Brain Science and Addiction

NCLS Opioid Policy Fellows
Second meeting: evidence and innovations

Wednesday June 13th, 2018

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Conflicts of Interest: Dr. Sakai received reimbursement in 2012 for completing a policy review for the WellPoint Office of Medical Policy & Technology Assessment (OMPTA), WellPoint, Inc., Thousand Oaks, CA. He also served as a board member of the ARTS (Addiction Research & Treatment Services) Foundation until 2015.

Lab sources of support:
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National Institute on Drug Abuse (R01DA031761, R25DA033219, DA009842, DA011015).

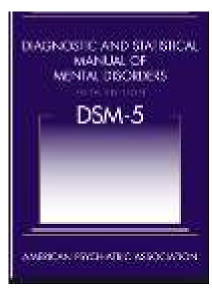
Defining terms…what is addiction?
Is it the amount used?
Frequency of use?
Is it something else?

Addiction, substance use disorder:

<u>Substance Use Disorder</u>

- **Role failures**
- **Hazardous use**
- **Interpersonal problems**
- **More than intended**
- **Cut down**
- **Time spent**
- **Activities limited**
- **Use despite consequences**
- **Tolerance**
- **Withdrawal**
- **Craving**

2-3 mild;
4-5 moderate;
≥6 severe



Common in general population

	Alcohol abuse	Alcohol dependence	Drug abuse	Drug dependence
Lifetime	17.8%	12.5%	7.7%	2.6%
12-month	4.7%	3.8%	1.4%	0.6%

Grant et al Arch Gen Psychiatry 61: 361-368 J Clin Psychiatry 66:677-685
Hasin, D. S. et al. Arch Gen Psychiatry 2007;64:830-842.
Compton, W. M. et al. Arch Gen Psychiatry 2007;64:566-576

Even more prevalent in clinical populations…

COMORBIDITY (odds ratios – alcohol dependence):

	Men	Women
Depressive symptoms	2.7	4.1
Manic symptoms	8.1	4.7
Generalized anxiety symptoms	3.7	2.8
Social anxiety symptoms	2.0	2.6
Post-traumatic stress sx's	2.7	3.4

Kessler et al *Arch Gen Psychiatry* 54(4): 313-321

Even more prevalent in clinical populations…

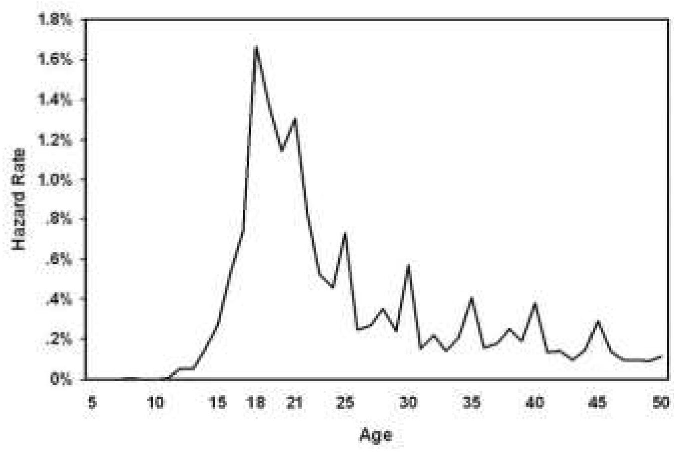
General medical clinics
- 1/5 non-tobacco substance abuse problem

Inpatient medical services
- 23% current smokers
- 14% alcohol misuse
- 12% drug misuse

Common also in ED setting

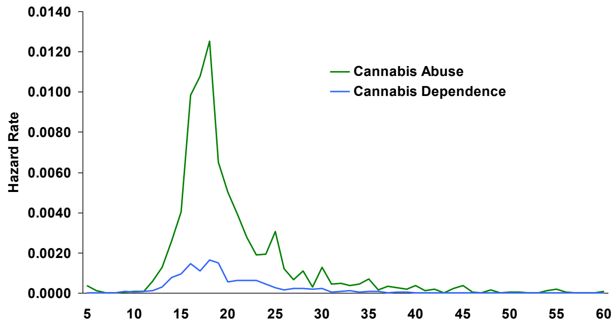
Cherpitel & Ye, Drug & Alcohol Dependence 2008; 97:226-230
Mercy, 2003
Kouimtsidis et al., 2003

With a common onset in adolescence…

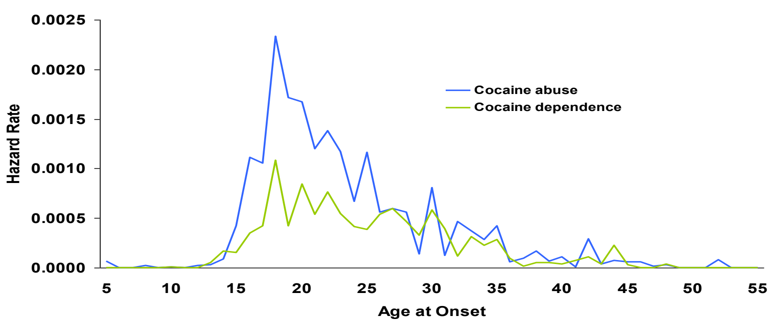


Age at onset of alcohol dependence from Li et al., Biological Psychiatry 56:718-20

With a common onset in adolescence…



Age at onset of cannabis abuse and dependence – from Grant Psychological Medicine 36:1447-1460.



Age at onset of cocaine abuse and dependence – unpublished data

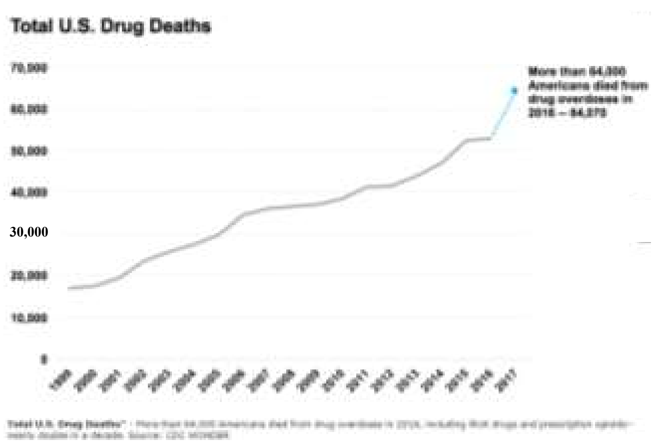
Common cause of preventable death…

Preventable causes of death in 1990:
- #1 Tobacco (400,000 deaths per year)
- #3 Alcohol (100,000 deaths per year)
- #9 Illicit drugs (20,000 deaths per year)

Actual causes of death in 2000:
- #1 Tobacco (435,000 deaths per year)
- #3 Alcohol (85,000 deaths per year)
- #9 Illicit drugs (17,000 deaths per year)

Mokdad et al. JAMA 2004; 291:1238-45

Dramatic rise in drug-related deaths…



Historically, physicians have not consistently addressed addiction…

Physicians generally – poor job of screening

Survey of FP's (n=648)
- **90% failed dx substance abuse when presented with early symptoms of alcohol abuse in an adult patient**
- **40% of pediatricians presented with classic description of drug abusing teen – did not include substance abuse in their differential**

Another study in primary care practices – patients with alcohol dependence received assessment and referral to treatment only 10% of the time

Only about 3% of those with alcohol use disorder in past 12-months report that they had received help from a physician or other health care professional

National Center on Addiction and Substance Abuse, 2000
McGlynn et al. NEJM 2003; 348:2635-2645
Hasin, D. S. et al. Arch Gen Psychiatry 2007;64:830-842
National Center on Addiction and Substance Abuse, 2000

A biological basis…

- **A disorder historically relatively ignored…**
- **More difficult to have compassion for…self-induced vs. a victim…a behavioral component.**
- **Not a "moral failing" or "willful misconduct"**

A biological basis…

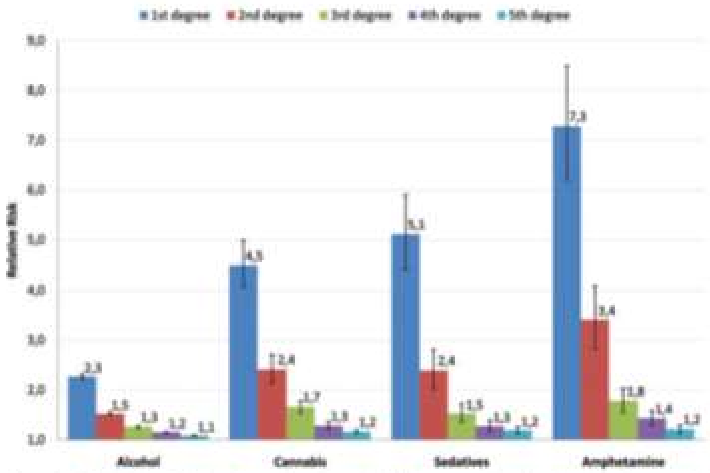


Figure 2. Relative risks of substance dependence in first- to fifth-degree relatives, given that the index person is dependent on the same substance. The 95% confidence intervals are provided as error bars for each RR estimate. (In color in *Annals* online.)

Tyrfingsson et al., 2010

A biological basis…

- Twin and adoption studies ~50% of variance in the population related to genes
- Animal studies –
  - rats become addicted to the same substances that humans do
  - rats can be bred to create strains that are likely to become quickly and severely (measured in level presses/dose) addicted to substances

Cloninger, 1999; American Journal on Addictions 9: 285

A biological basis…

Table 2. Relative risks for substance disorders

Substance A	NA	Substance B	NB	Mates
Alcohol	15,361	Alcohol	15,361	3.40 [3.23, 3.59]
Cannabis	3185	Cannabis	3185	14.48 [12.41, 16.97]
Sedatives	1759	Sedatives	1759	6.24 [4.61, 8.10]
Amphetamine	1619	Amphetamine	1619	19.42 [15.67, 29.46]
Cannabis	3185	Alcohol	15,361	6.52 [5.99, 7.08]
Sedatives	1759	Cannabis	3185	9.32 [7.79, 11.11]
Sedatives	1759	Alcohol	15,361	3.81 [3.47, 4.18]
Amphetamine	1619	Sedatives	1759	13.32 [10.88, 16.30]
Amphetamine	1619	Cannabis	3185	14.39 [12.23, 16.89]
Amphetamine	1619	Alcohol	15,361	6.60 [5.96, 7.30]

RR values reflect the risk of dependence on substance B observed in mat
For each condition the number of cases is provided, and the 95% confid

Tyrfingsson et al., 2010

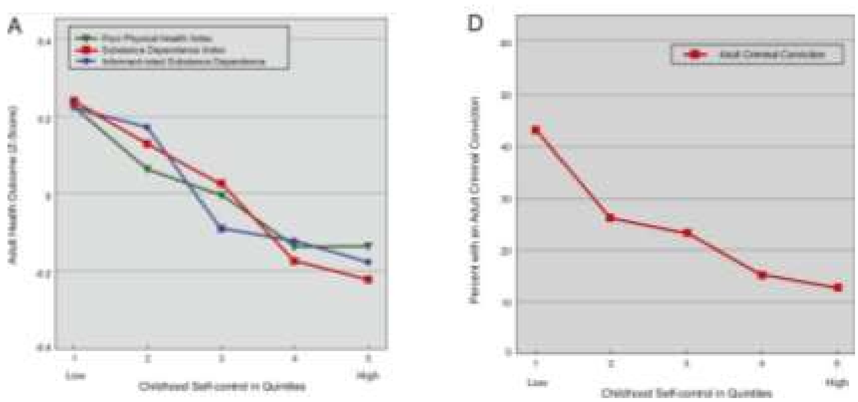
Many youths try substances of abuse, why do some progress to a clinical diagnosis of a substance use disorder?

Pre-Existing Risk:

- N=1,000
- Enrolled from birth to age 32 years
- Self Control - 3, 5 yrs observational; 5, 7, 8, 11 parent, teacher and self report of impulsive aggression, hyperactivity, lack of persistence, inattention, and impulsivity.

Fig. 1. Design of the Dunedin Multidisciplinary Health and Development Study.

Pre-Existing Risk:

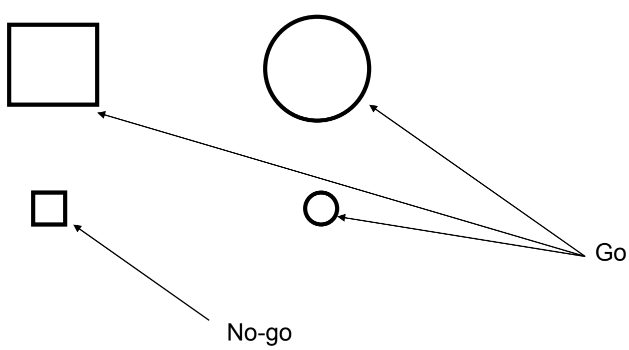


Moffitt et al., PNAS 2011; 108:2693

Behavioral Disinhibition: Liability for Externalizing Spectrum Disorders and Its Genetic and Environmental Relation to Response Inhibition Across Adolescence

Susan E. Young, Naomi P. Friedman, Akira Miyake, Erik G. Willcutt, Robin P. Corley, Brett C. Haberstick, and John K. Hewitt
University of Colorado at Boulder

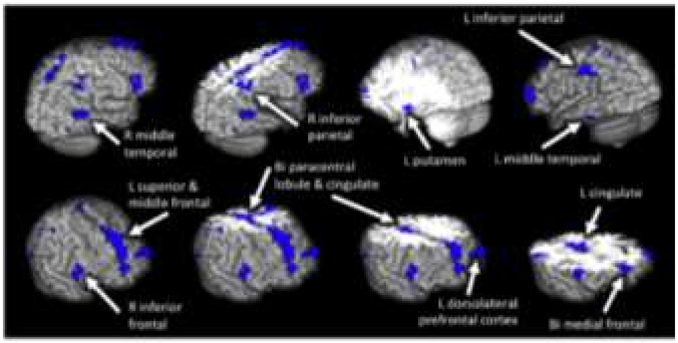
Adolsecent-onset SD:



Pre-Existing Risk:

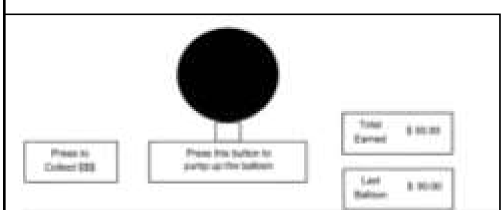
12-14 years, very limited substance use; Scanned using Go/No-Go at baseline

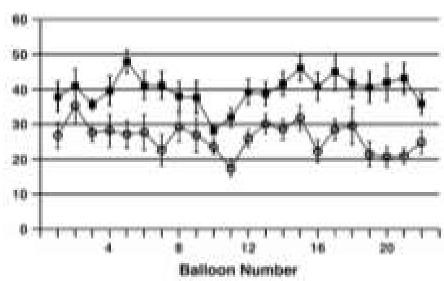
Followed into adolescence and categorized based on progression to heavy substance use



Norman et al., DAD 2011

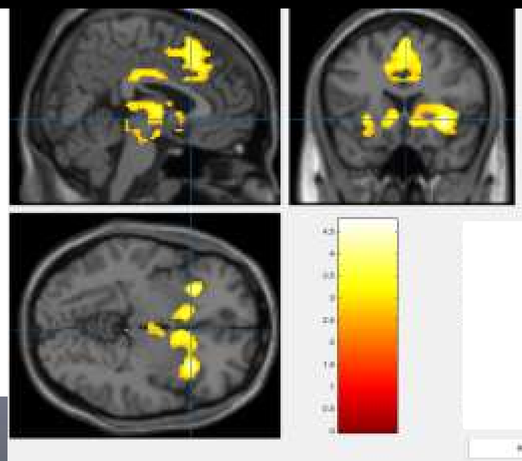
Adolescent-onset SUD:





Lejuez et al. J Exp Psychol Appl 2002; 8:75
Crowley et al., J Am Acad Child Adolesc Psychiatry 2006; 45:175

Figure 1. Negative relationship between brain activation and externalizing behavior scores. Children 9-11 years old are imaged as they decide to take risks. Significant areas include the reward-related circuitry (including midbrain and bilateral caudate and nucleus accumbens) and frontal regions (including inferior frontal gyrus superior frontal gyrus and cingulate gyrus).



Adolescent-onset SUD:

Laboratory studies using various modalities such as:

Delay discounting

Measures of impulsivity

Measures of inhibition

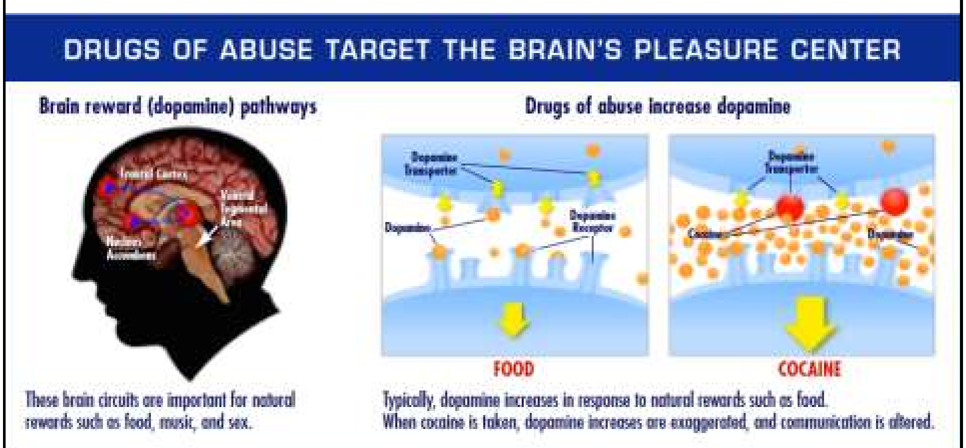
Measures of executive function

Emotion regulation and anger

Show that adolescent patients with SUD perform more poorly than controls.

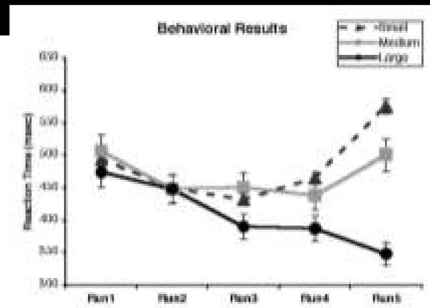
A biological basis…

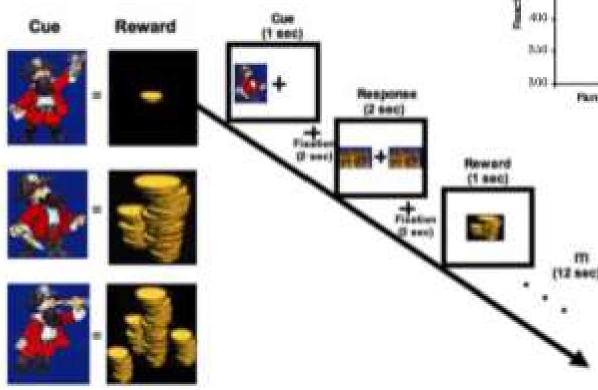
- We are not all equally likely to develop a substance use disorder…some pre-existing risk
- What brain changes are associated with developing addiction…



Brain Development:

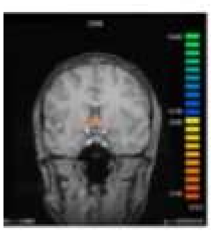
Reward-related behavior:

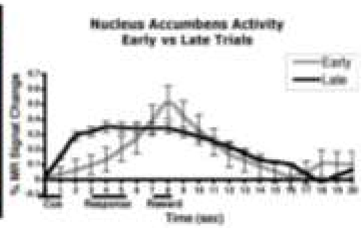




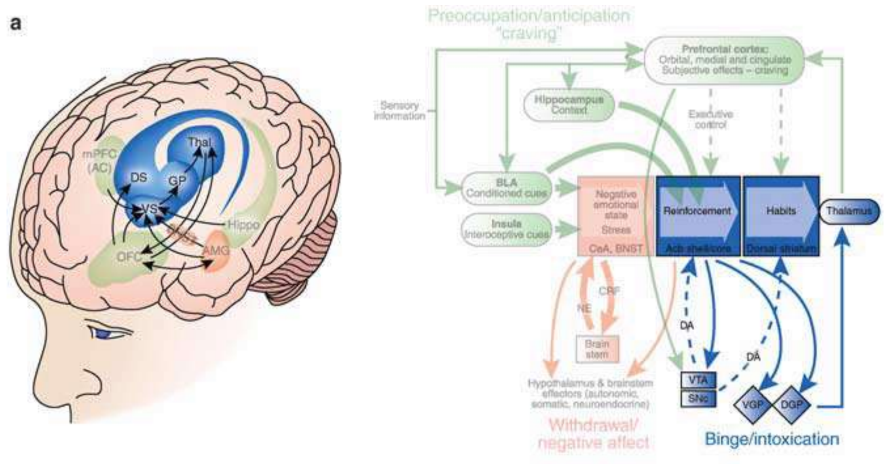
Brain Development:

Reward-related behavior:



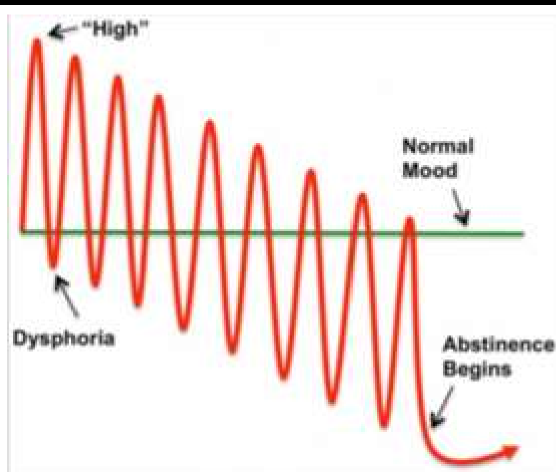


Galvan et al., J Neuroscience 2005; 25:8650



Koob & Volkow, 2010

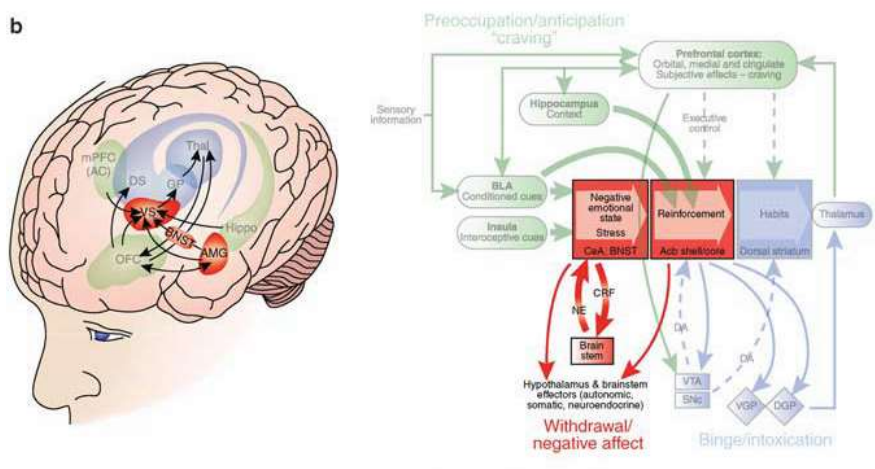
Adolescent-onset SD:



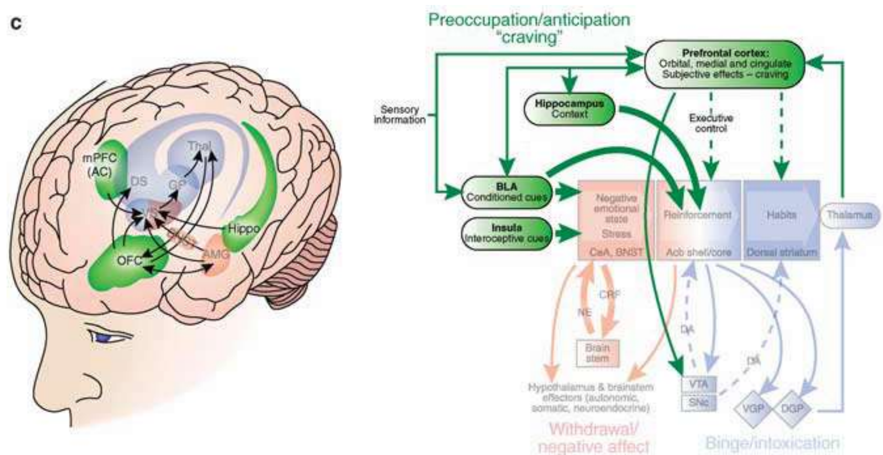
Koob & Volkow Neuropsychopharmacology 2010; 35:217
Crowley et al., PLoS ONE 2010; 5(9):e12835

Case:

"It's not even fun anymore. I just feel like I have to use it to feel normal."



Koob & Volkow, 2010



Koob & Volkow, 2010

"Cortically regulated cognitive and emotional processes, which result in the overvaluing of drug reinforcers, the undervaluing of alternative reinforcers, and decifits in inhibitory control…"

Goldstein & Volkow, 2002 (review) Am J Psychiatry 159:1642

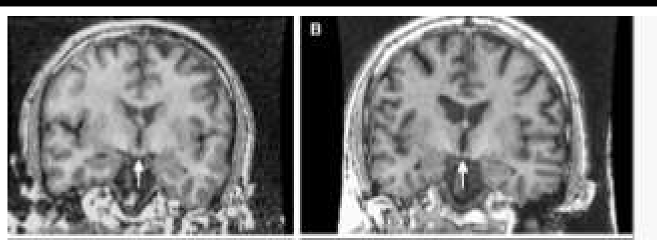
Adolescent-onset SD:

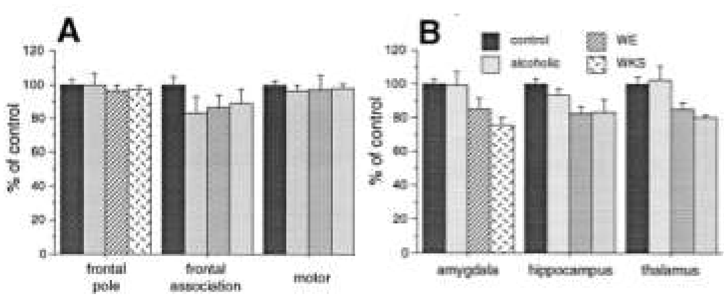
Brain differences cause drug use

Vs.

Drug use causes brain problems

Alcohol effects on brain:





Kril et al., Neuroscience 1997; 79:983
Sullivan & Pfefferbaum Alcohol Alcohol 2009; 44:155

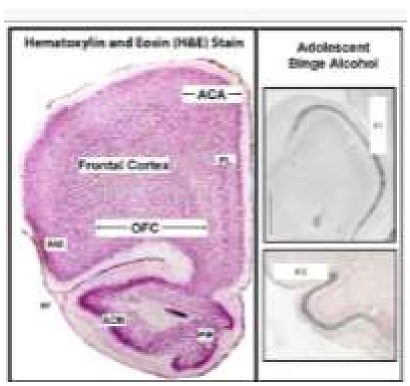
Inhalant-related brain injury:

- Toxic Leukoencephalopathy

Filley et al., NEJM 2001; 345(6):425

Adolescent-onset SD:

The adolescent brain may be particularly vulnerable to substance induced damage



Crews & Boettiger Pharmacol Biochem Behav 2009; 93:237

Adolescent-onset SUD:

Not all youths are equally likely to develop SUD
Problems of inhibition, high novelty seeking, poor delay discounting, affective regulation and rewards sensitivity etc. are related to increased risk
Early data suggest less GM volume and hypoactivation in both reward related pathways and frontal control circuits in those at risk or with early SUD
Exposure to substances then causes further brain changes in both reward, frontal control circuits and circuits important to stress, memory and learning

The Future:

- https://www.drugabuse.gov/related-topics/adolescent-brain/longitudinal-study-adolescent-brain-cognitive-development-abcd-study