

Addiction-related behavioral traits and neuroimaging

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Disclosure: Dr. Oberlin and Mr. Nelson, founders of Relate XR, LLC, an STTR NIDA awardee, are inventors on a patent filed by Indiana University on the technology described in this presentation



Outline

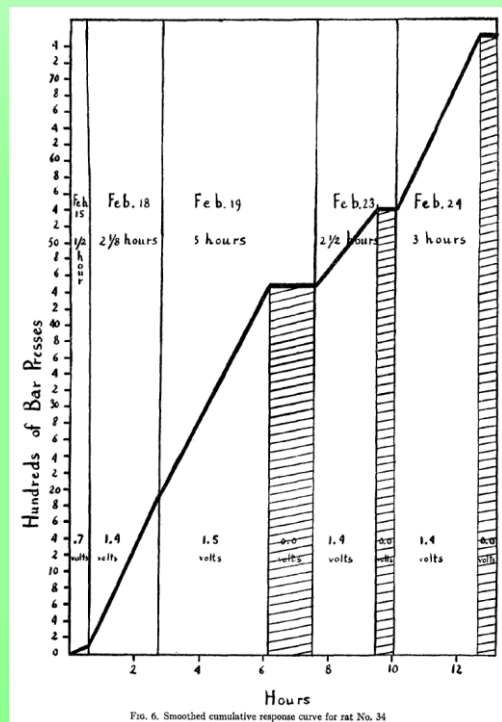
- ❖ Neural substrates of addiction-like behavior
- ❖ Dopamine: wanting and liking
- ❖ Impulsive choice
- ❖ Cognitive control
- ❖ Introspection





Neural Substrates

❖ “Reward” pathway: Olds and Milner 1954

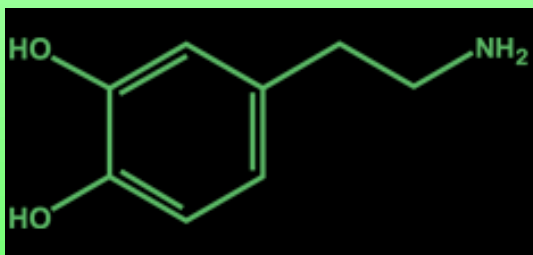


- ❖ Electrode stimulates nucleus accumbens
- ❖ >700 lever-presses per hour (every 5 sec)
- ❖ Rats preferred barpressing over water, food, or sex (even biting the experimenter upon disconnection)
- ❖ This obsessive motivational drive resembles human addiction



Neural Substrates & Neurochemistry

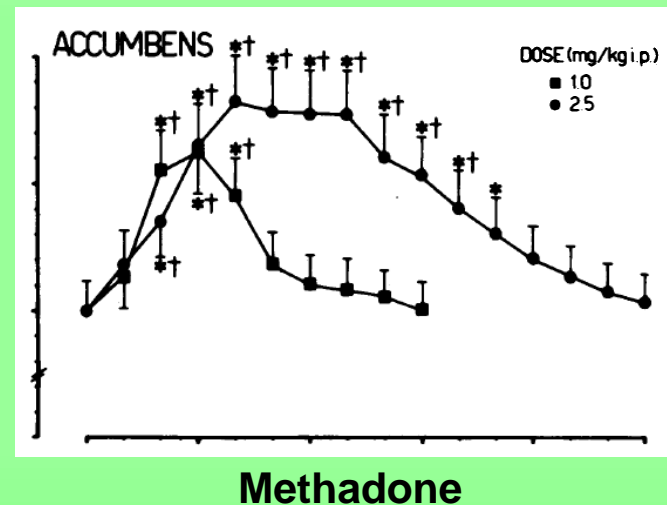
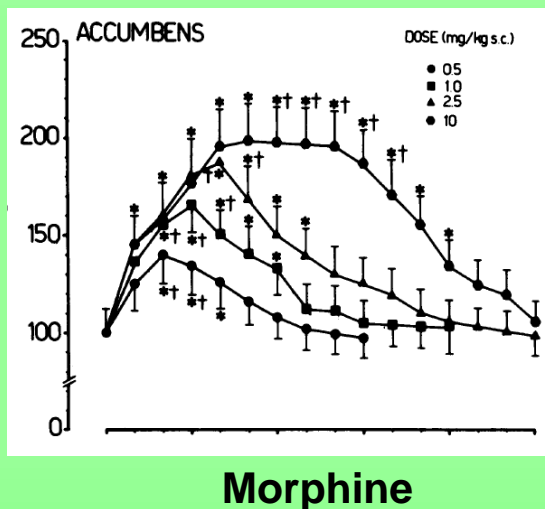
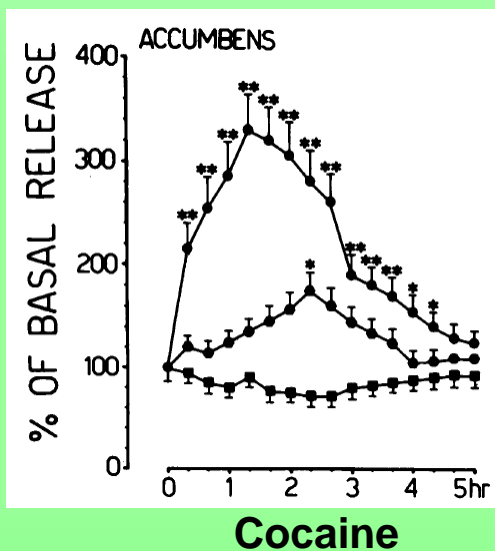
- ❖ The nucleus accumbens is the target of midbrain dopamine projection neurons
- ❖ Nucleus accumbens is rich in dopamine receptors
- ❖ Dopamine = pleasure (Wise and colleagues 1980)





Neural Substrates & Neurochemistry

❖ Drugs of abuse increase mesolimbic dopamine (Di Chiara & Imperato 1988)

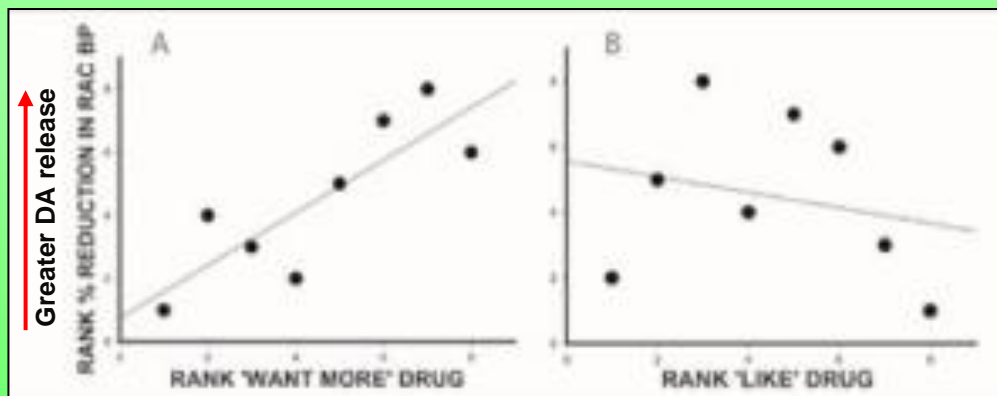


❖ Drugs that do not increase accumbens dopamine do not have abuse potential (e.g., histamine and muscarinic antagonists)

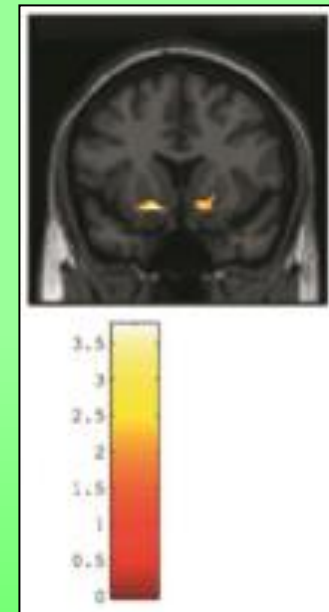


Dopamine \neq Pleasure

- ❖ Dopamine not required for “liking” (taste reactivity and 6-OHDA lesions; Berridge & Robinson 1998)
- ❖ Footshock increases dopamine in accumbens (Kalivas & Duffy 1995)
- ❖ Increased dopamine increased “wanting” but not “liking” (Pecina et al., 2003)
- ❖ L-dopa increases “wanting” but not “liking” in Parkinson’s patients (Evans et al., 2006)



(Evans et al. 2006)

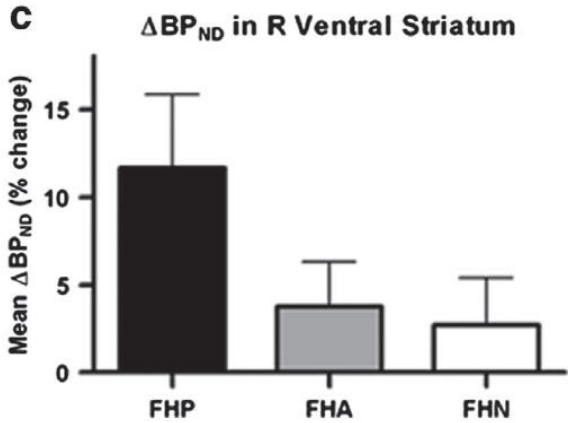
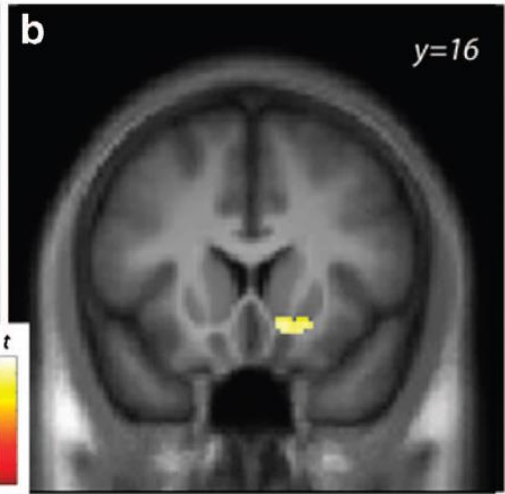
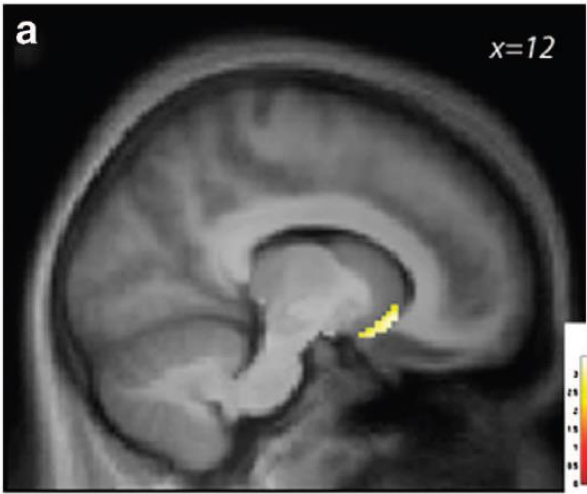
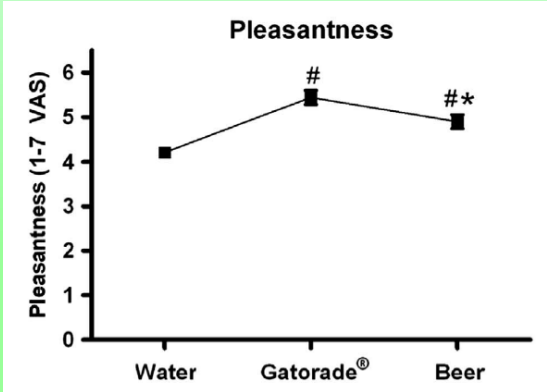
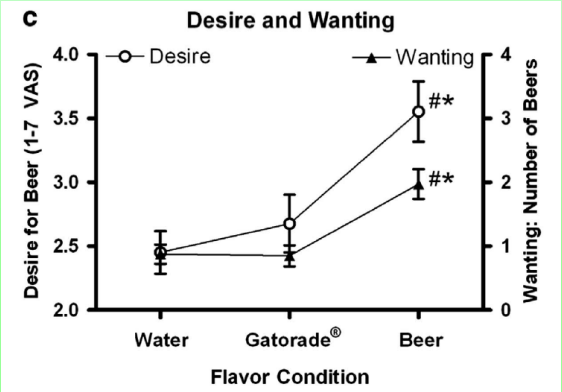


(Evans et al. 2006)



Dopamine = Wanting

- ❖ Dopamine appears to increase motivational drive for drug-related stimuli (“Incentive Sensitization”, Berridge & Robinson)





Competing Rewards Across Time

a.k.a. “delaying gratification”

- ❖ Natural rewards satiate (think hunger after big meal)
- ❖ Drug rewards often sensitize (the opposite of satiation)
- ❖ Why aren't most humans addicted?
- ❖ Humans are good at imagining the future (vs. e.g., chimps)



Myopia for the future and addiction

Table 2. *Future time perspectives of heroin addicts and controls*

Predicted life-events (group mean values)	Heroin addicts	Controls
Extension	18 years*	26 years
Mean predicted	5.4 years*	8.8 years
Coherence	0.51*	0.81
Stories (median times)		
Story 1	1.3 hours	2 hours
Story 2	1.7 hours	3 hours
Story 3	1 hour*	7 days
Story 4	9 days*	4.7 years

* $p < 0.01$.

Petry et al. (1998)

Story 4: “Here the last story that I’ll give you. I want you to finish it any way you wish, just like you did on the other stories.

Here it is: ‘After awakening, Bill began to think about his future. In general he expected to...’ Now you start there and finish it for me.”

[“How long a time was involved in the actions described in the story”]

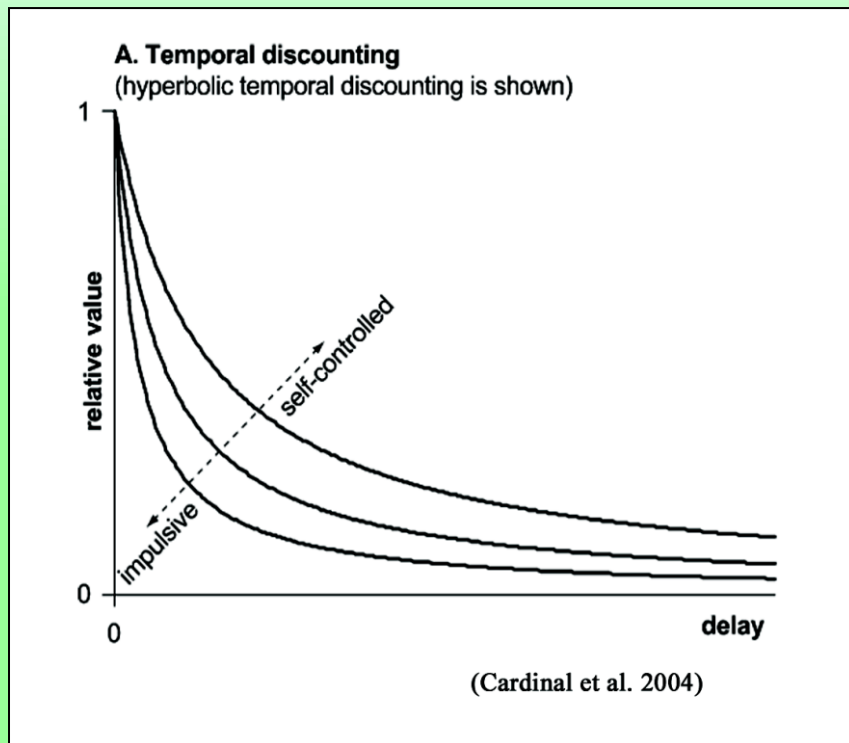


Delay Discounting: impulsive choice

- ❖ “Myopia for the future”
- ❖ Choosing smaller immediate reward over a larger delayed reward (Rachlin & Green 1972)
- ❖ DD uses a method of bargaining to measure how much a delayed reward is ‘discounted’ by a given delay.



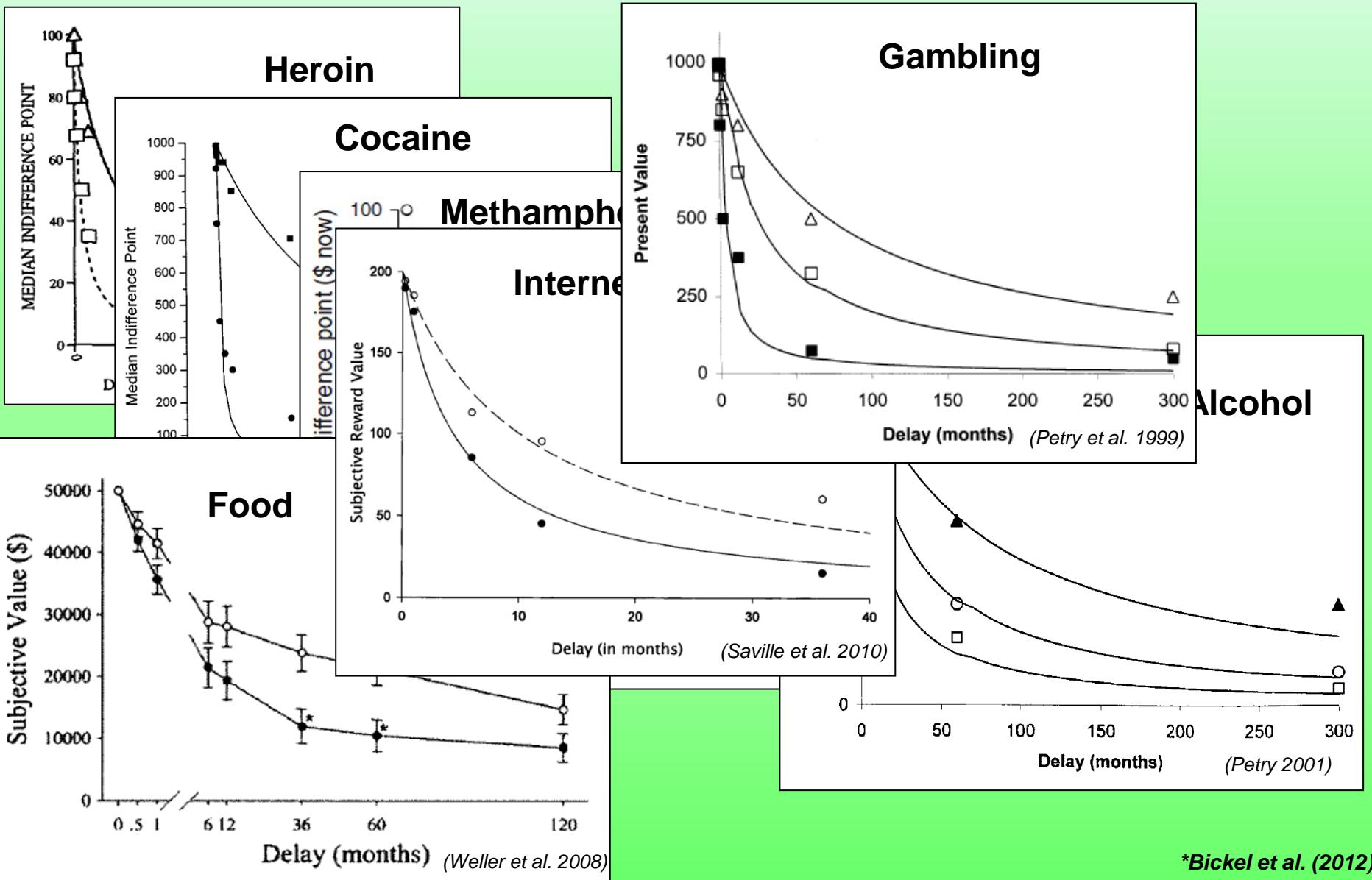
Impulsive Choice: Delay Discounting



Steeper discounting (smaller indifference points)
indicates greater impulsivity, i.e., larger k .



Impulsive Choice: A Trans-disease Process*





Intertemporal Choice in Addiction

Intoxicants

High Intensity

Immediate

Direct reward: brain activation
(receptor binding)

Reliable
(100% chance of reward)



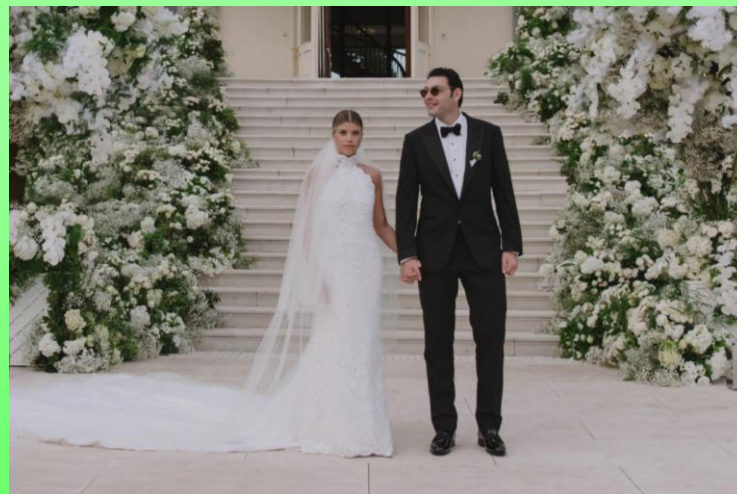
Prosocial Future Rewards

Variable intensity

Distant

Indirect: reward representation
(constructed, exists in imagination)

Uncertain
(unknown future: <100% chance)





Intertemporal Choice in Addiction

How can prosocial future rewards possibly compete with immediate drug reward?

- *Decreasing the value of drug reward
(focus attention on drug-mediated punishment)

- *Increasing the value of prosocial future rewards
(focus attention on benefits of investing in delayed rewards)

Drug punishment and recovery reward EXIST IN THE FUTURE and can only be imagined.

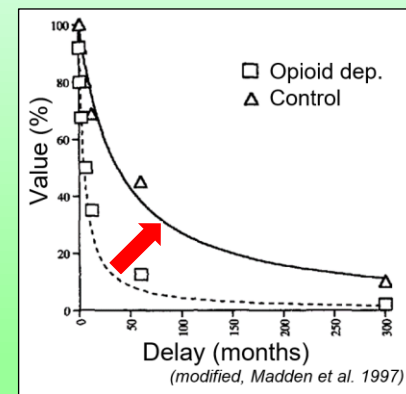
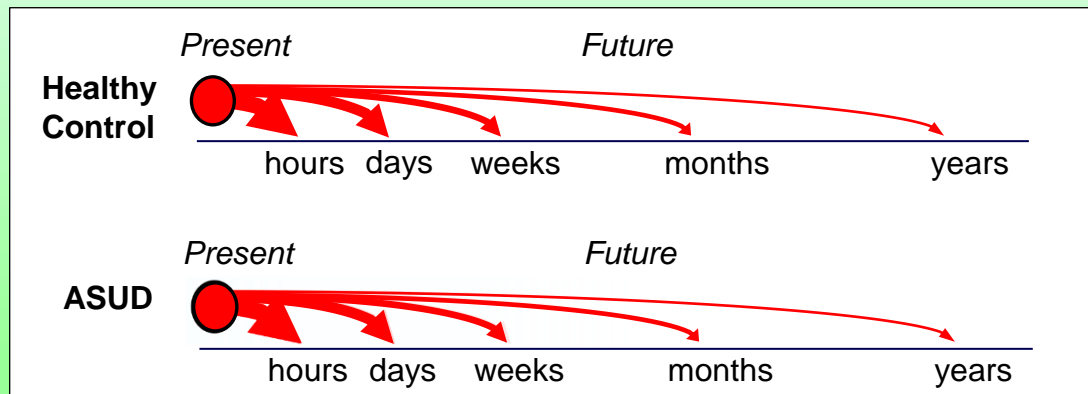
“When you’re trying to help someone let go of a drug, you are competing with a powerful and long-practiced reinforcer.

People change when they see an alternative that is better”.

-William Miller, PhD



Increasing Future Thinking



- ❖ Increasing episodic future thinking is effective
(meta-analysis; Rung & Madden 2018)



\$10 **OR** **\$100**
now **after 1 month**

- ❖ Evoke autonoetic future consciousness (“mental time travel”) through cueing and sensory rehearsal of specific future events (Atance & O’Neill 2001)



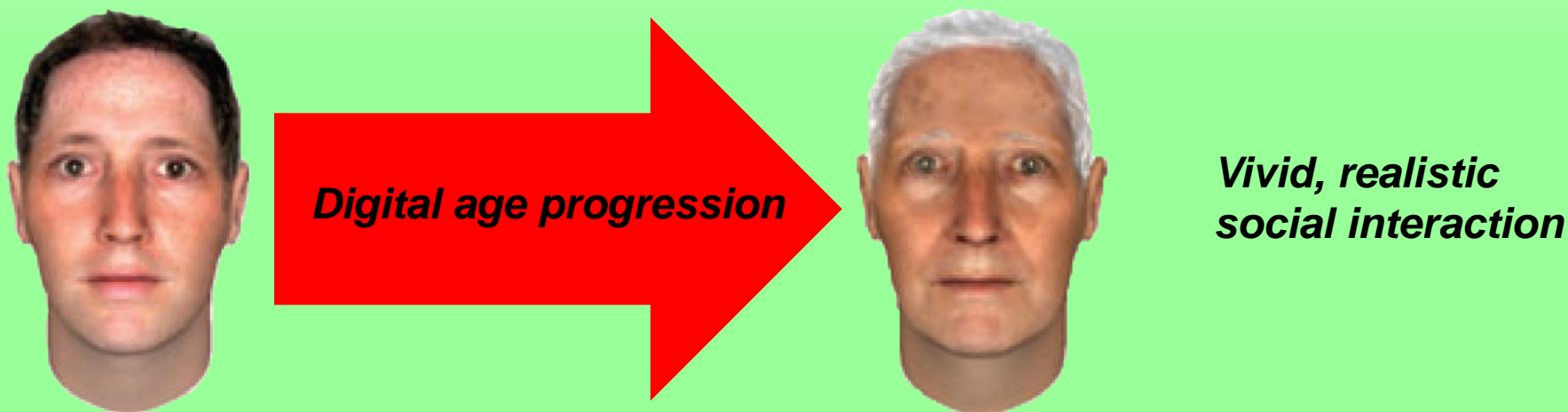
Evoking Future Thinking: “active ingredients”

- ❖ **Episodic**; Personal narrative story, i.e., versus semantic future thinking (*Atance & O'Neill 2001*)
- ❖ **Autobiographical**; Features and elements specific to the self and self-relevant (*Daniel et al., 2013*)
- ❖ **Future-oriented**; Prospective future events (*Lin & Epstein 2014*)
- ❖ **Vivid**; Generate stronger affective responses and perceived as more plausible (*Rösch et al. 2021*)
- ❖ **Content-specific**; Incorporate future payoff; evoke imagination of actual outcomes, e.g., health-related (*Chiou & Wu, 2017*)



Instantiating the Future Self with VR

“...neglect of the future self can arise from a failure of the imagination”
(Parfit 1971, Hershfield *et al.* 2011)



Hershfield's subjects interacted future selves (~70 yo) in immersive virtual reality.

Subjects allocated more money to savings, retirement, and discounted less after interacting with their older self in VR, relative to subjects interacting with their present self in VR.



Making the Future Real for SUD

- ❖ Can we create an experience to assist early recovery?
- ❖ Leverage future self-continuity and discrepancy
- ❖ Integrate effective episodic future thinking elements
- ❖ Increase attention and valuation of the future
- ❖ Personally relevant (details, punishments, rewards)



A Novel Method and Pilot Study

Discover Mental Health



Research

Virtual reality intervention effects on future self-continuity and delayed reward preference in substance use disorder recovery: pilot study results

Yitong I. Shen^{1,2} · Andrew J. Nelson³ · Brandon G. Oberlin^{1,2,4,5}

Funded VR Clinical Trials:

- ❖ **NIAAA R01**
(Alcohol: Single & 30-day VR; 30-day & 6 mo follow-up—VR control)
- ❖ **NIDA R34**
(Stimulants: Single VR; 30-day & 6 mo follow-up—TAU control)
- ❖ **NIDA R41 (STTR)**
(Opioids: Single VR; 30-day follow-up—TAU control)

Future Reality Portal

Design:

- Body transfer and personalization [autobiographical]
- Decision point [choice behavior]
- Time travel [episodic; future-oriented; script and object schema]
- Neutral [prototype schema maximizes inclusivity]
- Fixed order to highlight agency and optimism [positivity]

❖ Future Self-Continuity

- ❖ Visual presentation of future selves [vivid; autobiographical]
- ❖ Future selves invoke personalized salient details about future outcomes [content specificity, future-oriented]
- ❖ Future selves speak to them in their own voice, using their terminology [vivid; autobiographical]

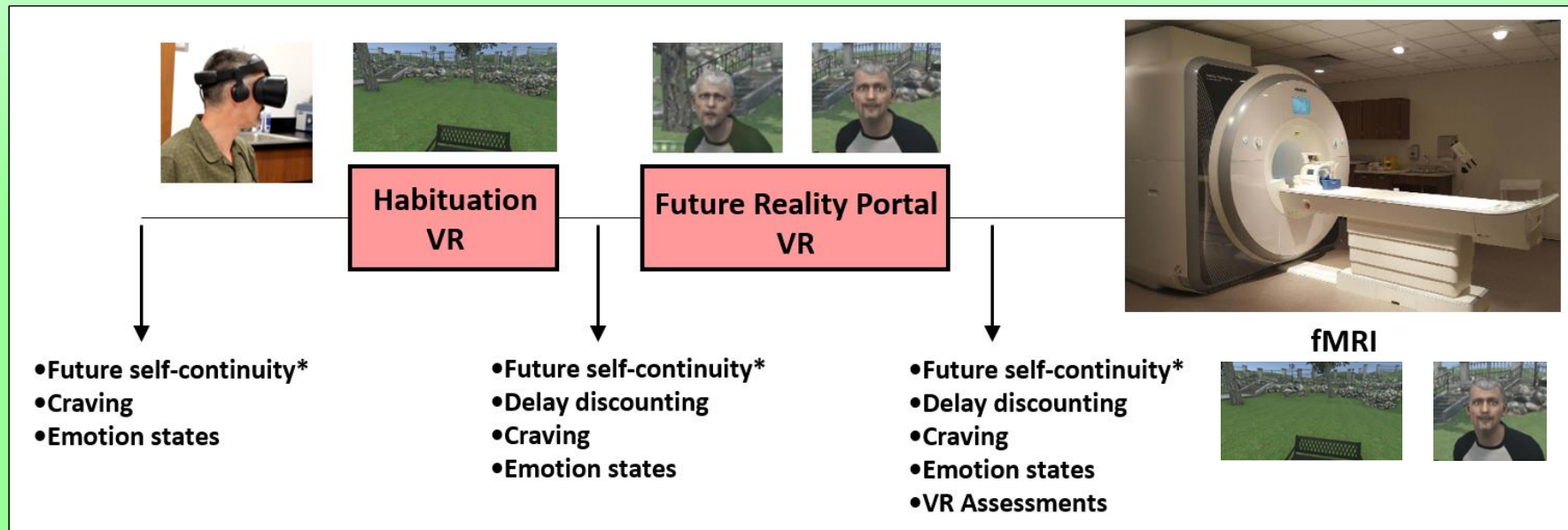
❖ Self-Discrepancy

- ❖ Specific focus on drug/alcohol misuse [script schema; content specific]
- ❖ Strong non-verbal messaging [content specific]
- ❖ Powerful visual contrast between the two future selves [social and script schema]

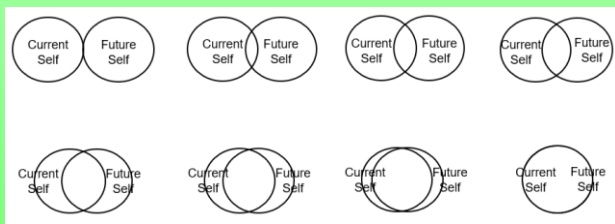


The Future Reality Portal

Open-label pilot study



*

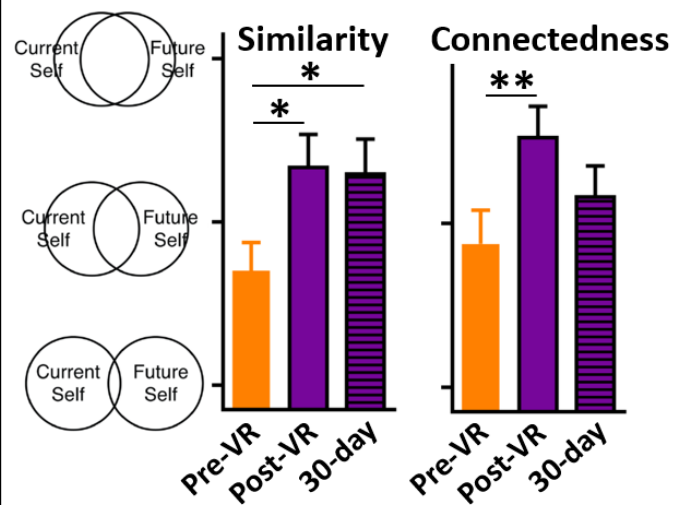


- 30 daily smartphone visual reminders (retrieval cues), with single item
- 30-day follow-up: inventories, DD, and drug use/abstinence assessment



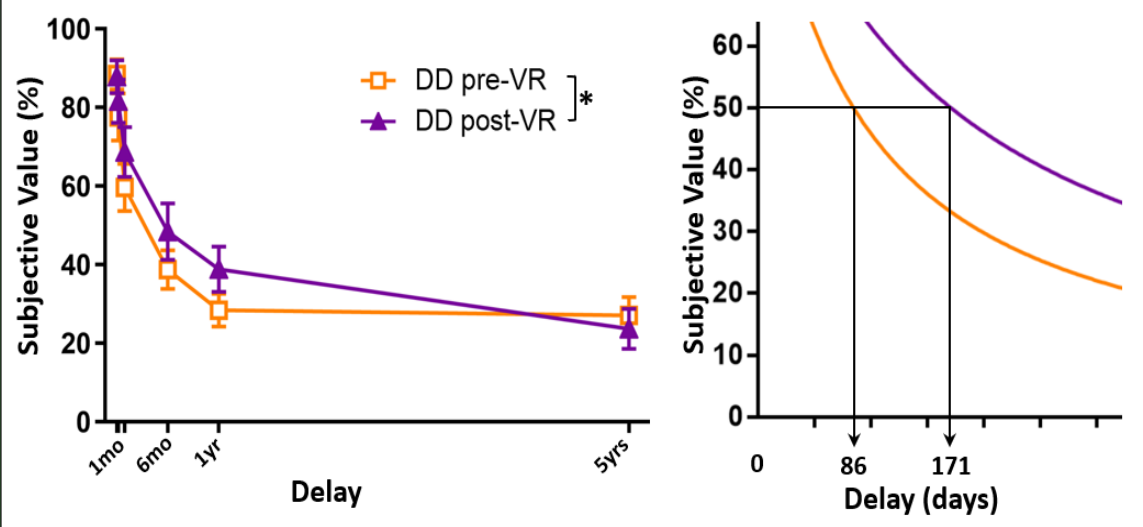
Future Reality Portal Effects

Future Self Continuity

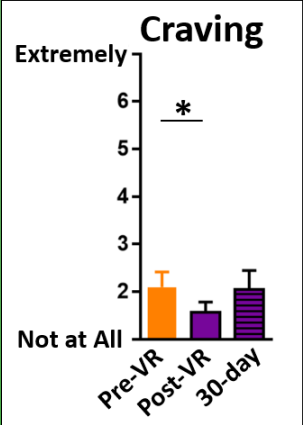


Post-VR increases in Future Self Continuity lasted 30 days (Similarity).

Delay Discounting, \$100



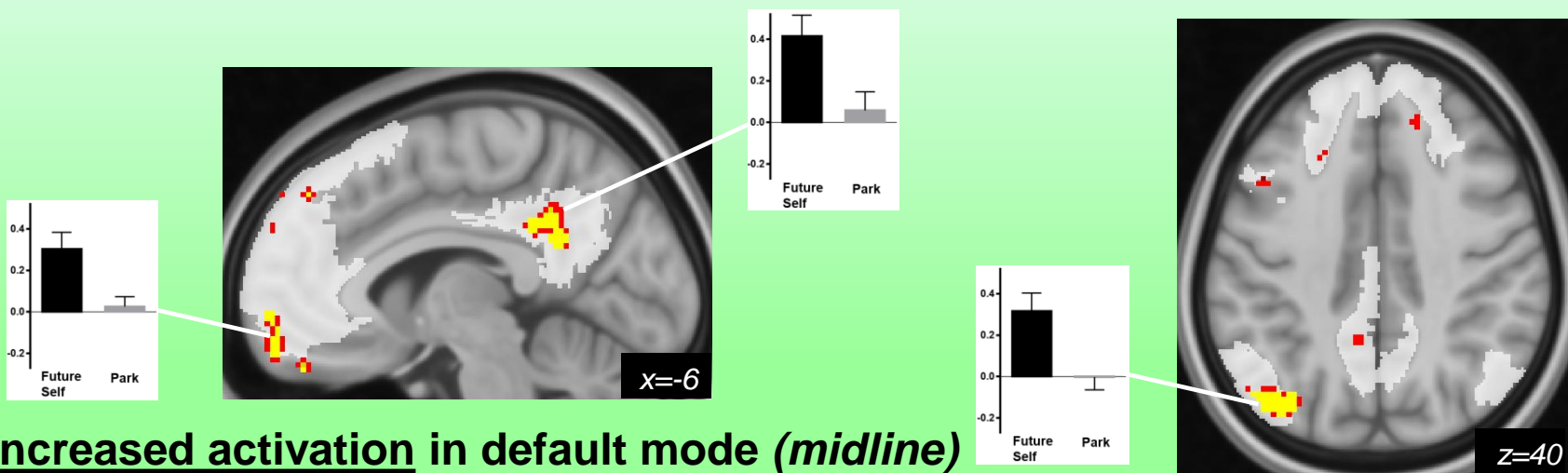
Post-VR, 71% (15/21) participants showed decreased discounting: near doubling of delay tolerance (DD reverted to pre-VR 30 days later).





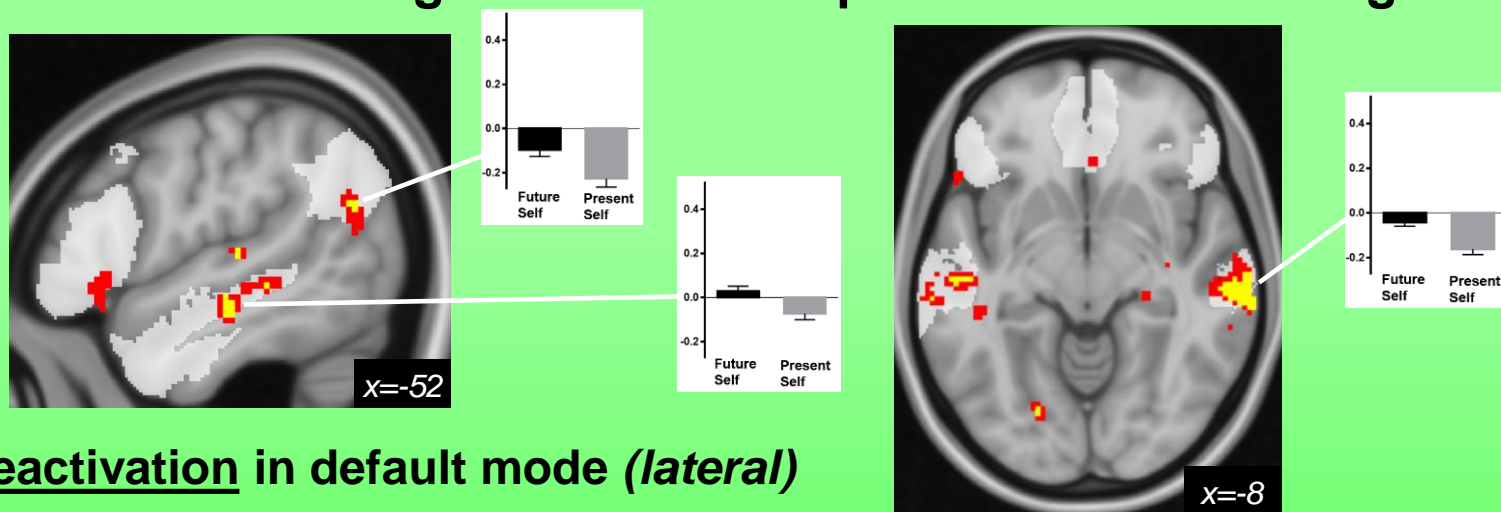
The Future Self and the Brain

Passively viewing and thinking about the Future Self, task-free...



Increased activation in default mode (*midline*)

Viewing the Future Self during active intertemporal decision making...



Decreased deactivation in default mode (*lateral*)



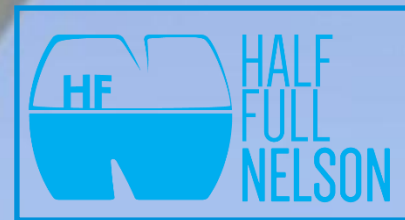
Conclusions

- ❖ The nucleus accumbens is the brain site supporting self-administration.
- ❖ Accumbens dopamine relates to wanting/craving.
- ❖ Accumbens dopamine response to drug cues is heritable.
- ❖ Impulsive choice is an addiction endophenotype.
- ❖ Attention on future outcomes promotes better choices.
- ❖ VR future self intervention increased future thinking, reduced discounting, and corresponded with high rates of abstinence.
- ❖ Future selves elicited default mode engagement (suggesting introspection as a mechanism of action)



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Thank you



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Questions?

