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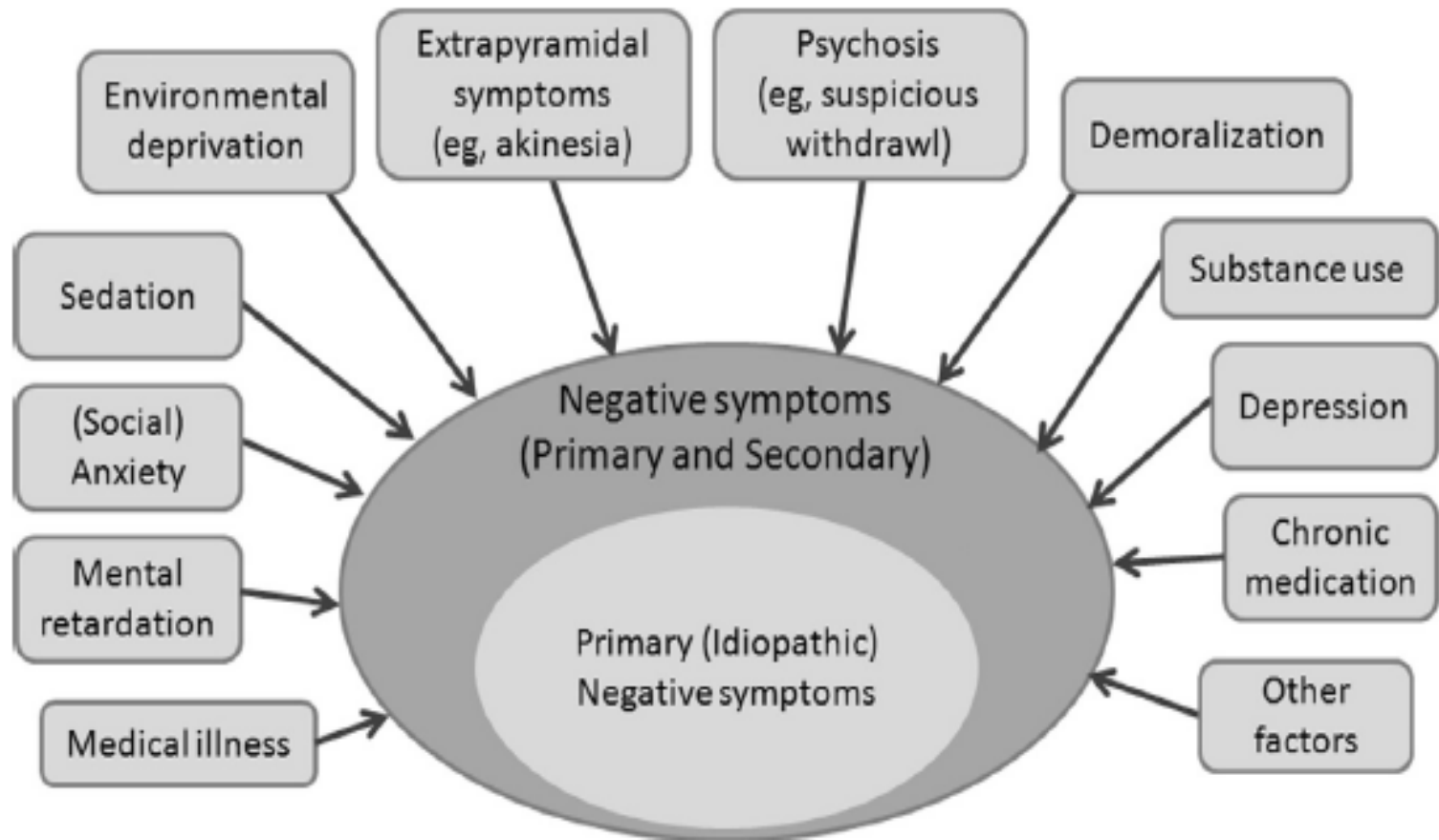
Supreme Court Justice Potter Stewart's Comment on Pornography

“I can't tell you what it is,
but I know it when I see it.”

Negative Symptoms as Pathological Features of SCZ

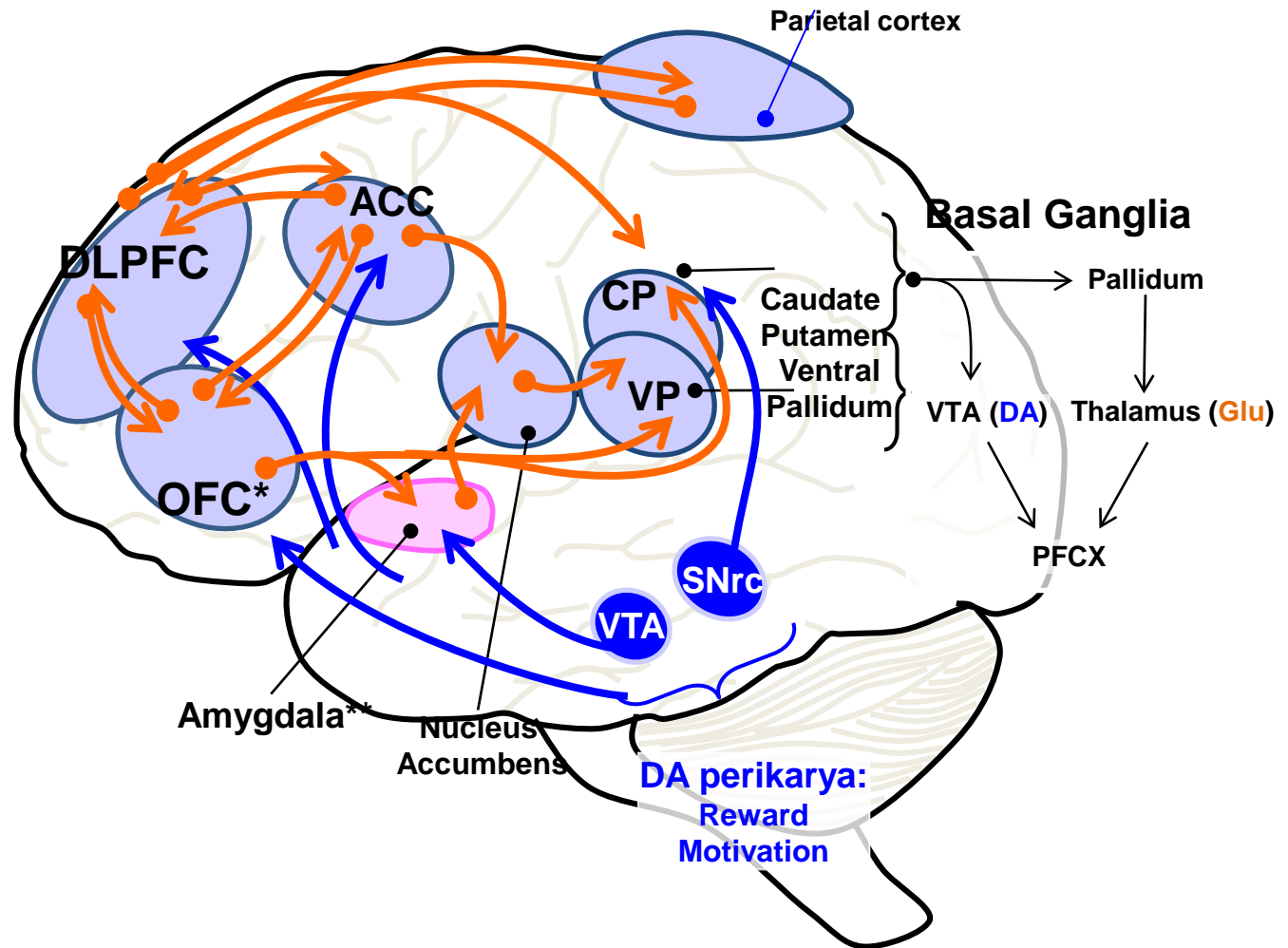
- Kraepelin: “we observe a weakening of those emotional activities which permanently form the mainsprings of volition... The result is emotional dullness, .. Loss of mastery over volition, of endeavor, and ability for independent action. The essence of the personality is thereby destroyed”
- Bleuler “patients appear lazy and negligent because they no longer have the urge to do anything either of their own initiative or at the bidding of another.... In mild cases, where wishes and desires still exist, they will nevertheless do nothing toward the realization of these wishes”

Primary and Secondary Negative Symptoms



Fervaha et al, European Psychiatry 2014

Where in the brain are negative symptoms based?



Neurobiological background of negative symptoms

Silvana Galderisi¹ · Eleonora Merlotti¹ · Armida Mucci¹

Methods of Assessment of Negative Symptoms

- Clinical Assessment Instruments
- Behavioral Biomarkers
- Neuroimaging

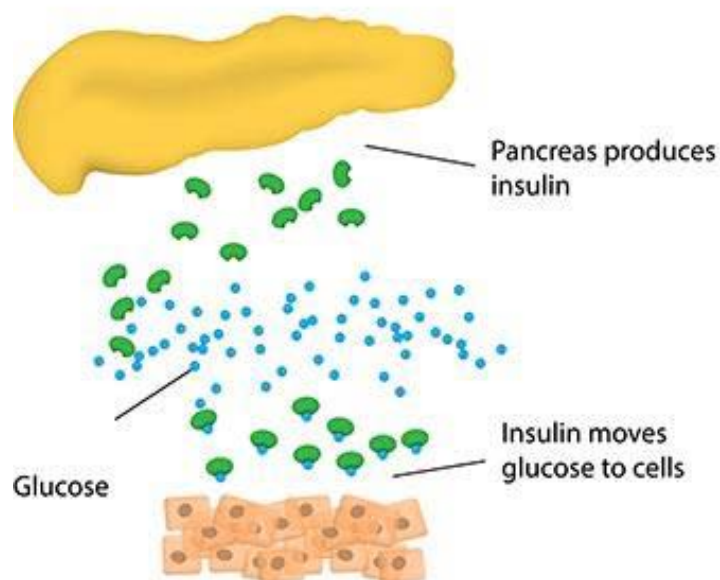
Pathways to Progress in Understanding and Treating Negative Sxs

- Core Readout or Biomarker
- Genetic Association
- Gene Product as Biomarker or Therapeutic Target
- Animal Models to Deconstruct Cognitive Components
or Neural Basis

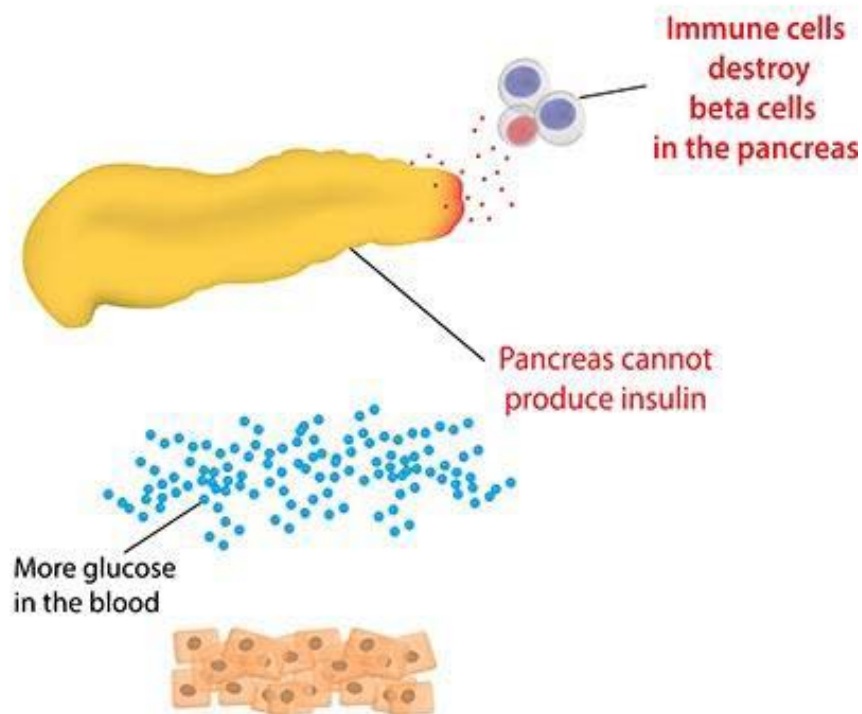
Schizophrenia: target “circuitry” and core readout?

Type 1 Diabetes

Healthy



Diabetic

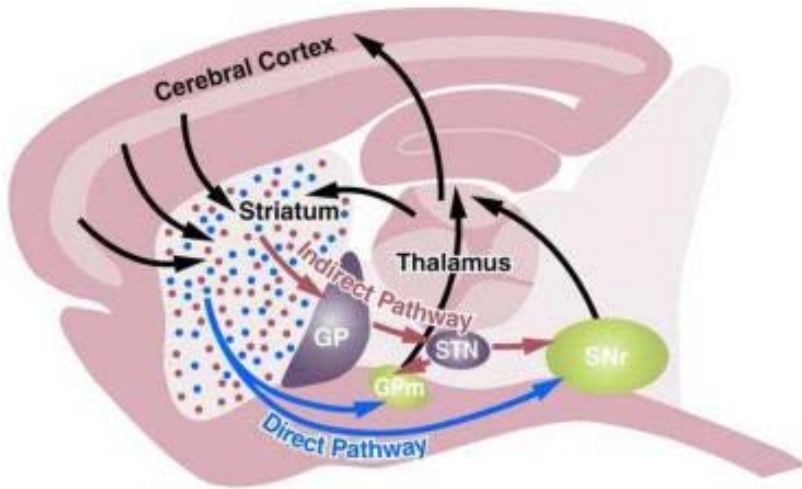


Targets of Interest for Cognitive Enhancement

MATRICS Neuropsychopharmacology Committee

n	Alpha-7 nicotinic receptor agonists	31
n	DA-D1 receptor agonists	30
n	AMPA glutamatergic receptor agonists	14
n	NMDA glutamatergic receptor agonists	12
n	Metabotropic glutamate receptor agonists	12
n	Glycine reuptake inhibitors	8
n	M1 muscarinic receptor agonists	7
n	GABA A R subtype selective agonists	5

DA receptors in nucleus accumbens regulate motivated behavior. Selective stimulation of D1Rs in direct pathway or increased D2Rs in indirect pathway of adult NAc enhances motivation and reward seeking behavior.



Kreitzer and Malenka, *Neuron* 2008.

• Different gene expression patterns:

Direct	Indirect
D1R, M4, dynorphin, substance P	D2R, A2AR, enkephalin

• Different functions:

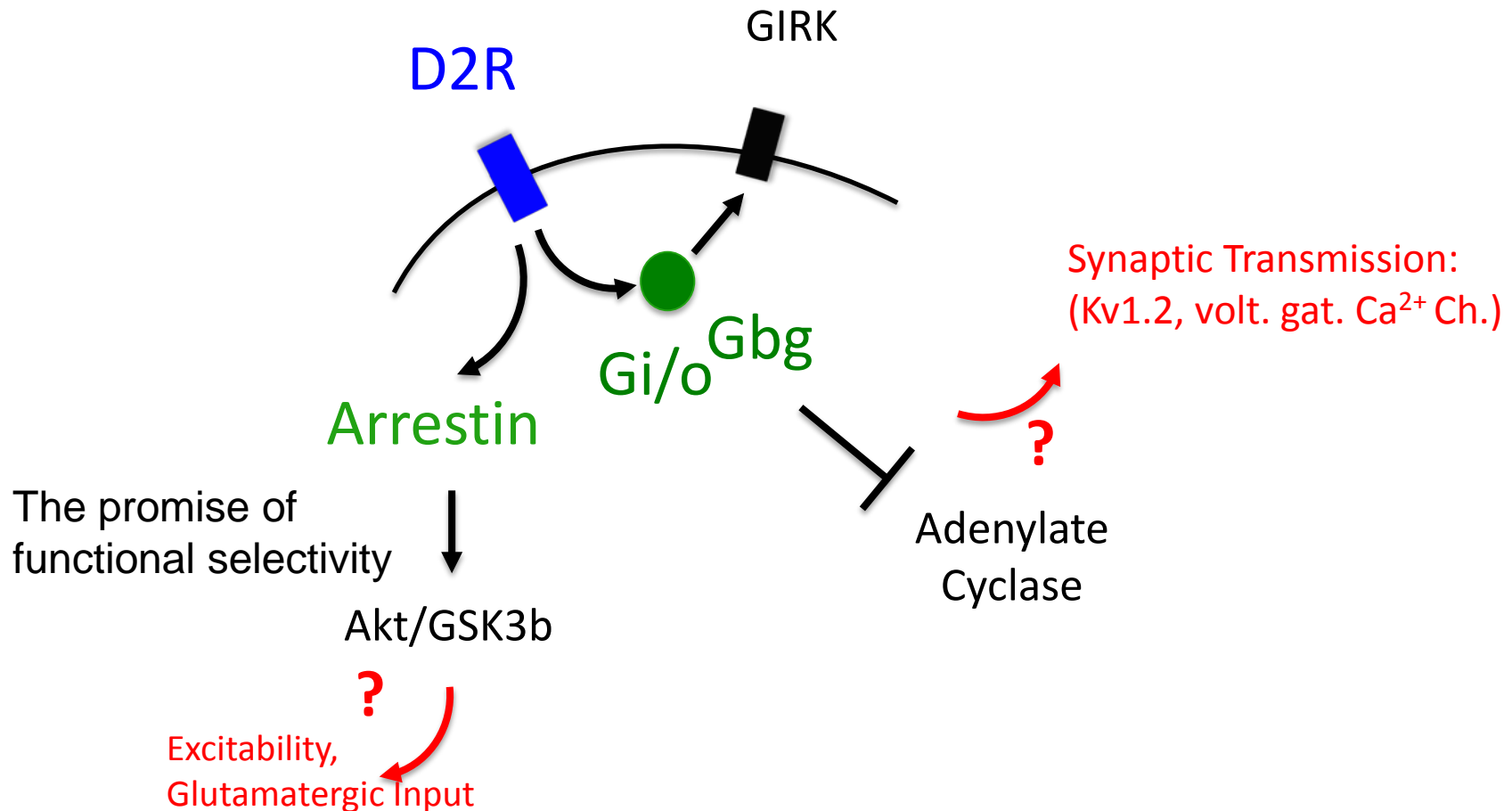
Direct	Indirect
GO!	No GO!

• Receptors differ in their signaling:

D1	D2
↑ PKA	↓ PKA
↑ Cav1 L-type Ca ²⁺ channels	↓ Cav1 L-type Ca ²⁺ channels
↓ K ⁺ channels	↓ Na ⁺ channels
↓ Cav2 Ca ²⁺ channels	↑ K ⁺ channels

Developing D1R agonists possibly through allosteric modulation

Targeting D2R in Medium Spiny Neurons function: a cell-selective approach
D2Rs Signal Via G-protein Dependent and Independent (Arrestin) Pathways



Factors Affecting Negative Sxs Response in Clinical Trials

- Inclusion Criteria
 - Sx Severity
 - Illness Duration
- Number of Study Arms and Sites
- Centralized Ratings
- Adjunctive vs Monotherapy
- Industry Sponsorship
- Commercial vs Academic Sites
- **Better Models of Pathophysiology, Targets, Therapeutics**

Discussion

First let's hear from the FDA