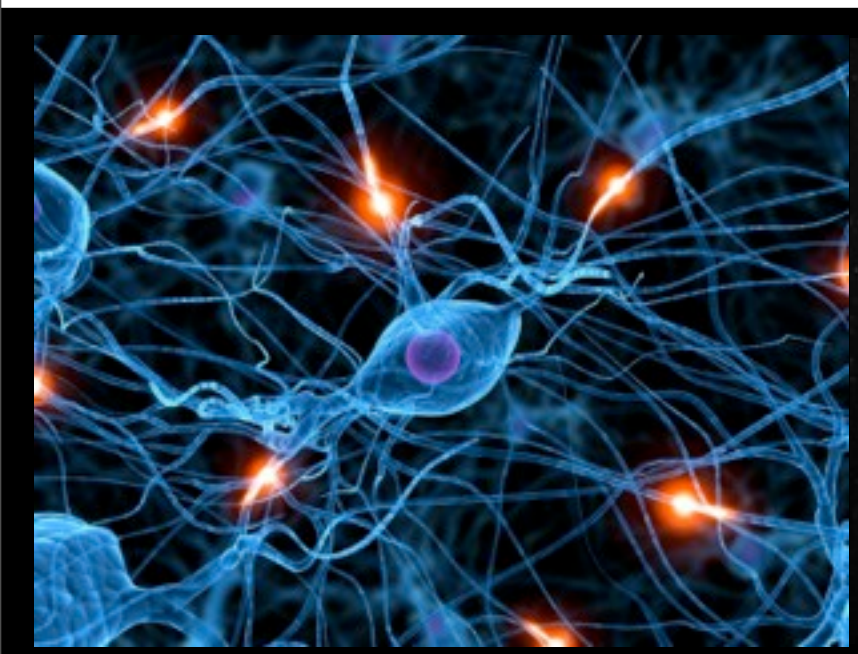
The Neuroanatomy of Fear



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VA GRECC Neuropsychology Postdoctoral Research Fellow

February 7, 2014

The Neuroanatomy of Fear

Defining Fear

Fear is a biologically basic emotion of all humans and many animals, however differs among phylogenetically divergent levels of neural complexity.

Ralph Adolphs (2013) "The Biology of Fear", *Current Biology*

- Fear is an intervening variable between sets of context-dependent stimuli and behavioral responses. A central state of an organism leading to conscious and unconscious experience, often behavior, caused by particular sets of stimuli.
- Caused by particular patterns of threat-related stimuli, and in turn causing particular patterns of adaptive behaviors to avoid or cope with that threat.

Joseph LeDoux (2014) "Coming to terms with fear", Proc Natl Acad Sci

- Recently addressed conflation of two phenomena labeled "fear":
  (1) behavioral and physiological fear responses elicited by threats, such as a mugger
  (2) conscious feelings of fear, occurring in the same situation but controlled by a different brain system.
- Problems arise when terms are conflated referring to conscious experiences with those that refer to the processing of stimuli. the brain mechanisms that underlie the two kinds of processes are the distinct.

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Major Conceptions of Fear

Type of Theory	Key Features
Motivation/Personality	5 types of fear: evolutionary danger, novelty, intensity, learning, social
Neurofunctional	2 systems: fear and panic
Adaptive/Evolutionary	Fear is an instance of a more basic and broader survival system
Basic Emotion	Fear is one of a small set of basic emotions, which are cross-cultural
Modular	Phobias (to snakes, spiders, etc.) reflect the operation of modules
Modular	Pain, predators, and conspecific aggression are 3 types of fear
Dimensional	Fear is one location in a 2-D space of arousal and valence ("core affect")
Dimensional	Fear is one location in a 2-D space of reward and punishment
Social Construct	The experience of fear in humans is constructed from core affect

Ralph Adolphs (2013) "The Biology of Fear", Current Biology

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Types of Fear Responses

Fear is commonly thought to have adaptive functions in terms of both cognition and behavioral response.

Defensive Aggression: response a threatening situation response based on the presence of elements of either fear and/or threat, which may be real or perceived. “Flight”

Active/Predatorial Aggression: unprovoked response a purposeful and goal-directed attack with absence of sympathetic arousal “fight”

Passive Response: Passive fear responses (freezing). Fearful situations can produce immobility

Approach/ Avoidance Behavior:

Approach-avoidance conflicts occur when there is one goal or event that has both positive and negative effects or characteristics that make the goal appealing and unappealing simultaneously.

Example = Marriage :)

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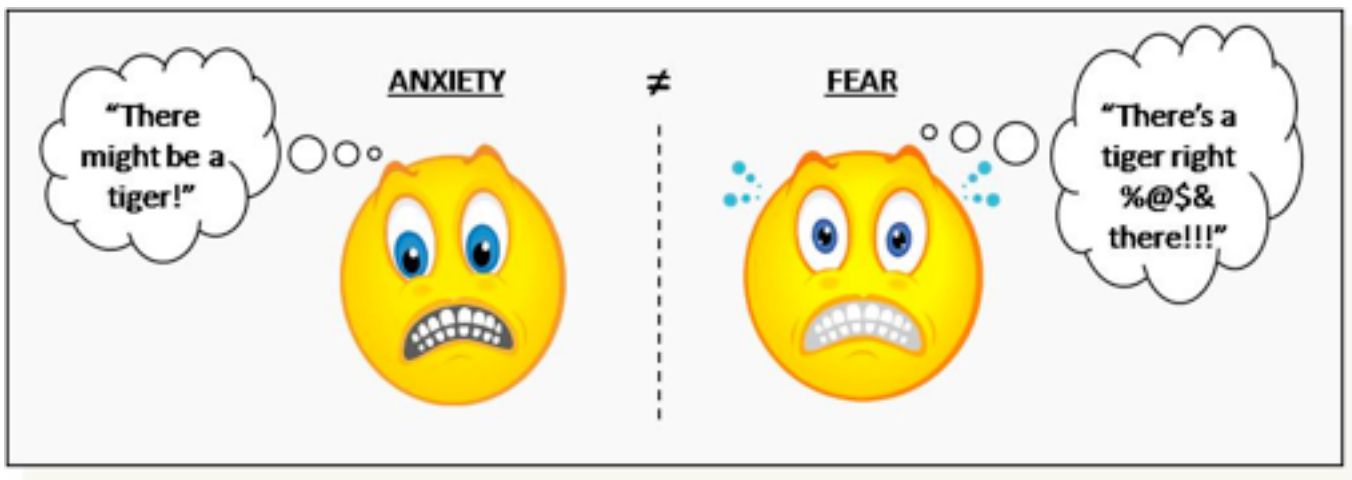
Distinguishing Fear versus Anxiety

- Fear is conceptualized as an adaptive but phasic (transient) state elicited through confrontation with a threatening stimulus
- Anxiety is a more tonic state related to prediction and preparedness--the distinction is similar to the one between emotions versus moods.
- Not necessarily neuroanatomically dissociable, but more likely variations of fear systems based upon with varying levels of threat imminence (from more distal to proximal) and types of environmental stimuli (Adolphs, 2013).



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Theories of Fear Processing

Pavlovian Fear Conditioning

- Presenting a neutral conditioned stimulus (CS) (e.g., a tone) with an aversive unconditioned stimulus (US) (e.g., a shock).
- After repeated pairings, the CS alone elicits a conditioned fear response (e.g., increased freezing, startle).
- Extinction occurs when a CS that previously predicted a US no longer does so, and over time, the fear response decreases.

Operant/ Instrumental Conditioning

- Uses positive/negative reinforcement or punishment to change behavior
- Behavior is modified by its antecedents and consequences.

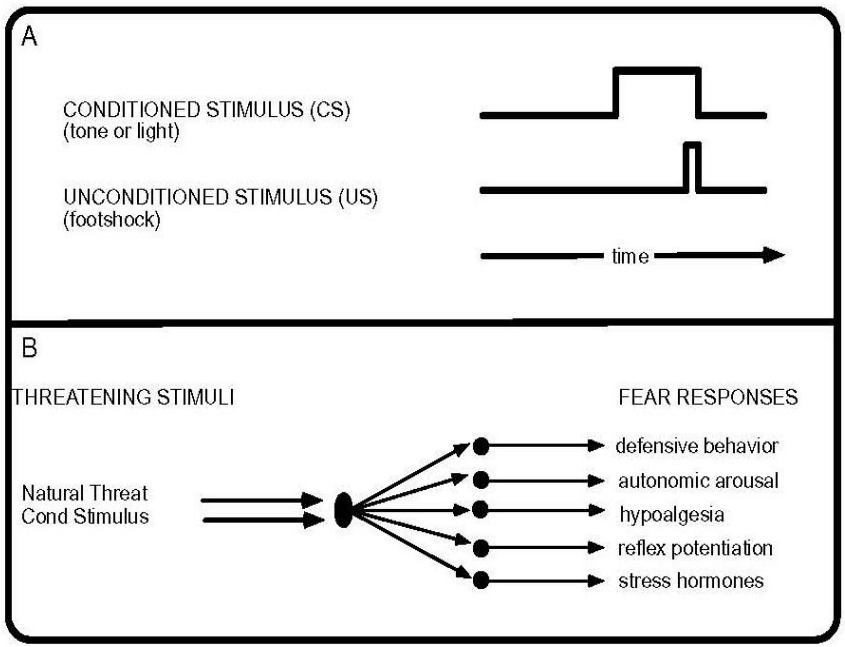
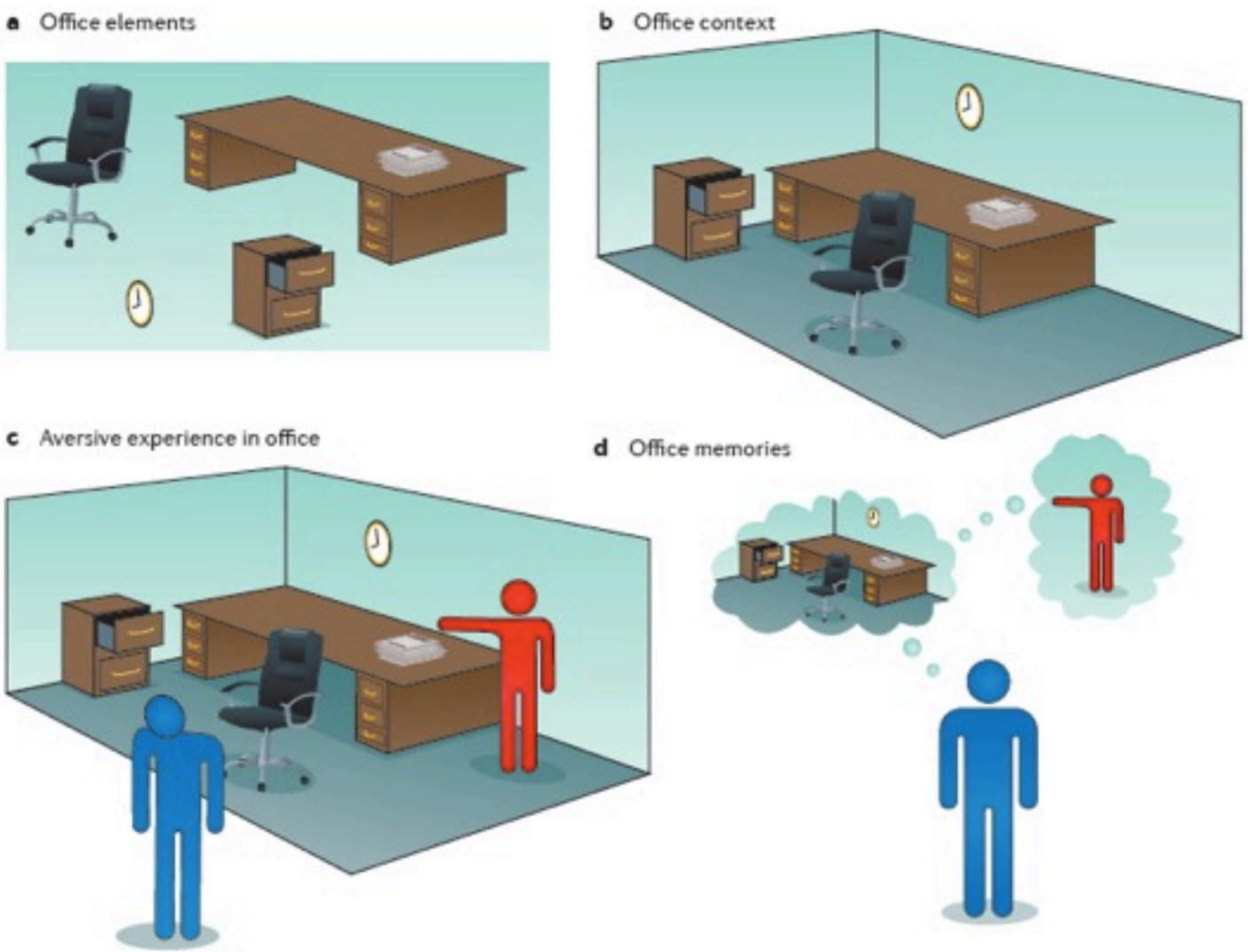


Figure 1 Fear conditioning involves the presentation of a noxious unconditioned stimulus, typically footshock, at the end of the occurrence of a relatively neutral conditioned stimulus (CS), such as a light or tone (*top*). After conditioning, the CS elicits a wide range of behavioral and physiological responses that characteristically occur when an animal encounters a threatening or fear-arousing stimulus (*bottom*). Thus, a rat that has been fear conditioned will express the same responses to a CS as to a natural threat (i.e. a cat).

LeDoux, J. E. (2000). Emotion circuits in the brain. Annual Review of Neuroscience, 23(1), 155-184.

Fear Processing ~ Contextual Conditioning

- Eliciting circumstances (e.g., flight available or not, environmental cues)
- Type of threat (predator, unknown)
- Distance to the threat (imminence)
- Time elapsed since threat



The contextual brain: implications for fear conditioning, extinction and psychopathology
Maren, Phan, & Liberzon, NATURE REVIEWS| NEUROSCIENCE VOLUME 14 | JUNE 2013

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Theories of Fear Processing

Appraisal Theories (e.g., Arnold, 1960; Frijda 1986; Lazarus, 1966)

- The cognitive aspect involved in elicitation of emotion is unconscious or otherwise automatic, and occurs immediately after the stimulus, prior to the bodily response.

Network Theories (Berkowitz, 1990; Bower, 1981; Lang, 1985)

- Activation of memory is the principal cause of emotions. A limited number of stimuli elicit unconditioned emotional responses; however the range of stimuli that evoke emotions is elaborated through conditioning. Emotions are represented in schemas, in which each has a localist representation (node).

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Cognition and Emotion

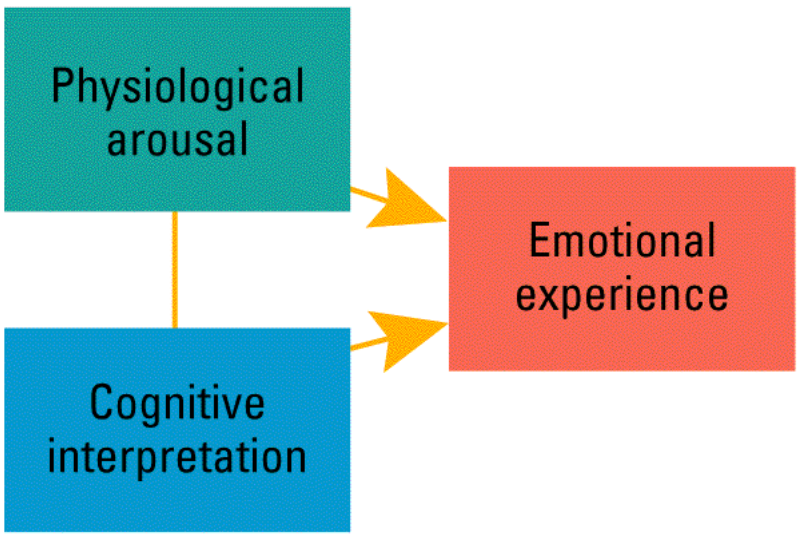
Barrett's Theory (2006)

- **Two factor theory:** (1) A stimuli elicits core affect. (2) Core affect is cognitively categorized. Internal categorization of core affect is a form of perception that is influenced by prior conceptual knowledge. Whether a core affect is categorized as anger, fear, or sadness depends on acquired emotion scripts.

Physiological arousal
- Sweaty palms
Increased heart rate
Rapid breathing

Cognitive Interpretation
- Attribute arousal to cause

For emotion, both factors are required



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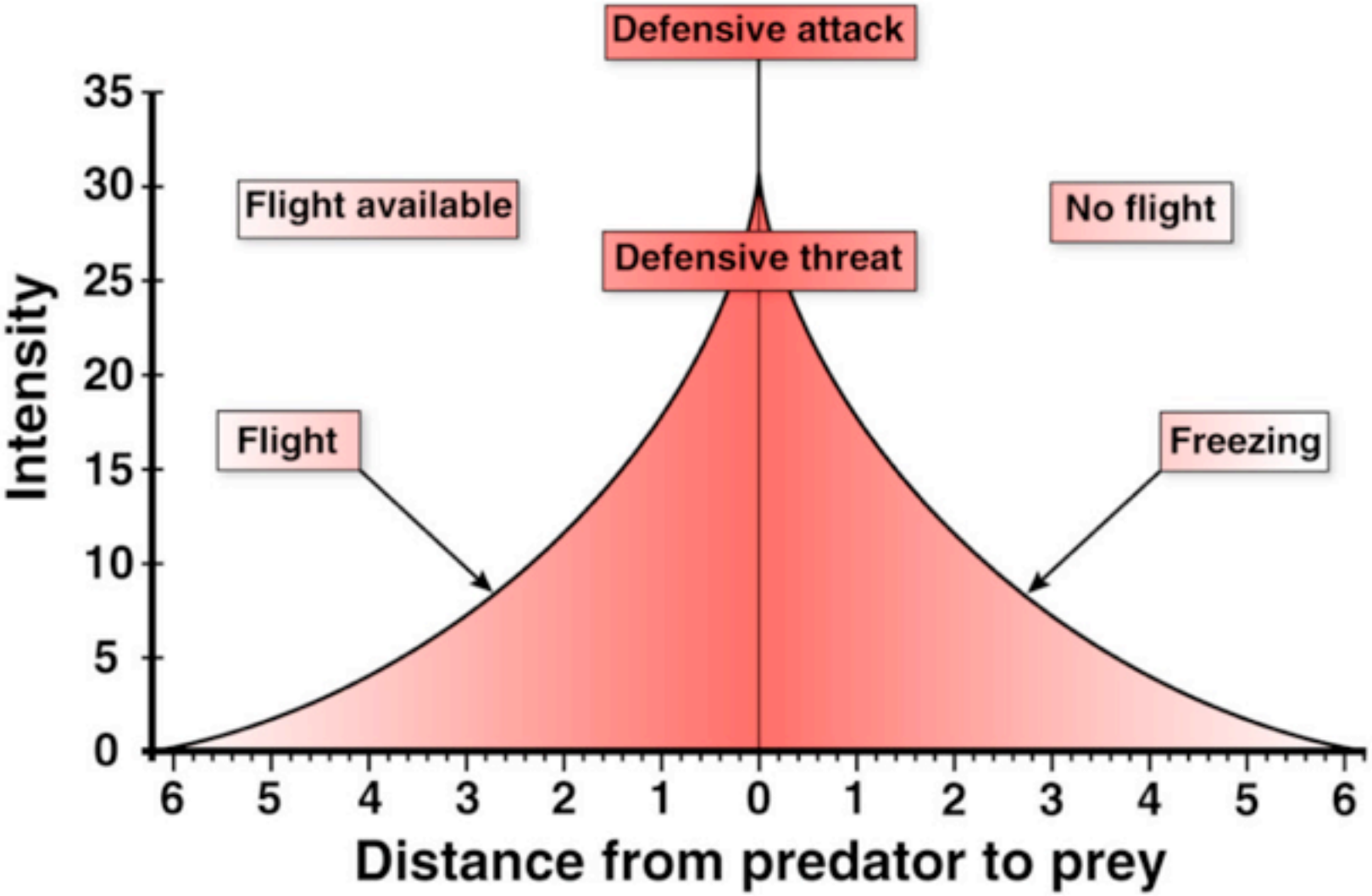
Types of Fear Responses ~ **Fight, Flight, Freeze Response**



Blanchard, RJ.; Blanchard, DC. In Fear and Defence. Brain, PF.; Blanchard, RJ.; Parmigiani, S., editors. London: Harwood Academic; 1990. p. 89-108.

VIDEO

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Theories of Fear Processing

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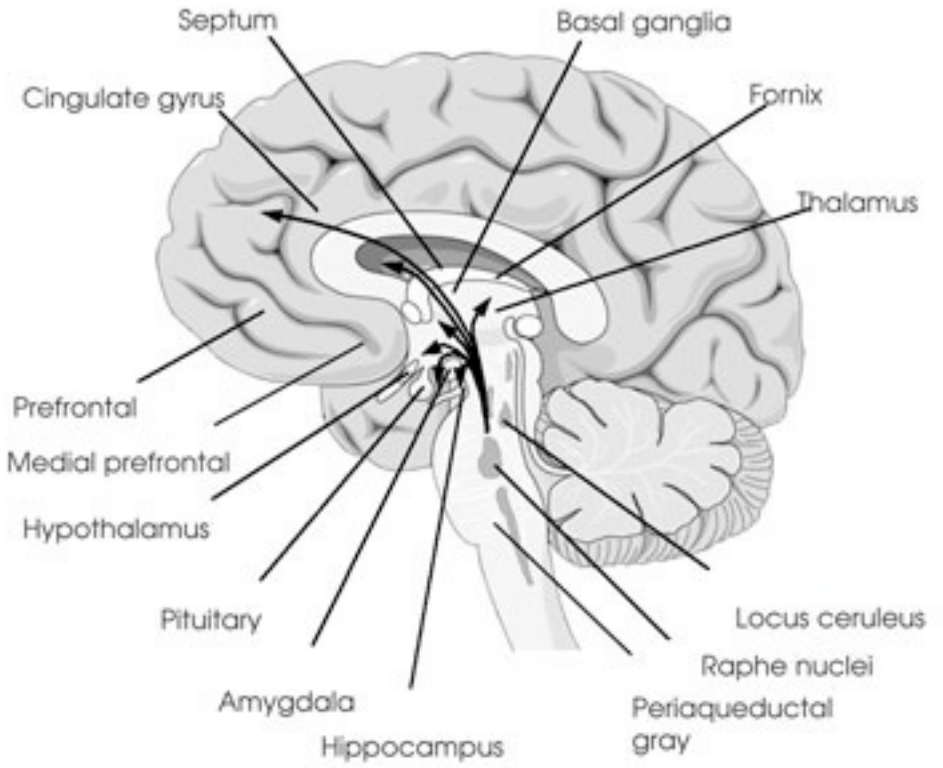
Limbic System

Includes:

amygdala, hippocampus,
fornix, thalamus, raphe nucleus
nucleus accumbens,
anterior hypothalamus, cingulate,
mammmillary bodies

- Provides higher levels of the brain stem.
- Integrates brain stem with higher cortical areas.
- Considered the “emotional center” brain, thought term is debated

Figure 1
Gross Anatomical Structures Involved in the Fear Circuitry*



*Arrows indicate movement of sensory input.

Berlant JL. *Primary Psychiatry*. Vol 10, No 10. 2003.

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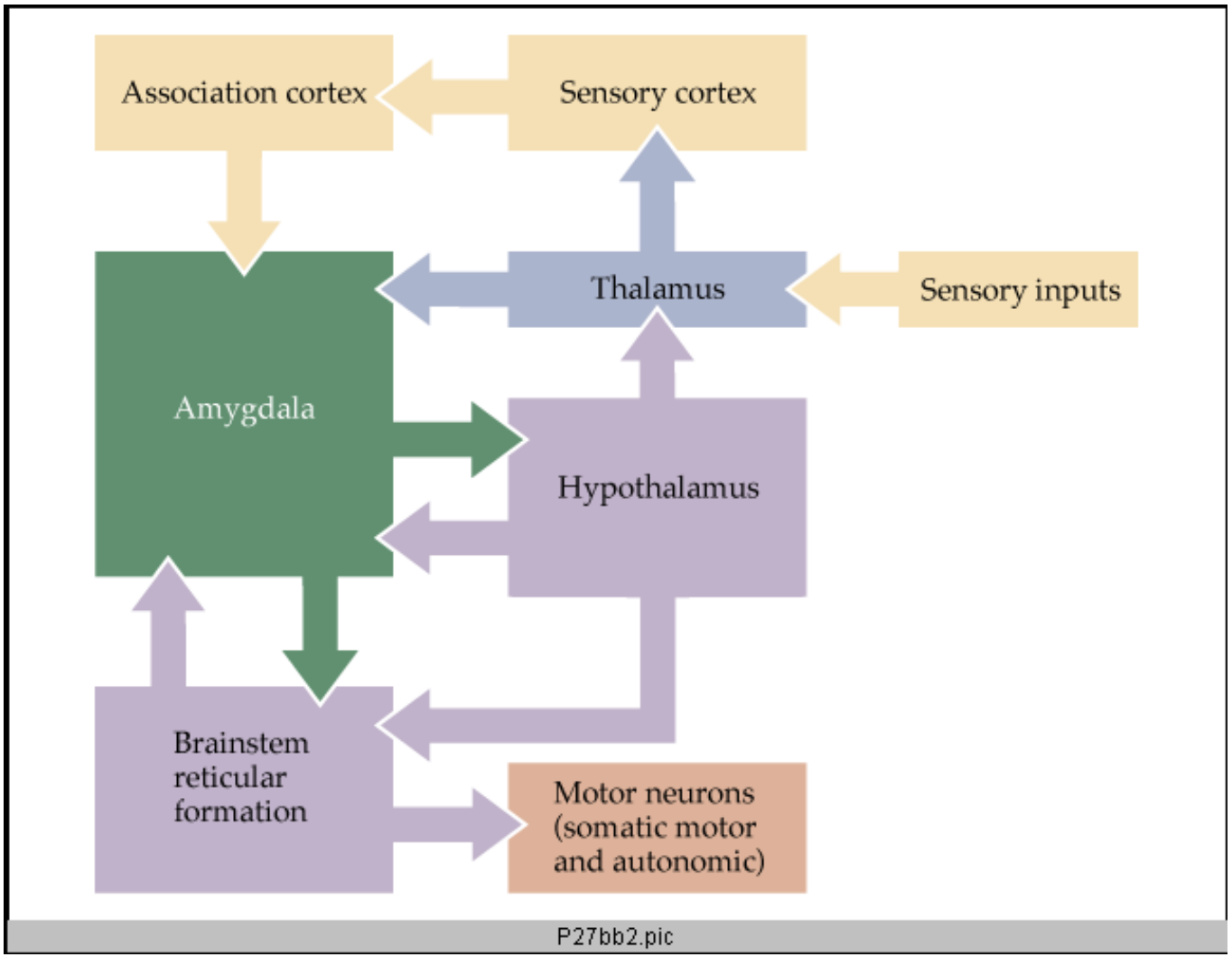
Neural Regions



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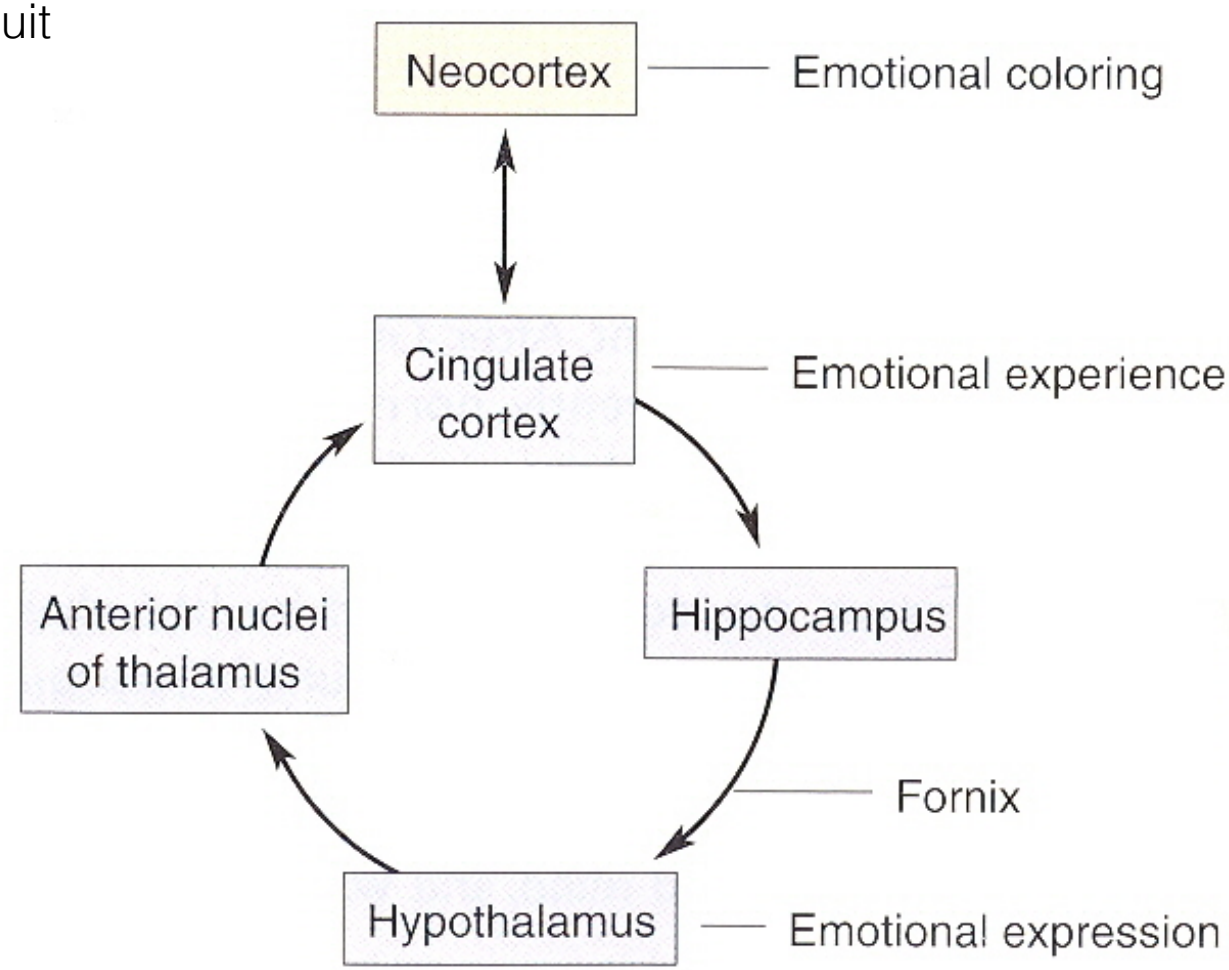
- Papez Circuit

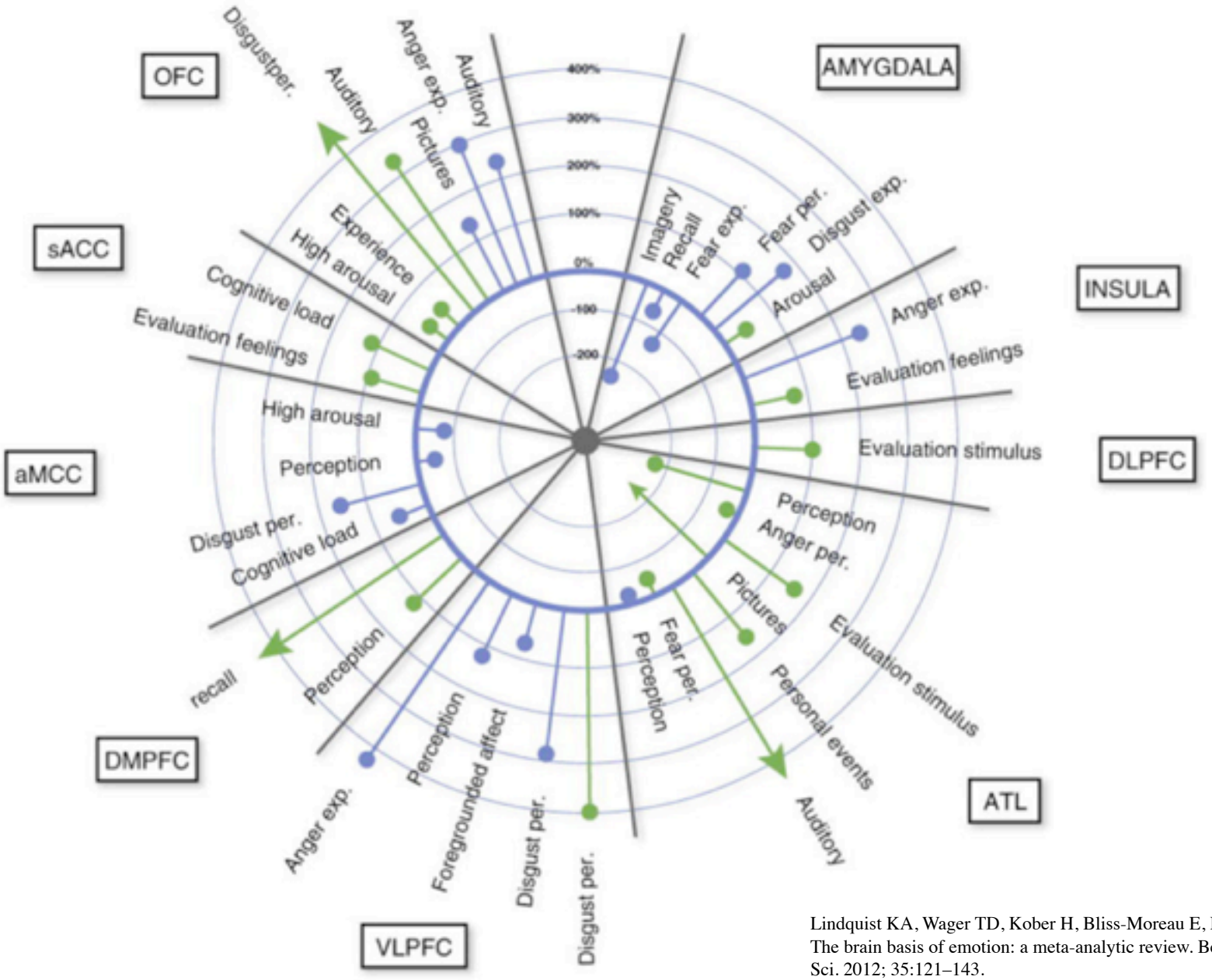


From: Bear et al., 2007

Overview of limbic regions involved in fear response

- Amygdala involved in emotional arousal and conditioned fear; ACC and insula also active during increased fear states
- Ventromedial prefrontal cortex (vmPFC) involved with extinction of the fear response, modulated during reappraisal inverse to amygdala
- Both hippocampus and insula are associated with extinction of fear
- Ventrolateral PFC involved in labeling, conscious appraisal of affect, inversely correlates with amygdala
- Dorsal, superior and dorsomedial PFC correlates positively with amygdala activity- accentuates
- Dorsal ACC associated with anticipatory anxiety
- Rostral ACC associated with regulation and control of anxiety

Overview of limbic regions fx



Lindquist KA, Wager TD, Kober H, Bliss-Moreau E, Barrett LF. The brain basis of emotion: a meta-analytic review. Behav. Brain Sci. 2012; 35:121–143.

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Neural Regions

Amygdala

- Activation during fear conditioning even when the CS is presented below perceptual thresholds (Critchley et al, 2002; Knight et al, 2009; Morris et al, 2001) and even when more complex USs are used (Doronbekov et al, 2005; Klucken et al, 2009).
- Activity has been associated with skin conductance changes during fear conditioning (Cheng et al, 2006; Phelps et al, 2001).
- Lesions of amygdalar sites have been shown to reduce unconditioned defensive responses during exposure to a live predator (Canteras, Mota-Ortiz & Motta, 2012)

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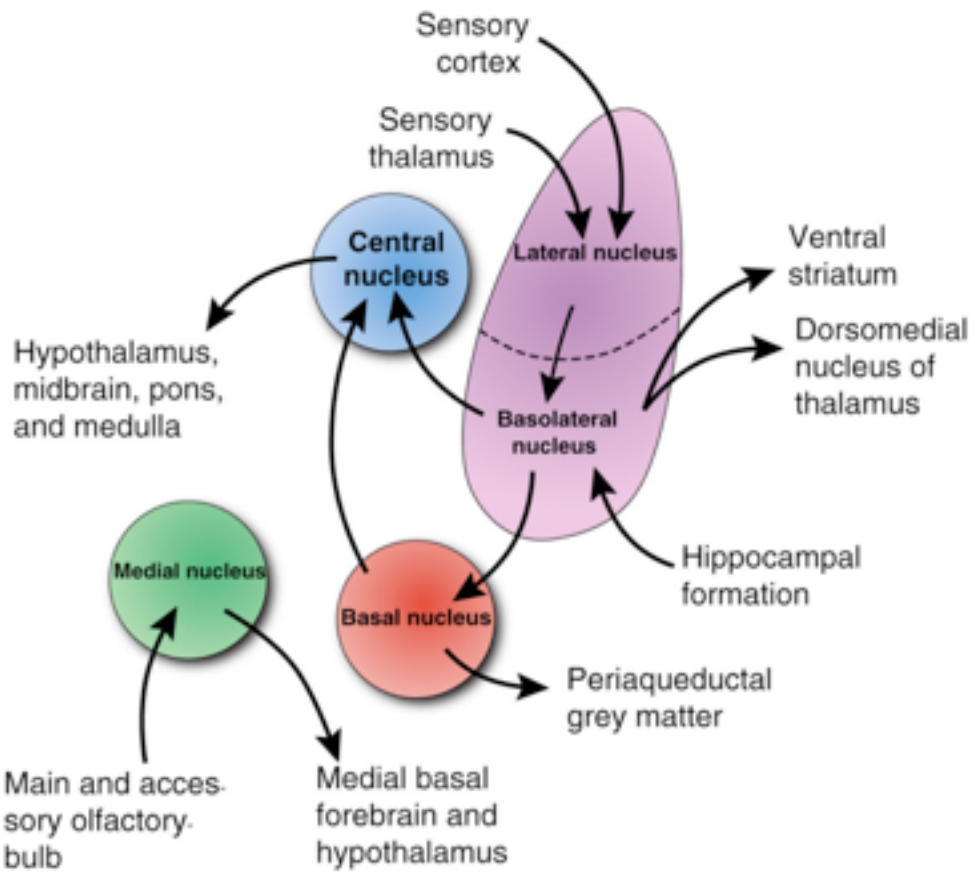
Neural Regions
Amygdalar Circuits & Function



Basolateral amygdala - receives sensory inputs that specify fear associations and selective activation of neurons within this nucleus is sufficient to associate the incoming sensory information with unconditioned fear responses.

The central nucleus is considered the main output regulator for mediating fear responses. Inhibits cholinergic targets mediating cortical arousal and promote freezing through projections to the periaqueductal gray.

outputs to fear generating structures in the hypothalamus and brainstem. (LeDoux et al 1988).

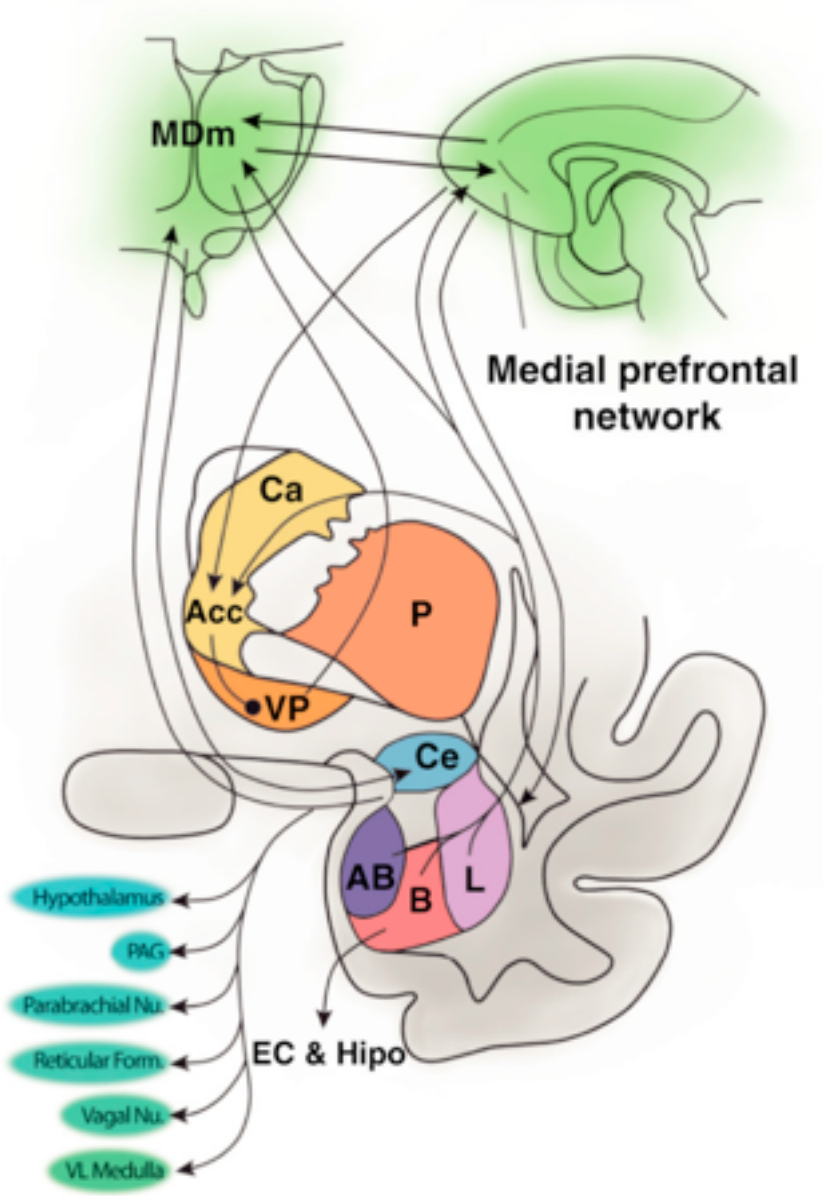
The central nucleus (CE), in contrast, is viewed as the major output region of the amygdala.

LA is seen as the site of fear memory, while Ce is seen as the site of fear expression (LeDoux, 2000).

The LA communicates with the CE directly, but the connections between these two nuclei are somewhat modest and other amygdaloid nuclei also help mediate between these two.

Limbic Arousal and Regulation

- Medial and ventral lateral PFC: inhibit emotional response
- Major medial PFC connections to the amygdala
- MPFC connections to amygdala, HC and BG in non-human primates



Price and Drevets, Neuropsychopharmacology, 2009

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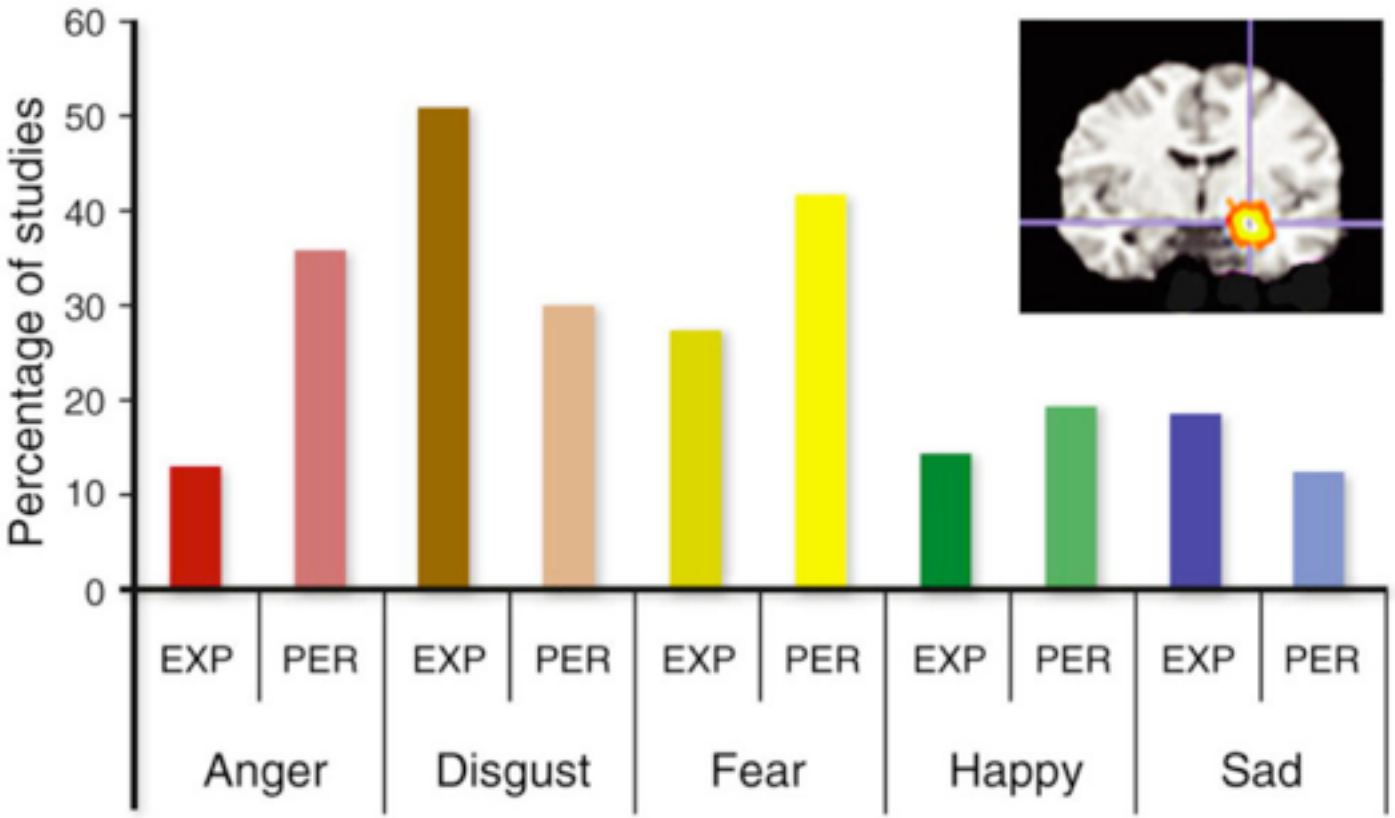
Neural Regions

Amygdala



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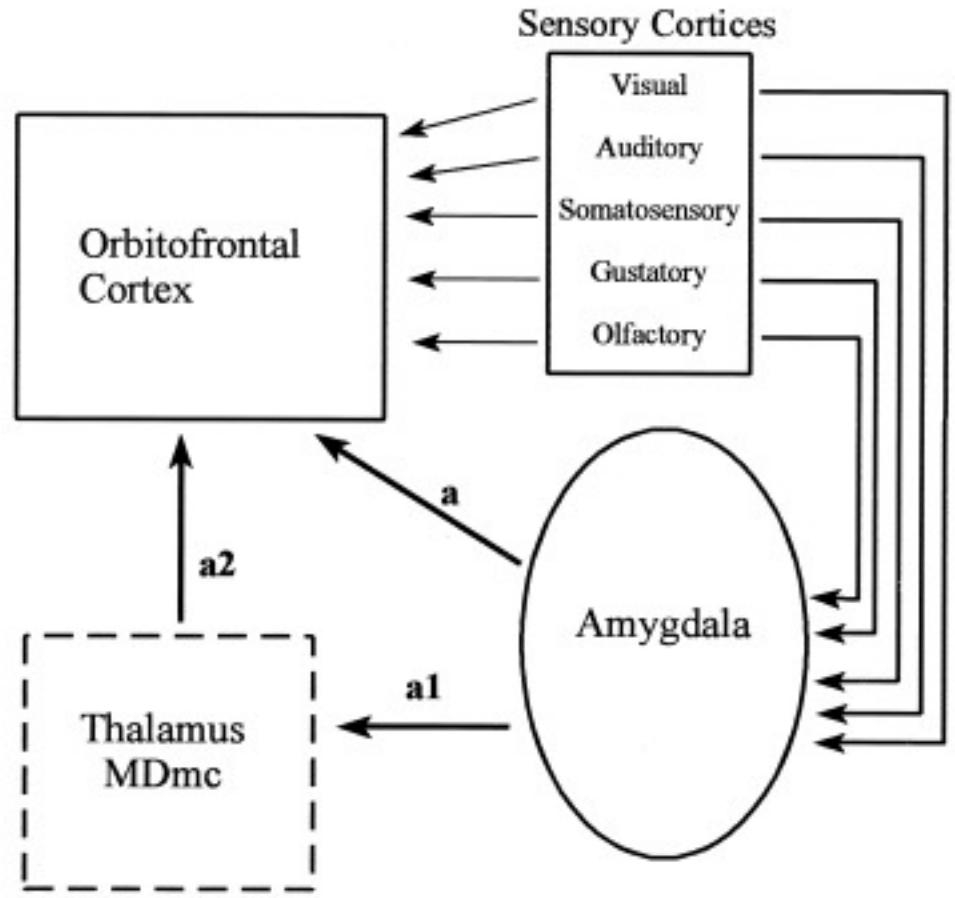


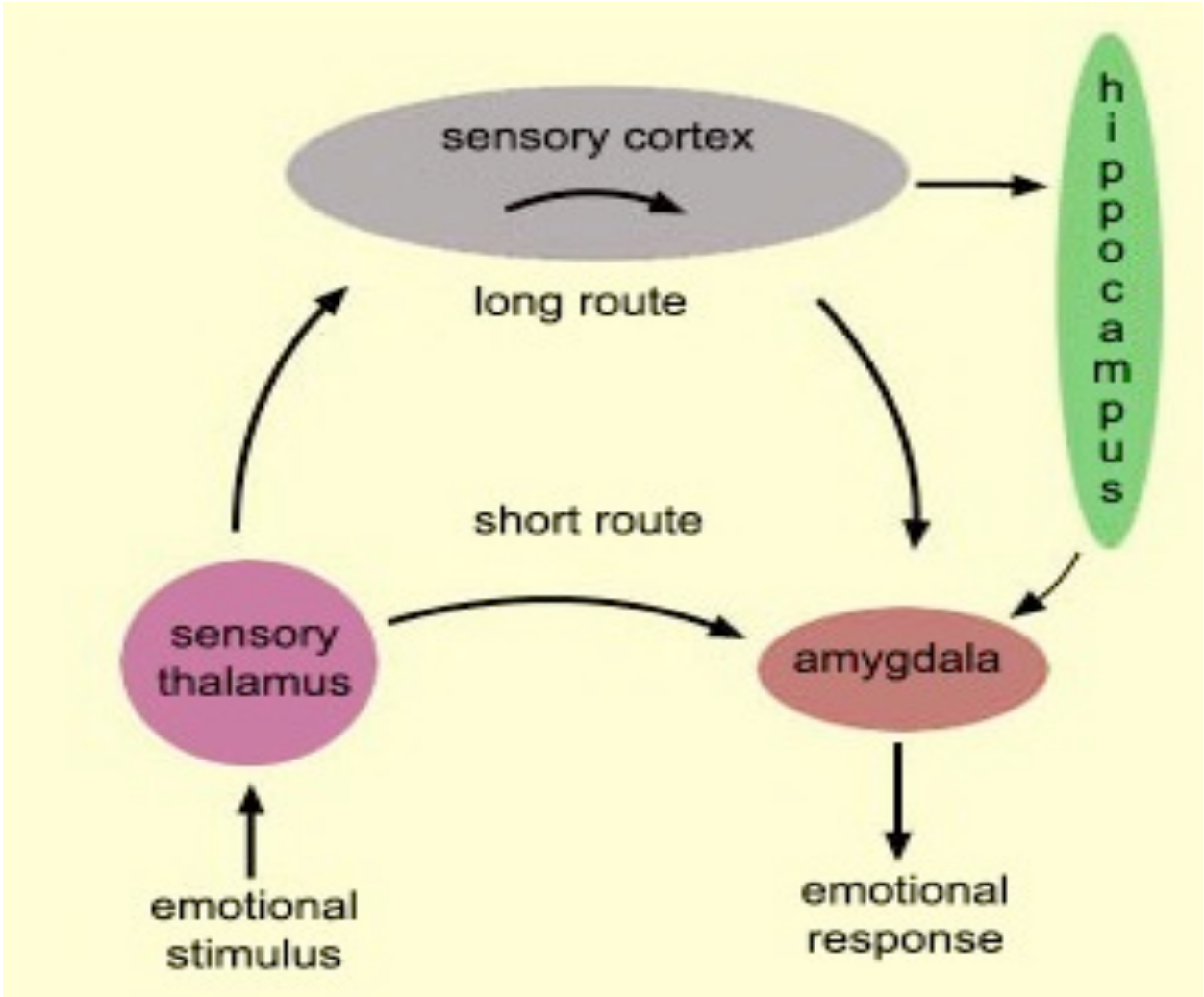
FIG. 3. Direct and possible indirect projections associated with sensory processes and emotion to orbitofrontal cortices in rhesus monkeys. Orbitofrontal cortices receive direct projections from visual, auditory, somatosensory, gustatory and olfactory cortices and possible indirect sensory input through the amygdala (a). Projections from the amygdala reach the orbitofrontal cortex directly (a) and possibly indirectly through the thalamic MDmc (a2), which receives projections from the amygdala (a1). MDmc, magnocellular mediodorsal nucleus.

Proceedings of the Human Cerebral Cortex: From Gene to Structure and Function

Connections underlying the synthesis of cognition, memory, and emotion in primate prefrontal cortices

Barbas (2000)

Short and Long Routes via the Amygdala



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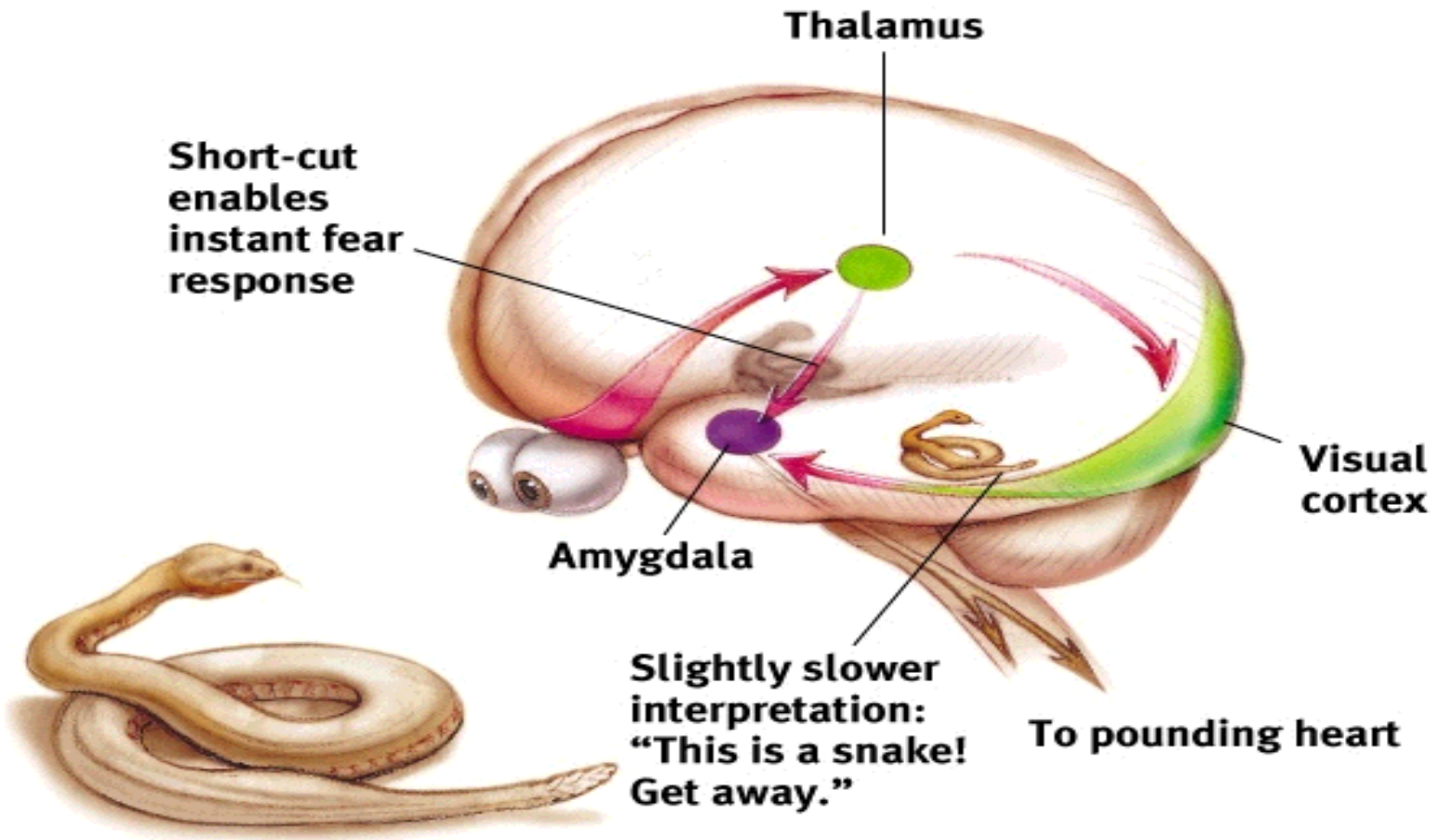
Fear Processing



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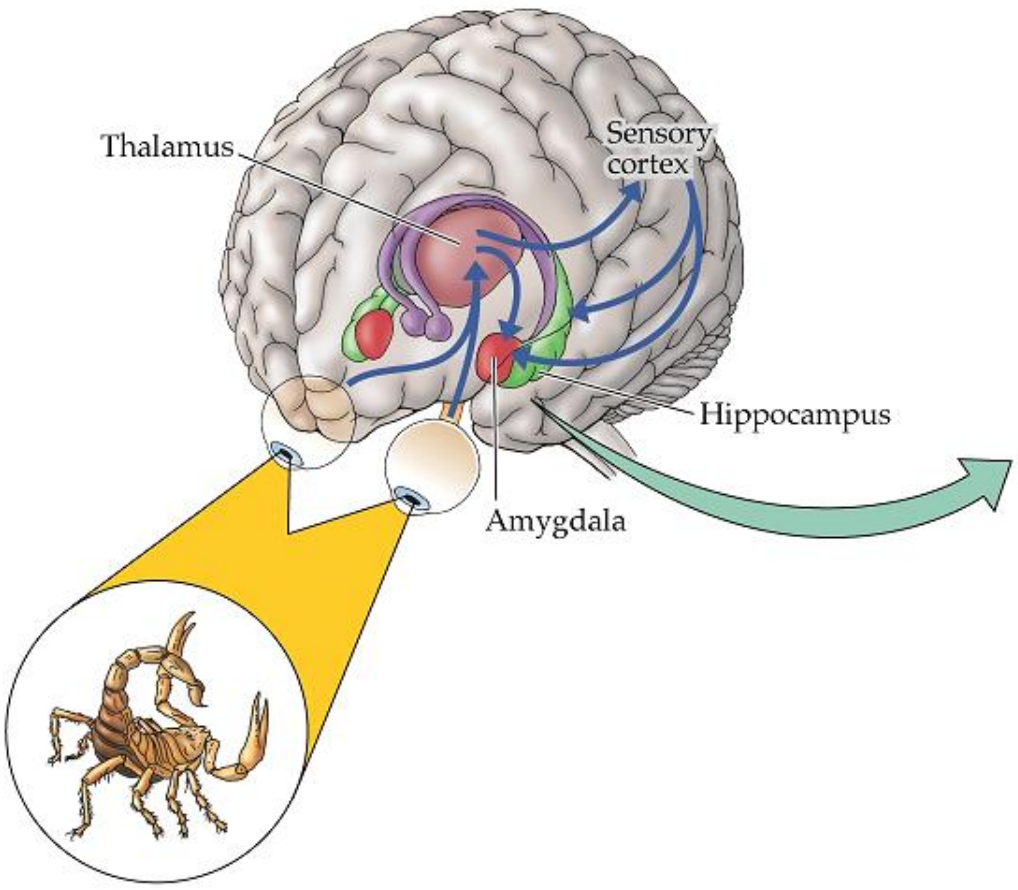
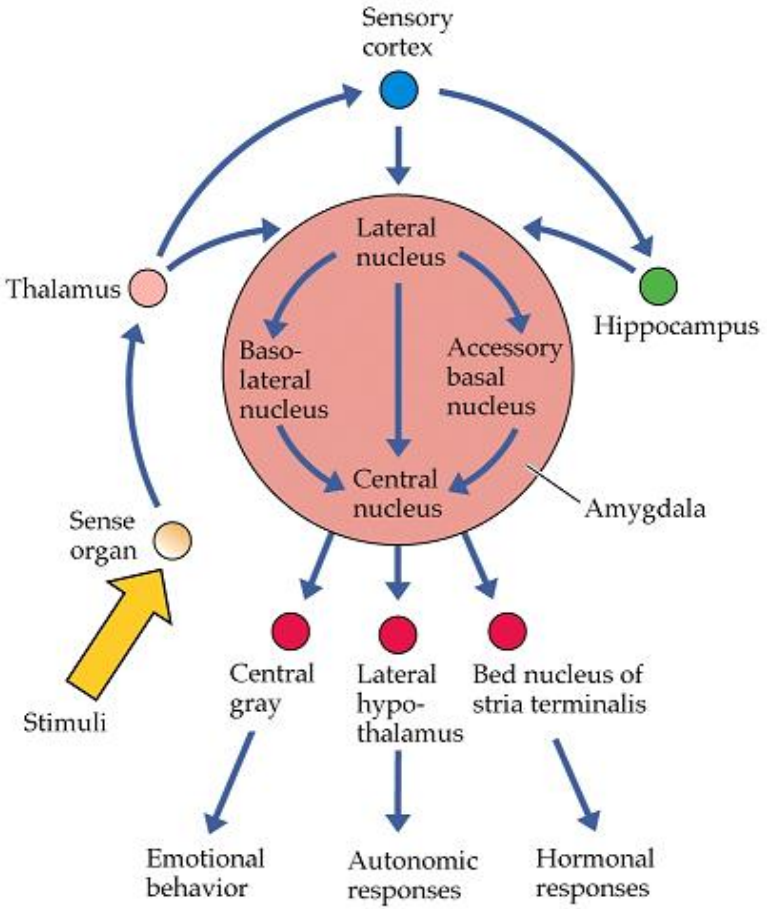
Fear Processing





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Fear Conditioning (LeDoux, 1995)

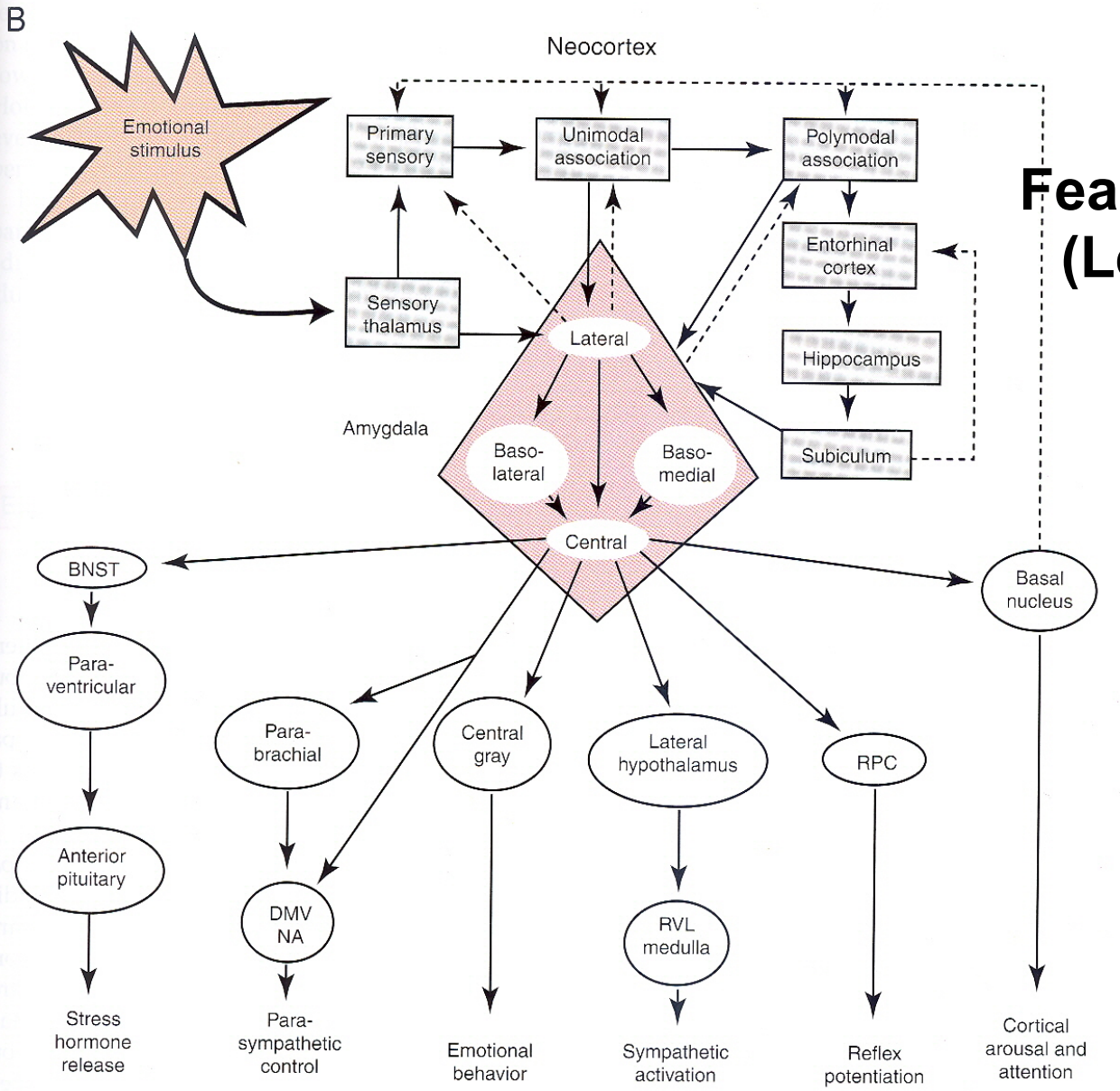

FIGURE 51.12 Fear conditioning. (A) Prior to training, the tone produces a transient orienting response. During training the tone is followed by a brief foot shock. Following training, the rat is reintroduced into the chamber and freezes when the tone is presented. (B) Anatomical pathways that mediate fear conditioning. A hierarchy of sensory inputs converges on the lateral amygdala nucleus, which projects to other amygdala nuclei and then to the central nucleus, which send outputs to several effector systems for emotional responses. BNST, bed nucleus of the stria terminalis; DMV, dorsal nucleus of the vagus; NA, nucleus ambiguus; RPC, nucleus reticularis pontis oralis; RVL, rostral ventral nucleus of the medulla. From LeDovx (1995).

From: Squire et al., 2003

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Hippocampus and Connections

Data suggest that the amygdala has a general role in aversive conditioning and that context conditioning additionally recruits the hippocampus.

Hippocampal lesions do not necessarily disrupt context fear conditioning when made before conditioning. Stimulus elements that make up a context represented outside the hippocampus are sufficient for learning, but these representations are normally overridden by a representation of context in the hippocampus.

Hippocampal lesions in rodents produce deficits in freezing behavior during exposure to a shock-paired context.

Deficits in fear memory following hippocampal damage appear due to a deficit in forming and storing the contextual representation itself rather than a deficit in forming the context–US association (i.e., context conditioning).

Hippocampal activation to CS occurs in the extinction context but not in the conditioning. Hippocampal-vmPFC interactions may be important for the contextual modulation of extinction (Kalisch et al, 2006).

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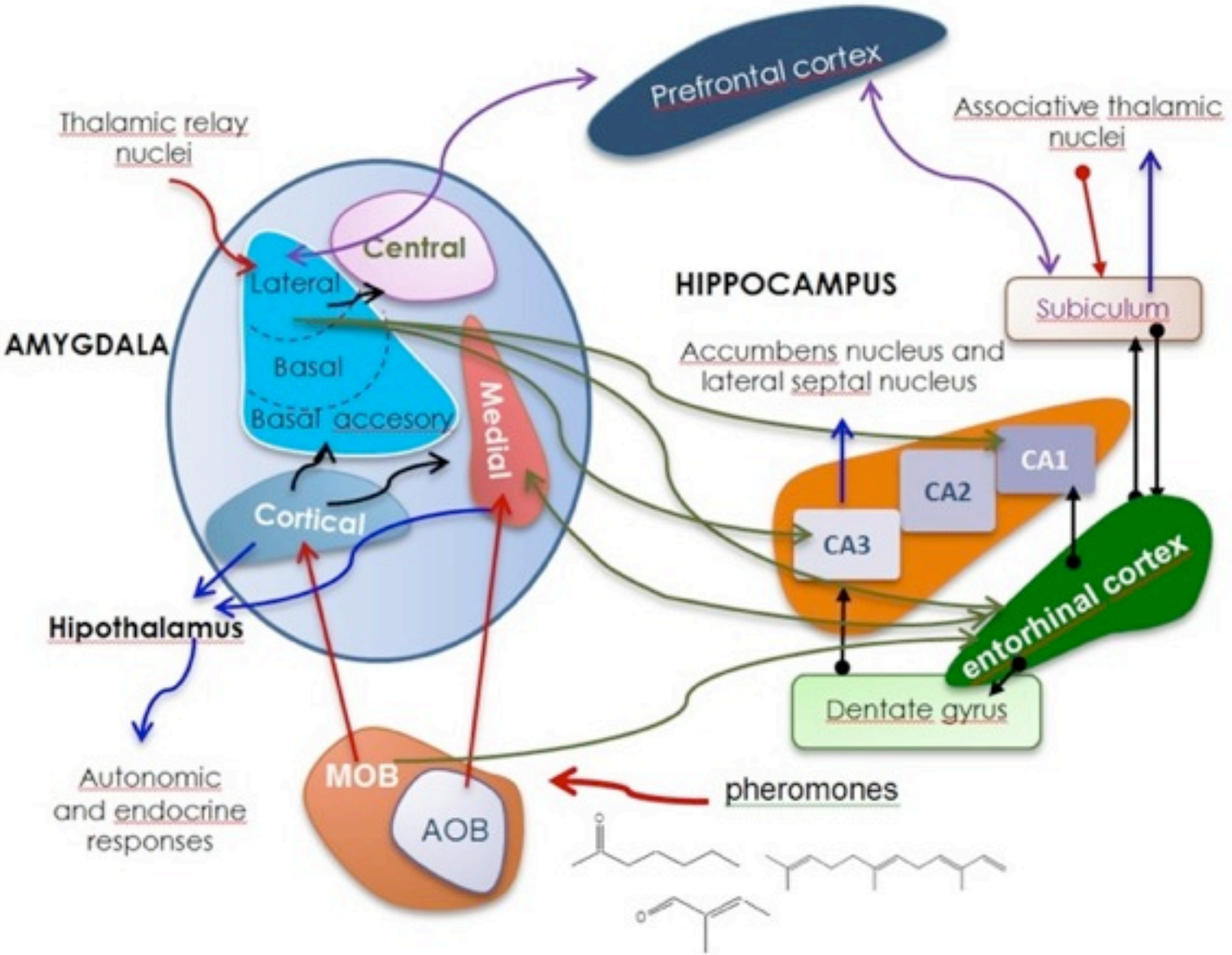

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Ventromedial Prefrontal Cortex

- Functional neuroimaging studies of healthy humans have reported vmPFC activation during extinction (Barrett and Armony, 2009) and the later recall of extinction (Milad et al, 2007).

- Skin conductance measures of extinction memory are positively correlated with vmPFC activation (Phelps et al, 2004) and vmPFC cortical thickness (Milad et al, 2005).

Cingulate Cortex

- Fear conditioning is also associated with increased activation in the dACC and rACC (Alvarez et al, 2008; Buchel et al, 1998, 1999)

- Activation in the dACC and rACC also occurs during observational fear learning (Olsson et al, 2007).

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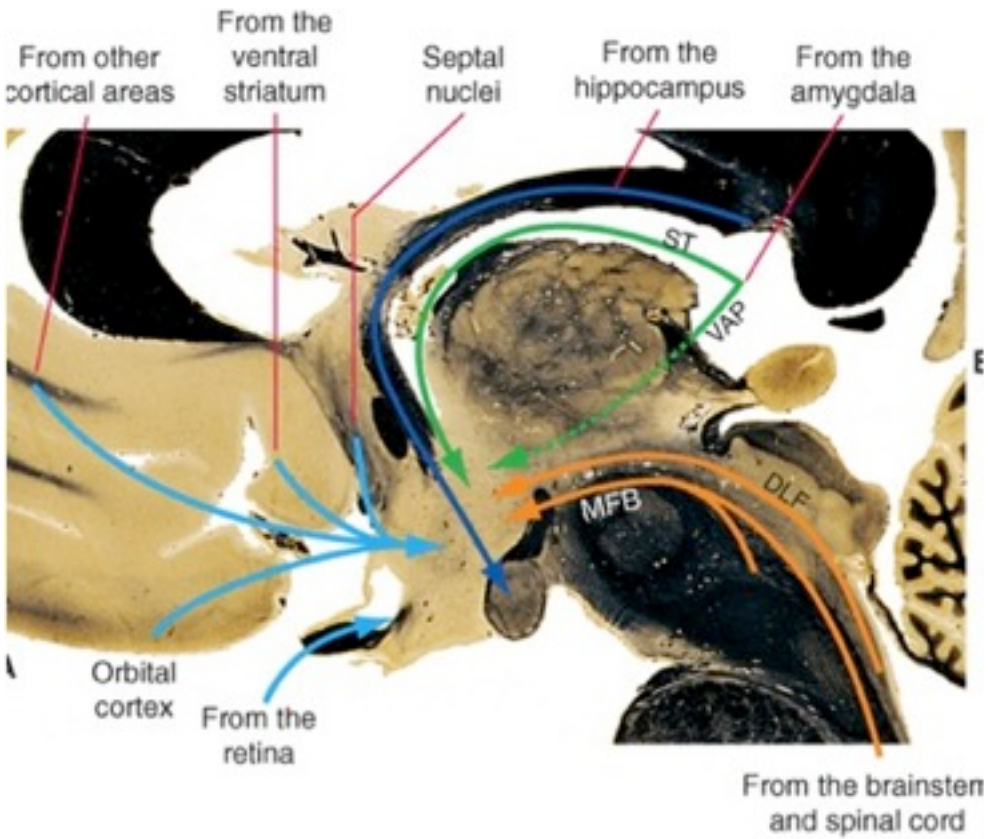
Hypothalamus

- Hypothalamic nuclei receive extensive exteroceptive and interoceptive sensory information and innervate and regulate brain stem structures.
- Through the paraventricular nucleus of the hypothalamus, helps coordinate endocrine activity
- Ventromedial hypothalamus exerts descending inhibitory influence on cell groups in the PAG responsible for defensive aggression.



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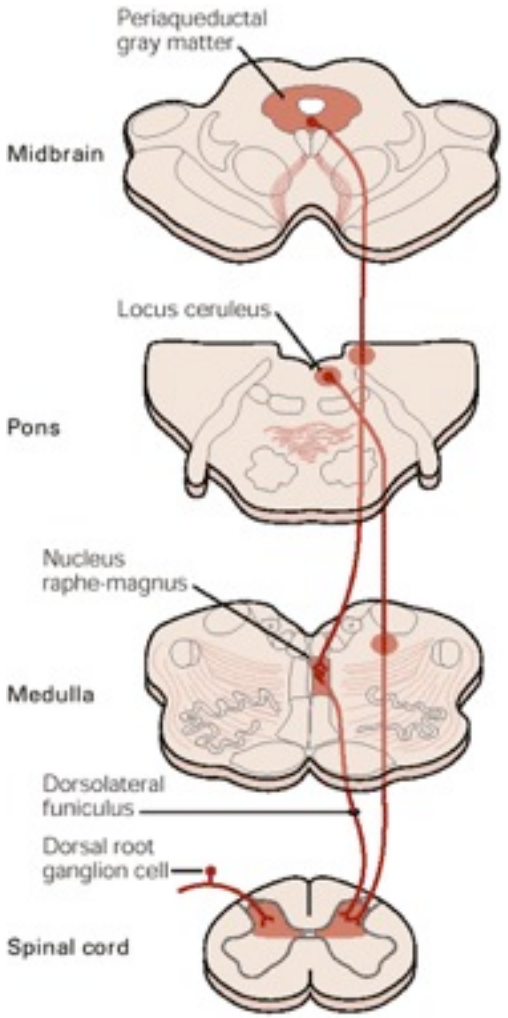
Periaqueductal Grey

- Mobilizes defensive behavior given proximal sources of threat when there is little time for analysis.
- Descending projections to somatic autonomic cell groups to help coordinate activities from motivational states.
- Columns relate to different motivational patterns.
- Stimulation of the lateral column elicits confrontational or defensive aggression and blood flow to the face.
- Stimulation of the caudal area of the lateral column elicits flight behavior and increased blood flow to the limbs.
- Adjacent ventrolateral column facilitates passive strategy in response to pain (such as playing dead).



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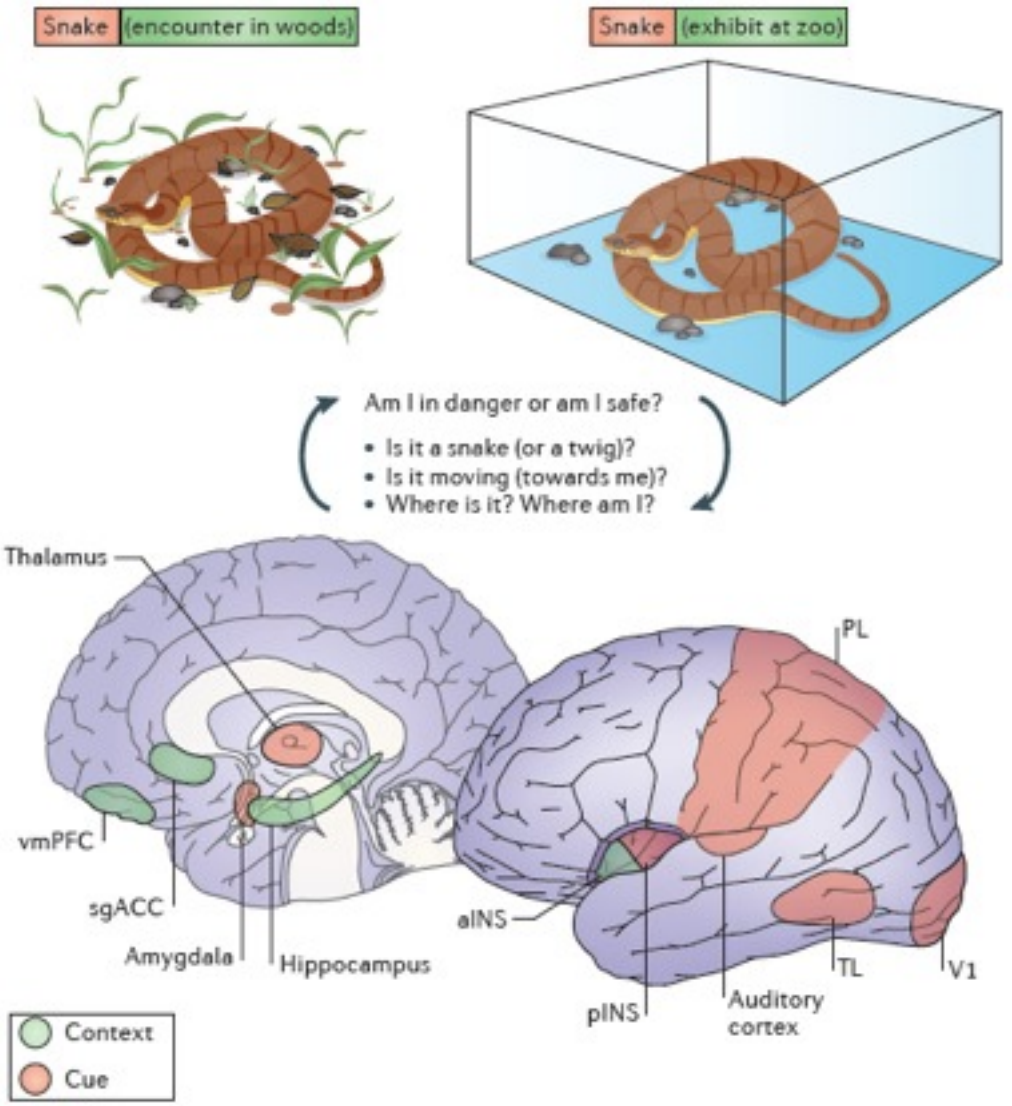
Brain circuits involved in cue and context processing in the human brain



The contextual brain: implications for fear conditioning, extinction and psychopathology
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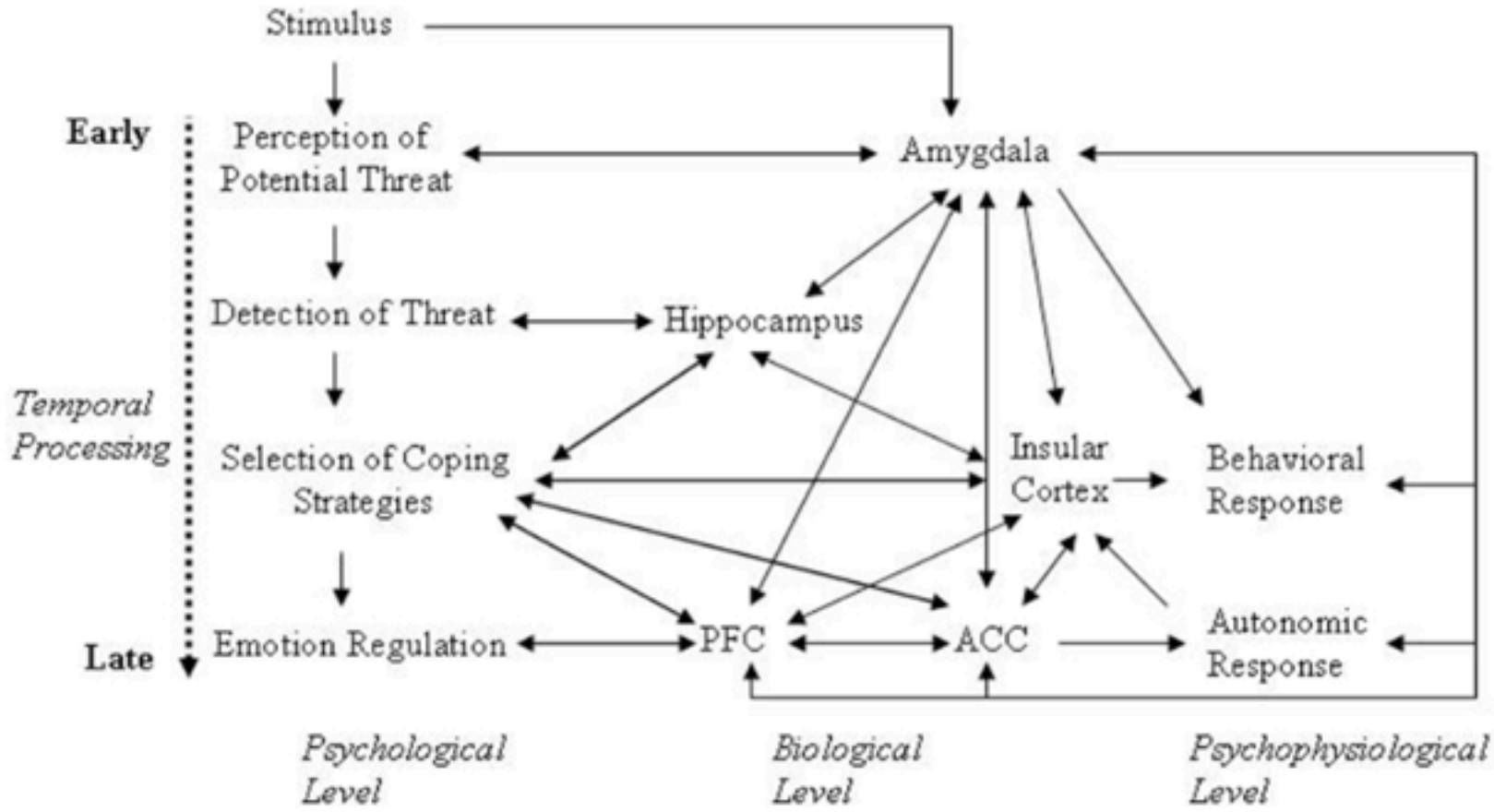
Figure 1



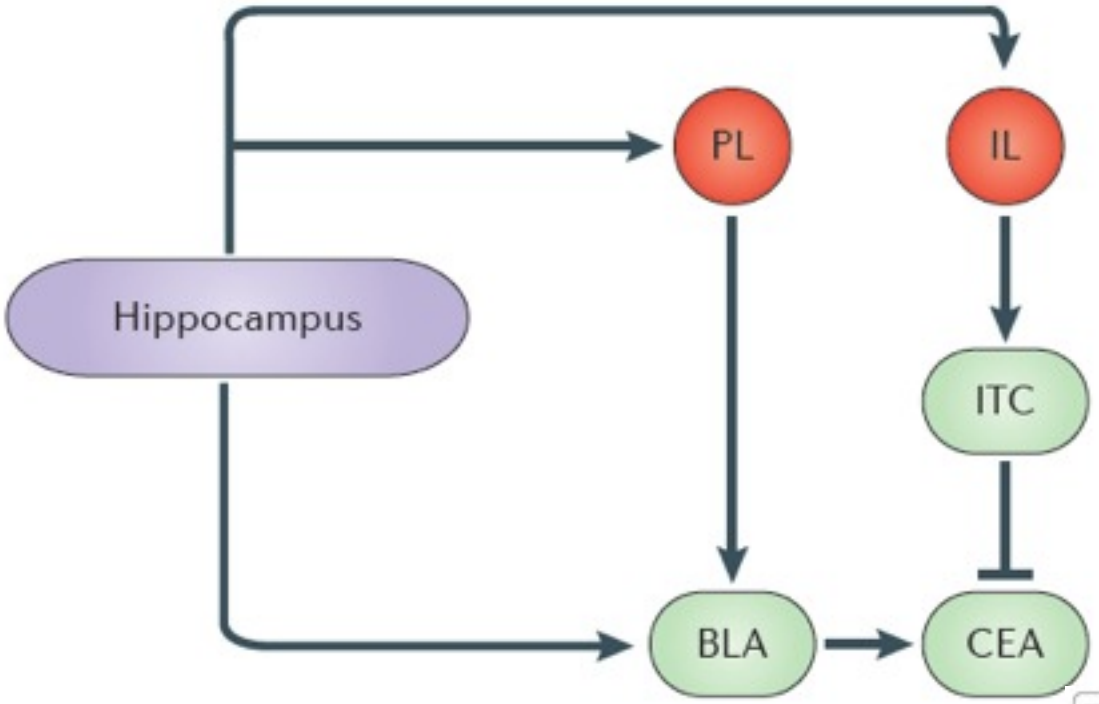
Cogn Emot. 2012 ; 26(2): 282–299. doi:10.1080/02699931.2011.579414.

Neurobiological Correlates of Cognitions in Fear and Anxiety: A Cognitive-Neurobiological Information Processing Model

Stefan G. Hofmann[1], Kristen K. Ellard[1], and Greg J. Siegle[2]

Fear and Memory

Regulation & Extinction of Fear Memories



infralimbic cortex (IL)

prelimbic cortex (PL)

basolateral amygdala (BLA)

central amygdala (CEA)

Intercalated (ITC) cells)

The contextual brain: implications for fear conditioning, extinction and psychopathology

Stephen Maren[1], K. Luan Phan[2] and Israel Liberzon[3]

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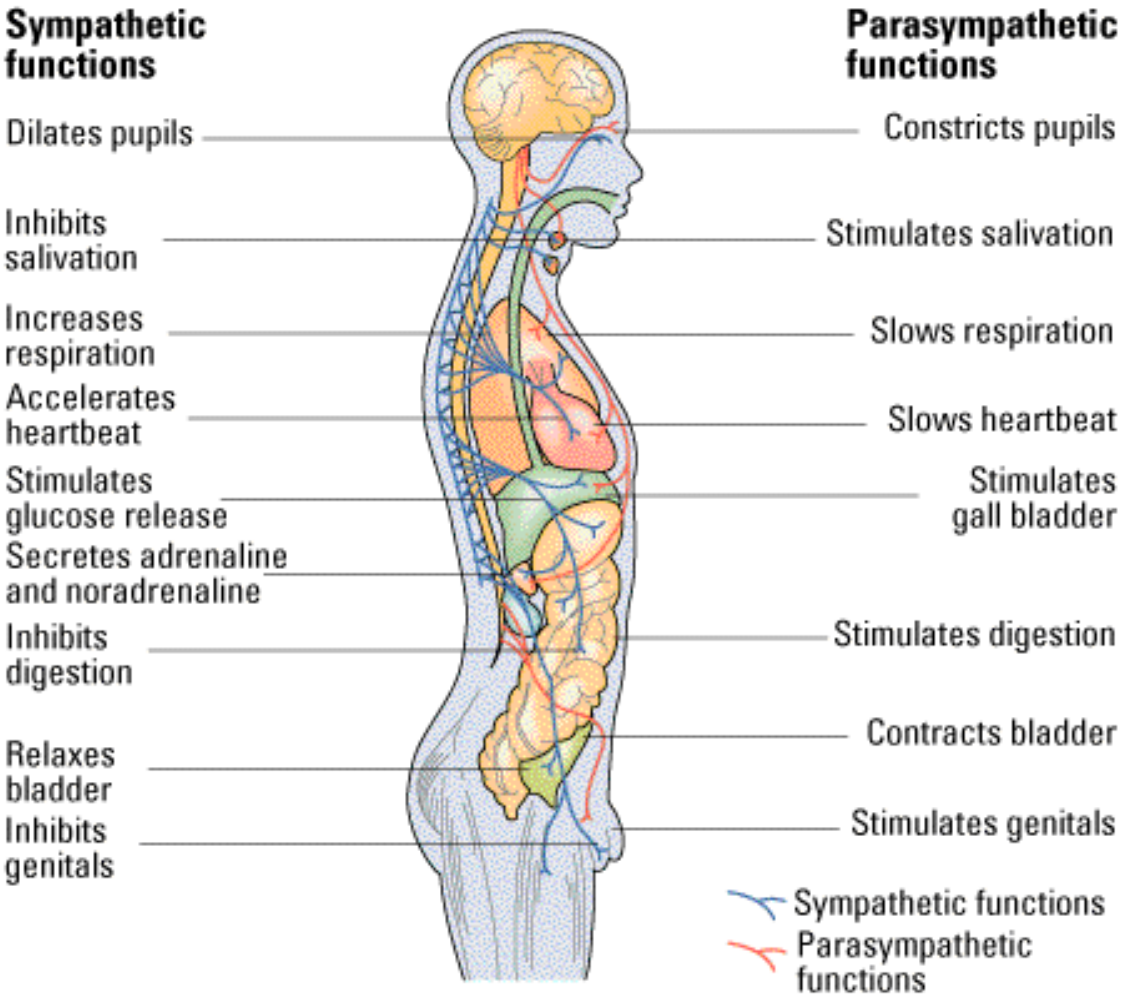
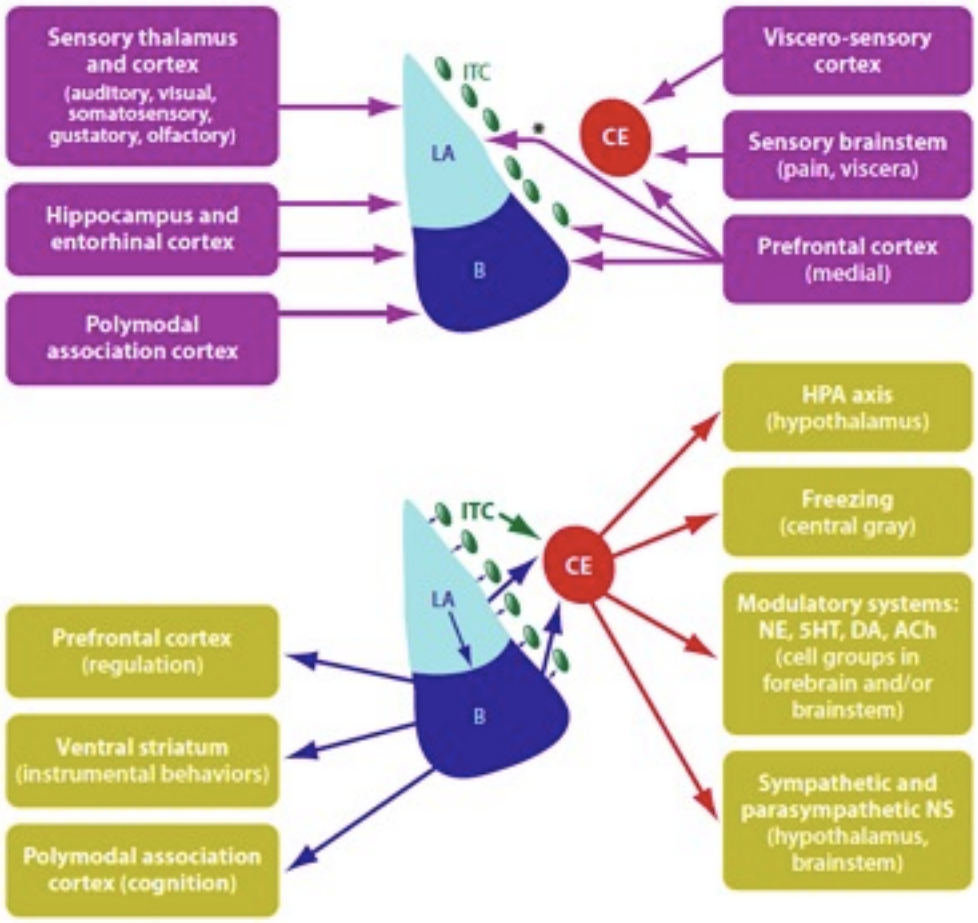
The Neuroanatomy of Fear

Emotions and the Body



- Somatic NS responses (defensive behaviors such as freezing)
- Autonomic NS responses (heart rate, blood pressure)
- Endocrine responses (hormone release)
- Hypoanalgesia (reduced pain sensitivity)
- Reflexive alterations (startle)

Fear and Hormones



The Influence of Stress Hormones on Fear Circuitry

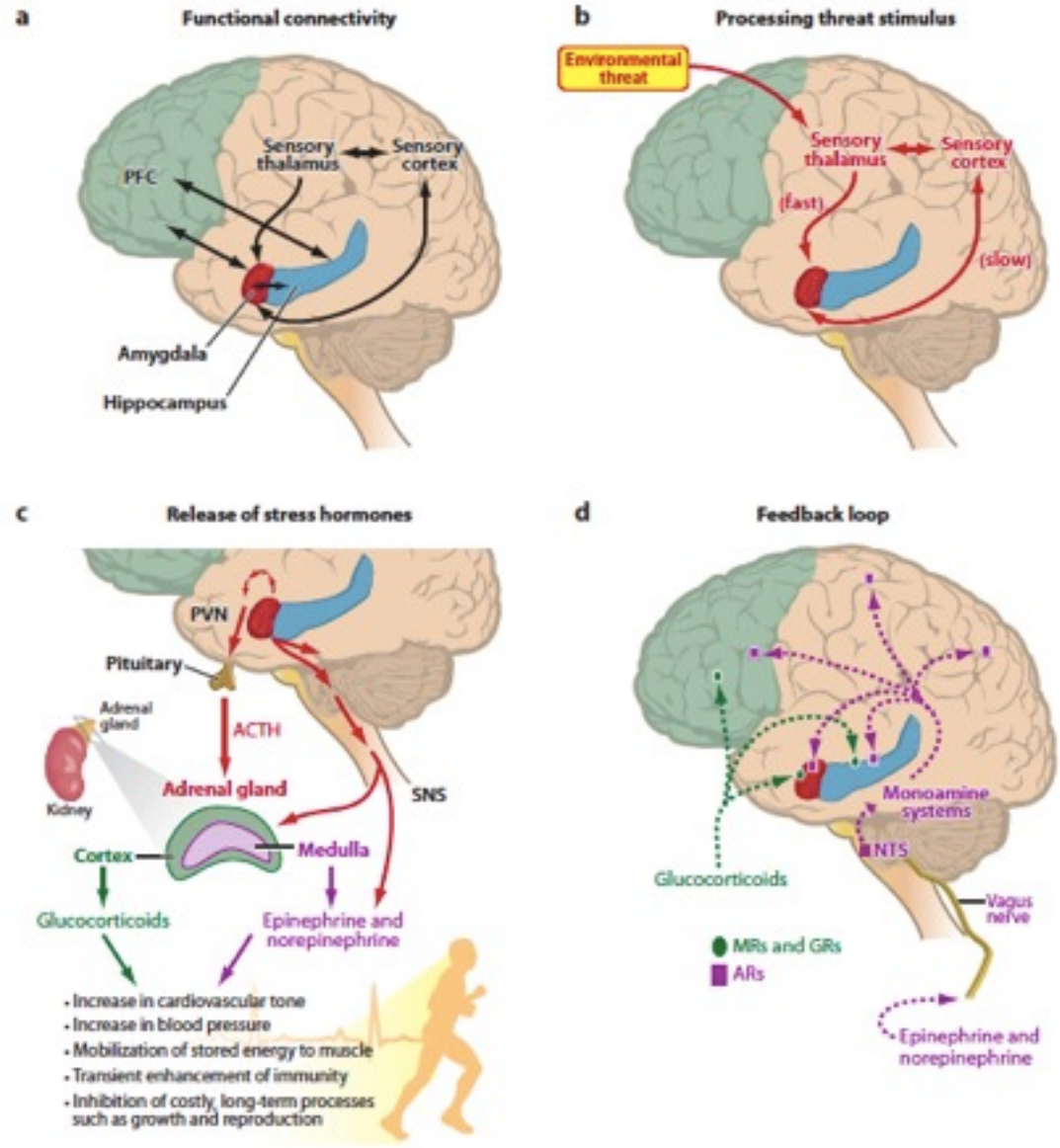
Sarina M. Rodrigues,[1] Joseph E. LeDoux,[2,*] and Robert M. Sapolsky[3,*]

Annu. Rev. Neurosci. 2009. 32:289–313

Figure 1

(*Top*) Inputs to some specific amygdala nuclei. Asterisk (*) denotes species difference in connectivity. (*Bottom*) Outputs of some specific amygdala nuclei. 5HT, serotonin; Ach, acetylcholine; B, basal nucleus; CE, central nucleus; DA, dopamine; ITC, intercalated cells; LA, lateral nucleus; NE, norepinephrine; NS, nervous system.

Fear and Hormones



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Neurologic Disorders of Fear

Several Neurological Disorders Associated with Disrupted Fear/ Anxiety Processing:

- Epilepsy - with limbic/temporal foci
- Williams Syndrome
- Autism
- Frontotemporal Dementia
- Huntington's Disease
- Traumatic Brain Injury
- Alzheimer's Disease
- CVA
- Klüver–Bucy syndrome

- Patients with damage to hippocampus and areas of medial temporal lobe demonstrate deficits in acquisition of fear responses (e.g., temporal lobe epilepsy).
- Conversely, patients with selective damage to the hippocampus and areas of the medial temporal lobe show impaired declarative memory for fear conditioning but intact implicit emotional response to the conditioned stimulus.

Psychiatric Disorders of Fear

PTSD

Neuroimaging findings in PTSD:

- Hyperactivation in amygdala, dACC and insular cortex may be hyperresponsive (Etkin and Wager, 2007).
- Hypoactivation in emotional regulation areas including the ventromedial prefrontal cortex, anterior ACC, and rostral ACC, implicated in failure to inhibit the amygdala.
- Small number of studies show reduced ACC volumes and gray matter densities
- Diminished hippocampal volumes and abnormal function, although direction of the abnormality depends on the type of task completed on neuroimaging.
- Abnormal hippocampal function may contribute to deficits in contextual processing and impairments in memory and neuroendocrine dysregulation.

The Neurocircuitry of Fear, Stress, and Anxiety Disorders, Liberzon & Shin Neuropsychopharmacology Reviews 2010; 35:169–191

Psychiatric Disorders of Fear

Panic Disorder

Neuroimaging findings:

- The 'fear network,' which includes the amygdala, hippocampus, thalamus, and brain stem structures, is hypersensitive.
- Several studies have provided evidence consistent with amygdala and brain stem hyperresponsivity.
- Activation in rACC and dACC appears to be increased, and gray matter volumes in these regions appear to be decreased.
- Several studies have reported decreased GABA and 5-HT1A receptor binding in the amygdala, medial prefrontal cortex, insular cortex, and brain stem in panic disorder.
- A common limitation is inclusion of participants taking psychiatric medications (Domschke et al, 2006, 2008).

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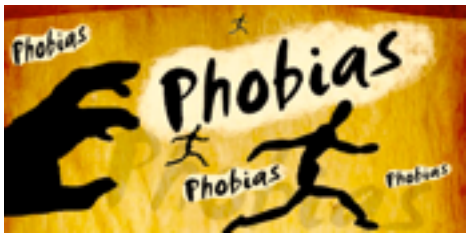
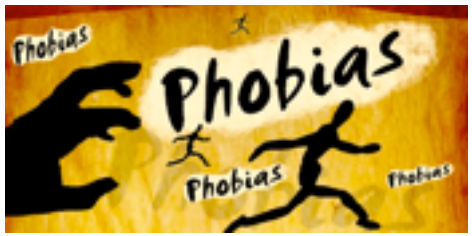
Psychiatric Disorders of Fear

Social Phobia

- Exaggerated amygdala activation is a consistent functional finding in the literature.
- Several studies reported exaggerated rACC and insular cortex activation, other studies have reported contradictory findings.
- Future research will have to: (1) address questions regarding ACC/mPFC and insular involvement, (2) identify neurocircuitry specific to regions that contribute to the perception of social stimuli as particularly fear inducing.



Specific Phobia(s)



- Early models of the etiology of phobias centered on fear conditioning and extinction, and implicated the amygdala and medial prefrontal cortex.
- Fear conditioning models are likely to be incomplete given:
  (1) many individuals with phobias cannot recall a conditioning event
  (2) only a small number of common stimuli are objects of phobias (Fyer, 1998).
- The amygdala, dACC and insular cortex all appear to be hyperresponsive to phobia related stimuli in specific phobia. These abnormalities tend to normalize with successful treatment.

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Psychiatric Disorders of Fear
Generalized Anxiety Disorder (GAD)

- Studies have implicated amygdala, VLPFC, medial prefrontal cortex, and anterior cingulate cortex.
- Exaggerated amygdala activation in response to fearful (McClure et al, 2007b) and masked angry facial expressions (Monk et al, 2008) and during anticipation of aversive photographs (Nitschke et al, 2009).
- In a mixed cohort with GAD and social phobia, those with low tolerance for uncertainty had elevated amygdala, rACC and subgenual ACC activation during a decision-making task (Krain et al, 2008).
- In a treatment study, greater pre-treatment left amygdala activation to fearful faces was associated with a less favorable response to venlafaxine (Whalen et al, 2008)
- Activation in dACC and rACC appears to be elevated in response to fearful facial expressions in adolescents with GAD (McClure et al, 2007b).

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Psychiatric Disorders of Fear

Table 1. Summary of the Direction of Functional Neuroimaging Findings in Anxiety Disorders

	Amygdala	rACC	dACC	Hippocampus	Insular cortex
Posttraumatic stress disorder	↑	↓	↑*	↑ ↓	↑ ↓
Panic disorder	↑ ↓*	↑*	–	↑ ↓	–
Social phobia	↑	↑ ↓*	↑ ↓	–	↑
Specific phobia	↑	↑ ↓*	↑	–	↑
Generalized anxiety disorder	↑ ↓*	↑*	↑*	–	–

rACC = rostral anterior cingulate cortex; dACC = dorsal anterior cingulate cortex.
↑ = increased function in the disorder (relative to control groups).
↓ = decreased function in the disorder (relative to control groups).
↑ ↓ = mixed findings.
* = based on a very small number of studies.
– = too little information available.

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