



**ARTICLE**

# Pharmacokinetics trumps pharmacodynamics during cocaine choice: a reconciliation with the dopamine hypothesis of addiction

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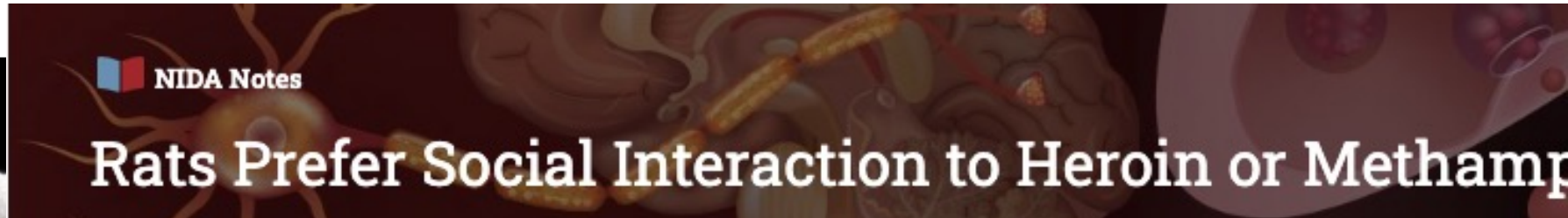
# Background

- Dopamine hypothesis of addiction:
  - Drugs of abuse stimulate DA release in the ventral striatum, leading to:
    - Reductions in electrophysiological activity of DA neurons
    - Downregulation of dopamine receptors
    - Decreased release of endogenous DA
- However, when given the option between drug and food, rats tend to choose food

# Background

## Is sugar even more addictive than cocaine?

by Mari A. Schaefer, Posted: August 28, 2017



**WEIRD NEWS** 10/18/2013 12:55 pm ET | Updated Oct 18, 2013

## Oreos More Addictive Than Cocaine? Shows Cookies Might Produce More Than Coke In Rats



By Simon McCormack

# Background

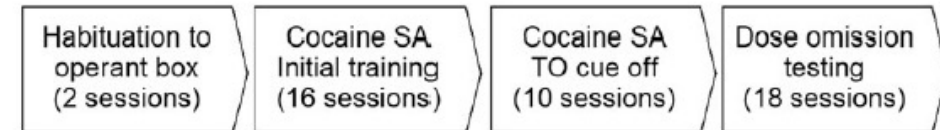
- Role of Pharmacokinetics
  - Rats prefer smaller rewards sooner to larger rewards later (high delay discounting)
  - Drug reward takes tens of seconds to “kick in” compared to sucrose
    - Impossible to reduce this lag time
    - Hard to increase time to food reward without knowing the exact timing of drug reward
  - When both rewards are delayed enough, rats will choose the larger reward: **preference reversal**

# Methods

- 55 male Wistar rats
- Acquired cocaine self-administration, followed by drug reward omissions
- Preference reversal:
  - Alternate operant training (10% sucrose solution)
  - Programmed delay to both options (10, 20, 40, 60s)

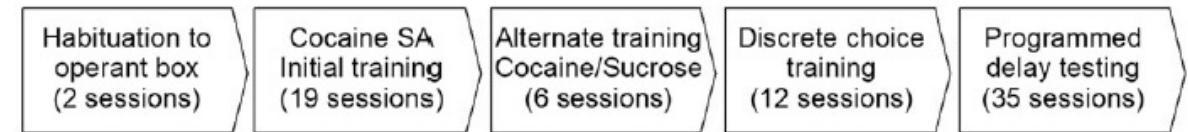
A

Experimental timeline of drug omission experiment



B

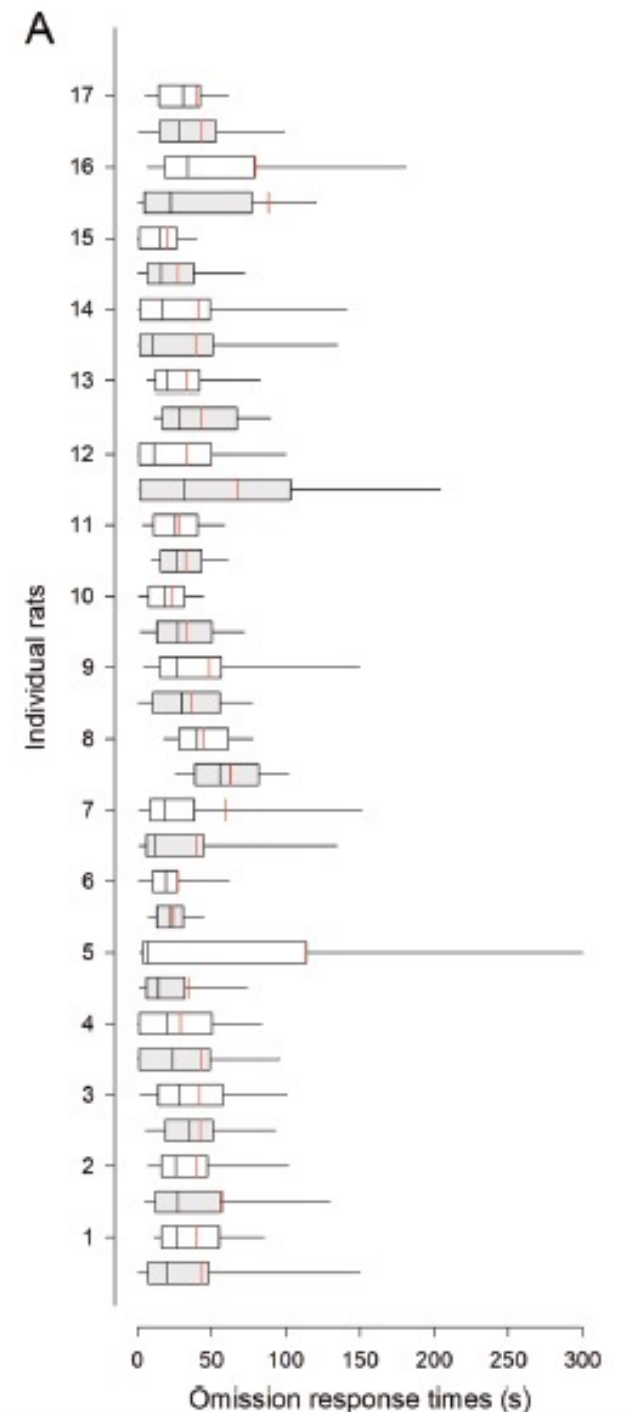
Experimental timeline of preference reversal experiment



# Results

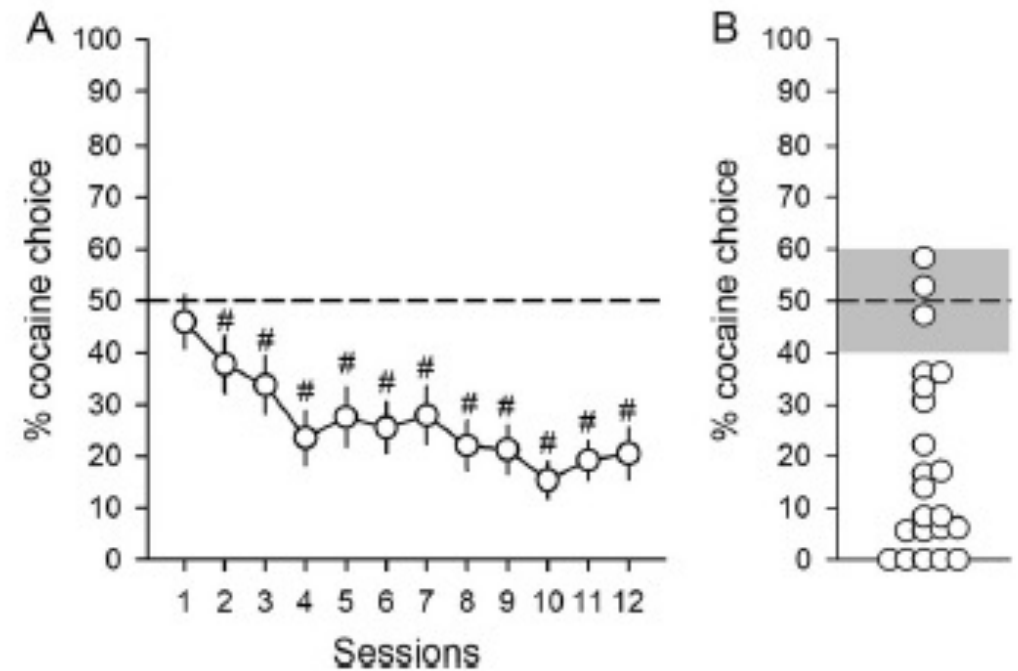
Omission response times hypothesized to be a reflection of the delay to cocaine reward

- most omission response times were relatively long and variable (CVs > 50 %), but did not change significantly with dose
- Individual mean omission response times ranged from ~20s to ~90-110s depending on dose.
- adding a programmed delay between the response and drug infusion increased omission response time by a duration that was close to the added delay
  - suggests that without the delay, the omission response time may roughly be the underlying delay to cocaine reward



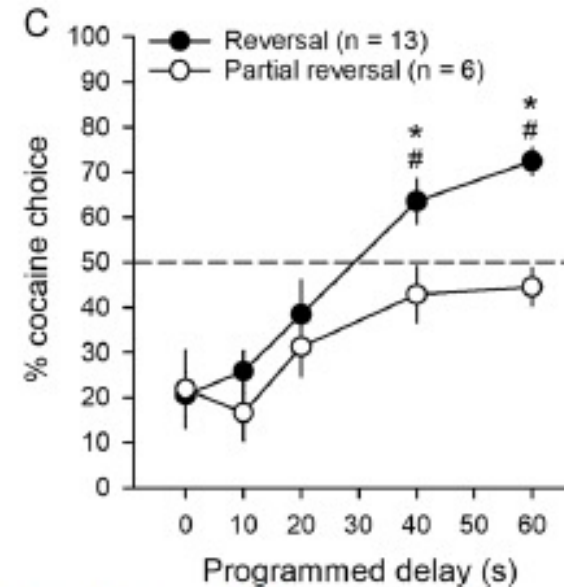
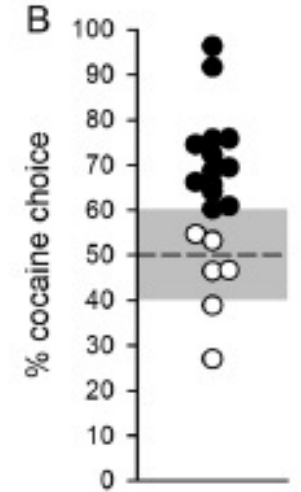
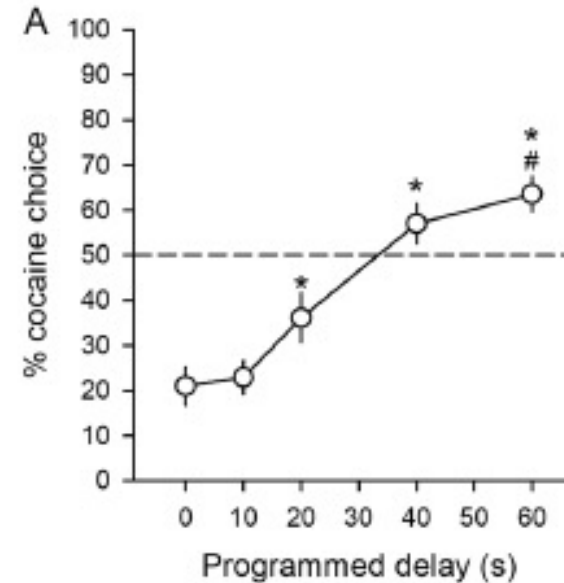
# Results

- Cocaine/Sucrose choice
  - Rapid development of preference for sweet water
  - By the end of training, only three rats were 'indifferent,' and none showed a preference for cocaine
  - Amount of food reward consumed per choice of sweet water was maximal for all



# Results

- Preference Reversal
  - Programmed delay added to both choices (up to 60s)
  - Rats became slower to make their choice and sometimes didn't choose at all
  - Overall, cocaine choice increased and eventually reversed in comparison to sweet water (some rats were merely indifferent, 2 still preferred sweet water)
    - **Not** due to sucrose choice decreasing – still stayed high, but cocaine overtook
  - Increase in response latency to sweet water, such that at 60s rats responded more quickly to cocaine





# Discussion

- Still don't know exact length of delay to cocaine reward, and still cannot shorten it to match non-drug reward delay
  - Intra-striatal infusion does not seem to reproduce cocaine reward, rats don't differentiate from IV
  - Optogenetics/photostimulation?
- Explains the apparent disconnect between the choice of sucrose (or non-drug) rewards over more potent substances.
  - Despite greater impact on dopamine release, is a “less desirable option” due to the longer delay
  - Prior studies were effectively unintentional delay discounting studies rather than actual choice