Genetics and behavior

How many genes?
What molecules and pathways?
What kinds of modifications?
How do they affect behavior?

founders of neuroethology

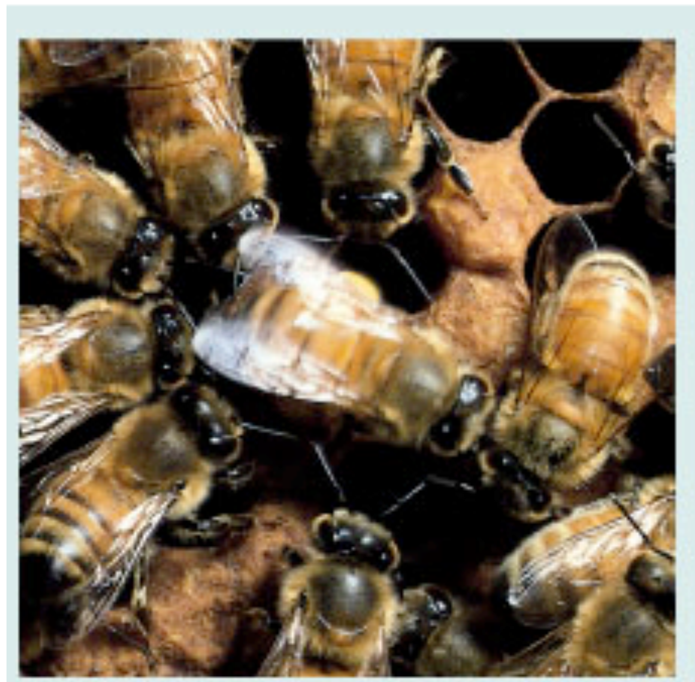
sensory stimuli elicit stereotyped behaviors

courtship, aggression

learning occur in specific behavioral contexts

imprinting

social communication



pheromones, dances

Nature. 2006 Oct 26;443(7114):931-49.
Insights into social insects from the genome of the honeybee Apis mellifera.

Honeybee Genome Sequencing Consortium.

Collaborators (328)

Weinstock GM, Robinson GE, Gibbs RA, et a;

Here we report the genome sequence of the honeybee Apis mellifera, a key model for social behaviour and essential to global ecology through pollination. Compared with other sequenced insect genomes, the A. mellifera genome has high A+T and CpG contents, lacks major transposon families, evolves more slowly, and is more similar to vertebrates for circadian rhythm, RNA interference and DNA methylation genes, among others. Furthermore, A. mellifera has fewer genes for innate immunity, detoxification enzymes, cuticle-forming proteins and gustatory receptors, more genes for odorant receptors, and novel genes for nectar and pollen utilization, consistent with its ecology and social organization. Compared to Drosophila, genes in early developmental pathways differ in Apis, whereas similarities exist for functions that differ markedly, such as sex determination, brain function and behaviour. Population genetics suggests a novel African origin for the species A. mellifera and insights into whether Africanized bees spread throughout the New World via hybridization or displacement

Nature. 2001 Feb 15;409(6822):860-921.
Initial sequencing and analysis of the human genome.

Lander ES, Linton LM, Birren B, Nusbaum C, & al.
International Human Genome Sequencing Consortium.

The human genome holds an extraordinary trove of information about human development, physiology, medicine and evolution. Here we report the results of an international collaboration to produce and make freely available a draft sequence of the human genome. We also present an initial analysis of the data, describing some of the insights that can be gleaned from the sequence.

The genomic landscape shows marked variation in the distribution of a number of features, including genes, transposable elements, GC content, CpG islands and recombination rate….

There appear to be about 30,000–40,000 protein-coding genes in the human genome—only about twice as many as in worm or fly….

The full set of proteins (the 'proteome') encoded by the human genome is more complex than those of invertebrates. This is due in part to the presence of vertebrate-specific protein domains and motifs (an estimated 7% of the total), but more to the fact that vertebrates appear to have arranged pre-existing components into a richer collection of domain architectures.

Hundreds of human genes appear likely to have resulted from horizontal transfer from bacteria at some point in the vertebrate lineage. Dozens of genes appear to have been derived from transposable elements.

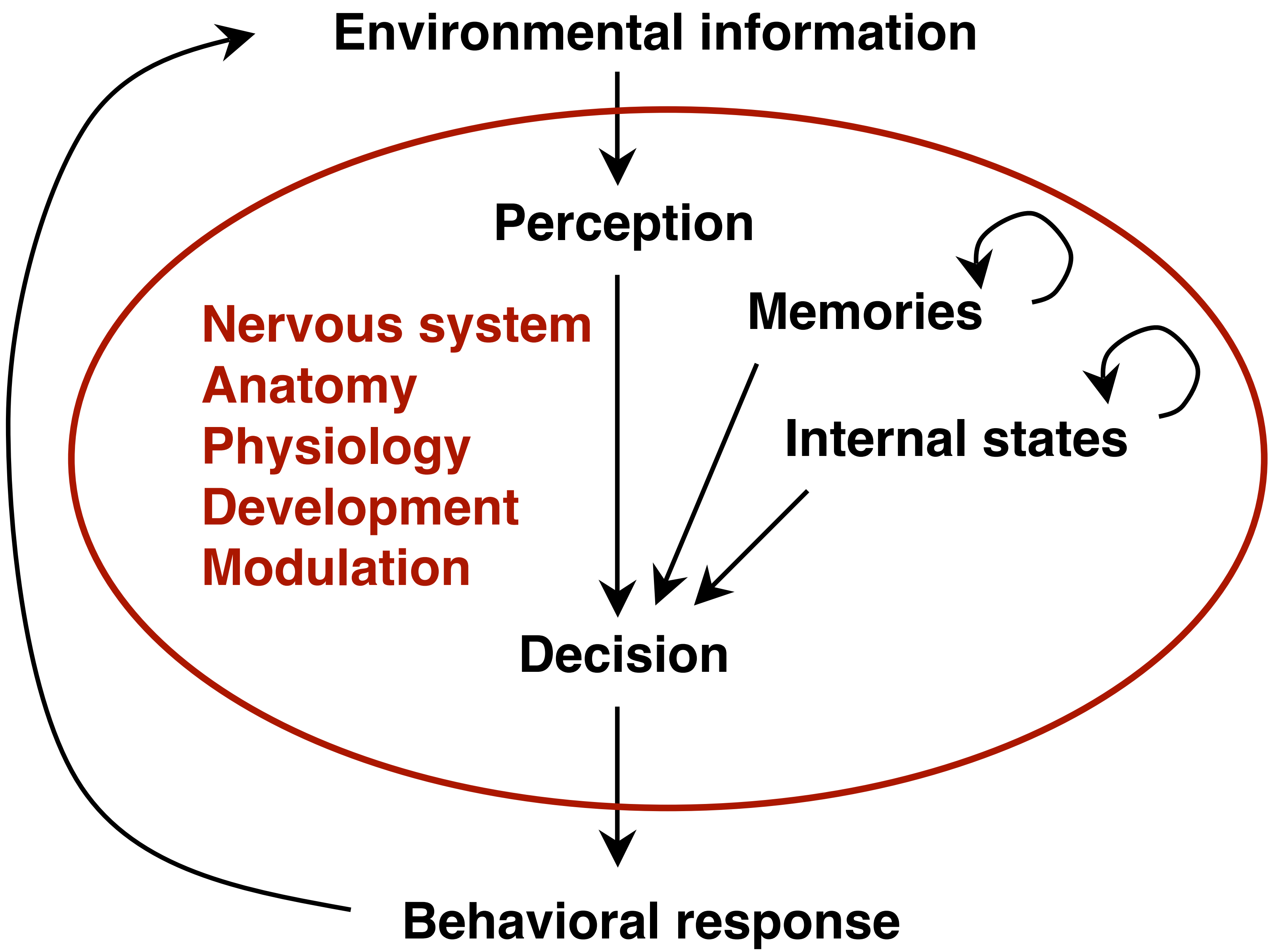
Although about half of the human genome derives from transposable elements, there has been a marked decline in the overall activity of such elements in the hominid lineage. DNA transposons appear to have become completely inactive and long-terminal repeat (LTR) retroposons may also have done so.

Analysis of the organization of Alu elements explains the longstanding mystery of their surprising genomic distribution, and suggests that there may be strong selection in favour of preferential retention of Alu elements in GC-rich regions and that these 'selfish' elements may benefit their human hosts.

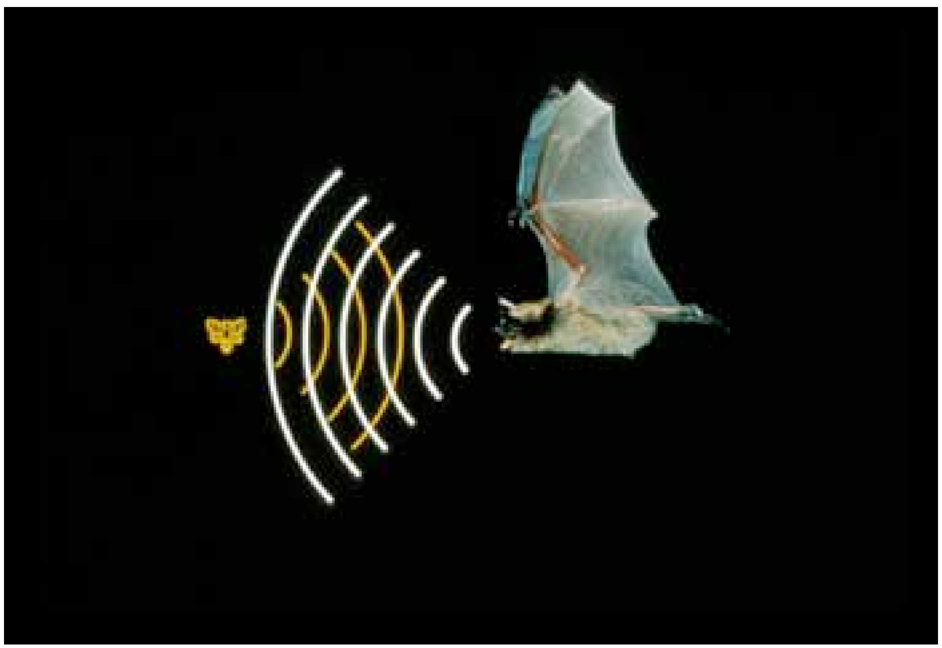
The mutation rate is about twice as high in male as in female meiosis, showing that most mutation occurs in males.

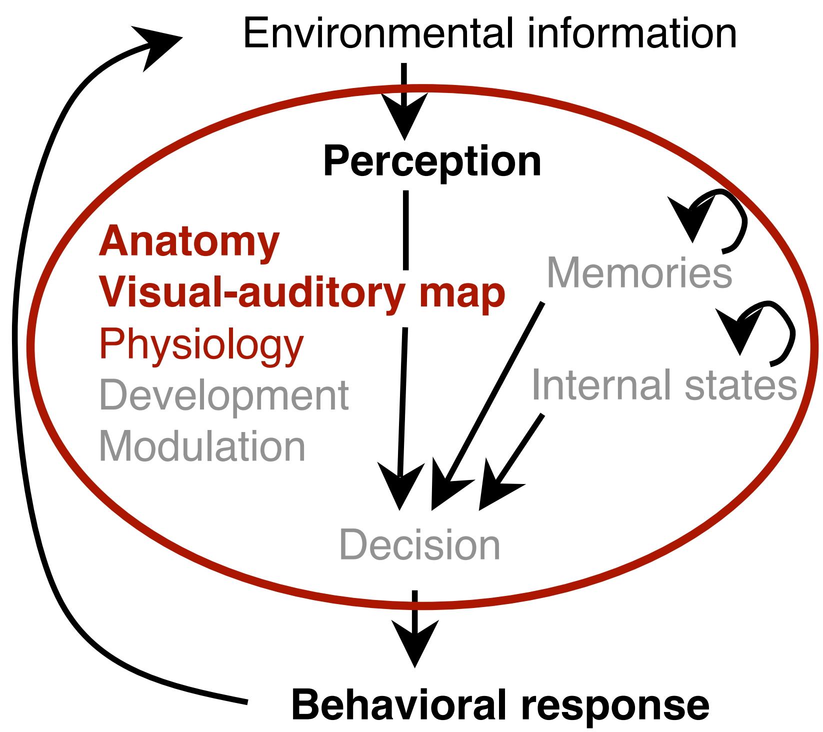
Complex behaviors begin with core behaviors

- common themes across systems/animals
- sources of variation between systems/species
- variation between individuals
- variation within individuals

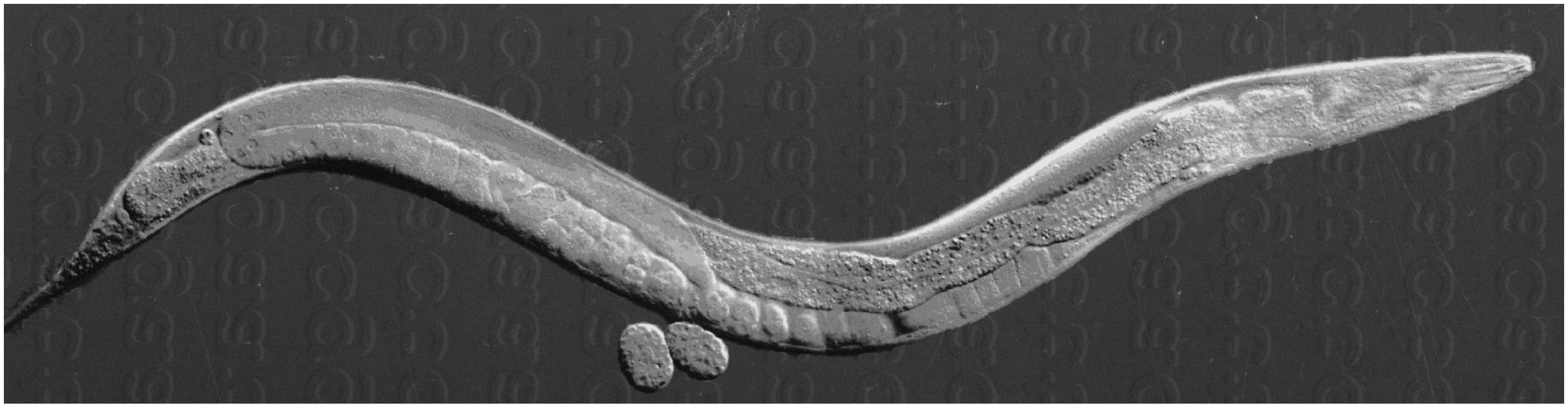

Environmental information
Perception
Nervous system
Anatomy
Physiology
Development
Modulation
Memories
Internal states
Decision
Behavioral response

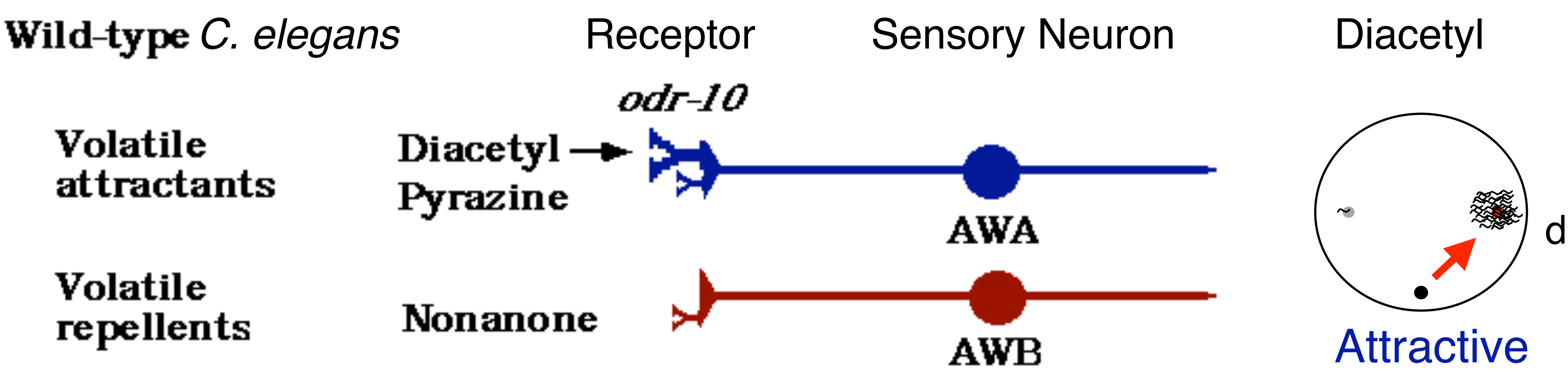
Complex behaviors begin with core behaviors



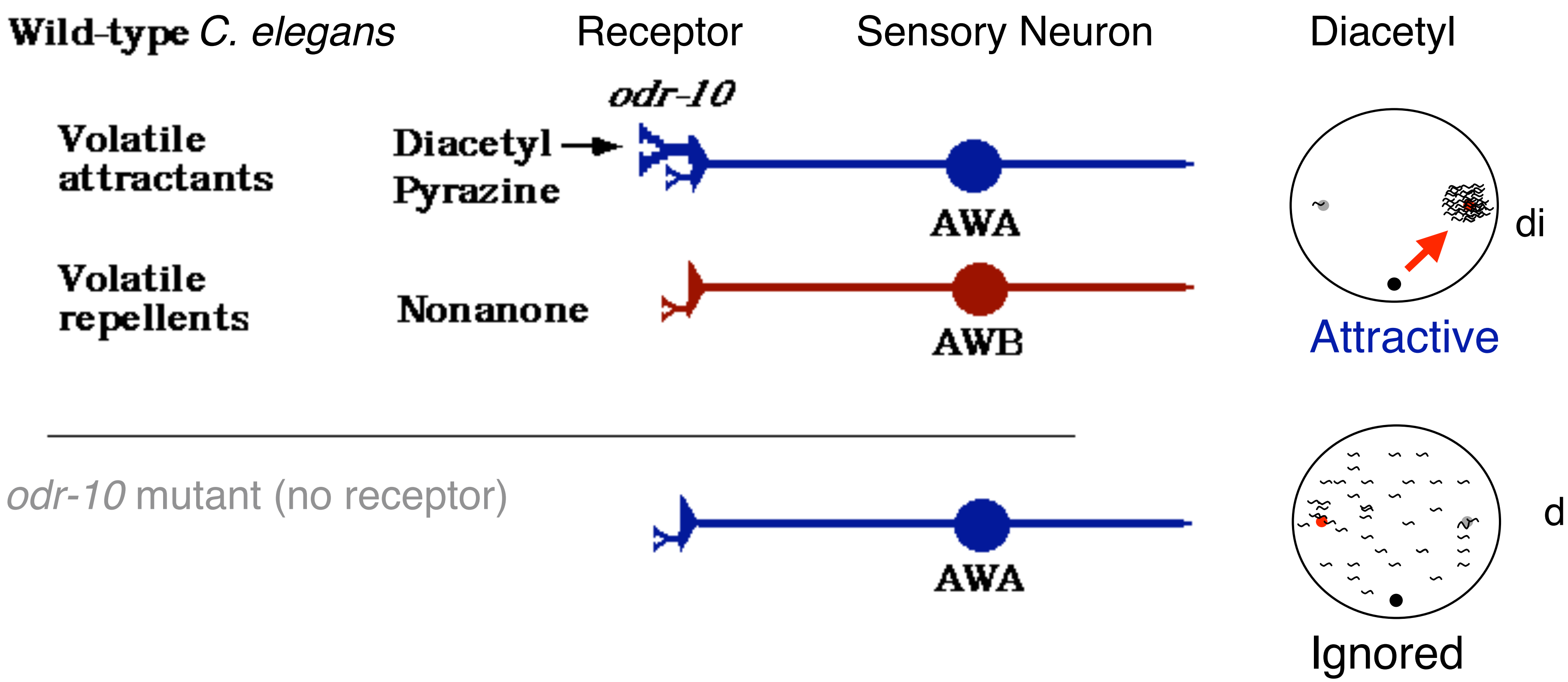


Core behaviors start with innate circuits & preferences

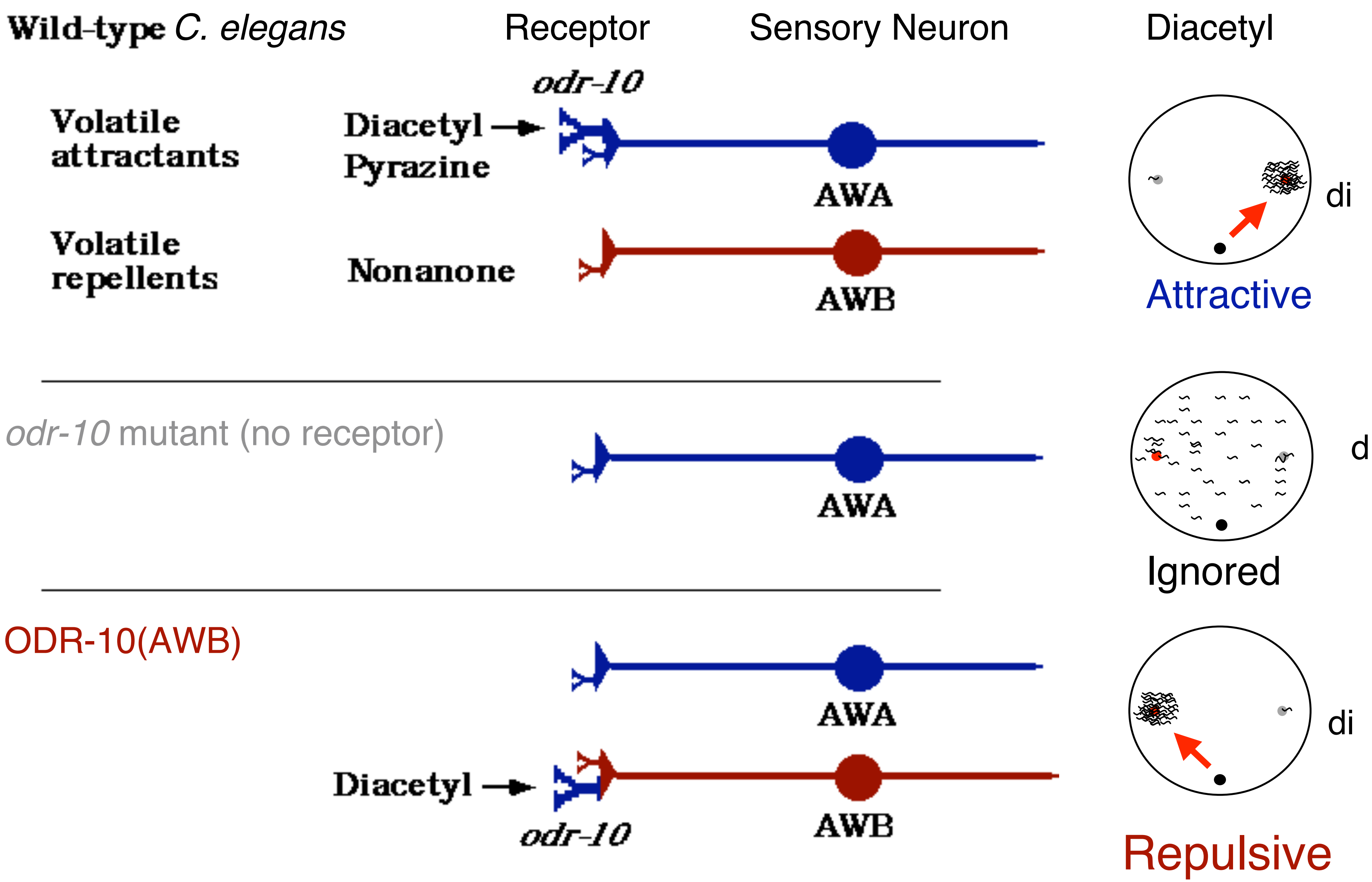




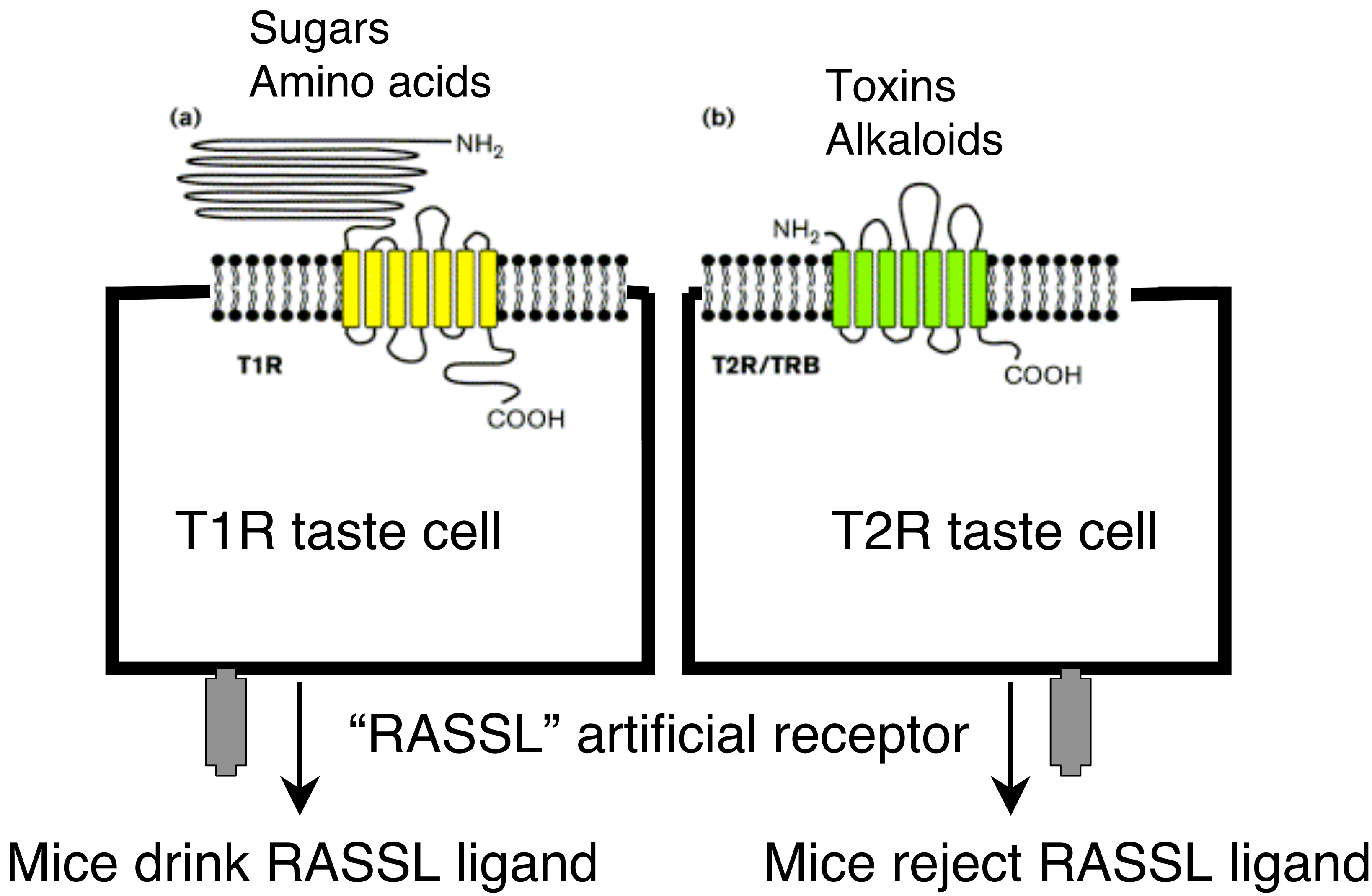
How is an attractive response specified?



How is an attractive response specified?

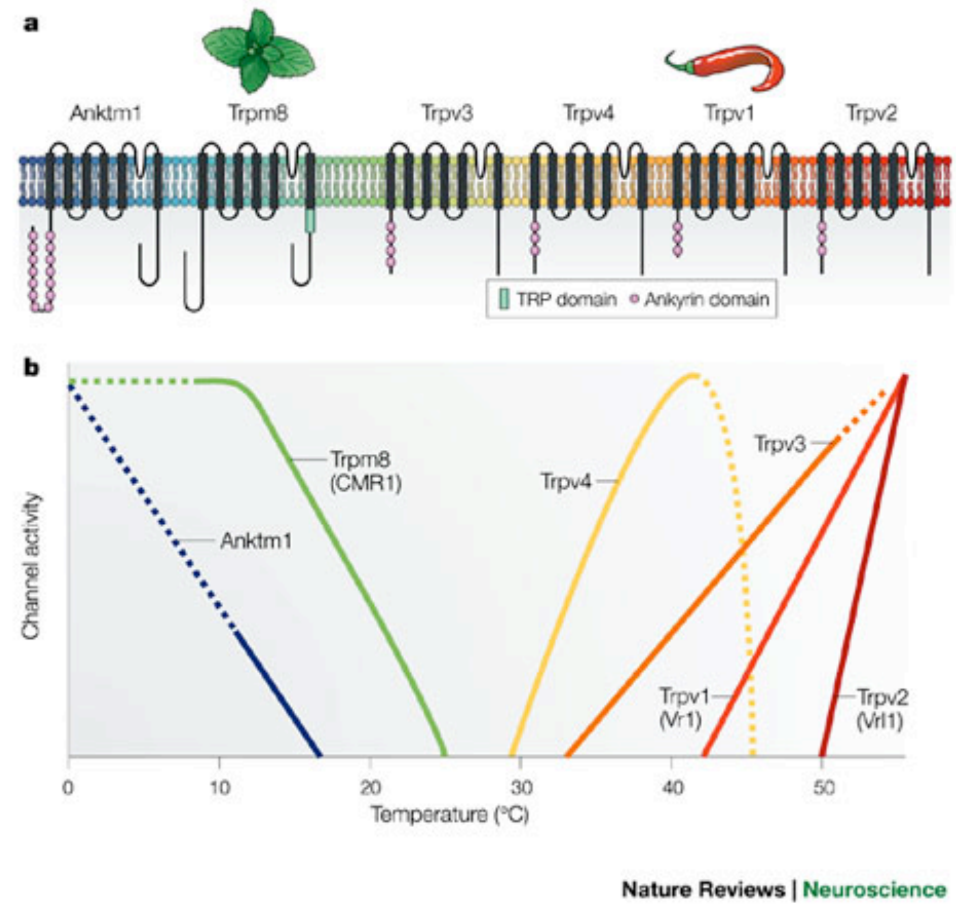


Mammalian taste responses are hard-wired too



Zuker, Ryba and colleagues

Sensory inputs link to anatomical pathways for innate preference



nb Not very appealing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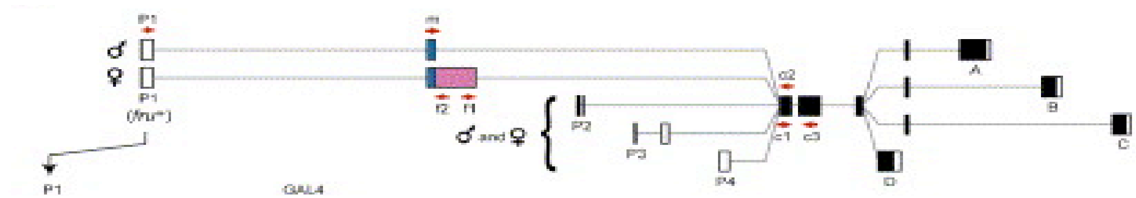
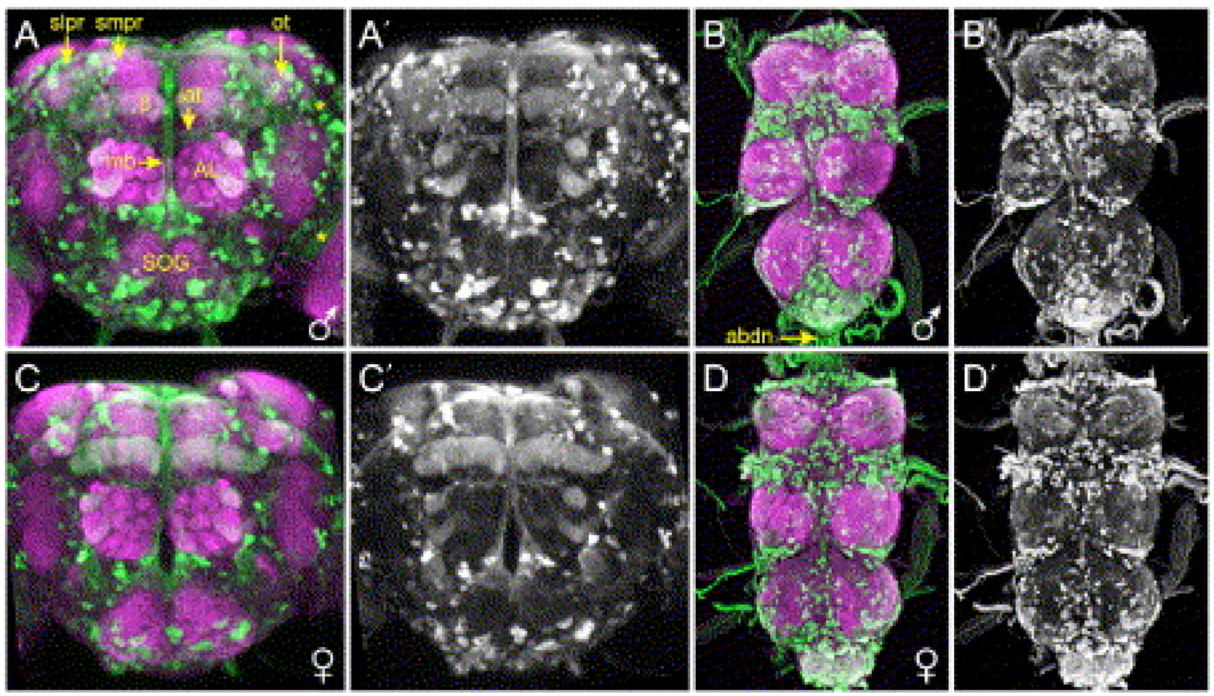
The alternatively spliced gene fru drives male behaviors



Fru is in 2% of neurons, mostly overlapping m/f

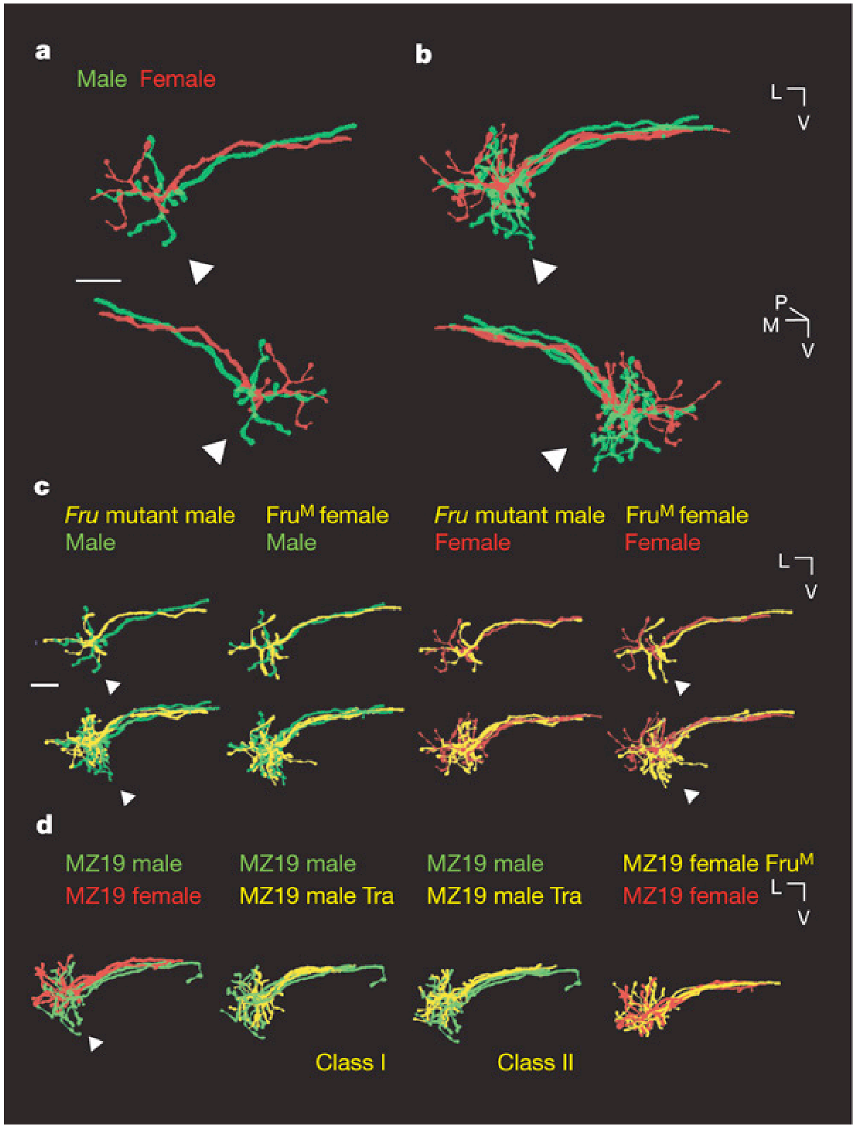
Males

Females



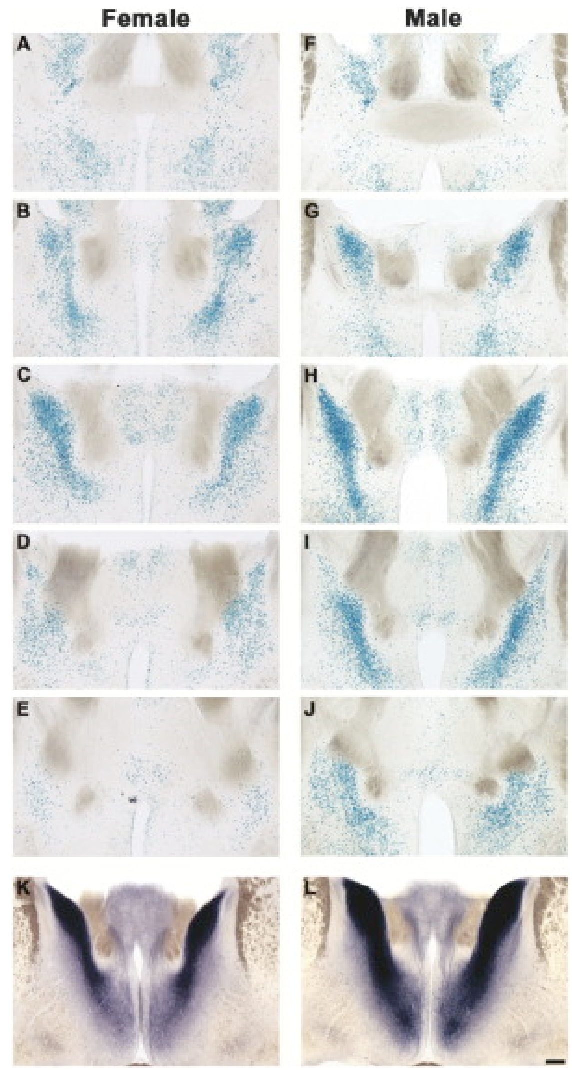
Anatomical dimorphism is subtle

Fru flies

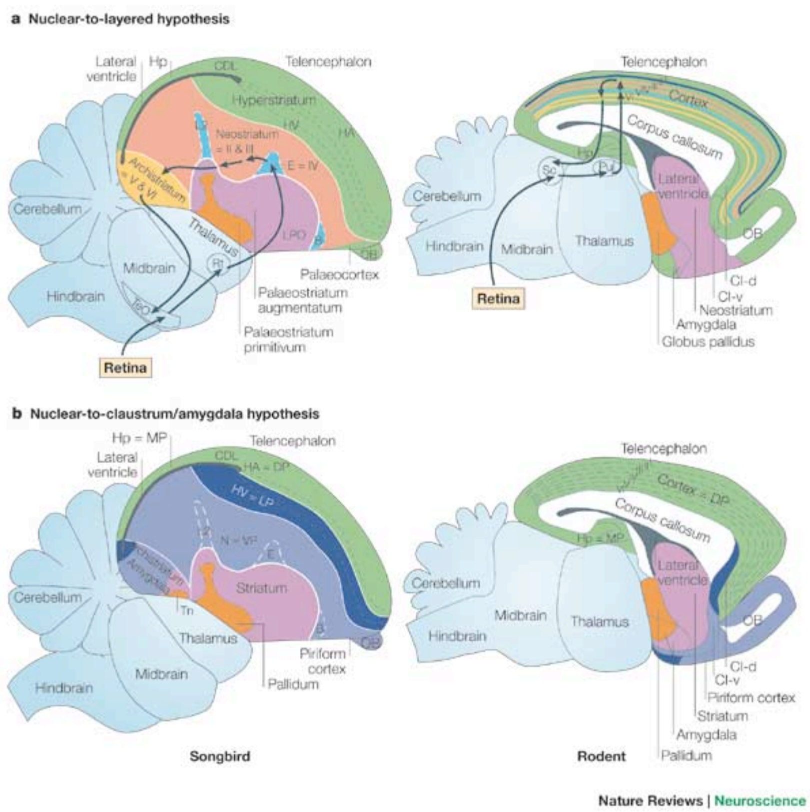


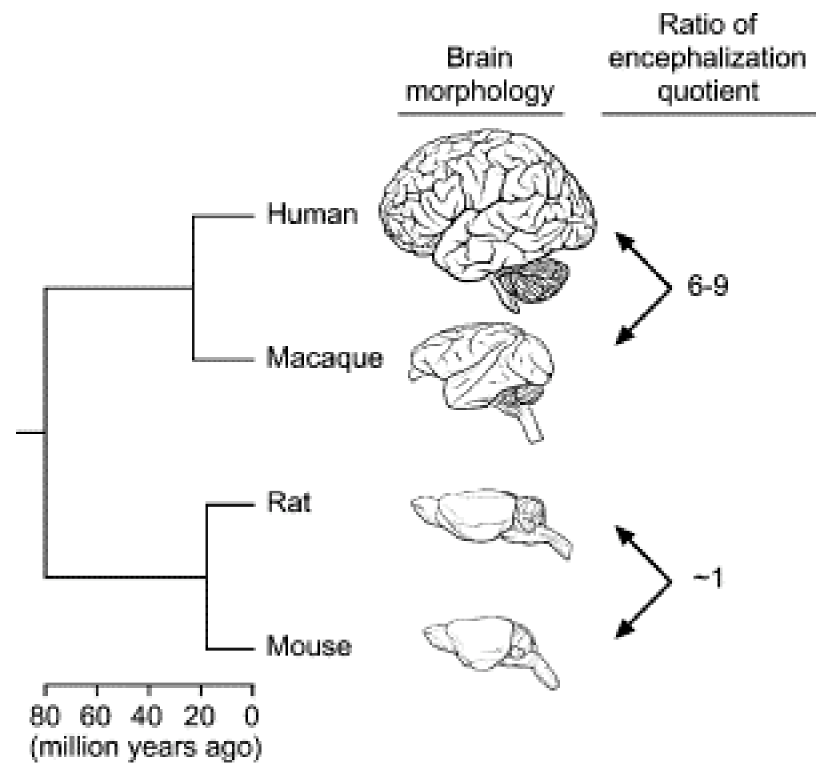
Androgen receptor cells

Mouse BNST, needed for male mating



Anatomy changes incrementally





If anatomy doesn't change quickly, what does?

Polygamous and monogamous social behavior in voles

Meadow vole:
Mostly solitary
Limited maternal care
No paternal care
Non-territorial, non-aggressive
Low separation stress

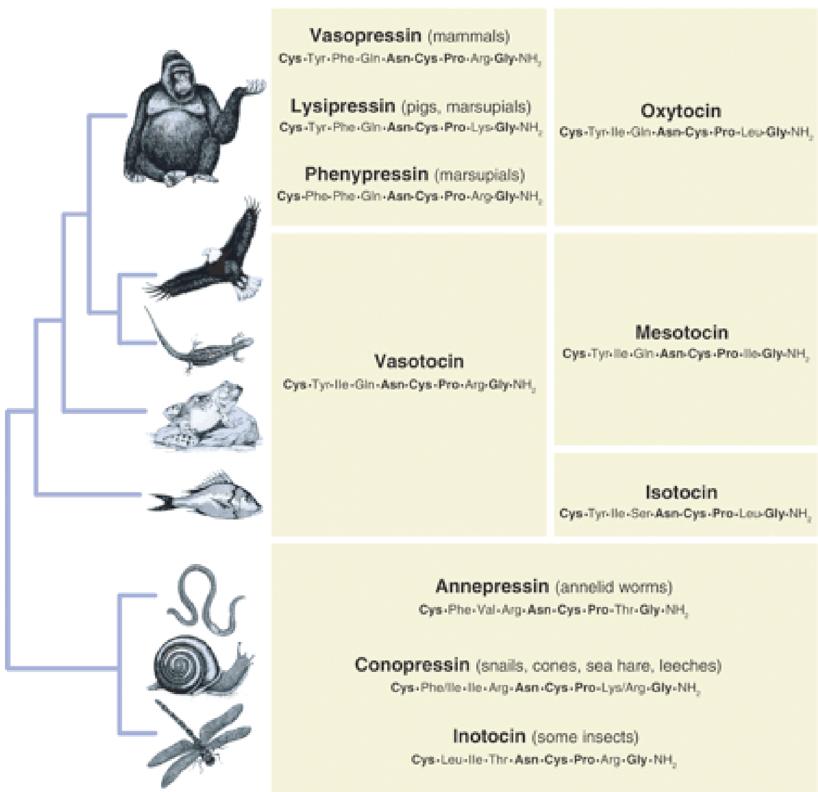
Prairie vole:
Colonial
High maternal, paternal care
High pair-bonding
Territorial, aggressive
High separation stress

Insel, Young and colleagues

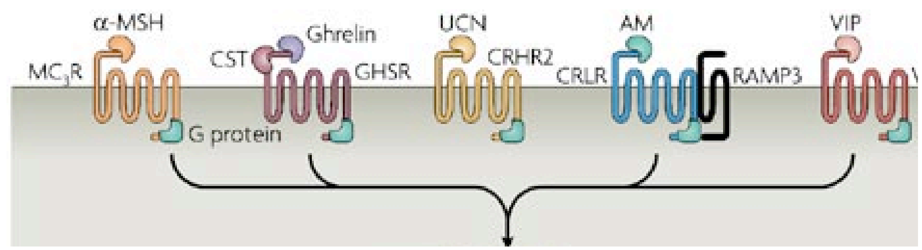
Oxytocin/vasopressin neuropeptides

Osmotic regulation (hypertonic)

Social behaviors: earthworms, fish, birds, mammals

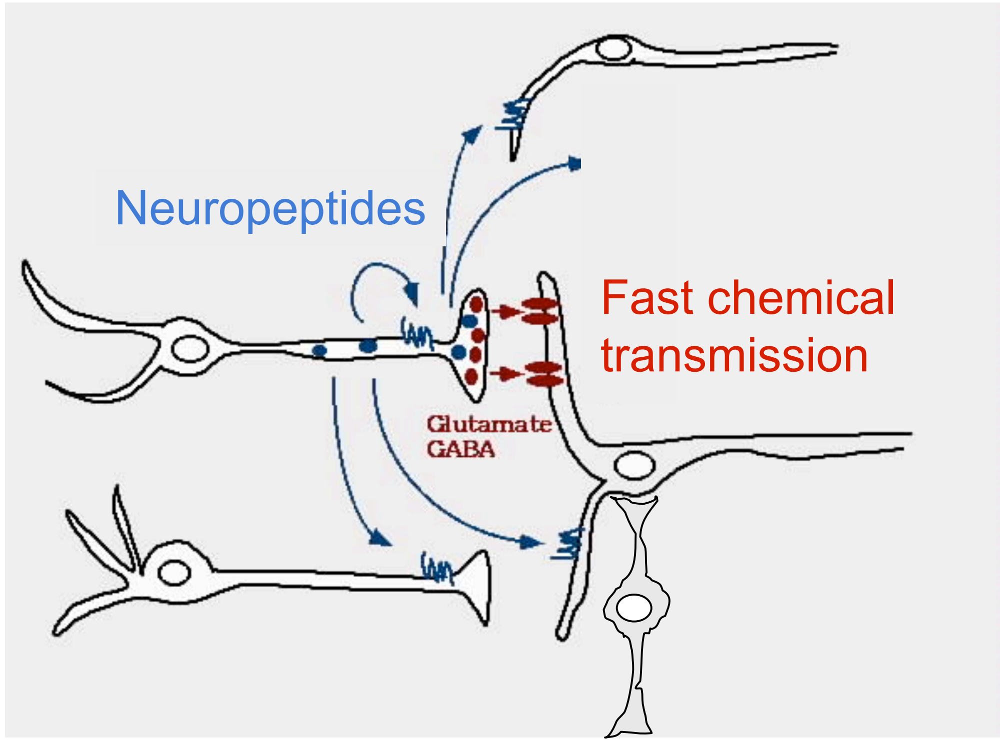


multiple G protein-coupled receptors for each peptide



Both montane and prairie voles have and express peptides

Different kinds of neuronal communication

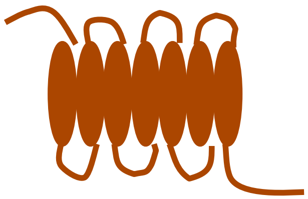


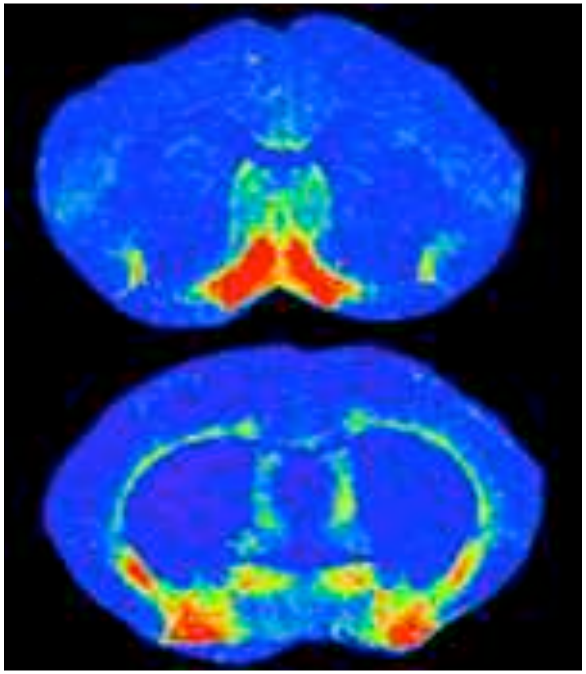
<u>Classical transmitters</u>
Fast (ms)
Act locally (synapse)
Instructive (depol/hyperpol)
Few, highly conserved

<u>Neuropeptides</u>
Slow (sec-min)
Can act at a distance
Modulatory (GPCR)
Many, rapidly-evolving

Vasopressin/oxytocin receptors are expressed differently in monogamous and polygamous voles

Vasopressin V1 receptor





Accumbens shell
(Nacc) - prairie vole (pair-bond)

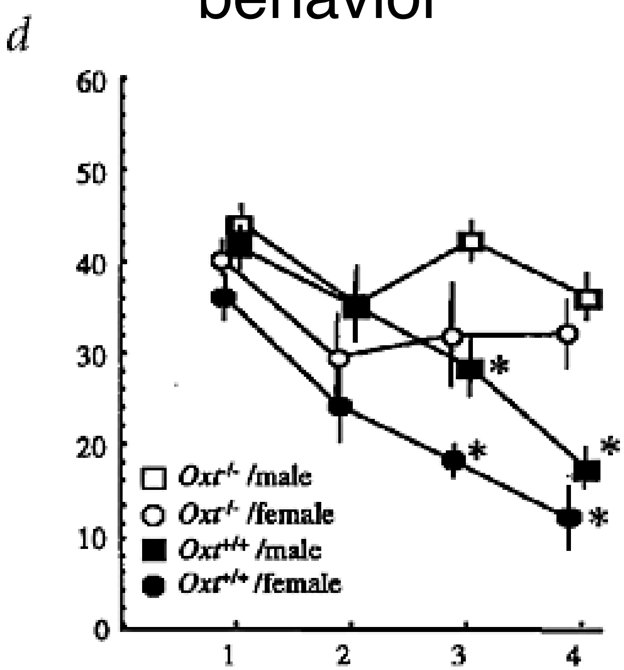
Lateral septum-montane vole

Oxytocin receptor in accumbens-
prairie vole, not montane vole

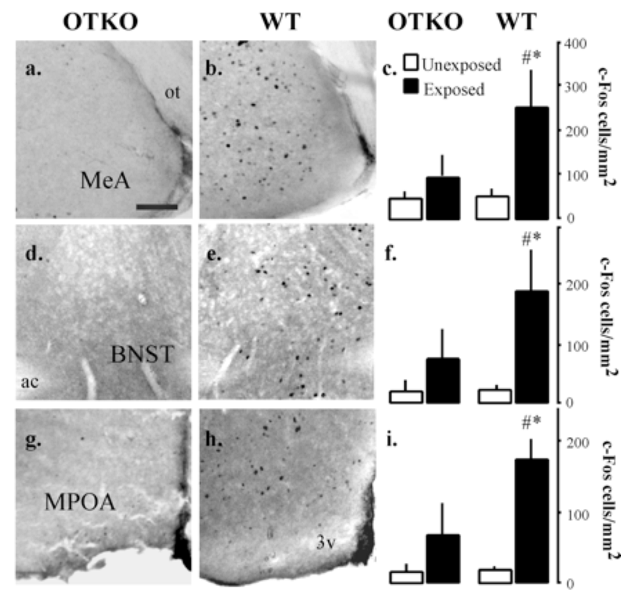
Insel, Young and colleagues

Oxytocin mutant mice have social amnesia

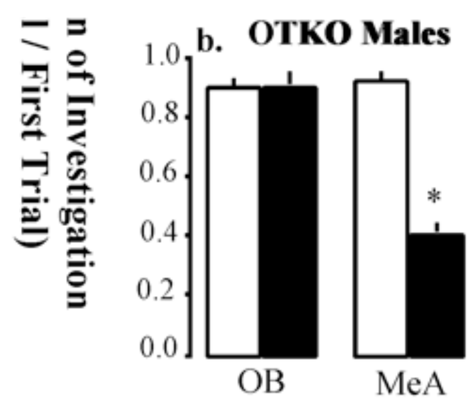
behavior



amygdala activation



rescue by regional
OT infusion into amygdala



Ferguson et al., 2000, 2001

Differences between species

Can involve new genes (pheromone receptors)

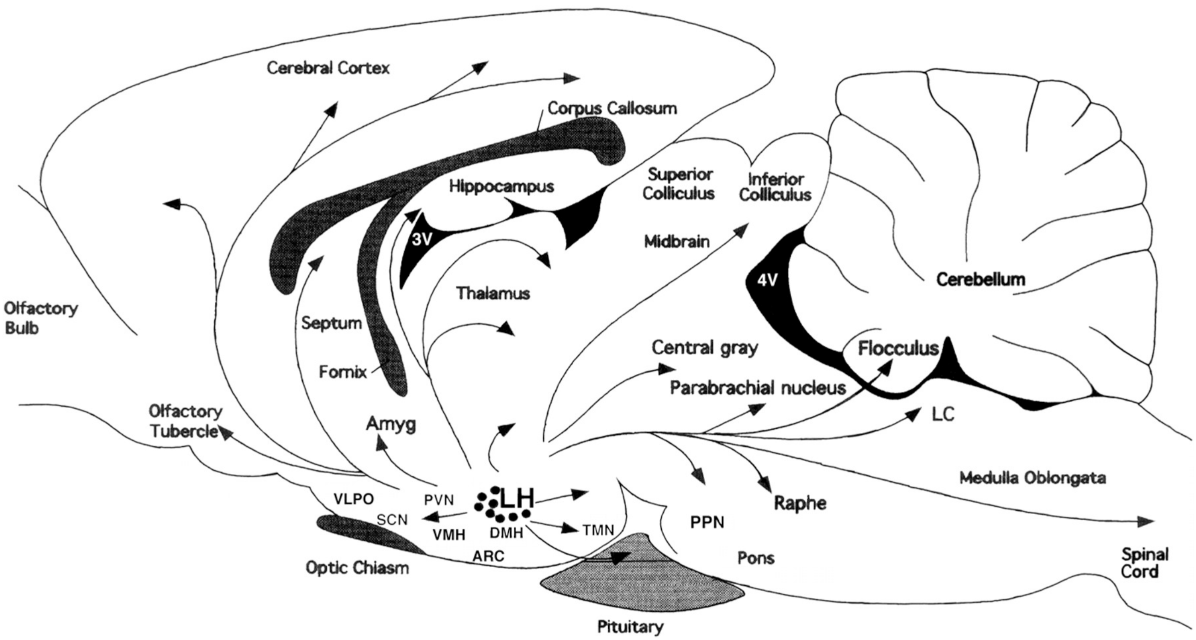
More likely to reconfigure existing genes

Relationship between sensory input, internal state, decision

Narcoleply/cataplexy
Reduced sleep latency, premature entry into REM sleep
Waking hallucinations
Loss of muscle control with excitement

Dog: hypocretin-2 (orexin) receptor
Mouse: hypocretin/orexin
Humans: autoimmune destruction of hypocretin neurons

~2000 hypocretin/orexin-producing neurons in the hypothalamus project to many regions involved in sleep and arousal



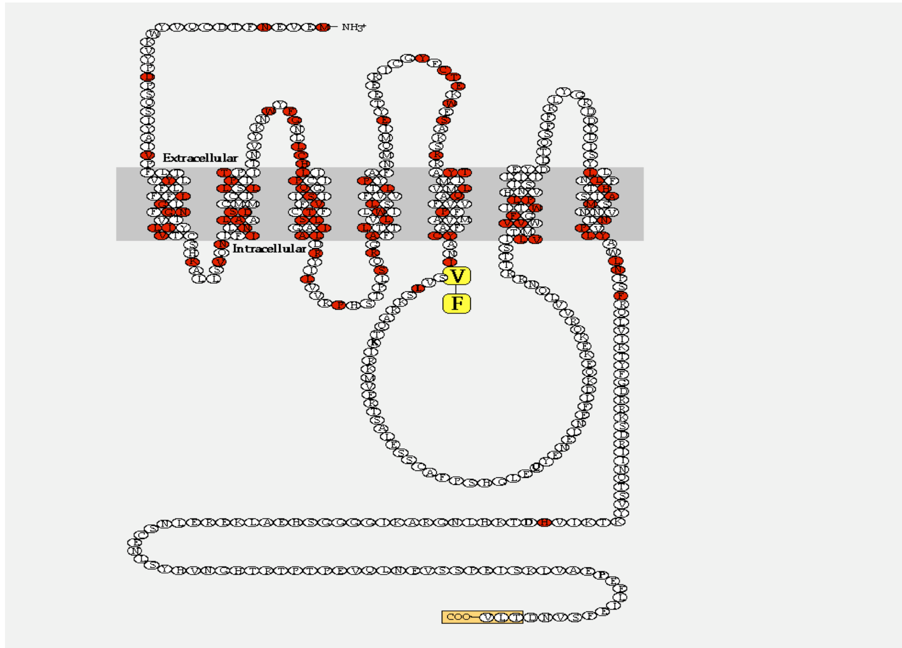
In fish, hypocretin receptor is not on arousal neurons

Variation in wild-type *C. elegans* aggregation behavior

Solitary feeding
N2, lab strains
(mostly)

Social feeding
Wild strains
(mostly)

Social and solitary strains
have different alleles of the neuropeptide receptor gene *npr-1*



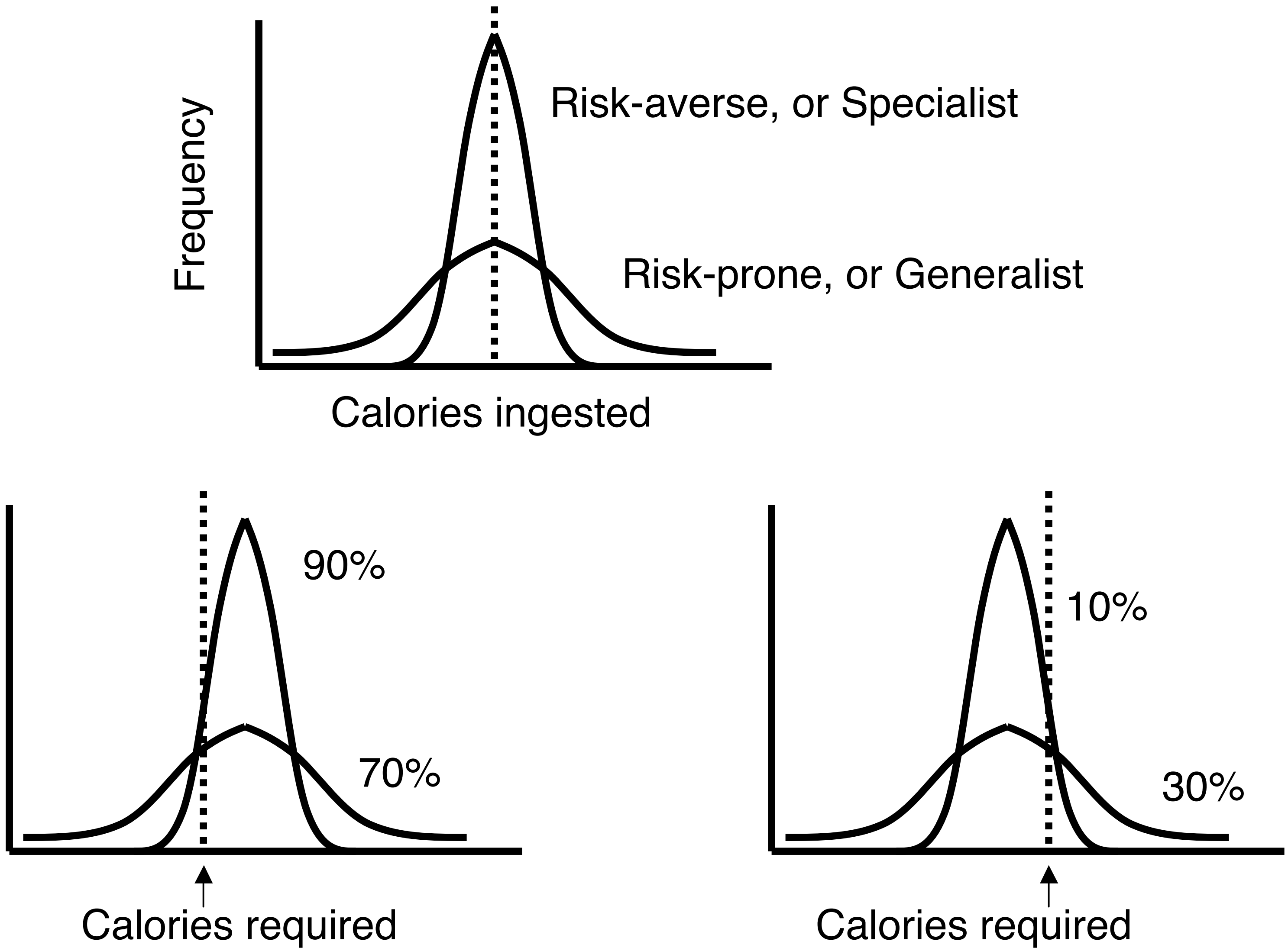
npr-1(215V) is necessary for solitary behavior:
If the gene is inactivated, solitary strains become social

npr-1 (215V) is sufficient for solitary behavior:
Introducing this one gene makes wild social strains become solitary

Neuropeptides can account for differences
Between species (voles, expression pattern)
Between individuals (worms, protein activity level)
Within one individual (us, asleep or awake)

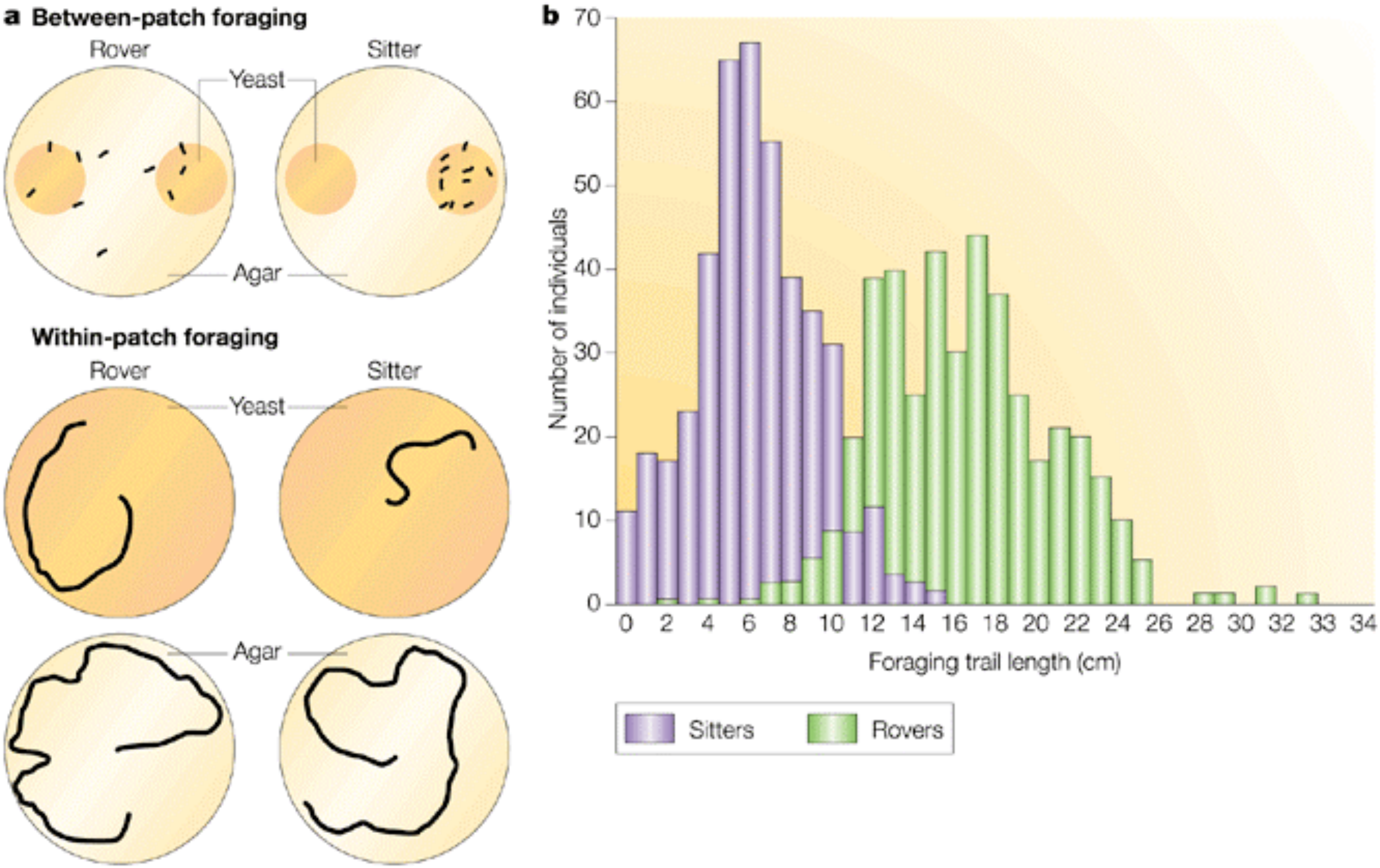



One species can use multiple behavioral strategies



Giraldeau and Livoreil, Game theory and social foraging (1998)

Drosophila larvae can be rovers or sitters



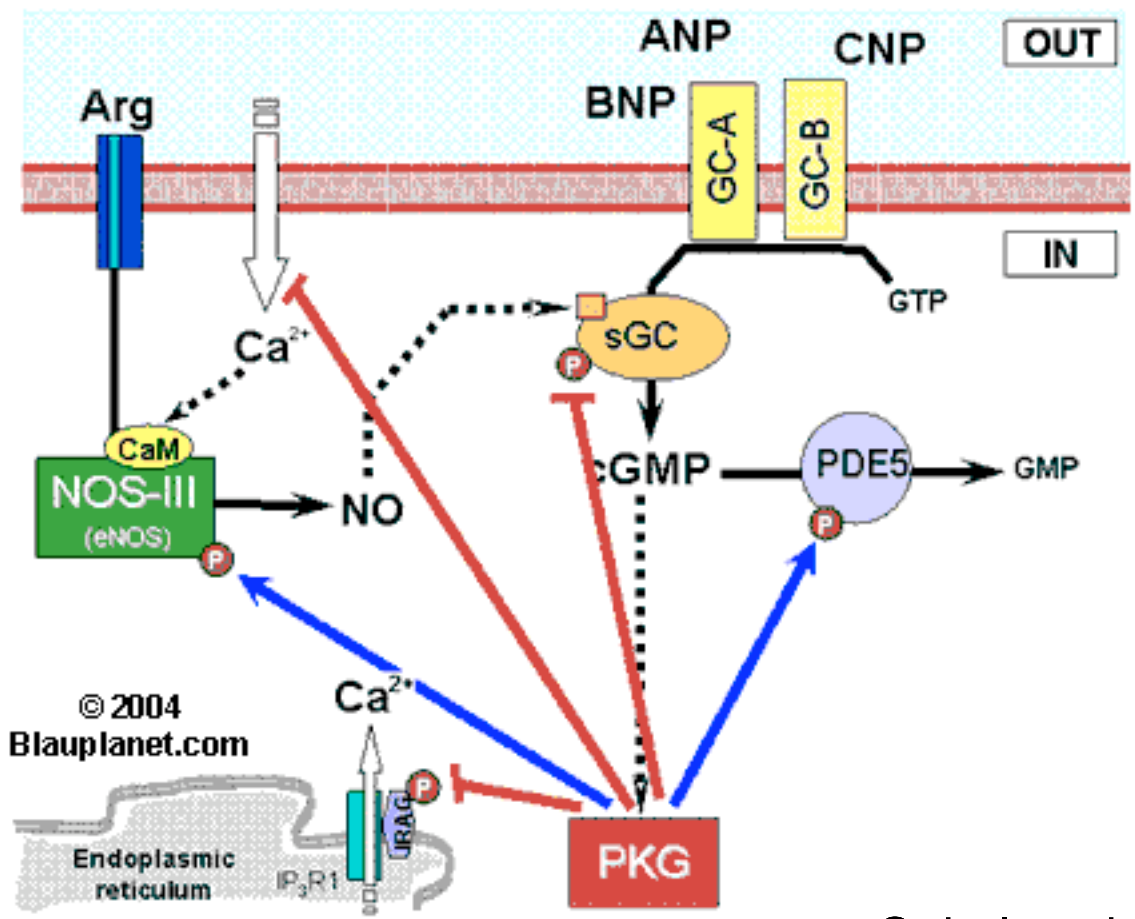
Nature Reviews | Genetics

forager locus encodes cGMP-dependent kinase:

High=Rover, Low=Sitter, Off=Dead

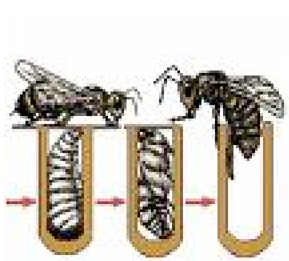
Activation: sensory, physiological pathways

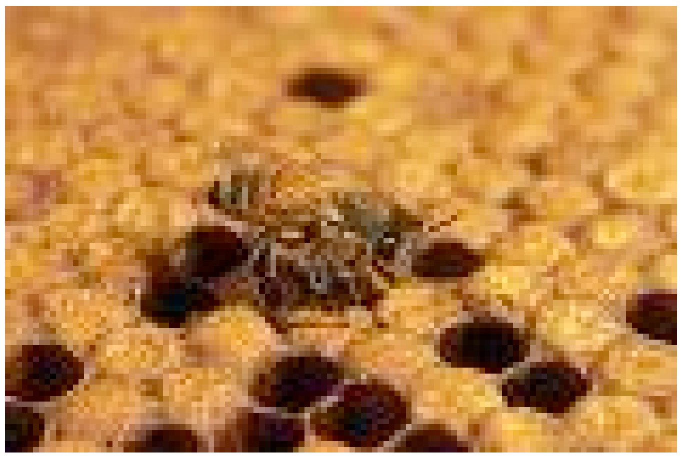
Targets: channels, signaling, neuronal excitability

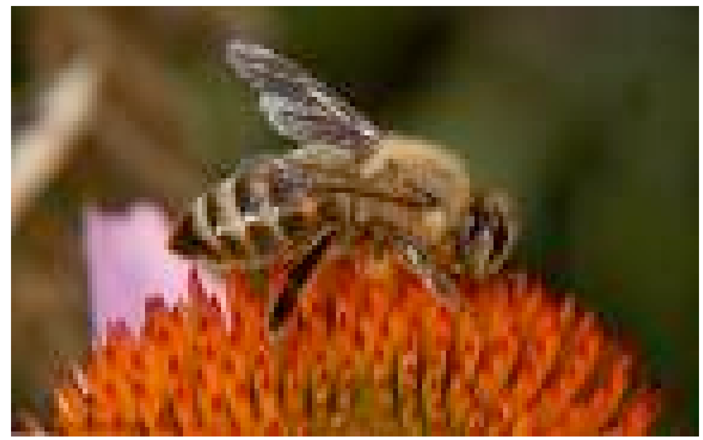


Sokolowski and colleagues

Intraspecies variation can be temporal as well as personal



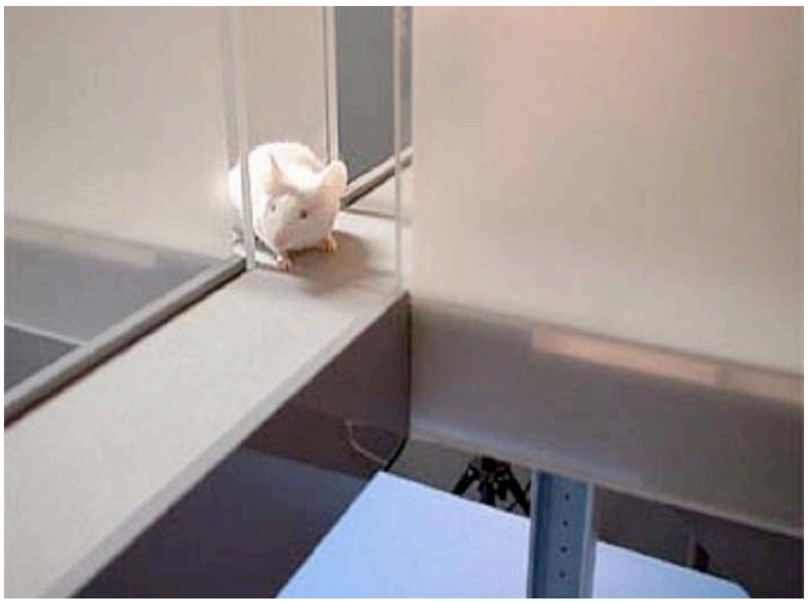


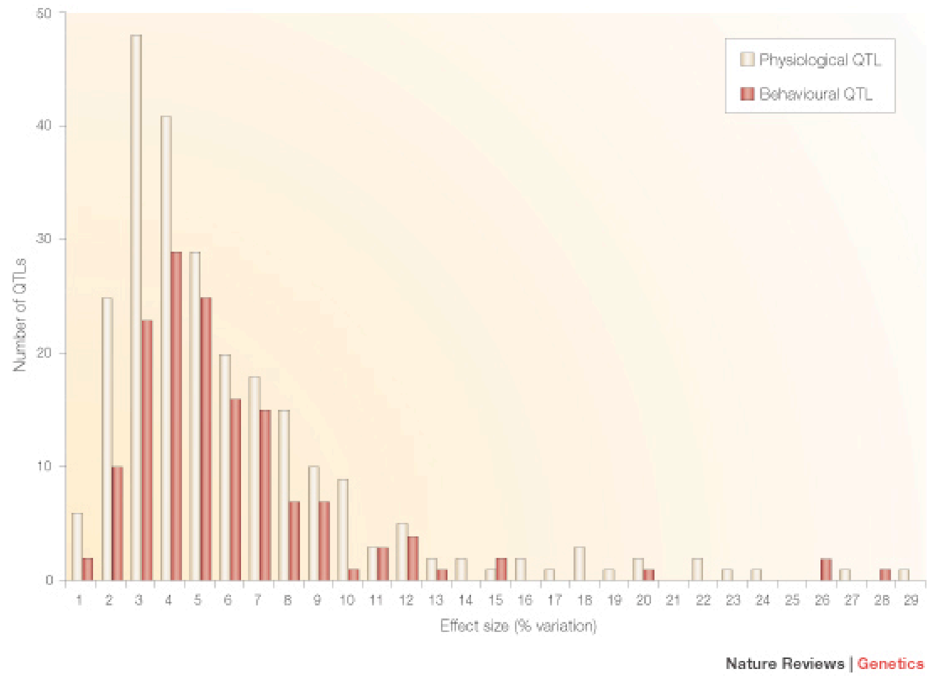


Honeybee workers: nurse (young) or forager (older)
Different activity levels of cGMP-dependent protein kinase

All of this is an oversimplification

Many genes affect anxiety-related behaviors in wild-type mouse strains





Only one is defined, a regulator of G protein-signaling

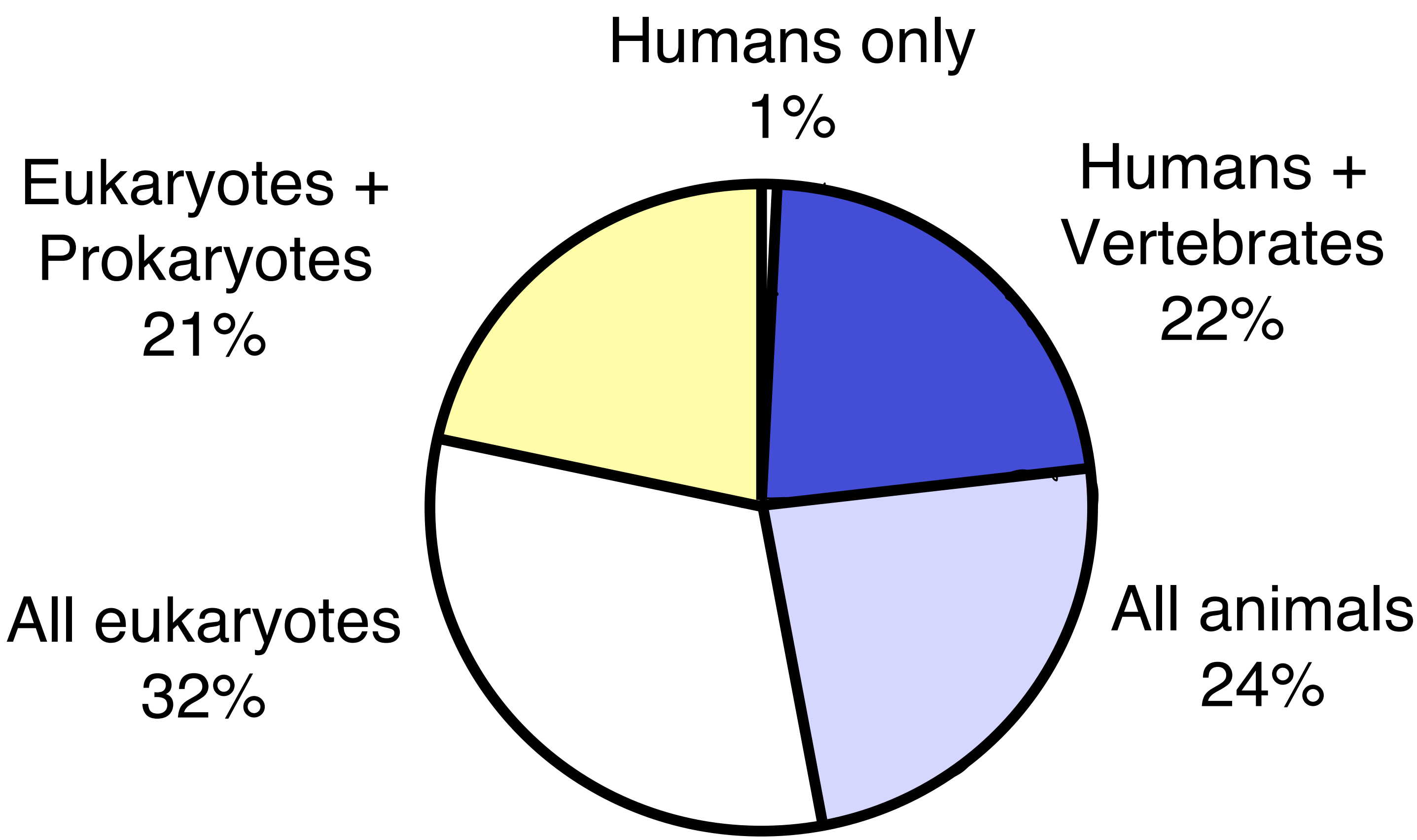
Differences within a species

Probably mostly not in core pathways
(rapid transmission, action potential, development)

More likely in modulatory pathways: tolerate highs/lows

We know about some individual genes-
but most variation is probably polygenic

Most human genes are shared with other organisms



Increased risk of psychiatric illness over the general population

	Identical twin	Sibling
Autism	2000-fold	50-150 fold
Schizophrenia	48-fold	9-fold
Bipolar disorder	60-fold	7-fold
Depression	8-fold	2-5 fold
Type 2 diabetes	16-fold	2-3 fold

Heritability of psychiatric disease

1. Shared environment? No
   Minnesota twin study (Bouchard)

2. Single-gene mutations like cystic fibrosis? No
   Linkage studies in 1980s, 1990s

3. Common low-risk alleles, like ApoE/Alheimer's? No
   Failure of whole-genome association in 2000s.

Whole-genome association studies

Haplotype: 10 kb of linkage disequilibrium
Human genome: $3x10^6$ kb

SNPs: 500,000-600,000 to cover haplotypes
25,000 to 30,000 will be "P<0.05"
Correction for multiple comparisons --
Need enormous numbers if small effects

	# of patients needed if allele is common (~30%)	rare (~5%)
30% increased risk	5000	30,000

4. Many rare risk alleles? A few validated examples
   Autism -- neuroligin (synaptic plasticity)
   Schizophrenia -- neuregulin (barely, inhibitory neurons)
   Attention deficit -- DRD4 dopamine receptor
   each, maximally, 1-3% of total cases

5. New mutations? Discussion paper