JoCl

RK

outline

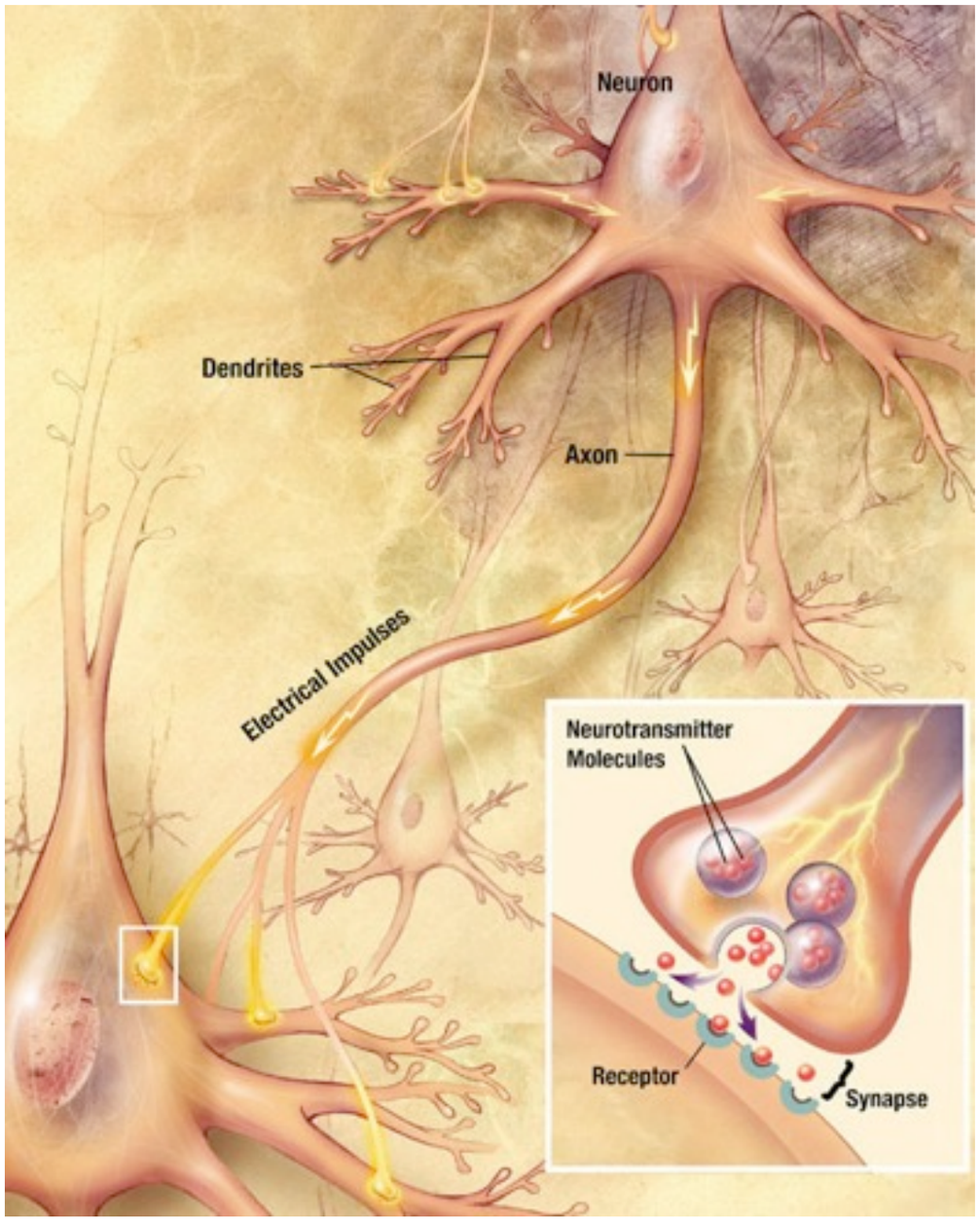
1. signalling, the synapse, and the brain
2. psychiatric disorders - schizophrenia & DISC1

the neural network

node == neuron
edge == synapse

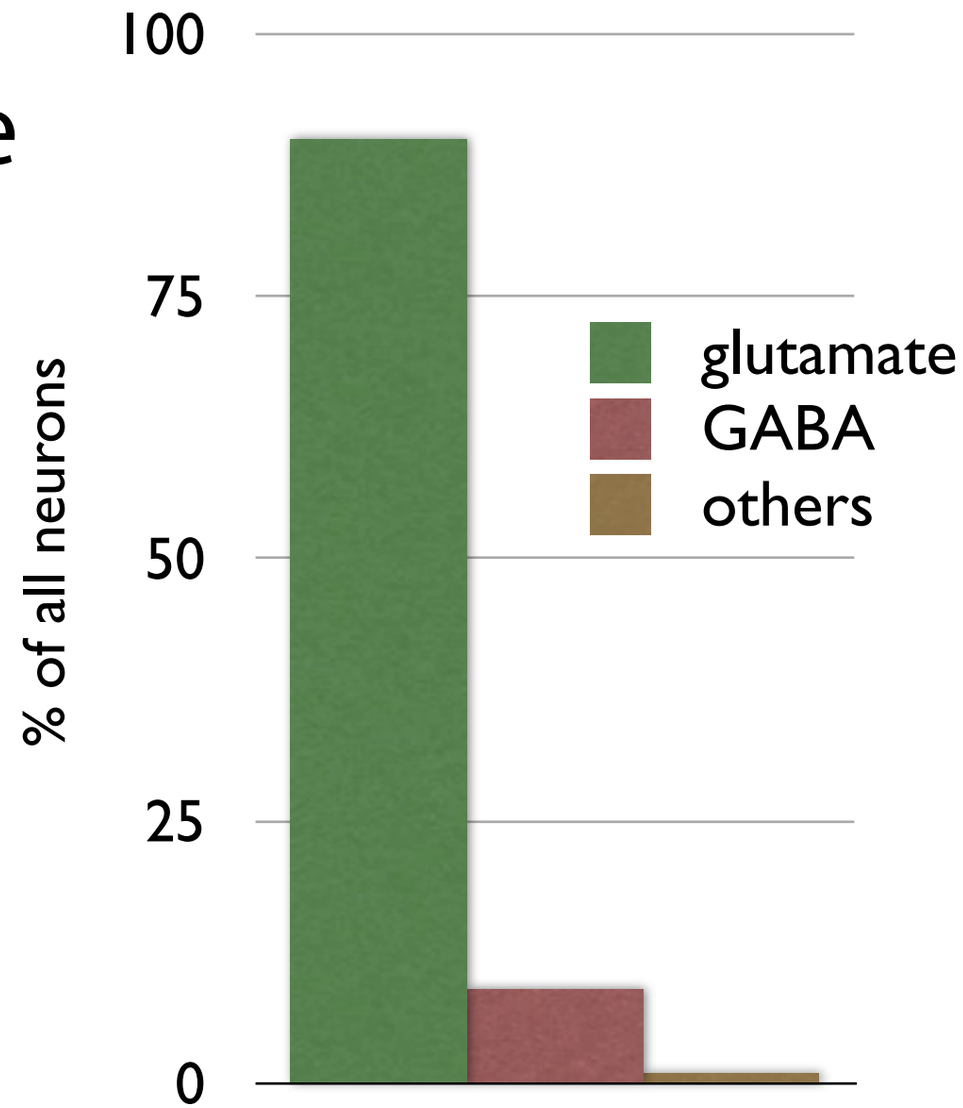
- neurons generally release one type of transmitter molecule

- transmitters regulate the flow of charge between connected neurons and downstream targets



neurotransmitters

- transmitter molecules are either excitatory or inhibitory
- network complexity & function achieved by localisation and connectivity

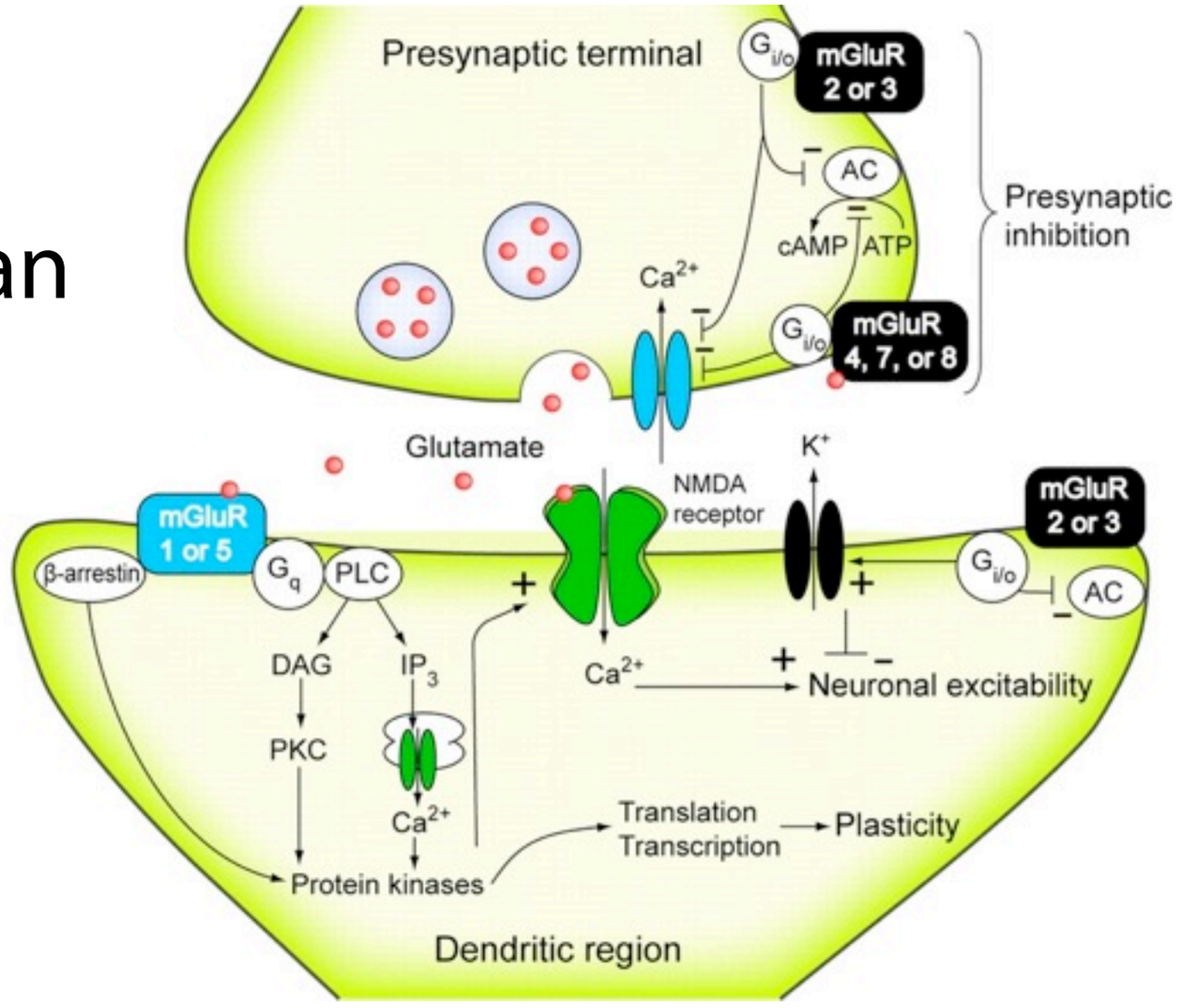


neurotransmitters

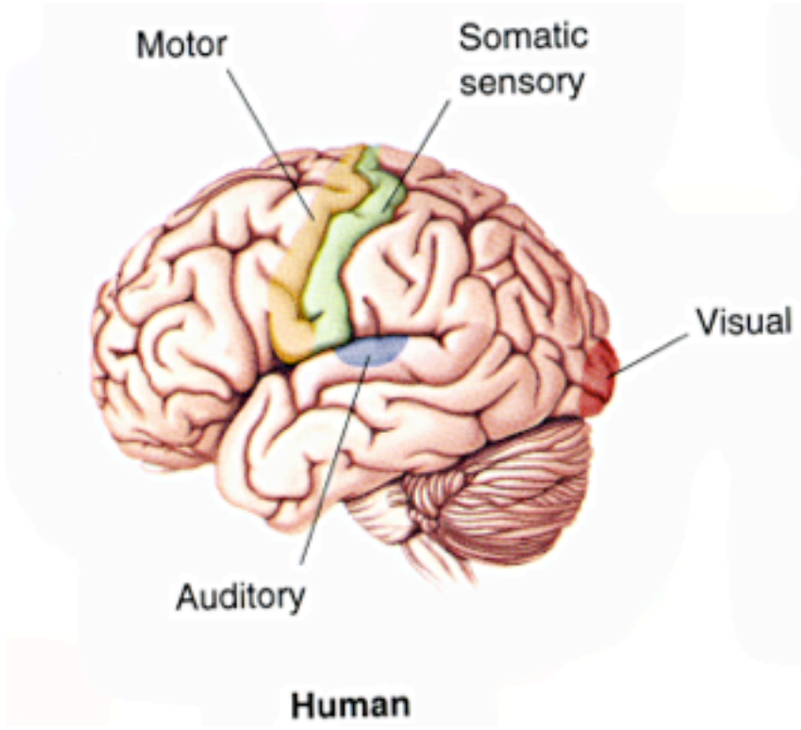
chemical	[example] functions
glutamate	general excitatory & memory
GABA	general inhibitory & sleep
acetylcholine	memory & movement
serotonin	mood, sleep, & appetite
norepinephrine	arousal & mood
dopamine	movement & pleasure
endorphins	pain relief

neuroreceptors

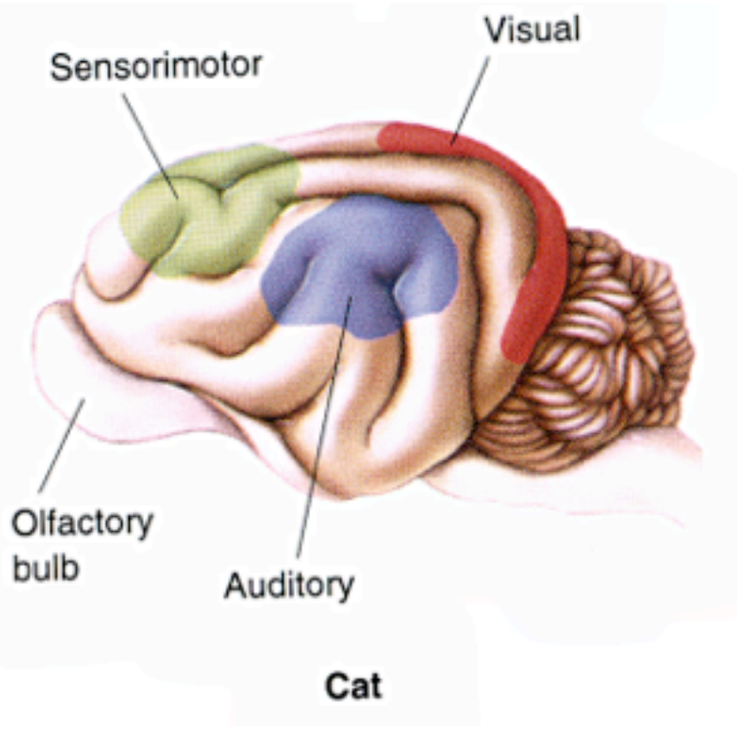
- to add complexity, the receptor for a given transmitter can be either excitatory or inhibitory
- receptors can be presynaptic or postsynaptic



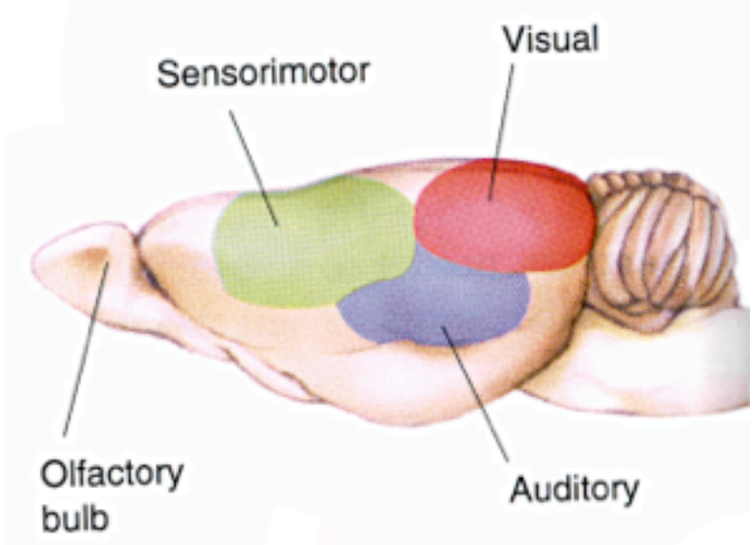
brain structure



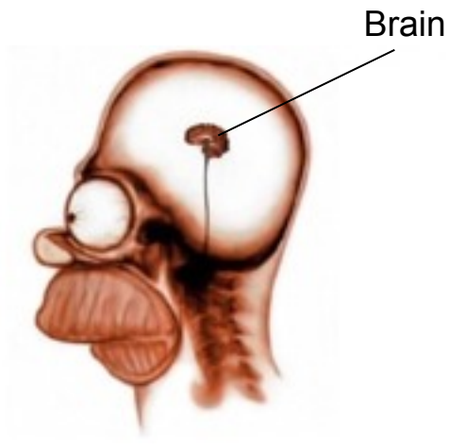
Human



Cat



Rat

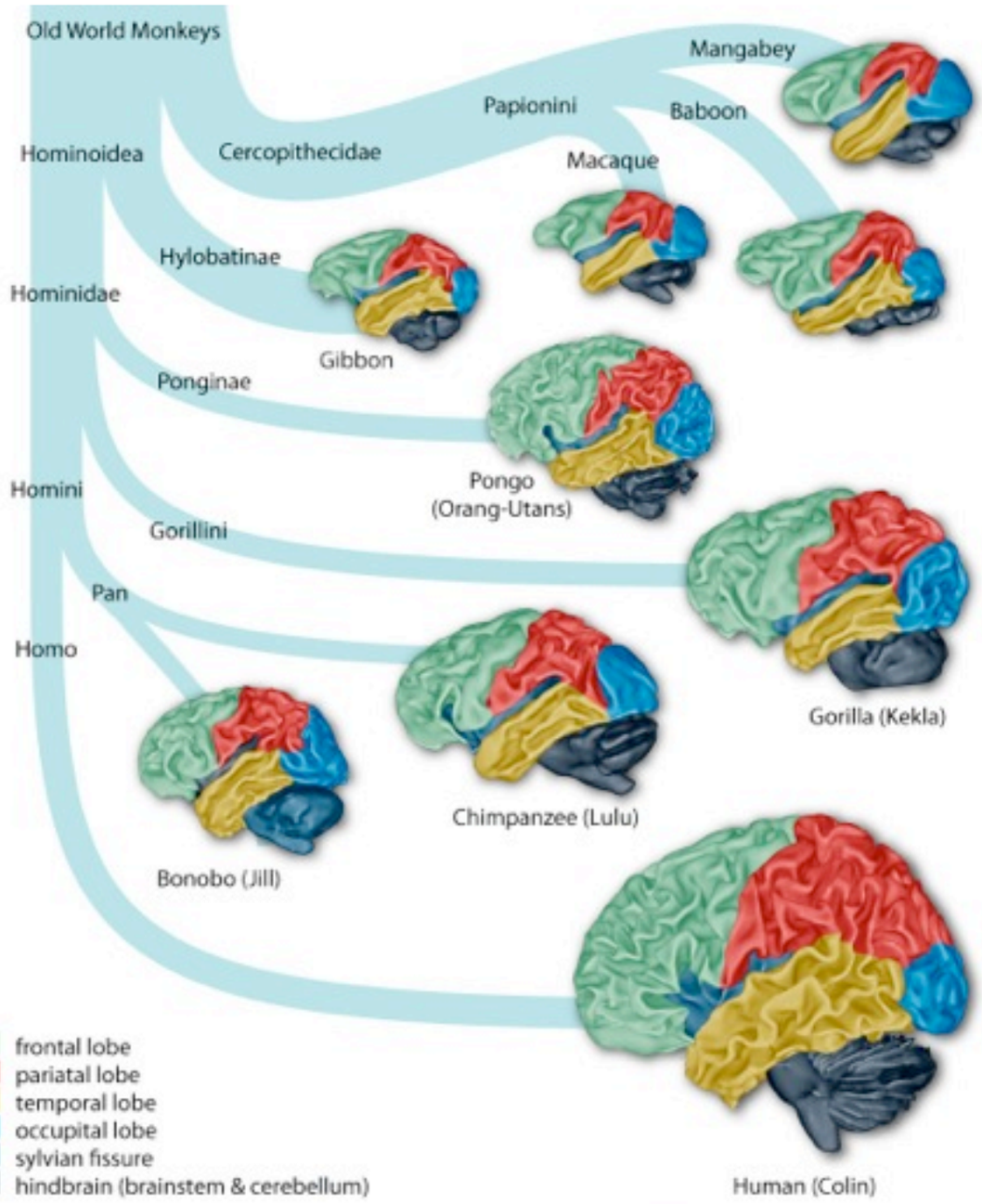


Homer

cortical function

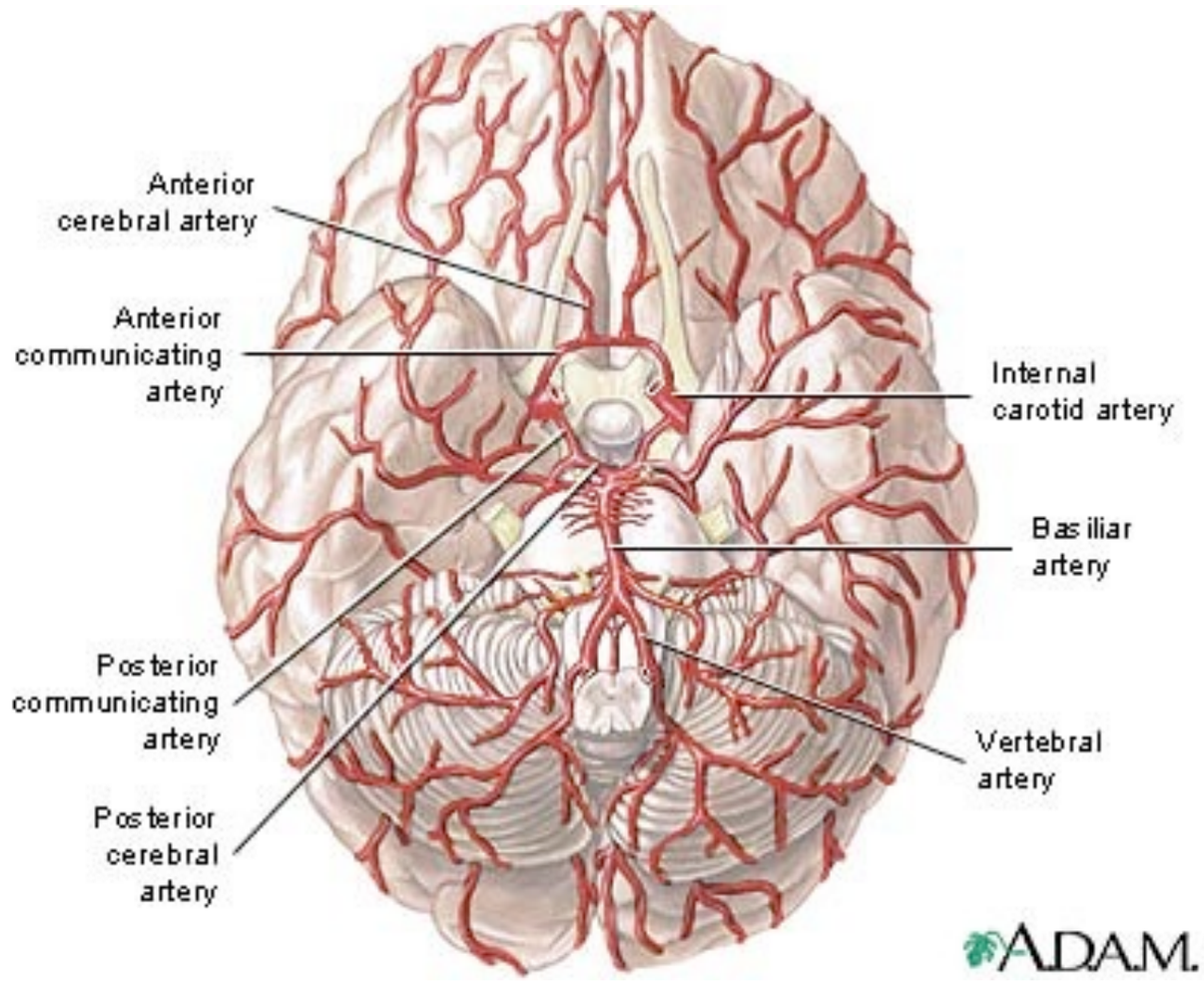
- frontal - forward planning and conscious thought
- parietal - integration of sensory info
- occipital - sight
- temporal - processes complex stimuli & memory

cortical conservation



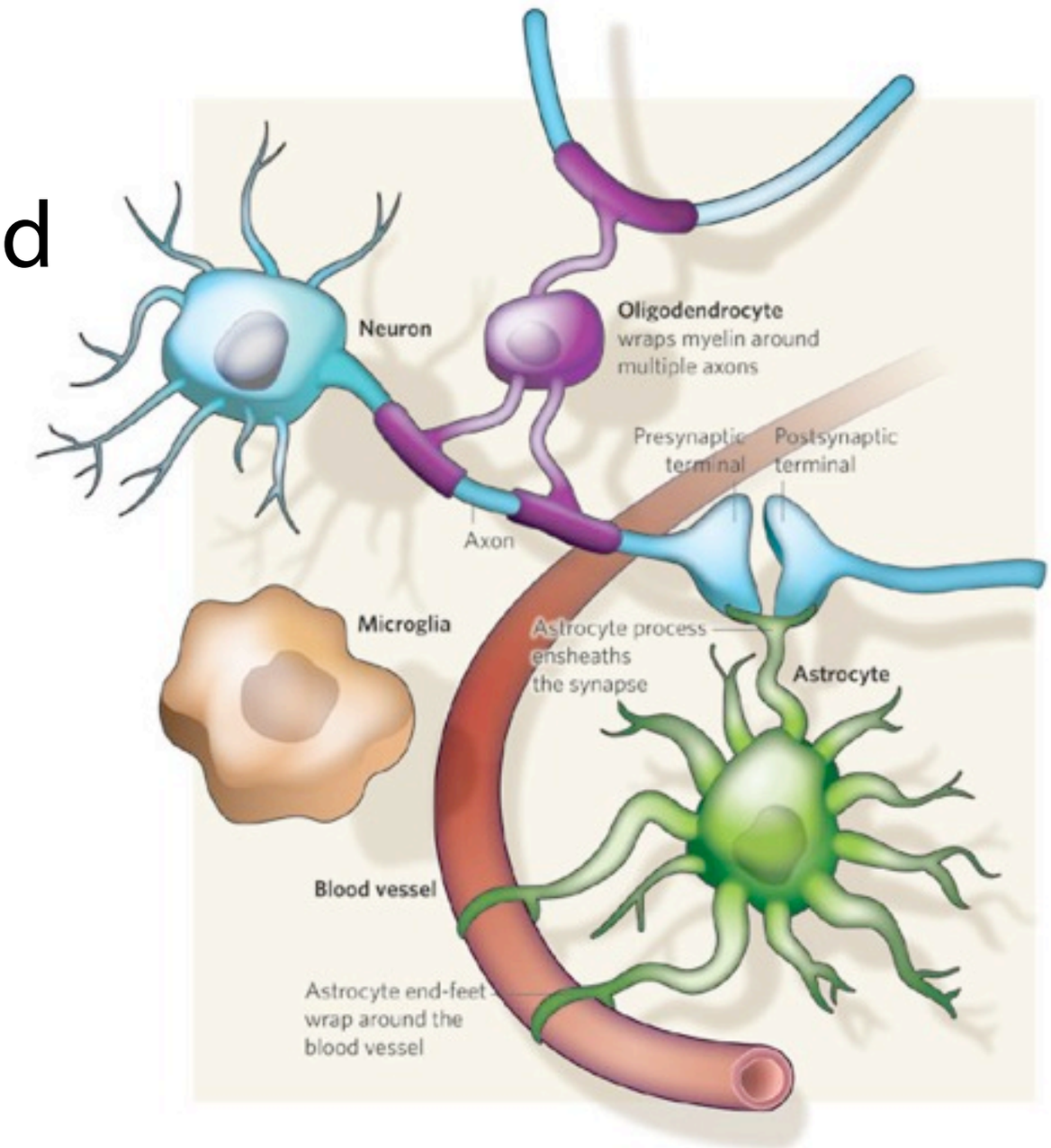
supporting cast - blood

- brain consumes 25% of the body's oxygen
- requires continual supply of glucose



supporting cast - glia

- astrocytes
  the link between blood and neurons
- oligodendrocytes
  insulate the axon to improve conductivity
- microglia
  immune cells

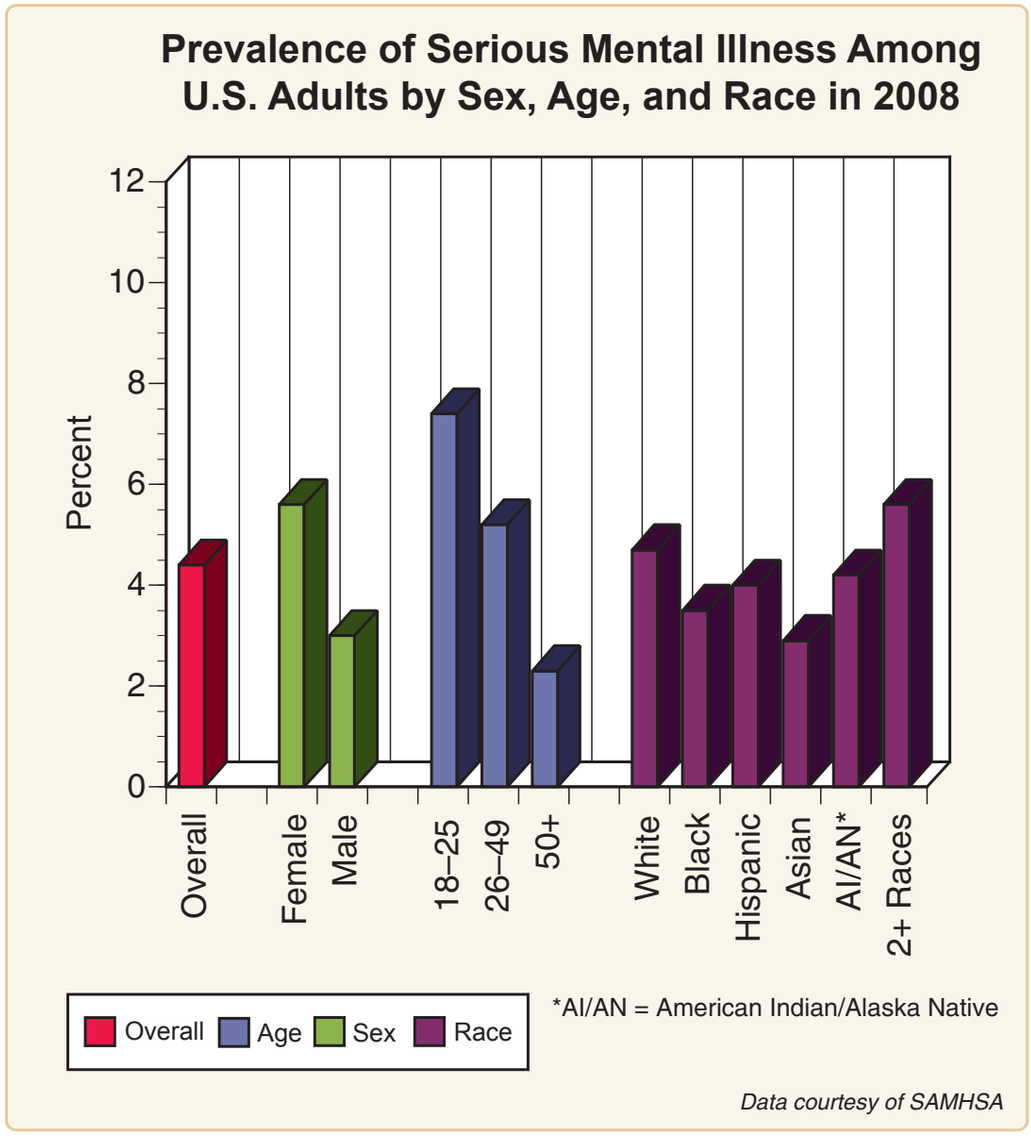


outline

1. signalling, the synapse, and the brain
2. psychiatric disorders - schizophrenia & DISC1

psychiatric disorders

- all disorders carry 25% lifetime risk for people in the developed world
- serious disorders in US (~4% of pop)
- complex disorders with developmental, genetic, and environmental risk factors

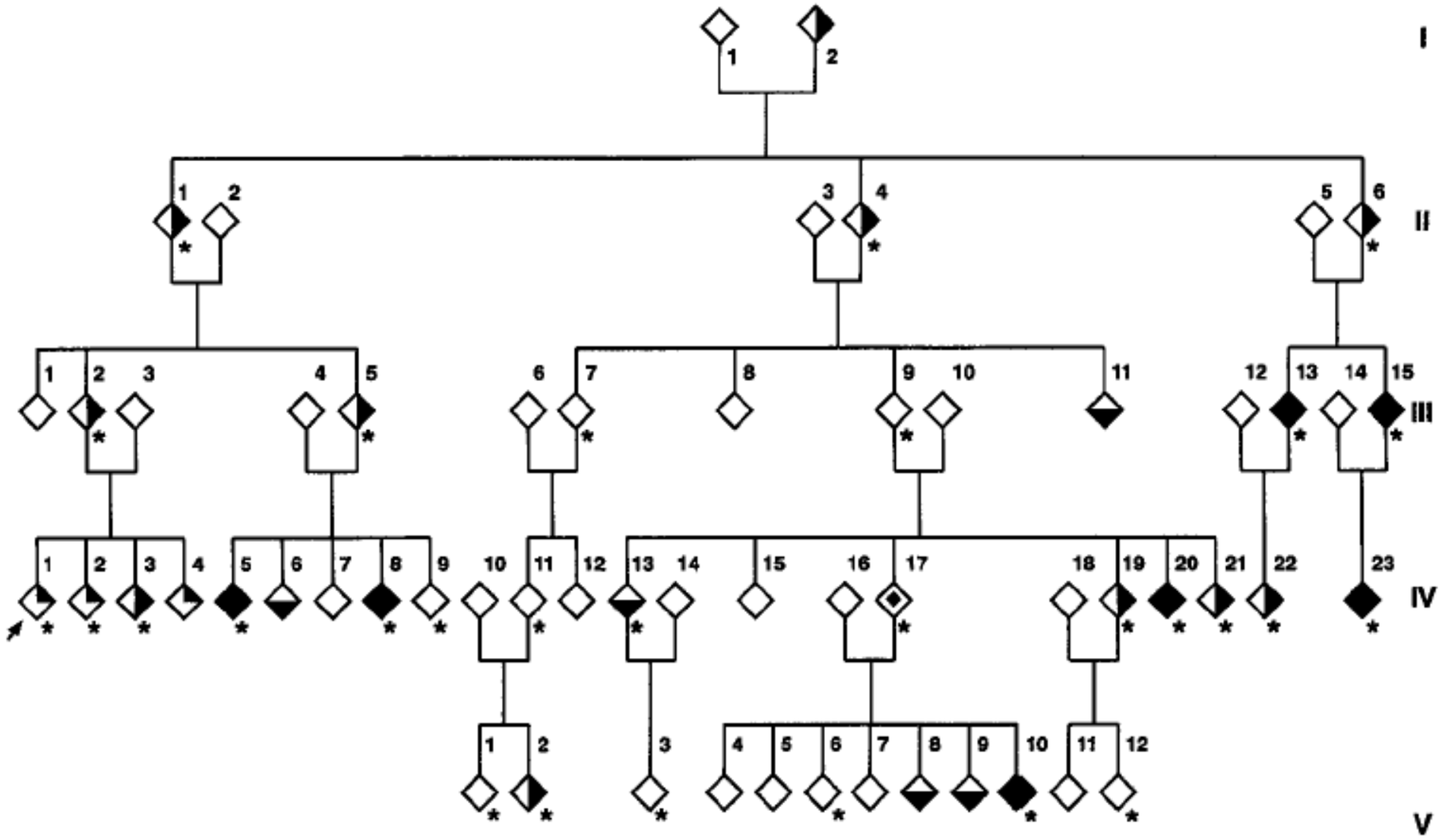


source: NIMH

schizophrenia (SZ)

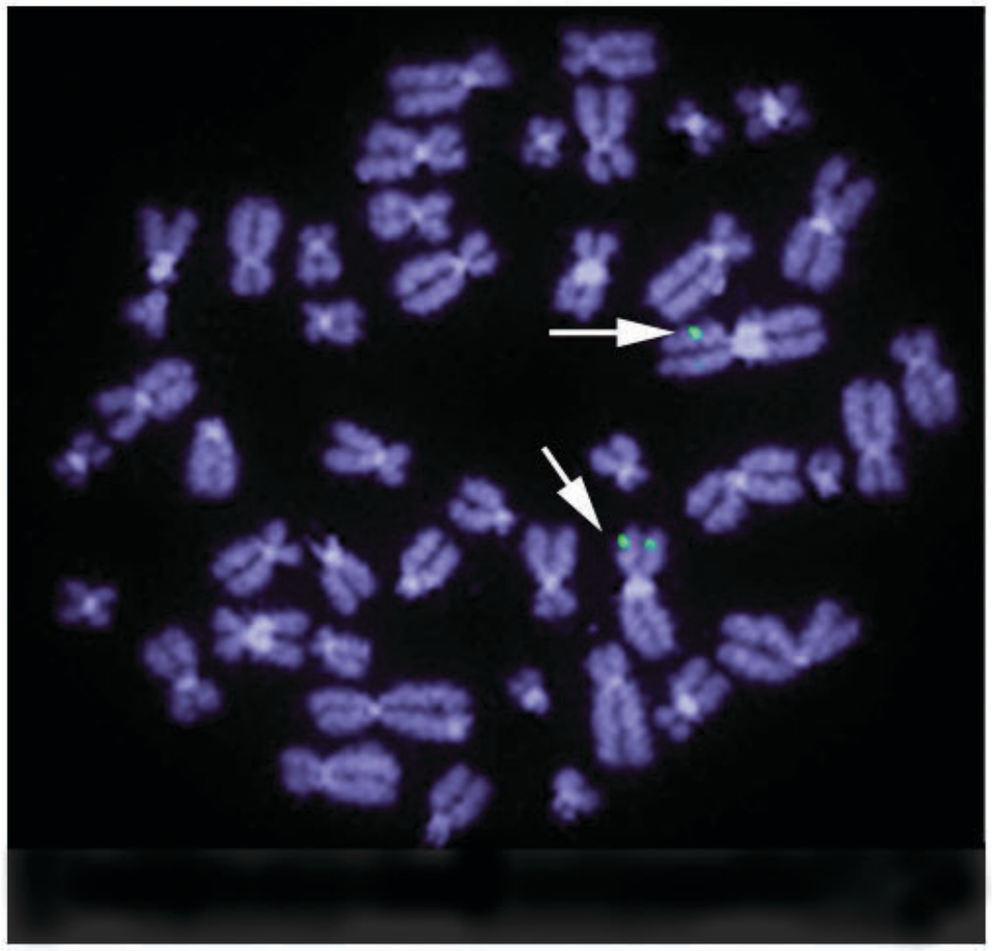
- involves multiple brain regions
- symptoms have three components:
  - ‘positive’: hallucinations & delusions
  - ‘negative’: depression & withdrawal
  - cognitive: working memory deficits
- no single known cause, +ve symptoms likely result from overabundant dopamine

DISC1 & SZ


I
II
III
IV
V
Schizophrenia
Bipolar Disorder
Recurrent Major Depression
Adolescent Conduct Disorder
Anxiety, Alcoholism, Minor Depression
Translocation t(1;11) Carrier

DISC1

- inherited non-lethal mutation
- discovered that all affected family members have a balanced translocation between chr1 & chr11
- major gene interrupted is DISC1



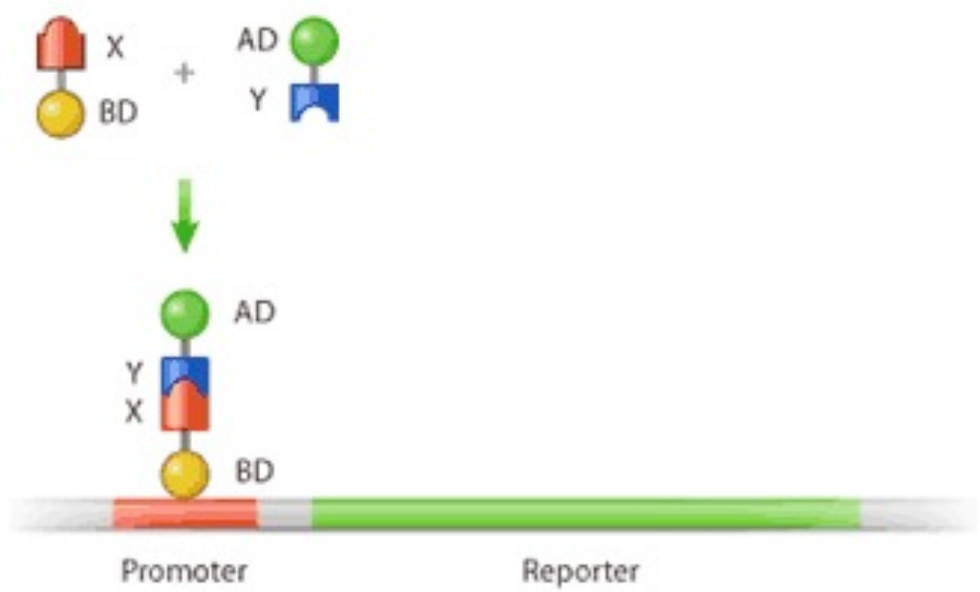
DISC1

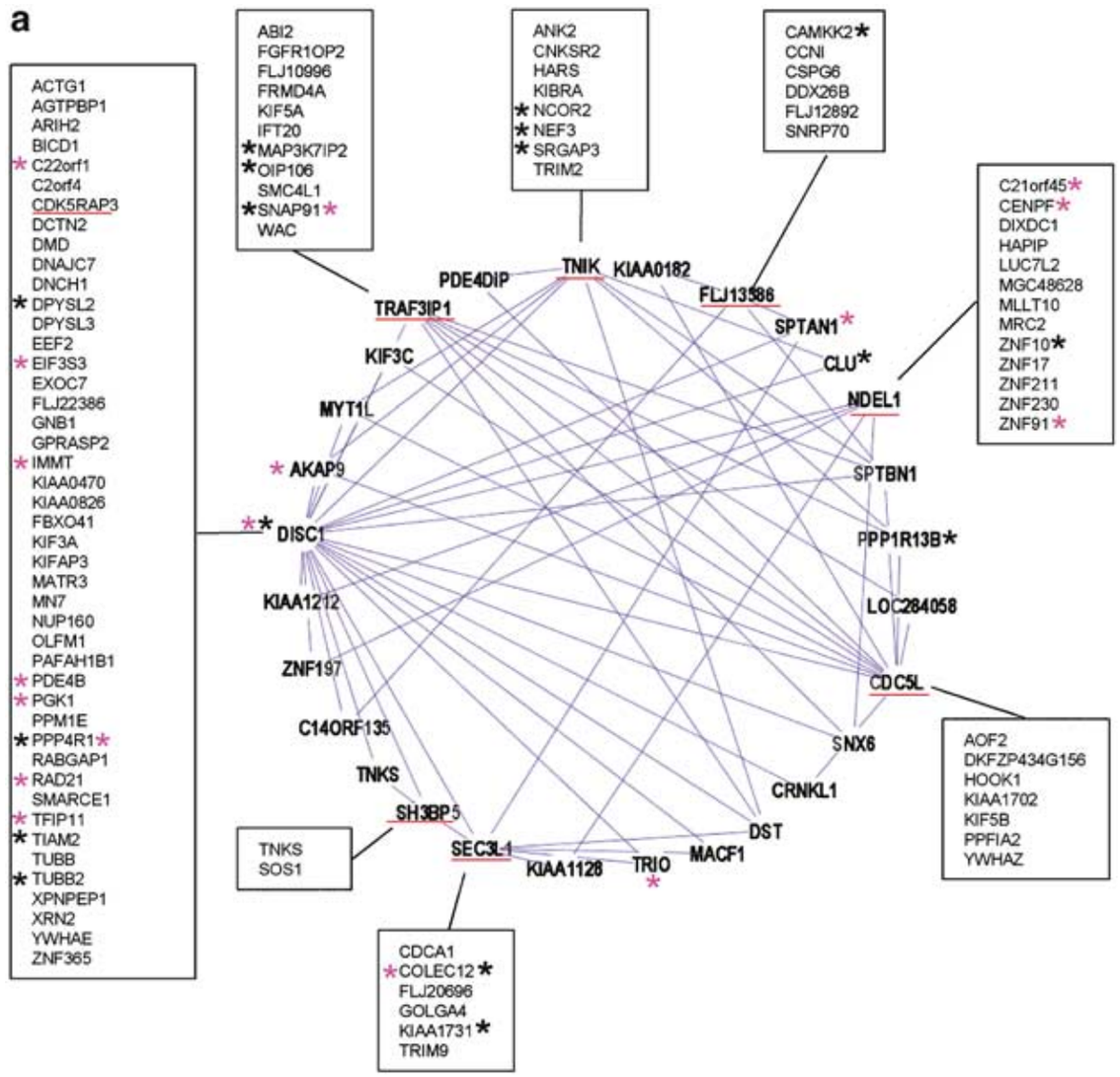
from year	analysis	reference
2000	protein interaction screens	Millar 2005 Science
2002	association studies	Bradshaw 2011 Neuropharmacology
2002	protein structure & prediction	Soares 2011 ACS Chem Neurosci
2003	animal models	Hikida 2007 PNAS
2006	expression analysis	Lipska 2006 Hum Mol Genet
2008	CNV / 2GS	Song 2008 Neuroscience Letters

protein interactions

Camargo et al. (Mol Psych '07)

- used yeast 2 hybrid screen to elucidate protein network





association studies

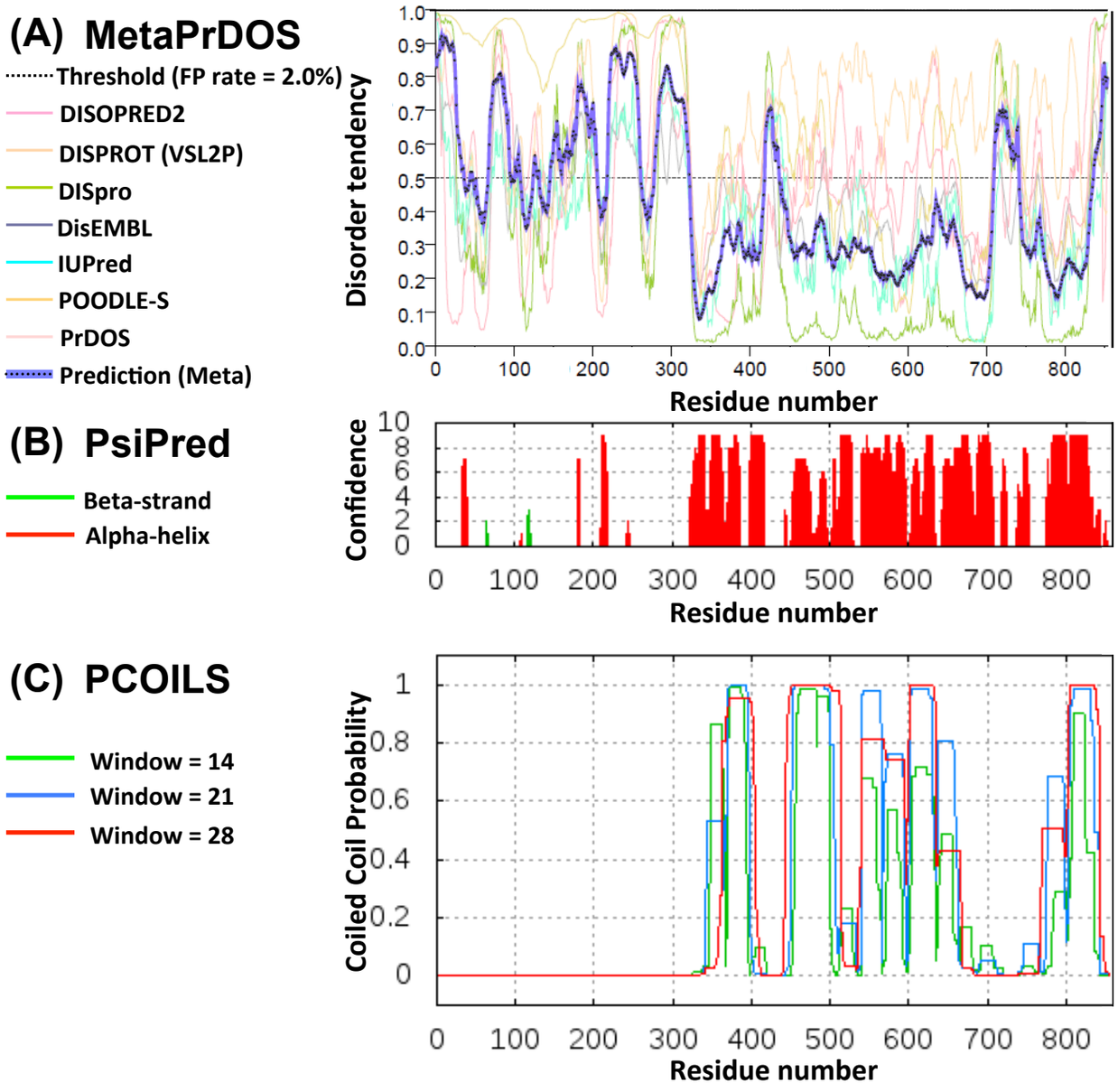
Reviewed in Bradshaw et al. 2011 Neuropharmacology

- used to establish DISC1 as a risk factor in the general population
  - 36 published positive studies (5 negative)
  - positive associations across: multiple populations, disorders, symptom domains, and endophenotypic traits
  - conditioning for risk SNPs in DISC1 increases significance of SNPs in interacting proteins

protein structure

Soares et al. 2011 ACS Chem Neurosci

- nobody has managed to crystallise the DISC1 protein
- prediction based on computation, but DISC1 has little conservation with other proteins



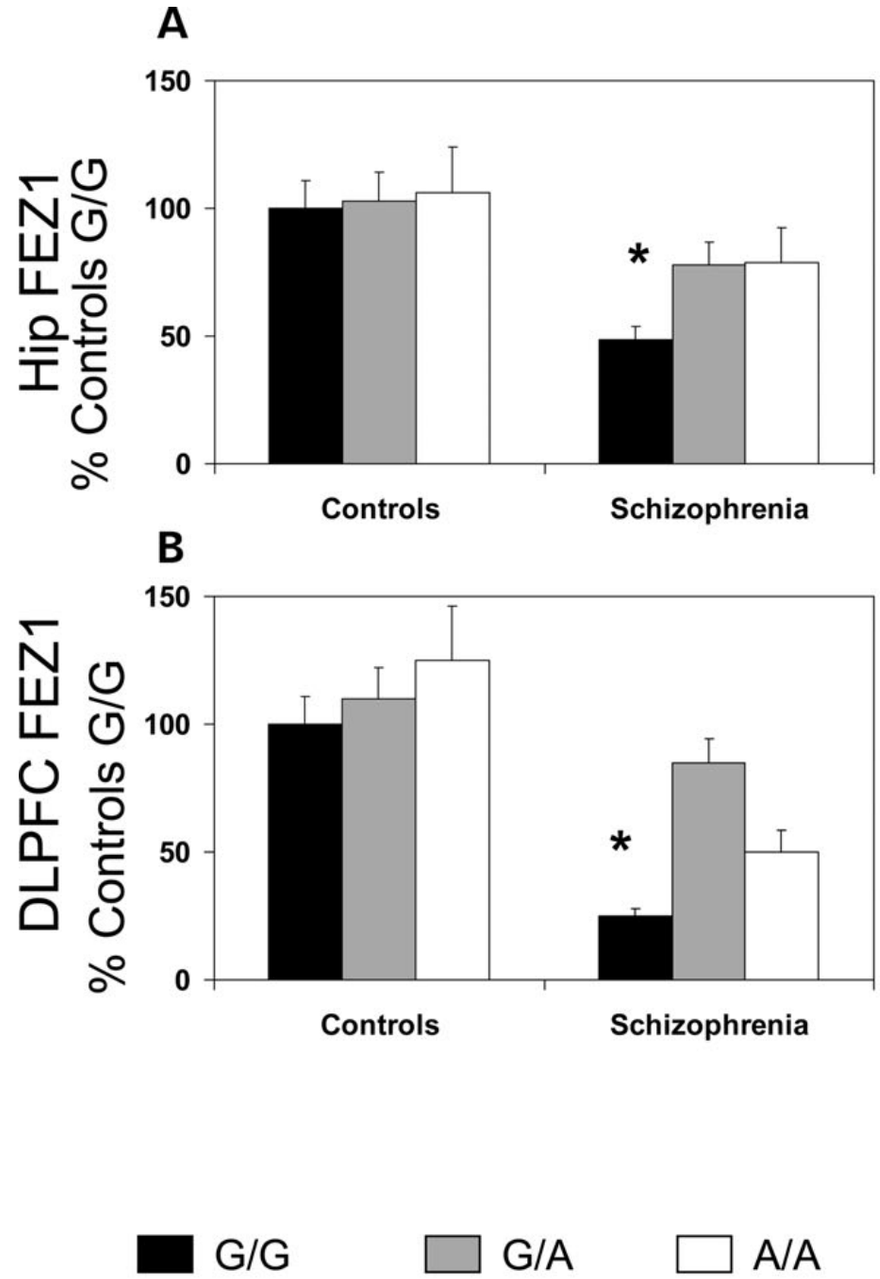
animal models

- full knockout produces similar phenotype to Huntington's disease models
- dominant negative & point mutations recapitulate many aspects of psychiatric phenotype incl. changes in dopamine metabolism
- brain anatomy shows neural migration phenotype, resulting from abnormal brain development, implicating GABAergic interneurons

mRNA expression

Lipska et al. 2006 Hum Mol Genet

- qPCR in human tissues with risk allele shows decrease in binding with partner mRNA
- [small scale] arrays run on mouse point mutants shows changes in neuronal migration factors



CNV / 2gs

Song et al. 2008 Neuroscience Letters

- compared bipolar and SZ to 5000 HapMap samples
- confirmed risk of 2 common structural variants w/ SZ
- found ultra rare point mutants in important binding areas for BP and SZ
- CNVs associated with autism (not seen in 1.5k controls)

summary

- brain is much more complex than alluded to in these slides
- disorders most likely reflect combination of genetic risk and environmental catalysts
- DISC1 is an example of a simple genetic finding that has led to new discoveries about SZ pathophysiology whilst linking in risk pathways for other disorders