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PSYCHIATRY ACADEMY

Neurobiology of Addiction & Genetics of Substance Use Disorders

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Faculty Disclosure

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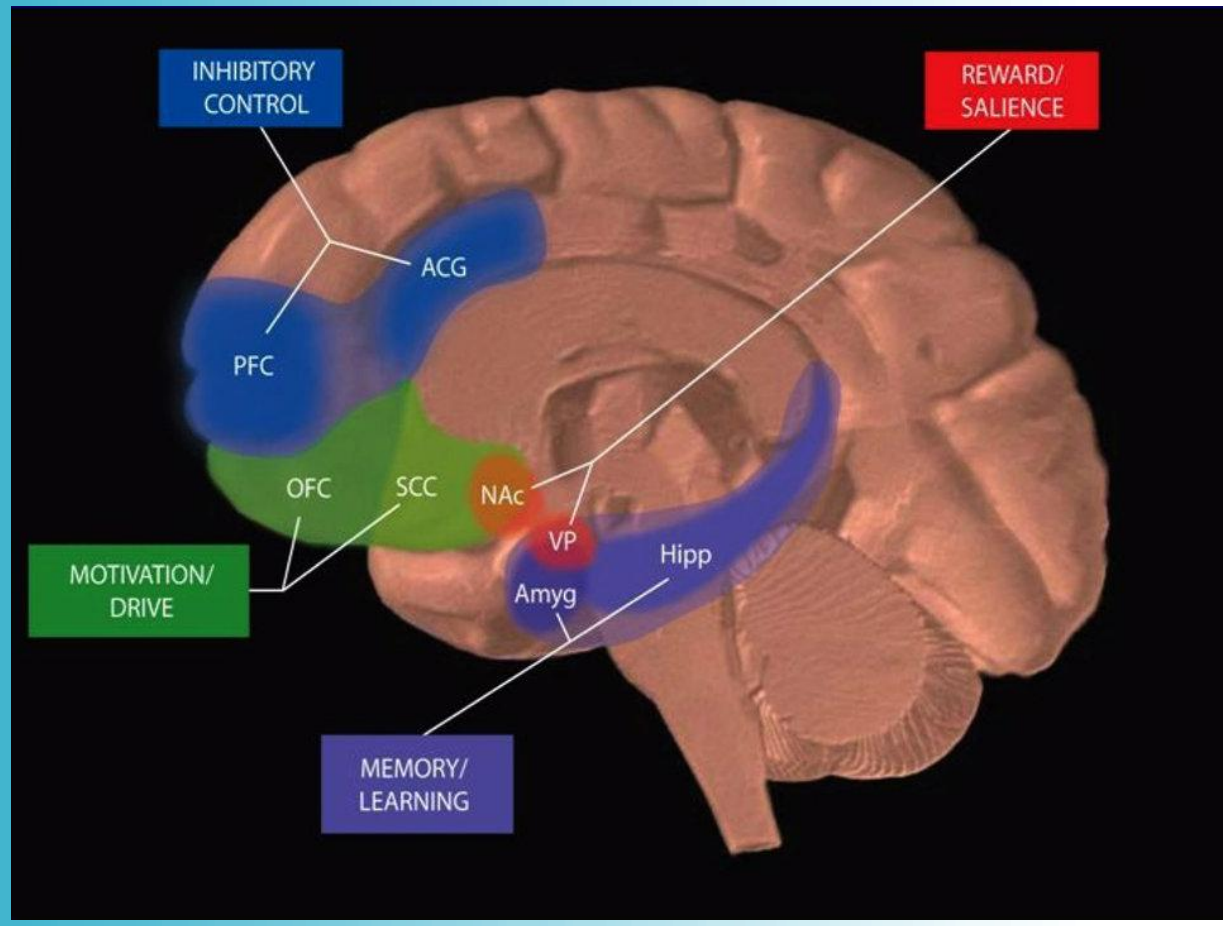
I have the following relevant financial relationship with a commercial interest to disclose:

- I receive or have received research support from NIMH, NIDA, and the Klingenstein Third Generation Foundation
- I have ownership equity in WISER Systems, LLC as a partner.

Agenda

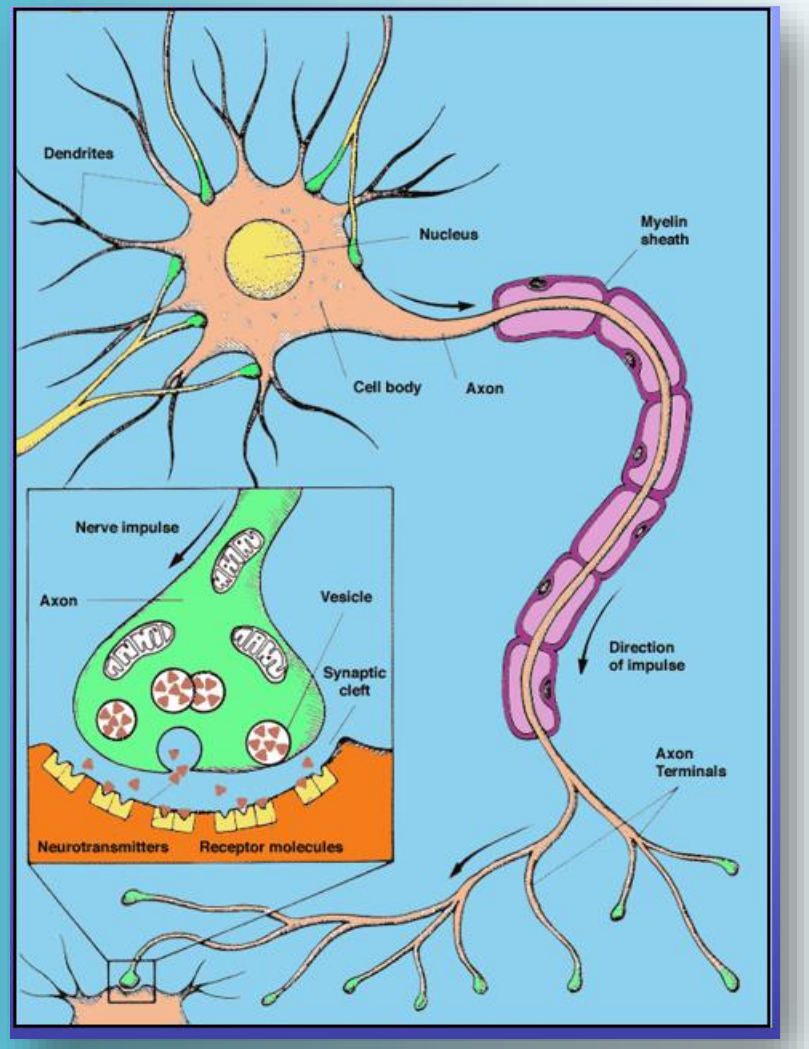
- Briefly review the brain regions and mechanisms of substance use and addiction
- Briefly review the concepts of genetics and genetic epidemiology
- Discuss heritability of substance use disorders
- Discuss specific genes and neurobiological systems associated with substance use disorders

Addiction is a Brain-Based Disorder



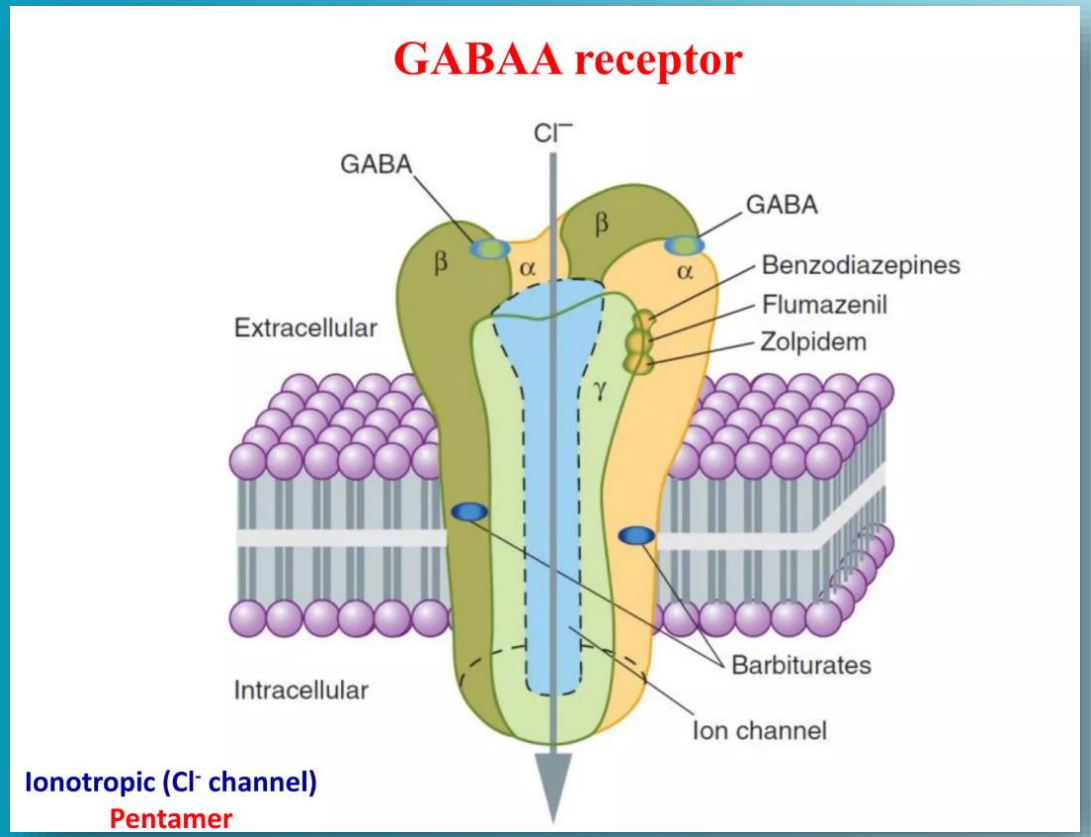
Source: NIDA

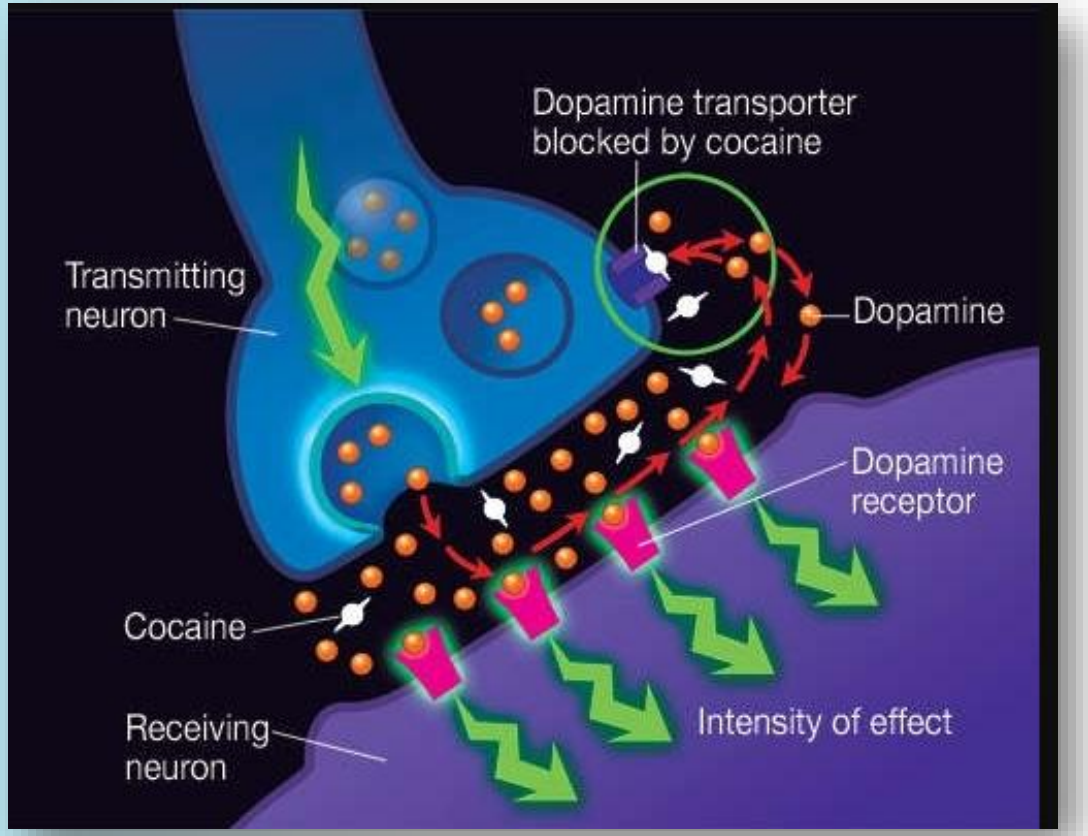
Addiction is a Brain-Based Disorder



Source: NIDA

Addiction is a Brain-Based Disorder





Source: NIDA

Neurobiological Systems Involved in SUD

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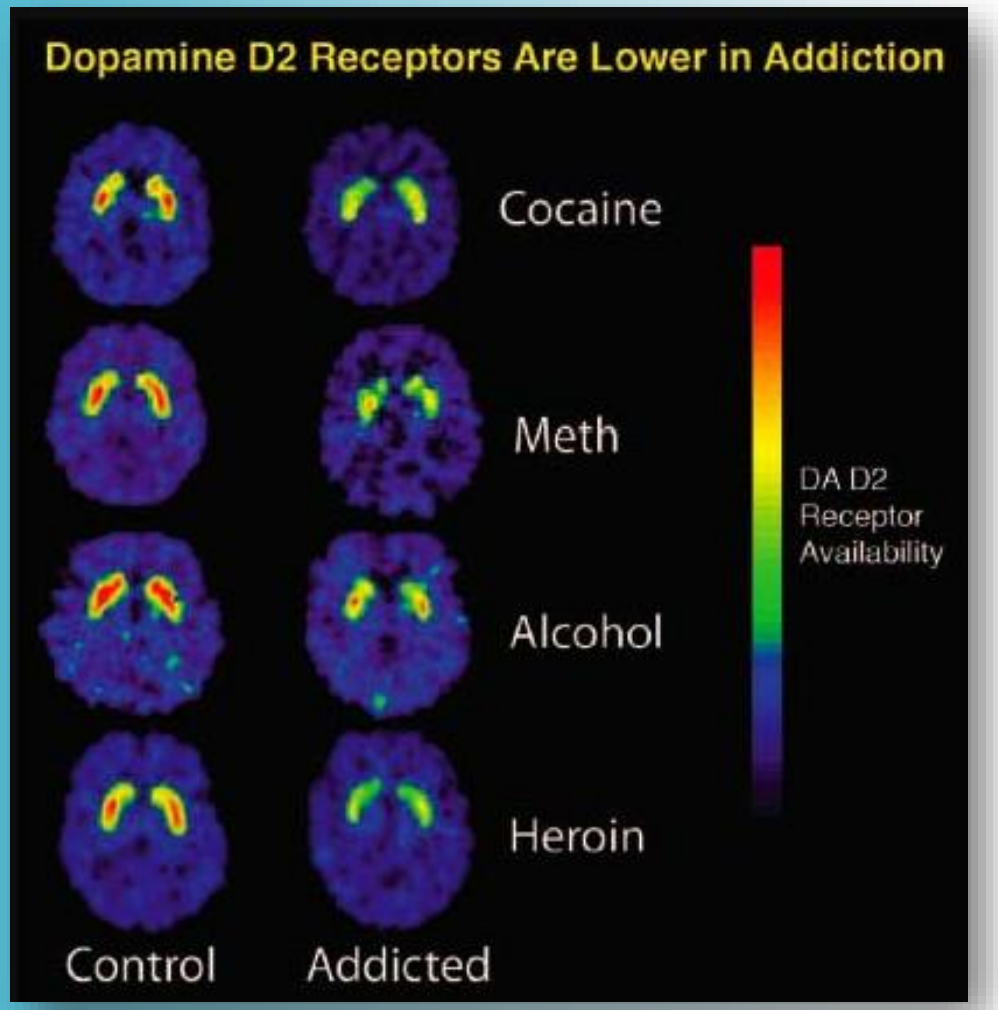
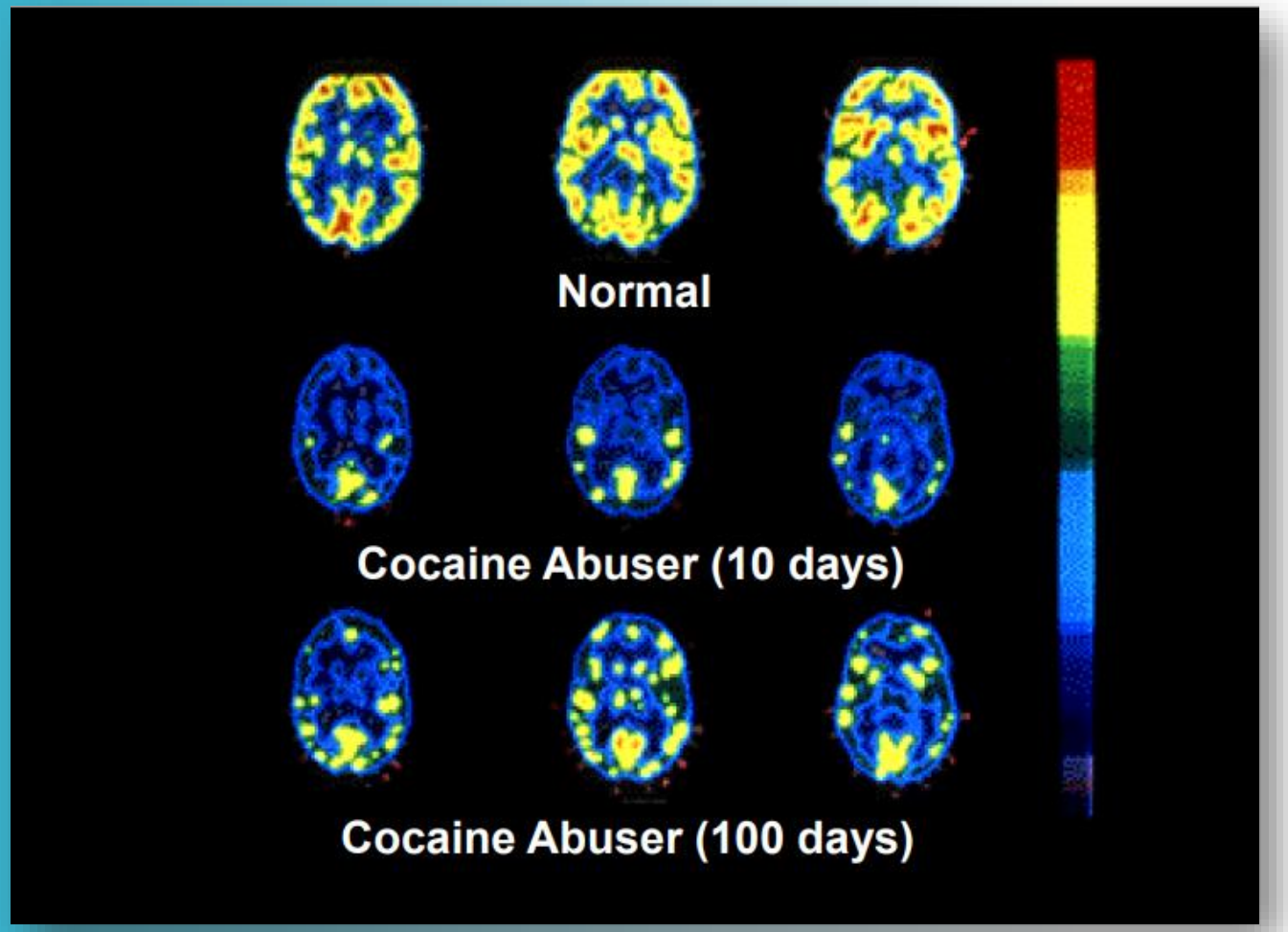
Substance	Mechanism of Action
Alcohol	GABA and opioid agonist; NMDA antagonist
Cocaine	Blocks re-update of dopamine
Amphetamines	Stimulate dopamine (and NE) release
PCP, ketamine (Psychedelics)	NMDA antagonist
Opioids	Mu, delta, kappa opioid agonists
Cannabis	CB1 and CB2 agonist
MDMA	Serotonin release and reuptake inhibition; mild dopamine and NE reuptake inhibition
LSD	5HT2a agonism leading to increased glutamate

Neurobiological Systems Involved in SUD



Source: NIDA

Neurobiological Systems Involved in SUD



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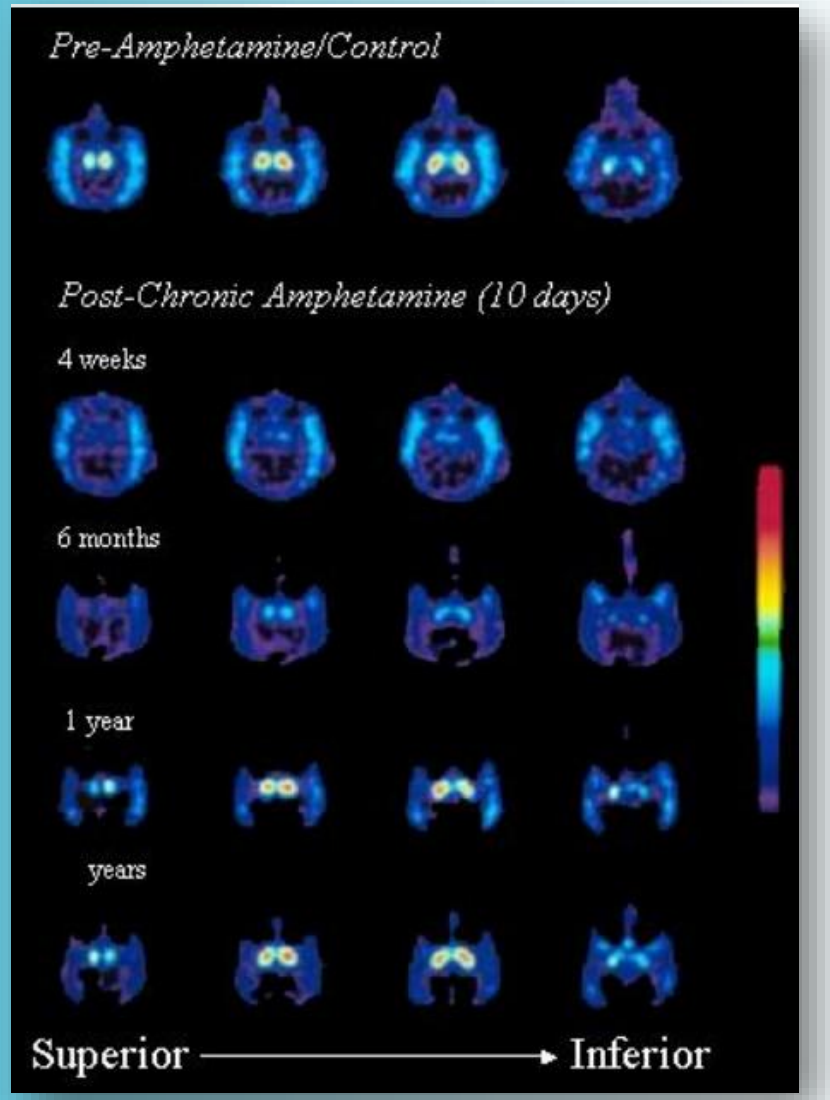
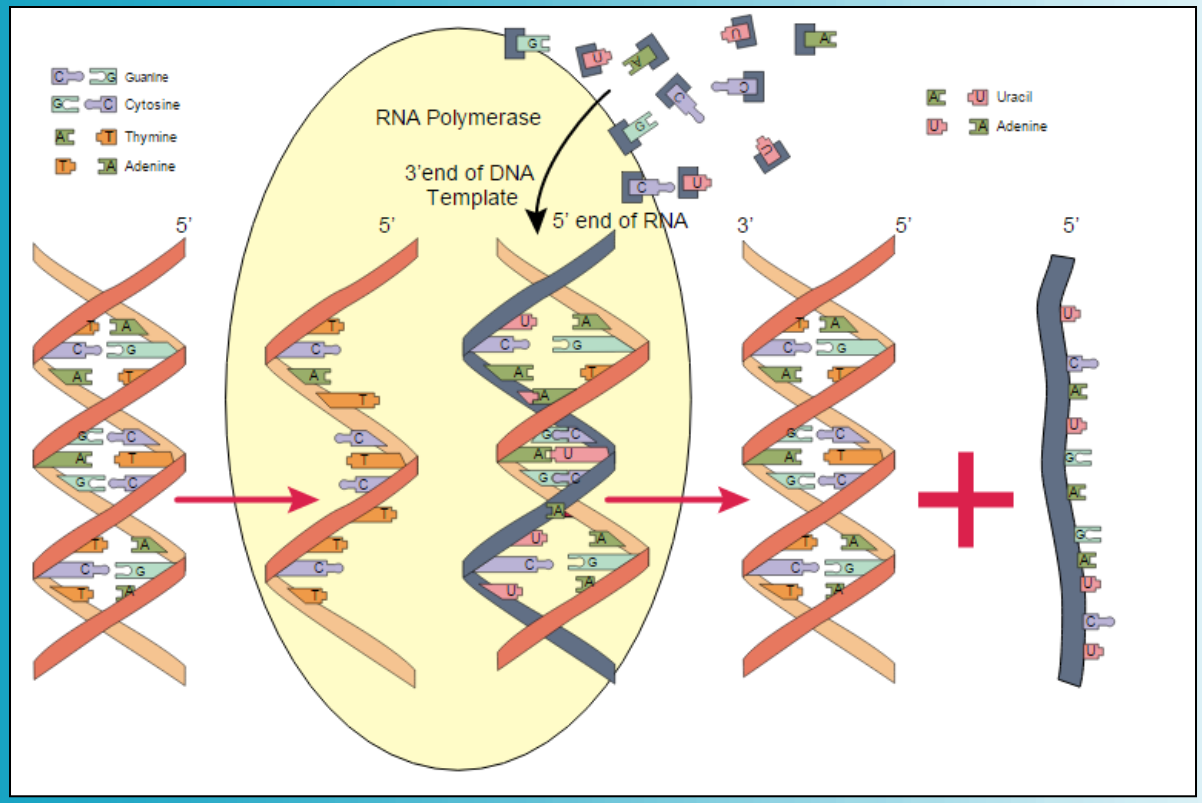
Neurobiological Systems Involved in SUD



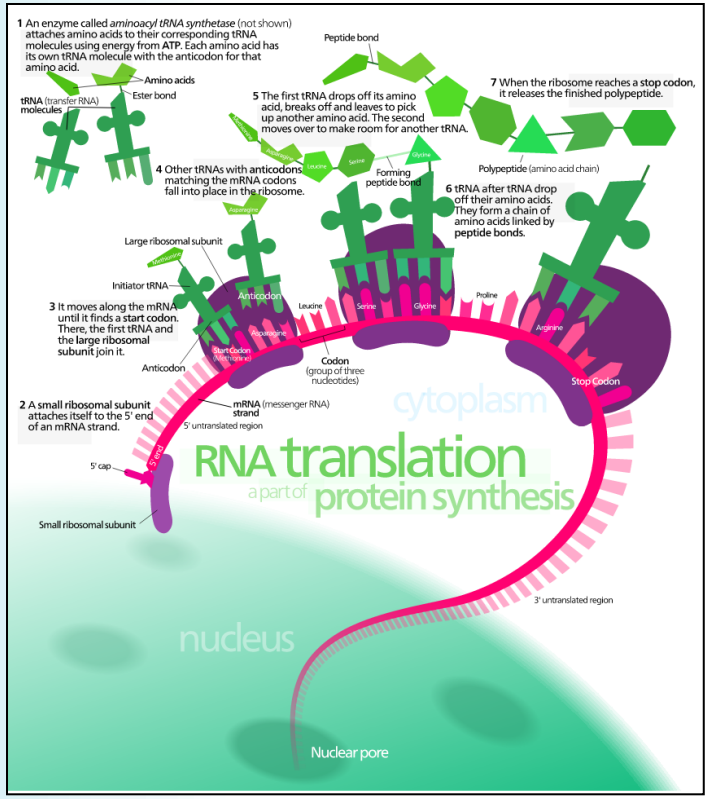
Source: NIDA

Genetics: Central Dogma

- DNA →RNA →Protein



"Rna syn" by Fred the Oyster. The source code of this SVG is valid. This vector graphics image was created with Adobe Illustrator.. Licensed under GFDL via Wikimedia Commons - https://commons.wikimedia.org/wiki/File:Rna_syn.svg#/media/File:Rna_syn.svg



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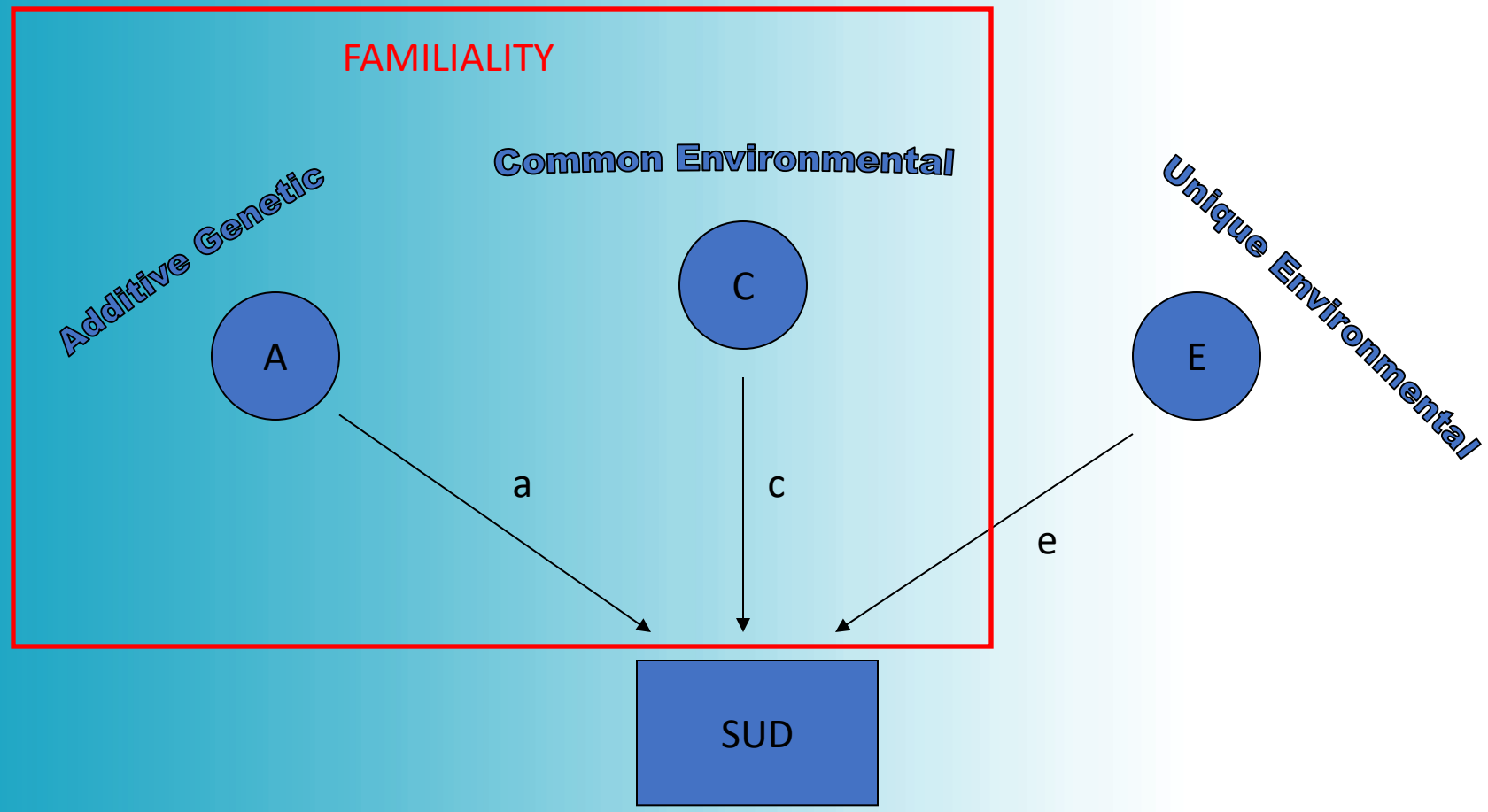
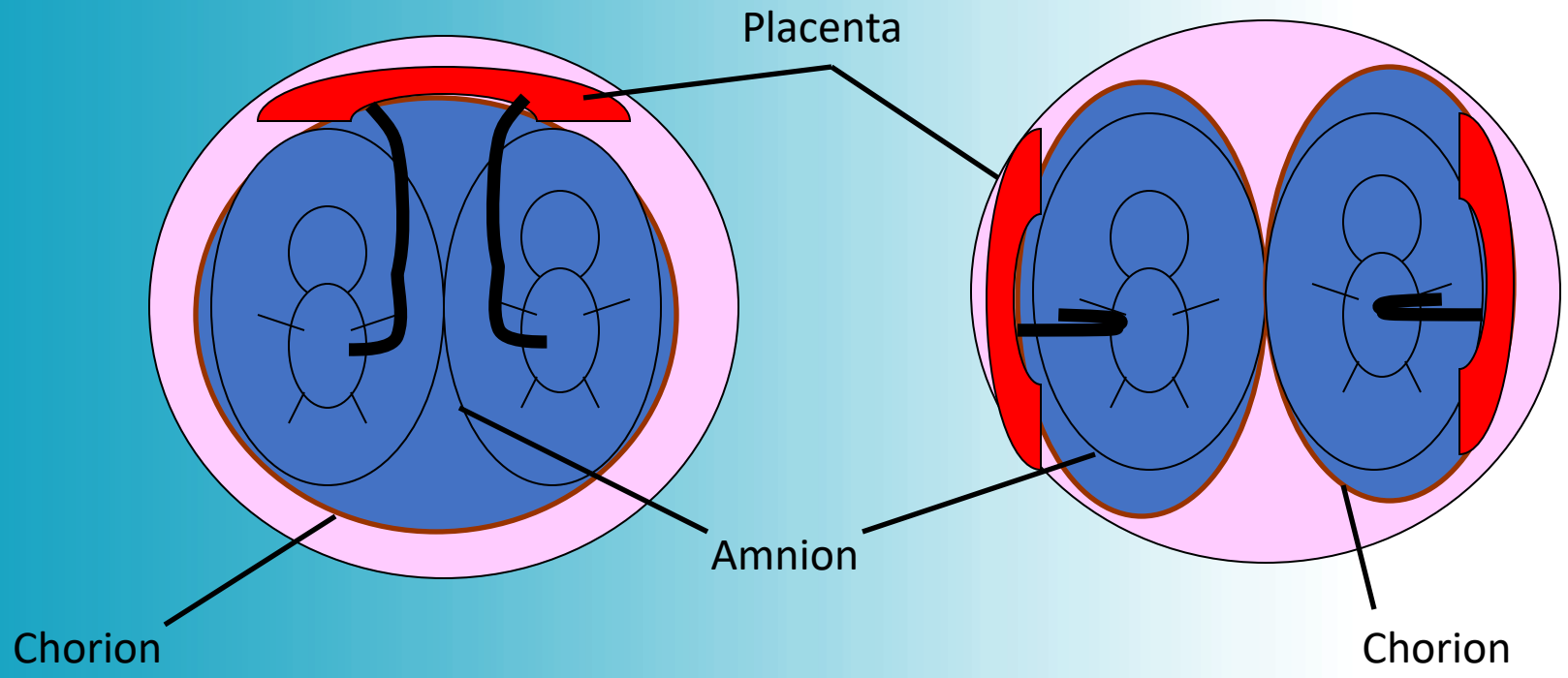
Genetic and Environmental Contributions to SUD



Twin Studies

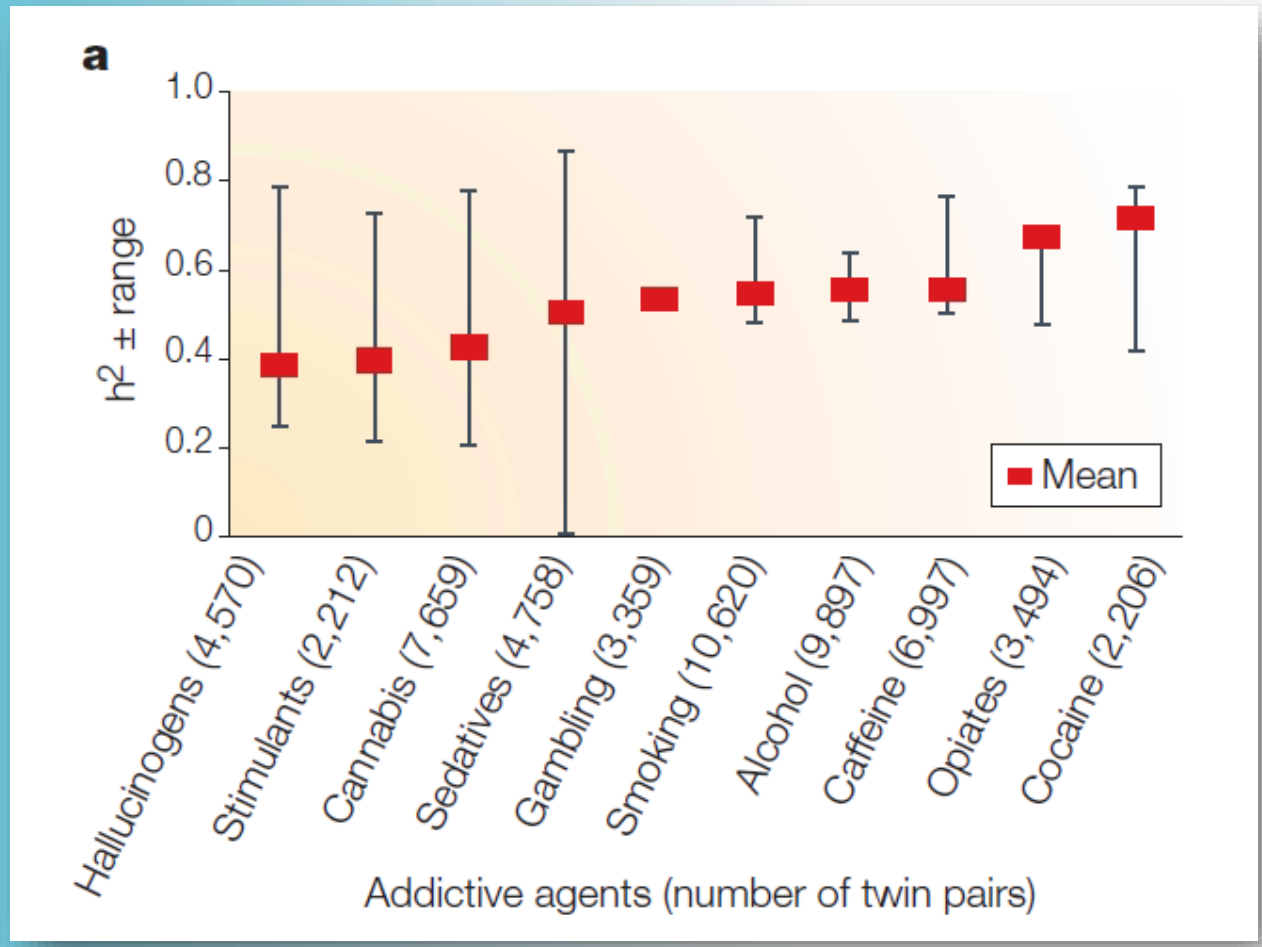


Monozygotic (MZ) twins
Share 100% of DNA

Dizygotic (DZ) twins
Share 50% of DNA

Heritability of SUDs

Heritabilities range from 40-70% for all substances, with the highest numbers being for cocaine abuse



From Goldman, Oroszi & Ducci (2005)

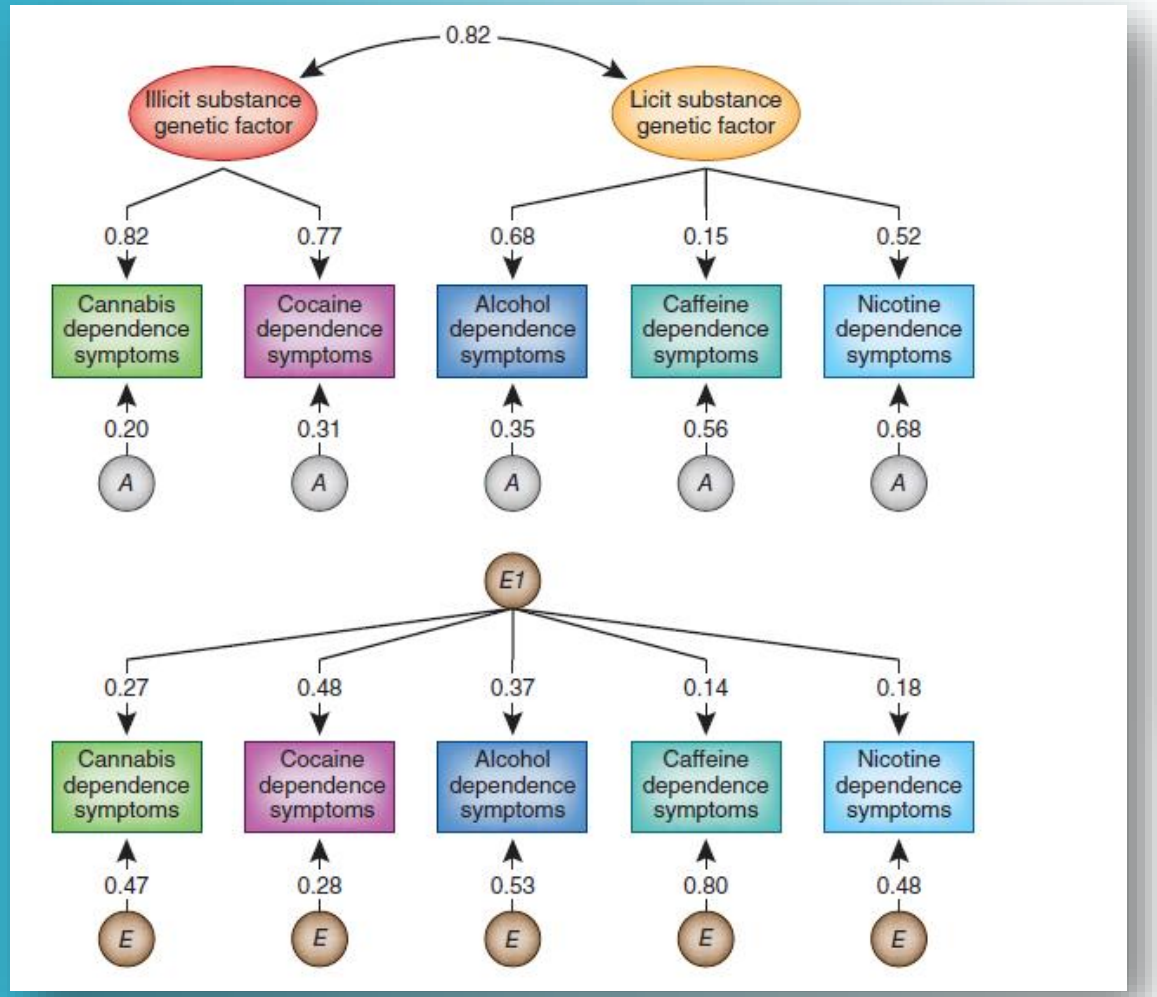
How Specific is the Heritability?

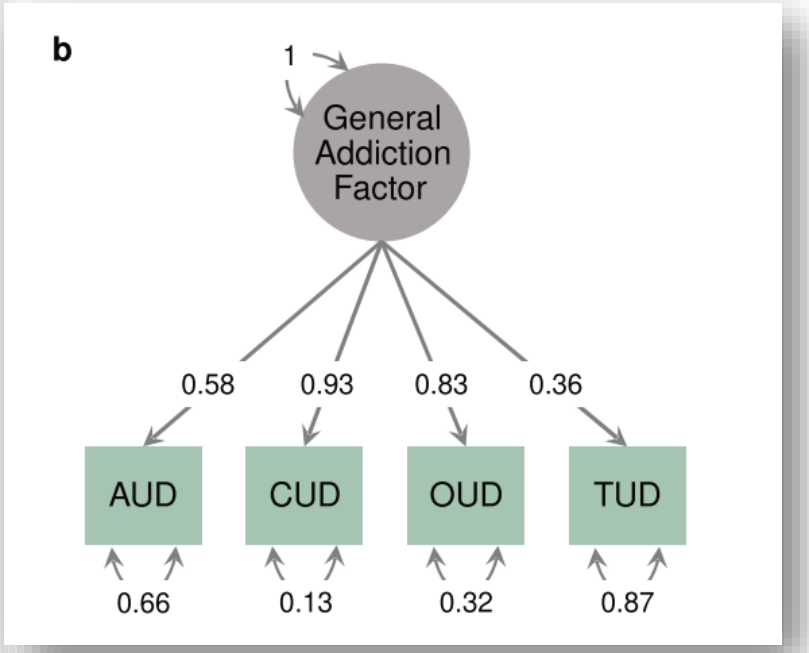
Fairly specific for nicotine and caffeine.

Not as much for others.

So, there are some general factors associated with broad liability.

There are also broad genetic associations with other psychiatric disorders such as externalizing disorders.





From Kendler et al (2012); Hatoum et al (2023)

How Specific is the Heritability?

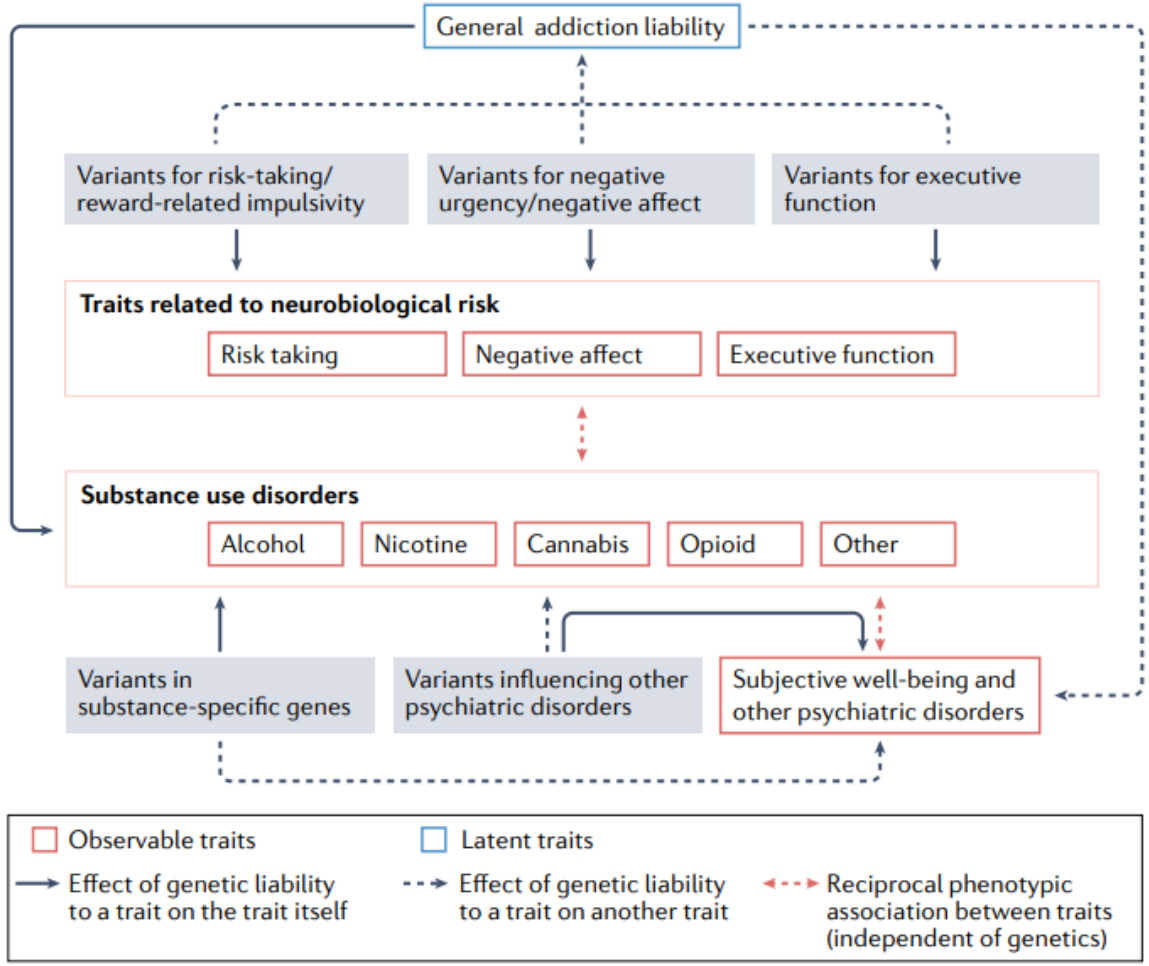


Fig. 2 | The genomic architecture of SUDs. The genetic contribution to individual substance use disorders (SUDs) is attributable to variants that influence general addiction liability and substance-specific variants[63]. General addiction liability is driven by variants influencing traits that correspond to the three stages of the neurobiological model of addiction: reward and risk-taking, negative affect and urgency, and executive functioning. By contrast, variants in receptors that respond to the psychoactive components of individual substances or those in genes metabolizing individual drugs directly influence each SUD in a substance-specific manner. Furthermore, genetic variants that influence other psychiatric disorders may also independently influence SUDs. Reciprocally, the genetics underlying general addiction liability may impact risk of other psychiatric disorders. Small effects of substance-specific genetic variants on other psychiatric disorders are also predicted. In addition to these genetic pathways, prolonged substance use and SUDs may phenotypically influence risk-taking, negative affect, executive functioning, and psychiatric health and well-being (double headed dashed red arrows depict phenotypic associations). Of note, alcohol, nicotine, cannabis, cocaine and opioid use disorders are shown as there are current large genome-wide association studies of these SUDs; however, the genetics of many other SUDs could be similarly classified.

From Bogdan et al. *Nat Reviews Neurosci* (2023)

The Environment

What is inherited is the manner of reaction to a given environment

- Dr. Elmer G. Heyne (1912 – 1997), Wheat Geneticist

Possible Roles for the Environment

- Direct effects on initiation and maintenance of SUDs
  - For example, heritability of smoking is almost zero at age 13, but increases with age
  - As twins age, genetic factors emerge
- Gene-environment correlation
  - Genetic factors associated with SUDs and with environments that promote them are correlated
  - For example, antisocial behavior
- Gene-environment interaction
  - Genetic risk only evident when placed in a fertile environment

Gene–Environment Interaction

- Factors that reduce genetic risk of SUD:
  - Religiosity
  - Rural settings, neighborhoods with less migration
  - High parental monitoring
  - Legislative restrictions
  - Social restrictions (e.g., increased heritability of tobacco use disorders in women over the past half century)

Specific Molecular Genetic Risks

- Broad heritabilities not useful clinically
- Are there specific genes that place one at risk?
- Results from either:
  - Candidate gene studies: studies that examine specific genes thought to be associated
  - Genome-Wide Association Studies (GWAS): studies that look at markers across the entire genome
  - There has been one very large GWAS of alcohol and smoking (N = 3.4 Million) published in *Nature* in December 2022
  - There was a large GWAS of opiate use disorder (N = ~639K) published in *Molecular Psychiatry* in July 2022
  - There was a multivariate GW meta-analysis on over 1 Million participants published in 2023 showing heritability of the general addiction factor with strongest association in *PDE4B* which mediates neurotransmitters

Molecular Genetic Findings: Cannabis

- To date:
  - *FOXP2* – a gene regulator associated with cannabis use and speech/language delay
  - *Chromosome 8 locus* – near *CHRNA2* and *EPHX2*
  - Others include *ANKFN1, INTS7, PI4K2B, CSMD1, CST7, ACSS1,* and *SCN9A*
  - Certainly nothing that could be considered a biomarker
  - May be different for cannabis use vs. cannabis use disorder

Molecular Genetic Findings: Nicotine

- Single-nucleotide polymorphisms (SNPs) most likely to be involved have been associated with:
  - *CHRNA5, CHRNA3, CHRNB4* – all subunits of nicotine receptor
  - *CACNA1B* – which has been associated with psychiatric disorders
  - However, these may also be associated with risk for alcohol, cocaine, and opiate use/misuse.
  - Effect sizes are small (Odds Ratios ~1.2 - 1.4)
  - Additional variants include *NRTN* (dopamine neurons), *PAK6* (GABA interneurons),

Molecular Genetic Findings: Alcohol

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- Less convincing GWAS data. To date:
  - *GABRA2*- a GABAa receptor subunit gene
  - *PECR* – involved in fatty acid metabolism
  - question of *ALDH2, ADH1A, ADH1B, ADH1C* – alcohol dehydrogenase genes and *CDH13* – a cadherin
  - *ECE2* – involved in cortical development and neuropeptides

  - Certainly nothing that could be considered a biomarker
  - Heritability 60%, SNP heritability 33% (Mbarek et al 2015)

Molecular Findings Alcohol and Smoking

Table 1 | Non-synonymous sentinel variants

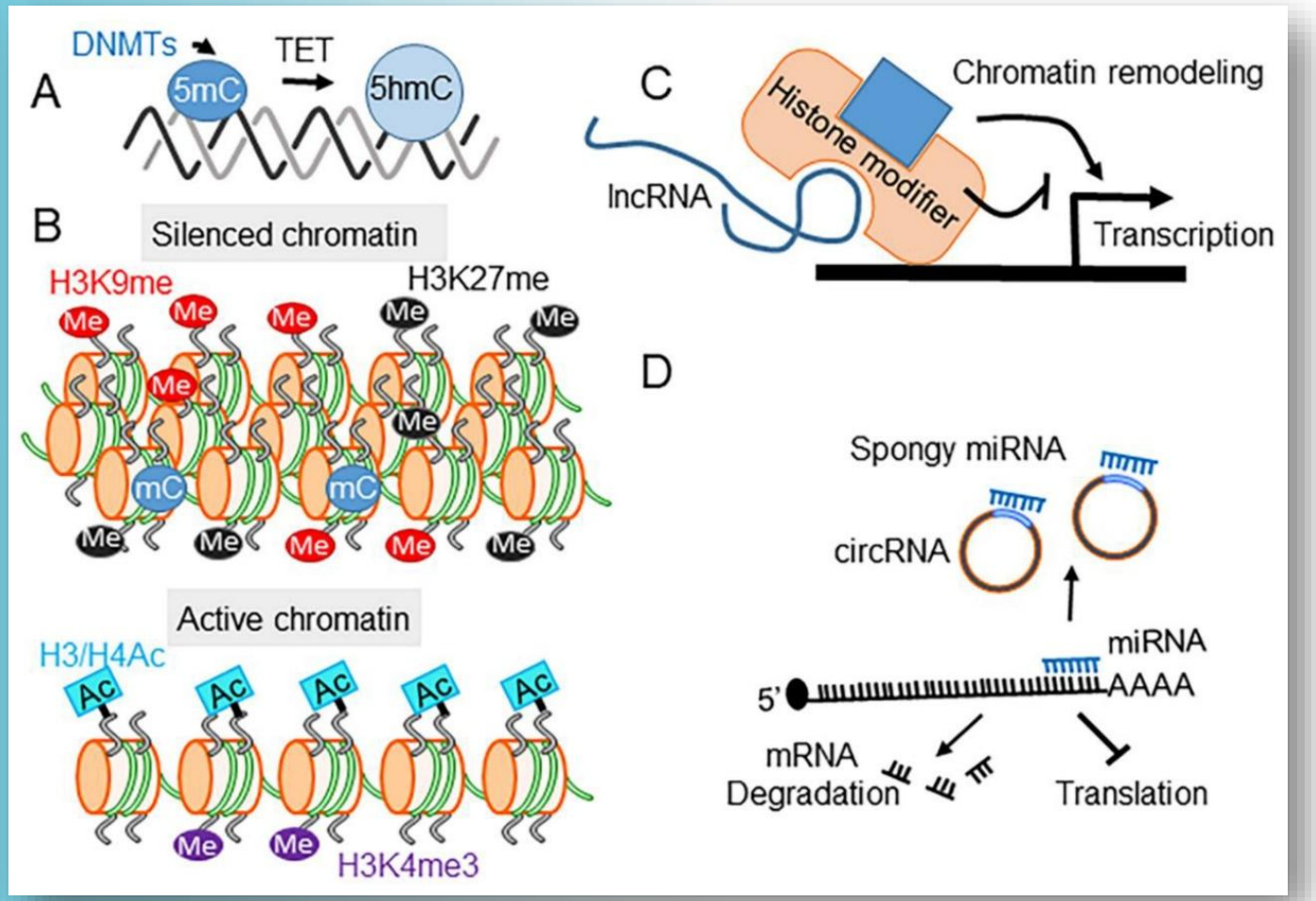
Phenotype	Gene	rsID	Chr	Position	REF	ALT	AF	Beta	P	N	Q
CigDay (SmkCes)	*CHRNA5*	rs16969968[a]	15	78,882,925	G	A	0.34	0.075	1.2×10^{-278}	330,721	0.34
CigDay	*HIST1H2BE*	rs7766641	6	26,184,102	G	A	0.27	−0.014	2.9×10^{-10}	335,553	0.78
CigDay (AgeSmk)	*GRK4*	rs1024323	4	3,006,043	C	T	0.38	−0.012	8.7×10^{-9}	337,334	0.17
SmkInit	*REV3L*	rs462779[a]	6	111,695,887	G	A	0.81	−0.019	4.5×10^{-29}	1,232,091	0.67
SmkInit (DrnkWk)	*BDNF*	rs6265	11	27,679,916	C	T	0.20	−0.016	2.8×10^{-19}	1,232,091	0.13
SmkInit	*RHOT2*	rs1139897	16	720,986	G	A	0.23	−0.012	1.8×10^{-15}	1,232,091	0.61
SmkInit (DrnkWk)	*ZNF789*	rs6962772[a]	7	99,081,730	A	G	0.15	−0.015	2.1×10^{-14}	1,232,091	0.92
SmkInit	*BRWD1*	rs4818005[a]	21	40,574,305	A	G	0.58	−0.010	3.9×10^{-14}	1,232,091	0.75
SmkInit	*ENTPD6*	rs6050446	20	25,195,509	A	G	0.97	0.035	8.8×10^{-13}	1,225,969	0.33
SmkInit	*RPS6KA4*	rs17857342[a]	11	64,138,905	T	G	0.38	−0.010	9.8×10^{-12}	1,232,091	0.16
SmkInit	*FAM163A*	rs147052174	1	179,783,167	G	T	0.02	0.037	2.3×10^{-10}	1,232,091	0.59
SmkInit	*PRRC2B*	rs34553878	9	134,907,263	A	G	0.11	0.016	1.2×10^{-9}	1,232,091	0.28
SmkInit	*ADAM15*	rs45444697[a]	1	155033918	C	T	0.21	0.010	5.3×10^{-9}	1,232,091	0.46
SmkInit	*MMS22L*	rs9481410[a]	6	97,677,118	G	A	0.76	0.010	1.1×10^{-8}	1,232,091	0.04
SmkInit	*QSER1*	rs62618693	11	32,956,492	C	T	0.04	−0.020	2.1×10^{-8}	1,232,091	1.00
DrnkWk	*ADH1B*	rs1229984	4	100,239,319	T	C	0.96	0.060	2.2×10^{-308}	941,280	0.05
DrnkWk	*GCKR*	rs1260326	2	27,730,940	T	C	0.60	0.008	8.1×10^{-45}	941,280	0.10
DrnkWk	*SLC39A8*	rs13107325	4	103,188,709	C	T	0.07	−0.009	1.5×10^{-22}	941,280	0.33
DrnkWk	*SERPINA1*	rs28929474	14	94,844,947	C	T	0.02	−0.012	1.3×10^{-11}	941,280	0.50
DrnkWk (SmkInit)	*ACTR1B*	rs11692465	2	98,275,354	G	A	0.09	0.008	2.5×10^{-11}	937,516	0.40
DrnkWk	*TNFSF12-13*	rs3803800	17	7,462,969	A	G	0.79	0.004	1.5×10^{-10}	941,280	0.67
DrnkWk	*HGFAC*	rs3748034	4	3,446,091	G	T	0.14	−0.005	1.7×10^{-8}	941,280	0.65

The sentinel variant in approximately 4% of loci was non-synonymous. Shown here are all non-synonymous sentinel variants, and all non-synonymous variants in near-perfect LD with a sentinel variant. If the listed gene was also associated (through single variant or gene-based test) with another phenotype, that phenotype is listed in parentheses. Several genes have been implicated in previous studies of substance use/addiction, including *CHRNA5*, *BDNF*, *GCKR*, and *ADH1B*. Phenotype abbreviations are defined in Fig. 1. Chr, chromosome; REF, reference allele; ALT, alternate allele; AF, allele frequency of ALT; Q, Cochrane's Q statistic P value. [a]These variants were not themselves sentinel, but were in near-perfect LD with a sentinel variant ($r^2 > 0.99$, from the 1000 Genomes European population). The scale of Beta is on the unit of the standard deviation of the phenotype. For binary phenotypes the standard deviation was calculated from the weighted average prevalence across all studies included in the meta-analysis (available in Supplementary Table 7).

Epigenetics

A. DNA methylation
B. Histone modification
C. Non-coding RNAs
D. Micro RNAs

Chronic use of substances may have effects on all of these processes within the opioid receptor system



Reid KZ, Lemezis BM, Hou TC, Chen R. *Int J Mol Sci.* 2022

Summary

- Substance use disorders are brain disorders and involve brain regions associated with reward, motivation, inhibitory control, and memory
- Different classes of drugs affect different receptors in these regions
- Receptor systems change over time with exposure to drugs and with removal of that exposure
- Substance use disorders are heritable, but probably due to multiple genes with additive effects
- Personality, life history, family history continue to be more reliable and cost-effective screens

Thank you!

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Email me at: robert.althoff@uvmhealth.edu

Visit our website: http://www.med.uvm.edu/vccyf

Image Credit: U.S. Department of Energy Human Genome Program