

From Impulsivity to Altruism:  
*What psychopharmacology can learn from  
12 Step Recovery*

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# Wizard of Oz

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# Why do people start taking drugs? <sup>1</sup>

<sup>1</sup> This is not a trick question

# Why do people start taking drugs?

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- **Intense pleasure**

- To feel better – alleviate negative affects


- Enhance performance

- Curiosity

In the Wizard of Oz, Dorothy is carried to Oz by a tornado

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Why do people keep  
taking drugs?

# Why do people keep taking drugs?

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- Pleasure
- **Alleviate negative affects**
  - Craving
- Block withdrawal
- Social reinforcement

# How might addiction treatments work?

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- Block pleasure – Naltrexone, Buprenorphine, Methadone
- Decrease craving – Naltrexone, Varenicline
- Interfere with social reinforcement - Methadone
- Decrease abstinence syndrome – Acamprosate, Varenicline



In the Wizard of Oz, Dorothy is carried to Oz by a tornado

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# Treatments To Block Reward

*'I get no kick from champagne'*

# NATURAL REWARDS

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■ Food

■ Water

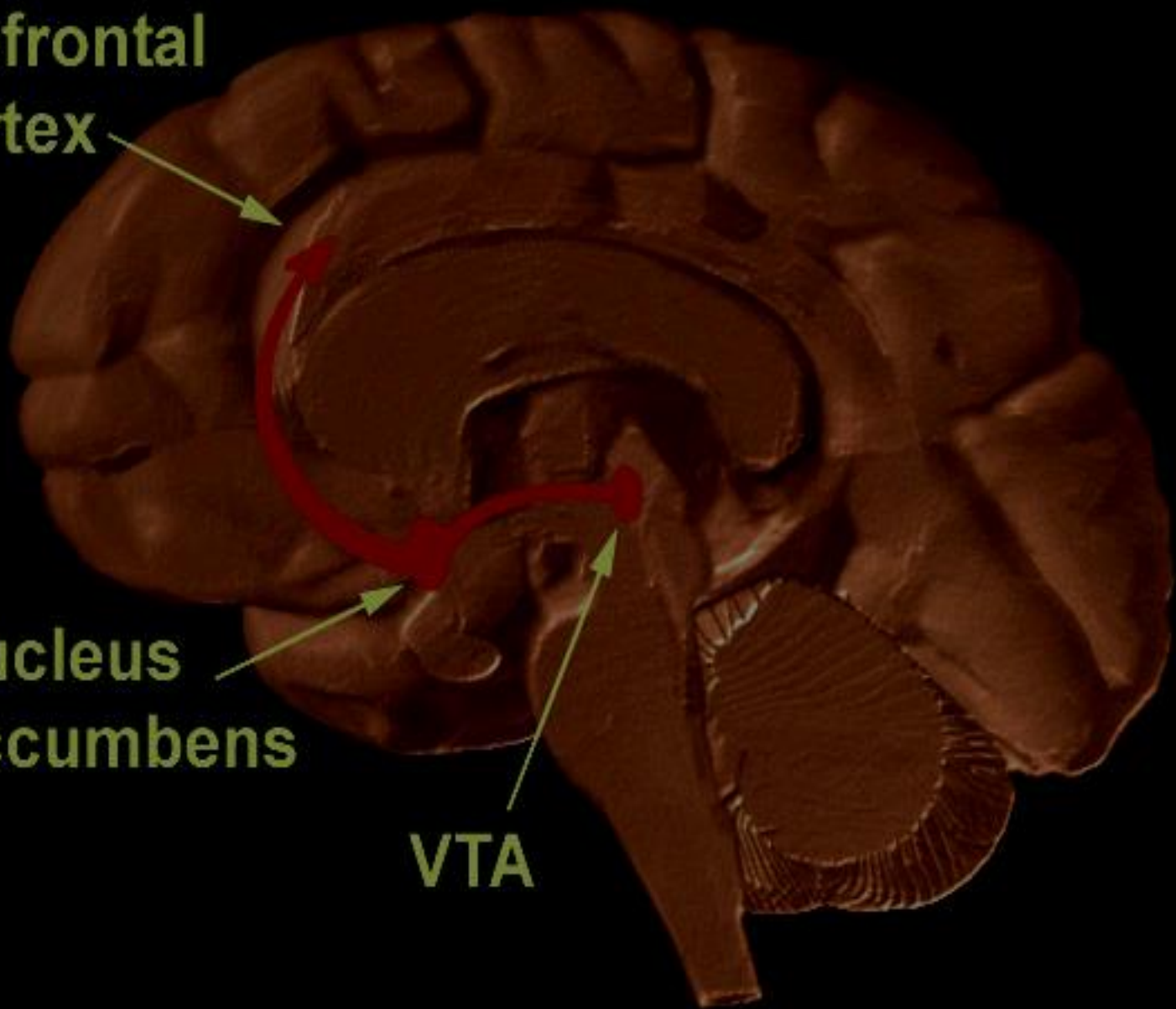
■ Sex

■ Nurture

**prefrontal cortex**

**nucleus accumbens**

**VTA**



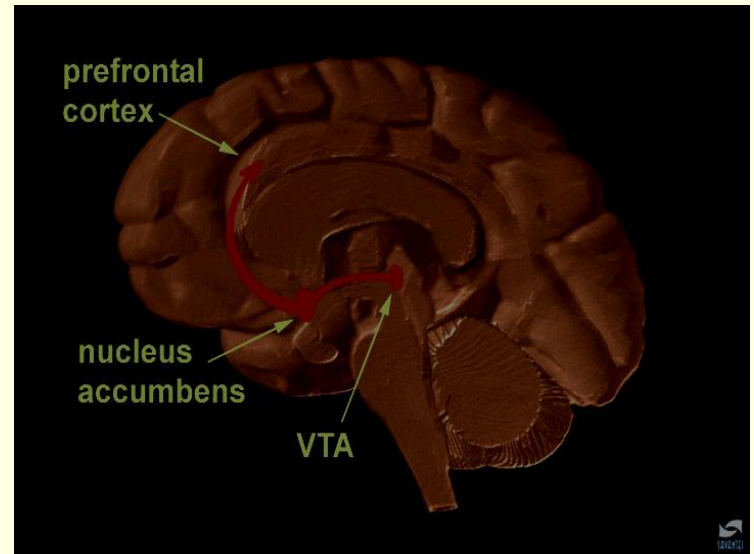
# VENTRAL TEGMENTUM AREA

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- Dopamine cell bodies of the mesocorticolimbic dopamine system
- Drug and natural reward circuitry of the brain
- Important in cognition, motivation, drug addiction, intense emotions relating to love

# NUCLEUS ACCUMBENS

- Reward & pleasure
- Laughter
- Addiction
- Aggression
- Fear

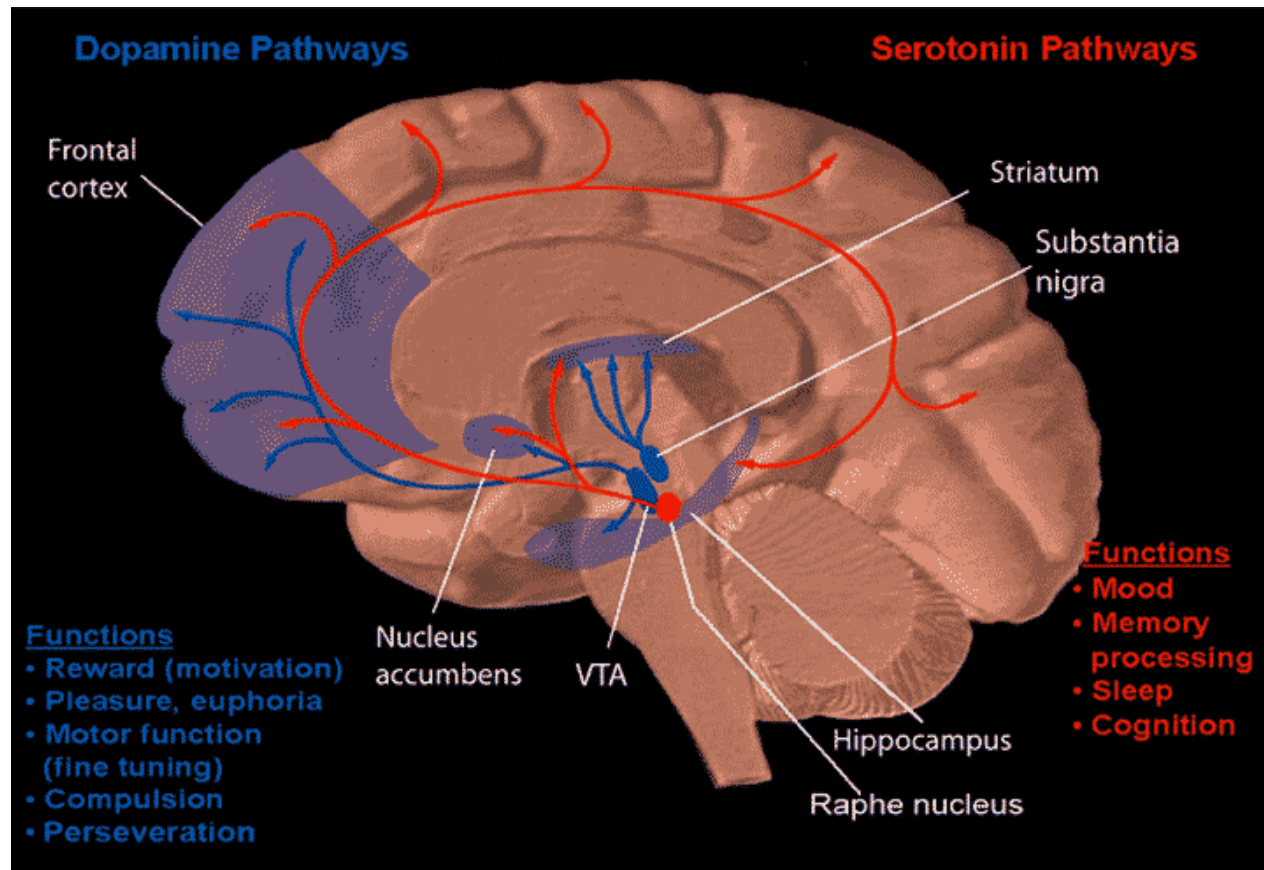


# PREFRONTAL CORTEX

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- Inhibits immediate reaction –
- “Metacognition”
- Executive function - determine good and bad, better and best, same and different, future consequences of current activities, working toward a defined goal

# The Reward System





# Dopamine (DA) and the Reward System

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- DA containing cells in the Ventral Tegmental Area (VTA) project to the Nucleus Accumbens (NAc)
- NAc processes motivated behavior
- NAc DA is essential for reward related learning
- DA mediates non-drug rewards (food, sex) and drug rewards

# Dopamine Hypothesis of Addiction

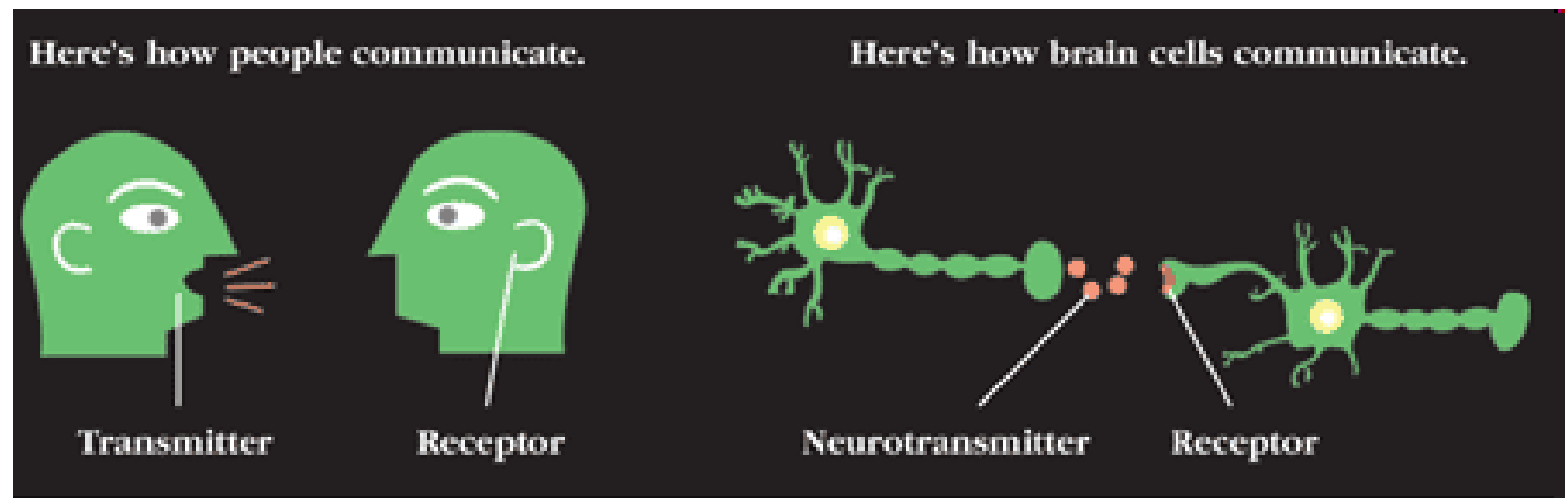
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- Activation of the mesocorticolimbic dopamine system is key to mediating the reinforcing effects of drugs of abuse
- DA mediates the euphoria elicited by drugs
- Blocking DA receptors attenuates euphoria/reward of drugs
- Other areas of the brain – amygdala, hippocampus and hypothalamus are associated with emotional memories and drug addiction

# Pharmacological Treatment of Cocaine Dependency

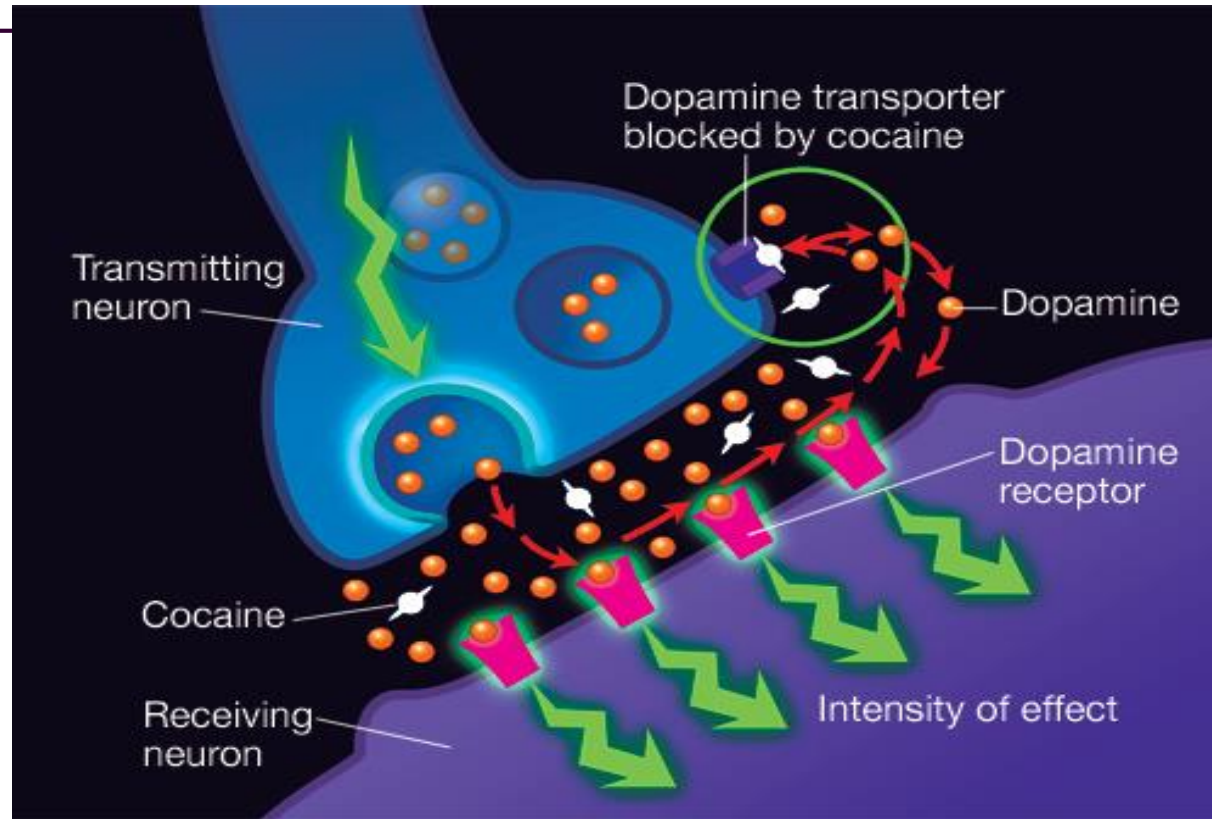
A case study in the DA hypothesis as it  
relates to treatment

# Neurotransmitters – Chemical Signal from One Nerve Cell to the Next



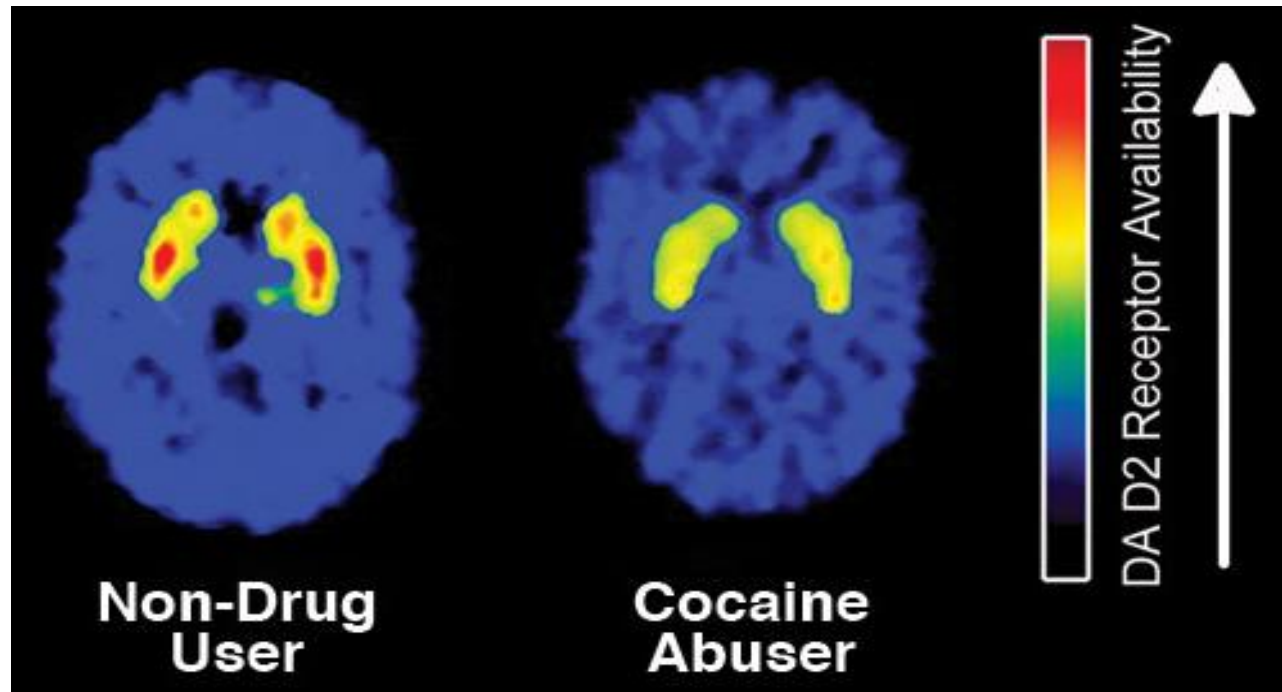
*Concept courtesy: B.K. Madras*

# How Cocaine Affects Dopamine



- Cocaine blocks the DA transporter
- Markedly increases DA in synapse

# The Consequence of Chronic Cocaine



- Decreases DA (D2) receptors in the brain, depletes DA
- Impairs motivation, natural rewards less effective

# Cocaine: A test case for dopaminergic treatments

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- Cocaine most directly and selectively affects the DA system
- Causes intense euphoria and craving
- Brain DA production is reduced and D2 receptors decreased

*Is enhancing DA function in cocaine dependency effective?*

# Enhancing DA activity

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- Agonists – drugs that mimic DA
- Indirect agonists – drugs that cause DA to be released
- Increase DA synthesis
- Drugs that block the breakdown of DA
- Outcome measures
  - Retention in treatment
  - U/A for cocaine metabolites



# Drugs that Raise Dopamine Levels

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- Enhance synthesis
  - L-dopa/cabidopa (Sinemet)
- 3 failed trials (no difference from placebo)
- Inhibit breakdown
  - MAO inhibitor
    - Selegiline – no benefit
  - COMTI
    - Withdrawn hepatotoxicity
  - DBH inhibitor
    - Disulfiram (Antabuse)
    - Only effective in patients with comorbid alcohol dependency

# Agonists

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- Amantadine (Symmetrel)
  - Indirect agonist
  - Did not improve retention
  - Did not improve abstinence
  - Did not decrease number of positive urines
- Desipramine (Norpramin)
  - NE transporter inhibitor, also inhibits DA re-uptake in frontal cortex
  - No increase in retention
  - No increase in Abstinence

# Agonists (cont.)

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- Bromocriptine
  - Direct D2 agonist
  - Did not decrease positive urines
- Bupropriion (Welbutrin)

# Promoting DA has failed.

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- Agonists failed
- Precursors failed
- Blocking breakdown failed



# Opiates and Reward

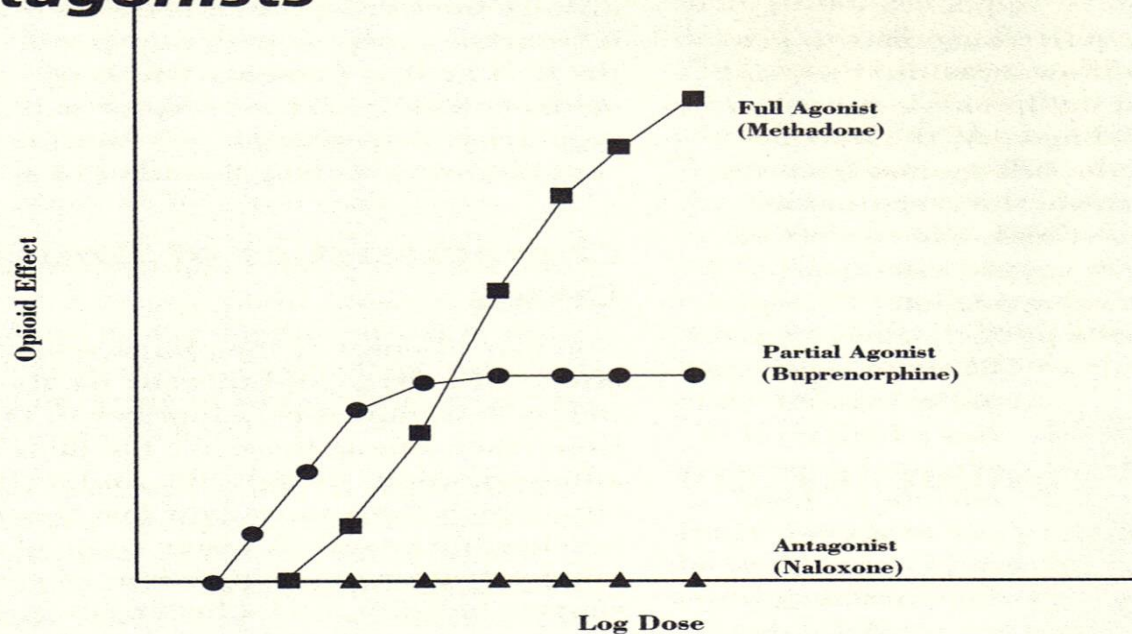
# Approved Treatments For Opiate Dependency

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- Methadone
  - Full  $\mu$  receptor agonist
  - Binds tightly and activates receptor
- Naltrexone
  - Full antagonist
  - Binds tightly to receptor and blocks activation
- Buprenorphine (Subutex, Suboxone)
  - Partial agonist
  - At low concentrations binds to receptor and activates it
  - At high concentrations blocks the receptor

# Relative Effects on Opiate Receptor

## Conceptual Representation of Opioid Effect Versus Log Dose for Opioid Full Agonists, Partial Agonists, and Antagonists\*



\*Conceptual representation only, not to be used for dosing purposes.

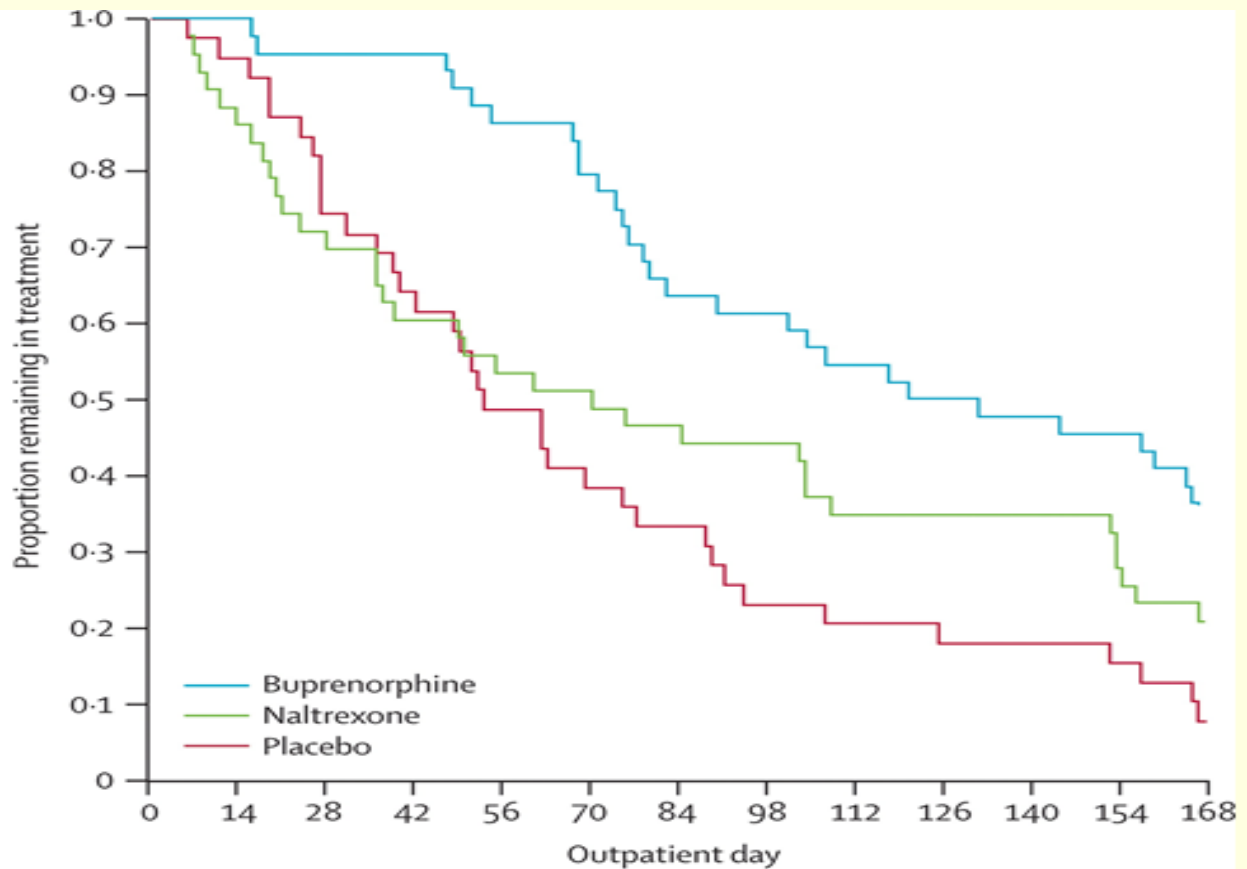
# ...Itself and Its Opposite

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- Methadone and naltrexone have similar results when it comes to blocking the reward from the opiate receptor by opposite means
- Methadone causes massive tolerance, meaning insensitivity of the receptor
- Naltrexone sits on the receptor so no opiate agonists can bind to it



# Limits of Success



## Number remaining in treatment

|               |    |    |    |    |    |    |    |
|---------------|----|----|----|----|----|----|----|
| Buprenorphine | 44 | 42 | 38 | 28 | 24 | 21 | 18 |
| Naltrexone    | 43 | 30 | 23 | 19 | 15 | 15 | 9  |
| Placebo       | 39 | 29 | 19 | 13 | 8  | 7  | 5  |

# Why Don't Reward Treatments Work Better?

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- Hedonic/Reward responses are critical to drug initiation but not maintenance
- Changes in learning and memory are only partially related to changes in Dopamine
- Maintenance of drug dependency is caused by complex behavioral differences in addicts that precede drug use and are worsened by drug use



The way into forest....

Is not necessarily the  
way out of the forest!

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What are we treating and why are we treating it?

# What is addiction?

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- A disorder of the brain's reward system
- A spiritual malady of self-centeredness
- Genetic disease of impulsivity
- An expression of poor nurturance, abuse, neglect
- An attempt to cope with intra-psychic distress

# New Path – Stay Close to Treatments

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- 12 Step Recovery
  - Increases long term abstinence
  - Results in meaningful social and behavioral change
  - Active processes of 12 step recovery are understudied
    - Number and duration of participation
    - Do you have a sponsor

# Why is AA Understudied?

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- AA does not consider itself a treatment program
- It exists to carry the message to those who still suffer with the disease
- Very limited infrastructure by design
- Remain forever non-professional
- Investigators have limited understanding of recovery
- Secular humanists distrust spirituality
- Limited access to the process (closed meetings etc.)
- Focus has been on the number of meetings and whether one has a sponsor

# Can 12 Step Programs Tell Us Where To Look?

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- Sharing/Learning
- Caring/Empathy
- Service/Altruism



# WHAT IS IMPULSIVITY?

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A predisposition toward rapid, unplanned reactions to internal and external stimuli without regard to the negative consequences of those reactions to oneself or others.

Non-planning impulsiveness

▣ Response inhibition

▣ Delayed discounting



# NON-PLANNING

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- Do things on the spur of the moment
- Without thinking about the future
- ‘heat of the moment’
- Buying a car, even when it means you won’t have the rent

# RESPONSE INHIBITION

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- Ability to suppress a previously learned response
- When the rules change we have to be able to change
- Go-No Go tasks used to measure it

# DELAYED DISCOUNTING

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- Universal human trait to value any reward that is immediately available over any reward that is delayed
- Think about 2 TVs: one costs \$1500 now, the other cost 1600 now, but comes with a \$200 rebate. Which would you choose?
- Delay discounting is a measure how much one values a delayed reward

# IMPULSIVITY PRECEDES ADDICTION

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- Children of drug addicts score high on impulsivity questionnaires
- Do worse on response inhibition tasks
- Discount future rewards more
- Young adults with steeper discounting drink more
- Genetics accounts for about 40% of differences in delayed discounting

# DRUGS MAKE PEOPLE MORE IMPULSIVE

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- Whether its cocaine, opiates, alcohol or tobacco – drug addicts discount future rewards more
- Delayed discounting caused by drugs improves but very slowly, many months
- Contributes to relapse

# TWO BRAIN SYSTEMS INVOLVED

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- Delayed discounting involves reward pathways
  - Striatum (NAc), prefrontal cortex
- Response inhibition involves executive controls systems
  - Anterior cingulate cortex and related areas
- Impulsive individuals (as measured by DD) show LESS activation in the medial PFC and striatum (reward pathways) when presented with a future reward



# HOW DOES IMPULSIVITY CONTRIBUTE?

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- More impulsive youth take their first drink/cigarette/mj at a younger age
- Impulsivity is linked with other psychological problems that are associated with drug abuse
  - Conduct disorder
  - Attention deficits
  - Aggressiveness



# Treating Impulsivity

# AA AND Impulsivity

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- One day at a time
- Slow and easy
- Sharing in meetings

# TWO WAYS TO BECOME LESS IMPULSIVE

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- Improve memory
- Prospection

# IMPROVE MEMORY

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- Valuing a future reward requires that you remember what it's worth
- In both animal and humans impaired memory causes increased impulsivity
- Memory training decreases impulsivity in newly abstinent amphetamine addicts
- AA improves memory through repetitions, steps and practice

# MEMORY TRAINING AS TREATMENT

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- Frequent memory training exercises improve working memory
- Decrease impulsivity on a DD task
- Not yet known whether it will improve clinical outcomes but it should!
- We are piloting computer based memory training in some programs to improve outcome

# PROSPECTION

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- Ability to project yourself into the future
- Mental time traveling
- Thinking about what will happen in the future
- Sharing at meetings is about prospection – wanting what the guy has

# Treatments For Impulsivity

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- Dopamine stabilizers that will decrease the 'push' toward relapse
- Memory enhancers that improve our ability to value what we have and what we want



# Empathy, Altruism and Substance Abuse

*We Care*

# What is Empathy

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- Involves insights into the thoughts/feelings of others
- “to project yourself into what you observe”
- The way in which we perceive what others feel

*“Empathy is central to what it means to be fully human. It allows us to tune into how someone else is feeling.”*

# The Social Role of Empathy

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- Associated with morality, altruism, pro-social behavior and cooperation
- Critical to moral development

# Empathy is Impaired in SA/ETOH

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- Callous-unemotional children are at greater risk for conduct disorders, antisocial personality and substance abuse
- Alexithymia, the inability to identify and describe feelings occurs in 40% of Alcoholics compared with 5-7% of population
- Empathy in detoxified alcoholics is significantly lower than controls

# Loss of Empathy: State or Trait

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- Diagnosis of alcohol dependence (and by extension other SUDs) is intrinsically characterized by impaired capacity for empathy
- Drugs create a pseudo-empathic experience among users related to the synchronous emotional experience induced by the high/intoxication
- Empathy for others diminishes as craving and withdrawal dominate the addict's emotional state
- Alexithymia is a stable trait among substance misusers related to impaired empathy

*Loss of empathy precedes drug use and is made worse by drug use*

# AA: A Behavioral Plan That Restores Empathy

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- *A spiritual malady of self-centeredness*
- Step 4. A fearless moral inventory of ourselves
- Step 5. Admitted to God, ourselves and another human being the exact nature of our wrongs
- Step 8. Make a list of persons we have harmed and become willing to make amends to them
- Step 9. Make direct amends wherever possible

# Biological Basis of Empathy

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- Oxytocin (OT) is the most abundant neuropeptide in the hypothalamus
- Peripheral effects include uterine contractions, milk ejection in lactation
- OT is released locally in amygdala and septum, areas associated with emotional memory
- OT receptors are found in many sites related to drug seeking
  - Nucleus accumbens, ventral tegmental area, amygdala, hippocampus

# Behaviors Regulated by Oxytocin

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- Sexual arousal and orgasm
- Monogamous pair bonds
- Maternal Behavior
- Peer-to-peer social interaction
- Promotes attachment, trust and reciprocity among strangers
- Social memory and anxiety reduction



# OT in Humans

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- Can be administered intranasally
- Increases trust
- Decreases amygdala response to fear stimuli
- Increases the recognition of social cues
- Critical to the development of maternal-infant attachment
- Increases ability to infer mental states
- Less likely to show decreased trust after breaches of trust

# Generosity in Humans

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- Definitions:
  - Altruism is helping another at a cost to oneself
  - Generosity is offering more to another than he or she expects or needs
- Evolutionary theories of giving include kin selection, direct and indirect reciprocity, group selection and strong reciprocity
  - But most charitable giving is not reciprocal
- Empathy believed to prompt altruistic acts

# Does OT Affect Generosity in Humans

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## ■ Ultimatum Game

- Decision Maker 1 gets \$10 endowment and told to offer a split to Decision Maker 2 who has no endowment
- If Decision Maker 2 accepts the offer the money is paid out to both
- UG measures **generosity**

# Does OT Affect Generosity?

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- OT increased generous behavior in the Ultimatum Game (offers exceeded the average)
- Generosity was 80% greater in the OT group

# Does Service Improve Outcomes?

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- How do you measure Service/Altruism
  
- In the past week:
  - How often have you been patient with others when others were irritating in their words/actions?
  - How often have you met the needs of friends or relatives?
  - How often did you think about the problems of others?

# Results

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- More time spent helping corresponds with higher abstinence rates at 6 and 12 months (Zemore SE 2006)
- Helping behaviors predicted remission at 3 years (Hazard ratio = 2.59,  $p = .01$ ) (Pagano ME 2006)
- Increased helping behaviors, resulted in greater AA/NA involvement at 6 months (Zemore SE 2004)

# Do brain chemicals mediate the benefits of service?

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- Experimental construct for Service is Altruism
- Empathy triggers the release of Oxytocin

AND AT THE SAME TIME

- Increases generosity by 50%

# Empathy and Altruism: Pharmacological Targets for Drug Treatment

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- Defects in empathy are common in addiction
- 12 step recovery targets moral behavior and increases empathy
- Research demonstrates a connection between service (altruism) and long term outcome
- Oxytocin promotes generosity, empathy and pro-social behaviors

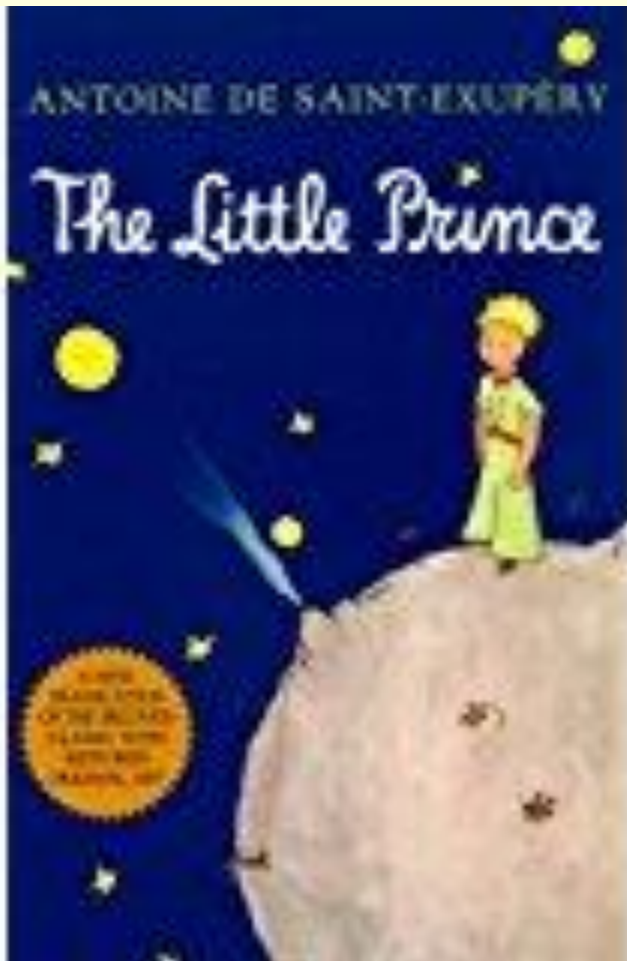




# A Memory Disorder

# Why do you drink?

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I drink to forget.

*What do you  
want to forget?*  
My problems.

*What are your  
problems?*  
I can't remember.

*Why don't you  
remember?*  
Because I drink to much.

# Alcohol and Learning

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- Alcohol causes cognitive deficits in 50-80% of alcoholics
- Memory deficits develop **after** prolonged drinking ceases and is worse in abstinent alcoholics
- Repeated periods of Alcohol followed by withdrawal impairs memory
- Alcohol impairs prospective memory/working memory
- Impairs the ability to learn complex novel information
- Caused by changes in grey matter microstructure and decreases in hippocampus volume

# 12 Steps and Memory

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- Sharing
  - Deficits in avoidance/negative reinforcement
- One day at a time
  - Deficits in short term and long term logical memory, executive function
- Steps
  - Deficits in working memory

# Why is Sharing important?

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- Alcohol impairs contextual learning
- When Tones are Paired with foot shock, rodents learning to fear the tone AND the environment associated with the shocks
- With ETOH animals fear the box but NOT the tone
- Binge drinkers failed to learn associations in aversive conditioning tests

*Looked at another way, Alcohol interferes with your ability to remember threatening situations.*

# Alcohol and State Dependent Learning

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- Learning under drugged conditions shows little or no transfer to non-drugged states
- Learning that occurs during a drugged state transfers to a similar drug state

*Things learned while 'high' are recalled poorly when sober.*

# Memory and Alcohol Dependency

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- If memory deficits are caused by alcohol...
- If impaired memory contributes to relapse...
- If AA exerts some of its benefits by compensating for the deficits in executive memory, prospective memory and avoidance memory.....

*Would Pharmacological Treatments That Prevent Alcohol Related Memory Deficits Treat Alcoholism?*

# Nimodipine (Nimotop)

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- Dihydropyridine approved for hypertension
- Binding sites on calcium channels that regulate glutamate and are associated with excitability after prolonged alcohol exposure
- Blocks withdrawal related hyperexcitability
- Reduces dopamine depletion after alcohol withdrawal
- Memory deficits are associated with effects of withdrawal



# Nimodipine and ETOH memory deficits

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- Rats were fed alcohol for 8 months
- Memory was tested 1 month after ETOH d/c
- 2 tasks
  - Object Recognition
  - T-Maze
- Nimodipine twice daily for two weeks during the last two weeks of alcohol exposure
- Nimodipine in a single dose immediately prior to alcohol withdrawal

# What the tests measure

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- Object recognition
  - Rats attracted to novel objects, and once they 'learn' an object they spend less time with it
- T-maze: prospective memory test
  - 'unlearning test' – non-matching to place
  - Placed in maze with one arm blocked and food in the other arm
  - Retested with blocking door removed
  - Count the number of times they return to the previously UNBLOCKED arm (errors)

# Results

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- One month after withdrawal, alcohol treated animals showed marked memory deficits on both tasks
- On the T-maze they make approximately twice as many 'bad' choices (perseverative errors)
- Nimopidine either for two weeks or as a single dose completely prevented memory loss due to alcohol

# Conclusions

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- Deficits in learning, empathy and altruism predispose to substance abuse and are worsened as a result of chronic substance abuse
- The benefits of 12 step recovery are related to the program's ameliorative effects on alcohol/drug related deficits in three key processes: learning, empathy, altruism
- We predict that pharmacological interventions that support normalization in these functions rather than reward regulation, will prove effective for treating drug dependency

# Wizard of Oz

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In the Wizard of Oz, Dorothy is carried to Oz by a tornado

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But with the help of friends whose apply their brain, heart and courage to her problem

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She is returned home .... through the recognition of the emotional bonds she has to the people there.

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