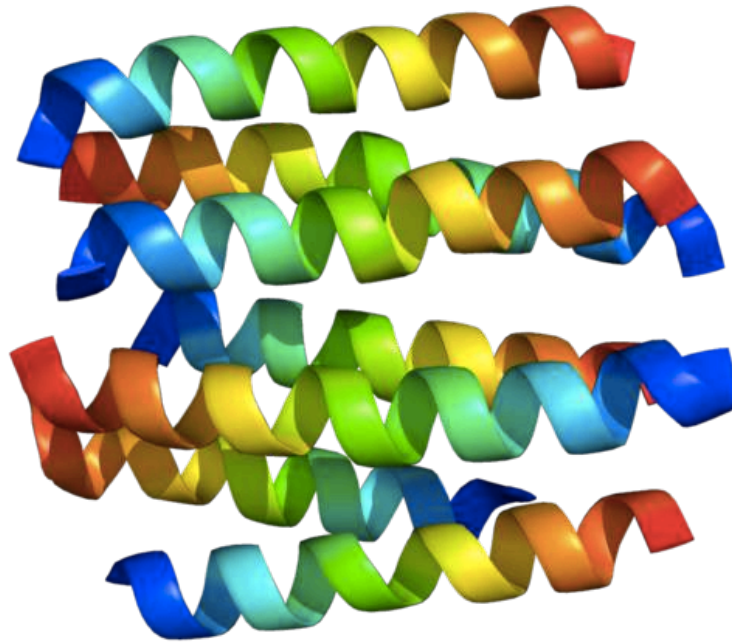


DRD2 and the Impulsivity Link

By: Shu Hui Lye



How is impulsivity defined?



https://boardgametime.files.wordpress.com/2012/04/table_flip.jpg

‘Rapid, unplanned reactions towards internal and external stimuli’

Impulsivity is a symptom in various psychiatric disorders



Addiction

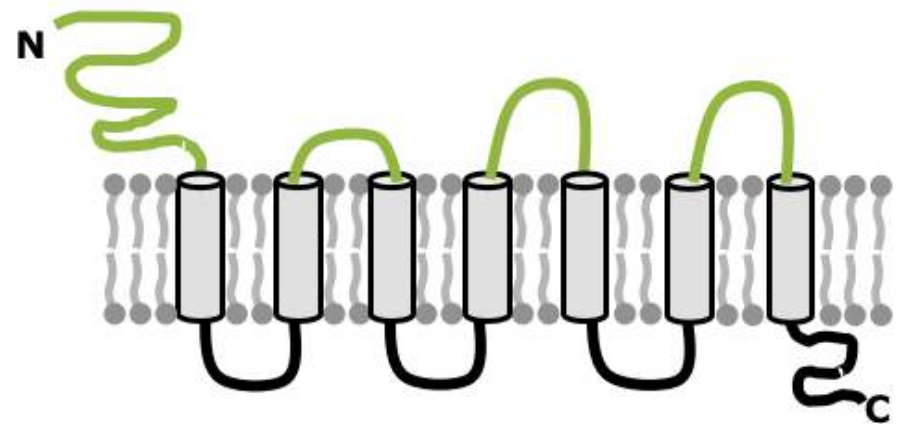
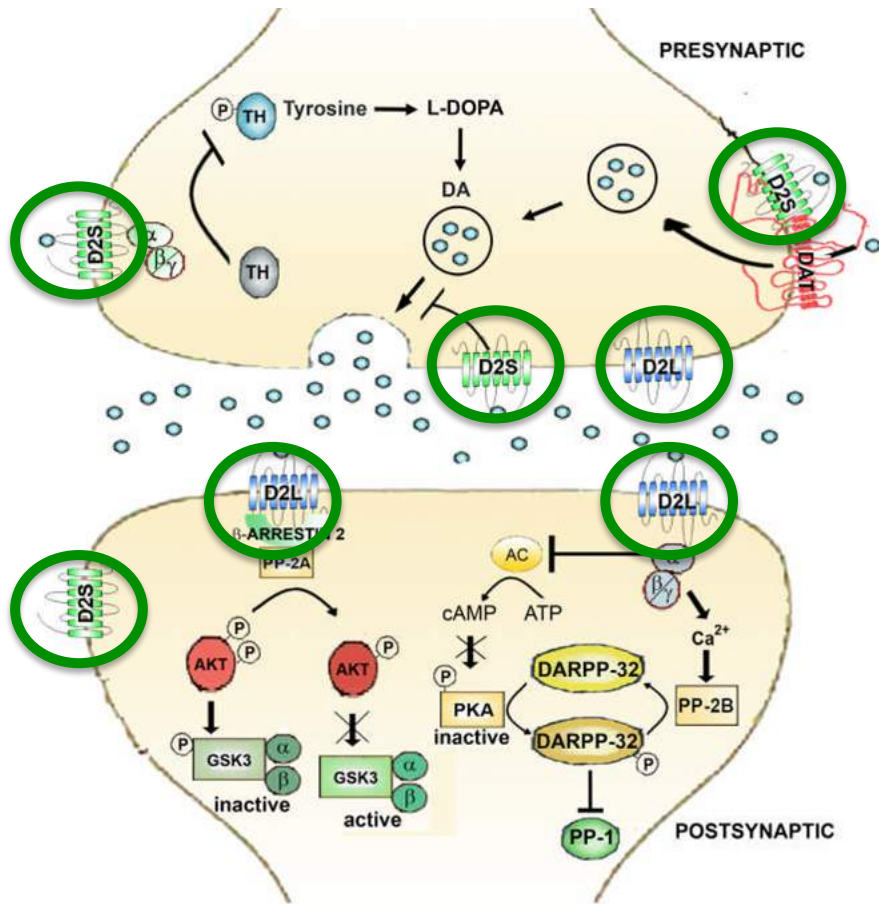


ADHD

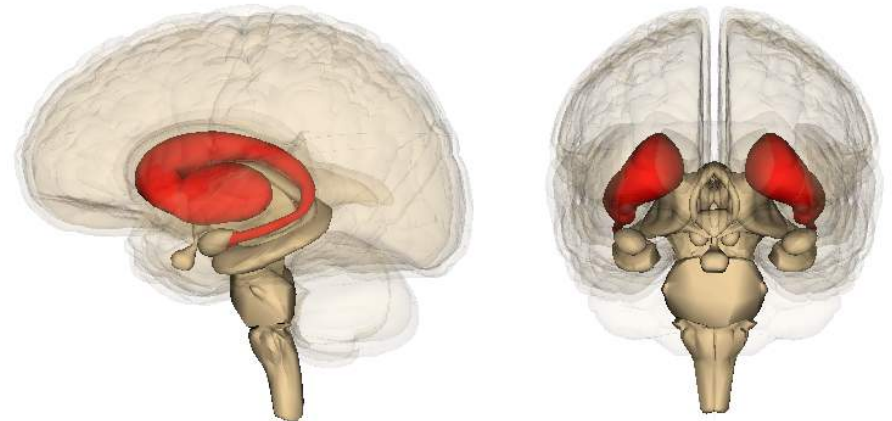


Schizophrenia

DRD2 codes for a dopamine receptor



DRD2 belongs to the GPCR superfamily

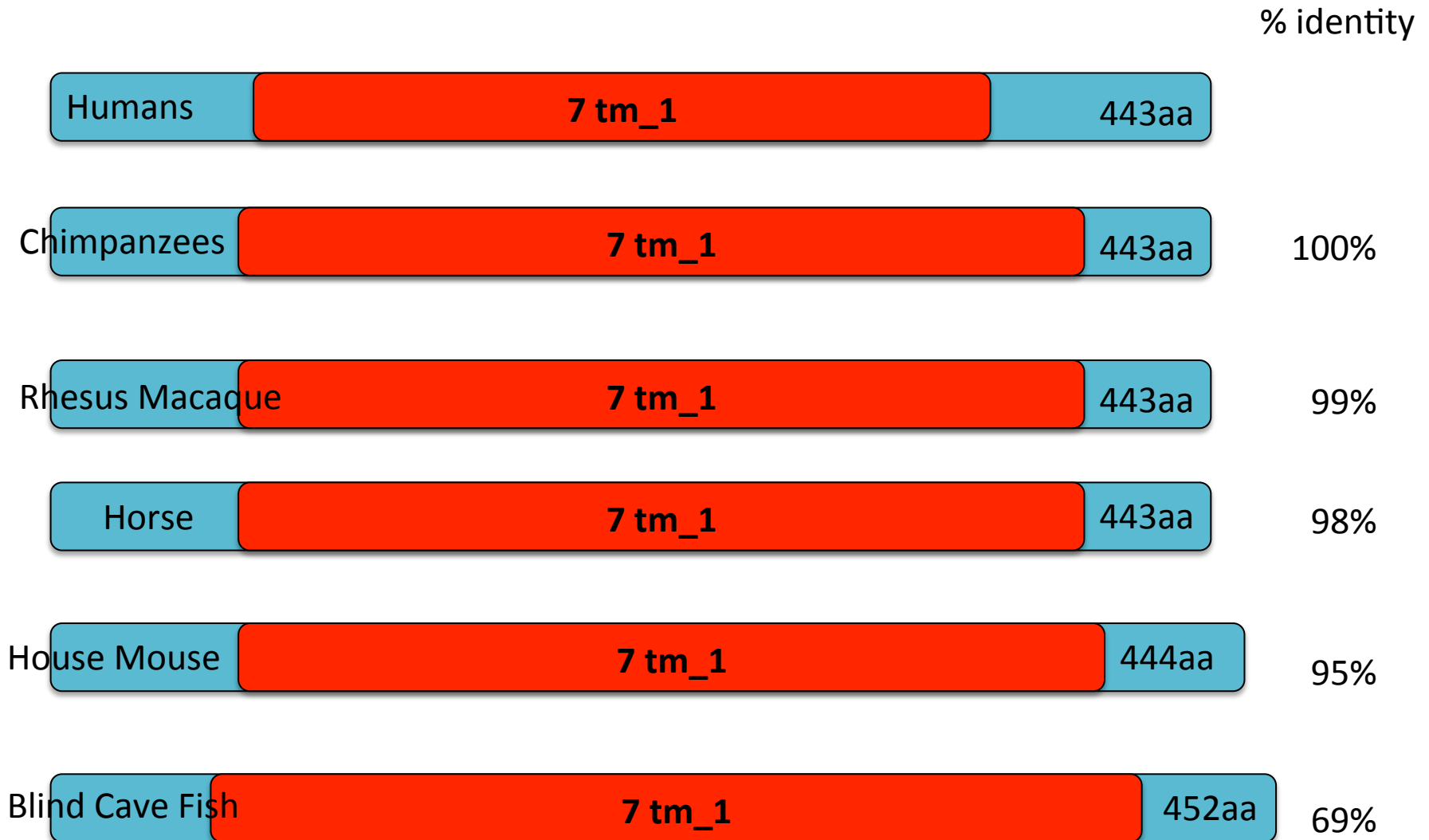


<http://static1.squarespace.com/static/52ec8c1ae4b047ccc14d6f29/t/54e0b408e4b0419b74cc5102/1424012297546/striatum.png>

De Mei, C., Ramos, M., Iitaka, C., & Borrelli, E. (2009). Getting specialized: presynaptic and postsynaptic dopamine D2 receptors. *Current opinion in pharmacology*, 9(1), 53-58.

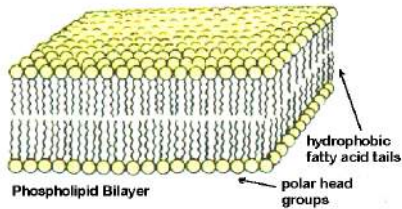
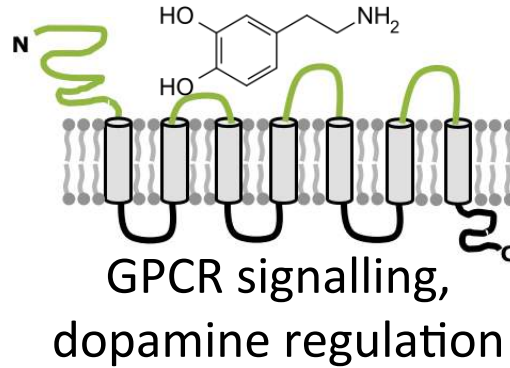
DRD2 is highly expressed in the **striatum**

DRD2 is well-conserved across vertebrates

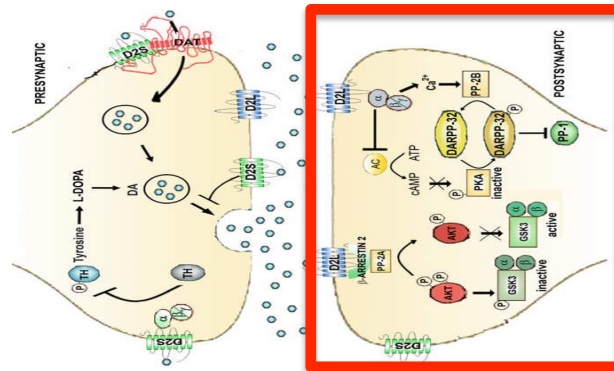


What does GO tell us about DRD2?

Biological Processes



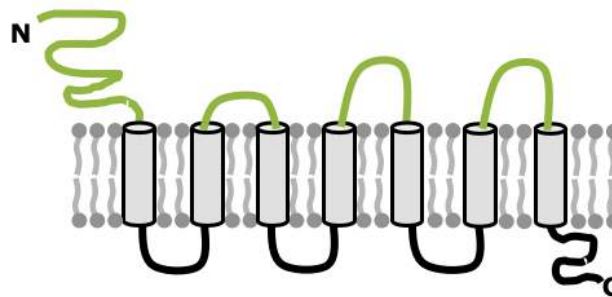
Cell membrane



Postsynaptic density

Cellular Component

Molecular Function



Dopamine activity via G
protein coupling

DRD2 is associated with impulsivity



Polymorphisms associated with drug addiction and smoking

Comings, D. E., et al. (1996), Najafabadi, M. S., et al. (2005)

Low **DRD2 levels** in obese subjects

Volkow, N. D., et al. (2008)



High drug self-administration in **DRD2 KO/KD** animals

Dalley, J. W., et al. (2007)

Knowledge gap: Why are there **conflicting studies** on associations?



<http://bipolarcaregivers.org/wp-content/uploads/2010/07/Computer-conflict-arrows.jpg>

May be due to complex regulatory mechanisms of DRD2

DRD2 **isoforms** have different functions.



Acts at postsynaptic sites



Acts at presynaptic sites

Possible antagonistic functions!

A **third isoform** has also been reported.



Acts at postsynaptic sites

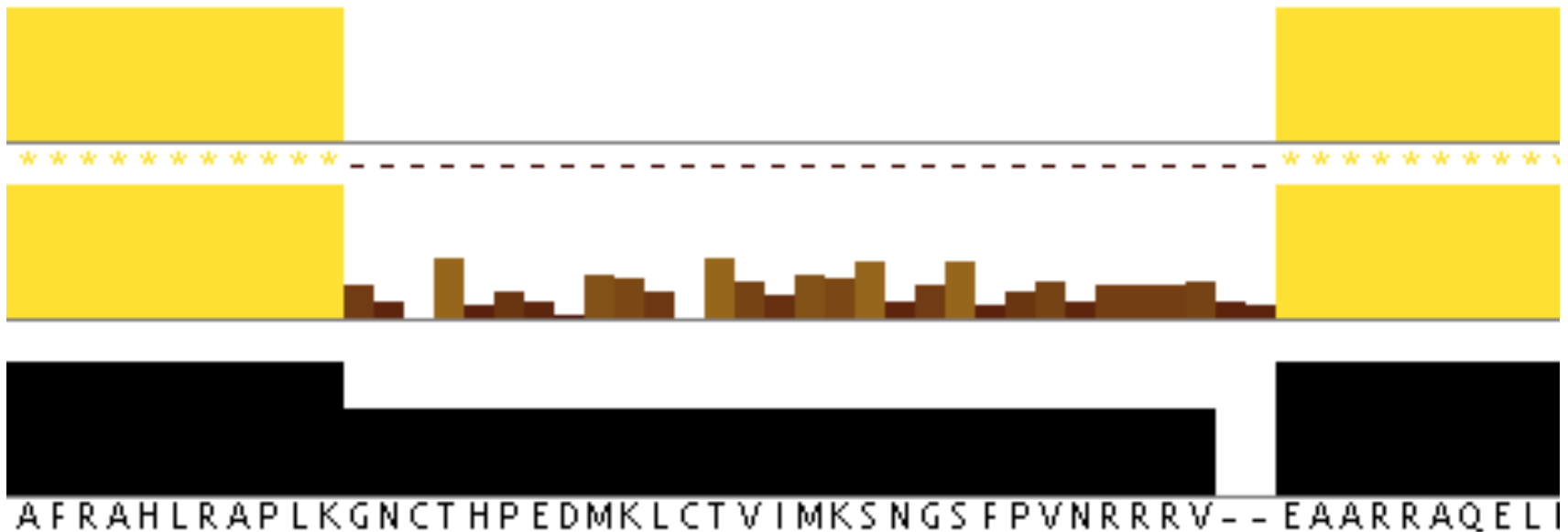


Acts at presynaptic sites



???

D2_{Longer} has two extra amino acids



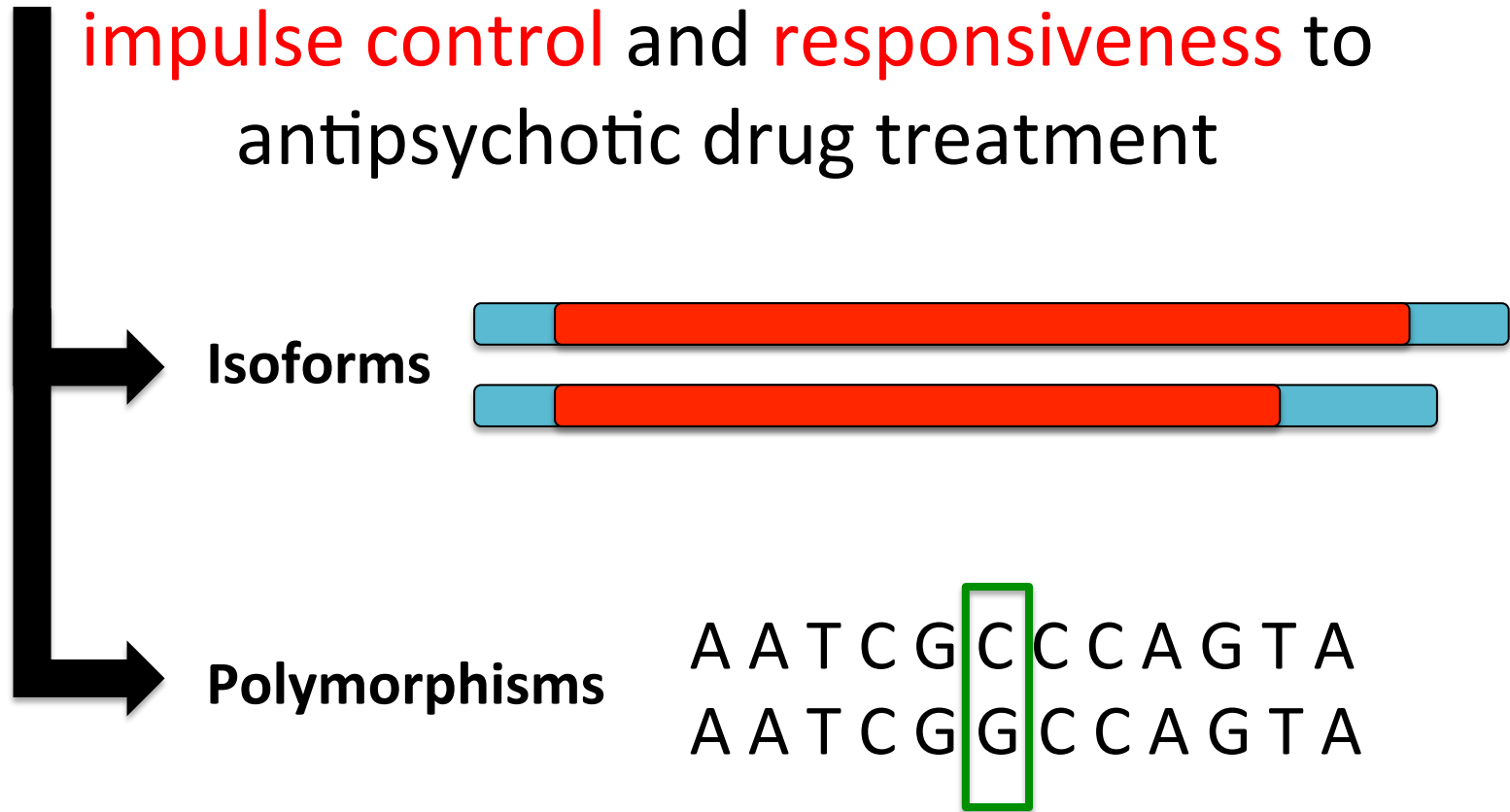
Extra amino acids may affect ligand binding

Hypothesis

Regulation of DRD2 expression is critical for **impulse control** and **responsiveness** to antipsychotic drug treatment

Hypothesis

Regulation of DRD2 expression is critical for **impulse control** and **responsiveness** to antipsychotic drug treatment



Aim 1: To study the prevalence and expression levels of D2_{Longer}



Long isoform



Short isoform

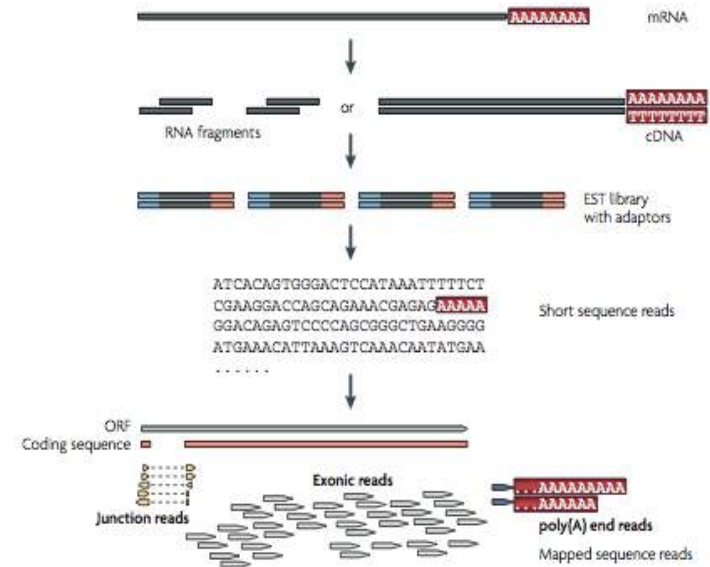


Longer isoform

Obtain samples (post-mortem brains)



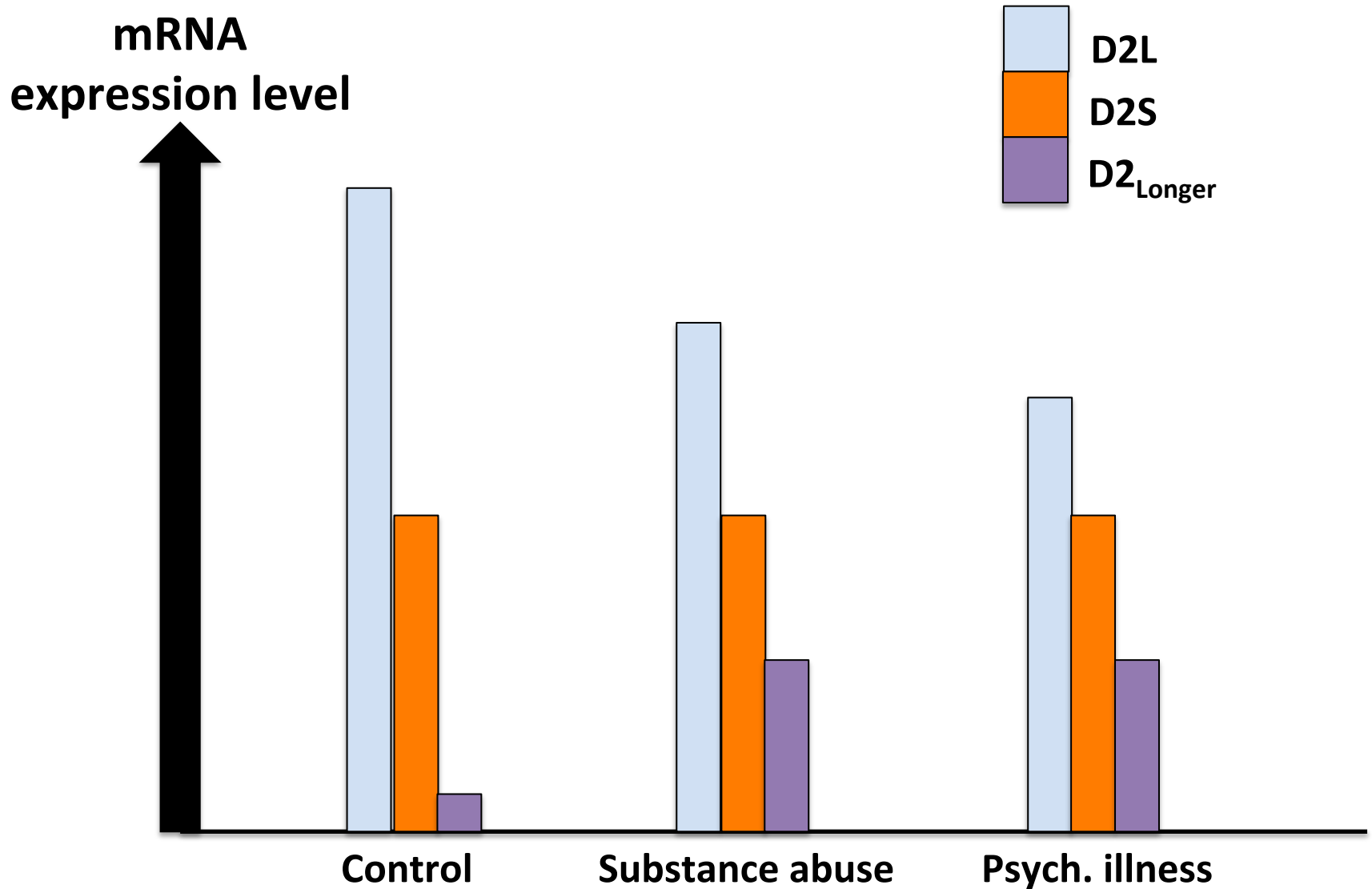
RNA-Seq: Quantify transcript abundance in different brain regions



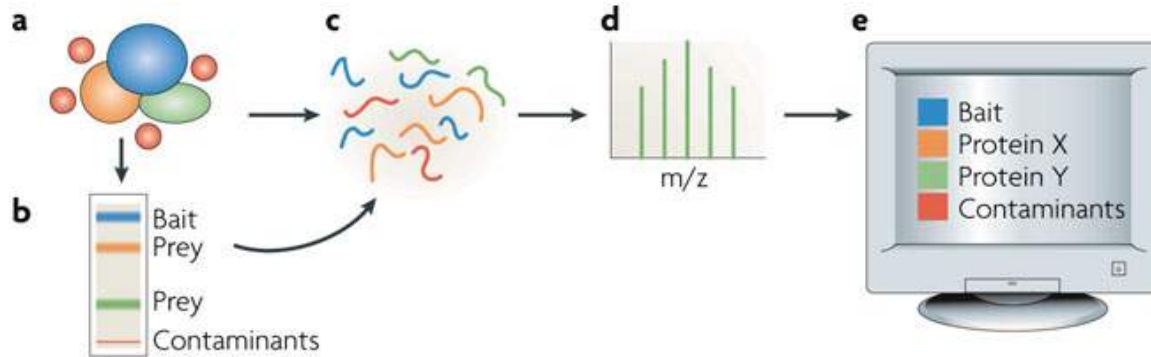
Proportion of DRD2 transcripts

	D2L	D2S	D2 _{Longer}
Control			
Substance abuse			
Psychiatric illness			

Example: DRD2 expression in striatum



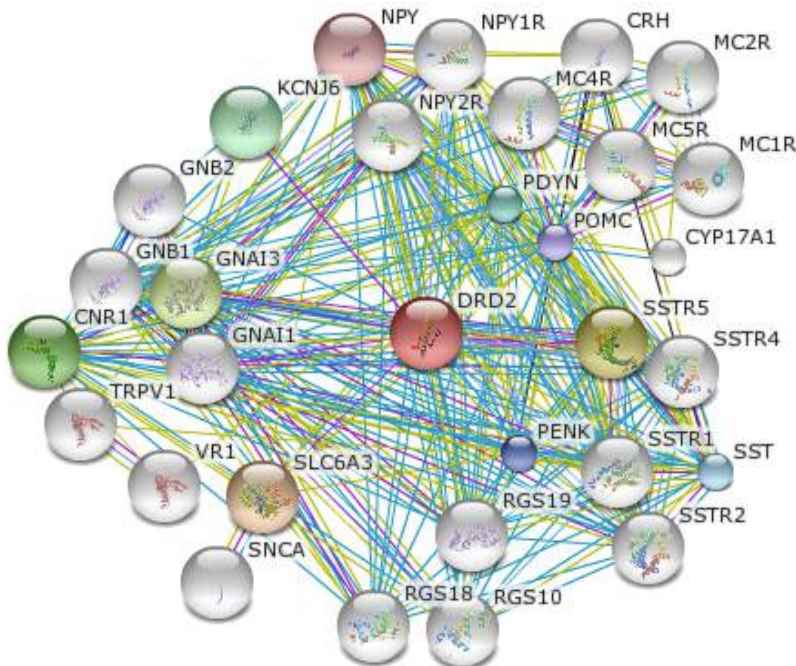
Aim 2: Study proteins interactions in D2S and D2_{Longer}



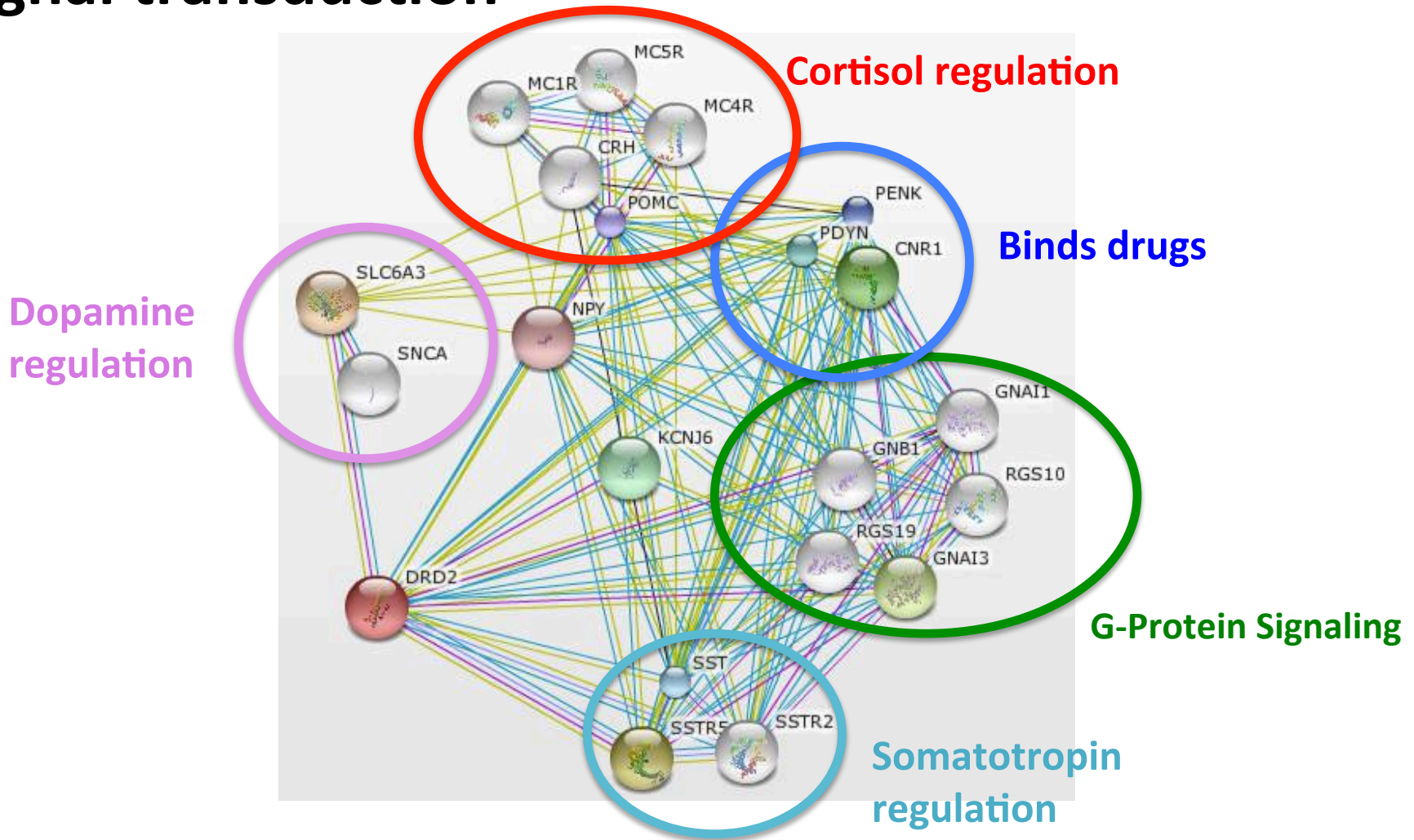
AP-MS with
TAP tagging



Compare to STRING

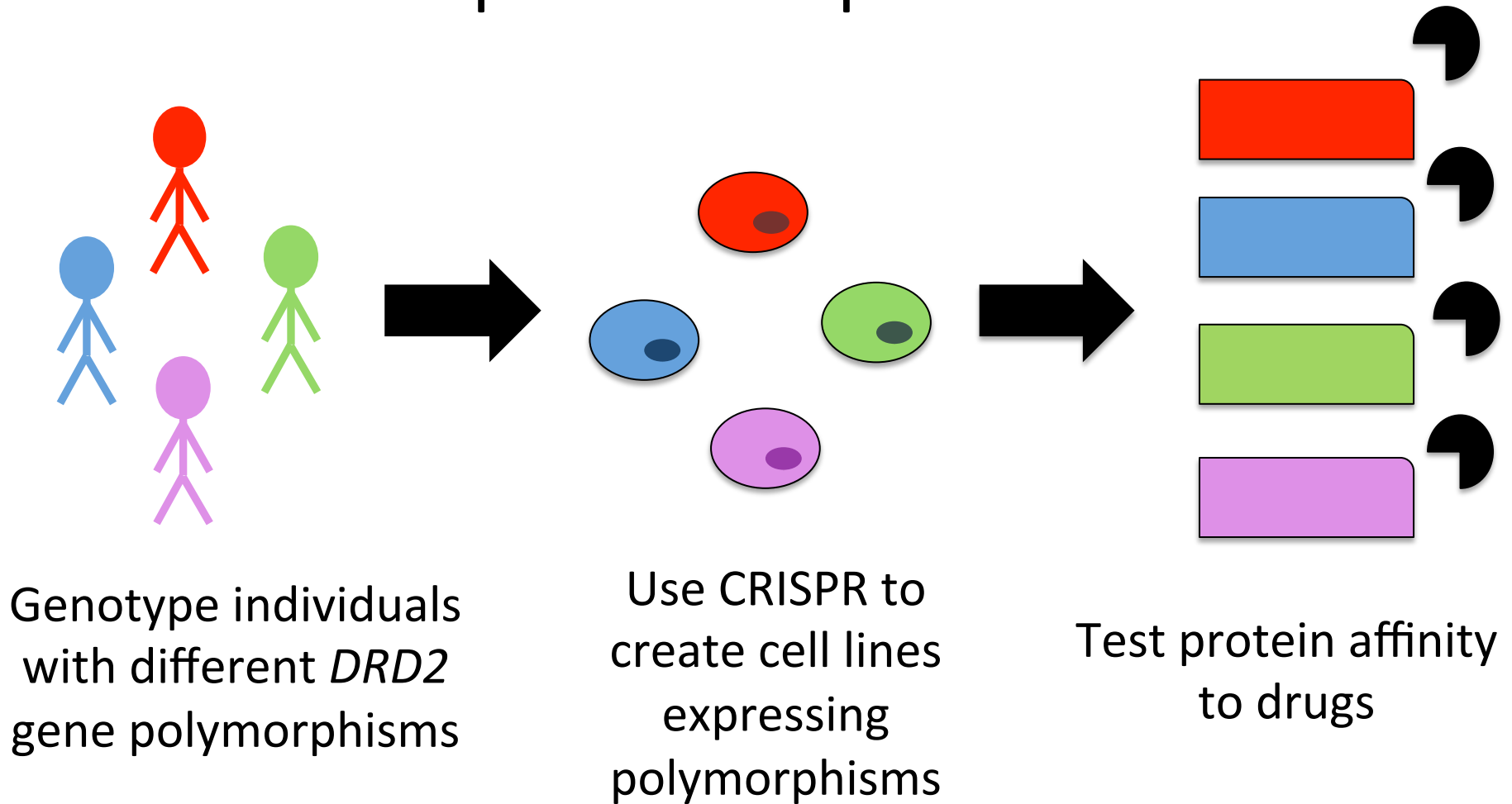


Proteins interacting with D2L are involved in signal transduction

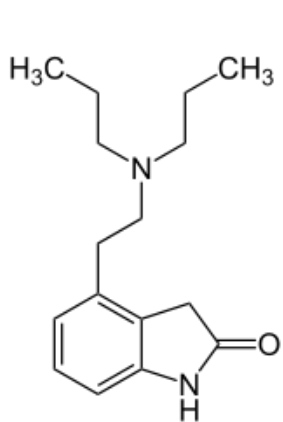


Hypothesis: Some proteins do not interact with D2S and D2_{Longer}

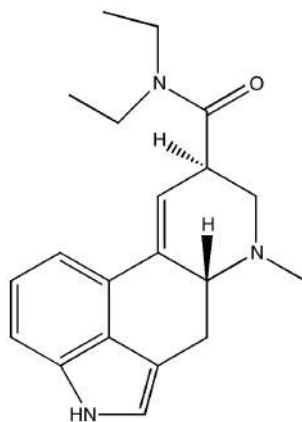
Aim 3: Study the relationship between gene polymorphisms and DRD2 protein affinity to specific compounds



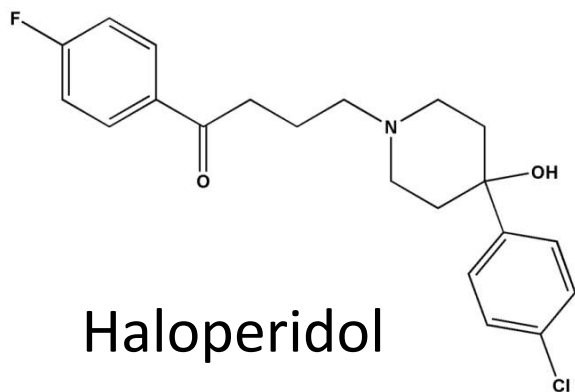
What drugs act on DRD2?



Ropinirole



LSD



Haloperidol

Pubchem

Filters

Activity Outcome

inactive (2,042,855)

unspecified (39,277)

active (12,054)

inconclusive (6,118)

Some Future Directions

Elucidate function and cellular localization of D2_{Longer}

KO/KD experiments

More association studies?

Long-term goal

Develop therapies to offset impulse control dysregulation that is characteristic of psychiatric illnesses

References

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- Volkow, N. D., et al. (2008). Low dopamine striatal D2 receptors are associated with prefrontal metabolism in obese subjects: possible contributing factors. *Neuroimage*, 42(4), 1537-1543