

Phenogenetics of dysregulation

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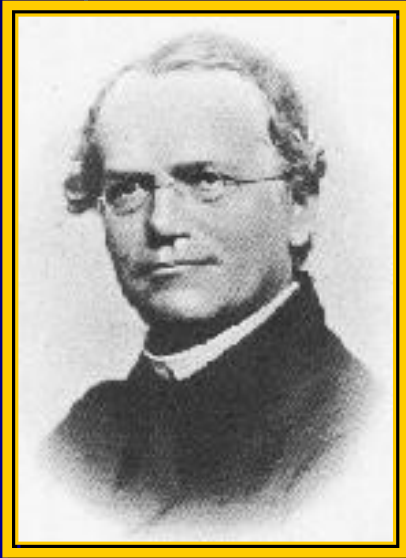
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Traits and genes



Genetics \Leftarrow good traits

- polymorphic
- monogenic
- discrete

Phenotyping SUD



Arbitrary phenotypes—ICD-m, DSM-n

Dx of substance dependence:
≥3 out of nine symptoms
→ **466 combinations**

$$\sum \frac{n!}{k_i!(n-k_i)!}$$

Staging—opportunistic; no specific “gateway”

Mixed effects: stimulants & depressants

What trait?

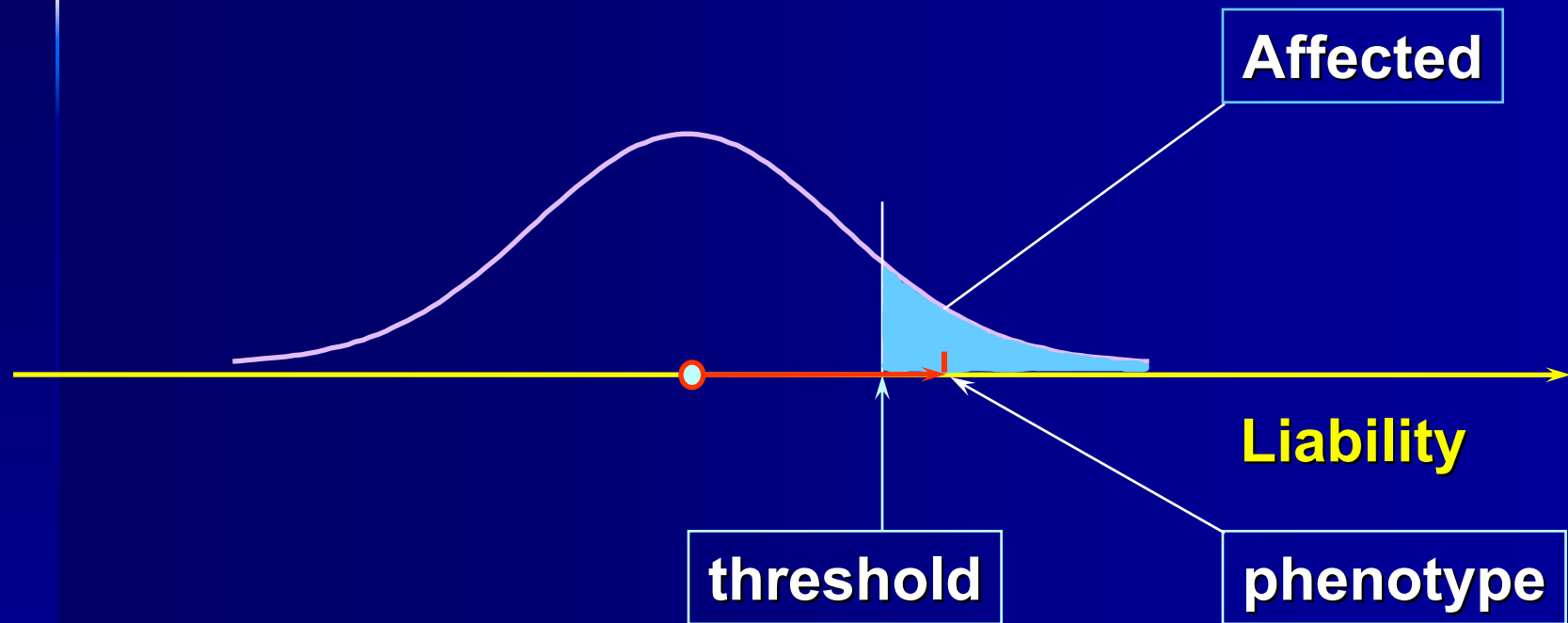


Liability, the concept

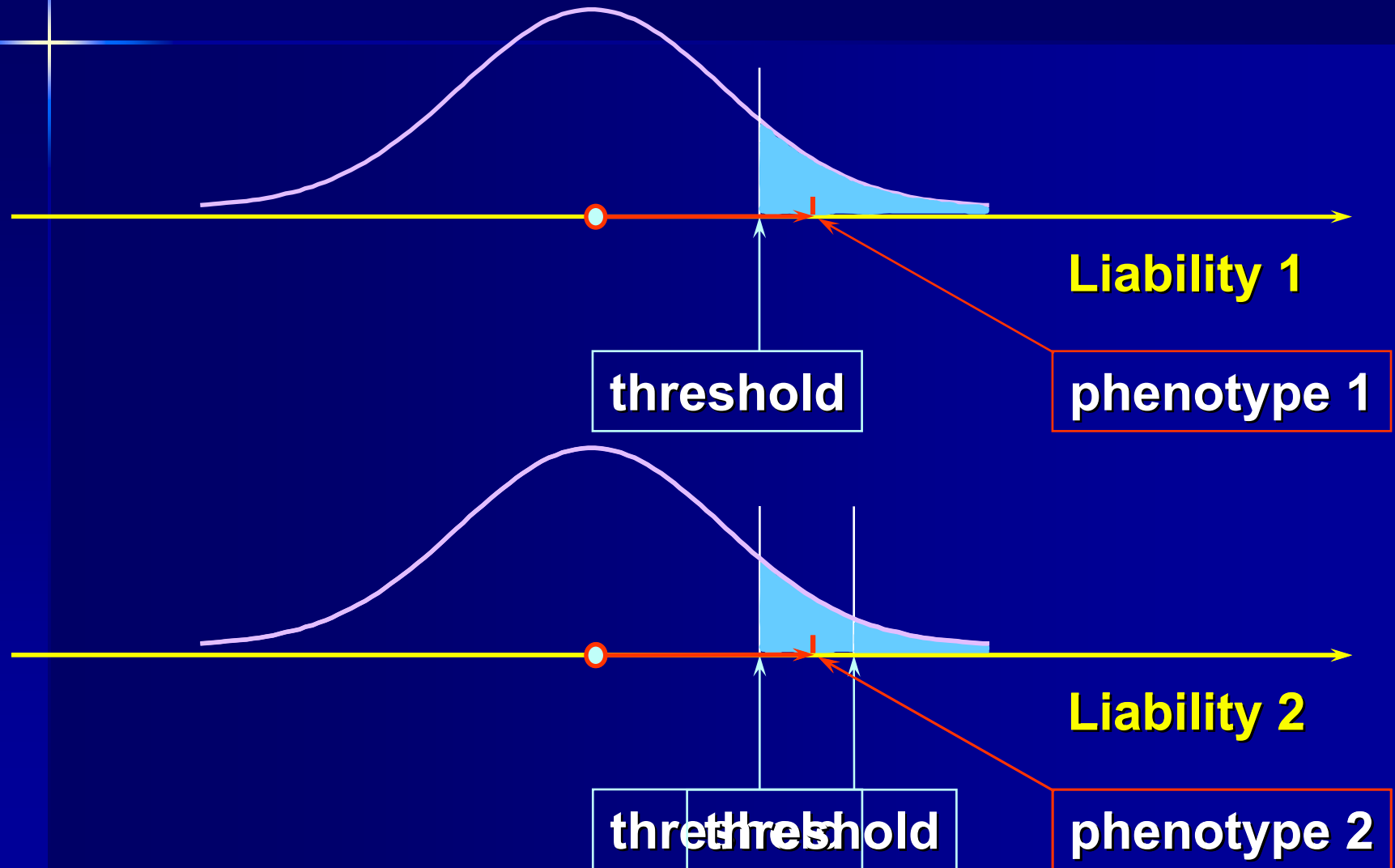
*“...to express not only the individual **innate tendency** to develop or contract the disease, i.e., his susceptibility in the usual sense, but also the **whole combination of external circumstances** that make him more or less likely to develop the disease...”*

Falconer (1965)

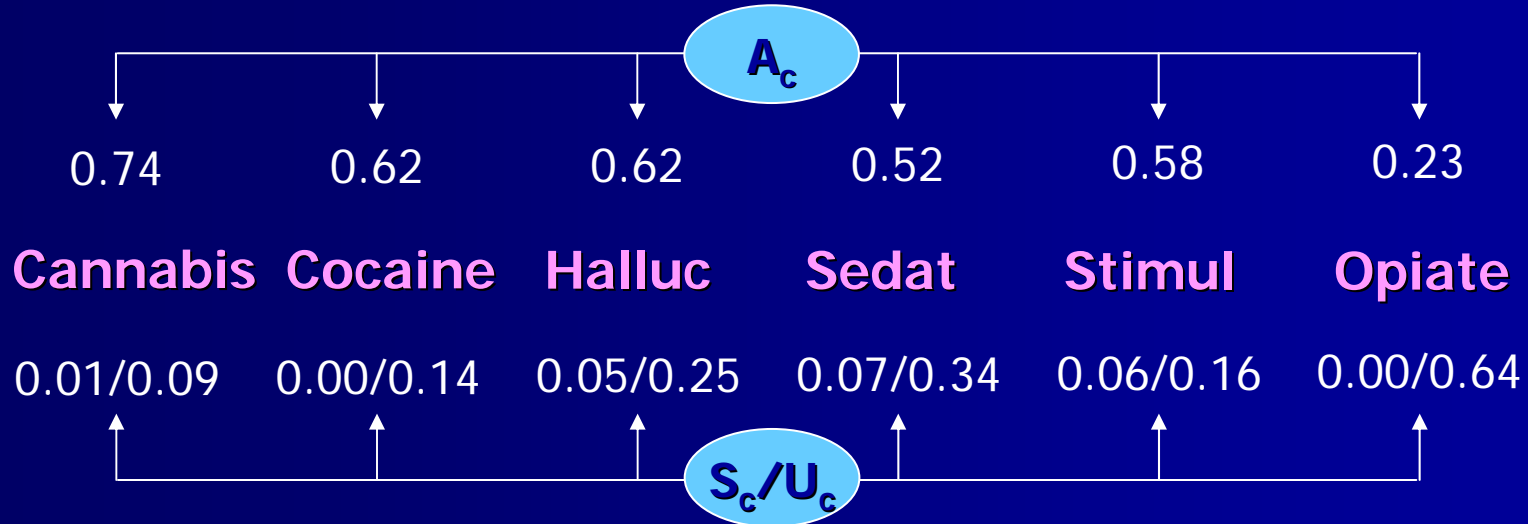
Liability distribution



Comorbidity & onset

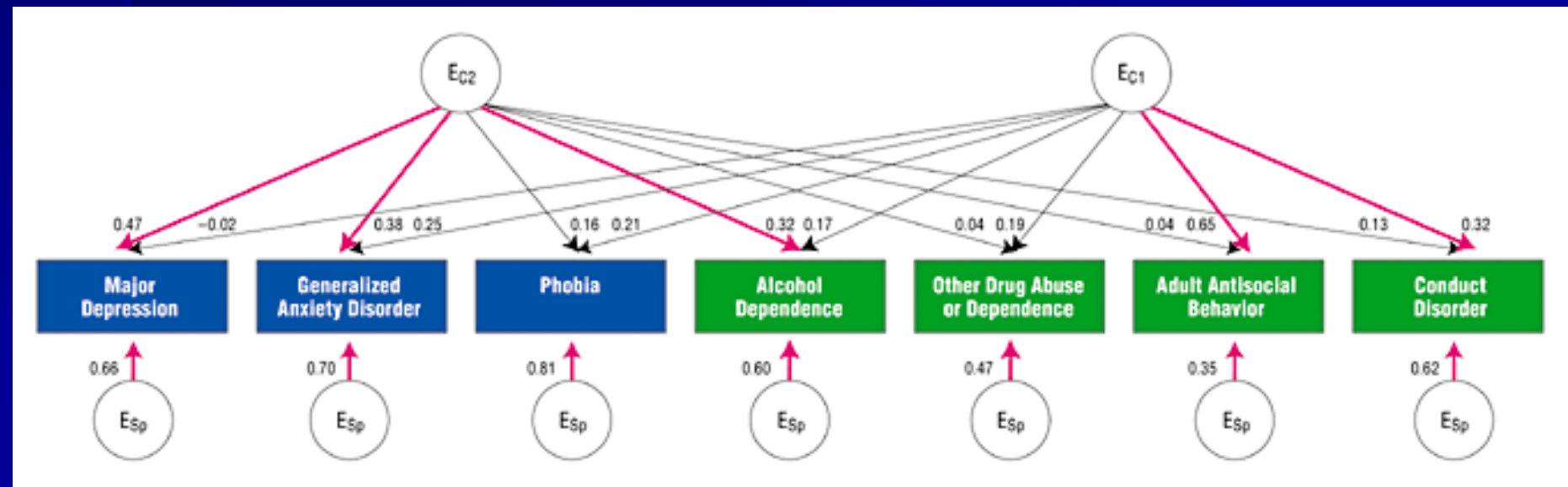
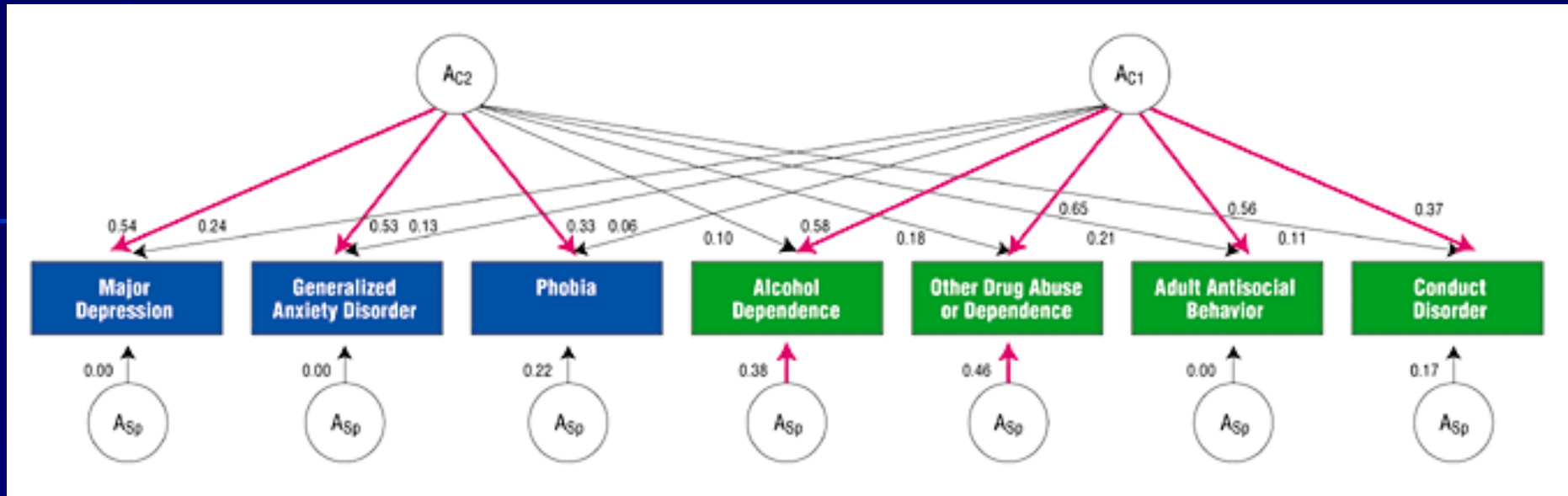


Shared causes of variation



Kendler et al., Am J Psychiatry 160: 687–695, 2003

Overlaps in liabilities to SUD and psychiatric disorders



Common sources of variation

Pre-use

- Temperament
- Personality
- Cognition
- Behavior
- Self-medication

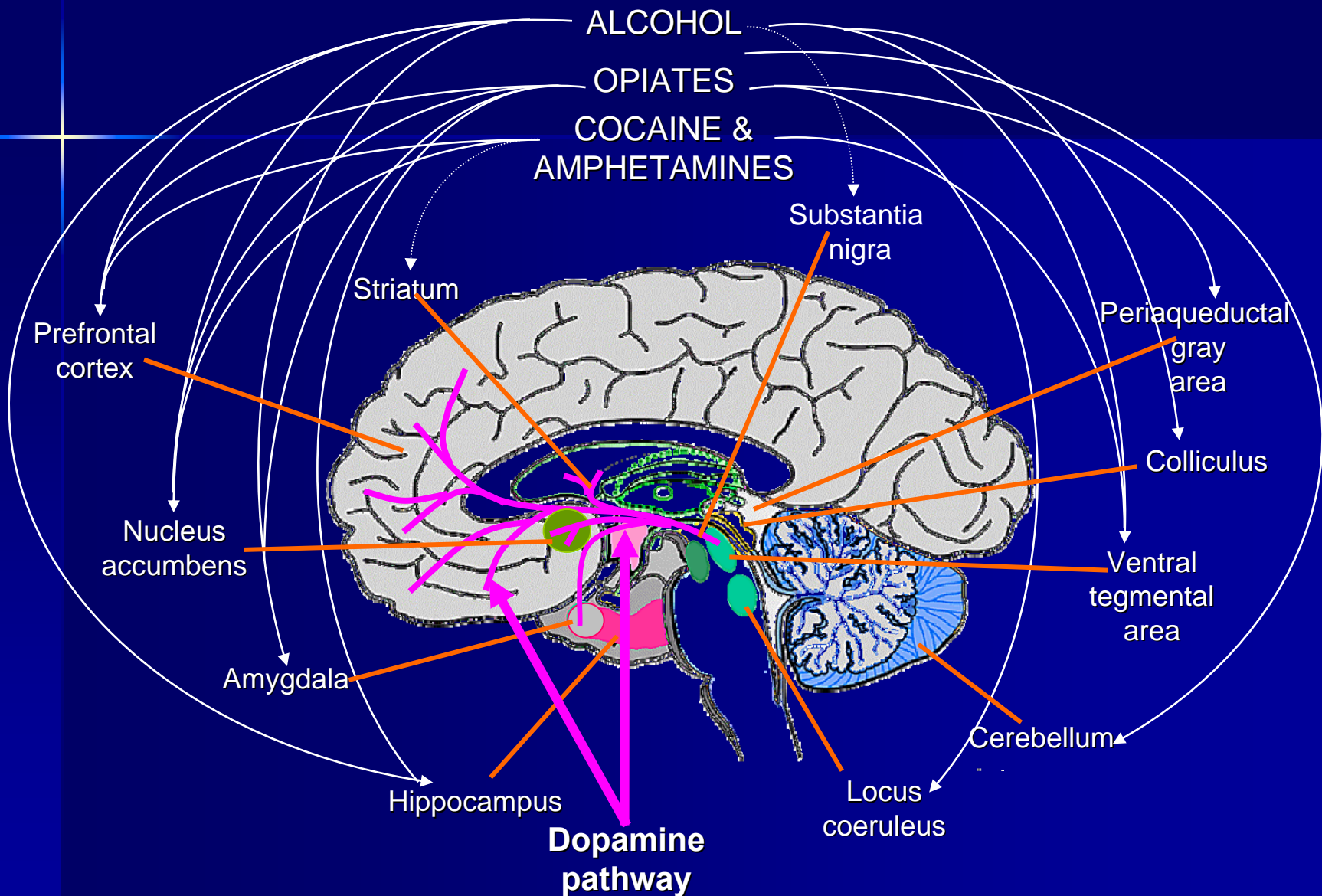
Post-use

- Positive reinforcement
- Negative reinforcement



Biobehavioral self-regulation

A substrate: the drug-activated mesocorticolimbic dopamine pathway



Genetics in SUD risk

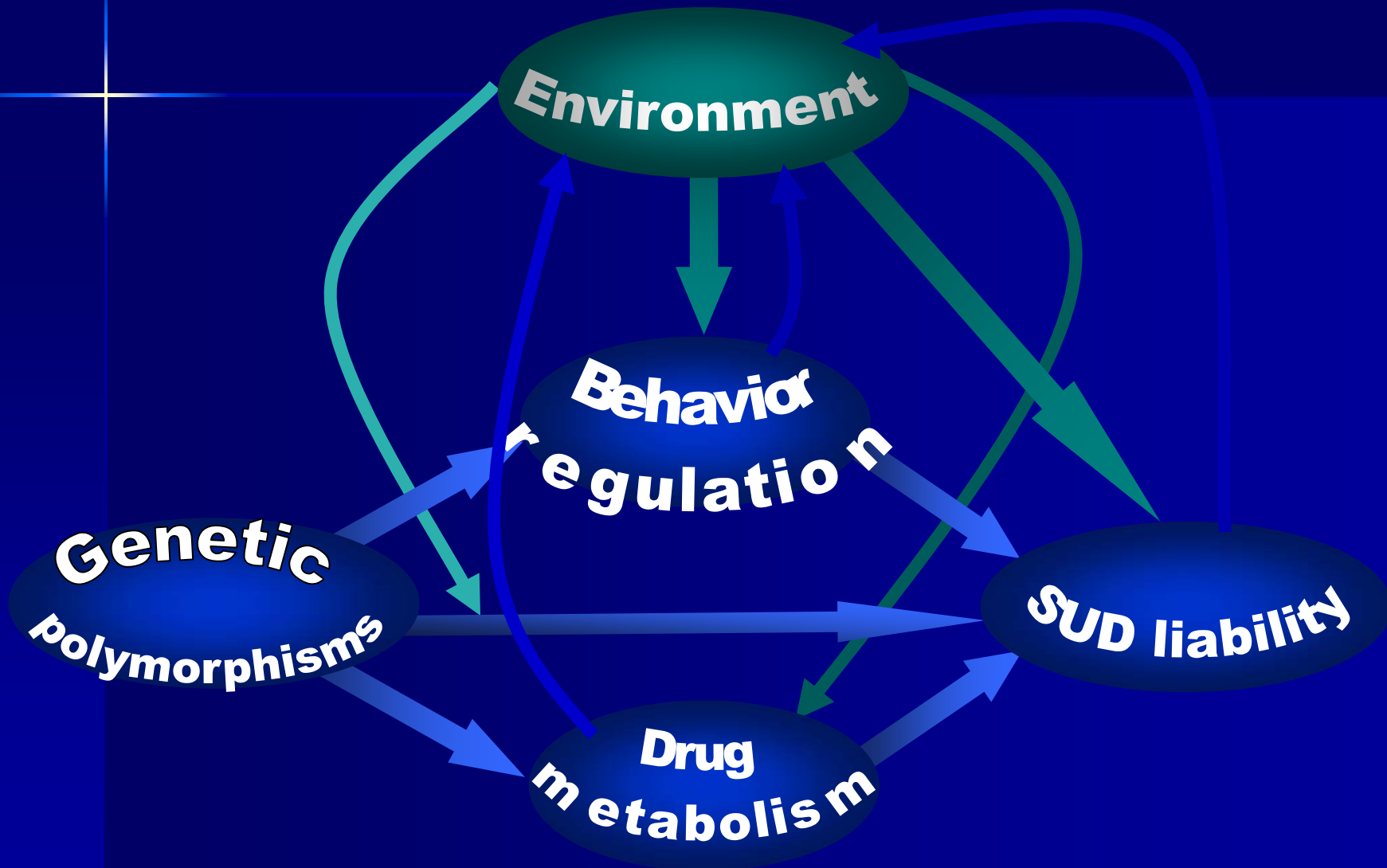
Genes

in determination
in variation

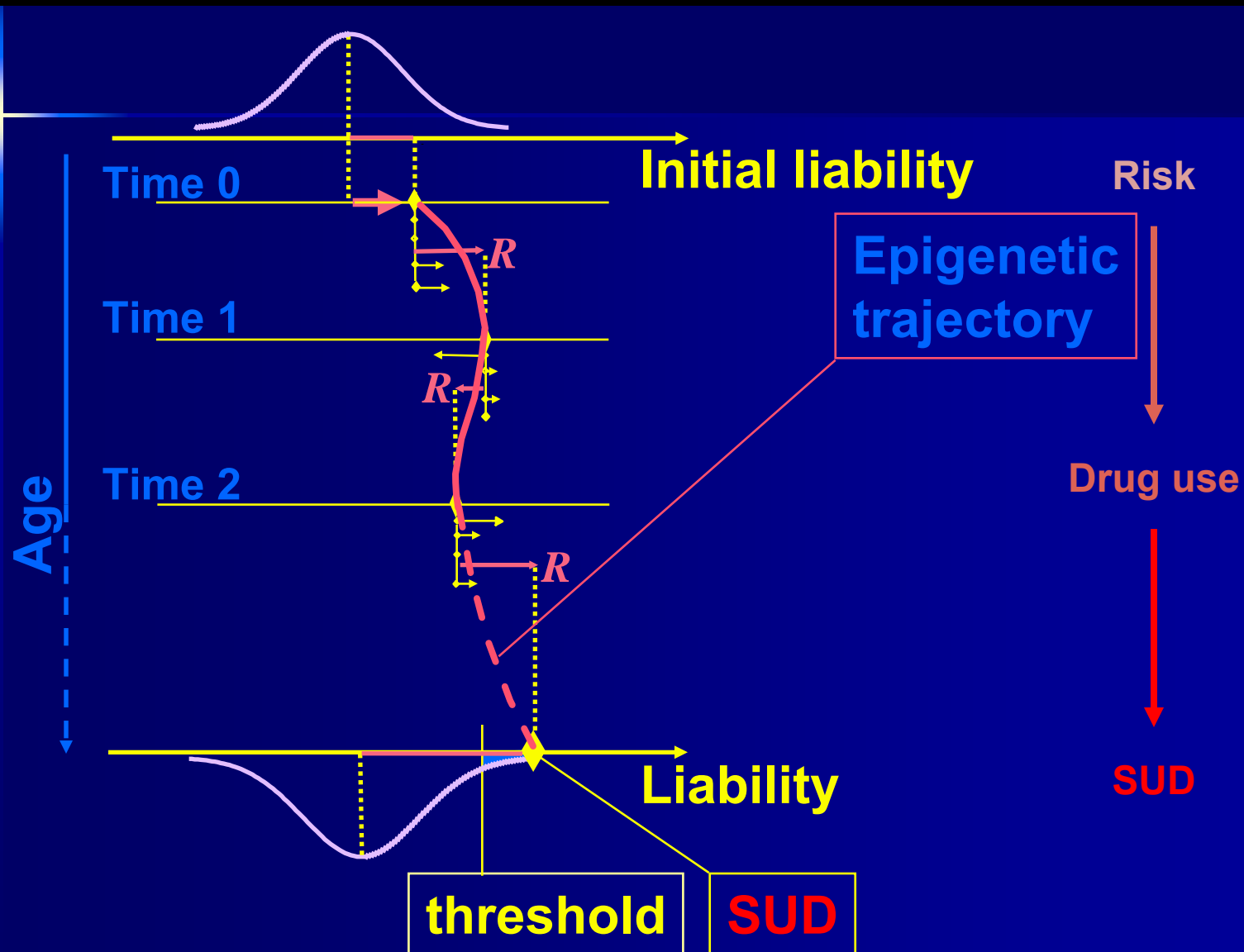
SUD liability



Sources of SUD risk variation



Dynamic liability: Tracking etiology and comorbidity of SUD

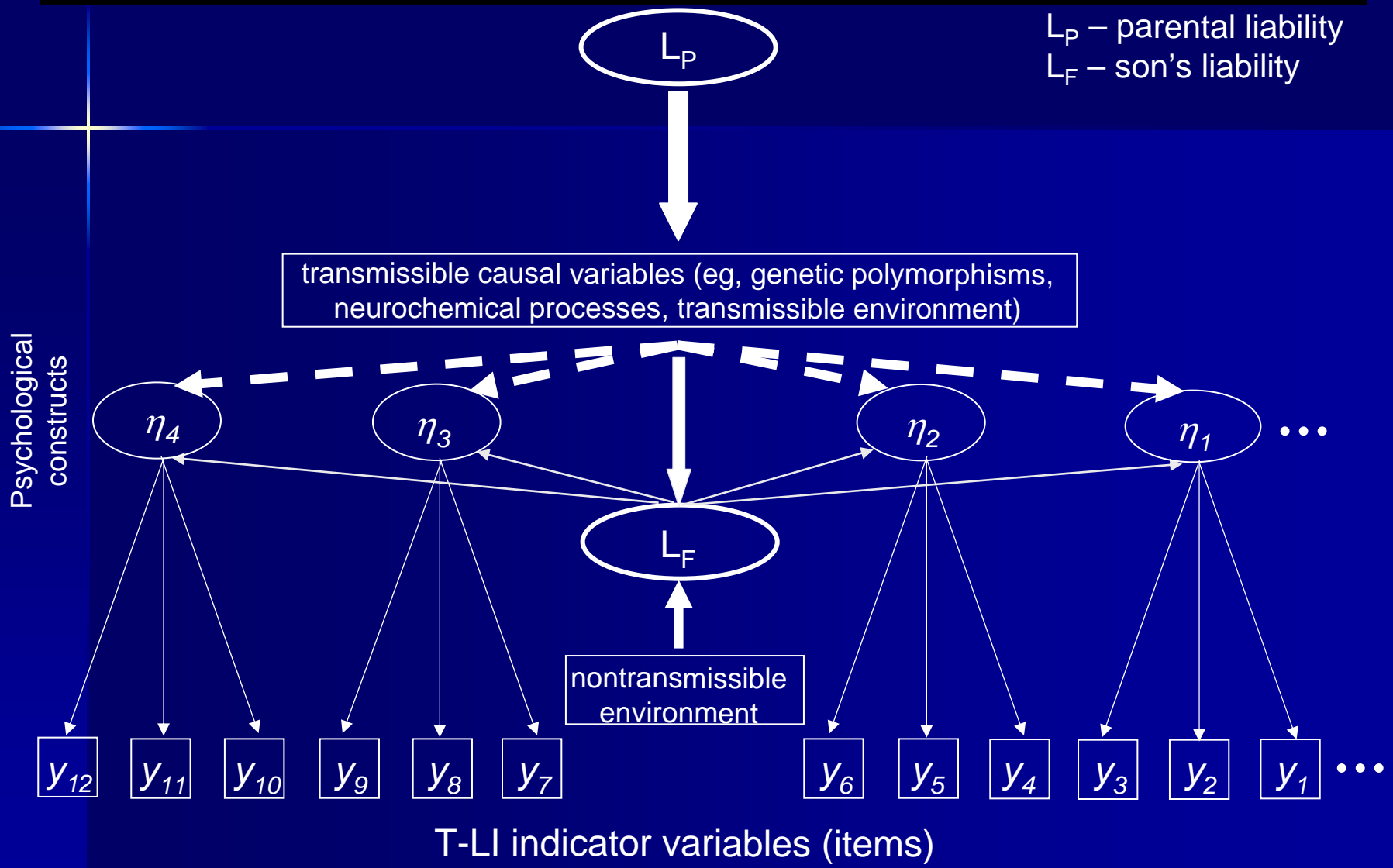


Family history: CEDAR

- Faster physiological maturation
- Detachment from parents
- Homophilic peer selection/contagion
- Dysregulation/disinhibition
- Maladjustment
- SU/SUD

Measurement of SUD liability

L_P – parental liability
 L_F – son's liability



Clinical indicators: DBD and the rate of SUD

<u>Diagnosis</u>	<u>HR</u>	<u>95% CI</u>	<u>P</u>
ADHD	2.81	1.42-5.55	0.003
CD	7.17	2.78-18.52	0.00005
ODD	2.20	1.04-4.63	0.038

dysregulation

Neuropsychological tests: Intermediate traits (“endophenotypes”)

Stroop Color Word Task (attentional control directed to a response requirement (e.g. color naming) while suppressing a more dominant response (word rendering)).

Vigilance task - measures of attention and impulsiveness.

Porteus Maze - planning ability and impulse control.

Actigraph - total motor activity

DRD4 (-521 C→T) FBAT

267 CEDAR triads (206 W, 61 B), age 10-12 (11.3)

	FBAT Z-stat	P-value
Stroop	3.775	.0002
Porteus Maze	3.105	.002
Activity Monitor	2.257	.02
Vig. Hit Rate	3.999	.00006
Vig. False Alarm Rate	1.951	.051

Continuous index: DRD4-ERP-Disinhibition

- Disinhibition \ni (affect, behavior, cognition)
- Highly heritable
- Highly predictive of SUD

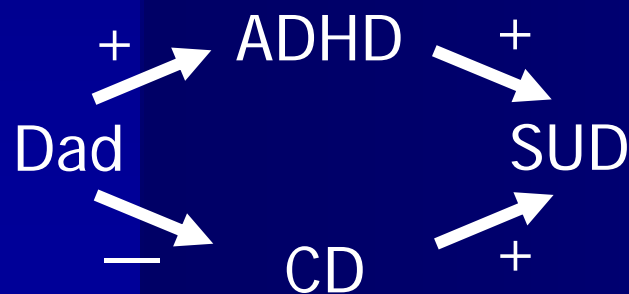
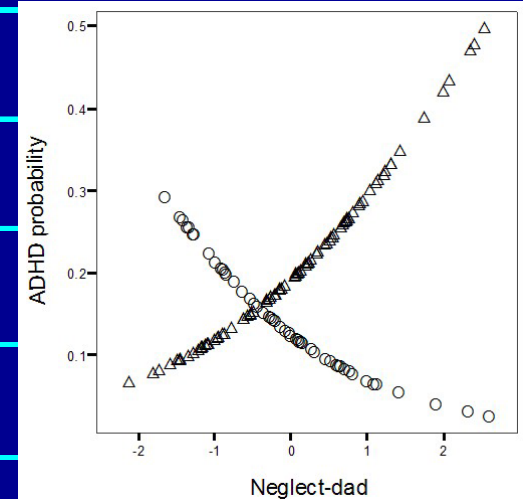
DRD4 \longrightarrow **ERP** \longrightarrow **Disinhibition**

mediation

Family-based analysis (FBAT)
Promoter region (-521) DRD4 SNP
ERP \rightarrow ND: $p = .02$
SNP \rightarrow P300: $p = .004$
SNP \rightarrow ND: $p = .003$
SNP \rightarrow ND|P300: $p = .85$

Parenting & MAOA: genes × environment

Dependent	Sample	Predictor	Hazard ratio (95% CI)	P
CD	full	dad	0.504 (0.289-0.879)	.016
		mom×dad	0.652 (0.456-0.932)	.019
	4R	dad	0.380 (0.179-0.805)	.011
		mom	1.601 (0.989-2.591)	.055
	3R	dad	0.796 (0.343-1.850)	.597
		mom	1.099 (0.534-2.265)	.797
ADHD	full	mom×dad	1.558 (1.031-2.353)	.035
		dad×MAO	3.299 (1.479-7.356)	.004
	4R	dad	1.974 (1.230-3.168)	.005
		mom×dad	1.799 (1.057-3.062)	.030
	3R	dad	0.574 (0.256-1.284)	.177
		mom×dad	1.604 (0.719-3.578)	.249
SUD	full	MAO	0.382 (0.155-0.940)	.036



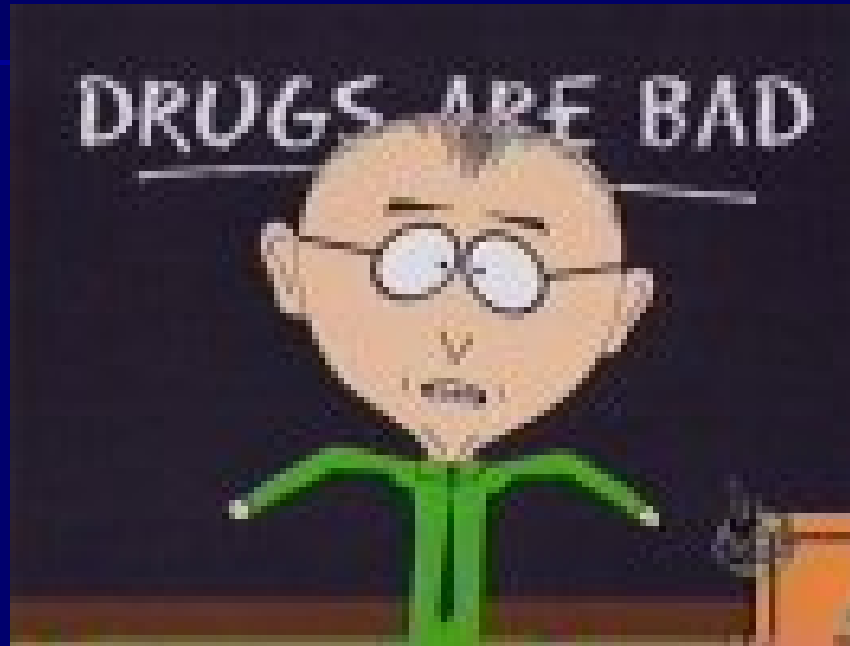
Vanyukov et al. (in press) Psychiatric Genetics

MAOA & SUD

Low MAOA activity 

- increase in the risk
- limbic volume reductions, hyperresponsive amygdala during emotional arousal, diminished reactivity of regulatory prefrontal regions (Meyer-Lindenberg et al., 2006)

Prevention applications



- Identification for targeted P.
 - Phenotypic
 - Genotypic
- Specific P.
- Genetic roots... environmental "Roundup"