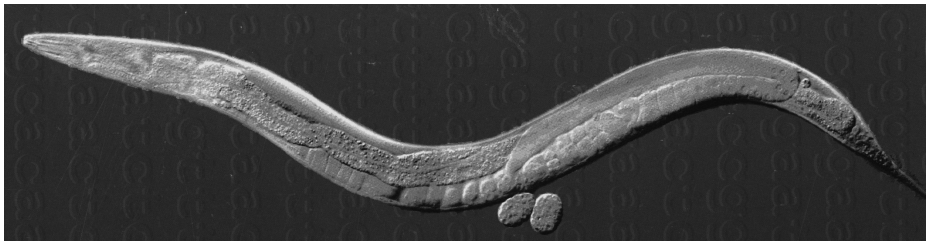
Genes, the brain, and behavior



Cori Bargmann
Howard Hughes Medical Institute
The Rockefeller University
New York, NY USA

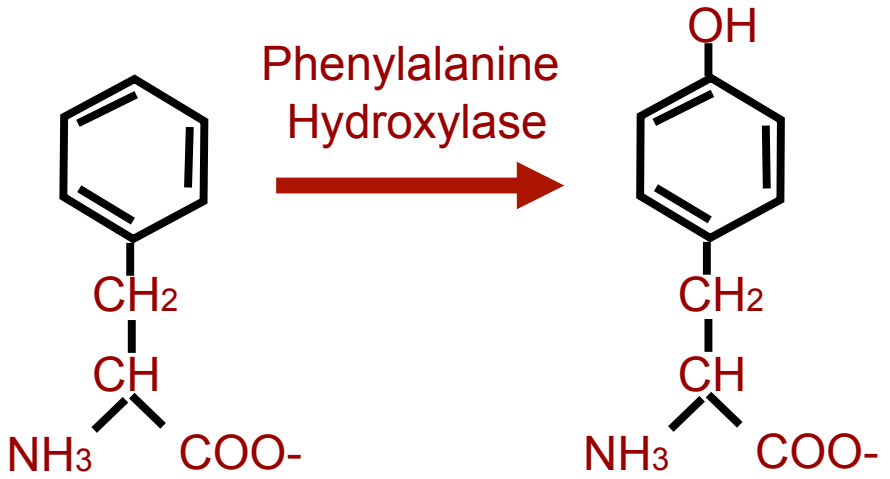
Familial risk of psychiatric illness

	Identical twin	Sibling	Population
Autism	69%	6%	0.6%
Schizophrenia	50%	9%	0.9%
Bipolar disorder	40%	5%	1%
Depression	44%	20%	6%
Anxiety disorder	40%	25%	6%

The first genetically-defined brain disorder

Phenylketonuria (PKU, 1934)

Mental retardation
Delayed social skills
Hyperactivity
Movement disorders
Seizures



L-Phenylalanine L-Tyrosine

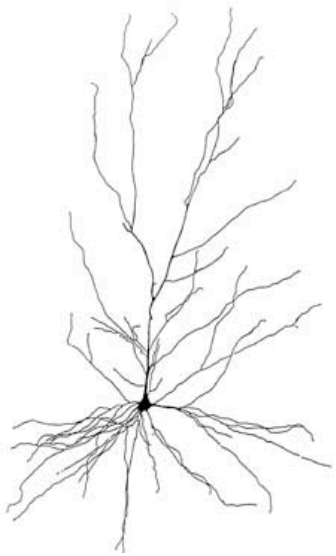
Diet

Gene → Neuron → Brain

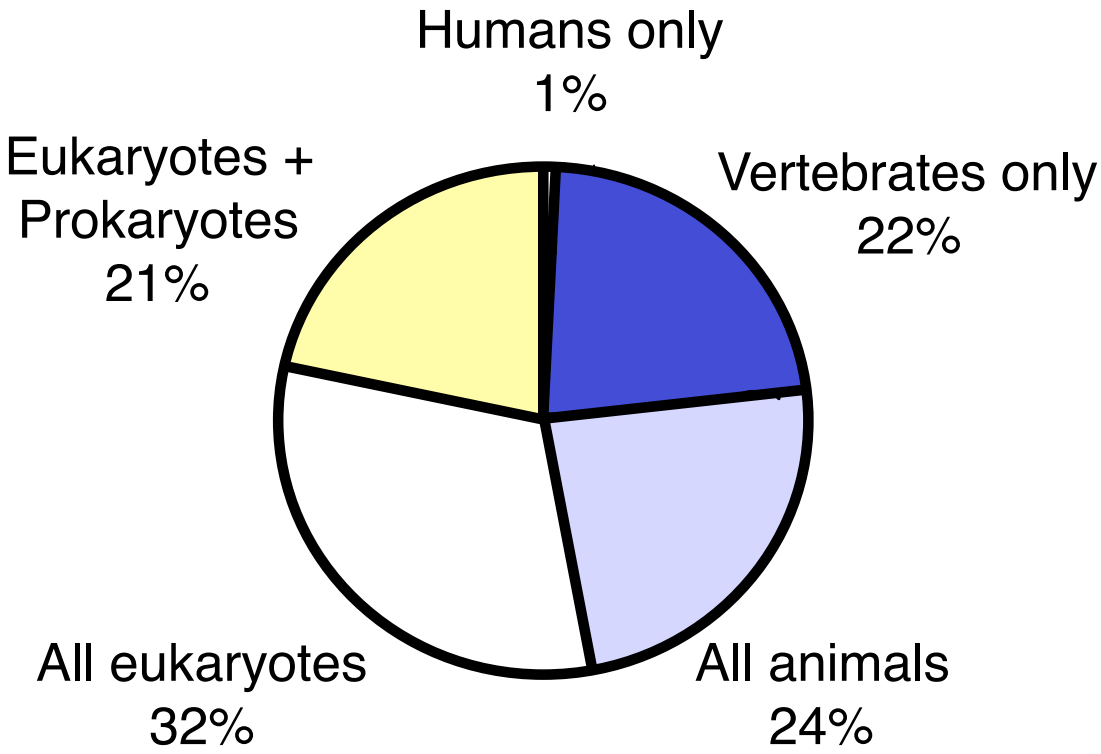
Mutation in phenylalanine hydroxylase

Smaller, fewer neurons

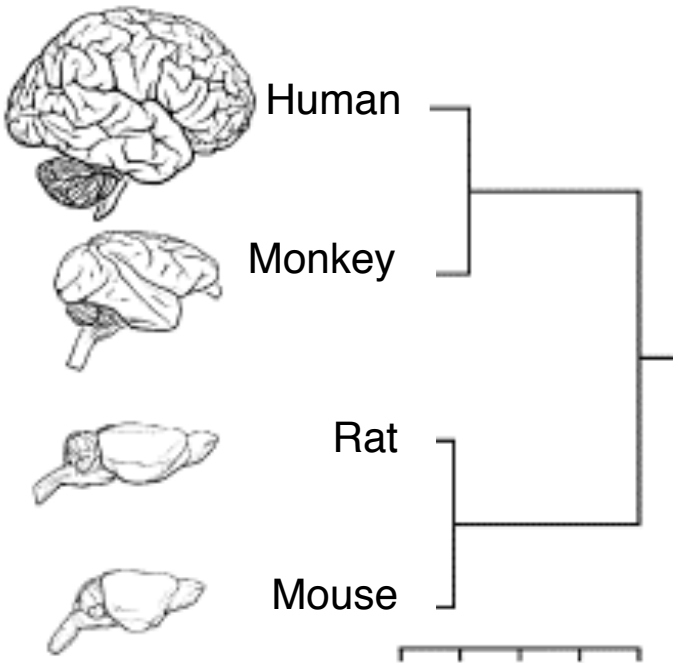
Altered function

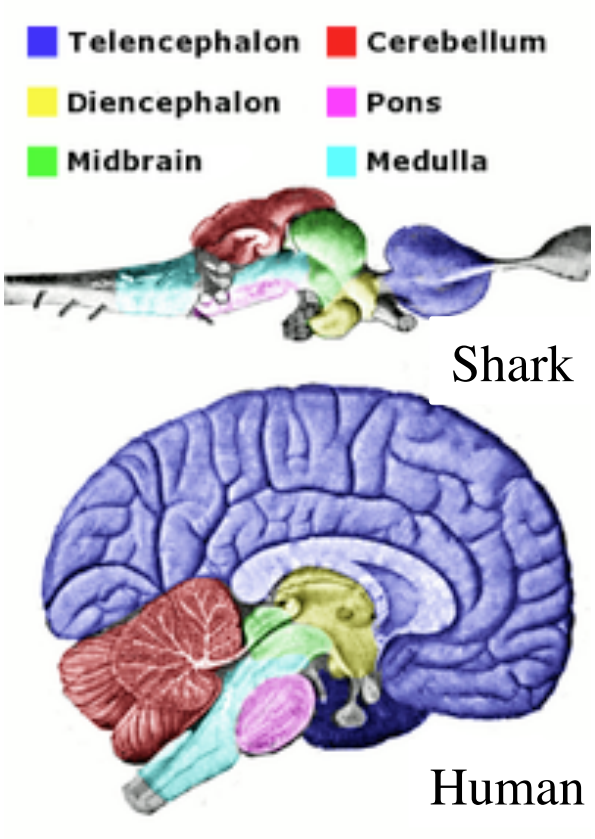


Humans share most genes with other organisms



Common brain regions in diverse animals





Neuroethology: the study of animal behavior

Sensory stimuli elicit
stereotyped behaviors

Examples: courtship, aggression

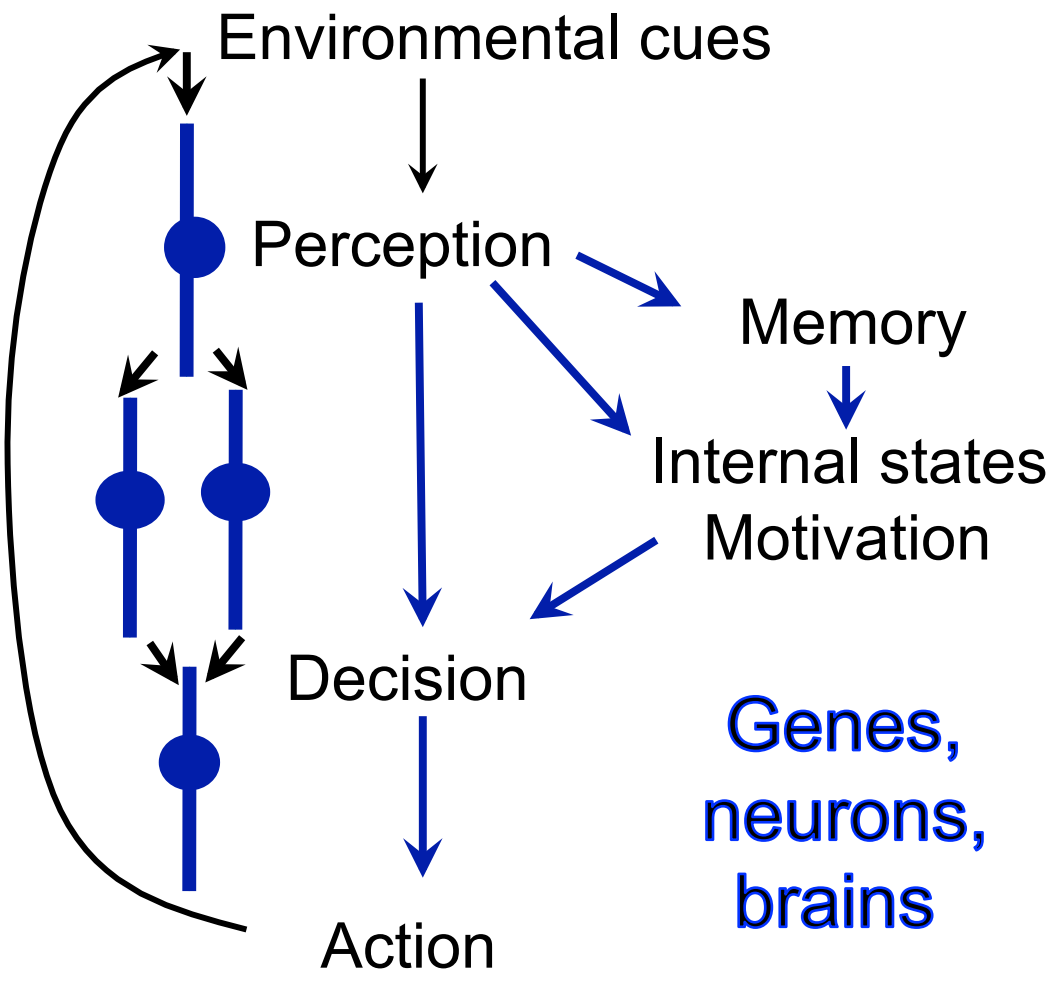
The brain has internal drives

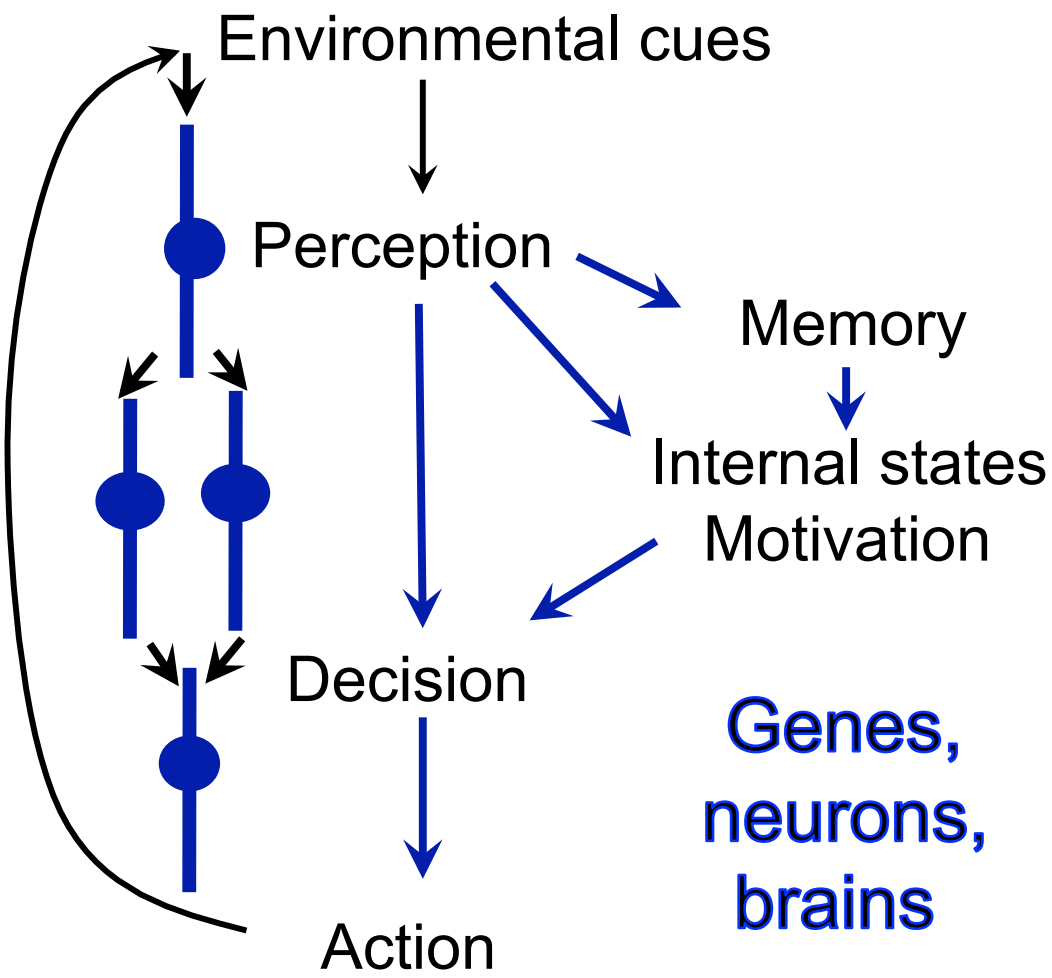
Examples: imprinting, songbird learning

Social behavior is widespread among animals

Examples: pheromones, dances

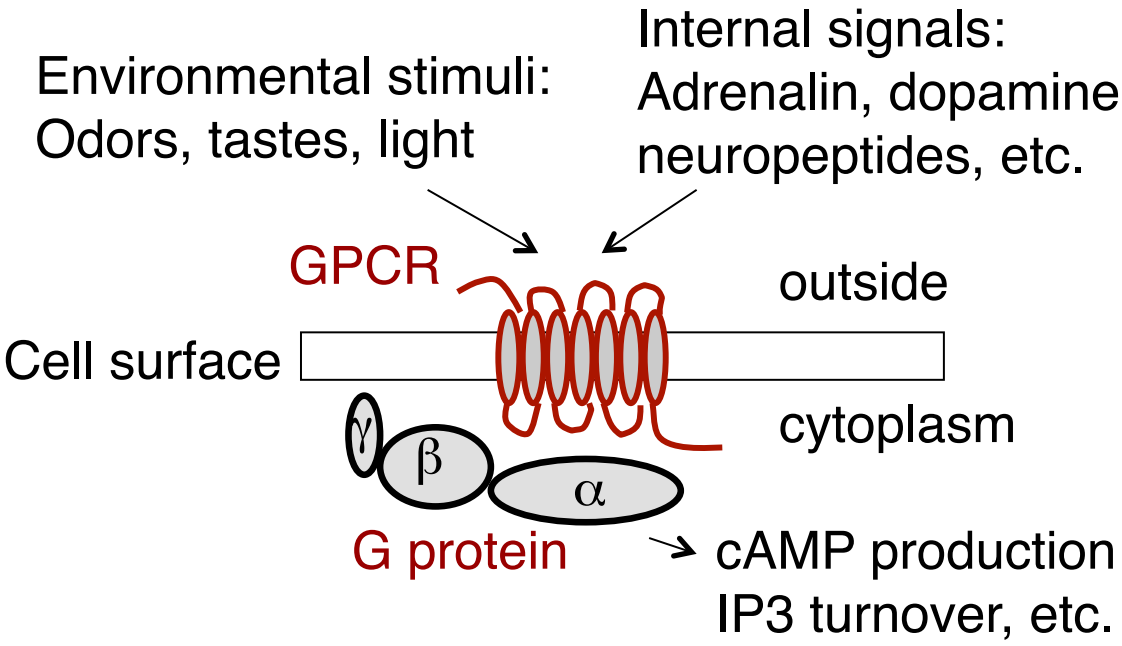
A framework for behavior

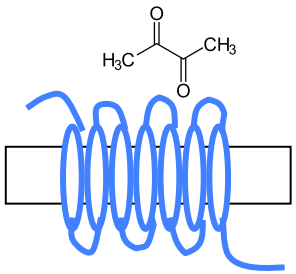




1. Sensation to action
2. Internal motivation
3. Natural variation

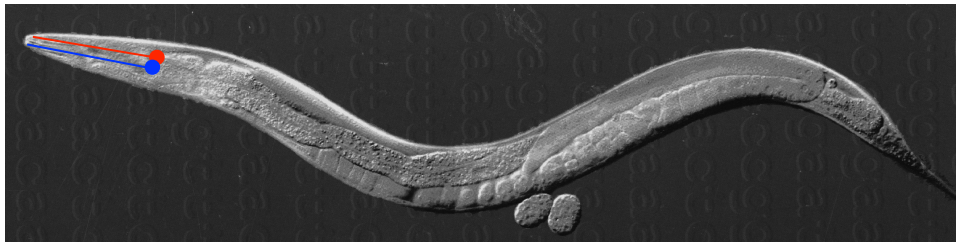
G protein-coupled receptors:
A class of molecules that affect behaviors



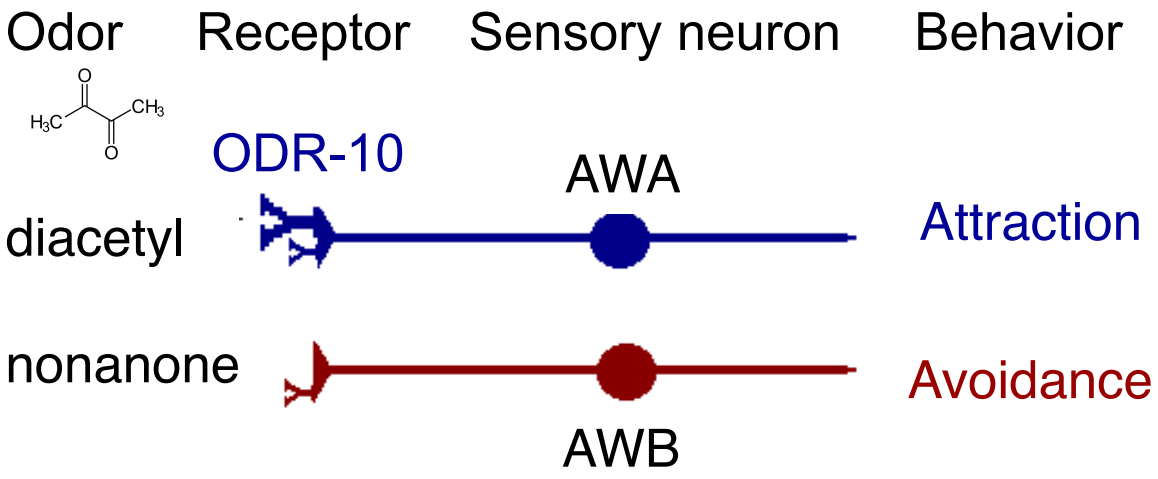


The odorant receptor
ODR-10

Behaviors start with innate preferences

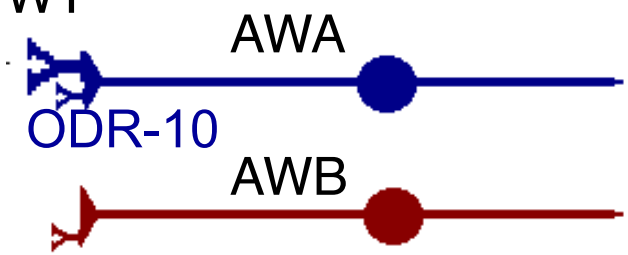


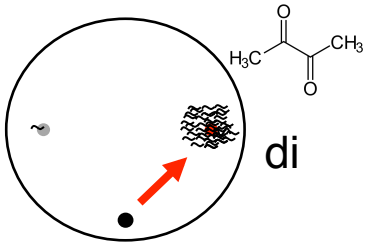
Caenorhabditis elegans



How is diacetyl attraction specified?

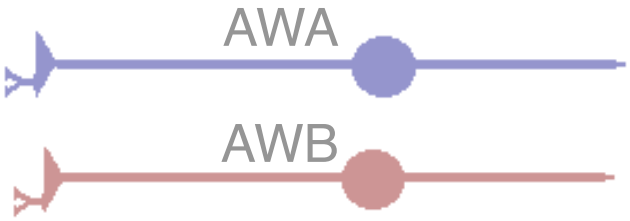
1. WT

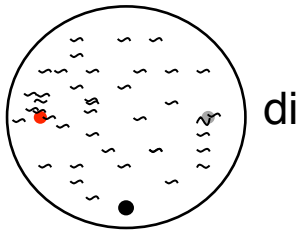




Attractive

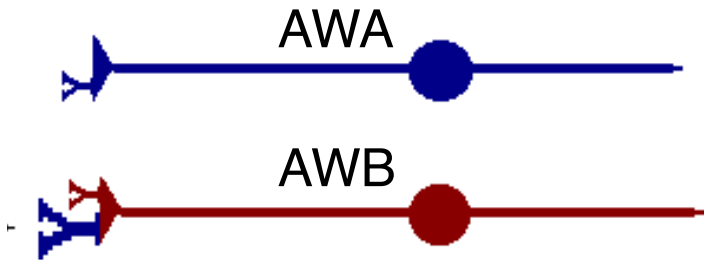
2. *odr-10* mutant (no receptor)

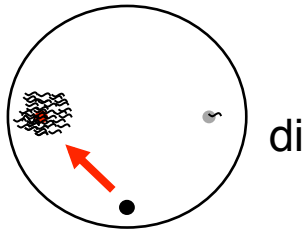




Ignored

3. AWB::ODR-10 transgene

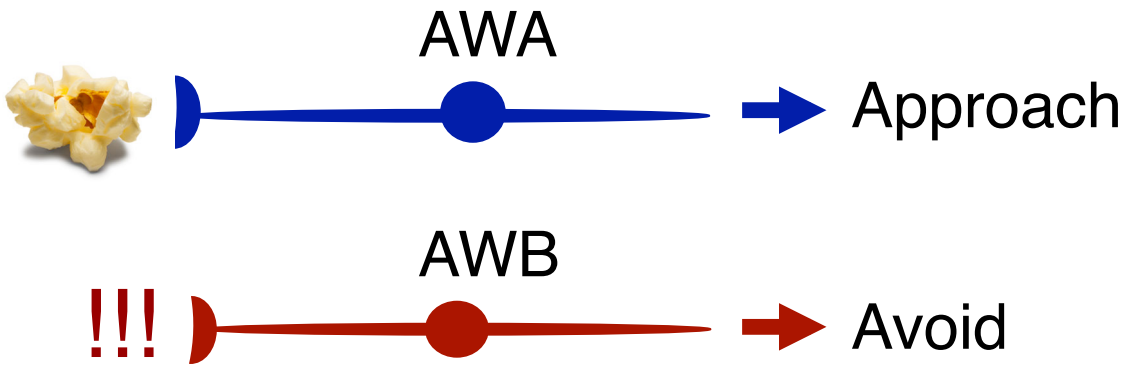




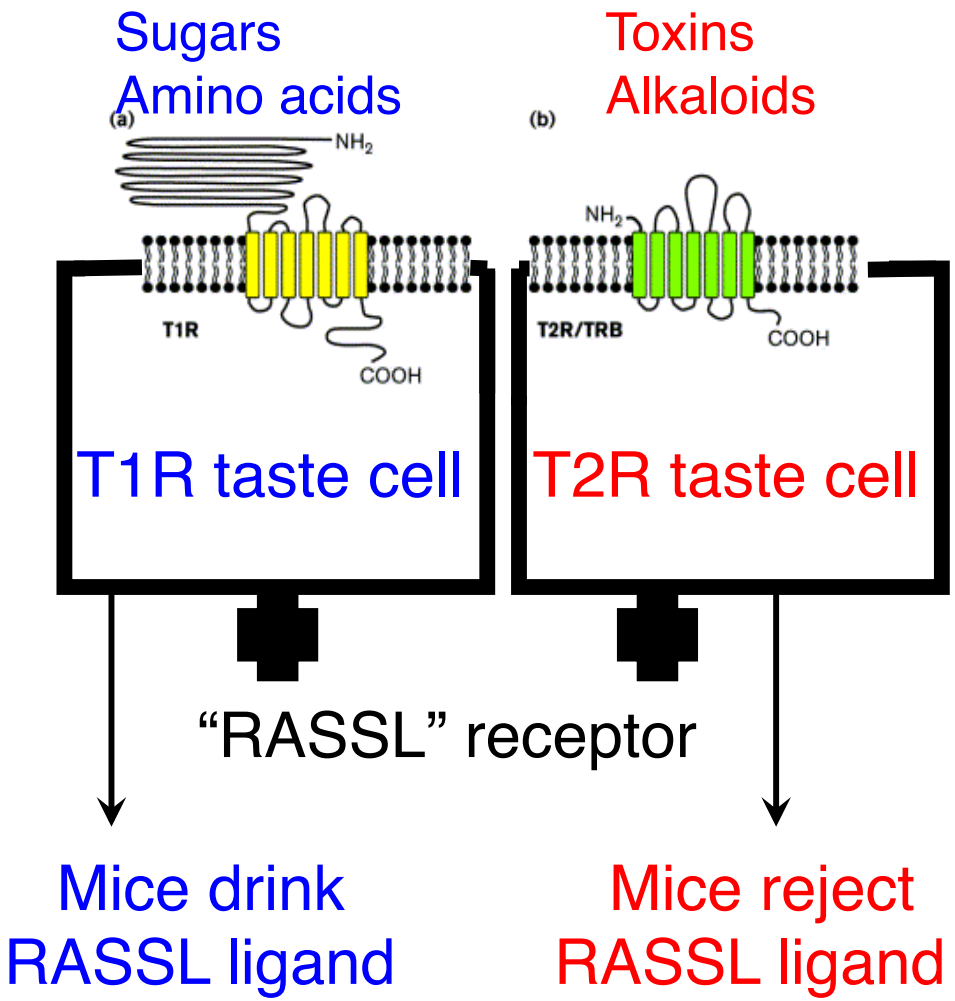
Repulsive

Troemel et al., Cell 1997

Sensory neurons encode behavioral responses

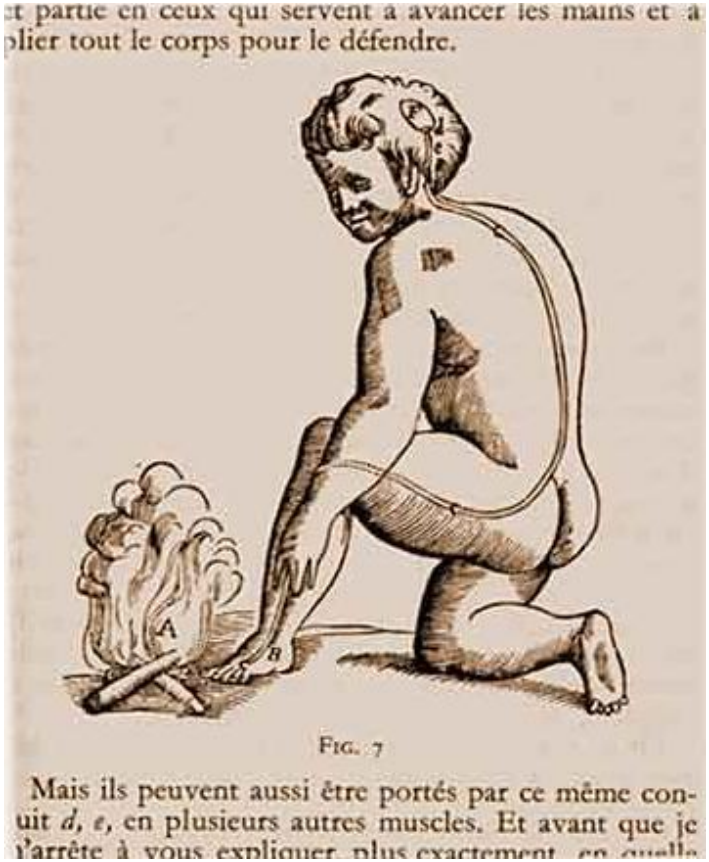


Mammalian taste responses are hard-wired too



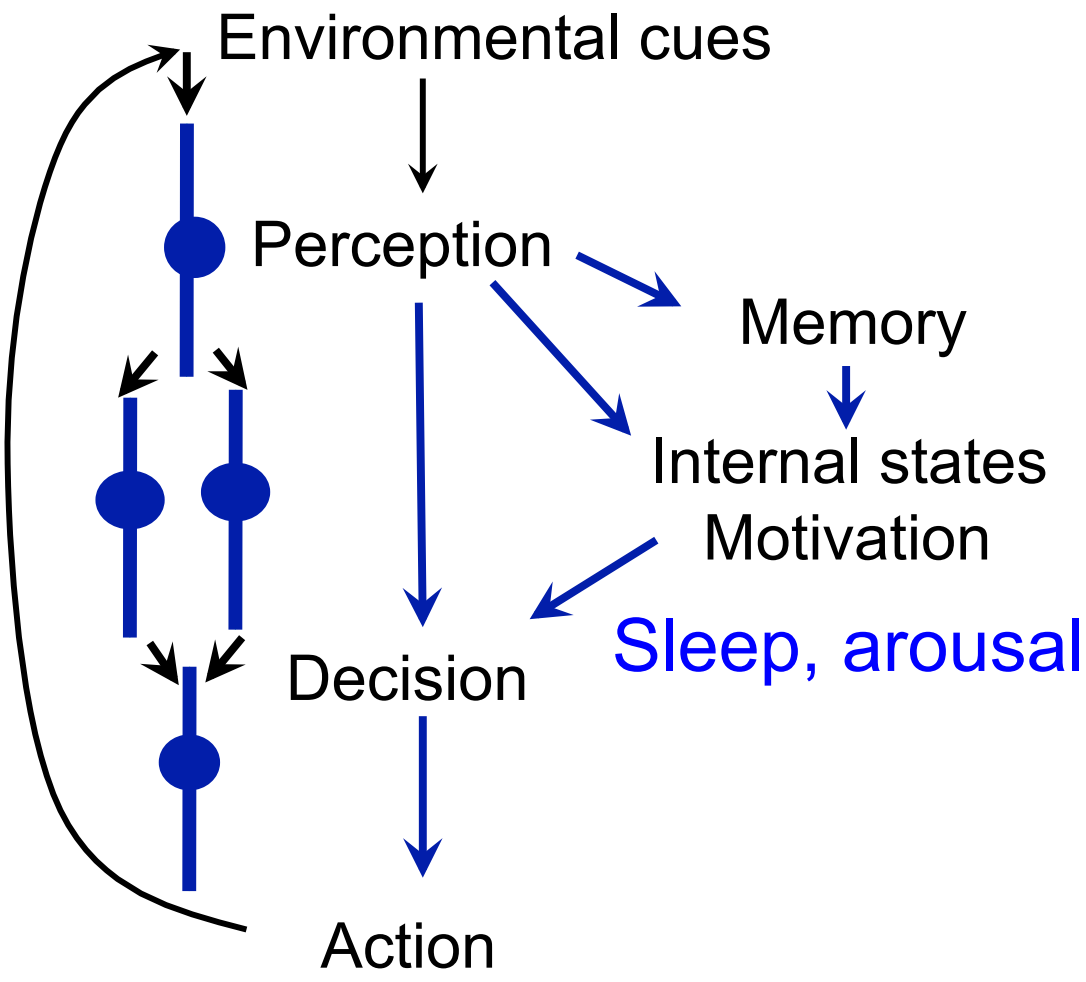
Zuker, Ryba and colleagues

Sensory neurons are wired to anatomical pathways for innate preferences



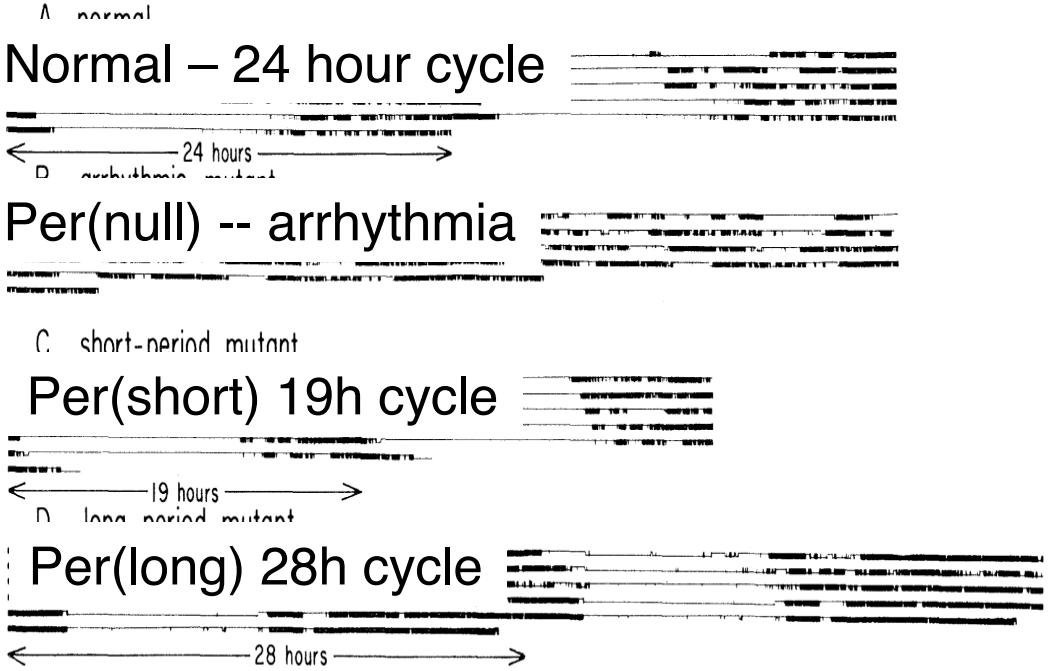
Genes, neurons, brains

A framework for behavior



The circadian clock

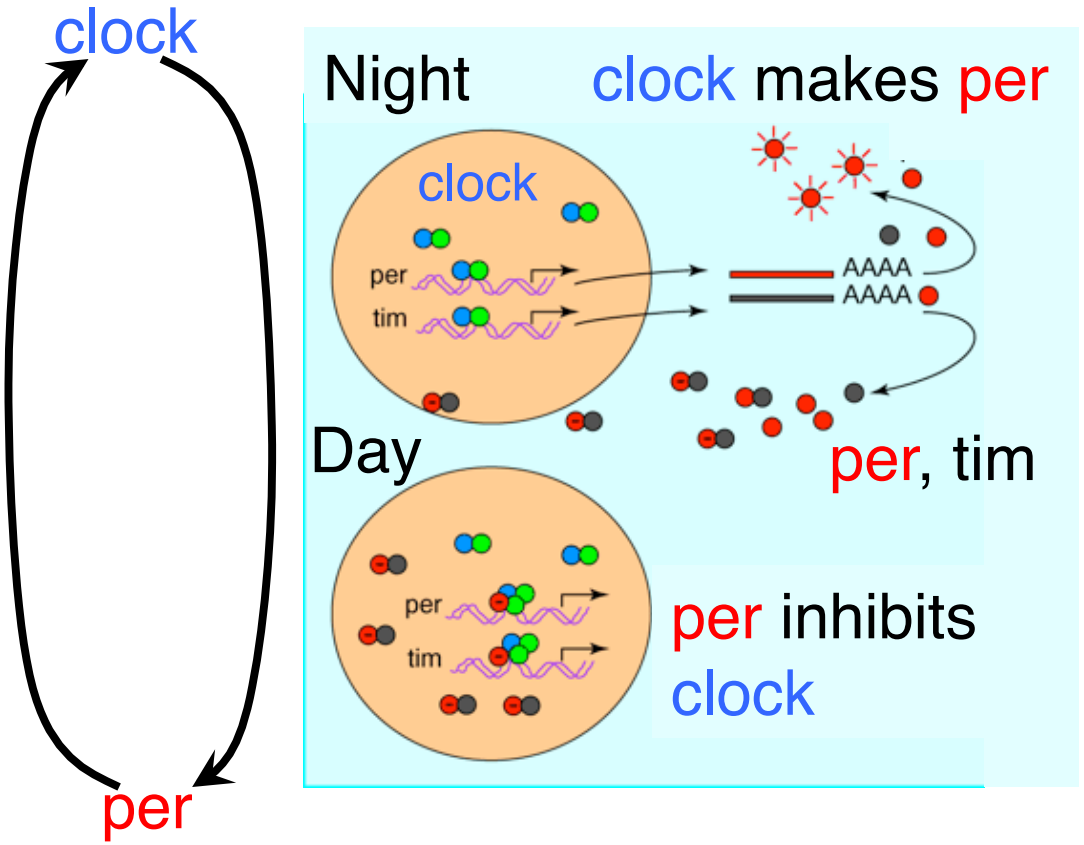
Fruit fly activity in constant darkness



Konopka and Benzer, PNAS (1971)

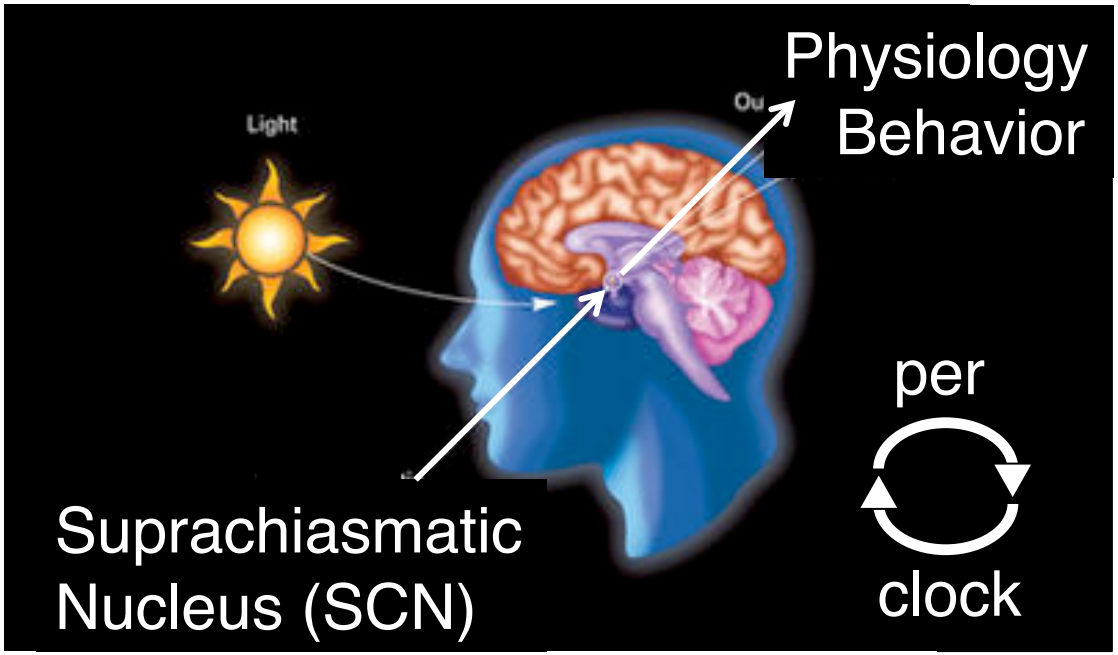
The intracellular circadian clock

A negative feedback loop,
similar in flies and humans



from Hastings, BMJ 317 : 1704 (1998)

Many cells have circadian clocks, but specific brain regions dominate



from www.wikipedia.org

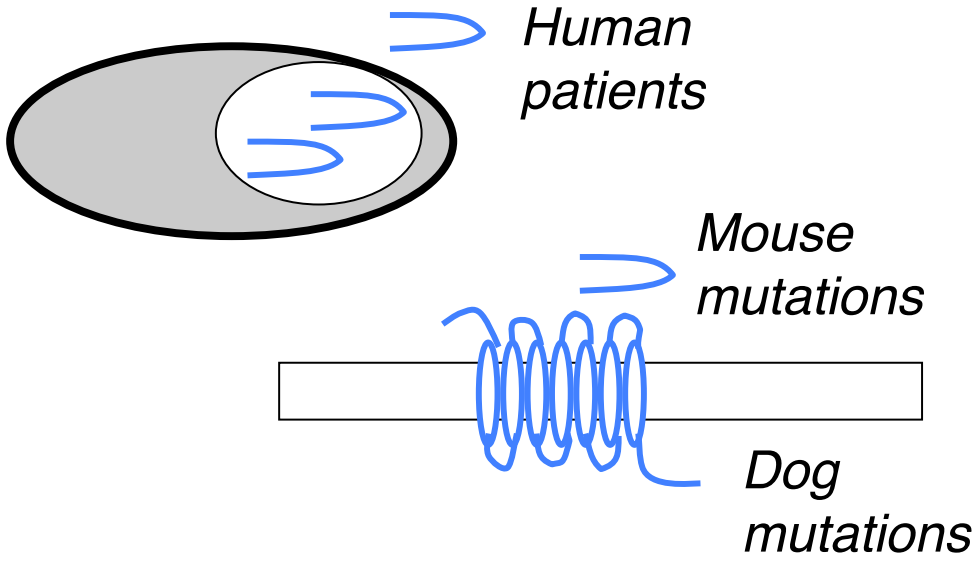
Advanced Sleep Phase Syndrome:
Mutations in human *per* genes

Narcolepsy with cataplexy

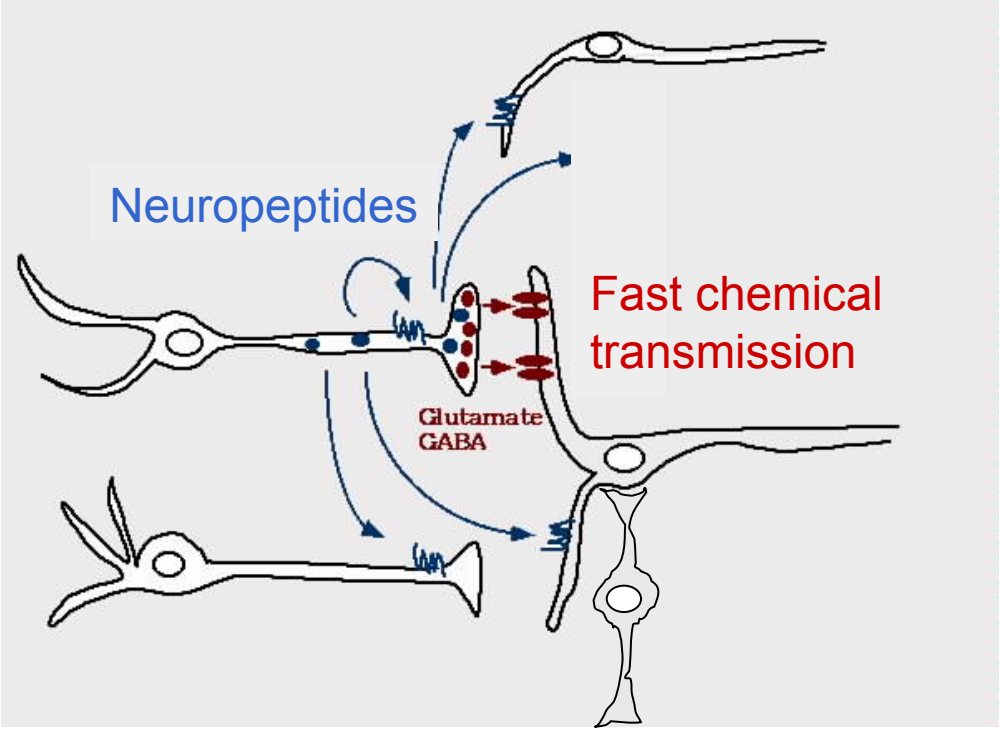
Reduced sleep latency
Waking hallucinations
Loss of muscle control with excitement

The genetic basis of narcolepsy-cataplexy is deficient neuropeptide signaling

Dog: hypocretin-2 receptor
Mouse: hypocretin peptide
Humans: autoimmune destruction of hypocretin neurons

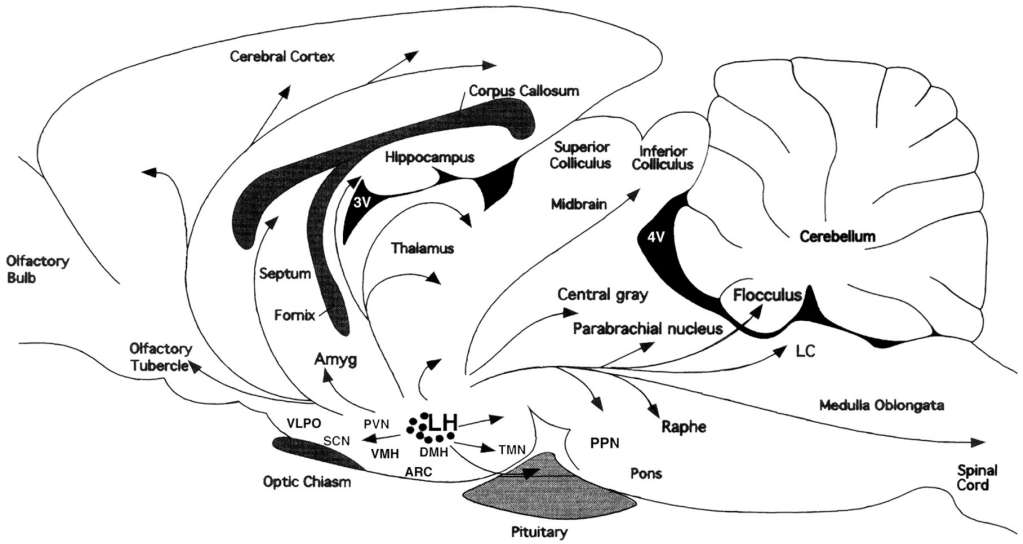


Different kinds of neuronal communication



Classical transmitters	Neuropeptides
Fast (ms)	Slow (sec-min)
Act locally (synapse)	Can act at a distance
Instructive (depol/hyperpol)	Modulatory (GPCR)
Few, highly conserved	Many, rapidly-evolving

Sleep is an internally-generated behavior

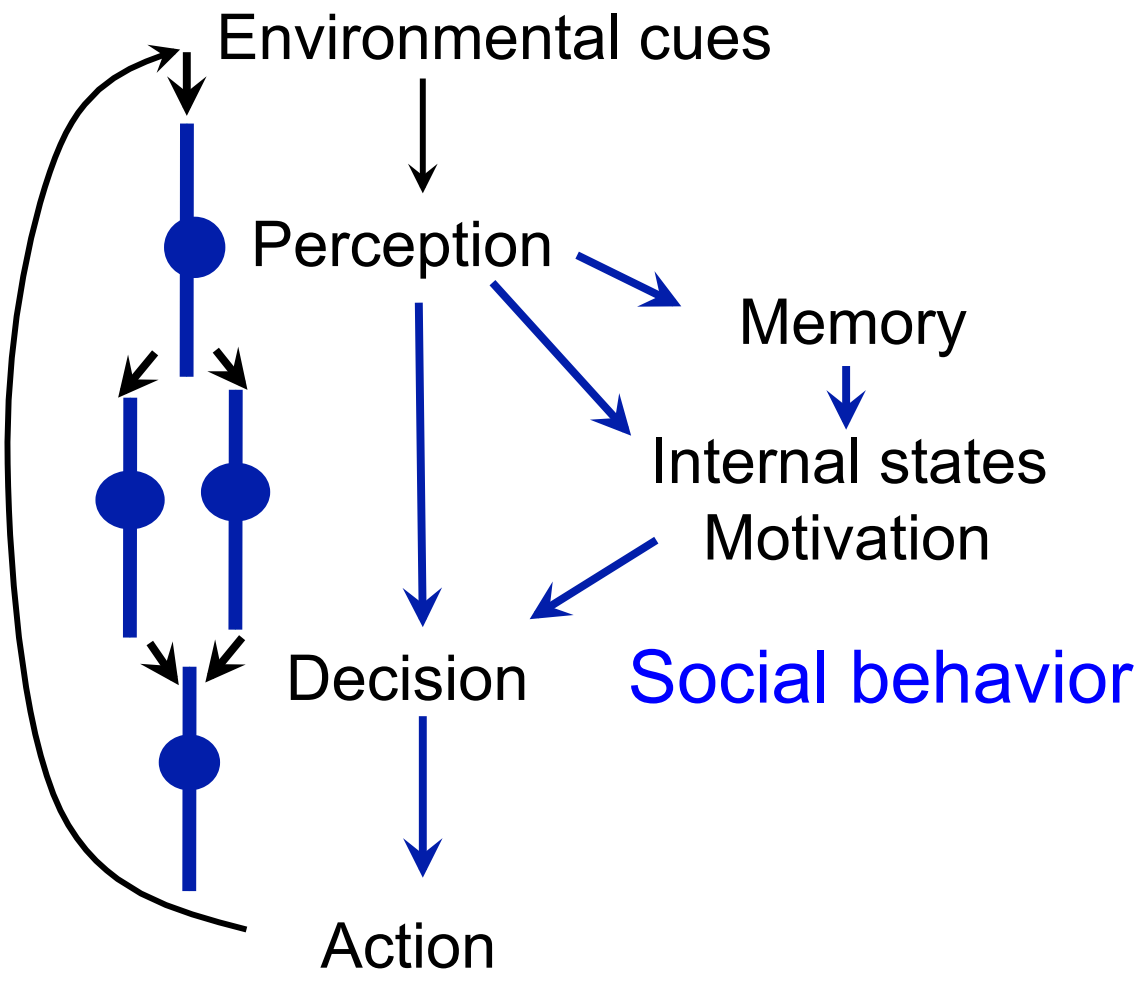


~2000 **hypocretin-producing neurons**

in the hypothalamus

project to many regions involved in sleep and arousal

A framework for behavior



Polygamous and monogamous rodents

Meadow vole:

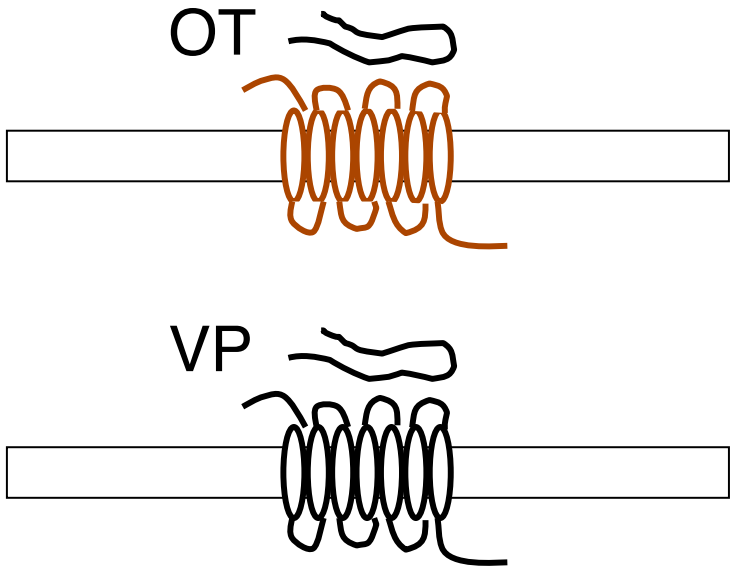
Mostly solitary
Limited maternal care
No paternal care
Non-territorial,
non-aggressive

Prairie vole:

Colonial
High maternal care
Paternal care
High pair-bonding
Territorial
Aggressive

Insel, Young and colleagues

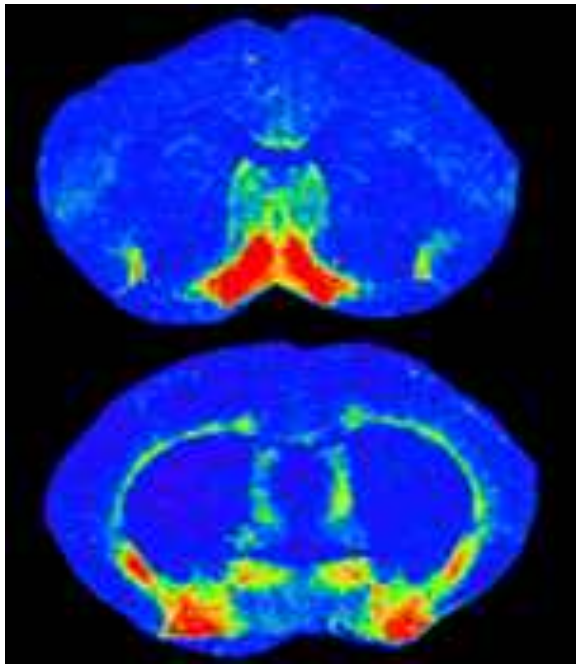
Oxytocin and vasopressin neuropeptides and their receptors regulate mammalian social behavior

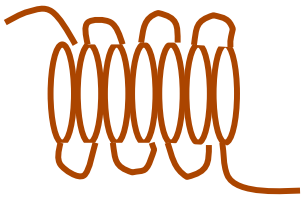


Both montane and prairie voles have these peptides and receptors

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

Vasopressin V1 receptor





Insel, Young and colleagues

A framework for behavior