Empathy, Altruism and Learning:

*What psychopharmacology can learn from 12 Step Recovery*

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Why do people start taking drugs?

- **Intense pleasure**
- To feel better – alleviate negative affects
- Enhance performance
- Curiosity
Why do people keep taking drugs?

- Pleasure

- Alleviate negative affects
  - Craving

- Block withdrawal

- Social reinforcement
How might addiction treatments work?

- Block pleasure – Naltrexone, Buprenorphine
- Decrease craving – Naltrexone, Varenicline
- Interfere with social reinforcement - Methadone
- Decrease performance enhancing effects – N/A
- Decrease abstinence syndrome - Acamprosate
The Reward System

Dopamine Pathways
- Frontal cortex
- Nucleus accumbens
- VTA

Serotonin Pathways
- Striatum
- Substantia nigra
- Raphe nucleus

Functions
- Reward (motivation)
- Pleasure, euphoria
- Motor function (fine tuning)
- Compulsion
- Perseveration

Functions
- Mood
- Memory processing
- Sleep
- Cognition
Dopamine and the Reward System

- DA containing cells in the Ventral Tegmental Area (VTA) project to the Nucleus Accumbens (NAc)
- NAc processes motivated behavior
- The shell of the NAc responds to primary reinforcers (food, sex)
- DA release in the NAc mediates the hedonic impact of rewarding stimuli
- NAc encodes goal directed behaviors for natural and drug rewards
- NAc DA is essential for reward related learning
- DA mediates non-drug rewards (food, sex)
Dopamine Hypothesis of Addiction

- 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 or 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
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

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

Is treating DA dysfunction in cocaine dependency effective?
Enhancing DA activity

- 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

- 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
Tried and Failed

- Direct agonists – L-Dopa
- Indirect agonists – Amantadine, Amphetamines, Antidepressants
- Metabolism inhibitors – MAOI (selegiline), COMT, Dopamine Betahydroxylase Inhibitor (Antabuse)
Why Increasing DA Is NOT Effective

- 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 often precede drug use and are also worsened by drug use.
The way into the forest....

Is not necessarily the way out of the forest!
New Path – Stay Close to Treatments

- 12 Step Recovery
  - Increases long term abstinence
  - Results in meaningful social and behavioral change
Why is AA Understudied?

- 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?

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

- 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.
- Impairs the ability to learn complex novel information.
- Caused by changes in grey matter microstructure and decreases in hippocampus volume.
12 Steps and Memory

- **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 prospective memory
Why is Sharing important?

- 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 tone but NOT the box
- 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

- 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

- 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)

- 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

- 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

Brooks, SP et al, 2008
What the tests measure

- 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 UNBLO ckED arm (errors)
Results

- 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.
Empathy, Altruism and Substance Abuse

We Care
What is Empathy

- 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

- Associated with morality, altruism, pro-social behavior and cooperation
- Critical to moral development
Empathy is Impaired in SA/ETOH

- 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

- 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

- 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

- 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

- 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

- 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

- 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

- 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?

- OT increased generous behavior in the Ultimatum Game (offers exceeded the average)

- Generosity was 80% greater in the OT group
Does Service Improve Outcomes?

- 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?

Pagano ME  2006
Results

- Helping behaviors predicted SUD 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)
- More time spent helping corresponds with higher abstinence rates at 6 and 12 months (Zemore SE 2006)
What brain chemicals mediates Service?

- Scientific construct for Service is Altruism
- Empathy triggers the release of Oxytocin
  AND
- Increases generosity by 50%
Empathy and Altruism: Pharmacological Targets for Drug Treatment

- 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 receptors are found in brain regions associated with drug misuse and interacts with DA and 5HT
- Oxytocin promotes generosity, empathy and pro-social behaviors
Conclusions

- 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
In the Wizard of Oz, Dorothy is carried to Oz by a tornado
But with the help of friends whose apply their brain, heart and courage to her problem.
She is returned home .... through the recognition of the emotional bonds she has to the people there.