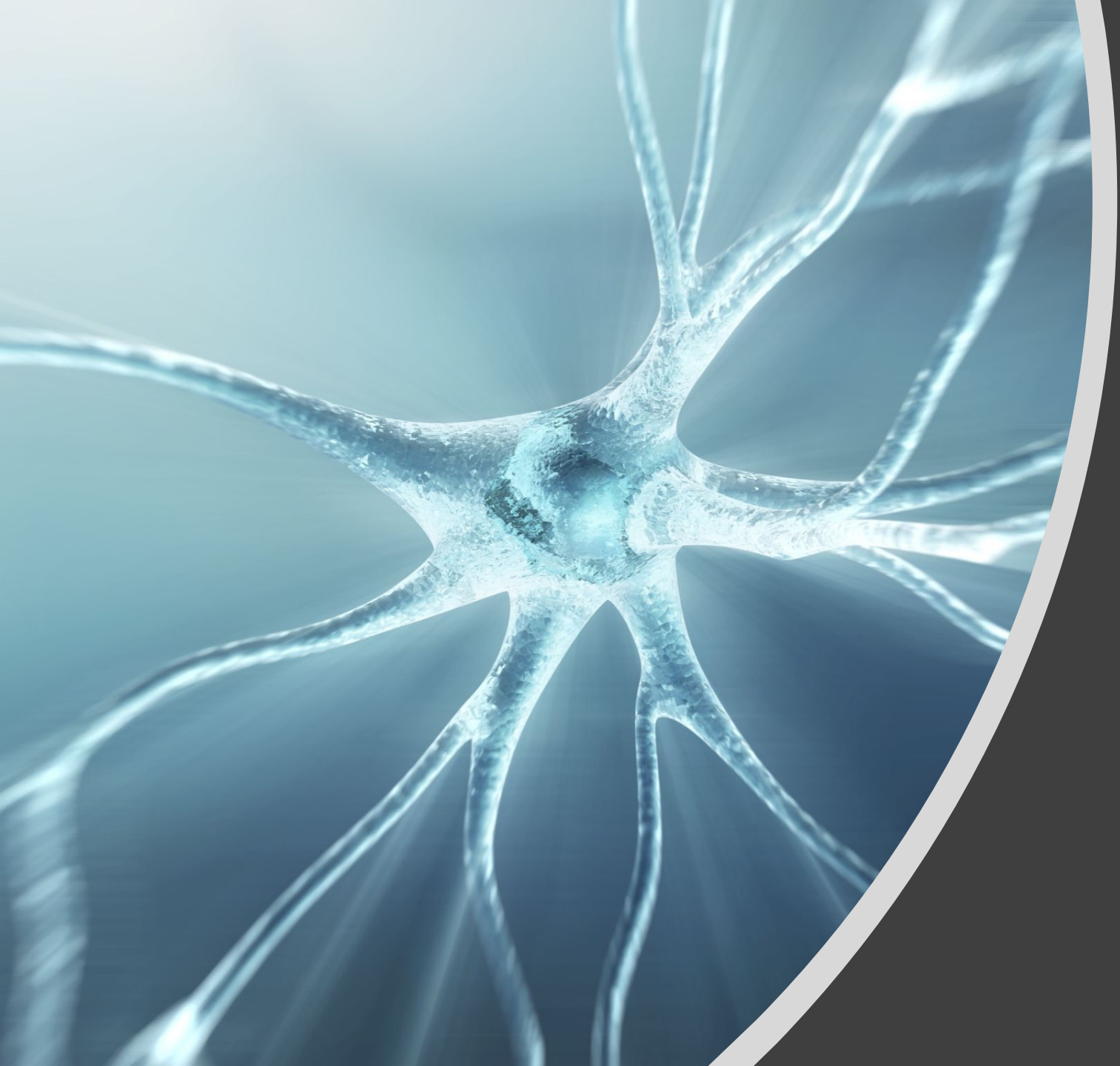
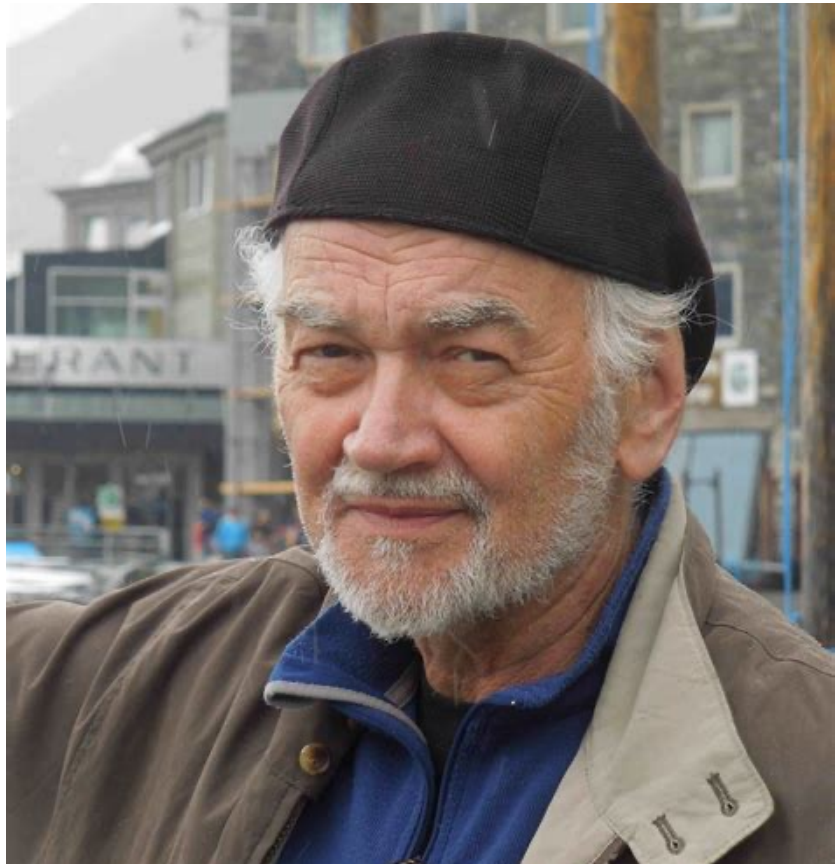


Affective Neuroscience

Brandon Roberts Ph.D.

Jaak Panksepp

- Coined the term “affective neuroscience”
- Mapped 7 primary process emotional systems
- Animals also have *feelings*
- Aided in the development of multiple approaches to treating psychiatric disorders



1943 - 2017

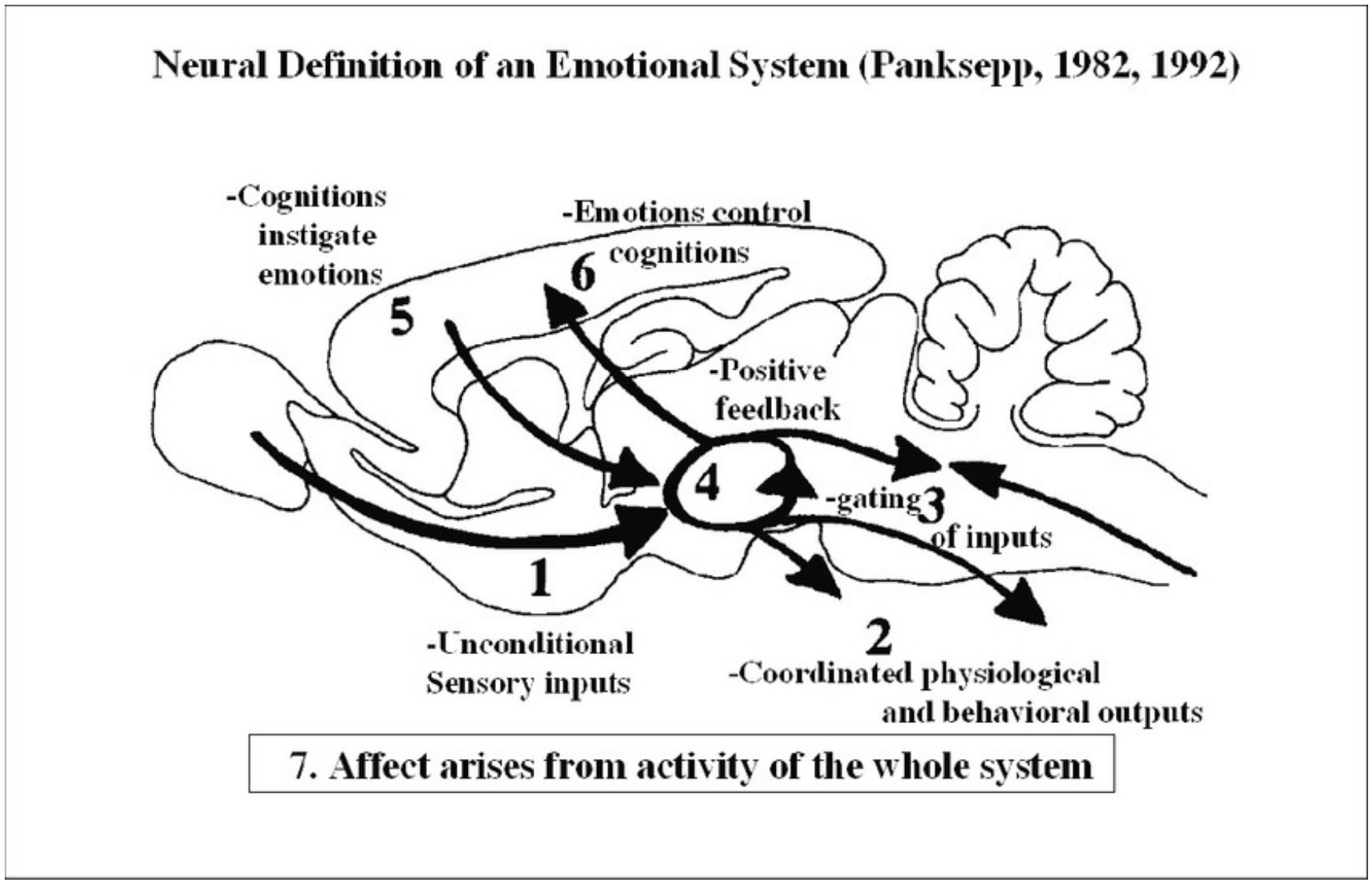
Mind archeology
(evolutionary perspective)

Triune brain

- **Primary process** emotions
- Secondary process learned behaviors
- Tertiary process interpretations, reflections, and foreshadowing

How can we understand the deep neural nature of human affects?

What do we mean by ‘Emotional System’?



Animal research may serve as a tool, but do animals have feelings?

Is the dog thinking:

- Nothing
- “You smell good”
- “I want to eat you”
- “I love you”

Walter Hess identified neural control of aggression, but called it ‘sham rage’ to avoid scrutiny

How can we measure affects?

Not possible without modern neuroscience

Dual-Aspect Monism
mental and physical are of the same substance

- Angry behavior reflects angry feelings
- Every time angry behavior is stimulated it serves as a punishment for an animal

How can we measure affects?

Positive affect (rewarding)

- Preference (place, object, individual, etc.)
- Self-stimulation of a circuit
- Positive vocalizations (50-kHz)

Negative affect (punishment)

- Avoidance (place, object, individual, etc.)
- Work to turn off stimulation of a circuit
- Negative vocalizations (22-kHz)

Primary process emotions

SEEKING – Exploration, desire, wanting

RAGE – Anger, irritability, resentment, hate

FEAR – Anxiety, trepidation, worry, PTSD

LUST – Sexuality, eroticism, libido, desire-love

PLAY – Joy, fun, games, friendship, euphoria

CARE – Nurturance, endearment, empathy, love

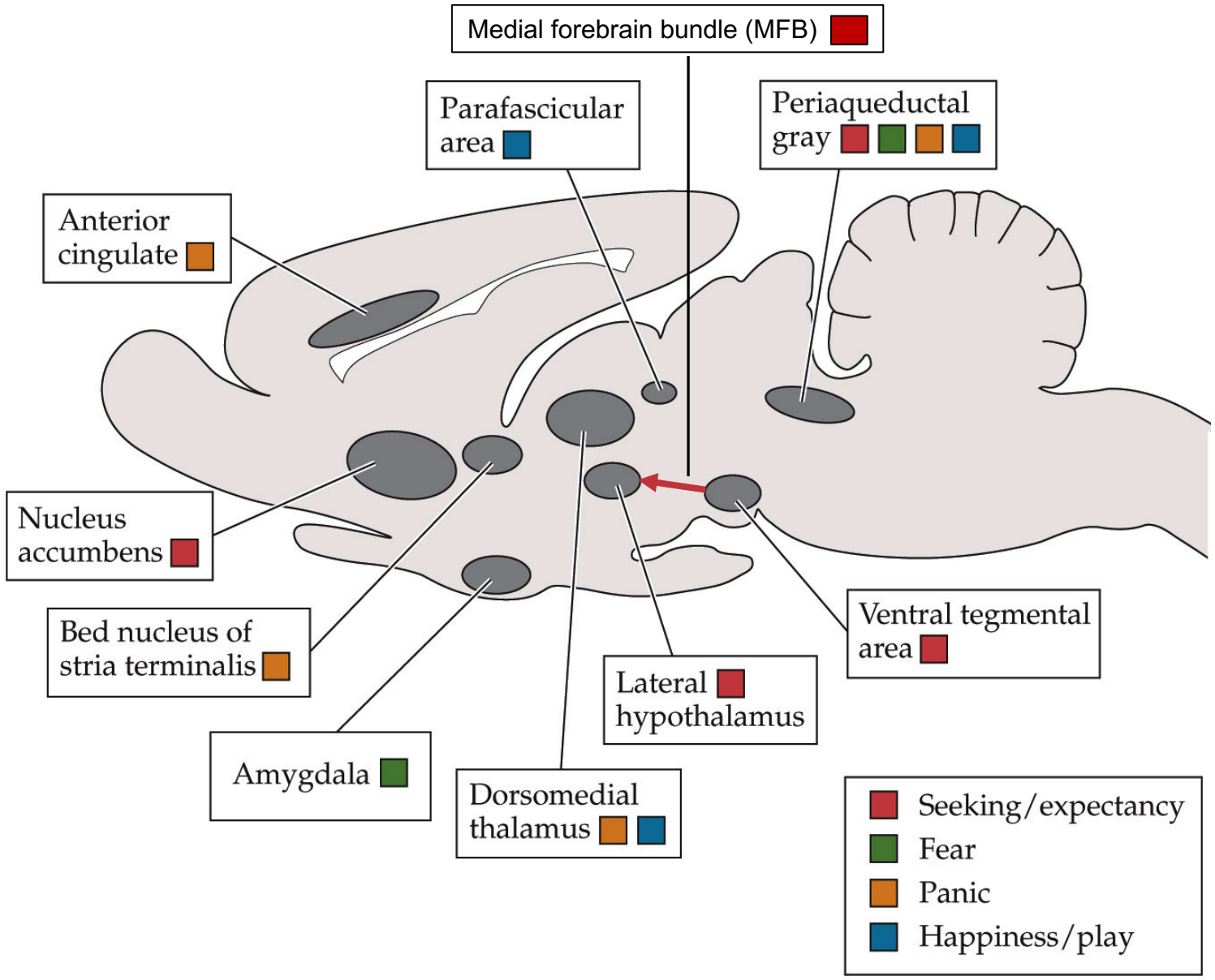
PANIC – Grief, sadness, psychic pain, depression

* Capitalization distinguishes distinct neural circuits that elicit a specific behavior when stimulated or inhibited

Emotional Systems	Emergent Emotions	Emotional Disorders
SEEKING (+ & -)	Interest Frustration Craving	Obsessive Compulsive Paranoid Schizophrenia Addictive Personalities
RAGE (- & +)	Anger Irritability Contempt Hatred	Aggression Psychopathic tendencies Personality Disorders PTSD variants
FEAR (-)	Simple anxiety Worry Psychic trauma	Generalized Anxiety Dis. Phobias PTSD variants
PANIC (-)	Separation distress Sadness Guilt/Shame Shyness Embarrassment	Panic Attacks Pathological Grief Depression Agoraphobia Social Phobias/AUTISM
PLAY (+)	Joy and glee Happy playfulness	Mania ADHD

(adopted from Panksepp, 1998)

Overview of brain regions involved in primary process emotional systems



Basic Emotional Systems	Key Brain Areas Concentrated in "Limbic System"	Key Neuromodulators (Peptides in Blue)
Appetitive Motivation **SEEKING**/ **(+) Expectancy** System	Nucleus Accumbens - VTA Mesolimbic and mesocortical outputs Lateral hypothalamus - **PAG**	**DA (+),** glutamate (+), opioids (+), **neurotensin** Many other neuropeptides
RAGE/Anger	Medial amygdala to Bed Nucleus of Stria Terminalis (BNST). medial and perifornical hypothalamic to **PAG**	**Substance P (+),** ACh (+), glutamate (+)
FEAR/Anxiety	Central & lateral amygdala to medial hypothalamus and dorsal **PAG**	Glutamate (+),**DBI, CRF,** **CCK, alpha-MSH, NPY**
LUST/Sexuality	Cortico-medial amygdala, Bed nucleus of stria terminalis (BNST) Preoptic hypothalamus, VMH, **PAG**	Steroids (+), **vasopressin,** & **oxytocin, LH-RH, CCK**
CARE/ **Nurturance**	Anterior cingulate, BNST Preoptic Area, VTA, **PAG**	**oxytocin (+), prolactin (+)** dopamine (+), **opioids (+/-)**
PANIC/ **Separation Distress**	Anterior Cingulate, BNST & Preoptic Area Dorsomedial Thalamus, **PAG**	**opiods(-), oxytocin (-)** **prolactin (-) CRF (+)** glutamate (+)
PLAY/Joy	Dorso-medial diencephalon Parafascicular Area, **PAG**	**opioids (+/-),** glutamate (+) ACh (+), TRH?

** Extensive list, need not memorize entire table*

SEEKING

Feeling of drive, exploration and anticipation

Required to “take action” in response to bodily needs or affective experiences

Stimulation in humans and rodents leads to desire to explore (not pleasure)

Dopamine and opioid systems play a central role

Dopamine spikes **before** a reward

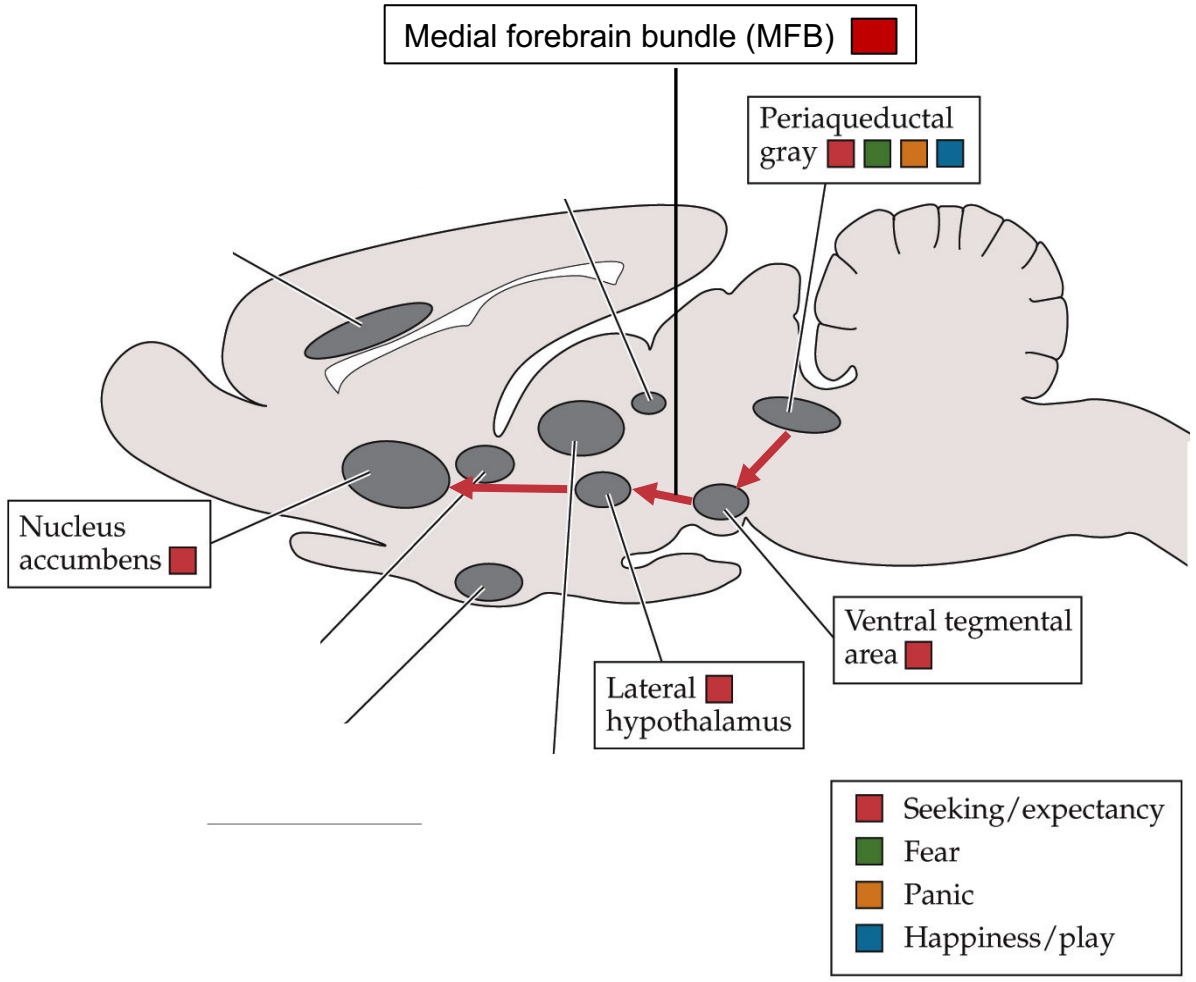
“Reward system” is potentially a misnomer

SEEKING

- Also known as “reward system”
- Originates in periaqueductal gray **(PAG)**
- **MFB** connects VTA to lateral hypothalamus (LH)

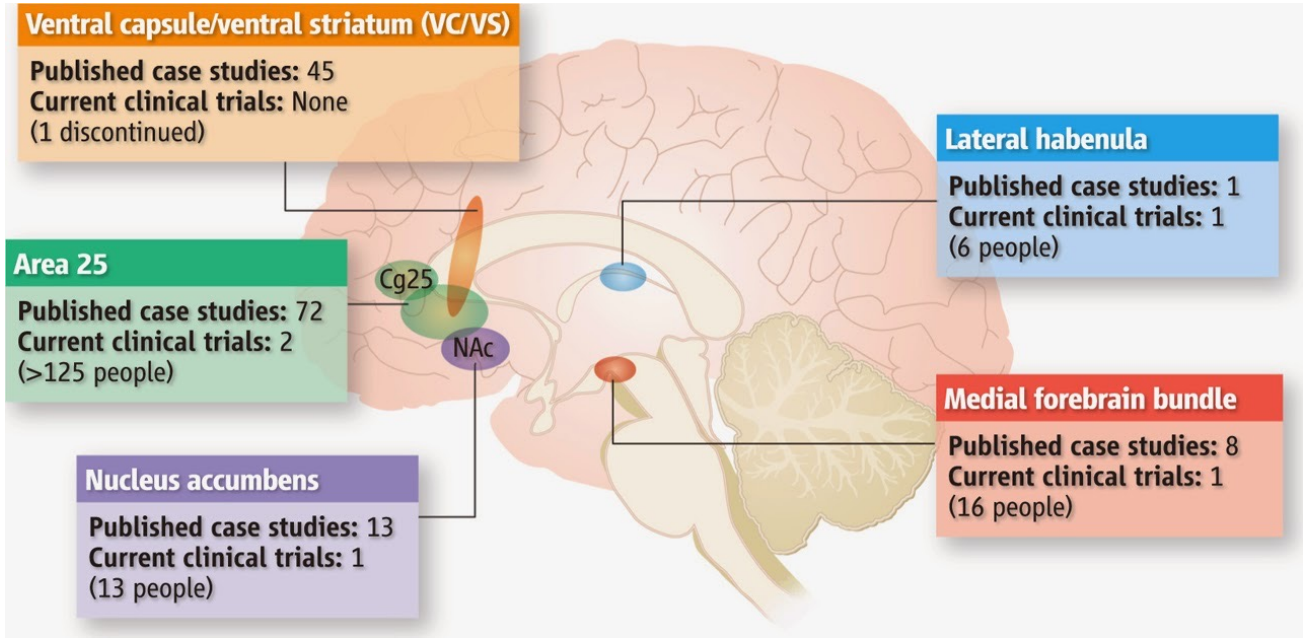
Primary neuromodulators:

- Dopamine
- Opioids



SEEKING

- Inactivation results in depression
- Deep brain stimulation (DBS) as a treatment for depression
- Most promising areas target SEEKING system
- Stimulation of **MFB** leads to desire to explore



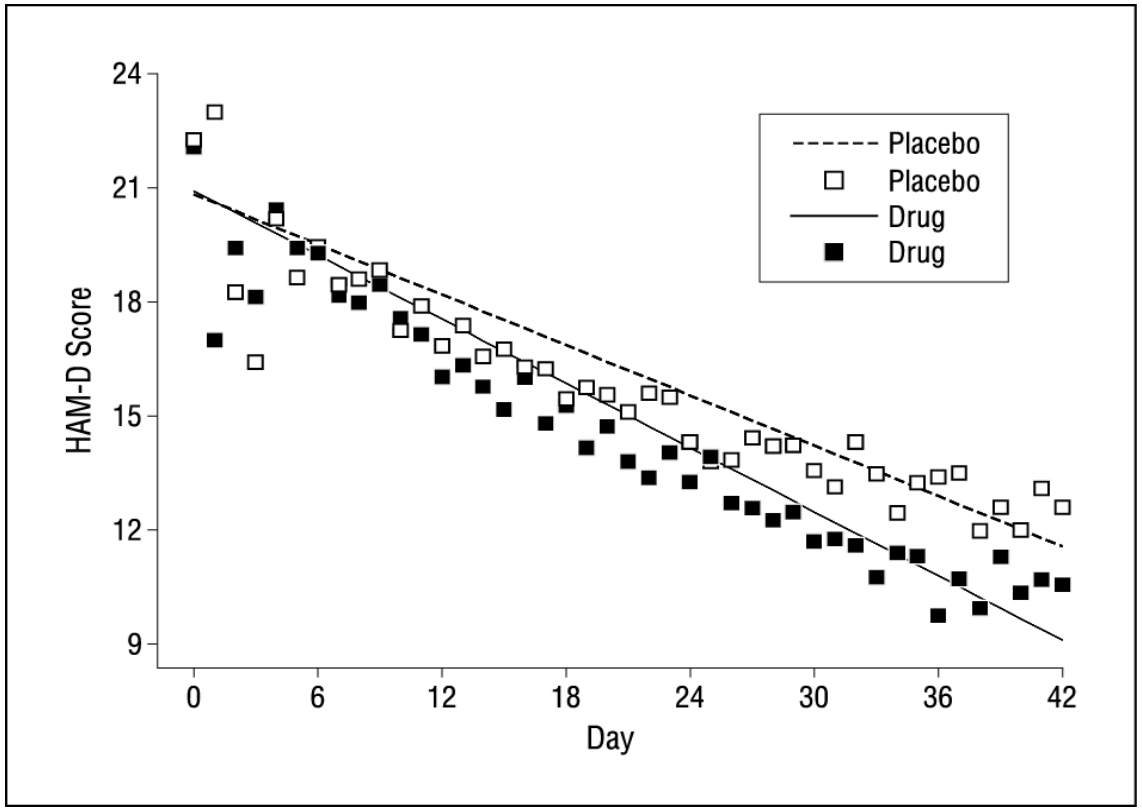
SSRIs often have low effectiveness compared to placebo

Serotonin is a general and broad regulator of neural function

Regulates incoming information and cross-talk between sensory systems

While SSRIs are helpful for some, serotonin does not regulate any specific emotional system

Fluoxetine (Prozac)

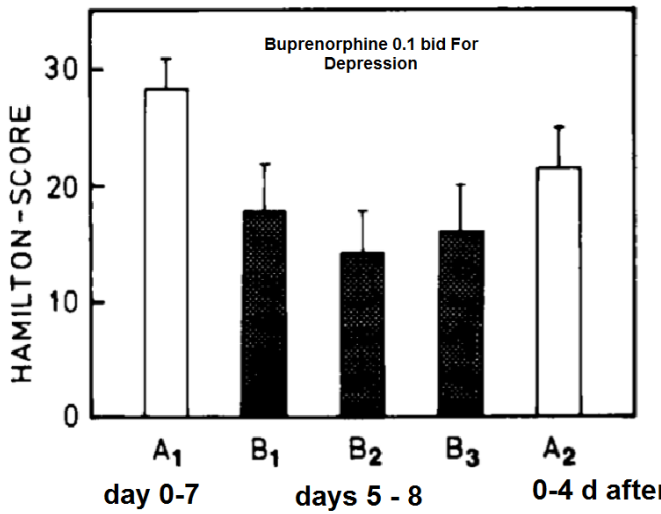


Gibbons, et. al. 2012

SEEKING (Clinical implications)

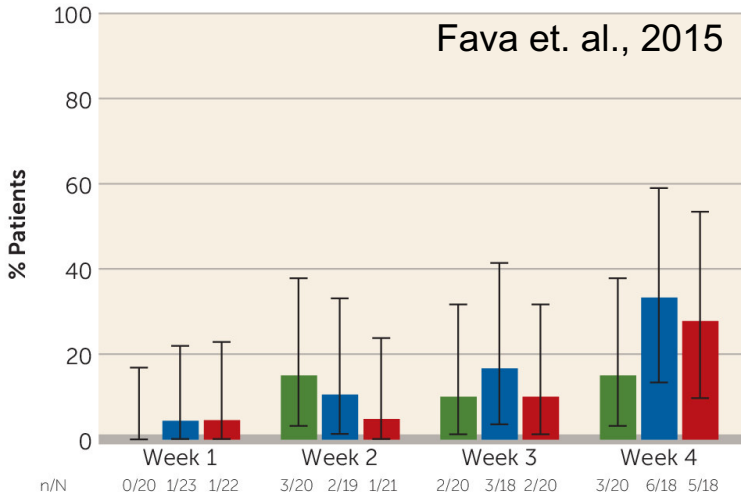
- Opioids are involved in SEEKING and PANIC systems
- Buprenorphine (partial opioid agonist) has shown promise in decreasing:
  - Depression symptoms
  - Suicidal thoughts
  - Anxiety
- Carries stigma of being an opiate

Emrich et. al., 1982



Emrich, H. M. et al. Possible antidepressive effects of opioids: action of buprenorphine. Annals of the new York Academy of Sciences 398.1 (1982): 108-112.

Patients with > 50% reduction in depression symptoms (HAM-D)



Measure	Baseline Mean score	Baseline SD	End Week 1 Mean score	End Week 1 SD	End Week 1 p (paired t-test with baseline)	Final Assessment Mean score	Final Assessment SD	Final Assessment p (paired t-test with baseline)
HAM-D	28.1	6.6	17.6	10.3	0.01	10.7	9.3	0.006
Global Assessment Scale	40.1	9.0	47.9	12.3	0.02	58.3	19.3	0.01
POMS Subscales*								
Tension	2.7	0.8	1.6	1.1	0.02	1.3	1.4	0.05
Anger	2.1	0.9	1.3	1.1	0.01	1.0	1.3	n.s.
Depression	3.4	0.3	1.6	1.3	0.01	1.5	1.5	0.02
Fatigue	3.4	0.8	1.6	1.1	0.02	1.4	1.6	0.05
Confusion	1.9	1.0	1.4	0.8	0.03	0.8	1.2	n.s
Elation	0.06	0.09	0.9	1.0	0.03	1.3	1.1	0.04
Friendliness	1.0	0.6	1.3	0.9	0.006	2.3	1.0	0.007
Vigor	0.4	0.3	1.0	1.0	0.04	1.7	1.2	0.05

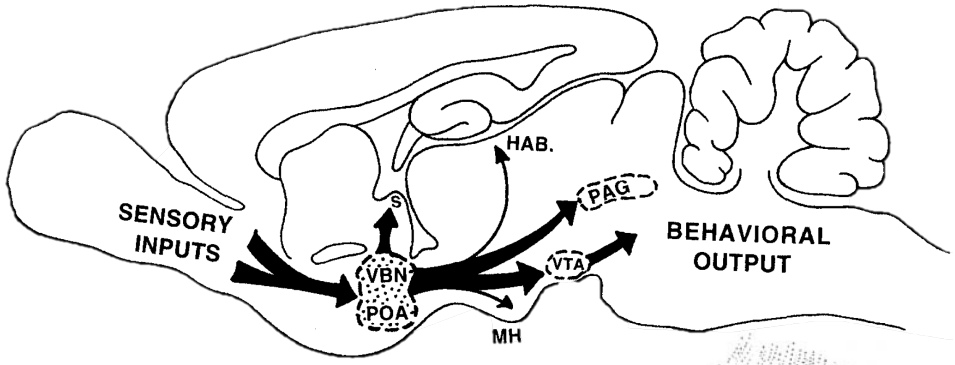
Bodkin et. al., 1995

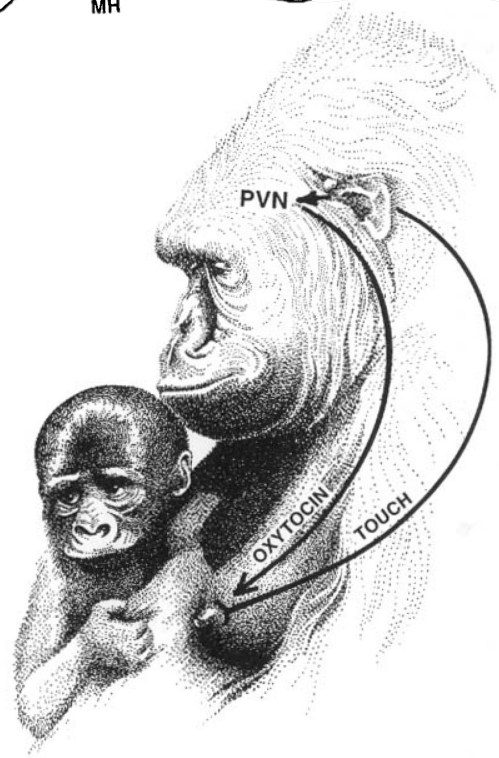
CARE

- Maternal bonding
- Social bonding
- Nurturing others

CARE

- **Oxytocin** is essential to a mother's selective bond to young
- Oxytocin produced in hypothalamus, released by pituitary
- Released by pituitary in response to breastfeeding, childbirth, and intercourse
- Oxytocin knock-out mice mothers are infanticidal, non-selective

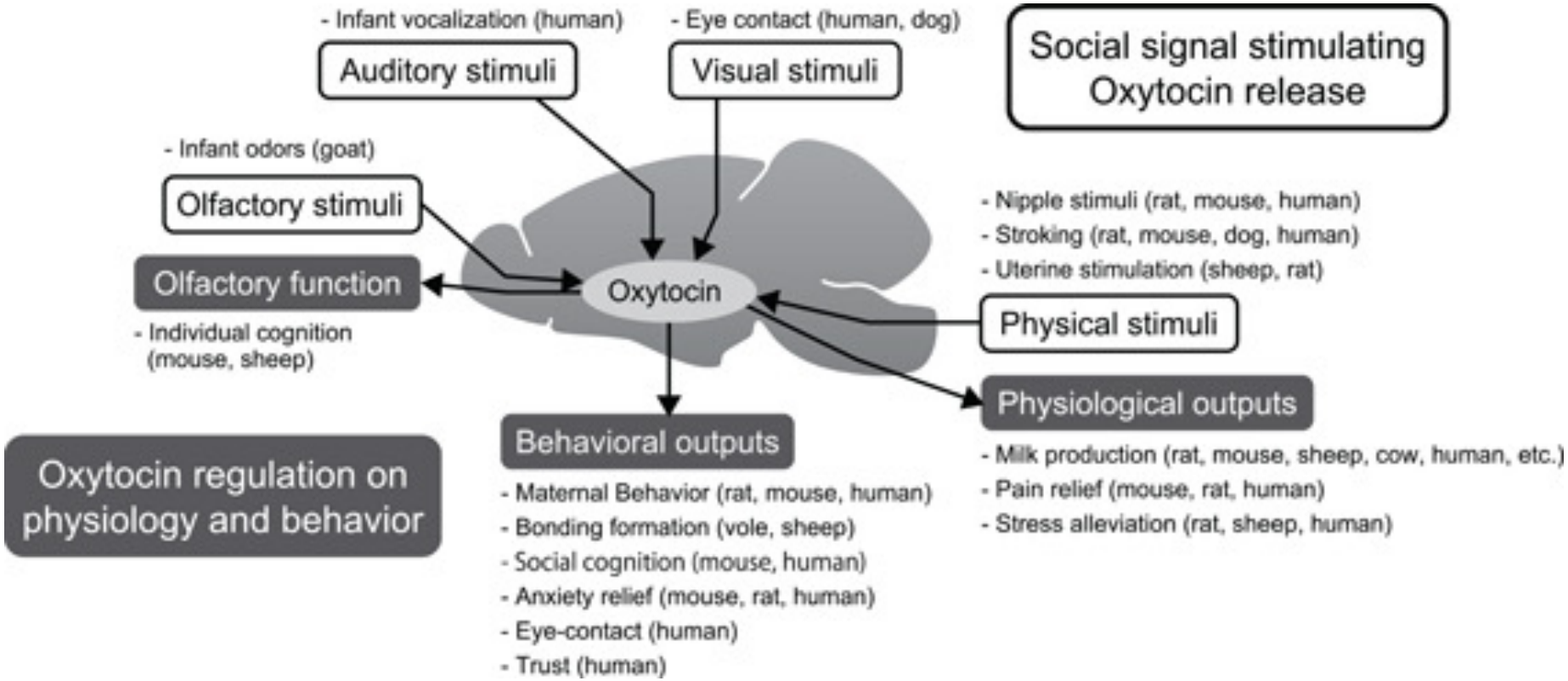




Kendrick et al. (1997) Brain Res. Bull.
Panksepp (1998)

CARE

- **Oxytocin** has numerous other functions



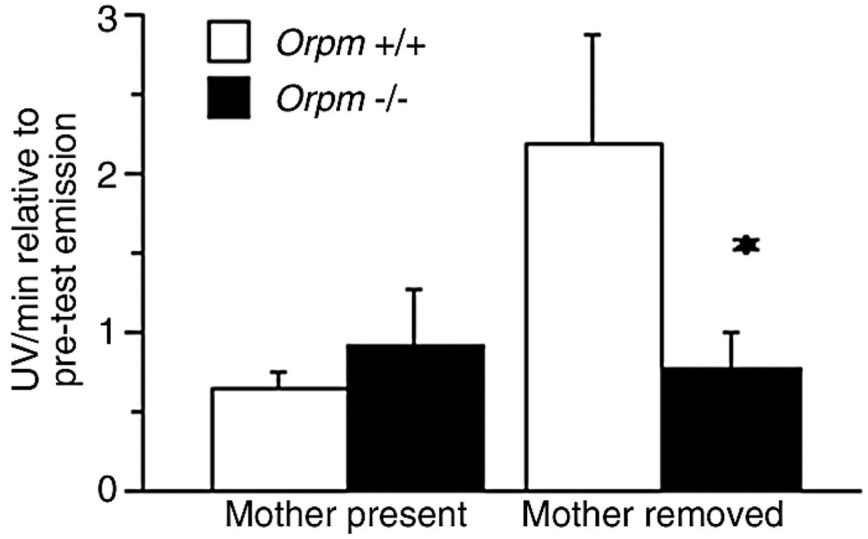
Nagasawa N., et al. (2012)
Frontiers in Human Neuroscience

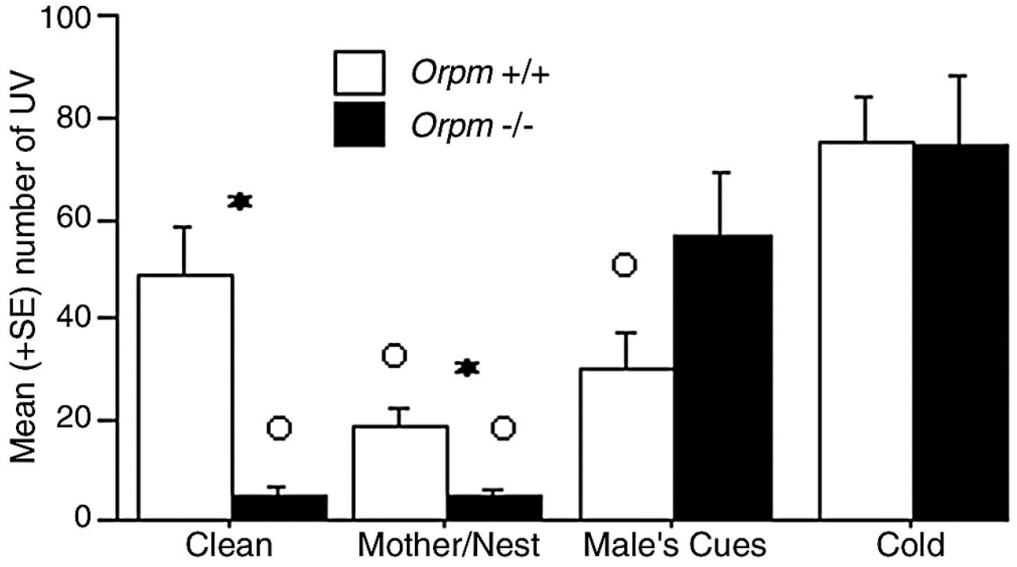
CARE

- **Opioids** are a reward associated with social comfort

<u>Knock-out</u> mice bred lacking μ - opioid receptors (*Orpm -/-*)

- Mothers spend less time with pups
- Infants less attached to mother
- Vocalizations are retained in response to cold and unfamiliar male odor





Moles et al. (2004) Science

SIMILARITIES BETWEEN

OPIATE ADDICTION & SOCIAL DEPENDENCE

1) Drug Dependence	1) Social Bonding
2) Drug Tolerance	2) Estrangement
3) Drug Withdrawal	3) Separation Distress

a) PSYCHIC PAIN	→	a) LONELINESS
b) LACRIMATION	→	b) CRYING
c) ANOREXIA	→	c) LOSS OF APPETITE
d) DESPONDENCY	→	d) DEPRESSION
e) INSOMNIA	→	e) SLEEPLESSNESS
f) AGGRESSIVENESS	→	f) IRRITABILITY

Fig. 13.5. AN

People and animals seek opioids to alleviate affective distress

PANIC/GRIEF

- **Separation distress**
- Social loss/loneliness
- Feelings of great despair
- Opioids are miraculous at filling this void (for better or worse….)

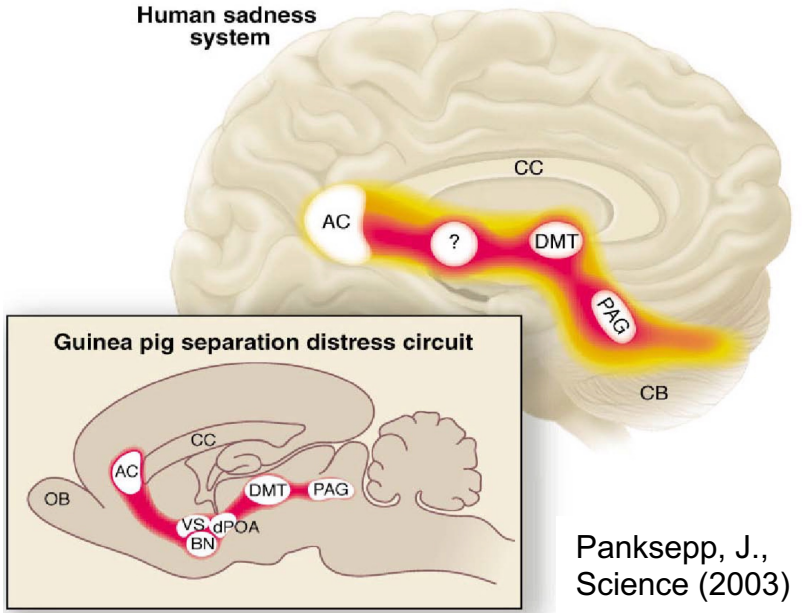
Emotional System	Emergent Emotions	Emotional Disorders
PANIC (-)	Separation distress Sadness Guilt/Shame Shyness Embarrassment	Panic Attacks Pathological Grief Depression Agoraphobia Social Phobias/AUTISM

PANIC/GRIEF

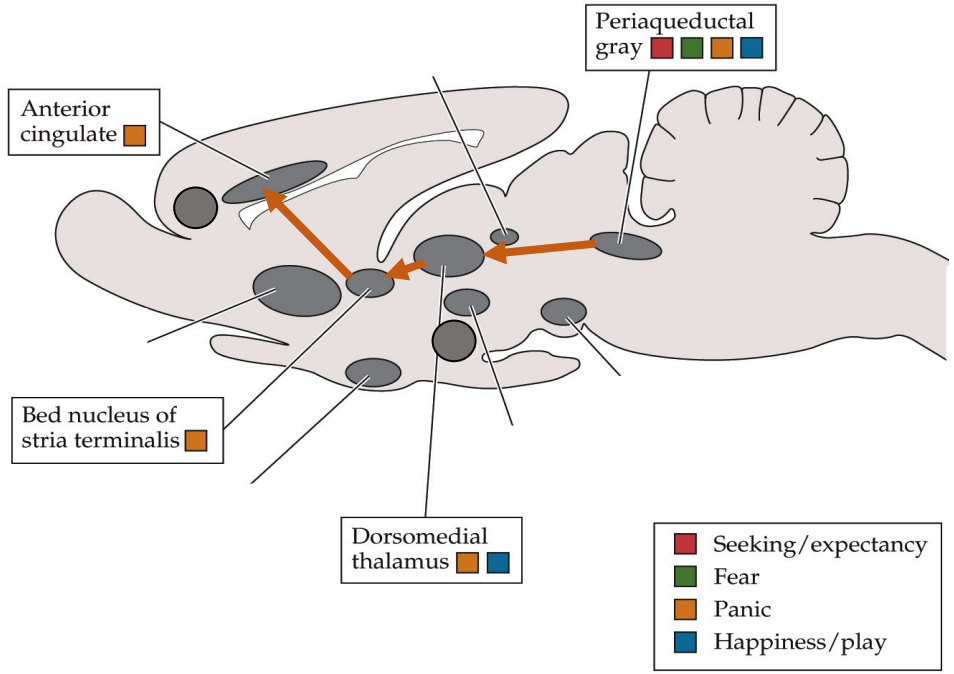
Acute stimulation of this system, particularly in the **PAG**, results in a strong flight response and negative vocalizations

Overactivation of PANIC/GRIEF results in depression (i.e. decreased activity of SEEKING system)

Removing chicks, pups, babies from their mother leads to separation distress calls that are alleviated with **opioids**



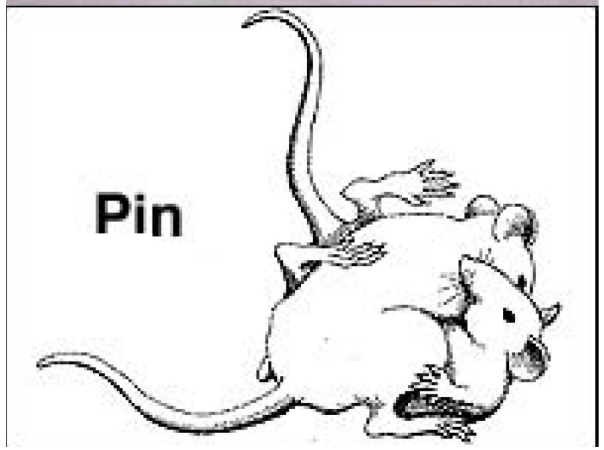
Panksepp, J., Science (2003)



PLAY

A ‘purposeless’ behavior lacking immediate benefits, appearing to not have serious intention or specific goal; often it may resemble modified adult behavior

Fagan, 1977; Pellegrini and Smith 2005



PLAY

- Does not require a learning phase
- Impulse for play is created from the spontaneous neural urges within the brain

Types of Play

- Locomotory
- Object
- Social or “rough and tumble”

PLAY

- 50-kHz vocalizations are elicited by a range of rewards
- When play is not regulated it can lead to bullying (measured by 22-kHz vocalizations)
- When inhibited it leads to ADHD symptoms
- Current ADHD medications reduce play in nearly all animals studied

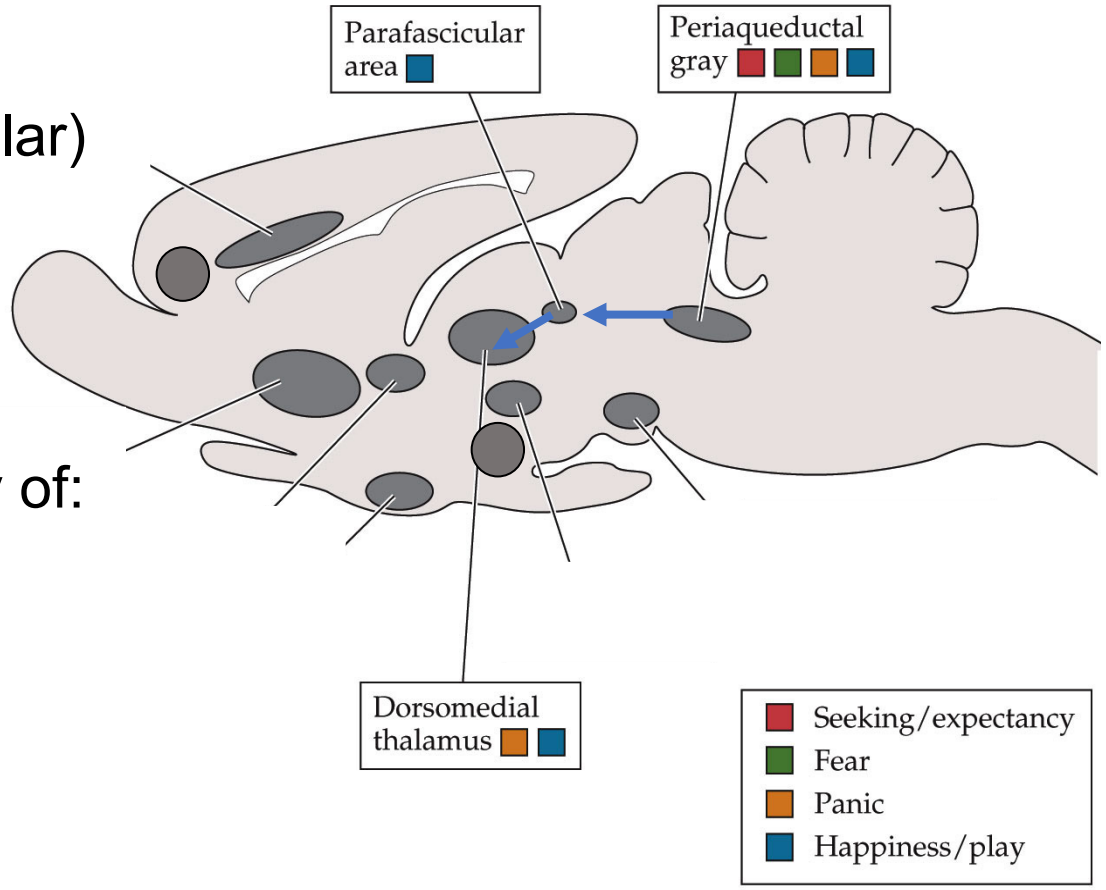
PLAY

Play elevates brain activity in:

- Thalamic areas (dorsomedial and parafascicular)
- Hippocampus (learning)
- Somatosensory cortex

Play can be altered by changing brain chemistry of:

- Dopaminergic system
- Serotonergic/noradrenergic systems
- Opioid systems



FEAR

- Fear is instinctual
  (pain, darkness, heights, spiders)
- Fear is also learned (PTSD)
- Fear conditioning interrupts play behavior

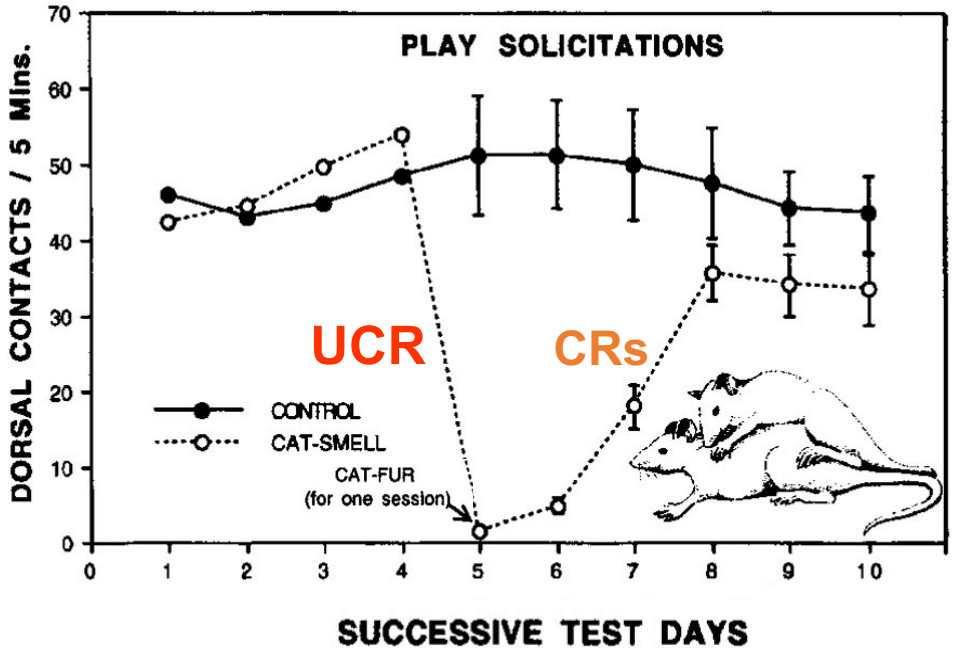
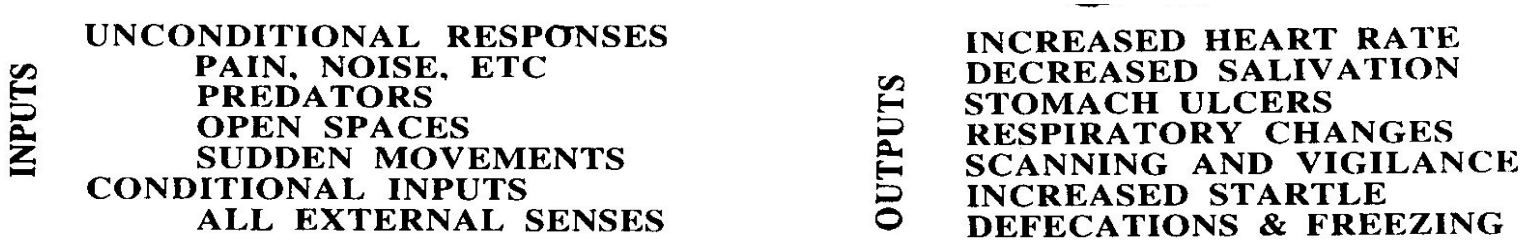


Fig. 1.1. AN



FEAR

Instinctual FEAR

UNCONDITIONED BEHAVIORS

Learned Fear/Anxiety

CONDITIONED BEHAVIORS

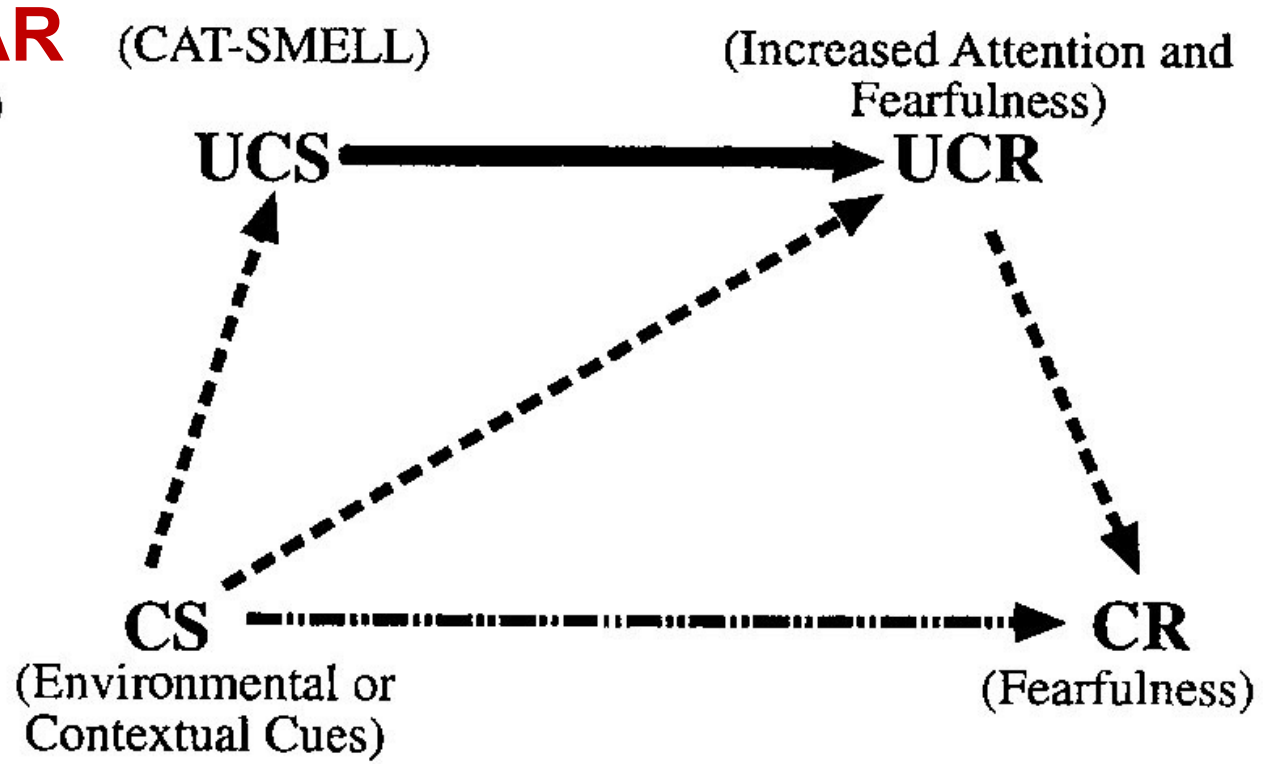
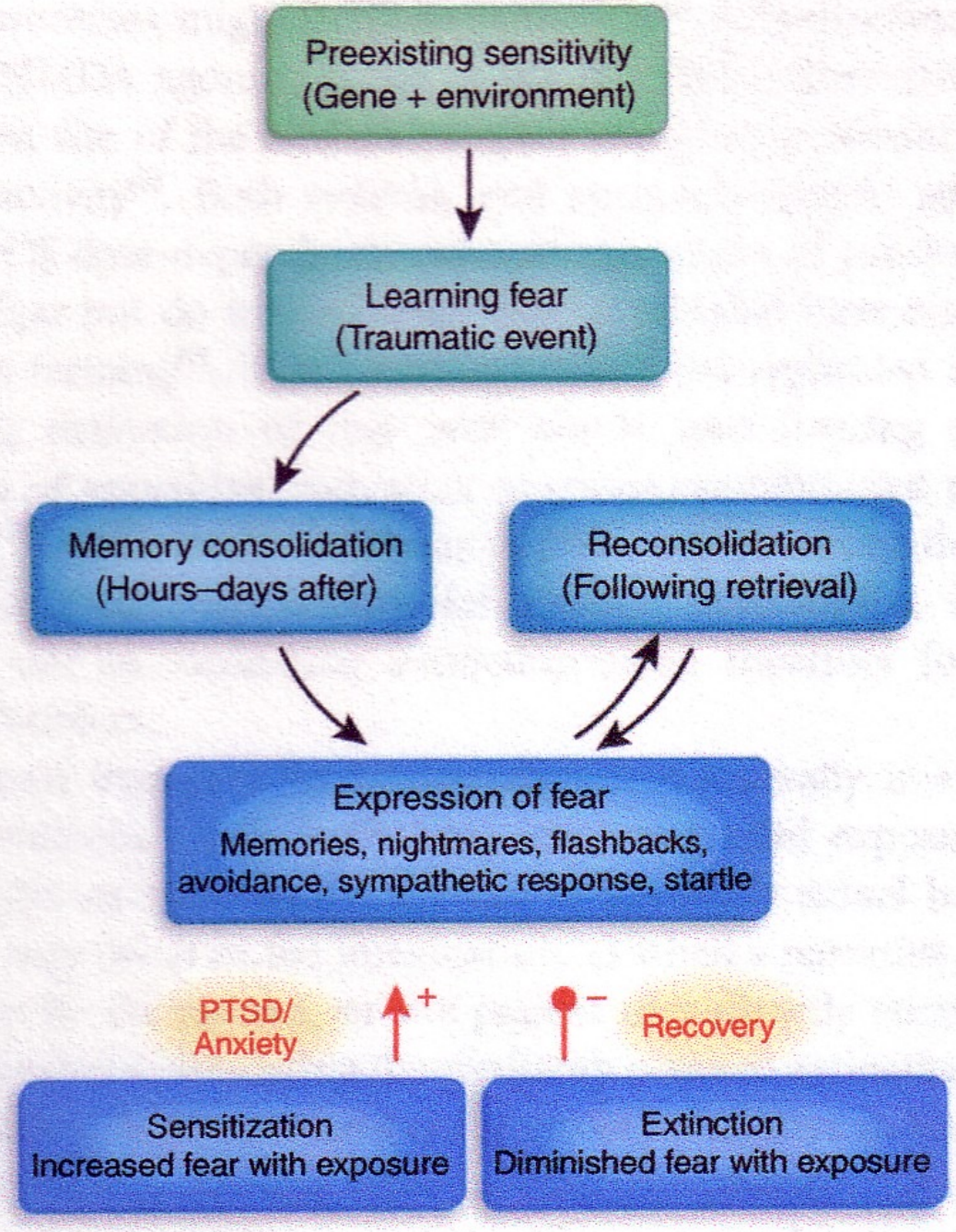


Fig. 1.2. AN



Fear & Memory

Fearful experiences alter past memories

1. Unconditioned stimulus & behavior
2. Fear exposure (trauma)
3. Forming a memory
4. Behavioral expression of fear upon recall

PTSD/Anxiety

Sensitization: repeated exposure = increased fear

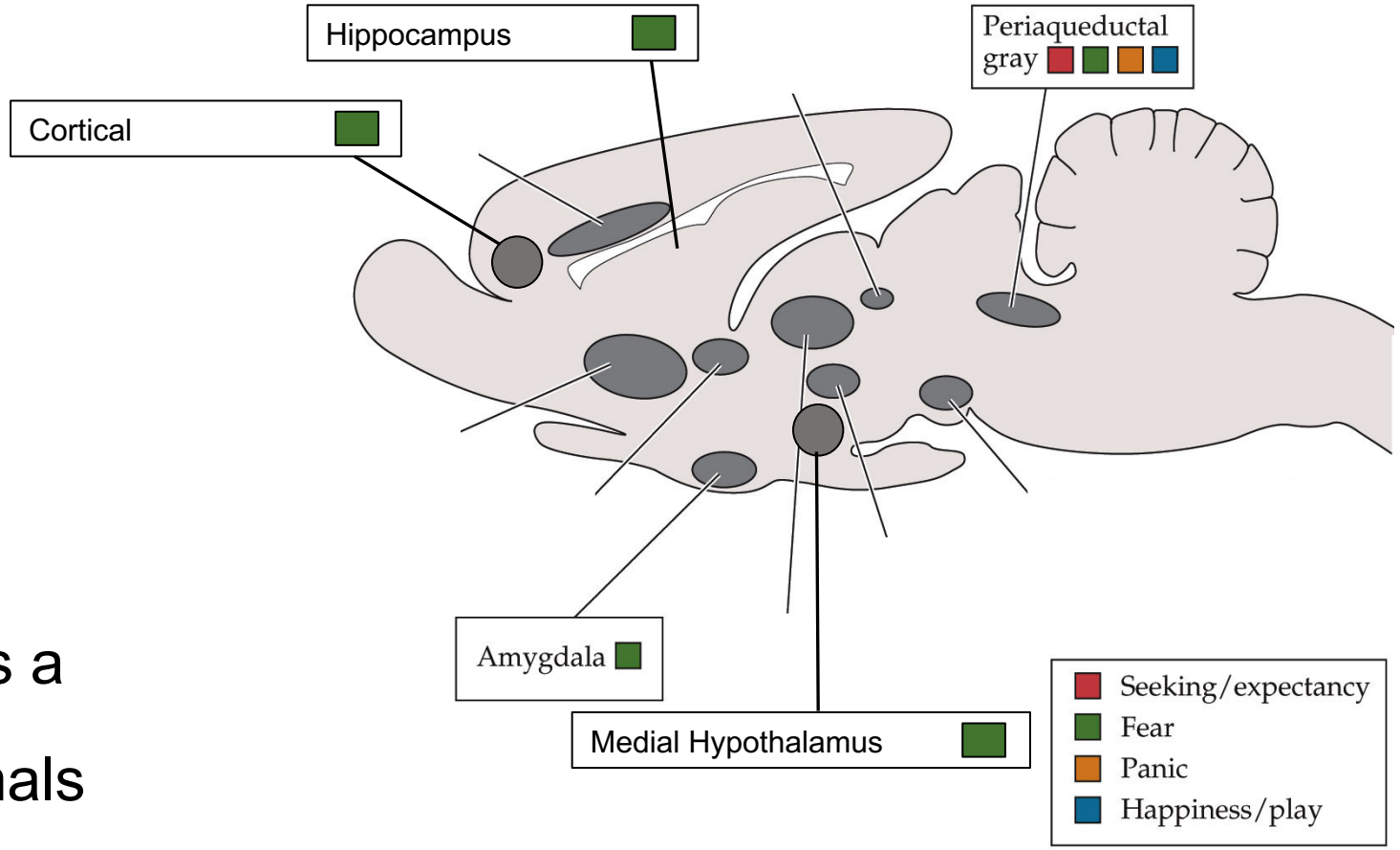
Recovery

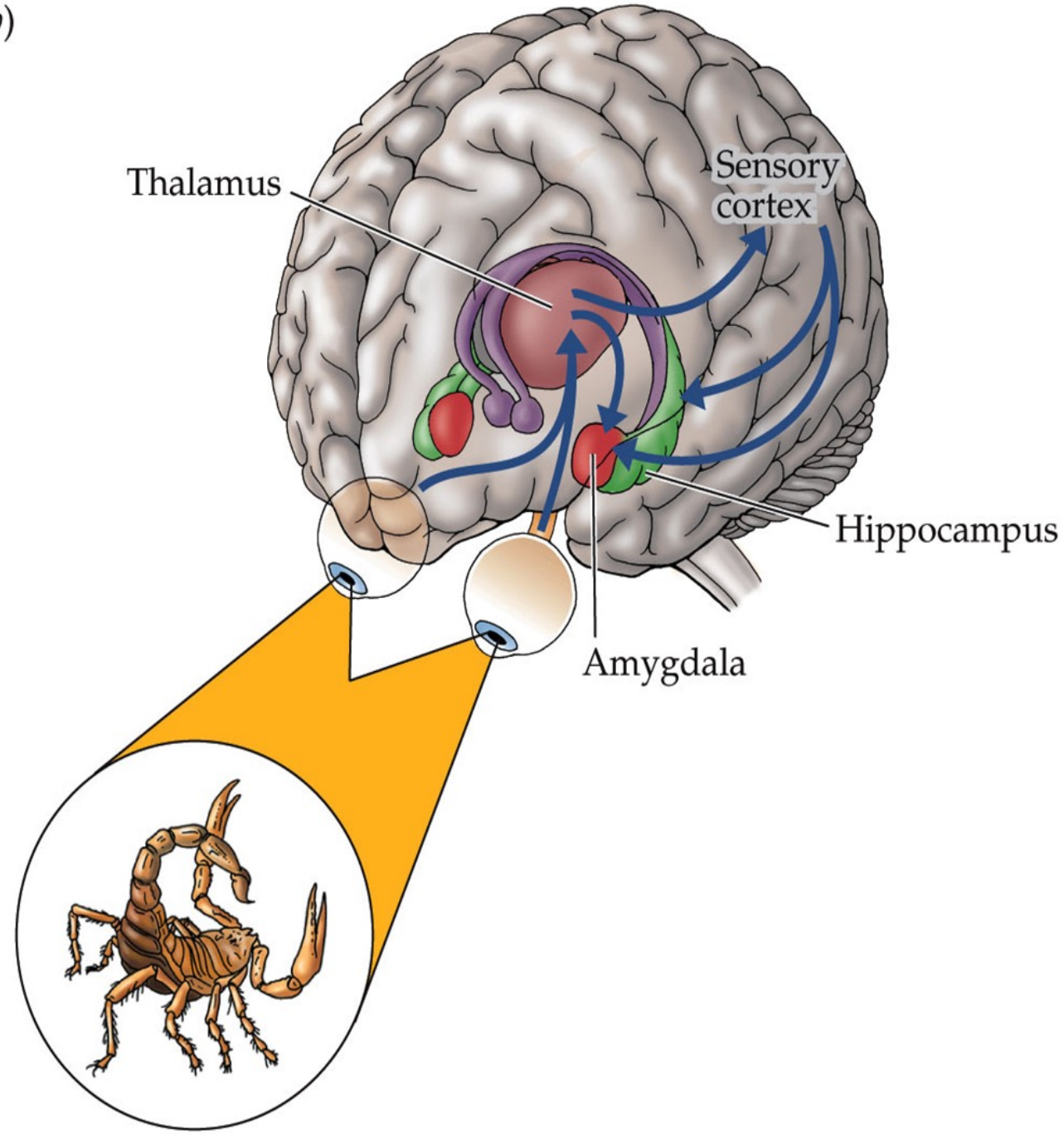
Extinction: repeated exposure = decreased fear

The Anxiety-Fear Connection

Brain regions involved in fear circuit across all vertebrates

Fear Learning can be used as a way to probe ”anxiety-like” behaviors in non-human animals





Anxiety & Fear

The basis for anxiety is primarily an <u>overactive FEAR circuit</u>

Sensory organ responds to a stimulus

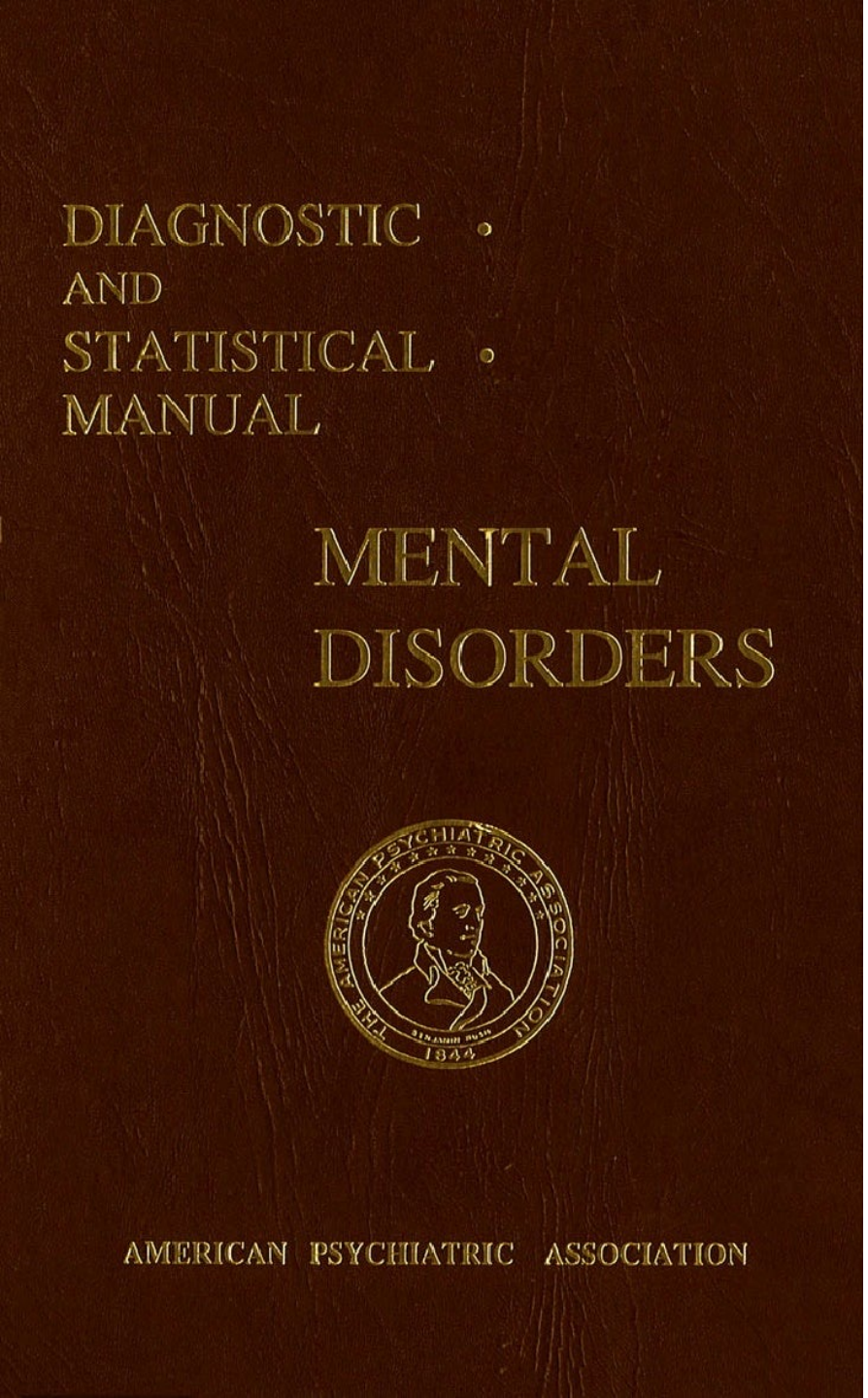
Thalamus receives input from sensory organs

Thalamus relays information to the **sensory cortex**, **hippocampus,** and **amygdala**

sensory cortex & hippocampus also send information to the amygdala

Amygdala sends information to brain regions that govern **emotional behavior**, and **autonomic & hormonal responses**

What is “normal” vs “pathological”?



DSM-I (1952)

- Axis I: Clinical disorders
- schizophrenia, depression, anxiety, etc.
- Axis II: Personality disorders
- borderline personality disorder
- Axis III: General Medical Conditions
- Axis IV: Psychosocial and Environmental Problems
- issues associated with lack of social support
- Axis V: Global Assessment of Functioning
- used to plan treatment and predict outcomes

DSM-5 DIAGNOSTIC CRITERIA FOR GENERALIZED ANXIETY DISORDER

Criteria	
1.	Excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least 6 months, about a number of events or activities.
2.	The individual finds it difficult to control the worry.
3.	The anxiety and worry are associated with three (or more) of the following six symptoms (with at least some symptoms having been present for more days than not for the past 6 months):
	a. Restlessness, feeling keyed up or on edge
	b. Being easily fatigued
	c. Difficulty concentrating or mind going blank
	d. Irritability
	e. Muscle tension
	f. Sleep disturbances (difficulty falling or staying asleep, or restless, unsatisfying sleep)
4.	The anxiety, worry, or physical symptoms cause significant distress or impairment in social, occupational, or other areas of functioning.
5.	The disturbance is not attributable to the physiological effects of a substance or another medical condition.
6.	The disturbance is not explained by another mental disorder.

Note. DSM-5 = Diagnostic and Statistical Manual of Mental Disorders *(5th ed.). Adapted from American Psychiatric Association, 2013.*

DSM-5 Anxiety Disorders and Obsessive-Compulsive Disorders

1. **Anxiety Disorders**

separation anxiety disorder, selective mutism, specific phobia, social phobia, panic disorder, agoraphobia, and generalized anxiety disorder

2. **Obsessive-Compulsive Disorders**

obsessive-compulsive disorder, body dysmorphic disorder, hoarding disorder, trichotillomania, and excoriation disorder

3. **Trauma and Stressor-Related Disorders**

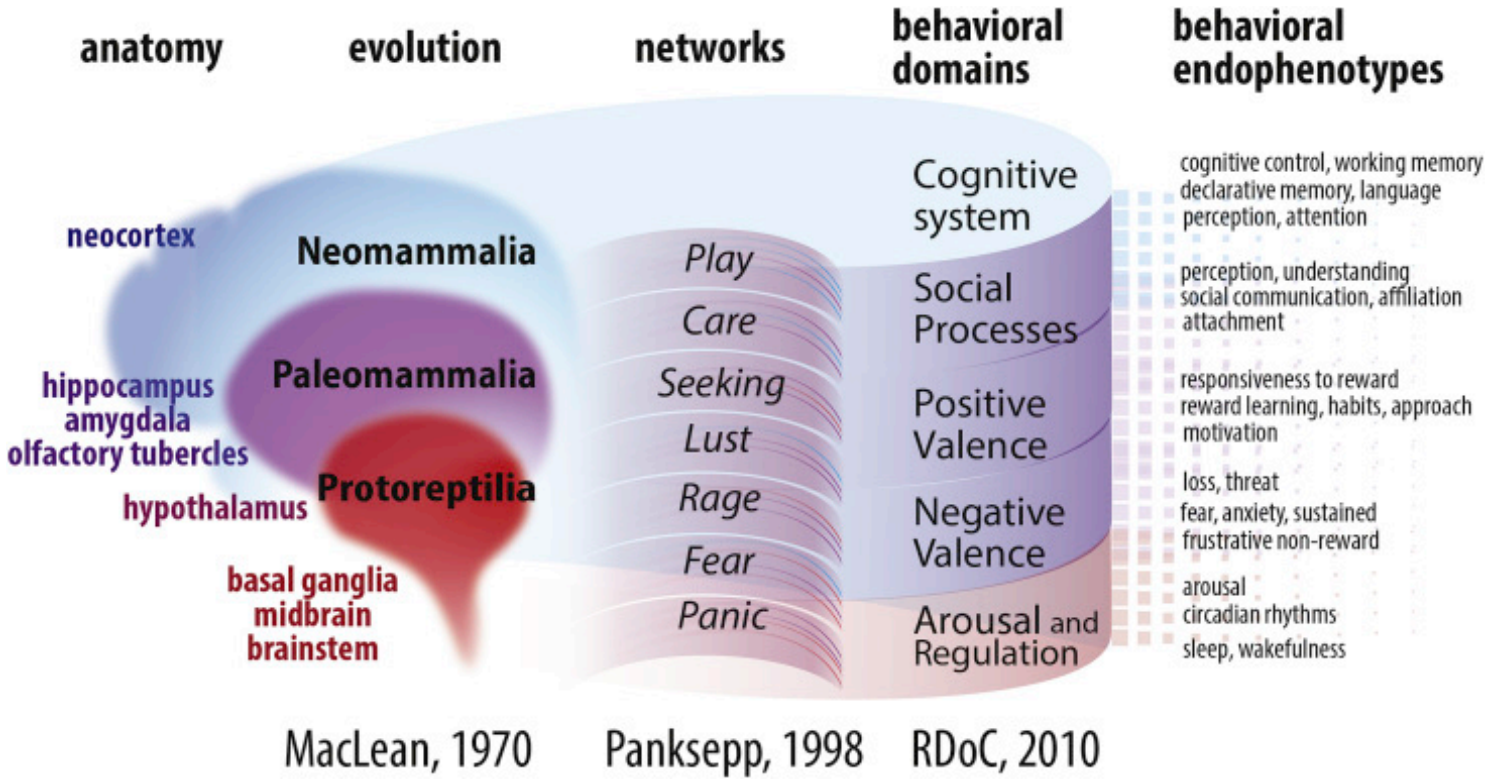
reactive attachment disorder, disinhibited social engagement disorder, PTSD, acute stress disorder, and adjustment disorder

National Institute of Mental Health

RDoC System

- Initiative to move away from DSM “categorical” approach to classifying mental illness
- DSM is based on lists of symptoms and does not incorporate modern neuroscience in understanding pathology
- RDoC is a dimensional approach that integrates genetics, neurobiology, imaging, and behavior
- Aims to construct valid and reliable phenotypes of mental disorders

Research Domain Criteria



Affective Conclusions

- Distinct primal subcortical brain regions and pathways control the affective mind
- Disruption of the affective mind underlies the overwhelming majority of psychiatric disorders
- Targeting these systems through neural stimulation and/or underlying neuromodulators provide a promising basis for treating psychiatric disorders

Questions?