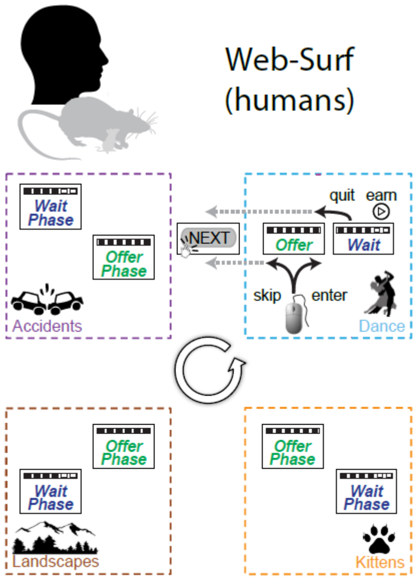
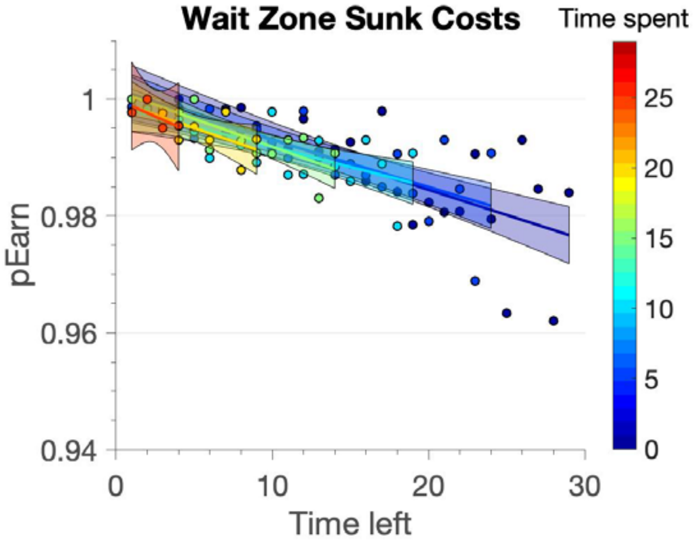
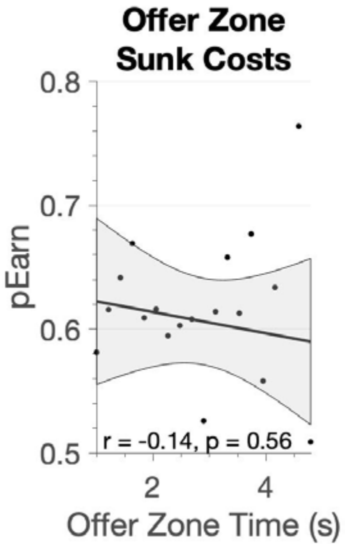






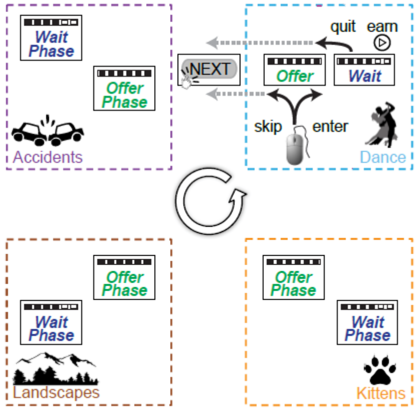
Rebecca Kazinka, Angus MacDonald, Redish (work in progress)

Sunk costs – human replications

amazon mechanical turk

N = 259 (after Bot removal)

Web-Surf (humans)

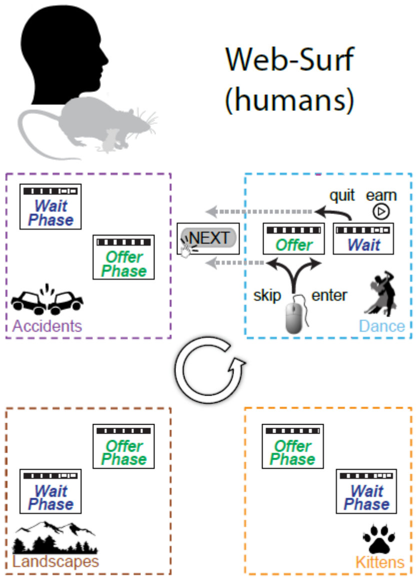


Rebecca Kazinka, Angus MacDonald, Redish (work in progress)

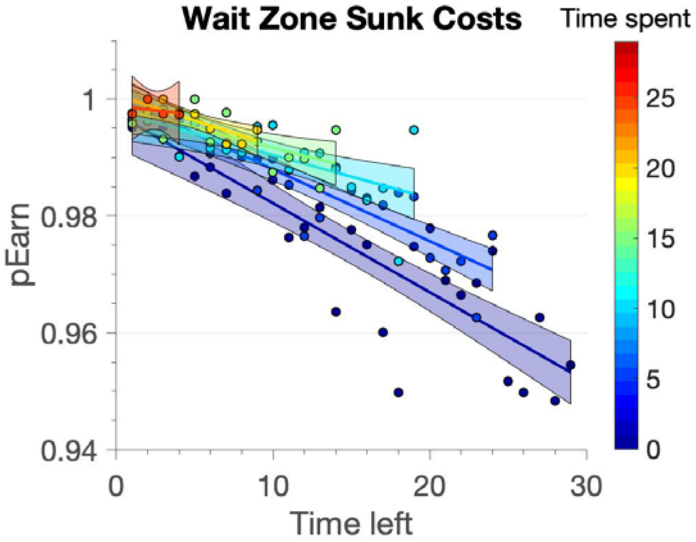
Sunk costs – human replications

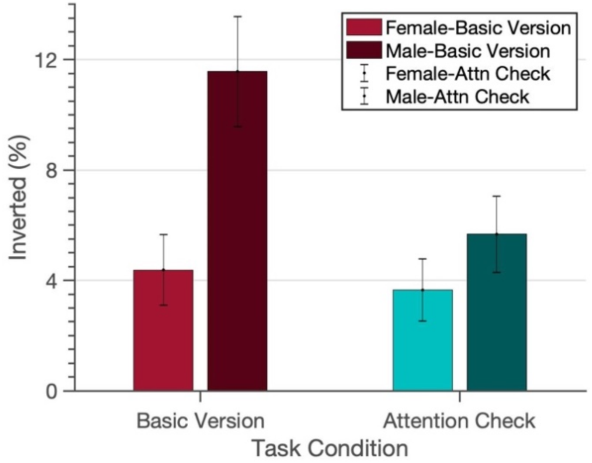
mechanical turk

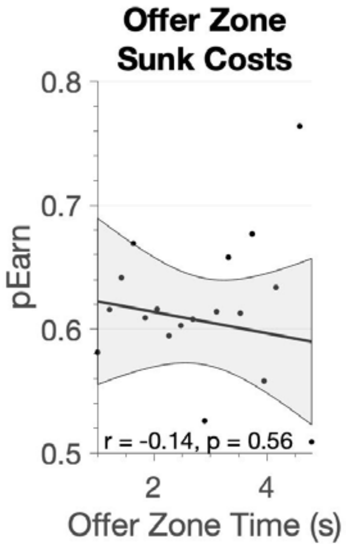
N = 259 (after Bot removal)



In an mTurk sample, sunk costs depend on the ability to attend to the delay.







Cross-species translation takes time

	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Cohort 5	Cohort 6	mTurk
Date	Spring 2014	Spring 2014	Fall 2016	Spring 2017	Spring 2017	Fall 2017	2019
Species	Rat	Human	Mouse	Rat	Human	Mouse	Human (mostly)
Breed	Brown-Norway	undergraduates	C57BL6J	Fisher Brown-Norway	undergraduates	C57BL6J	mTurk
Sample Size & Sex	22 (M) & 0 (F)	4 (M) & 13 (F)	32 (M) & 0 (F)	4 (M) & 6 (F)	24 (M) & 41 (F)	32 (M) & 0 (F)	>500 (47%M 53% F)
Age	8-12 months	19.63 years (mean)	13 weeks	6-10 months	20.23 years (mean)	13 weeks	18-60
Task Variant	wait zone only	wait phase only	offer zone + wait zone	offer zone + wait zone	offer phase + wait phase	offer zone + wait zone	OZ + WZ Attention & not
Experimenters & Gender	1 (M) & 1 (F)	3 (M) & 5 (F)	2 (M) & 3 (F)	2 (M) & 2 (F)	0 (M) & 6 (F)	3 (M) & 3 (F)	N/A
Length of Training	20+ days	5 minutes	70+ days	20+ days	5 minutes	70+ days	0 minutes
Food Deprivation	>80% free weight	N / A	>80% free weight	>85% free weight	N / A	>90% free weight	N/A

Two case studies

- Foraging and deliberation access different decision systems.
- Sunk costs accrue in foraging situations more than deliberation situations
- Sunk costs depend on attention to the delay and only start to accrue after investment.

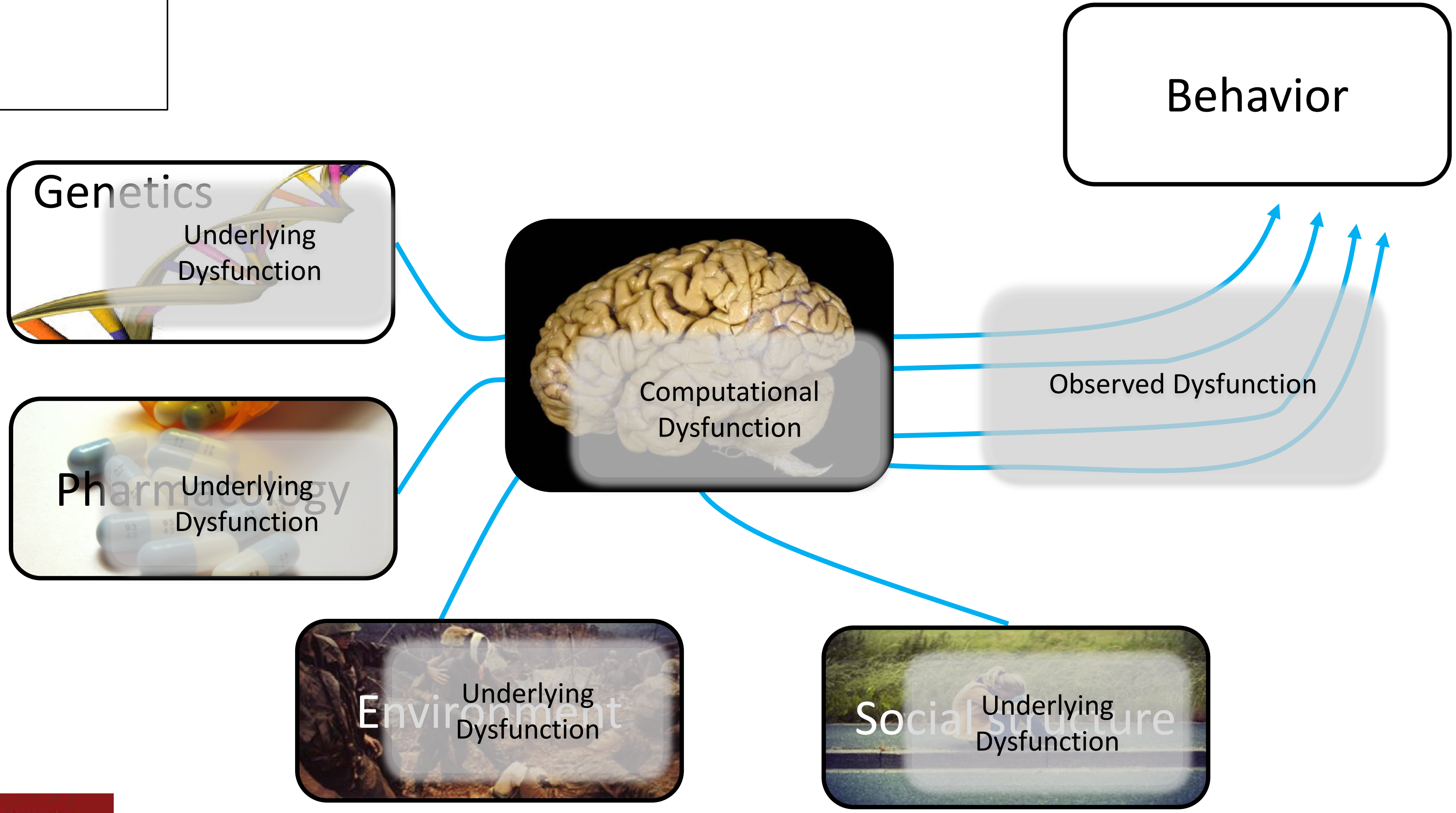
II Restaurant Row

What does this imply for psychiatry?

An engineer’s view on psychiatry

Computational psychiatry

This suggests
a new view
of psychiatry as
neurophysiological
computational
dysfunctions
in ***decision making***.



Failure modes

In reliability engineering,
a “failure mode” is
a vulnerability
inherent in
the machinery.

35W Bridge Collapse, 2007. startribune.com

Failure modes

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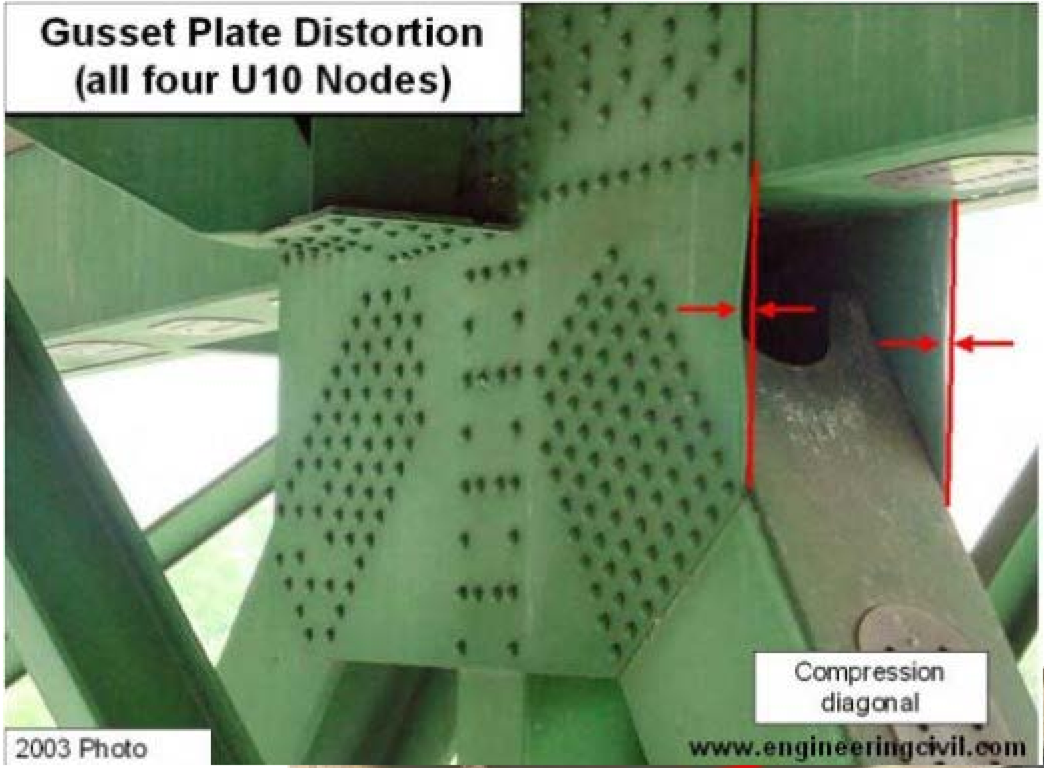
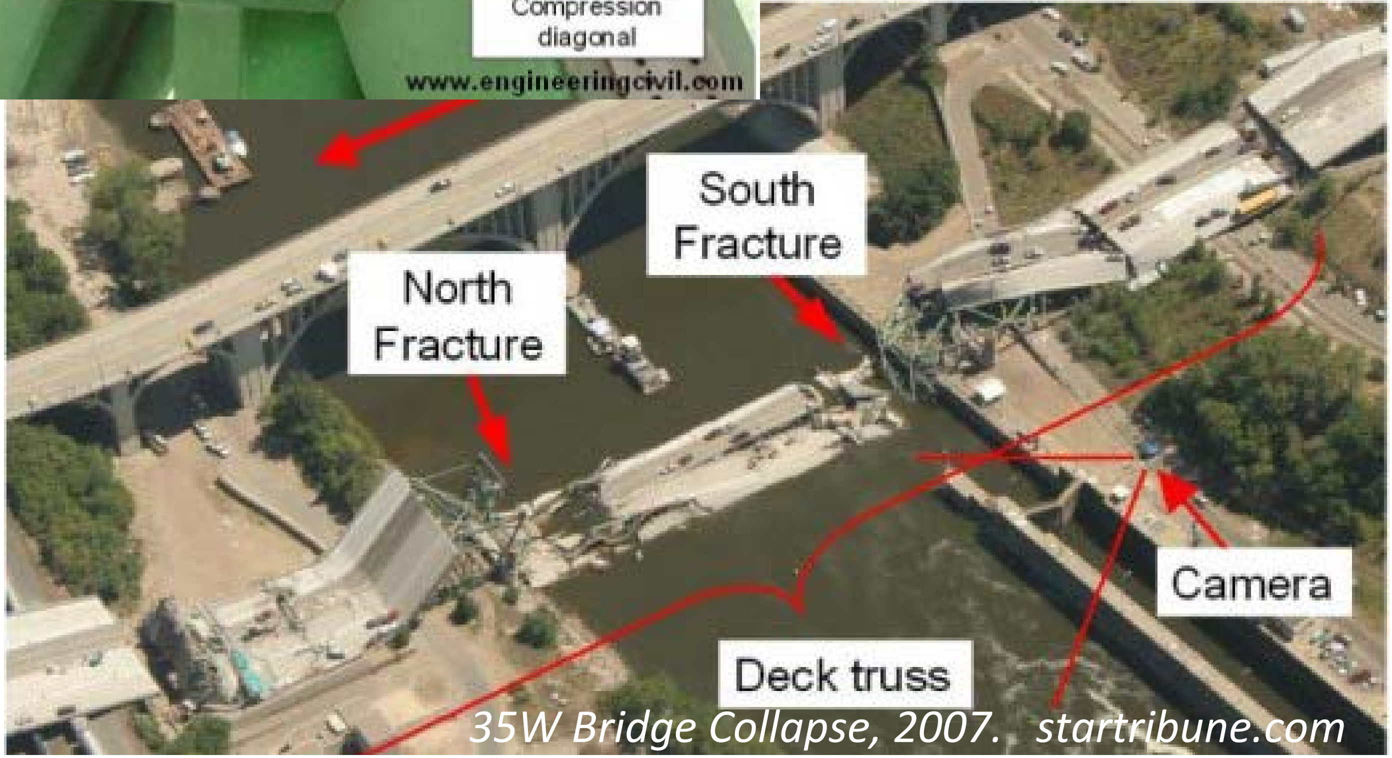




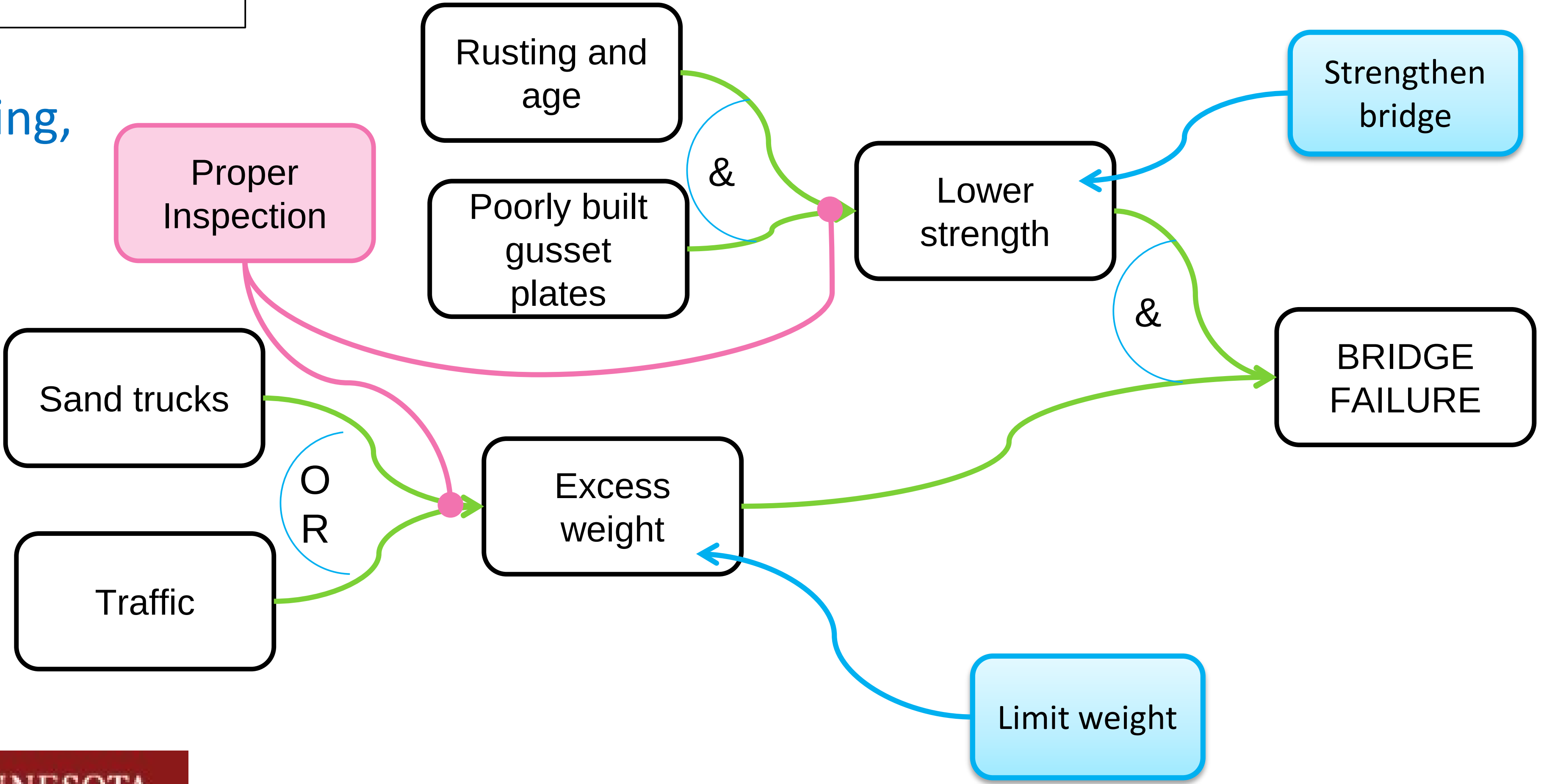
35W Bridge Collapse, 2007. startribune.com

Failure modes

If we know the failure modes, we can guide treatment.

***Computational Psychiatry** is about applying **reliability engineering** analyses to neural systems*

In reliability engineering, a "failure mode" is a vulnerability inherent in the machinery.



Psychiatric failure modes

All of these are **computational** failure modes.

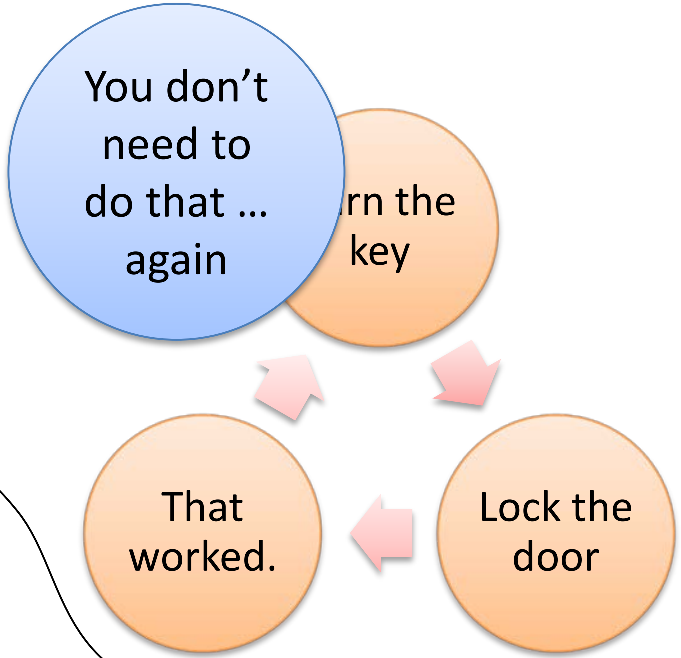
OCD

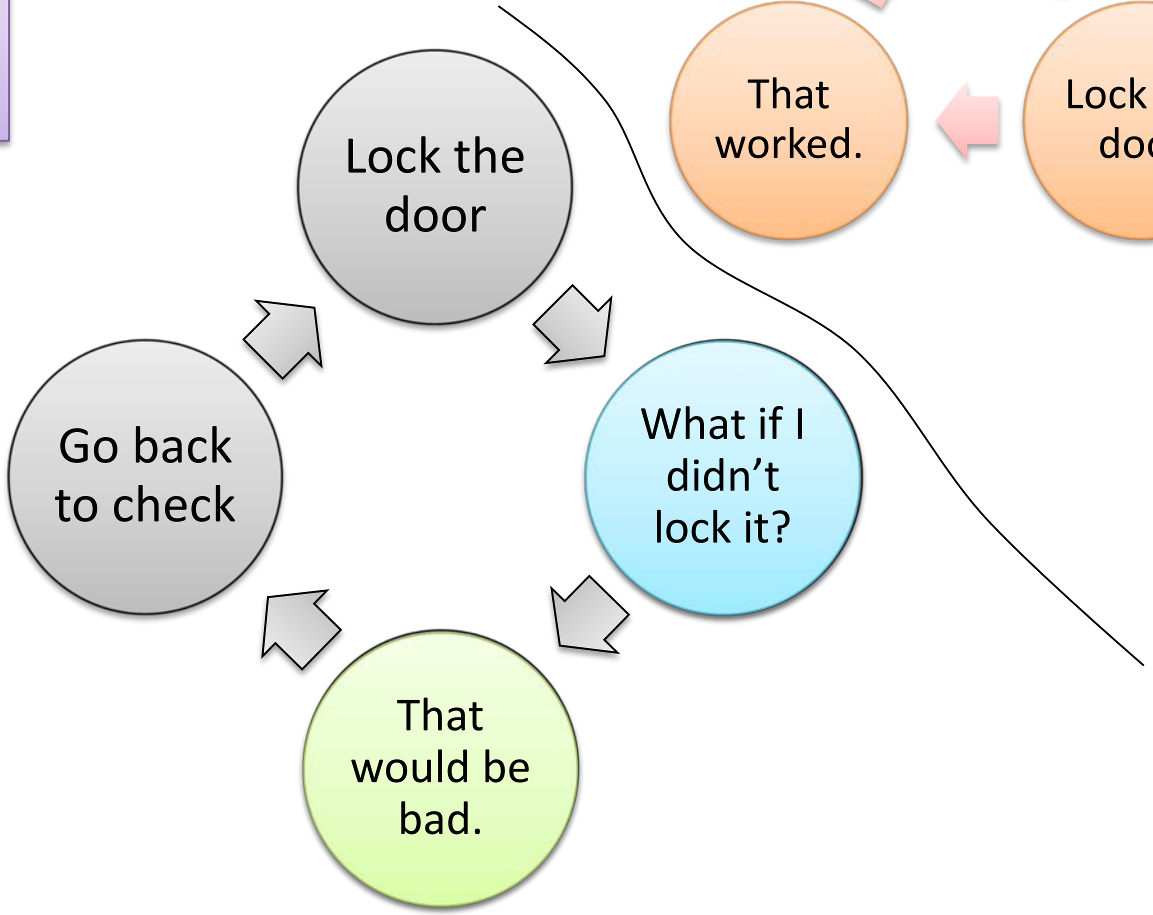
an imbalance between planning and habit modes,

perhaps via problems with *response inhibition,*

or an inability to recognize completion of a target,

or an over-intensity of anxiety predictions?





UNIVERSITY OF MINNESOTA

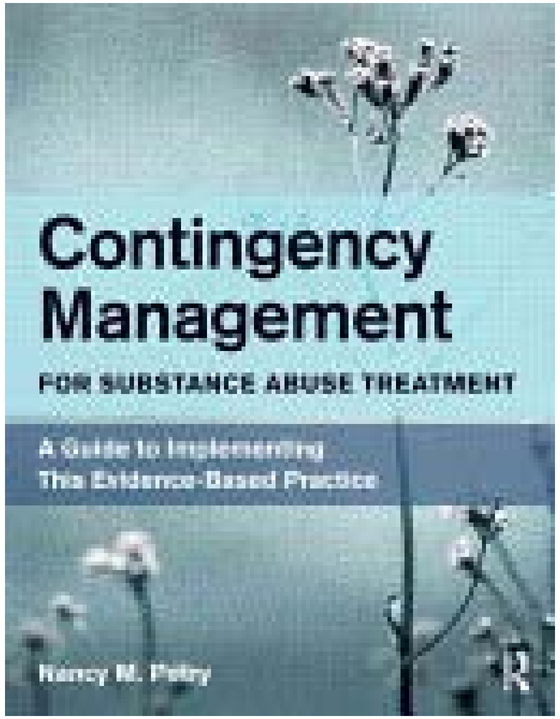
Coda: contingency management

Contingency management

Current theory:

- The reward is an ***alternate reinforcer***.
- Losing it increases the ***opportunity costs*** of the drug.

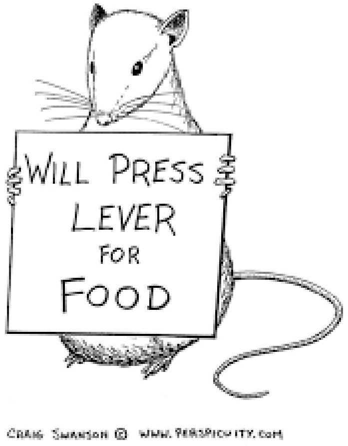
If you don't use drugs for a week (come in clean), then you receive a small reward.



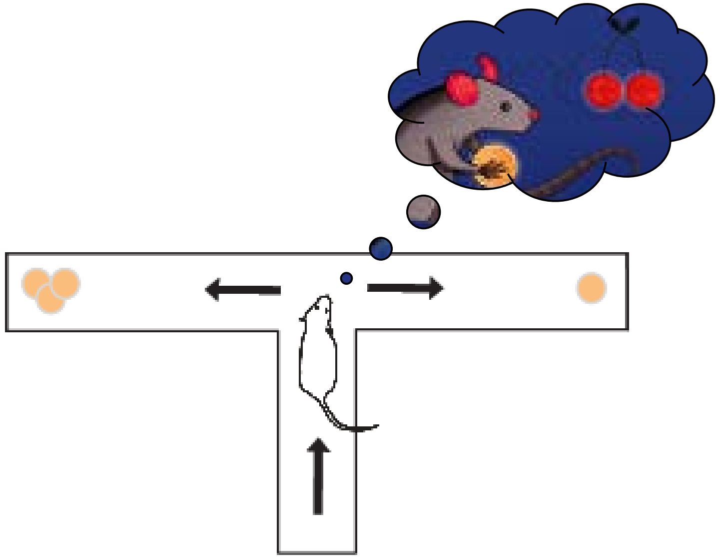
But the rewards are small.

Increasing the cost of the drug on the street by that amount has little to no effect.

Coda: contingency management



Is it worth it?

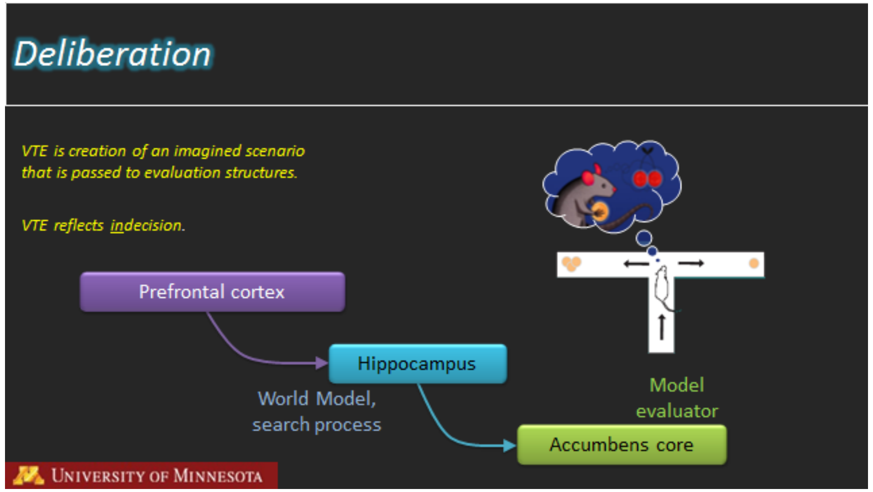


Which one?

Contingency management

CM will depend on **_working memory._**

We can train working memory.



Is it worth it?

Which one?

CM will depend on **_prefrontal cortex and hippocampus._**

We can test for prefrontal-hippocampal integrity.

How can we strengthen deliberation?

We can make the second option more concrete.

We can provide reminders.

- Diagnosis should align to **failure modes** of information processing.

- Treatment should modify that information processing
  - **Either** through changes in the patient itself
    OR through changes in the environment

- Translation across species requires computational validity.

Computational models of information processing as a link across species allowing translation from fundamental discoveries to clinical practice

- Diagnosis should align to **failure modes** of information processing.
- Treatment should modify info processing
  - **Either** through changes in the patient itself **OR** through changes in the environment
- Translation across species requires **computational validity**.

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