Dissecting Cognitive and Behavioral Processes Underlying Motivation

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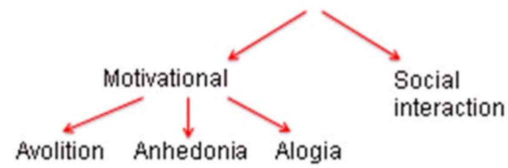
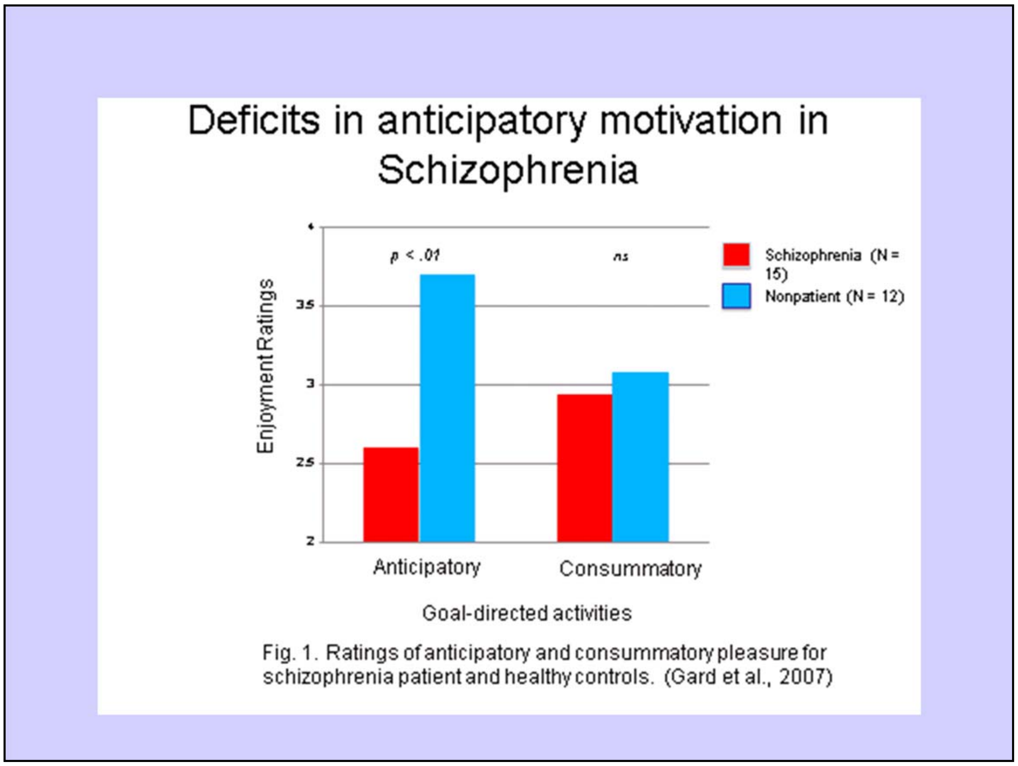
Symptoms in Schizophrenia

- Positive, **Negative** & Cognitive

- Negative symptoms: Two classes



- **Not responsive to medication or therapy; predictive of poor functional outcome**



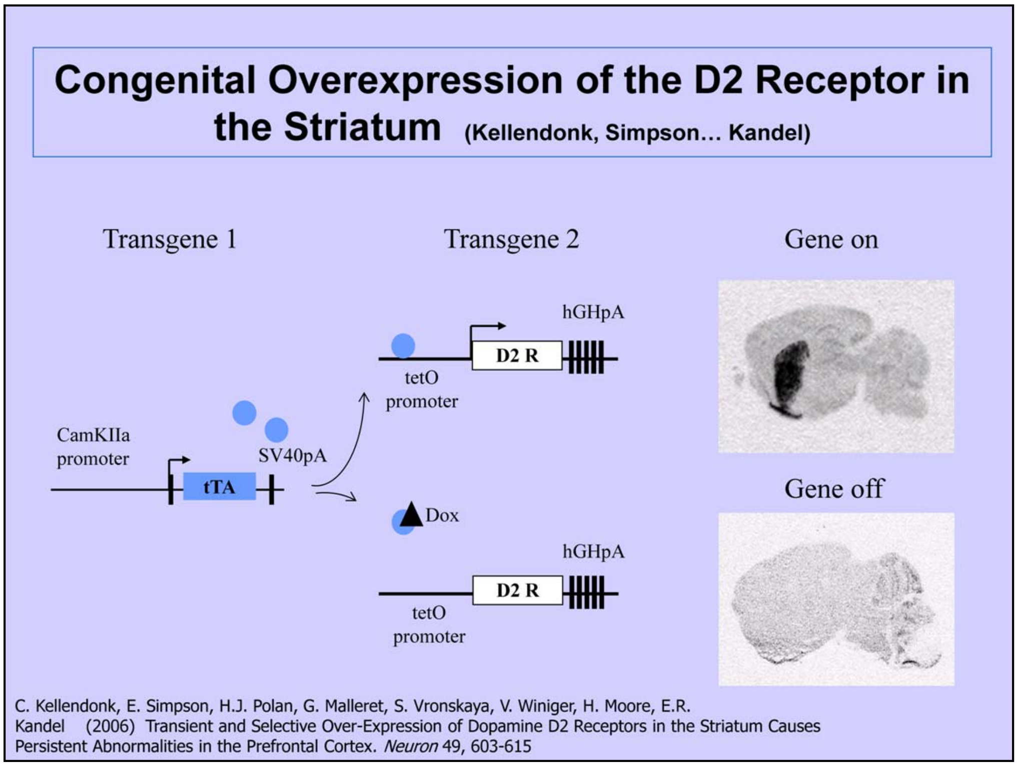
It appears that one aspect of the motivational deficit in patients is a deficit in anticipation not in subjective evaluation of the enjoyment of outcomes once they are experienced.

Outline of talk

Brief description of the mouse model I will use to illustrate the analysis

Talk about a task we have found useful as a global screen for cognitive/motivational deficits

Describe the dissection of the cognitive/behavioral processes that underlie motivation



Excess striatal D2 receptors in mice lead to cognitive deficits that resemble some of the cognitive deficits of schizophrenia

The overexpression alters the whole brain during development. For example, overexpression of D2 receptors in the striatum impacts dopamine levels, rates of dopamine turnover and activation of D1 receptors in the prefrontal cortex

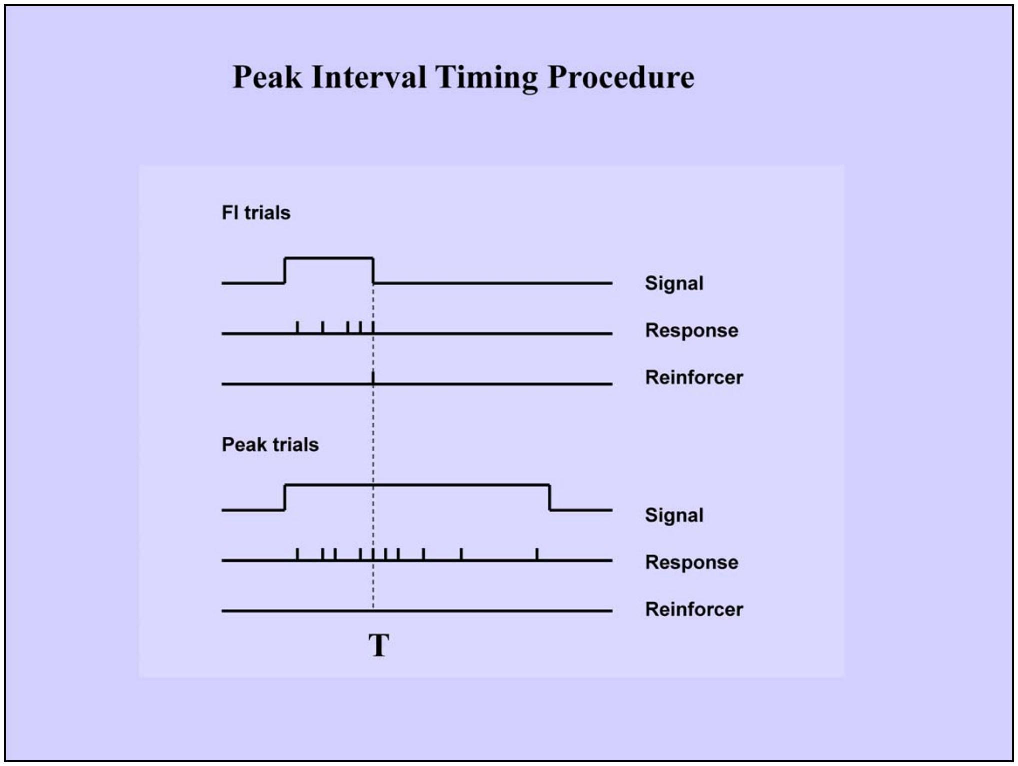
D2OE Have Cognitive and Behavioral Deficits

Working memory

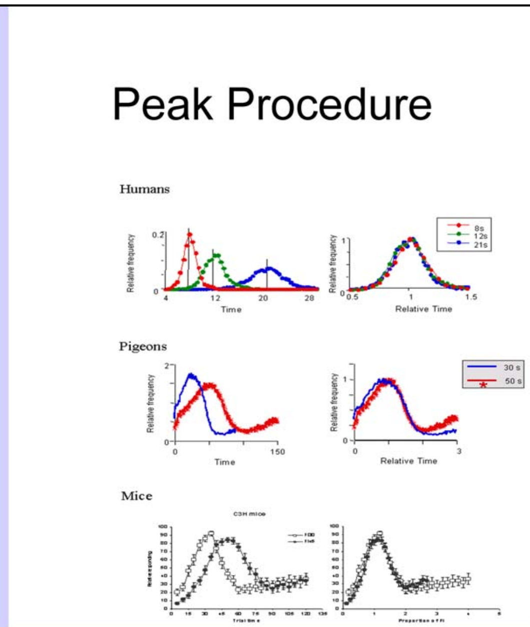
Behavioral Flexibility

Timing

Timing makes a good general screen when examining an animal model because accurate and precise timing depend on many cognitive processes. When we start with assessing a model it is perhaps best to begin with a general and sensitive screen for deficits to guide us in what directions to explore.



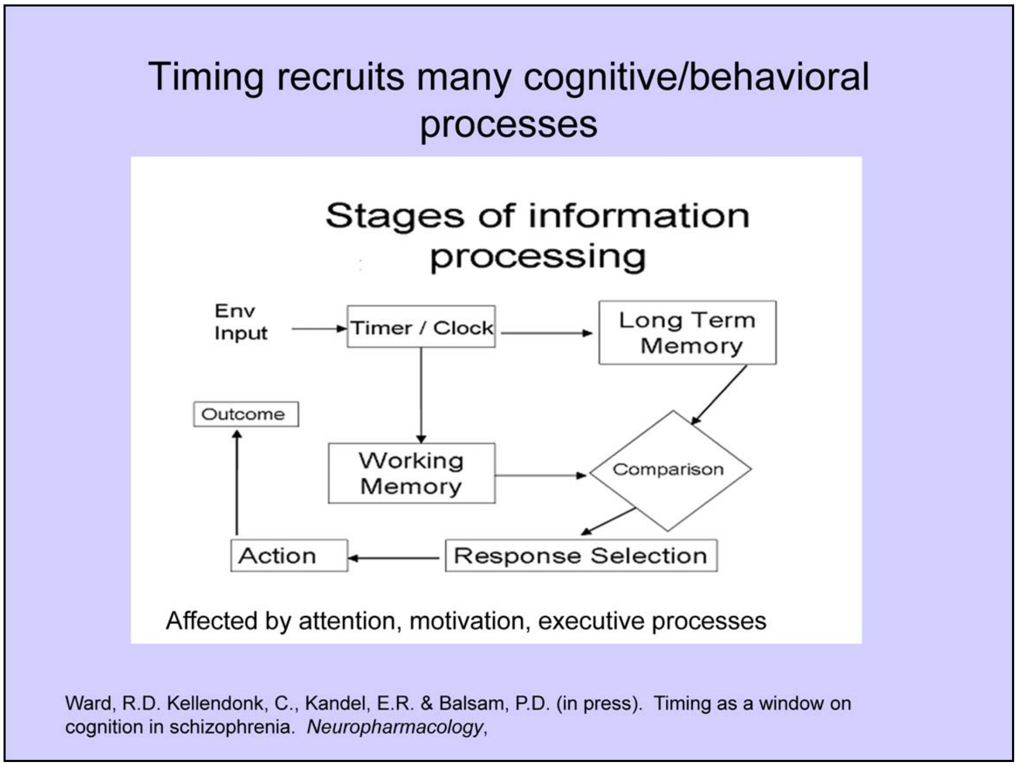
Two kinds of trials- During Fixed interval (FI trials) a cue comes on and animal is reinforced for first response after a fixed latency since cue onset. On Peak trials the cue stays on for a long time and no reinforcer is presented. If the animal has learned the time responding will become more likely as the expected time of reward approaches and then less likely once that time has passed.



Timed anticipation in humans (modified from Rakitin, Gibbon, Penney, Malapani, Hinton & Meck, 1998), pigeons (from Gibbon, Fairhurst & Goldberg, 1997), and mice (from Brunner, personal communication) shows the scalar property.

See movie on youtube

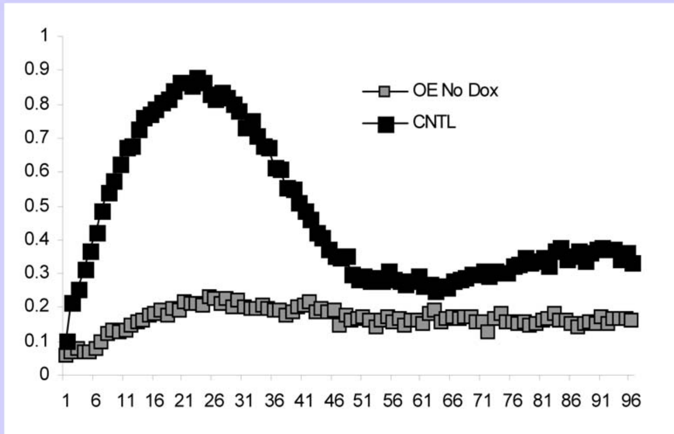
See movie on youtube. Note what the animal does shortly after the expected time of reward even though no pellet has been presented.



Timing requires intact perception, memory and decision processes. Accuracy and precision (variability) can also be affected by attention, motivation and executive processes

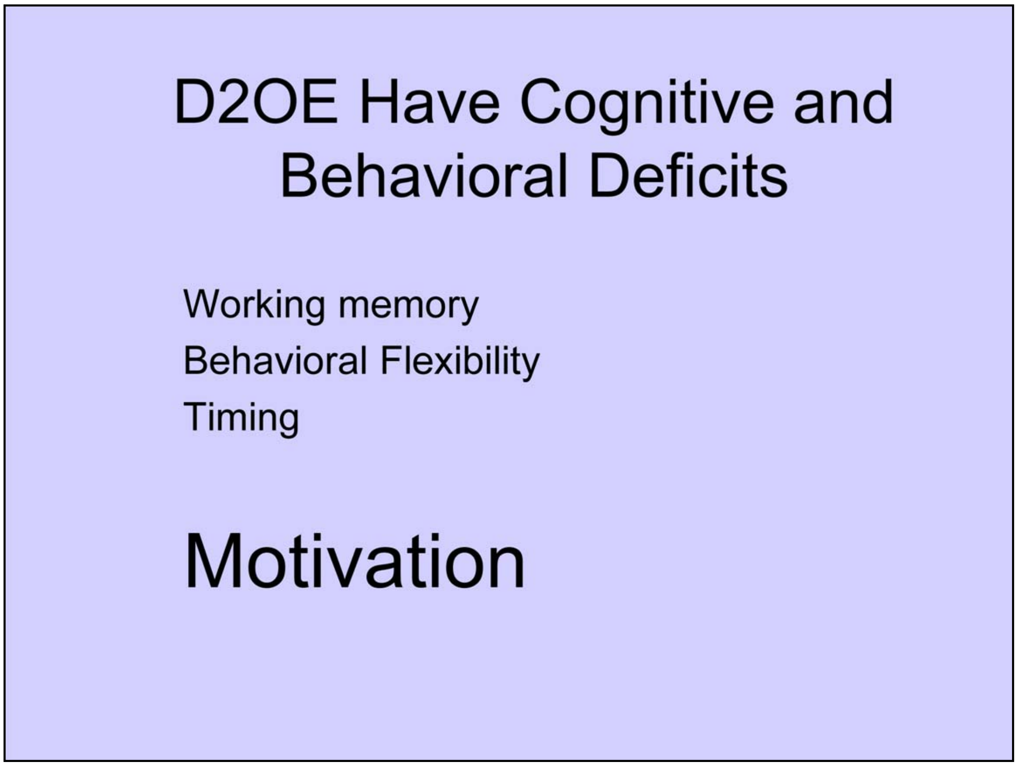
Overexpression of D2 receptor in striatum distorts temporal control

Drew, Simpson, Kellendonk, Herzberg, Lipatova, Fairhurst, Kandel, Malapani & Balsam (2007)



Perhaps, altered memory, attention, decision making and motivation

The model animals are less accurate and precise but also show a striking difference in the total response output. The latter may reflect a large deficit in motivation.



One striking difference between D2OE and controls is the lower rate of responding – perhaps reflecting a motivational deficit

Issues in analyzing behavior/cognition in animal models

Heterogeneity of tests

Multiple ways to solve problems-
No difference does not mean no difference

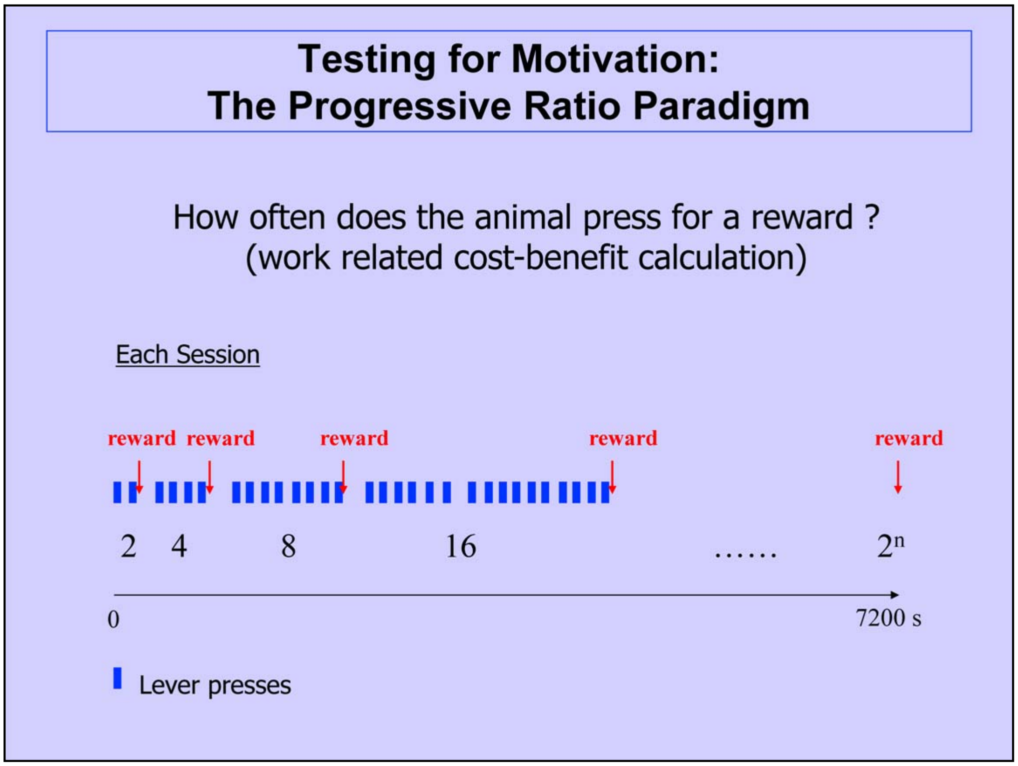
Learning – fear conditioning, working memory T-maze, spatial cognition- water maze, attention in an operant chanber

Differences in sensory cues, motivation, response requirements, etc.

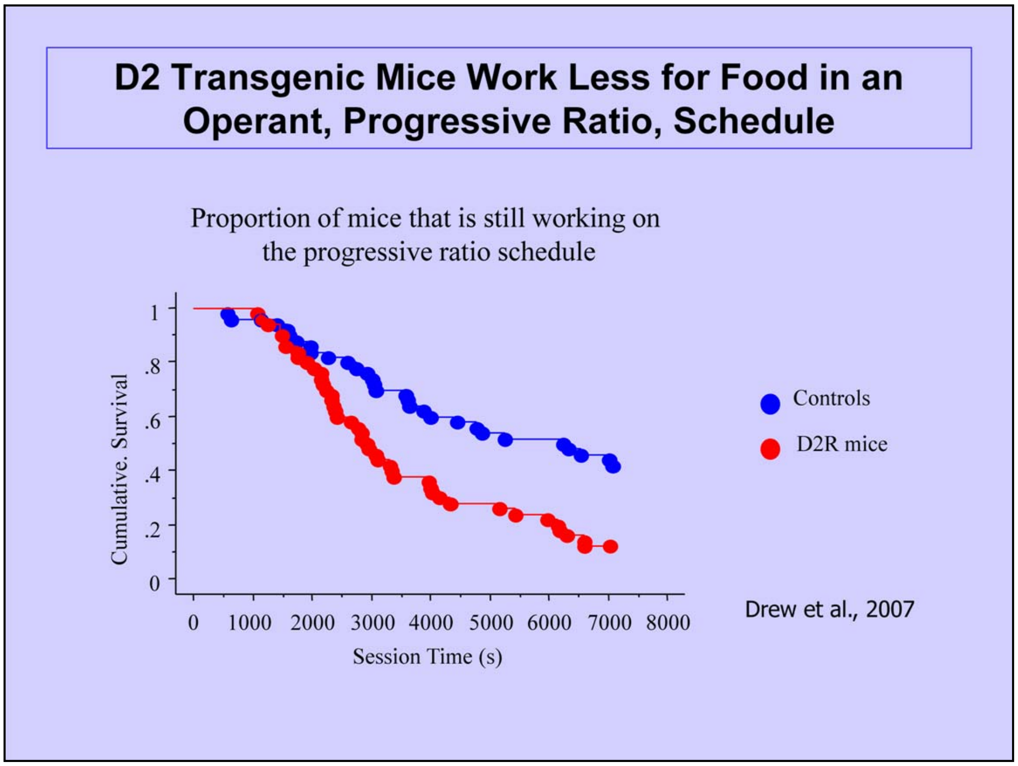
Overexpression of D2 receptor in striatum leads to decreased motivation

Drew, Simpson, Kellendonk, Herzberg, Lipatova, Fairhurst, Kandel, Malapani & Balsam (2007)

Image - http://www.frontiersin.org/behavioral_neuroscience/10.3389/fnbeh.2010.00171/full



Response cost increases after each successive reward. How long does the animal keep working?



D2OE quit working sooner during PR sessions

Dissecting Motivation

What does it mean to have less motivation?

Initiation

Maintenance
- Duration
- Vigor of responding

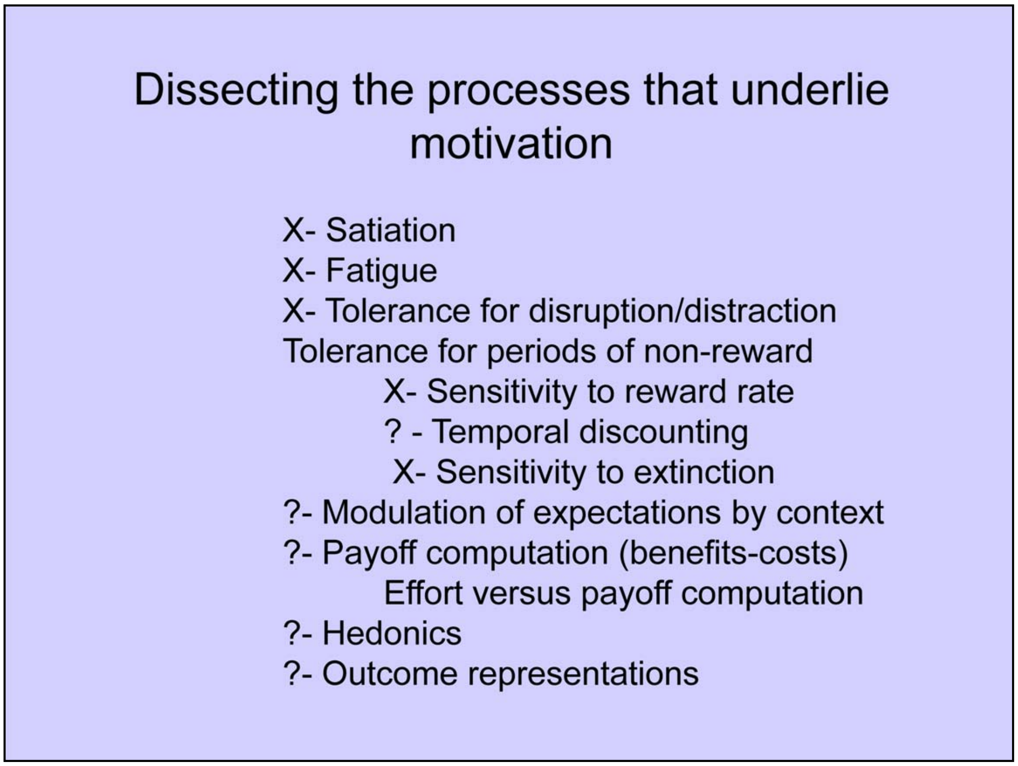
Perseverance (Behavioral Momentum)
- Resistance to disruption/distraction

Motivation will modulate all these dimensions of action. Our approach is to develop a set of tests that as much as possible hold stimuli, responses, motivation constant by devising tests for cognitive and behavioral deficits in which mice press bars to earn food reward (Ward, R.D., Simpson, E.S., Kandel, E.R. & Balsam, P.D. (2011). Modeling Motivational Deficits in Mouse Models of Schizophrenia: Behavior Analysis as a Guide for Neuroscience. *Behavioral Processes*, *87*, 149-156)

Dissecting the processes that underlie motivation

- Satiation
- Fatigue
- Tolerance for disruption/distraction
- Tolerance for periods of non-reward
  - Sensitivity to reward rate
  - Temporal discounting
  - Sensitivity to extinction
- Modulation of expectations by context
- Payoff computation (benefits-costs)
  - Effort versus payoff computation
- Hedonics
- Outcome representations

Possible processes that could contribute to differential performance of controls and model animals on the progressive ratio

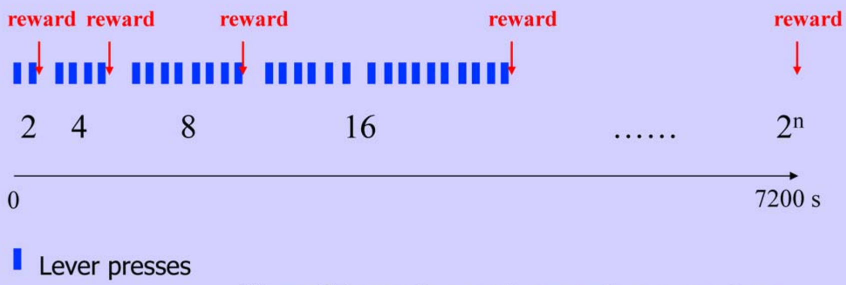


5 processes not responsible for the difference between our model and controls – marked by X

Testing for Motivation: The Progressive Ratio Paradigm

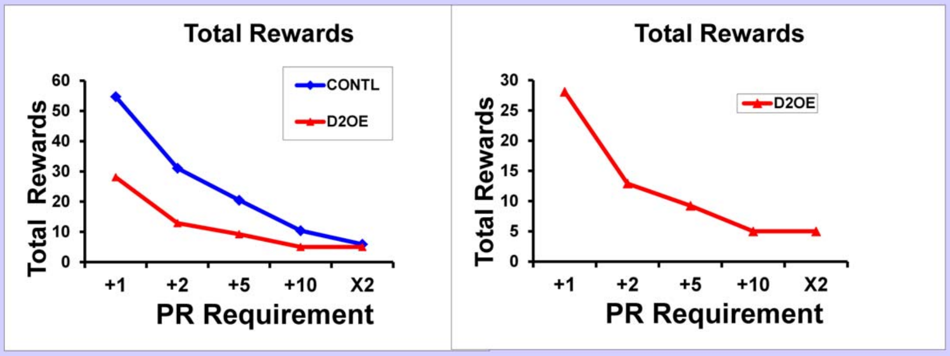
Do D2OE mice satiate or fatigue more easily?

Each Session



Vary PR work requirement across days

Do D2OE mice satiate more easily?

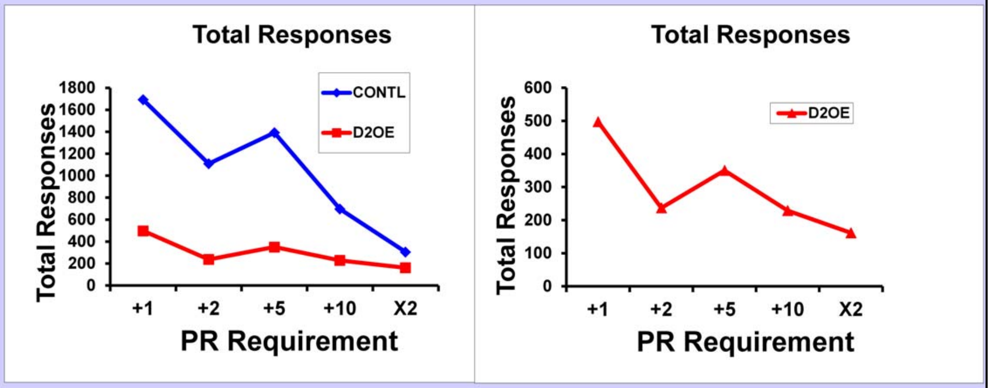


Progressive ratio performance of both D2R-OE and Control mice is sensitive to work requirement. Number of rewards depends on work requirement – D2OE do not quit because of satiation. They quit after an average of 8 rewards at X2 but earn nearly 30 rewards at +1

Simpson, E.H., Kellendonk, C., Ward, R.D., Richards, V., Lipatova, O., Fairhurst, S., Kandel, E.R. and Balsam, P.D. (2011) Pharmacologic rescue of motivational deficit in an animal model of the negative symptoms of schizophrenia. *Biological Psychiatry*, *69*, 928-935.

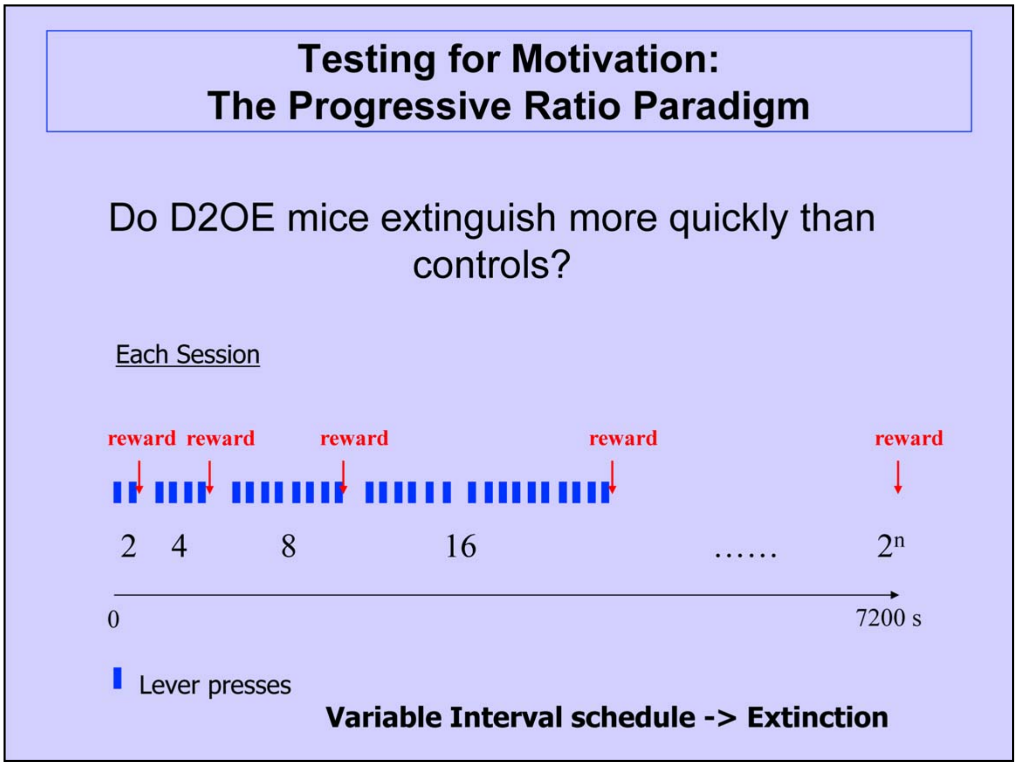
Note that parametric variation is very important. In this case the D2OE always quit sooner than controls but one can imagine how the a model animal and controls might not differ when requirements are too easy or too hard but differ at intermediate values.

Do D2OE mice fatigue more easily?



Number of responses depends on work requirement – D2OE do not quit because of fatigue. At X2 they quit after about 200 responses but make an average of 500 responses at +1

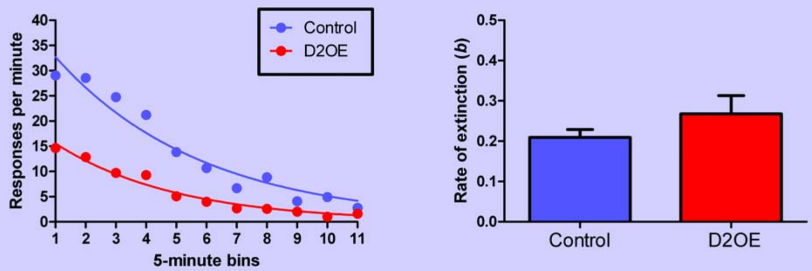
Simpson, E.H., et al. (2011) Pharmacologic rescue of motivational deficit in an animal model of the negative symptoms of schizophrenia. *Biological Psychiatry*, *69*, 928-935.



Model animals extinguish faster as the number of non-rewarded responses goes up after each successive reward. So we trained some on a variable interval schedule and then removed all reward to measure extinction rates.

Do D2OE mice extinguish more quickly than controls?

$$y = a * \exp(-bx)$$



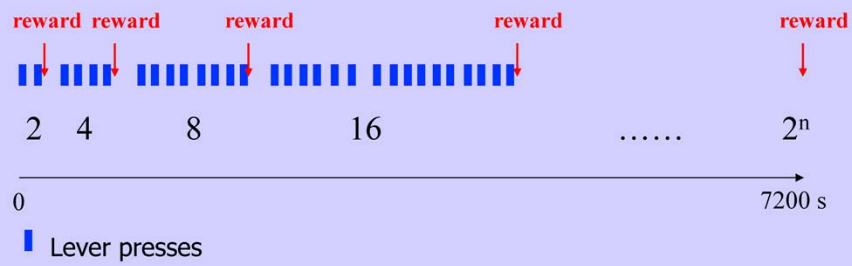
D2OE do not extinguish faster than controls

Individual extinction curves fit to negative exponential and rate of decline obtained from the decay parameter (b)

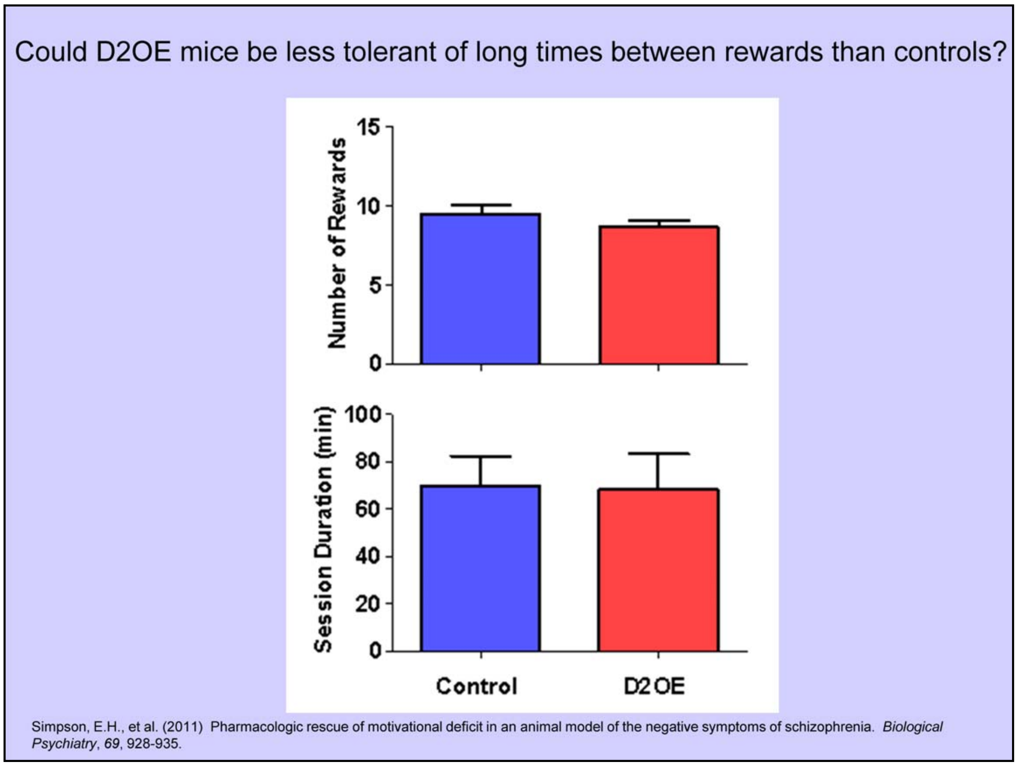
Testing for Motivation:
The Progressive Ratio Paradigm

- Do D2OE mice have less tolerance for increasing intervals between rewards?

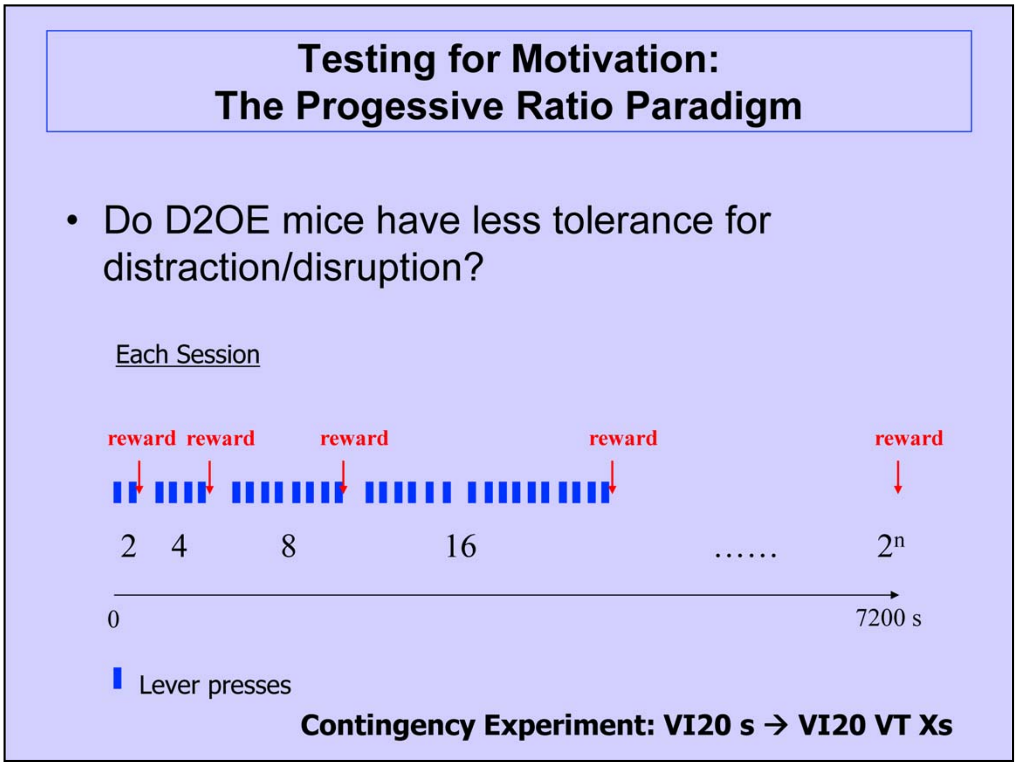
<u>Each Session</u>



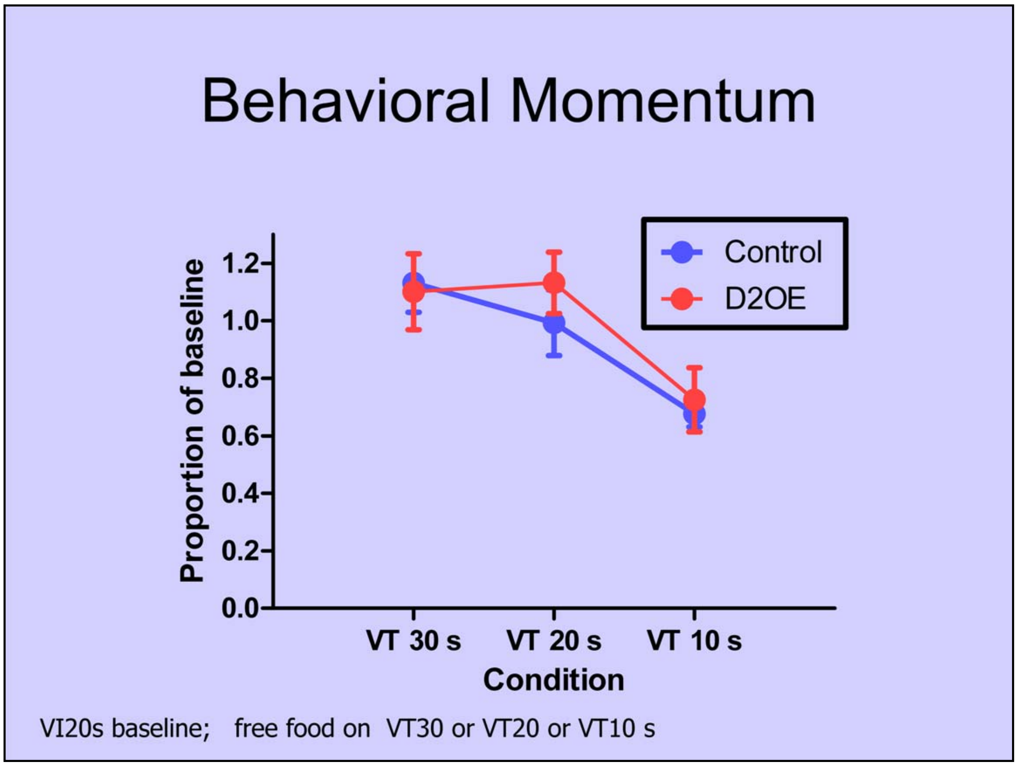
Progressive delay schedule: 1 response required; time between rewards double after each one



No difference in how long D2OE and controls work or how many rewards they obtain (max session duration is 120 min) on the progressive delay schedule in which the time between rewards doubles after each reinforcer but only a single response is required.



Animals were trained on a variable interval schedule and unpredictable free reinforcers were added to disrupt performance.



Animals earned rewards for bar pressing and the disruptive effects of free food were evaluated. Genotypes were equally disrupted by the added food. D2OE NOT more disrupted or distracted by change.

- D2OE mice show decreased motivation
- The motivational phenotype is not due to
  - Increased satiation
  - Greater fatigue
  - More rapid extinction
  - Decreased tolerance to delays of reward
  - Less behavioral momentum (easier disruption)
- Together these data suggest that the motivational phenotype in D2OE mice is due to a decreased willingness to work

Work vs. Free Food

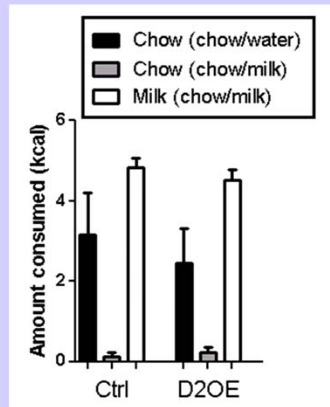
- Use method exploited by John Salamone to assess willingness to work for a preferred reward
- Mice choose between working for a preferred reward or consuming freely available home-cage chow
- In general, mice work more for preferred reward and consume less free chow

condense

Preference test

- 1 hour free access to milk and chow
  - Control test with 1 hour free access to water and chow

- Milk is a preferred reward for all mice



Mice earn the preferred condensed milk reward on a random ratio 20 (RR2) schedule while a pile of home cage chow is freely and continuously available in the chamber.   The model mice work less for the preferred reward but eat more of the free chow.

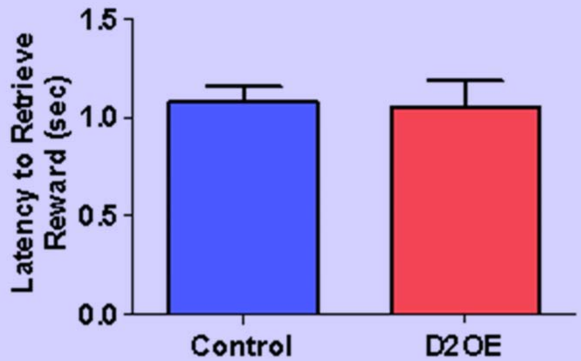
Why are D2OE less willing to work?

Outcome representation and anticipatory motivation

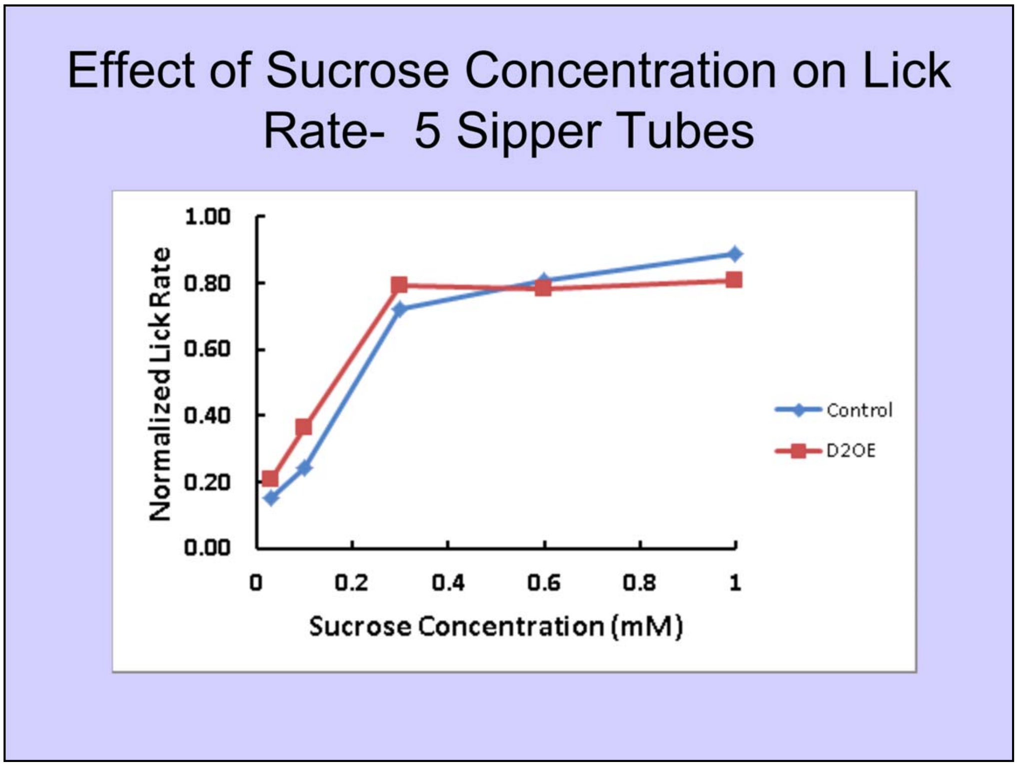
- Action involves calculating cost/benefit assessments to decide whether the effort required is worth the value of the anticipated outcome.
- Impoverished hedonic reaction might result in lower outcome representations and consequently decreased effort.

Podlesnik & Shahan 2008

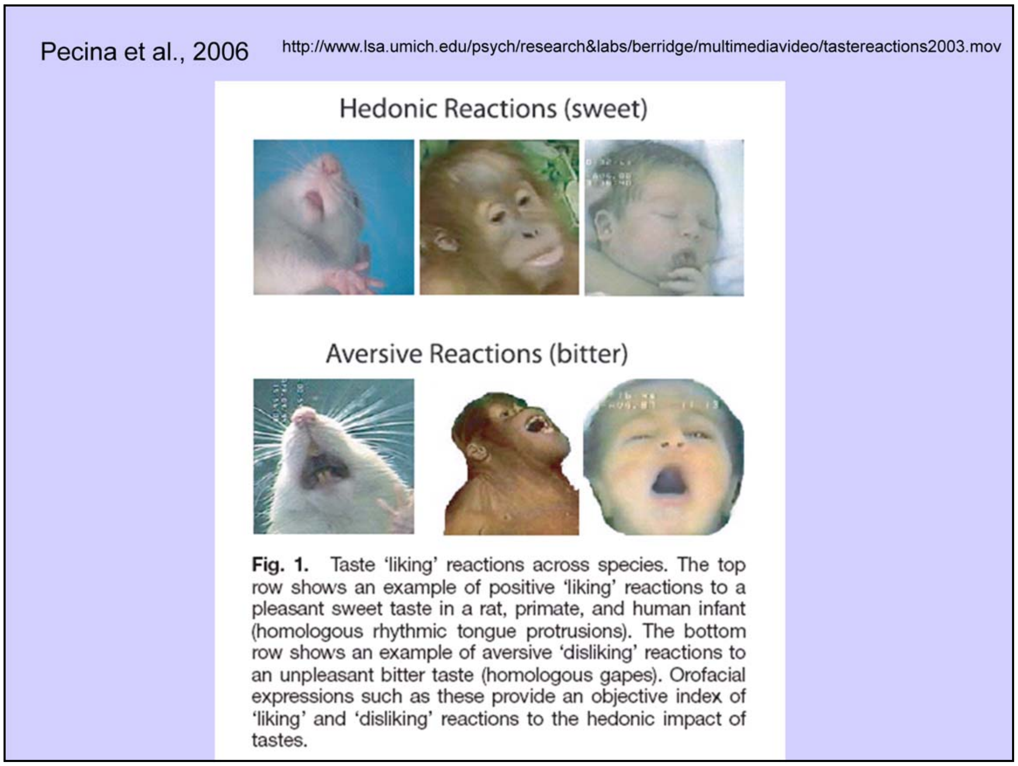
D2 Transgenic Mice make consummatory responses with the same vigor as WT



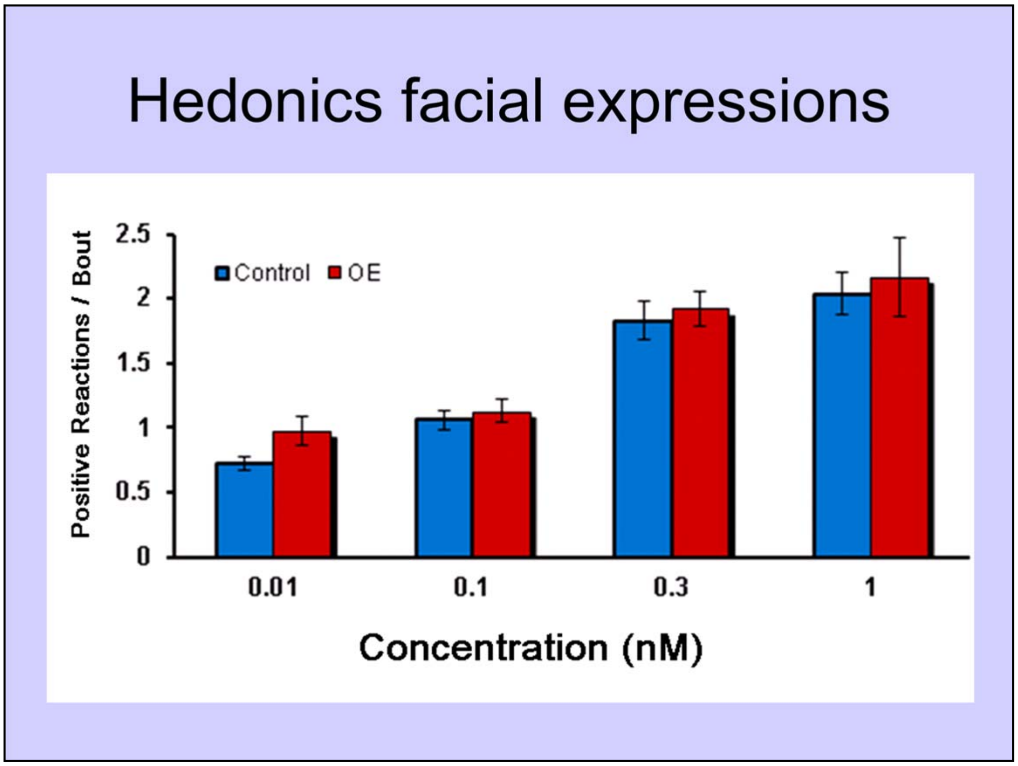
Drew et al., 2007



Controls and model mice show same sensitivity to sucrose concentration



Hedonic reactions can be measured by scoring facial reactions.

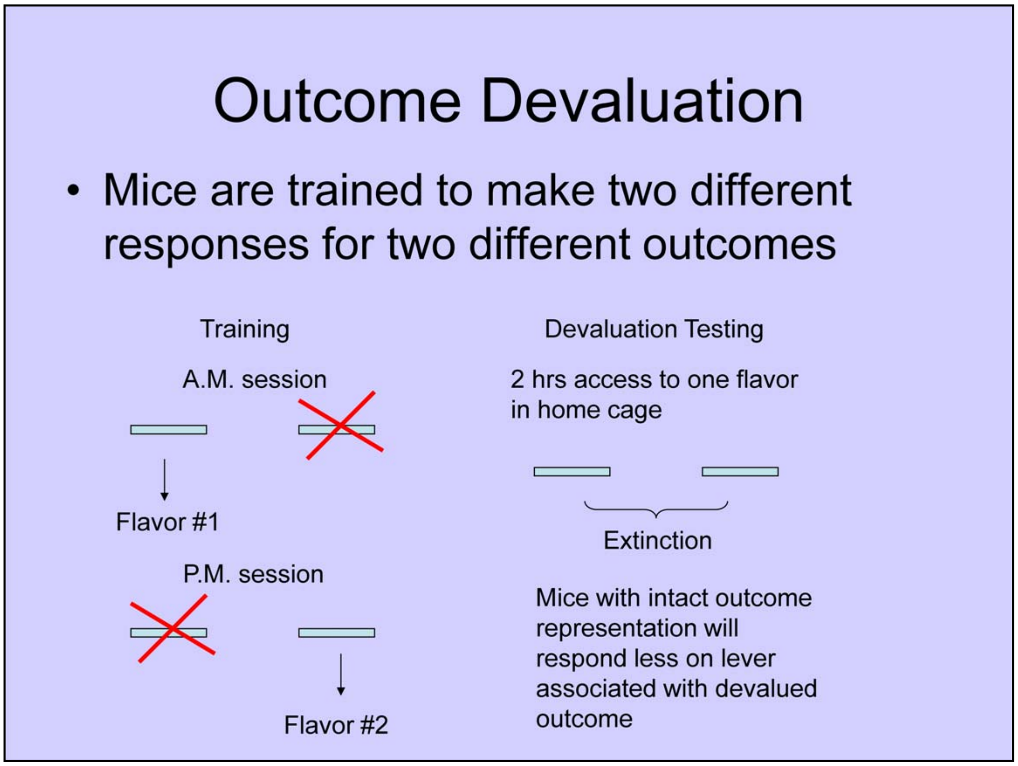


Neither latency to retrieve reward once it is present, lick rates to sucrose, nor positive hedonic reactions differ between D2OE and controls - Differences in motivation are NOT due to any difference in underlying hedonic reactions to reward.

- Cost/benefit assessments require a representation of the outcome of the work
- Hedonic reactions are intact
- Inability to accurately represent outcome value could lead to an imbalance in the cost/benefit assessment by decreasing the anticipated benefit, thus resulting in decreased effort

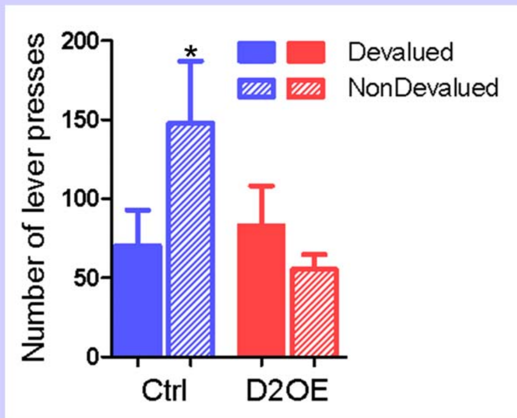
Outcome Devaluation

Thanks to Betsy Murray for the Paul Newman pictures



Only one bar and one outcome is presented in each of the two daily training sessions. On the test day both bars are presented to give animal a choice but not rewards are delivered.

D2OE have a deficit in representing outcome values



Controls work less on the bar that had previously produced the devalued food.
D2OE are indifferent.

Summary of D2OE Motivational deficit

- Hedonic reactions are intact
- Less willing to work for preferred outcomes
- Inability to accurately represent differential values of similar outcomes.
- Changed cost/benefit assessment perhaps by increasing the assessment of anticipated work and decreasing the assessment of anticipated benefit, thus resulting in decreased effort

Dissecting the processes that underlie motivation

Satiation – Parametric variation of PR
Fatigue - Parametric variation of PR
Tolerance for disruption/distraction – Added free reward
Tolerance for periods of non-reward –Progressive delay
Sensitivity to reward rate – Concurrent choice
Temporal discounting- Self-control procedure
Sensitivity to extinction - Extinction
Modulation of expectations by context – Pav to instr transfer
Payoff computation (benefits-costs) – Mixed outcomes PR
Effort versus payoff computation-Free food VS Wk
Hedonics- Facial expression, response vigor, latency
Outcome representations – Outcome devaluation

Neural substrates for these different aspects of motivation are different (though overlapping in part)

Thus if we want to relate behavior to the brain we must do this dissection

Translational Strategy

Neural substrates for these different aspects of motivation are different.

We must do a precise dissection of BOTH the behavioral and neurobiological processes in both patients and animal models