Fronto-executive functions in rodents: neural and neurochemical substrates

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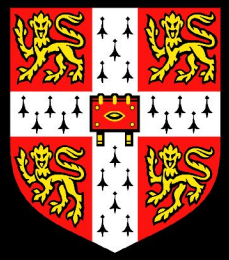

Saturday 26 April 2003, 9–9.20 am
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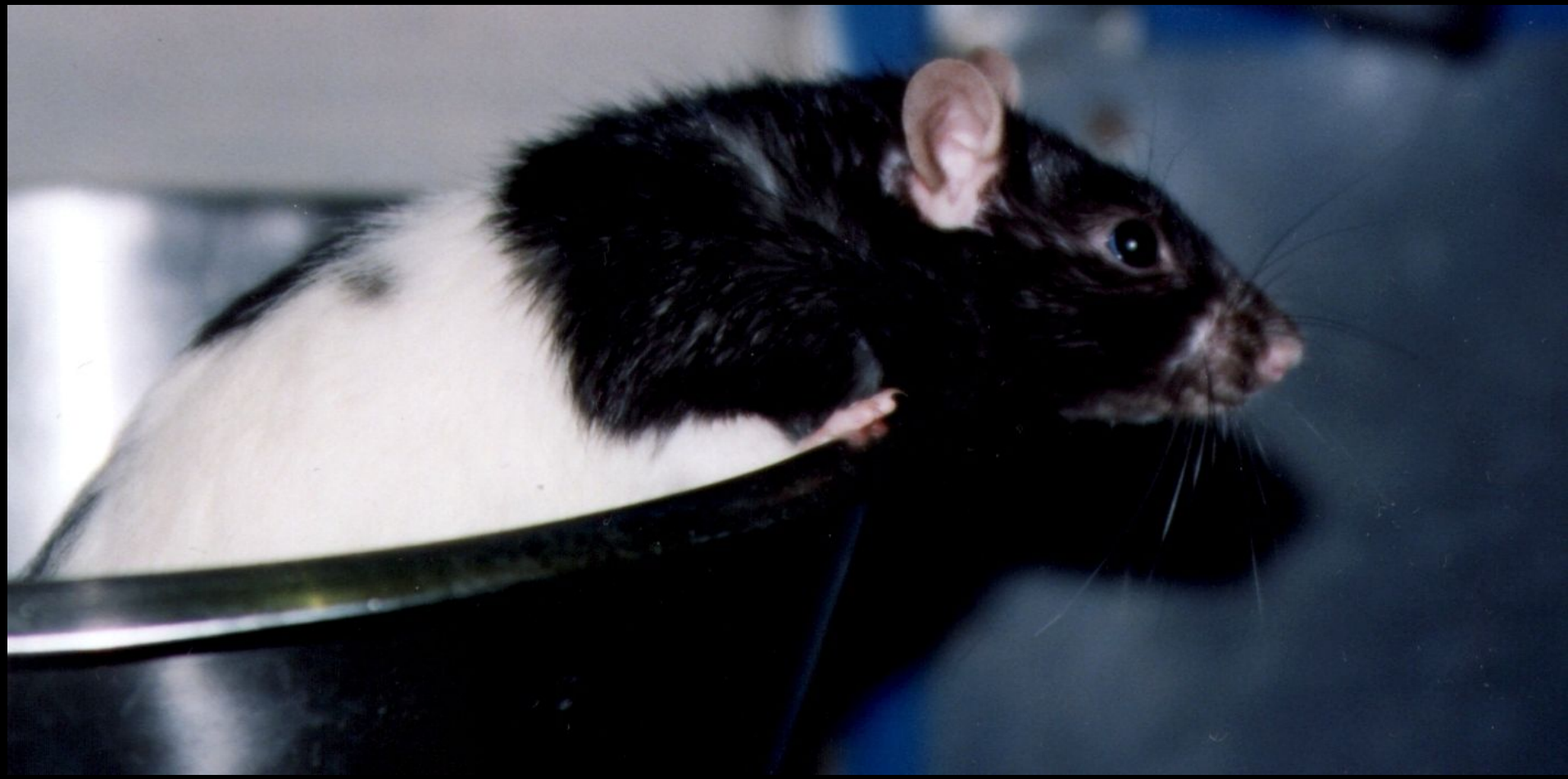


‘Executive’ function and its analysis

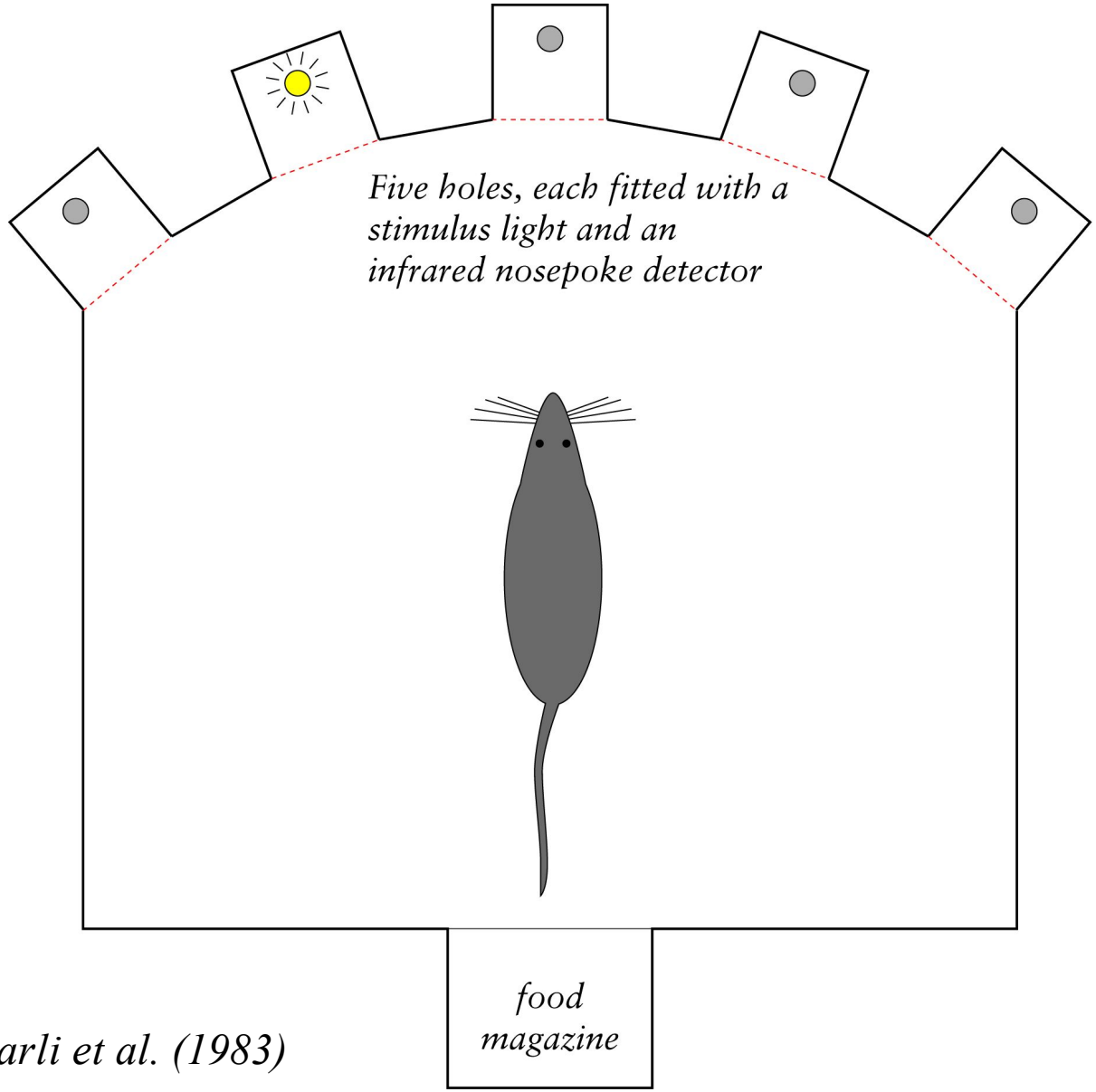
‘Executive’ functions may include:

- The ability to direct and sustain attention
- The ability to sequence and regulate ongoing behaviour (for example, inhibiting prepotent responses until they are required)
- The ability to perceive the consequences of one’s own actions — that is, the contingency between actions and their outcomes.

The neuroanatomical and neurochemical basis of these functions may be analysed in rats using both correlative techniques (e.g. microdialysis) and causal techniques (e.g. lesions).

Some behavioural tasks tax many psychological processes, and in this case optimal performance requires a coordination of ‘executive’ systems. However, many of these processes are separable behaviourally and neurally.

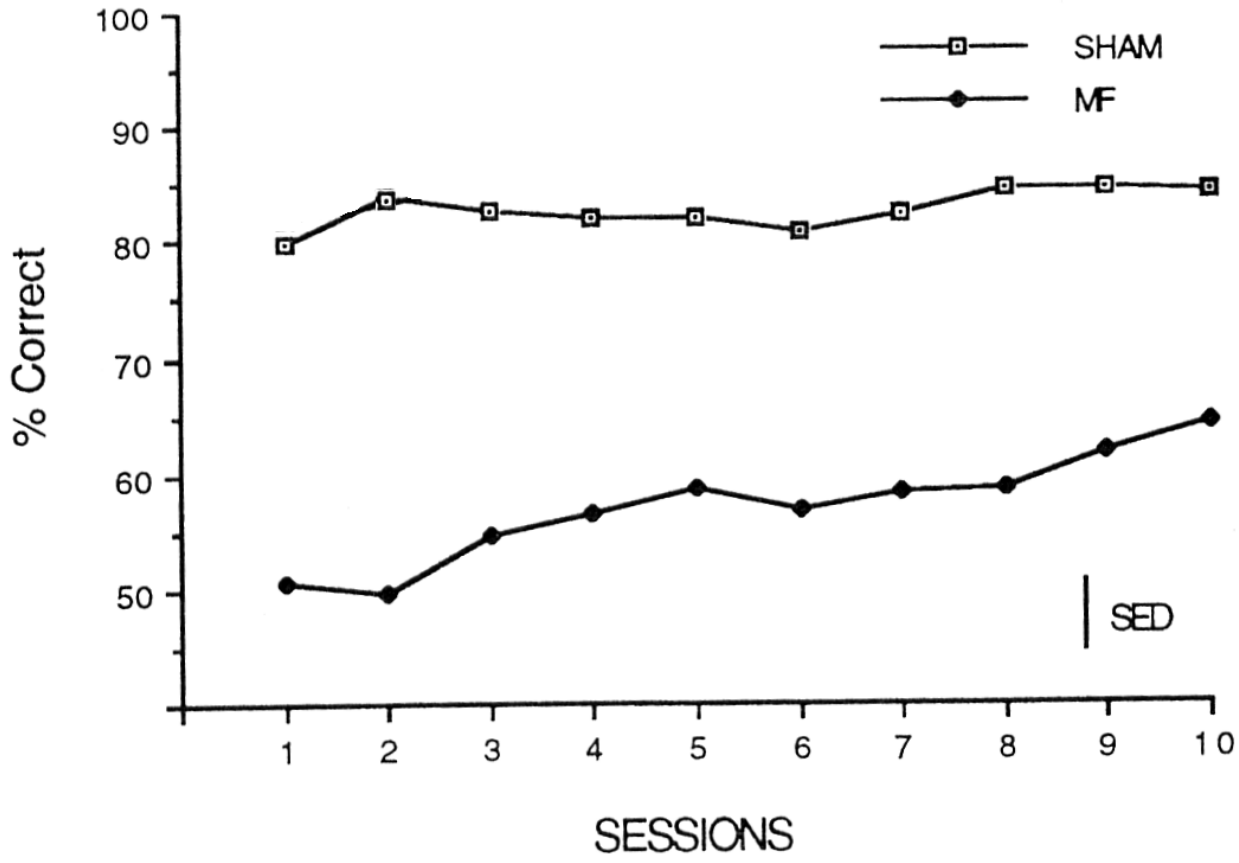
The five-choice serial reaction time task (5CSRTT): primarily a test of sustained and spatially divided visual attention

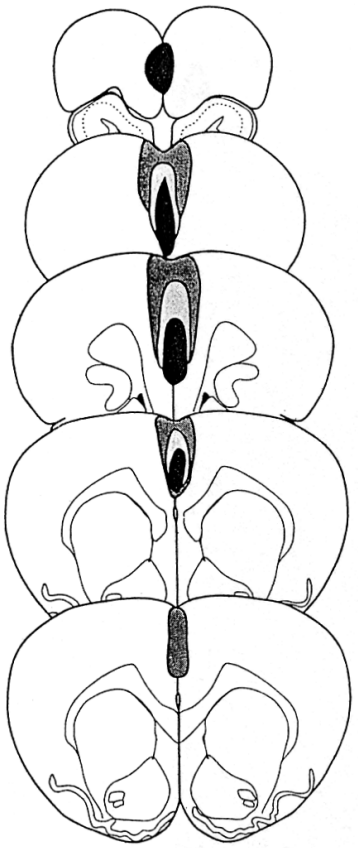


Carli et al. (1983)

- Animals are extensively trained.
- They must attend to multiple spatial locations, watching for brief stimuli.
- The task demands can be varied; for example, the event rate can be altered and white noise distractors can be added.
- The spatial and temporal predictability of the stimuli can be varied.

‘Frontal’ deficits: medial prefrontal cortex lesions impair accuracy

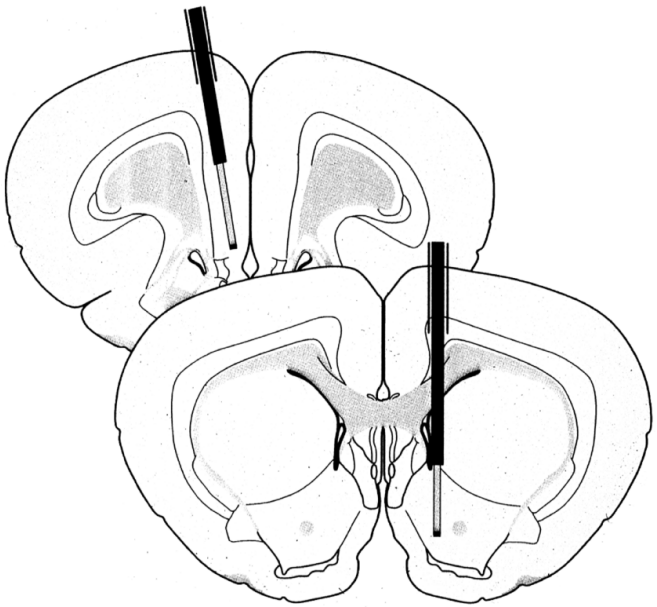


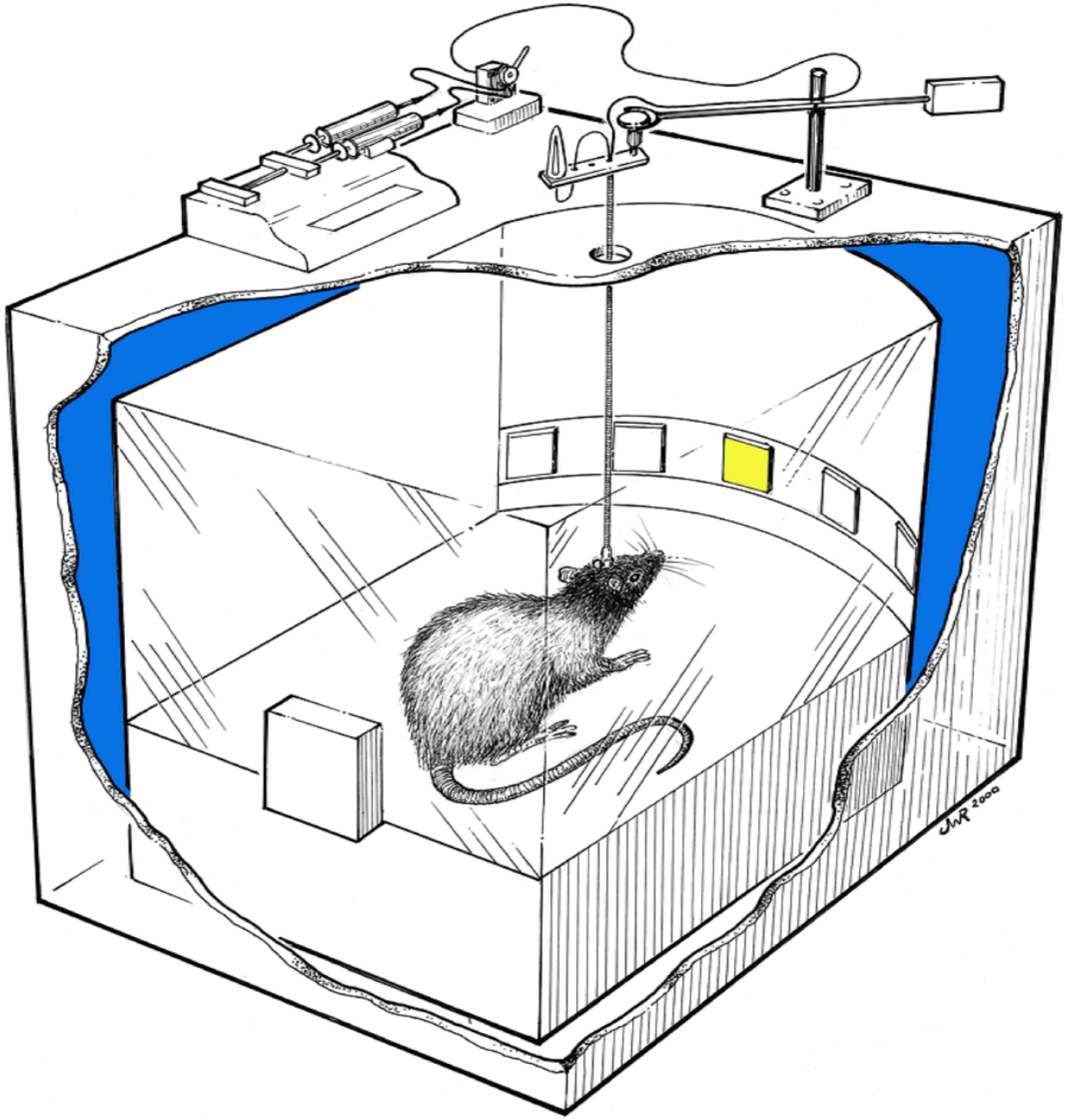


- mPFC lesions also increased **perseveration** at the response holes.
- Lesions of anterior cingulate cortex increased premature responding — a form of **disinhibited** or **impulsive** behaviour.

Muir et al. (1996)

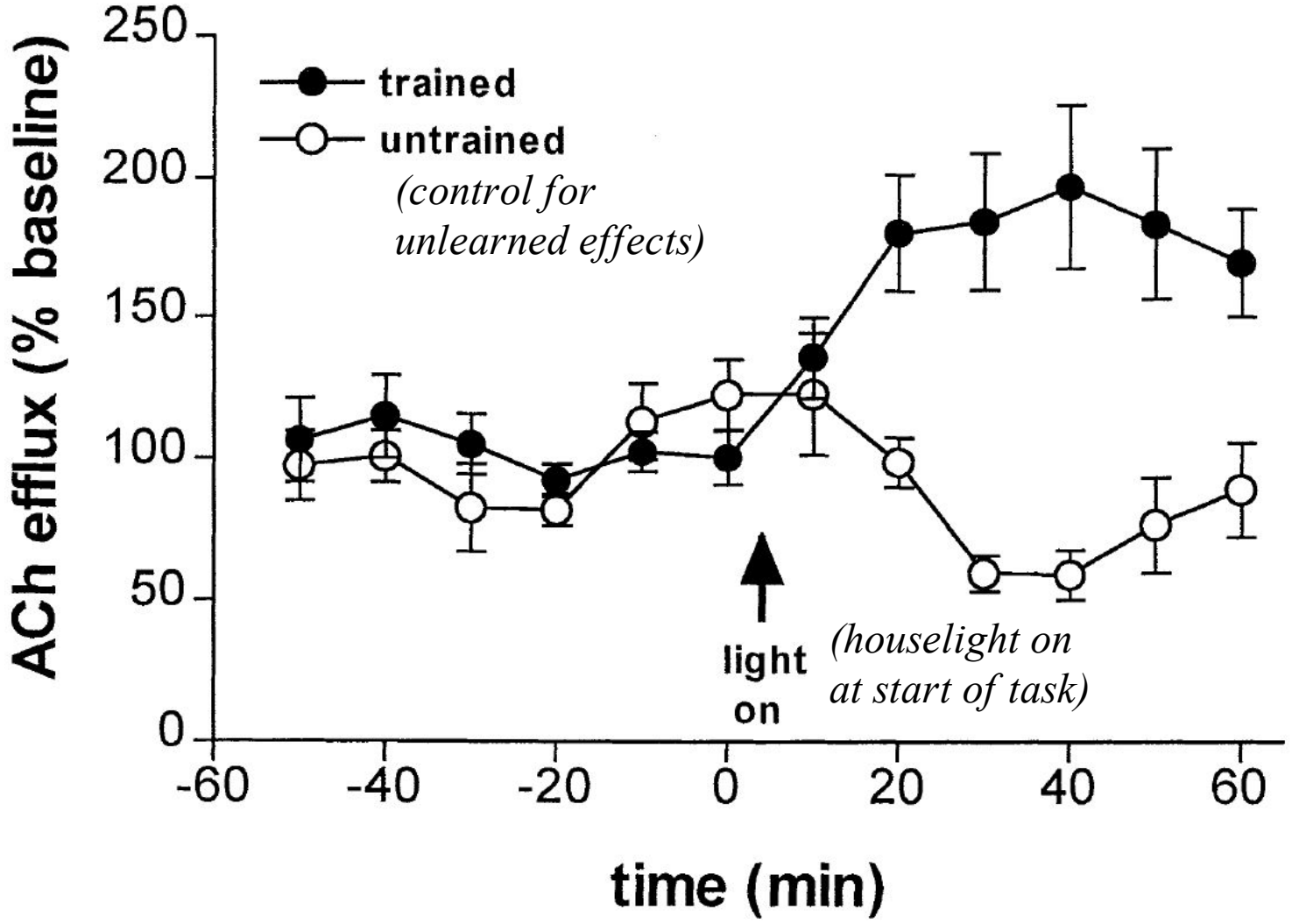
In vivo microdialysis in the 5-choice task





e.g. Passetti et al. (2000)

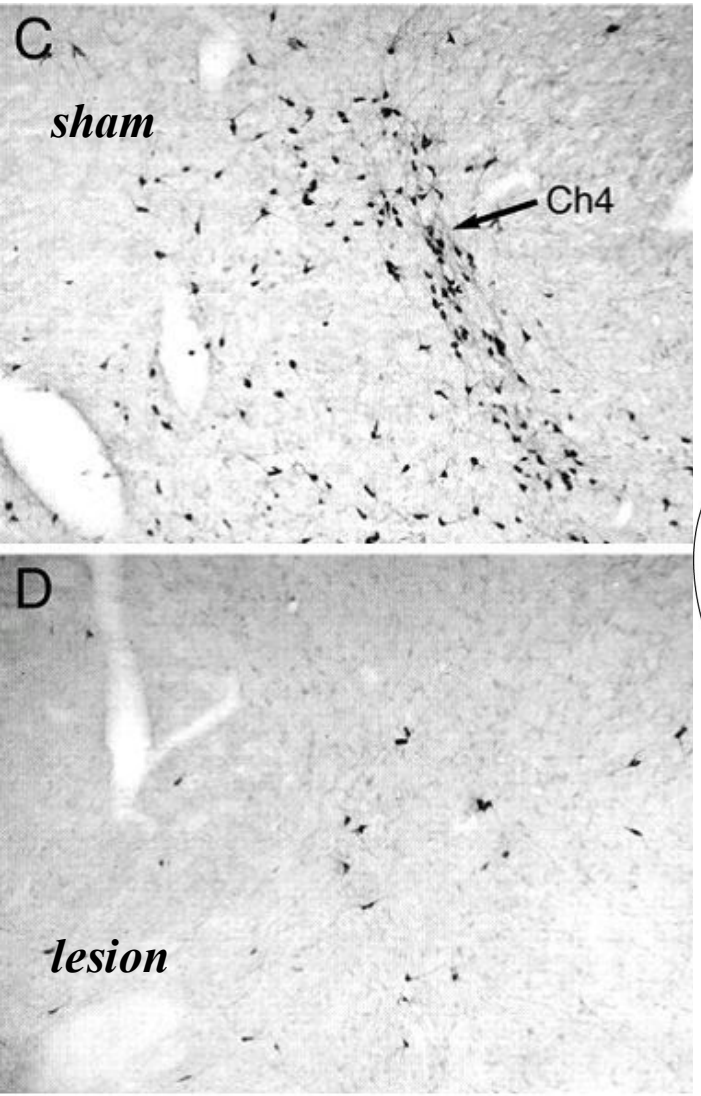
Increased ACh efflux in the prelimbic cortex during performance on the 5-choice task

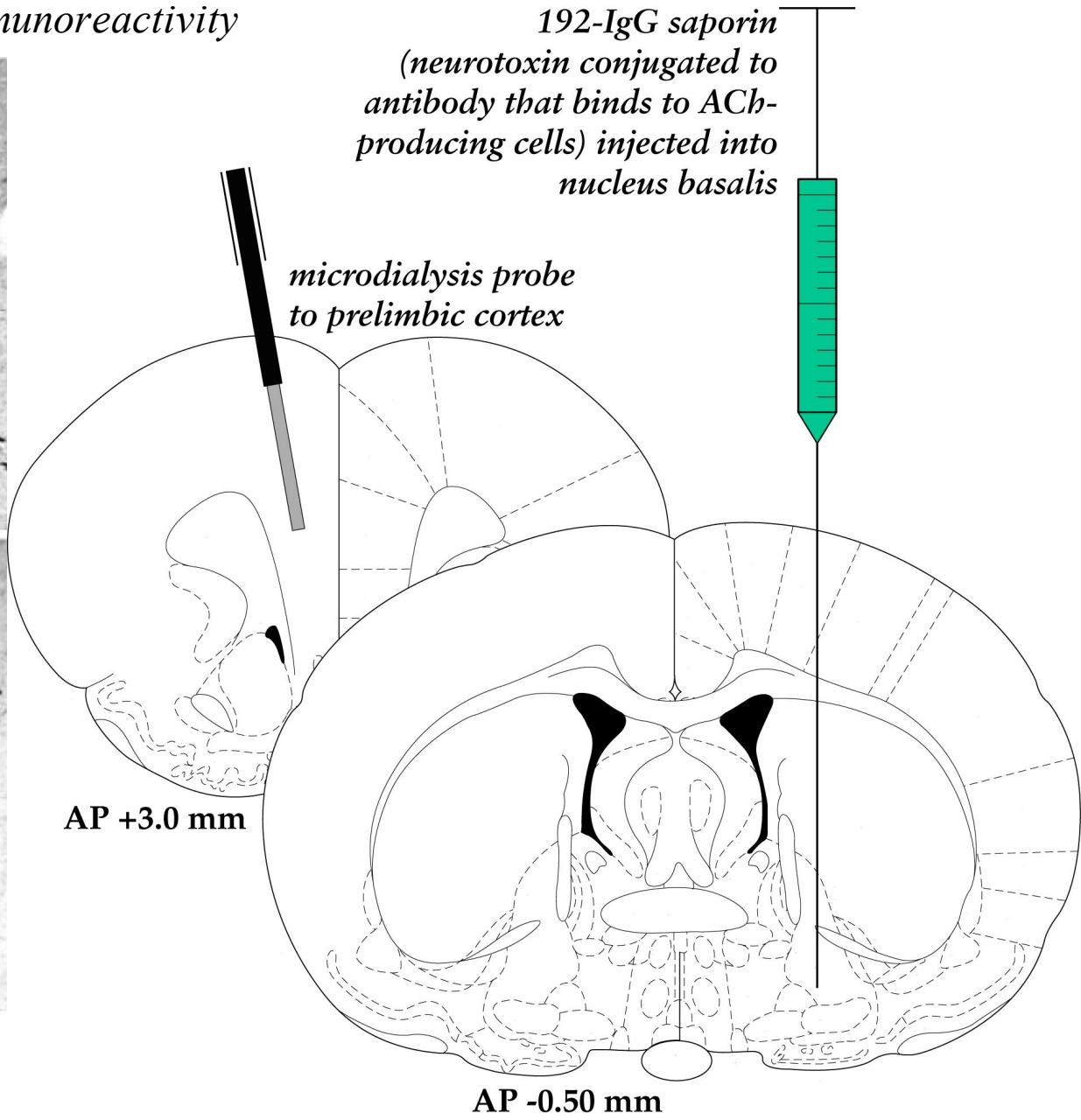


Passetti et al. (2000)

Intra-basalis saporin combined with in vivo microdialysis

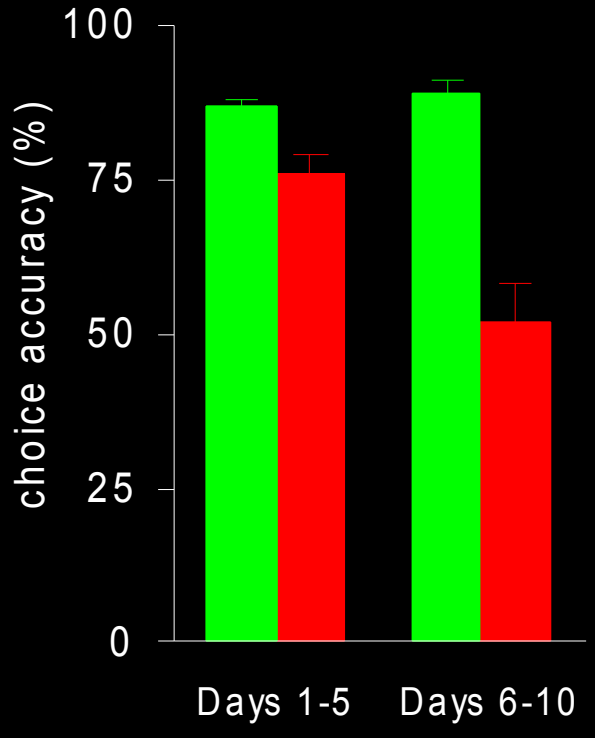
Acetyl cholinesterase (ChAT) immunoreactivity

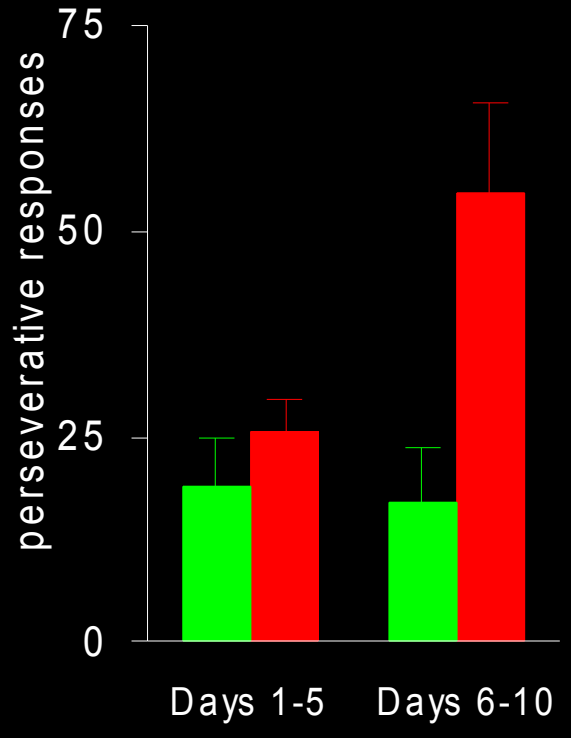


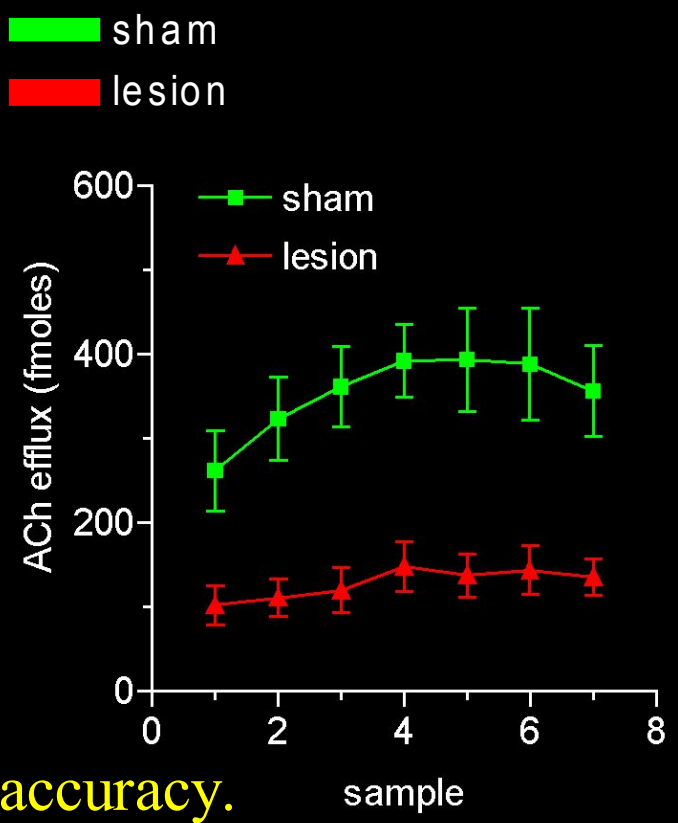


McGaughy et al. (2002)

ACh depletion induced attentional and 'executive' dysfunctions (an accuracy deficit and perseveration)







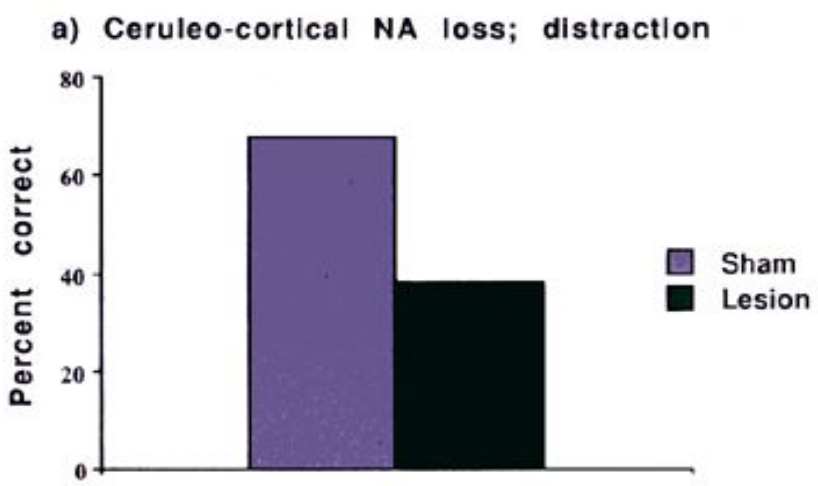
Basalis ChAT immunoreactivity correlated with accuracy.

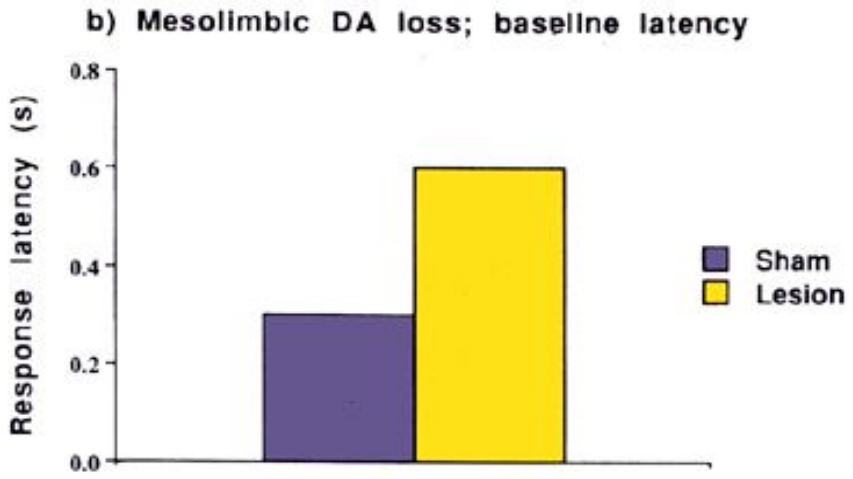
Task-related ACh efflux correlated with accuracy.

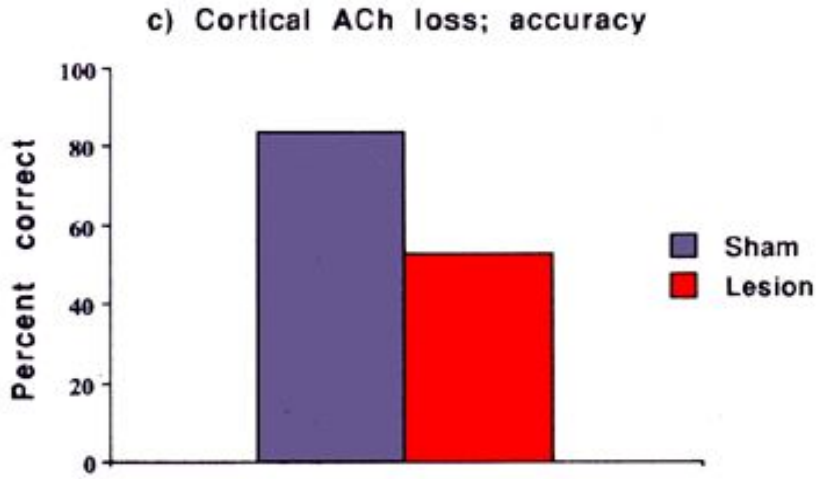
ACh efflux correlated with ChAT immunoreactivity.

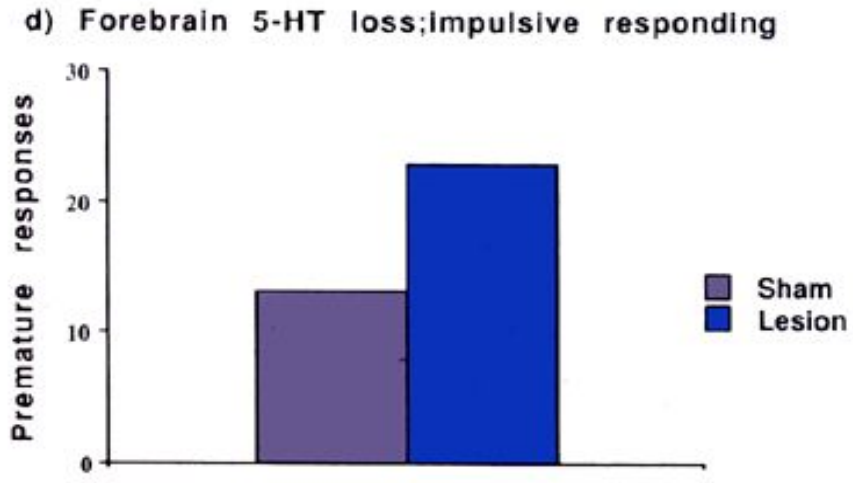
McGaughy et al. (2002)

Depleting forebrain neuromodulators produces dissociable effects on parameters of 5-choice task performance



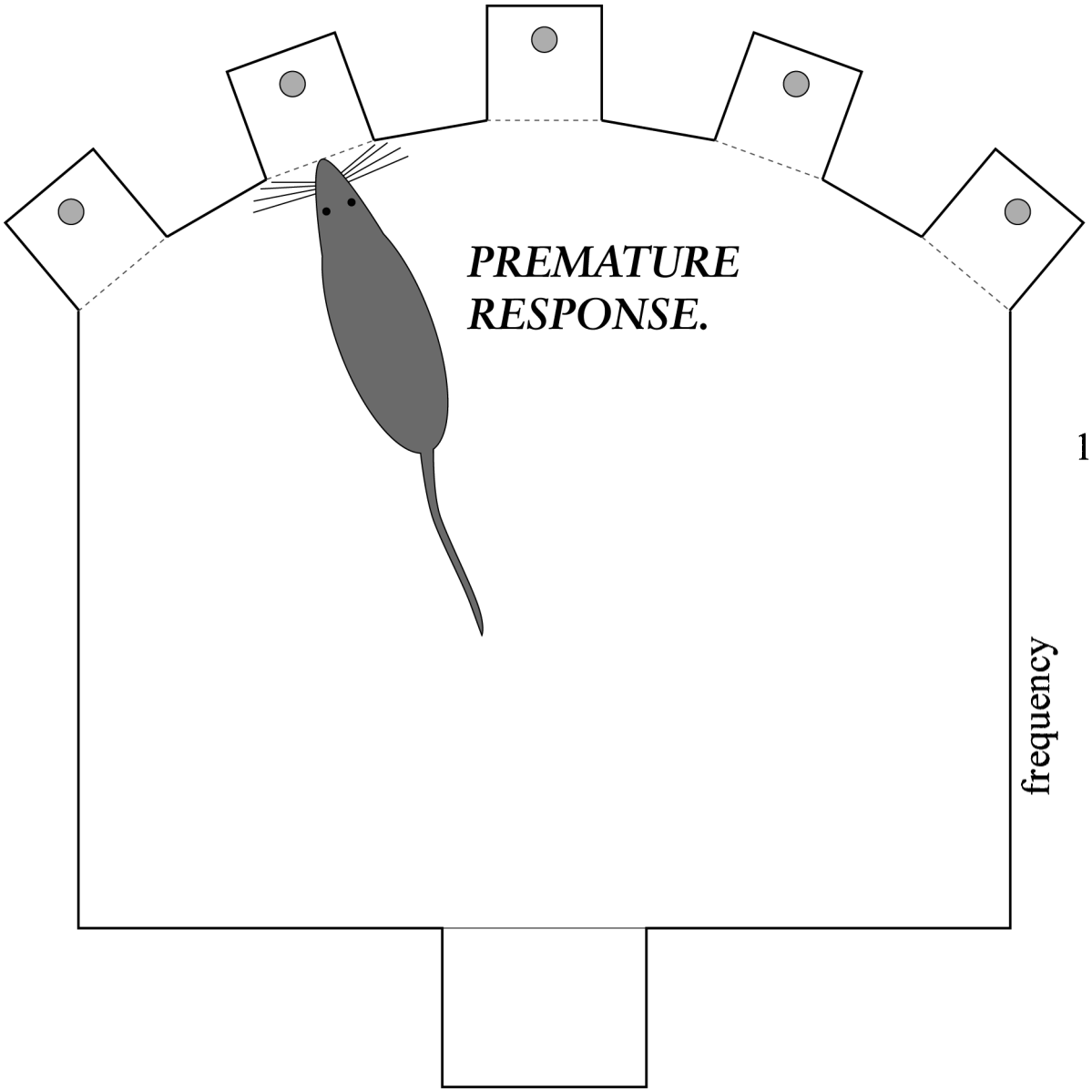




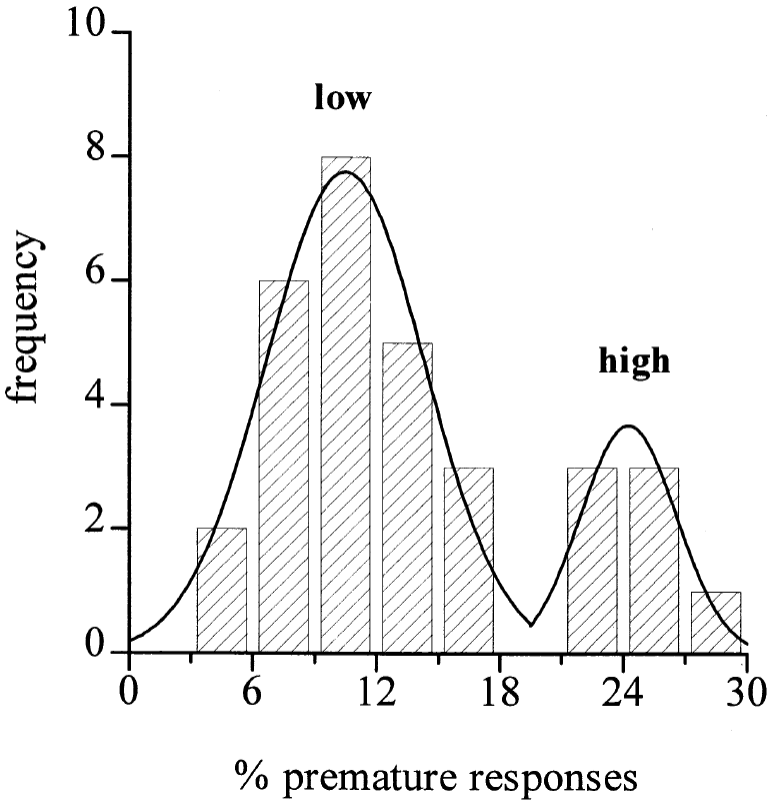


Carli et al. (1983), Cole & Robbins (1989, 1992); Muir et al. (1995), Harrison et al. (1997)

Motor impulsivity: premature responding in the 5CSRTT

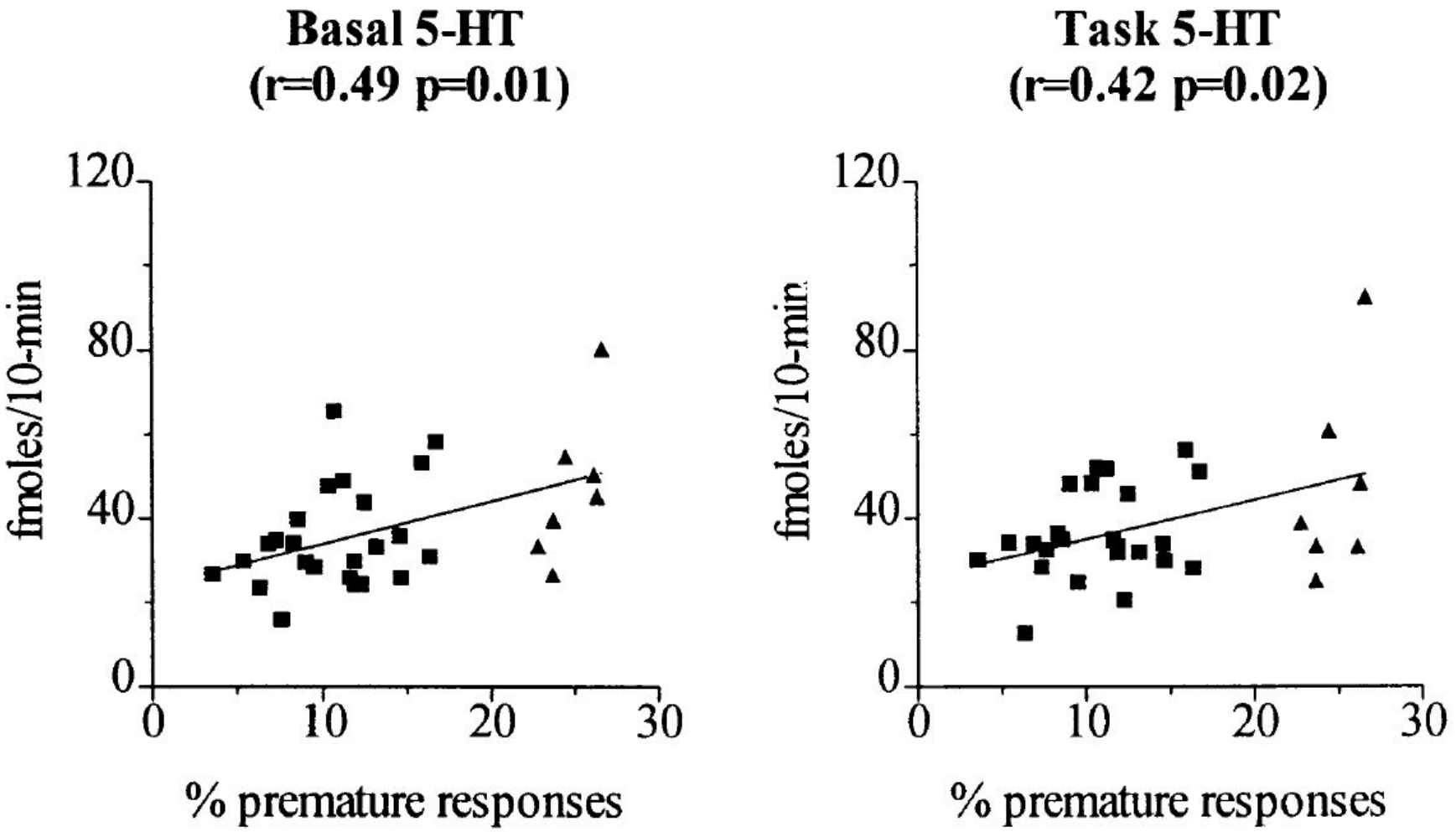


- Increased by anterior cingulate cortex lesions.
- Increased by forebrain 5-HT depletion.
- Bimodal distribution in normal rats.



Dalley et al. (2002)

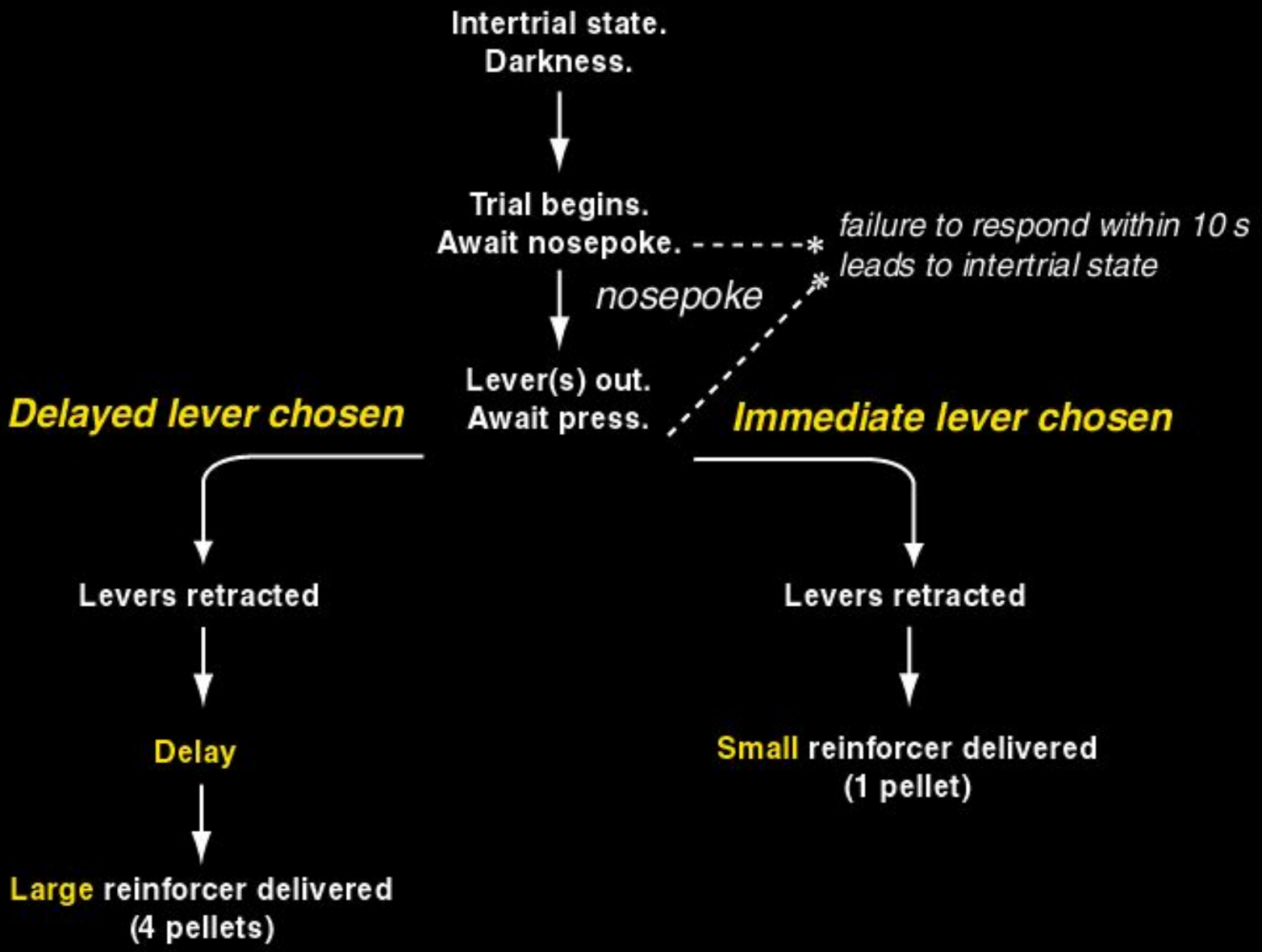
Premature responding *positively* correlated with 5-HT efflux



… though forebrain 5,7-DHT depletion (which reduces *tissue* 5-HT) *increases* premature responding. A puzzle under investigation.

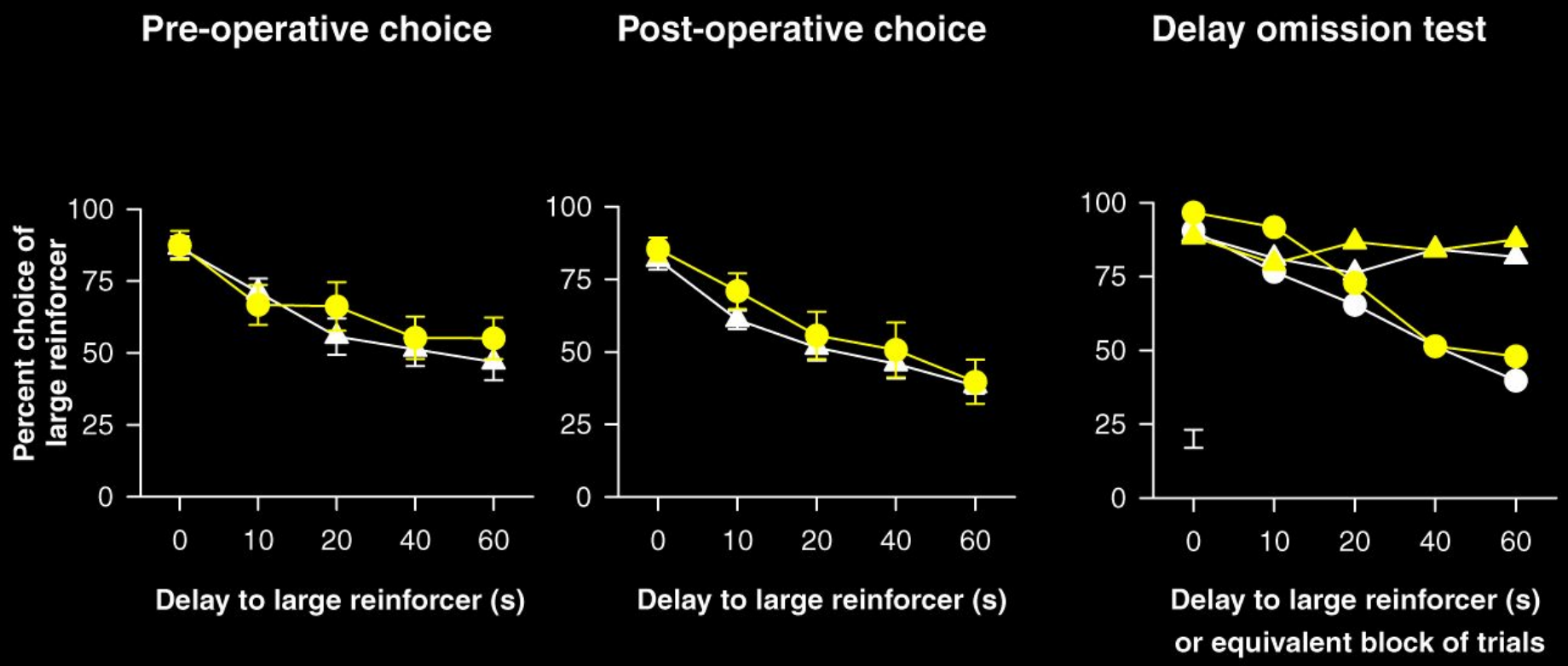
Harrison et al. (1997); Dalley et al. (2002)

Choice impulsivity: choice involving delayed reinforcement



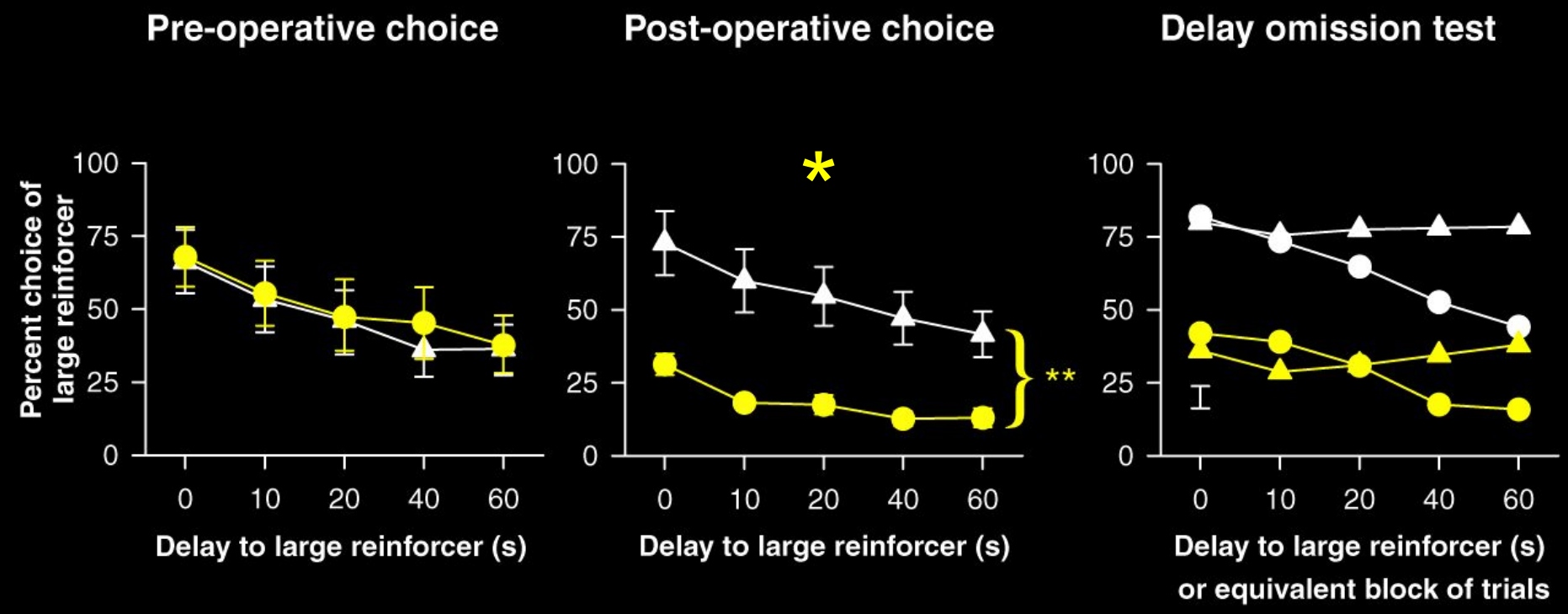
Cardinal et al. (2000), based on Evenden & Ryan (1996)

Anterior cingulate cortex (ACC) lesions, which have been shown to produced ‘motor impulsivity’ in the 5-choice task, had no effect upon responding for delayed rewards



Cardinal et al. (2001)

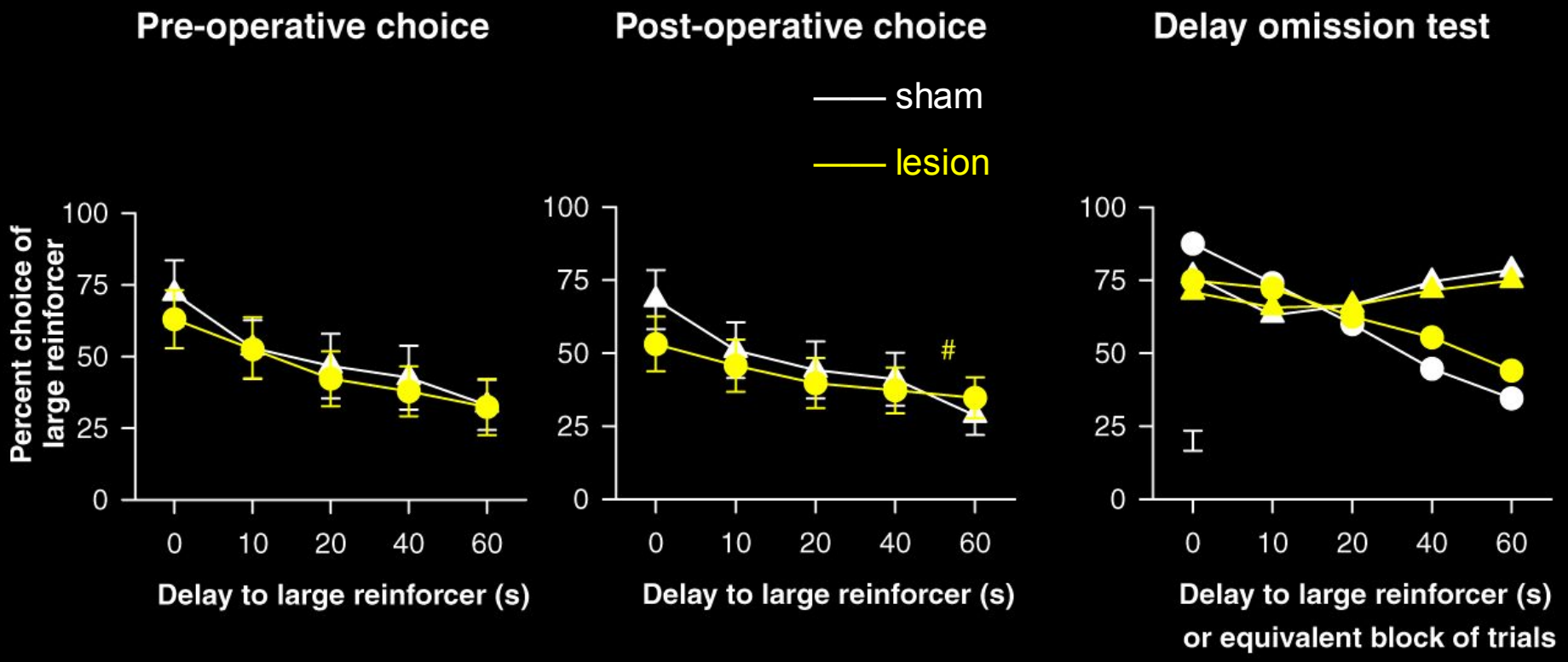
Nucleus accumbens core (AcbC) lesions severely impaired the ability of rats to choose a delayed reward



Cardinal et al. (2001)

Medial prefrontal cortex (mPFC) lesions induced an insensitivity to the task contingencies

Lesioned subjects chose the large reward *less* frequently at zero delay, and *more* frequently at long delays.



Cardinal et al. (2001)

Instrumental contingency knowledge requires prelimbic cortex

sham-operated rats

Test of action–outcome contingency knowledge.

Action A1 → outcome O1.
Action A2 → outcome O2.

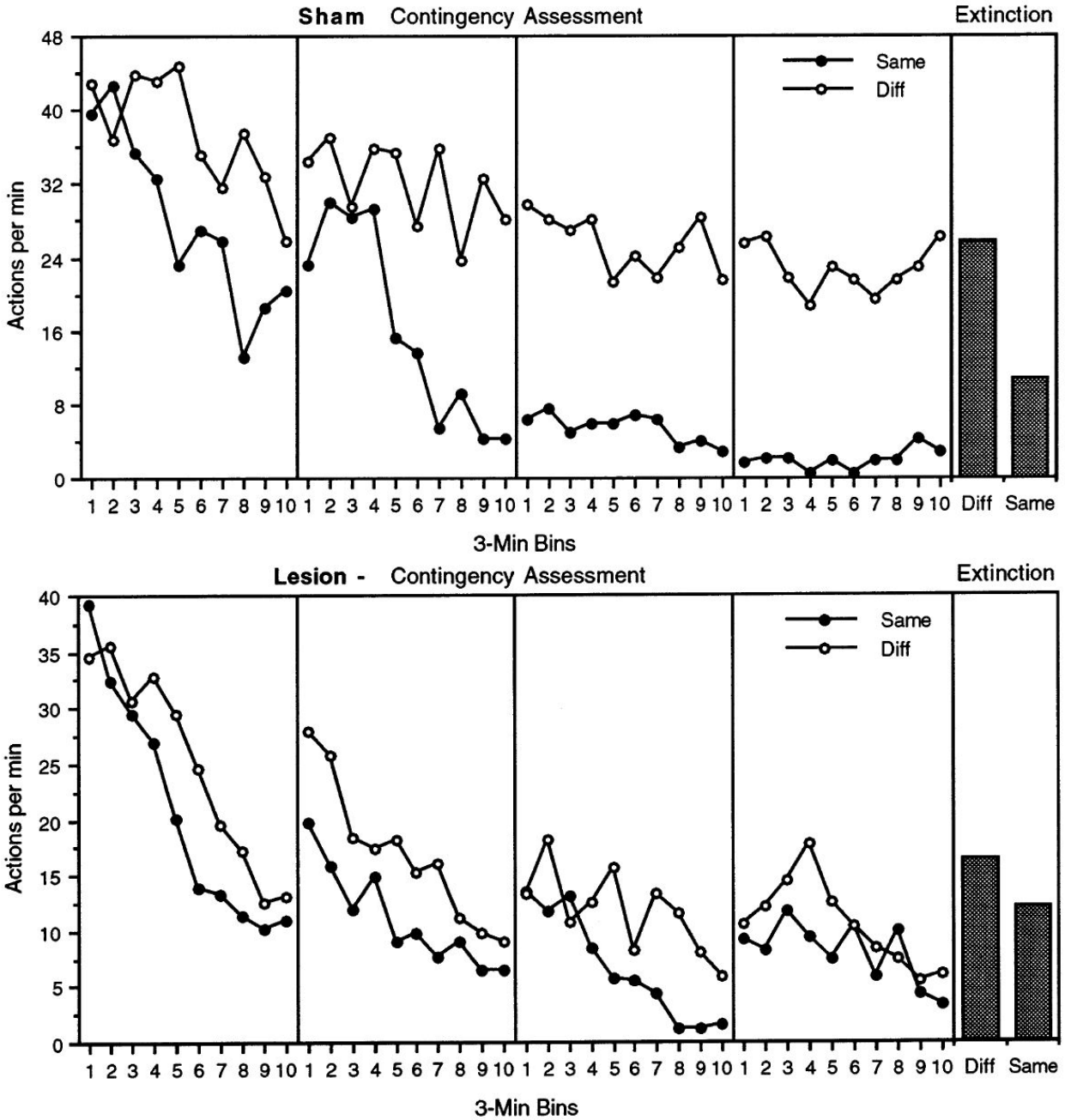
Contingency = p(O|A) – p(O|¬A).

Contingency is initially 1 – 0 = 1 for both A1 and A2. Outcome O1 is then delivered for free, reducing the contingency for A1.

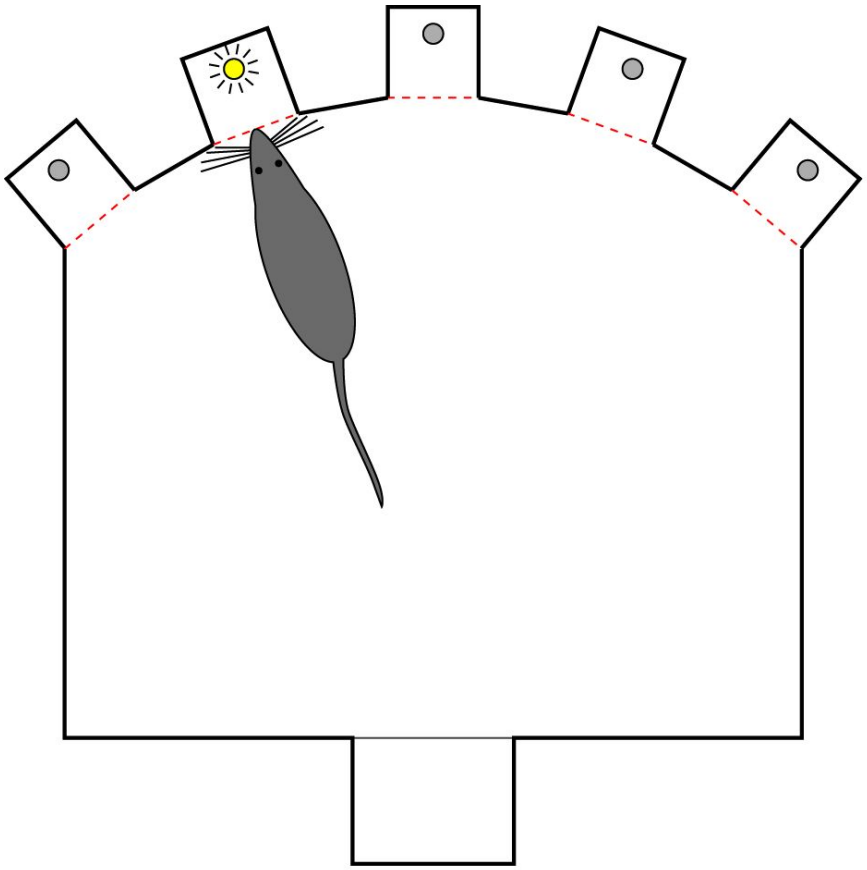
Normal rats respond by performing A1 < A2. Prelimbic-lesioned rats don't.

prelimbic-lesioned rats

Balleine & Dickinson (1998)



Degrading the instrumental contingency: yoked controls (1)



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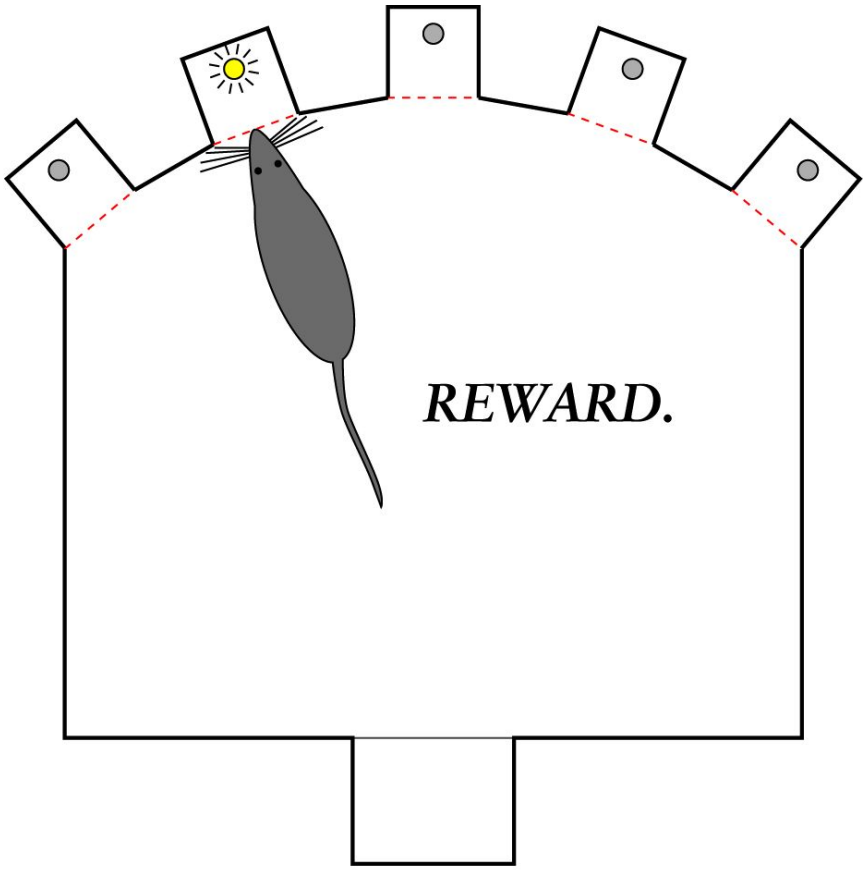
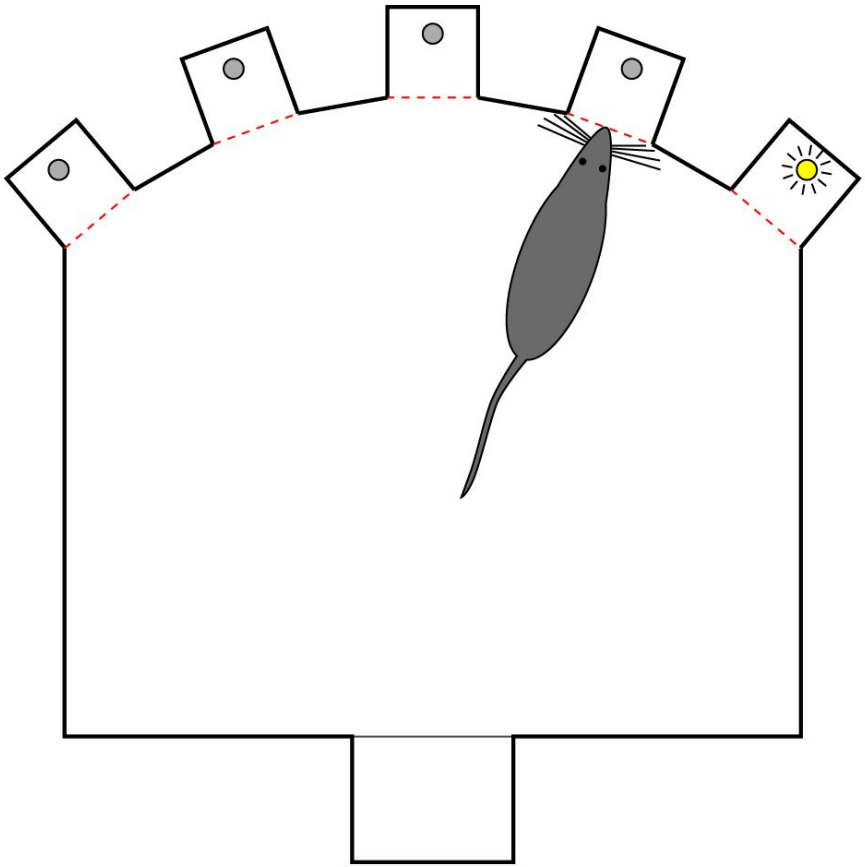


yoked control
(slave)

Dalley et al. (2001)

Degrading the instrumental contingency: yoked controls (2)



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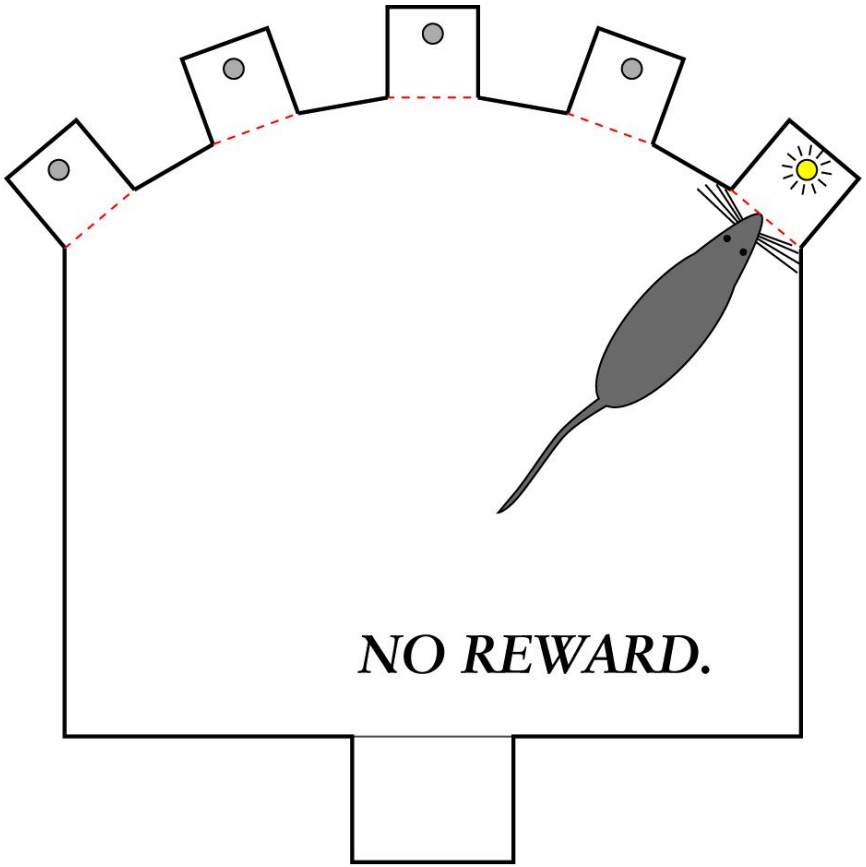
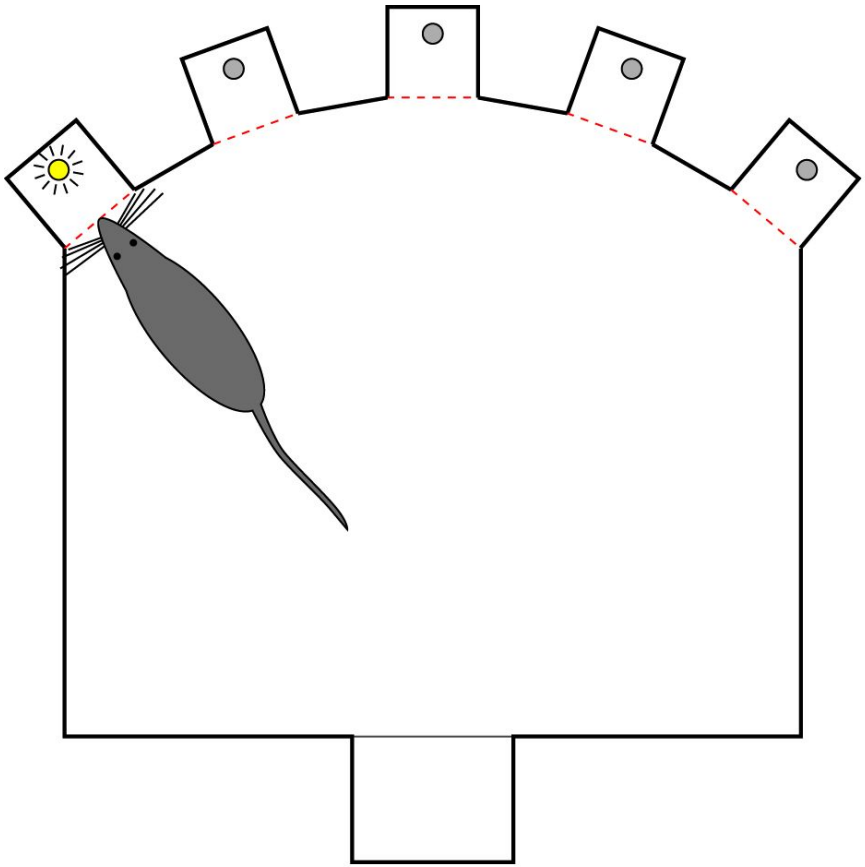


yoked control
(slave)

Dalley et al. (2001)

Degrading the instrumental contingency: yoked controls (3)



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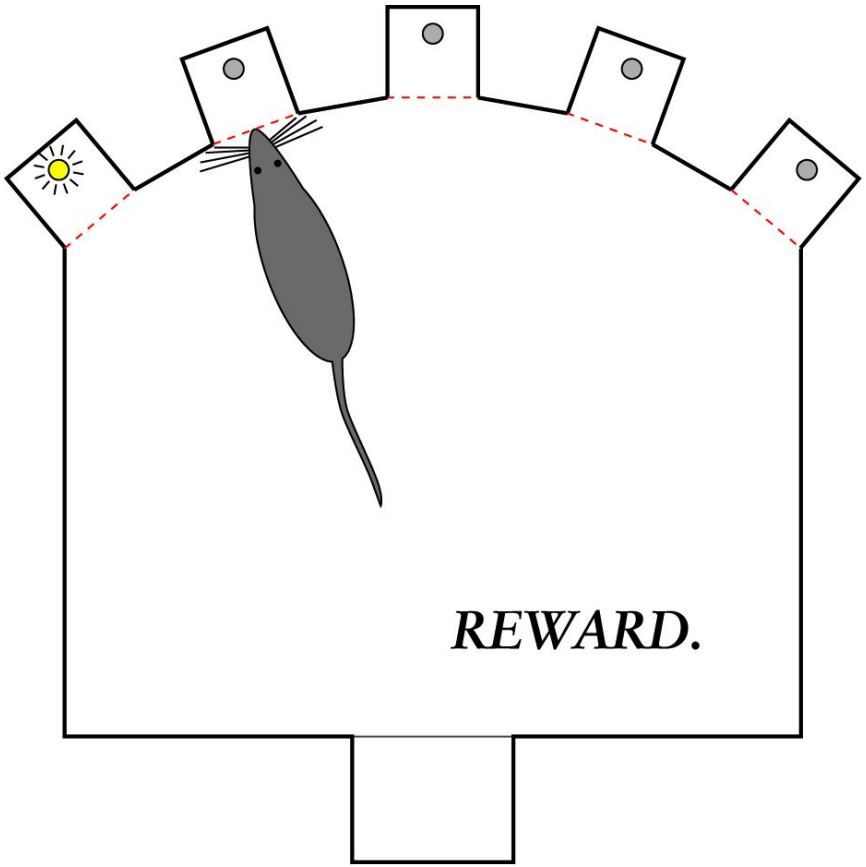
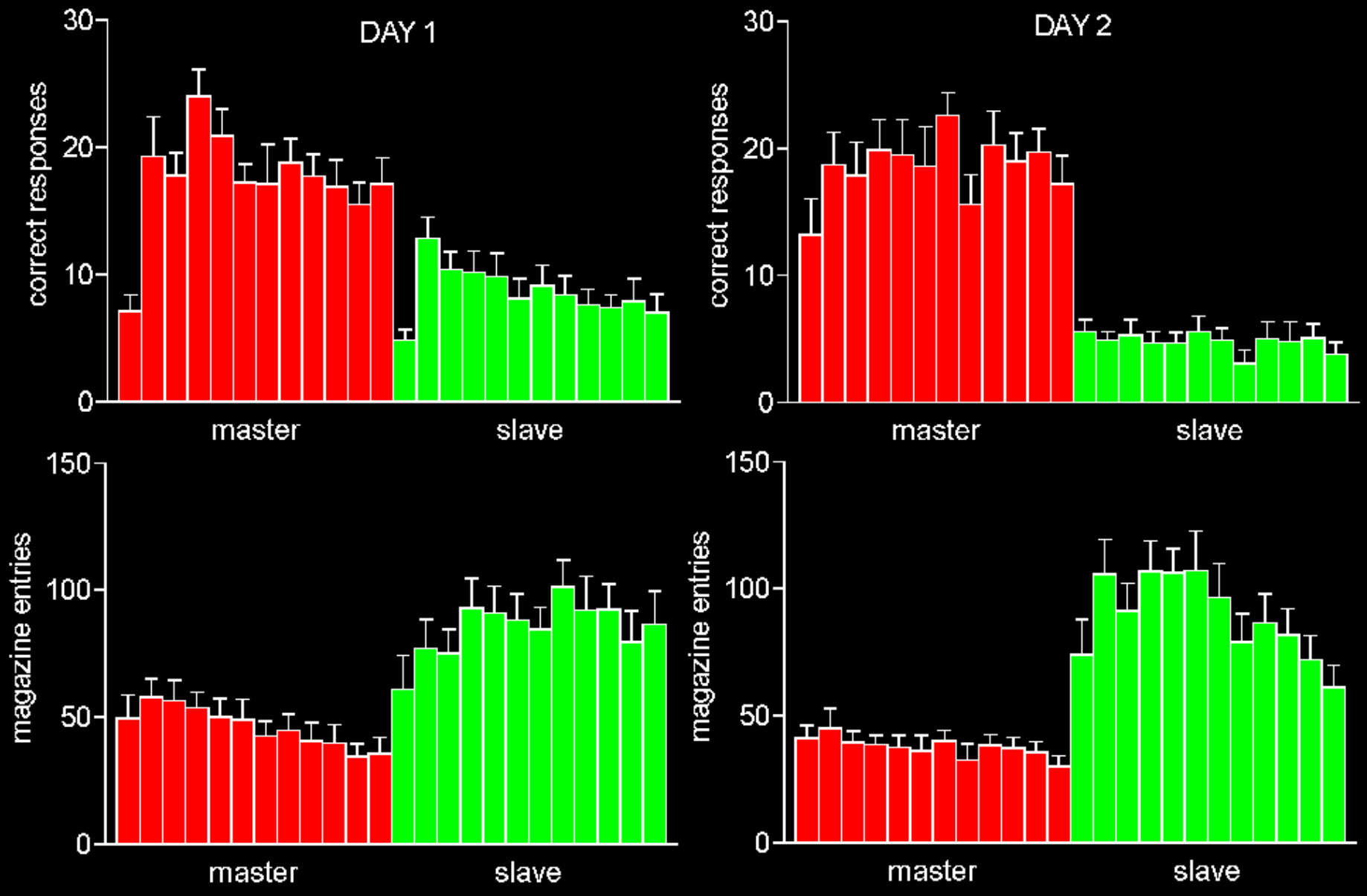


yoked control (slave)

Consummatory behaviour is controlled for.

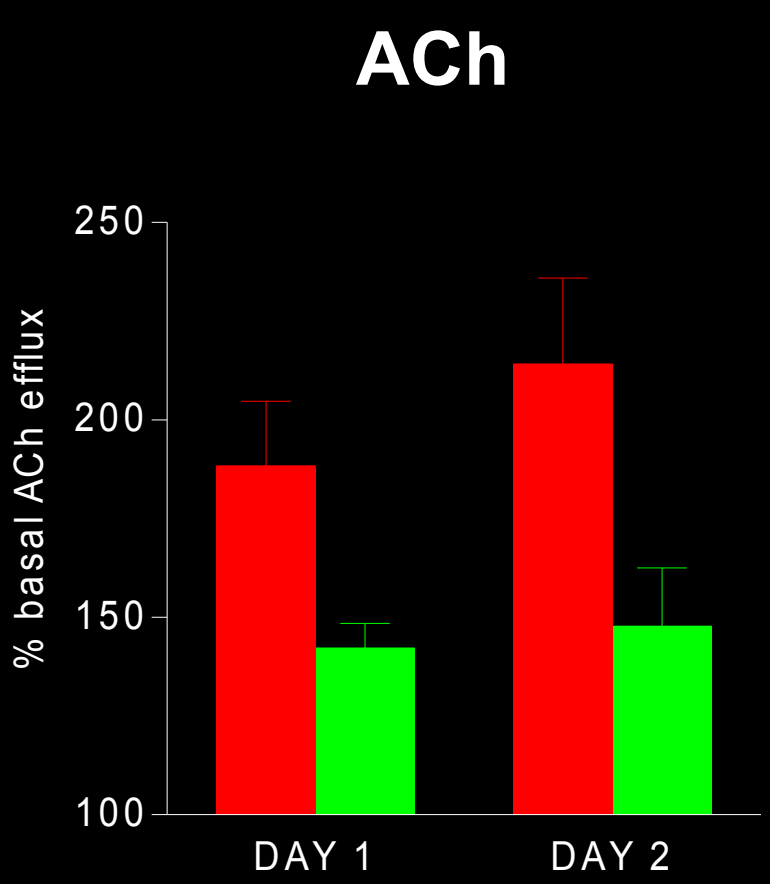
Dalley et al. (2001)

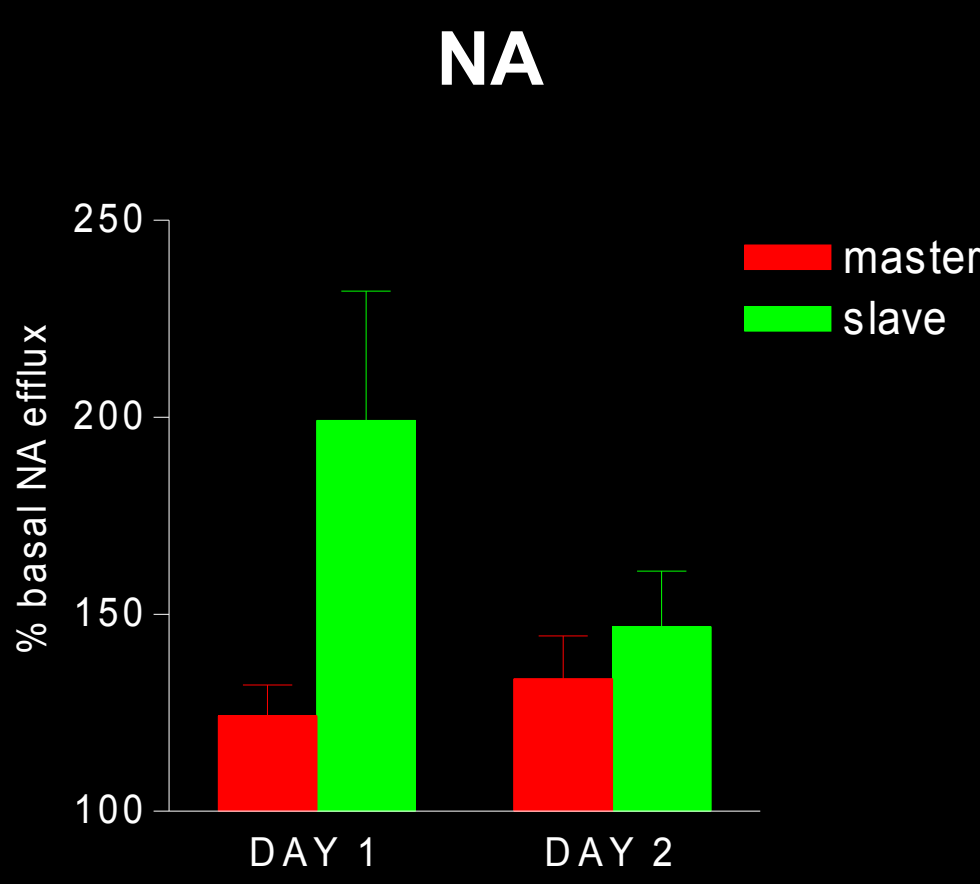
Behavioural performance of yoked controls



Dalley et al. (2001)

ACh efflux in prelimbic cortex was attenuated in yoked (noncontingent) subjects; NA efflux was transiently elevated in response to the contingency change



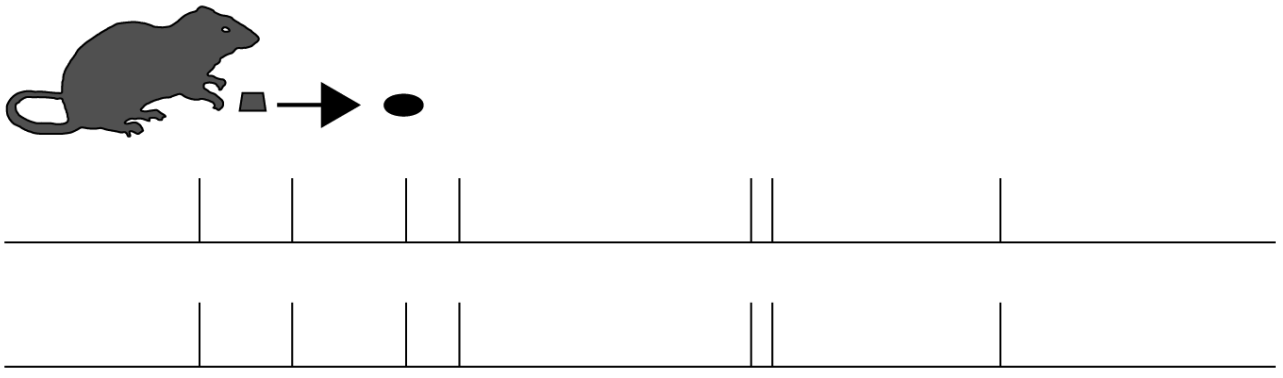


Dalley et al. (2001)

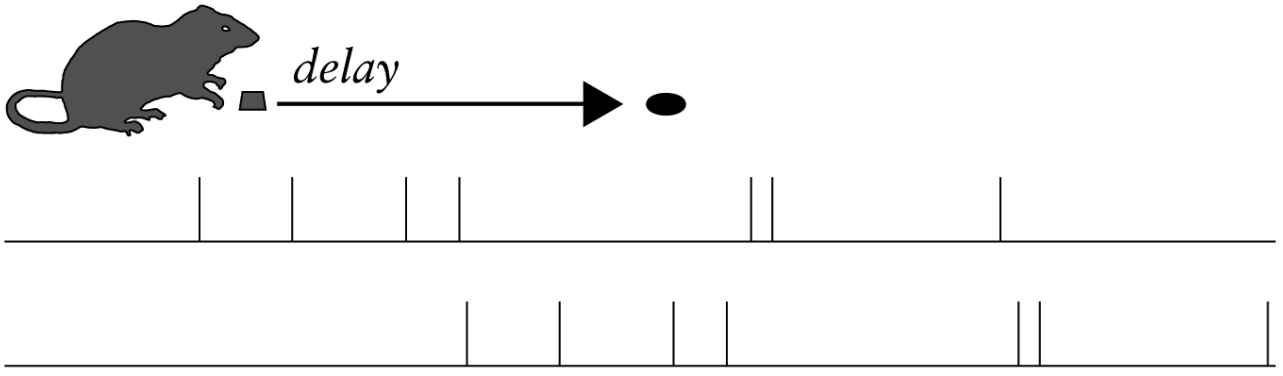
Instrumental contingencies are harder to detect with a delay

Acquisition of free-operant instrumental responding on a fixed-ratio-1 schedule

a) Zero delay

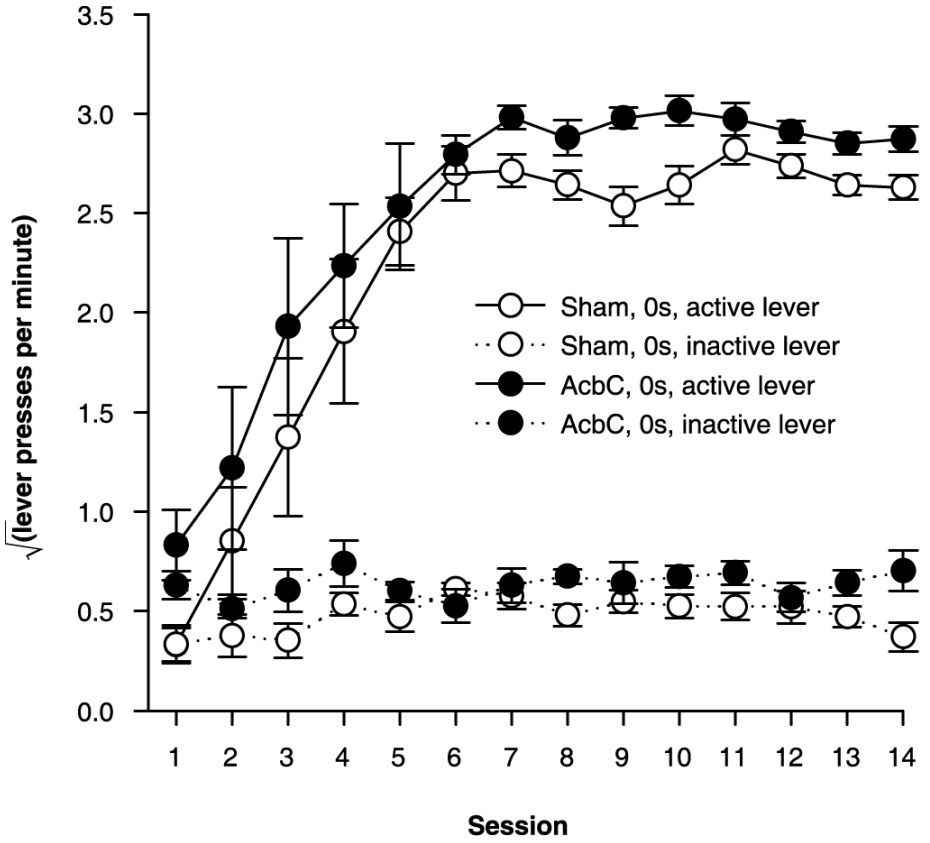


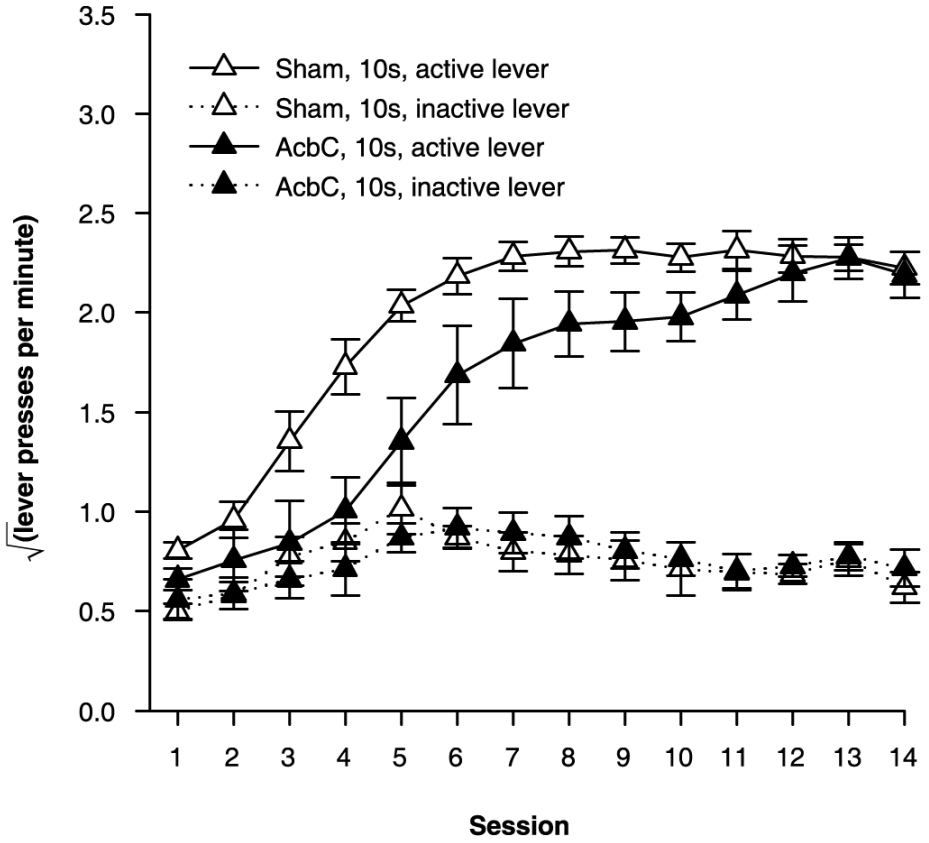
b) 10- or 20-second delay



We've seen that nucleus accumbens core (AcbC) lesions impair choice of delayed reward. Is this because they can't learn the contingency when reward is delayed?

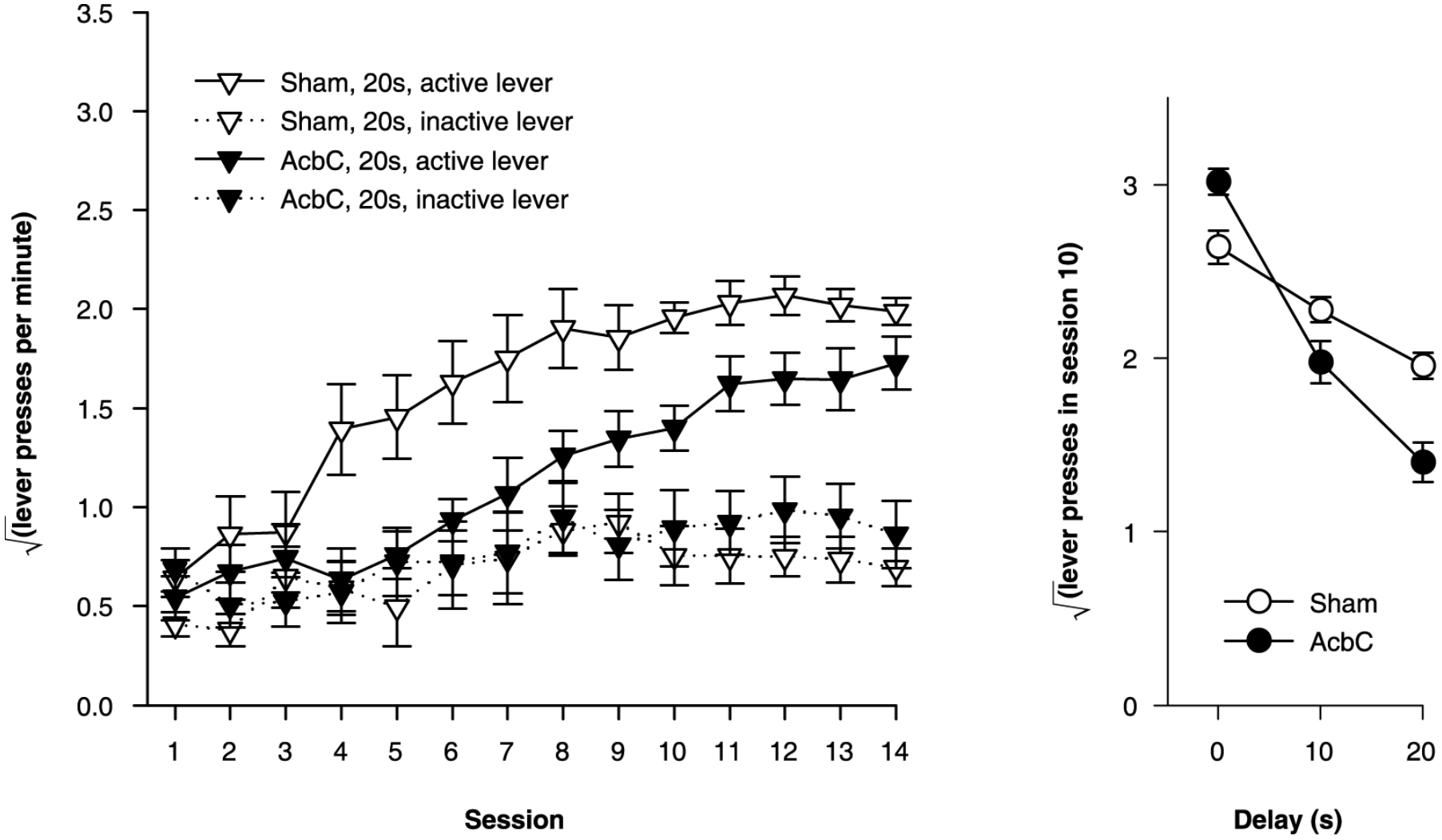
Instrumental acquisition requires the AcbC only when there is a delay between action and outcome (1)





Cardinal & Cheung (unpublished)

Instrumental acquisition requires the AcbC only when there is a delay between action and outcome (2)



Cardinal & Cheung (unpublished)

Summary

- The 'executive' is neither psychologically or neurally unitary.
- Accuracy in the 5-choice sustained attentional task
    - is impaired by lesions of prelimbic/medial prefrontal cortex;
    - is correlated with ACh release in prelimbic cortex;
    - is impaired by forebrain ACh depletion.
- The ability to inhibit 'premature' responses requires regions of the anterior cingulate cortex, and can be improved or disrupted following 5-HT manipulations. However, the 'motor' impulsivity (disinhibition) seen after ACC lesions is dissociable from 'choice impulsivity' (ability to choose a delayed reward), requiring the nucleus accumbens core (AcbC) and orbitofrontal cortex.
- The ability to detect instrumental action–outcome contingencies requires prelimbic cortex. This is a basic psychological process that may underpin performance on many tasks.
- Acquisition of instrumental responses appears normal following AcbC lesions, except when there is a delay between the action and the outcome.

Collaborators (in alphabetical order) and acknowledgements

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