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The neuroscience of fear and anxiety: a primer for clinicians

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THE NEUROSCIENCE OF FEAR AND ANXIETY:

A PRIMER FOR CLINICIANS

A clinical dissertation submitted in partial satisfaction

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Doctor of Psychology

by

Lionel Lee

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This clinical dissertation, written by

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DEDICATION

To Matthew Kenta Lee.

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Master of Arts in Psychology — 08/01
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PROFESSIONAL EXPERIENCE

Keylight Assessments — 11/12 – 12/15
Psychological Assistant — Beverly Hills, CA
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- Conduct comprehensive neuropsychological assessments for adults and children with mood and anxiety disorders, MCI and Alzheimer's patients
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Pediatric Minds Medical Center, Early Childhood Treatment Center — 09/11 – 03/12
Psychological Assistant — Torrance, CA
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- Worked as part of an interdisciplinary team including a pediatric neurologist, child clinical psychologists, board certified behavioral analysts, and speech and occupational therapists.
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- Conducted clinical intake interviews, provide individual and group therapy, and assist with social skills and communication training.
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Saint John's Health Center, Child and Family Development Center — 09/07 – 09/08
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- Worked as a member of an interdisciplinary team to provide evaluation and treatment of veterans with complex medical conditions, psychological, and social needs.
- Geriatric Psychology and Rehabilitation Program: co-facilitated groups ("Living with Disabilities", "Relaxation Group", "Weight Management"), assessed cognitive and emotional functioning, provided individual psychotherapy, and participated in weekly treatment planning meetings.
- Outpatient Mental Health: provided individual psychotherapy and care coordination for veterans with PTSD, anxiety, and depression; screened walk-in veterans.
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- Conducted intake interviews on at-risk middle school and high school students in an ethnically diverse area of Los Angeles.
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Multicultural Research Training Lab — 01/06 – 10/06
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Student Employment Office Los Angeles, CA
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- Formatted journal submissions for faculty researchers.
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- Coordinated researchers in Asian American mental health issues; contributed to book chapter on mental health and substance abuse treatment guidelines for Japanese Americans.
- Examined variations in state laws and funds allocation with respect to implementation of the Individuals with Disabilities Education Act.
- Contributed articles on mental health parity and quality of care for schizophrenia for the Center newsletter, the Community Update.
- Edited and prepared journal submissions and grant proposals.
- Conducted literature reviews and phone interviews.
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UCLA National Research Center on Asian American Mental Health, 08/95 – 09/97
Comprehensive Asian Youth Substance Abuse Prevention Program Los Angeles, CA
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- Supervised research team, assisted in grant writing, instrument development, survey administration, data entry and analysis, participant-observation training, and participant tracking.
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ABSTRACT

Over the last few decades, research in affective neuroscience has led to considerable insights into the biology of fear and anxiety. For those in the practice of psychotherapy, these advances hold the potential for explaining the evolutionary utility of these emotions and targeting psychotherapeutic interventions to neurobiological correlates when these emotions go awry. The conversation of neuroscience, however, has yet to find a comfortable place in the therapy room. Translational and conceptual disparities owing to the historical split between psychology and neuroscience, continue to present challenges to their integration. The present study seeks to reframe clinicians' understanding of the biological underpinnings of fear and anxiety from a static model governed by genetic predisposition and chemical imbalances, to a dynamic process that focuses on the environment's impact on biology. The following topics will be addressed: What are the neurobiological processes of fear and anxiety? Why did they evolve to serve adaptive purposes? What are the conditions in which disorders of anxiety and fear emerge? To answer these questions, this review of the literature discusses how fear and anxiety centers in the mammalian brain were shaped through phylogenetic development to respond to physical and interpersonal threat, and how fear and anxiety continue to benefit in learning and defensive action. An updated view of the neuroscience of fear and anxiety is also reviewed detailing the functions of known structures and involved pathways. Risk factors for panic and anxiety disorders, the neurological impacts of failure of coping with fear and anxiety are explored, and the application of psychotherapy are discussed. These findings will be applied towards a concise handbook on the neuroscience of fear and anxiety to provide a narrative of an adaptive model for use in the therapy room.

Chapter 1. Literature Review

Epidemiology

Disorders of anxiety and fear continue to pose serious health issues, constituting the most common class of psychiatric disorders in child and adult populations in the United States (Kessler et al., 2012). Lifetime prevalence data reflect that anxiety disorders affected over one quarter (25.1%) of children and adolescents between the ages of 13-18 (Merikangas et al., 2010) and 28.8% of adults (Kessler, Berglund, & Demler, 2005). Anxiety disorders also have a higher level of comorbidity than any other mental disorder in adults, most frequently co-occurring with mood and substance disorders (Barlow, 2002).

In 2005, panic disorders had a 12-month prevalence rate of 2.7% in the U.S. adult population (Kessler, Chiu, & Demler, 2005) and lifetime prevalence rate of 2.3% in children and adolescents ages 13-18 (Merikangas et al., 2010). In adults, panic attacks are highly comorbid with conditions across the anxiety disorders spectrum, with strongest associations found between panic attacks and post-traumatic stress disorder (PTSD), agoraphobia, generalized anxiety disorder (GAD), obsessive-compulsive disorder (OCD). Individuals suffering from panic attacks were also at higher risk of being diagnosed with at least two anxiety disorders, and significantly increased risk of being diagnosed with mental disorders across the diagnostic spectrum (Goodwin et al., 2004).

Search for the Biology of Fear and Anxiety

Despite the prevalence data, our understanding of the biology underlying fear and anxiety continues to evolve. The search for the biological origins of fear and anxiety has had a long-standing history, and originated from interest in their pathological forms. In the 17th century, disturbances of fear and anxiety, or *hysteria* at the time, were believed to originate from the

nerves and the brain. Given their myriad expressions and wide phenotypic overlap, shifts in the origin and meaning of their physical and mental expressions also presented an equally long-standing conundrum over time and cultural contexts. Before the late 19th century, symptoms of anxiety were found in medical classifications dedicated to the heart, ear, gut, and brain, and were treated as physical ailments (Berrios, 1999). At the turn of the 20th century, Freud, the neurologist, attempted to elucidate the neurobiological attributions of anxiety in *A Project for a Scientific Psychology.* This endeavor, however, was ultimately abandoned due to prevailing cultural ideas about fear and anxiety during his time (J. M. Woody & Phillips, 1995). Consequently, his influential conceptualization of pathological anxiety (anxiety-neurosis) was not attributed to the brain, but to sexual drives that formed the basis of virtually all psychological disorders (Berrios, 1999).

Biological explanations for fear and anxiety also proved elusive through the evolution of the Diagnostic and Statistical Manual of Mental Disorders (DSM). Since the first edition in 1952 through DSM-IV, references to the biological underpinnings of their pathologies centered largely on genetic heritability. Discussion of environmental impacts on physiology, however, was largely absent (American Psychiatric Association, 1952, 1994). Instead, the primary focus of the DSM relied on clustering and classifying features of pathological thoughts, emotions, and behaviors (clinical descriptors). Over subsequent iterations of the DSM, one artifact of relying on clinical descriptors was the expansion of diagnostic categories under the umbrella of Anxiety Disorders in both number and complexity, and shifts in the relationship between fear and anxiety (see Table 1; Barlow, Brown, & Craske, 1994).

Table 1

Anxiety Disorders Through the DSM

1952 DSM I PSYCHONEUROTIC DISORDERS		1968 DSM II NEUROSIS		1980 DSM III ANXIETY DISORDERS		1987 DSM III-R ANXIETY DISORDERS (or Anxiety and Phobic Neuroses)		1994 DSM IV ANXIETY DISORDERS		DSM IV-TR ANXIETY DISORDERS	
				Anxiety States (or Anxiety Neurosis)							
40.0	Anxiety Reaction	300.0	Anxiety Neurosis	300.01	Panic Disorder Generalized	300.21	Panic Disorder with Agoraphobia	---	Panic Attack (not codable)	---	Panic Attack (not codable)
40.1	Dissociative Reaction	300.1	Hysterical Neurosis	300.02	Anxiety Disorder	300.01	Panic Disorder without Agoraphobia	---	Agoraphobia (not codable)	---	Agoraphobia (not codable)
40.2	Conversion Reaction	300.13	Conversion Type	300.30	Obsessive Compulsive Disorder or Obsessive Compulsive (Neurosis)	300.22	Agoraphobia without History of Panic Disorder	300.21	Panic Disorder With Agoraphobia	300.21	Panic Disorder With Agoraphobia
40.3	Phobic Reaction	300.14	Dissociative Type			300.23	Social Phobia	300.01	Panic Disorder Without Agoraphobia	300.01	Panic Disorder Without Agoraphobia
40.4	Obsessive Compulsive Reaction	300.2	Phobic Neurosis			300.29	Simple Phobia	300.22	Agoraphobia without a History of Panic Disorder	300.22	Agoraphobia without a History of Panic Disorder
40.5	Depressive Reaction	300.3	Obsessive Compulsive Neurosis			300.30	Obsessive Compulsive Disorder (or Obsessive Compulsive Neurosis)	300.29	Specific Phobia (formerly Simple Phobia)	300.29	Specific Phobia
40.6	Psychoneurotic, Other	300.4	Neurosis Depressive					300.23	Social Phobia (Social Anxiety Disorder)	300.23	Social Phobia (Social Anxiety Disorder)
		300.5	Neurasthenic Neurosis (Neurasthenia)					300.3	Obsessive-Compulsive Disorder	300.3	Obsessive-Compulsive Disorder
		300.6	Depersonalization Neurosis (Depersonalization Syndrome)	Phobic Disorders (or Phobic Neurosis)		309.89	Post-traumatic Stress Disorder	309.81	Posttraumatic Stress Disorder (Acute, Chronic, or With Delayed Onset)	309.81	Posttraumatic Stress Disorder (Acute, Chronic, or With Delayed Onset)
		300.7	Hypochondriacal Neurosis	300.21	Agoraphobia with Panic Attacks	300.02	Generalized Anxiety Disorder	308.3	Acute Stress Disorder	308.3	Acute Stress Disorder
		300.8	Neurosis	300.22	Agoraphobia without Panic Attacks	300.00	Anxiety Disorder NOS	300.02	Generalized Anxiety Disorder	300.02	Generalized Anxiety Disorder
		300.9	Other Neurosis [Unspecified Neurosis]	300.23	Social Phobia			300.0	Anxiety Disorder NOS	300.0	Anxiety Disorder NOS
				300.24	Simple Phobia						
				308.30	Post-traumatic Stress Disorder, Acute						
				309.81	Post-traumatic Stress Disorder,						
				300.00	Atypical Anxiety Disorder						

To date, anxiety and panic disorders continue to form a complicated picture. In the fourth edition of the DSM, disorders of anxiety and panic encompassed 11 distinct categories, characterized by symptoms ranging from panic attacks in phobic disorders, to worry and rumination of generalized anxiety disorder, to intense somatic re-experiencing found in individuals suffering from post-traumatic stress (American Psychiatric Association, 1994). The shifting continued in DSM-5 as evidenced by the removal of Post-traumatic Stress Disorder and Obsessive Compulsive Disorder from the Anxiety Disorders umbrella, and establishing them as their own distinct disease entities, as well as the lowering of symptom thresholds in category of Anxiety Disorders (American Psychiatric Association, 2013). Berrios (1999) observed that despite these shifts, "none of the clinical phenomena or 'symptoms' included under the various 'anxiety disorders' was new. What had changed was their relative emphasis, the permutations and combinations in which they are clustered up, and their social meaning" (p. 83).

Though the promise of merging the biology and psychology of these emotions existed with the emergence of enhanced techniques to study the brain, discrepant views by psychology and neuroscience may have led to more of a conundrum. In part, the historical split between the study of the physical brain (neuroscience) and study of the mind (psychology) may have led to notable contrasts between fields in our understanding of anxiety and panic. Barlow et al. (1994) suggested that most biological investigators assumed that panic is fundamentally different from anxiety and most likely represents a form of brain dysfunction. In contrast, psychological and cognitive investigators assert that panic is not qualitatively different from anxiety, arguing instead that panic represents anxiety focused on somatic sensations that builds quickly in a positive feedback loop because of a misattribution of these sensations. Consequently, a lack of

symbiosis between psychology and neuroscience may have led to wide discrepancies in definitions, theoretical assumptions, and research focus (Cozolino, 2006).

Adaptive Relationship Among Stress, Fear, and Anxiety

Throughout evolution, living organisms have strived to maintain a complex and dynamic equilibrium of their internal environment that is believed to sustain life (Habib, Gold, & Chrousos, 2001). This balance, or *homeostasis*, is challenged constantly by external (environmental) and internal (psychological) demands. Hans Selye (1949) coined the term *stress* to describe the body's non-specific response to demands for change. Although he acknowledged that stress may have positive influences (eustress), stress more commonly refers to its negative influences (distress): a state of homeostasis that is threatened or perceived to be threatened.

To counter these demands, or stressors, the ability of an organism to adapt to its environment is of vital importance (McEwen, 1999). When confronted with more severe forms of stress, the brain recruits responses that promote adaptive, survival functions and a return to equilibrium or homeostatic patterns. These processes persist until an emergency has been survived and are considered adaptive if the emergency is transitory and the stress response is shut off quickly (Darnaudéry & Maccari, 2008). This process is of adaption is referred to as *allostasis* and is described as *maintaining stability through change* (McEwen & Gianaros, 2010; Sterling & Eyer, 1988).

Fear and anxiety. Fear and anxiety represent adaptive stress responses employed to achieve a return to homeostatic balance. They represent survival functions that address the immediate and preparatory needs of an organism to bring closure to a situation (LeDoux, 2012). Broadly, fear and anxiety signal the presence of threat and motivate an organism to take action aimed at adapting to or reducing the impact of the threat (Pêgo, 2010). Although intricately

related and often used interchangeably, animal and human studies reveal that fear and anxiety differ along several dimensions including their triggers, timing, and purpose (see Table 2).

Fear, or panic, is an emotional alarm to imminent, life-threatening danger (Öhman & Mineka, 2001; Schiller, Levy, Niv, LeDoux, & Phelps, 2008). It involves prior learning that specific contexts predict imminent adversity (Davis, Walker, Miles, & Grillon, 2010; Grillon, 2007). The onset of fear is rapid and results in a surge of physiological arousal characterized by a fight-or-flight response, or freezing with active attention (Barlow et al., 1994; Grillon, 2007; National Institute of Mental Health, 2009; Öhman, 2005; Schiller et al., 2008). The abruptness of fear responses suggest an absence of conscious processing of the immediate threat (Pêgo, Sousa, Almeida, & Sousa, 2009). Fear is thought to be adaptive when it is short in duration and abate upon termination of the threat (Davis, 1998a; Pêgo et al., 2009).

In contrast, anxiety is an emotional state elicited by distant, diffuse, or unspecific physical or psychological threat (Davis et al., 2010). Among its characteristics are feelings of tension, discomfort, apprehension, heightened anticipation, avoidance behaviors, and thoughts of uncontrollability and unpredictability (Barlow, 2002; Pêgo et al., 2009). Although anxiety is less intense than fear, it tends to last longer (Rennie, 1948). Whereas fear is quick (lasting milliseconds to seconds), the onset and offset of anxiety is slow, lasting from minutes to hours. Anxiety is considered adaptive when conscious, cognitive appraisal of threat occurs, and effective coping is employed. An individual's experience of anxiety is relative and individualized: s*tate anxiety* and *trait anxiety* refer to the differences between people in terms of their tendency to experience anxiety in response to the anticipation of a threat. While state anxiety describes temporary feelings of anxiety experienced by most people in response to perceived threat, individuals with trait anxiety experience more intense degrees of state anxiety

to specific situations, and to a broader range of situations or objects than do most people (Lazarus, 1991).

Table 2

Summary of Distinctions between Fear/Panic and Anxiety

Fear / Panic	Anxiety
Elicited by actual danger (e.g., presence of a predator)	Elicited by diffuse, distal, potential, or symbolic threats
Results in reflexive action or a fight-or-flight response	Results in general distress, apprehension, risk assessment behaviors, and avoidance
Triggered by short-lasting, explicit cues or contexts that predict imminent adversity	Triggered by diffuse, unspecific cues. Driven by anticipation, and perceptions of uncontrollability and unpredictability
Short-term state that generally abates upon termination of the adverse event	Long-term state
Narrows attention and inhibits competing responses	Increases overall sensory sensitivity towards confirming threat
Quick onset and offset	Slow onset and offset

Responding to Danger Through Phylogenetic Development

Phylogeny is a proposal of how organisms are related by their evolutionary history. Herbert Spencer proposed that higher life forms evolved from lower ones, and that human reasoning and thought evolved from the automatic responses of lower animals (Porges, 2001). This proposal applies to how we interpret human behavior from animal models that have encompassed our understanding of the brain's role in human emotions and behavior over the last 40 years. Inferences about the human brain from animal models stem from a theoretical assumption in comparative neuroanatomy stating that mammals share a common ancestry and may have evolved from a common progenitor (Cozolino, 2010).

From this common ancestry, primitive brain structures found in lower animals were conserved and later expanded upon in higher animals. Over time, sensory, emotional, and higher-order cognitive systems evolved together and new functions were integrated with existing systems (Aggleton, Everitt, Cardinal, & Hall, 2000). Further, according to the theory of recapitulation, often expressed as *ontogeny recapitulates phylogeny*, the brains of animals go through stages resembling or representing successive stages in the evolution of their remote ancestors in developing from embryo to adult.

The Triune Brain Model. MacLean's Triune Brain Theory (1990) serves as a useful heuristic to describe the hierarchical fashion in which brain structures involved in fear and anxiety evolved. MacLean details three distinct layers of the brain that developed in sequence over phylogenetic evolution from reptiles to humans (MacLean, 1990). These layers reflect the outward expansion of primitive brain structures found in lower animals (i.e., reptiles) to newer areas in mammalian species (see Table 3). Conservation of primitive structures is reflected in anatomical similarities in brains of different species from reptiles to lower mammals and ultimately to primates and humans.

Table 3

The Triune Brain

Neural Layer	Description and Function
The Reptilian Brain (R-complex)	The reptilian brain (R-complex)* is most primitive and innermost layer. It consists of the brainstem and cerebellum, and controls basic functions such as heart rate, breathing, body temperature, and balance.
The Limbic System (Paleomammalian brain)	The limbic system is the middle layer that emerged in mammals. It is an interconnected set of brain structures involved in the emotional and motivational aspects of feeding, reproduction, and parental behavior. The limbic system is thought to be the seat of unconscious values that exert a strong influence on behavior.
The Neocortex (Neomammalian brain)	The neocortex is the outermost layer and is characterized by two large cerebral hemispheres. It assumed prominence in primates and culminated in the human brain. The neocortex is considered to be flexible, with almost infinite learning abilities. Functions of the neocortex include sensory perception, generation of motor commands, and spatial reasoning. Development of human language, abstract and conscious thought, and imagination emerged with the rise of the neocortex.

*The reptilian brain has often been misinterpreted as soley representing the brains of reptiles, however, this is not entirely true. MacLean acknowledged that amphibians (Schumann, Bauman, & Amaral, 2011) and reptiles (Cory, 1999) have homologues or rudimentary elements of a limbic system. Therefore, the term *reptilian brain* is largely taxonomic.

Response to immediate physical threat. Survival circuitry inhabiting the spectrum of fear and anxiety responses may be embedded in the phylogenetic development of the brain from reptiles to humans. Parts of the reptilian and limbic brain involved in fear and anxiety are shared by mammals, and are part of an ancient system dedicated to facilitate defenses against predation (LeDoux, 2012; Öhman & Mineka, 2001). The reptilian brain may have first evolved to respond to immediate physical threats with reflexive behaviors such as fight-or-flight and freezing (Porges, 2001). The expansion of the reptilian brainstem to limbic areas reflected an increase in neural complexity over phylogenetic development, enriching an organism's behavioral and affective repertoire (Porges, 2007). By attaching emotional significance to incoming sensory stimuli, limbic structures aided in perception and memory of meaningful material and the

coordination of approach-or-avoid responses (Phan, Wager, Taylor, & Liberzon, 2004). Further, these connections may have led to associative learning that increased proximal and temporal space between self and threat enhanced one's chances of survival (Aggleton et al., 2000).

Among the earliest and most direct sensory-to-emotional connections formed were between neural fibers of olfactory bulbs and limbic structures. Characterized by close proximity and dense neural ties that allowed for rapid and efficient transmission of threat-related information for appraisal and response, this connection was adaptively appropriate as odor signaled close proximity of a predator (Aggleton et al., 2000; Pêgo et al., 2009). Connections from limbic structures to the visual cortex further enabled mammals to detect predators from afar and raise emotional alarms. This may have gave rise to more sophisticated visual abilities such as rapid discernment of threat from complex visual displays in humans (Öhman & Mineka, 2001). Other structures within the limbic system developed to handle continual internal monitoring of external threat, providing awareness of self through space and time.

Responding to interpersonal threats. Additional neural connections between the neocortex and the limbic system may have reflected further improvements in processing more subtle environmental cues. With the rise of the neocortex, reasoning abilities may have improved skills for evaluating dangerous situations, and planning on what to do about them, thereby enhancing predictability and control over one's environment, and ultimately keeping threat at a distance.

Neocortical growth has been found to correlate positively with social group size, with most prominent neocortical growth was seen in the human brain as compared to the brains of other animals (Bronowski, 2011). The neocortex evolved in part to meet the cognitive demands of competitive and cooperative relationships. As societies began to develop, the complexity of

social interactions in larger social groups may have led to increased internal and external resources to assist with recognizing more subtle interpersonal threats and supports. In many mammalian species, dominance rank provided a blueprint for social interactions that promoted self-preservation and reproductive success (Aggleton et al., 2000). In human subjects, activation of fear and anxiety centers has been observed in conscious and unconscious perception of fearful faces, in the processing of threatening words and vocalizations, and in the processing of outgroup versus ingroup facial stimuli (Adolphs, Russell, & Tranel, 1999). Fears and phobias may have developed as a means to appraise dominant or submissive group members (Öhman & Mineka, 2001).

Neocortical growth may have also been promoted by recognizing that cooperative relationships helped to promote survival. Beyond the invention of tools and weapons by humans that helped to procure resources and defend against physical threat, the advent of behavioral scripts, language, and communal activities (such as hunting) may have reflected refinements in identifying interpersonal supports that fostered cooperation and limited exposure to threat. The evolution of culture (i.e., sets of behaviors, rules, and traditions) and social norms may have increased predictability over physical and social landscapes, thereby enhancing one's perception of control and attenuating fear and anxiety. Art and storytelling served to pass on knowledge, further enhancing predictability of one's world and fostering anticipation of the future for generations (Bronowski, 2011). Over time, the recognition of these implicit, social cues reflected an adaptive advantage for enhancement of emotional perception, memory for emotionally meaningful material, and refinements in coordination of approach or avoidance responses (Phan et al., 2004).

Despite the flourish of the neocortex in primates and humans, the perseveration of early limbic mechanisms meant that more rudimentary actions (i.e., fight-flight-freezing) often still take precedence in the face of life-threatening danger. John Hughlings Jackson, in his Principal of Dissolution, proposed that phylogenetically newer neural circuits generally inhibit more primitive, phylogenetically older neural circuits. However, "when the higher are suddenly rendered functionless, the lower rise in activity" (Porges, 2007, p. 7). In the face of life-threatening circumstances, appraisal of imminent threat and generation of appropriate fear responses remain unconscious and automatic due to the ancient origin and location of the limbic system (Öhman & Mineka, 2001) and is relatively impenetrable to higher cortical reasoning (LeDoux, 1995). As survival continues to depend on involvement of early fear mechanisms, the handling of life-threatening events continues to rely on a quick process that occurs without neocortical involvement, and risks false positives rather than false negatives (LeDoux, 1996).

Immediate and Preparatory Systems

The brain is the central organ of stress and adaptation to stress because it perceives and determines what is threatening, as well as facilitates behavioral and physiological responses to a stressor (McEwen, Eiland, Hunter, & Miller, 2012). Joseph LeDoux described the biological underpinnings of fear and anxiety as *survival circuits* that serve specific adaptive purposes. Survival circuits are sensory-motor integrative devices that help organisms survive and thrive by organizing brain functions. These circuits are tuned to detect environmental challenges and opportunities, and they use this information to control behavioral responses and internal physiological adjustment that help bring closure to the situation (LeDoux, 2012).

Sympathetic nervous system. The first stage of coping with an acute stressor is characterized by the activation of the *sympathetic nervous system.* The sympathetic nervous

system is comprised of fibers from the spinal cord that go directly to internal organs in the main cavities of the body (especially those in the abdomen), blood vessels, or return to spinal nerves. These fibers supply the skin with secretory fibers to sweat glands, motor fibers to smooth muscle attached to hair follicles, and vasomotor fibers to the blood vessels of the limbs.

The activation of the sympathetic nervous system results in rapid, automatic responses to danger and produces fear behaviors such as a surge of physiological arousal resulting in a fight-or-flight response. During a general alarm reaction, numerous biological systems are activated to mobilize energy and halt energy storage. Increased functioning in the heart and lungs facilitate oxygen and glucose delivery, while digestion, growth, reproduction, and inflammatory and immune responses are suppressed. Cognition is altered simultaneously, with a tendency towards lowered sensory thresholds (Grillon, 2007). Following abatement of the threat, the *parasympathetic nervous system* is activated as a negative feedback response to reinstate the internal equilibrium of the organism. This is achieved through negative feedback mechanisms that counteract the reactivity produced by sympathetic activation, and allows the body to return to a state of homeostasis after experiencing stress (Darnaudéry & Maccari, 2008).

The HPA axis. The hypothalamic-pituitary-adrenal axis (HPA) refers to a complex set of interactions between the hypothalamus and pituitary glands in the brain, and the adrenal glands in the kidneys. The HPA axis plays a pivotal role in the stress response and is one of the primary biological responses to threat (Choi, Evanson, et al., 2007). The HPA is primarily involved the production of the stress hormones (cortisol in humans, or corticosterone in rats), which affect stress-related regulation of digestion, autoimmunity, emotions, sexuality, and the storage and expenditure of energy during stress (Dong & Swanson, 2004b). Models in comparative anatomy

suggest that the proteins, gene structures, and pathways of the HPA axis were present in the earliest vertebrates and have been maintained by natural selection (Denver, 2009).

The HPA axis evolved to respond to environmental and psychological threats, with threat type having differential effects on the HPA. Novel stressors typically activate the HPA axis. Subsequent exposure to the same, invariant stressor, however, has been found to promote habituation and the attenuation of the HPA response (Pêgo et al., 2009). An activated HPA also shows enhanced sensitivity to unpredictable stressors following one episode of HPA activation. Ohman proposed that sensitization represents time-limited enhanced responsiveness to evolutionarily relevant fear stimuli when the fear state is already activated (Öhman & Mineka, 2001). Woody and Szechtman (2011) proposed that because security motivation is geared for the immediate survival needs as well as uncertain future events, it makes adaptive sense to promote sensitization, where the activation of security motivation by threat enhances the sensitivity of the system to subsequent instances of potential danger. He further argues that sensitization is characterized by a memory for the future of potential threat, suggesting that anticipatory anxiety may be viewed as anxiety stemming from psychogenic stressors. A sensitized HPA response to psychological stressors may share mechanisms of sensitization to potential threats in the environment.

The Polyvagal Theory. In his Polyvagal Theory, Stephen Porges proposed several hierarchical stages that provide insights into the organization and functional nature of physiological states associated with fear and anxiety. The theory suggests that fear and anxiety are adaptive responses organized hierarchically along stages of *safe, dangerous, or life threatening events and contexts,* with each stage associated with a distinct biological system (Porges, 2007).

- The *Social Engagement System* represents the highest mode of operation. It is characterized by a set of mechanisms in the brain that facilitate responses for social interactions and operate largely in an environment safe from danger. This system is dominated by the parasympathetic influence.
- An organism attends to the environment because of novelty or potential threat. When danger is perceived to be imminent, the *mobilization system* removes dominant parasympathetic influences, activating the sympathetic nervous system and fight-or-flight responses if needed.
- When danger is life threatening, but fight-or-flight responses are not an option, then the most primitive sympathetic nervous system activity becomes dominant. The *immobilization system* triggers freezing responses such as *death feigning* and profound slowing of the heart and breathing (Barlow, 2002).

Neurochemistry of Fear and Anxiety

Neurochemicals consist of neurotransmitters and other molecules that influence the function of neurons and the networks, or structures, they form. In fear and anxiety processes, the time scale of actions in which these chemicals operate spans from seconds to hours, with (a) the rapid effects involving cell excitability while (b) the longer effects involving a genomic signaling cascade with minutes to hours for completion. When activated by threat, these chemicals potentiate brain mechanisms that heighten arousal and vigilance, enhance detection and analysis of threat cues, and facilitate future responding (Woody & Szechtman, 2011).

Norepinephrine. The stress hormone and neurotransmitter, norepinephrine, is produced in the brainstem. Norepinephrine has an excitatory effect on most of the brain, mediating arousal and priming the brain's neurons to be activated by stimuli. During times of stress, the release of

norepinephrine results in increases in sympathetic discharge and inhibition of parasympathetic tone. (Ramos & Arnsten, 2007). These actions support physiological elements of the fight-or-flight response. The release of norepinephrine increases the rate of contractions in the heart, triggers the release of glucose from energy stores, and increases blood flow to skeletal muscle the oxygen supplies to the brain. Increases in norepinephrine have been found to alter cognitive functions such as attention, motivation, and memory. Although norepinephrine can increase working memory, an excess may decrease working memory (Ramos & Arnsten, 2007).

Corticotropin-releasing hormone (CRH). CRH is a peptide found in cerebrospinal fluid and released during times of stress. CRH acts on the limbic system and produces a variety of behavioral and neuroendocrine effects similar to those seen in fear and anxiety. When circulating, CRH affects changes in heart rate, blood pressure, respiration, gastrointestinal responses, increases in norepinephrine and epinephrine, increased locomotor activity in a familiar environment, and decreased locomotor activity in unfamiliar environment (Davis, 1998b).

CRH is implicated in the production of glucocorticoids from HPA axis as well as the modulation of norepinephrine in the brainstem. CRH is produced in the paraventricular nucleus of the hypothalamus (PVN), which then induces ACTH release from the anterior pituitary and subsequent release of glucocorticoids from the adrenal glands (Ramos & Arnsten, 2007). CRH will feed back to inhibit its production, while feeding to the LC to increase norepinephrine production. Norepinephrine released from the brainstem will also feed back to inhibit its production (Aggleton et al., 2000; Benarroch, 2009). Its effects to natural stressors or conditioned fear can be blocked by CRH antagonists or benzodiazepines (Davis, 1998b).

Glucocorticoids. Glucocorticoids are a class of corticosteroid known to facilitate mechanisms that increase energy availability. Glucocorticoids are produced in the adrenal glands, as part of the HPA Axis and target numerous organ systems that are responsible for a variety of HPA functions, including energy mobilization and modulation of cardiovascular tone. Glucocorticoids also exert negative feedback on the HPA axis, thereby limiting its activation (Choi et al., 2008; Choi, Evanson, et al., 2007; Choi, Furay, et al., 2007; MacLean, 1990). The actions of CRH precede those of glucocorticoids, with adrenal release of glucocorticoids lagging minutes behind release of CRH (Droste et al., 2008). The delayed action of glucocorticoids involves changes in gene transcription and therefore requires more time to process (Sapolsky, Romero, & Munck, 2000; Schumann et al., 2011).

Two types of glucocorticoids actions are operative in the face of threat. *Modulating actions* alter an organism's response to the stressor that support the immediate physiological needs of an activated security motivation that include the increase of circulating glucose (the fuel needed in the brain, muscles, and other cellular works) and inhibition of glucose transport into storage to elevate circulating glucose. In contrast, *preparative actions* prime mechanisms that alter an organism's response to a subsequent stressor or aid in adapting to a chronic stressor (Cory, 1999) and require prolonged exposure (minutes to hours) to glucocorticoids and potentiate sympathetic effects on the cardiovascular system without producing an actual sympathetic activation. If potential danger does turn into an actual threat, however, glucocorticoids are readily mobilized because of the prior period of glucocorticoid exposure (Woody & Szechtman, 2011).

Neuroanatomy of Fear and Anxiety

The brain consists of billions of neurons that are organized by the principle that *neurons that fire together, wire together,* forming networks that manifest into discernable brain regions. Through phylogenetic development, conservation of primitive brain structures involved in fear and anxiety reflect lasting imprints on the brain of actions that promoted survival. Animal models have established that the neuroanatomical foundations and neurocircuitry of anxiety and fear circuitry are online at birth. These foundations are shaped both genetics and by subsequent experience.

The complexity of the brain necessitates the raising of several disclaimers. Although many brain regions are involved in a variety of functions (e.g., stress and also reward), discussion will be limited to their relationship to fear and anxiety for the purposes of this study. Further, despite rapid advances in neuroimaging that have allowed for a clearer understanding of human brain functioning, research in affective neuroscience is still considered to be in its nascent stages. This is primarily due to limitations in anatomical resolution in neuroimaging that continue to obscure finer details of neurocircuitry (LeDoux, 2012). With this in mind, animal studies are still regarded as first-line evidence for detailing structure to function in the human brain, but continue to pose challenges to hypothesis testing and generalizability to human populations (Davis et al., 2010).

Brainstem. The brainstem is a primitive network of brain structures involved in transmitting and processing sensory information from the periphery and motor impulses to muscles, tissue, and organs. It has been implicated in the reflexive regulation of heart rate, respiratory control, circulation, arousal and alertness, and consciousness. With regard to fear and

anxiety, the brainstem acts as a processing center of sensory and motor information between the brain and the spinal cord.

A number of brainstem regions are implicated in fear and anxiety responses. The locus coeruleus (LC) is responsible for mediating many of the sympathetic effects involved in stress and panic. Its role in the stress response is complex and multi-modal, given its far-reaching projections to the spinal cord, the brainstem, multiple limbic structures, and the neocortex. The LC is the principal site for brain synthesis of norepinephrine, and its activation has been implicated in increased arousal, increased vigilance, and increased attention (Davis, Walker, & Lee, 1997). In states of anxiety, the LC has been proposed to be involved in attentional bias, and enhanced detection and analysis of threat cues by optimizing scanning of the environment and shifting attentional focus towards potential threat (Porges, 2001; Woody & Szechtman, 2011).

Other brainstem regions have been implicated in fear and anxiety expressions, although the explanations for the mechanisms are still evolving. The trigeminal facial motor nucleus is involved in facial expressions of fear (Davis et al., 1997). Nucleus reticularis and pontis caudalis are involved in fear-potentiated startle (Aggleton et al., 2000; Davis, 1998a; LeDoux, 1995; Phan et al., 2004; Porges, 2007). Ventral periaqueductal gray and central gray are involved in freezing behavior, conflict test, conditioned emotional response, social interaction, and hypoalgesia (Öhman & Mineka, 2001). In more extreme expressions of fear, the parabrachial nucleus is involved in panting and respiratory distress. The dorsal motor nucleus of vagus and nucleus ambiguus are involved in parasympathetic effects that include ulcers, urination, defecation, and bradycardia (Davis, 1992, 1997).

Limbic structures. The limbic system is believed to be the center of emotional processing and is often described as the *emotional brain*. In fear and anxiety, limbic structures

are involved in the processing of threat salience, determination and relay of appropriate responses (i.e., fear or anxiety), as well as continued monitoring of the environment for threat. While much focus of the brain's role in fear and anxiety has centered on the amygdala, developments in neuroscience have allowed for increased specificity in detailing structure to function of limbic regions and how they facilitate fear or anxiety responses.

The thalamus. The thalamus is a limbic structure that serves as a processing center and relay station of sensory information between different subcortical areas and the cerebral cortex. The thalamus receives information from nearly sensory organ, with each sensory system including a thalamic nucleus. Sensory information related to threat is relayed from the thalamus to the sensory cortex, comprised of the visual cortex on the occipital lobes, the auditory cortex on the temporal lobes, the primary olfactory cortex in the temporal lobes, the gustatory cortex on the insular lobe, and the primary somatosensory cortex on the anterior parietal lobes. In addition, each of the primary sensory relay areas receives strong feedback connections from the cerebral cortex.

Of note, unlike other structures that go through the thalamic relay station, the sense of smell is unique. Although the olfactory bulbs receive sensory input from the olfactory nerves and route those signals throughout the brain, not all olfactory information is routed to the olfactory cortex. Some neural fibers are routed directly to limbic structures. Dense neural ties and close proximity between these structures allowed for rapid and efficient transmission of threat-related information for appraisal and response (Barton & Aggleton, 2000; Öhman & Mineka, 2001; Pêgo et al., 2009).

The amygdala. The amygdala is an ancient, almond-shaped cell mass shared by many higher and lower species that is widely regarded as one of the most important structures in

emotion (Öhman & Mineka, 2001). During the embryogenesis of rodents, the amygdala is online by the eighth month of gestation (Cozolino, 2006). Its early appearance in the mammalian brain both through evolution and embryogenesis suggest a primary role in survival.

The amygdala is located deep within the limbic system on both sides of the cerebral hemispheres. The right amygdala appears to be involved in emotional arousal below the level of awareness, whereas consciously perceived stimuli activate the left (Phan et al., 2004). Further, the amygdala is activated by both reward- or stress-related stimuli and has been proposed as an important structure in the detection of stimuli relevance (Davis & Whalen, 2001; Sander, Grafman, & Zalla, 2011).

Activation of the amygdala results in behavioral signs of fear and anxiety (Bronowski, 2011; Davis, 1998a; see Table 4). Animal studies using fear conditioning have determined its involvement in the detection and appraisal of threat, generation of fear-related emotions, and coordination of appropriate responses (Cozolino, 2006; Phan et al., 2004). In human subjects, amygdala activation has been observed in conscious and unconscious perception of fearful faces, processing of threatening words and vocalizations, and in the processing of outgroup versus ingroup facial stimuli. Damage to the amygdala in different animal species impairs emotional reactions of several sensory modalities, and in humans has been found to impair visual recognition of emotion in facial expressions (Adolphs et al., 1999).

Table 4

Functions of the Amygdala

Function	Source
Direct electrical stimulation of the amygdala produces behaviors associated with fear	(Davis et al., 1997; LeDoux, 1996)
Lesions of areas to which the central amygdala projects interfere with individual fear responses such as blood pressure changes, freezing behavior, or hormonal release.	(LeDoux, 2003; 2012)
Lesions to amygdala blocked fear-potentiated startle	(Davis et al., 1997; Grillon, 2007)
CRH injected intracisternally (through the cerebral ventricles) resulted in excitatory effect on acoustic startle. Lesions to the central nucleus of the amygdala block effects of CRH on acoustic startle reflex (pathway) when CRH was injected.	(Liang et al., 1992)
Acid lesions of the amygdala blocked the acquisition of fear-potentiated startle, but not its retention or expression	(Antoniadis, Winslow, Davis, & Amaral, 2007)

Although the amygdala is often discussed in the clinical literature as a whole, unilateral structure, ablasion and chemical lesion studies in animal models have parsed out the specific functions of its subregions. These subregions are highly connected to regions of the cortex, basal forebrain, thalamus, and brainstem, and possess specific connective parts that operate and control different mechanisms (Davis, 1997; Davis & Whalen, 2001). Three areas have been implicated in the acquisition of threat signals, storage and retrieval of implicit fear memories, and evaluation of threat salience to determine whether to employ fear or anxiety responses:

1. The basolateral amygdala (composed of the lateral and basolateral nuclei of the amygdala) is proposed to assign affective value to incoming or perceived threat cues. Salience of threat (e.g., whether it is immediate or distant) determines whether or not it requires an immediate response. The basolateral amygdala is known to have extensive connections going to the neocortex (Davis et al., 1997). Although pathways that connect the amygdala with the cortex provide a channel of communication between cognition and emotion, these connections are not symmetrical. Projections from the cortex to the

amygdala are considerably weaker than those from the amygdala to the cortex, and may explain why strong emotions are difficult to deactivate (LeDoux, 1995; Pêgo et al., 2009).

2. The lateral nucleus of the amygdala is a critical anatomical structure in the consolidation of conditioned fear memories. The lCeA (see below) has been proposed to be the site of fear memory storage (H. Li et al., 2013). Together, the LA-lCeA circuit work in a series in conditioned fear memory that incur a reflexive, defensive response (LeDoux, 1995; Öhman & Mineka, 2001; Schafe, Doyère, & LeDoux, 2005).
3. The central nucleus (CeA) is the primary output to the brainstem areas that control the autonomic nervous system and fight-flight responses (see Table 5). Recent studies have highlighted the CeA's greater role in responding to fear-conditioned-to-cue stimuli as compared to contextual stimuli, suggesting its greater involvement in fear as compared to anxiety (Davis et al., 2010; Pêgo et al., 2008; Porges, 2007; Woody & Szechtman, 2011). Its connections to the periaqueductal gray region in the brainstem modulate freezing or immobility. Its connections with the PVN control endocrine responses of the HPA axis (LeDoux, 1995). Its influence on the HPA axis, however, is considered to be limited (Graeff, 2007). While limbic regions such as the amygdala, influence HPA axis responses to stress, most of these limbic regions have limited to no direct projections to PVN, and instead use connections through intervening structures (Choi, Evanson, et al., 2007).

Table 5

CeA Targets and Physiological Responses

Target	Physiological Response	Reference
Lateral hypothalamus	Sympathetic autonomic responses: tachycardia, galvanic skin response, paleness, pupil dilation, blood pressure elevation Fear-induced bradycardia in rabbits	LeDoux, 1996 Davis, 1997 Ohman & Mineka, 2001
Dorsal motor nucleus of vagus Nucleus ambiguus	Ulcers, urination, defecation, bradycardia	Davis, 1997
Parabrachial nucleus	Panting, respiratory distress	Davis, 1997
Ventral tegmental area Locus coeruleus Lateral dorsal tegmental nucleus Basal forebrain	Arousal, increased vigilance, increased attention	Davis, 1997
Nucleus reticularis pontis caudalis	Fear-potentiated startle	LeDoux, 1996 Davis, 1998
Ventral periaqueductal gray in midbrain Central gray	Freezing behavior, conflict test, conditioned emotional response, social interaction, hypoalgesia	Ohman & Mineka, 2001; LeDoux, 1996; Davis, 1997
Trigeminal facial motor nucleus	Facial expressions of fear	Davis, 1997
Paraventricular nucleus (Hypothalamus)	Corticosteroid release (“stress response”)	Davis, 1997
Bed nucleus of the stria terminalis	Neuroendocrine responses	LeDoux, 1996

The bed nucleus of the stria terminalis. The bed nucleus of the stria terminalis (BNST) is a cell mass that forms a distinct region in the basal or non-cortical division of the cerebral hemisphere (Davis, 1998b; Dong, Petrovich, & Swanson, 2001). The BNST lies close in proximity to the amygdala, on the opposite side of the stria terminalis (Fudge & Haber, 2001). In rodents, the bulk of the BNST neurons are among the earliest born in the cerebral hemispheres (Dong et al., 2001).

Like the amygdala, subdomains of the BNST are highly connected to different parts of the brain, with afferent connections to regions in the cerebral cortex, rostral forebrain, thalamus,

hypothalamus (see Table 6), and brainstem. They similarly operate different mechanisms activated by both stress- and reward-related stimuli (Davis, 1998b; Fudge & Haber, 2001) and have been implicated in hunger, salt and water intake, stress, arousal, and reward (Shin, Geerling, & Loewy, 2008).

While the amygdala plays a key role in fear-conditioned-to-cue stimuli, the bed nucleus of stria terminalis (BNST) is implicated in anxiety behavior and responses to contextual stimuli (Pêgo et al., 2008). Electrical stimulation of BNST in rats produced stress-like behavior that was qualitatively similar to the behavior produced by restraint stress but differed in time course – the effects lasting longer (Casada & Dafny, 2010).

Table 6

Hypothalamic Targets and Functions

Hypothalamic Targets		
LeDoux, 1996; Davis, 1997; Ohman & Mineka, 2001	Lateral hypothalamus	Sympathetic autonomic responses: increased heart rate, galvanic skin response, paleness, pupil dilation, blood pressure elevation, fear-induced bradycardia
Davis, 1997	Paraventricular nucleus	Corticosteroid release

While limbic regions, such as the amygdala and hippocampus, influence HPA axis responses to stress, most of these limbic regions have limited to no direct projections to PVN, and instead use bisynaptic or multisynaptic connections through intervening structures (Choi, Evanson, et al., 2007; Radley, Williams, & Sawchenko, 2008). Numerous lines of evidence suggest that the BNST is well positioned to relay limbic information to the neuroendocrine system (Choi, Furay, et al., 2007; Crestani et al., 2013). Rodent models reveal that the BNST is connected extensively to the neuroendocrine system through its various subregions (see

Appendix: Connectivity of the BNST). The lateral anterior BNST sends projections to hypothalamic areas guiding autonomic and energy homeostasis and feeding behavior, whereas the posterior BNST projects to hypothalamic areas responsible for reproductive and defensive behaviors (Davis et al., 1997; Dong & Swanson, 2004a). The dorsalmedial division of the BNST generates the densest known inputs to the neuroendocrine system via the paraventricular nucleus (PVN) of the hypothalamus than any part of the cerebral hemispheres (Dong & Swanson, 2005b).

This connectivity suggests a primary role in the production and modulation of the HPA axis. By integrating the output of different stress-related brain networks, the BNST and PVN play a key role in the HPA stress response. The BNST is activated early after the arrival of stressful stimuli, resulting in the secretion of the adrenocorticotrophic hormone (ACTH), CRH, and arginine-vasopressin in the PVN. In turn, ACTH stimulates the synthesis and secretion of glucocorticoids by the adrenal glands (see Figure 1; Davis et al., 1997; Pêgo et al., 2009).

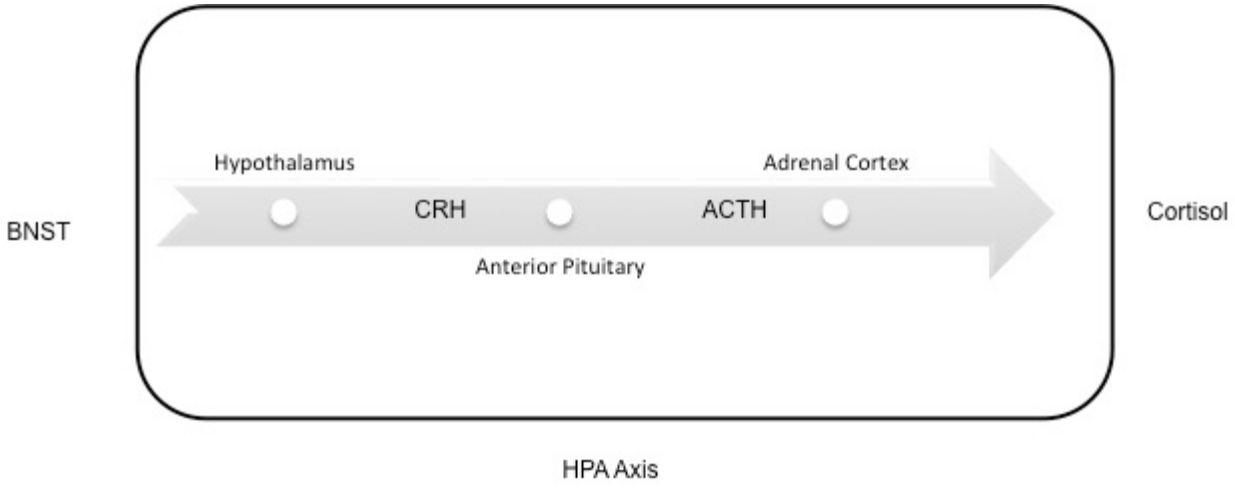

Figure 1. BNST to HPA production of cortisol.

The functional subdomains of the BNST play different roles in integrating and processing limbic information in response to stress and further suggest that excitatory as well as inhibitory

limbic information is funneled through these cell groups (Choi, Furay, et al., 2007). The anteroventral BNST appears to stimulate the HPA axis during acute stress, whereas the posterior BNST appears to be involved in its inhibition (Choi, Evanson, et al., 2007).

The excitatory and inhibitory effects of the BNST over the PVN ultimately impact the modulation of stress hormones. In rats, stimulation of the medial and rostral areas of the BNST resulted in a 24% increase in plasma corticosterone levels and a 36% increase 30-minutes post-stimulation. In contrast, stimulation of the lateral BNST resulted in 13% decrease in plasma corticosterone levels and a 22% decrease in levels 15-minutes post-stimulation (Dunn, 1987). Further, inhibitory influences of the BNST, such as the heart rate decreases following evoked restraint stress in rats, are a result of parasympathetic activation (Crestani, Alves, Tavares, & Corrêa, 2009; Öhman & Mineka, 2001).

Rodent models have shown that high-frequency stimulation of the BNST (simulating invariant, homotypic stress) has been found to decrease the size of the BNST (Pêgo et al., 2008), which in turn produces rapid and enduring depression of PVN responses. Through enhancement of inhibitory control from the BNST, this decreased responsiveness of neurons in or around the PVN may participate in of the HPA axis tolerance to repeated homotypic stress, which may suggest that habituation is occurring (Tartar, King, & Devine, 2006).

The hippocampus. The hippocampus is a limbic structure that plays a central role in learning and memory. It is involved in the processing of explicit and declarative memories, in contrast to the processing of implicit memories in the lateral amygdala. During periods of intense stress, threat cues activate the amygdala, which in turn triggers the production of glucocorticoids from the adrenal gland. These hormones modulate the strength of declarative memories formed in the hippocampus. In intense fear reactions, formation of conscious

memories (e.g., declarative and spatial) is impaired, whereas the ability to form unconscious (e.g., procedural or implicit) memories remains intact (LeDoux & Phelps, 2011).

The hippocampus is rich with receptors for CRH and glucocorticoids and is involved in regulating the release of glucocorticoids in response to environmental and psychogenic stressors (Woody & Szechtman, 2011). Both subtypes of CRH and glucocorticoid receptors are present in the hippocampus, as are both subtypes of receptors for glucocorticoids, with the two subtypes of each receptor often mediating functionally opposite effects. Differences in receptor subtypes and times of action of CRH and glucocorticoids in the hippocampus may serve different aspects of threat responding. One function may involve the envisioning future events by probing for possible danger that involves the creation of mental scenarios in which vague signs materialize as real threat and facilitating predictions about upcoming events. Another function is feedback inhibition of the HPA response where circulating glucocorticoids act on the hippocampus to limit or terminate HPA activation (Woody & Szechtman, 2011).

The insula. The insula is a limbic structure involved in evaluative, experiential, and expressive aspects of emotions. In fear and anxiety, the insula serves as an alarm center for internally sensed dangers to changes in the environment. It integrates information between somatic internal feelings and external cues, which is believed to be adaptive by providing internal awareness of the physical self across time to guide behavioral responses.

The insula receives integrated sensory information of the environment from various regions of the thalamus. The posterior insula connects reciprocally with the secondary somatosensory cortex and receives input from the ventral posterior inferior thalamic nuclei. This region also receives inputs from the ventromedial nucleus of the thalamus, which conveys homeostatic information such as pain, temperature, itch, local oxygen status, and touch. In

addition, a human imaging study revealed that the anterior insula is interconnected to regions in the temporal and occipital lobe, opercular and orbitofrontal cortex, and triangular and opercular parts of the inferior frontal gyrus (Phan et al., 2004).

Its emotional functions are suggested by its extensive connectivity to both the amygdala and BNST. In rhesus monkeys, widespread reciprocal connections bridge the insula and almost all subnuclei of the amygdala, with a particularly large input from the CeA. Through these shared connections, it is suggested that the insula relays internal, somatically sensed information to the amygdala where appropriate responses to danger are determined (Phan et al., 2004).

In highly anxious people, hypervigilant threat monitoring is a key symptom underlying many anxiety disorders. Together with the BNST, the insula appears to play a critical role in maintaining hypervigilance. In human subjects with elevated anxiety, the BNST showed greater overall recruitment and exaggerated tracking of threat proximity. The insular cortex tracked threat proximity, exhibited exaggerated responses in individuals with greater anxiety, and showed enhanced recruitment when threat proximity was controllable. Activity in the BNST and insula continuously monitored changes in environmental threat level and underlied hypervigilant threat-monitoring processes in more highly trait anxious individuals (Somerville, Whalen, & Kelley, 2010).

The hypothalamus. Located at the base of the brain, the hypothalamus is a coordinating center for the motor control of visceral activity. One of its many functions is the regulation of body temperature. In the stress response, the hypothalamus is the gateway to the hypothalamic-pituitary-axis involved in the production of the stress hormone, cortisol. The hypothalamus has connections with the pituitary gland by virtue of which it influences the pituitary and, through

the pituitary gland, the other endocrine glands. The hypothalamus also sends nerve fibers to lower centers in the brainstem.

The anterior cingulate. The anterior cingulate cortex (ACC) plays a role in the experiential aspects of emotion. It serves as a relay area of cognitive and emotional information, facilitating top-down organization of emotional information. It is involved in assessing the salience of emotion and motivational information and appears to be especially involved in early learning and problem-solving. Cerebral blood flow from human PET studies suggest a key role in determining speed reaction in behavioral tasks (Fuchs & Flügge, 2003). It has also been implicated in motivation for decisions and producing gut reactions (Cozolino, 2010). The posterior dorsal ACC is responsible for response selection, whereas the anterior dorsal ACC is involved in evaluation of the response. Activity in this region has been shown to increase when uncertainty is higher (Banich, 2009).

The ACC is broadly described as belonging to the limbic lobe given its expansive connections to subcortical structures (Fuchs & Flügge, 2003; Phan et al., 2004). It has extensive connections with multiple brain structures, including the hypothalamus, amygdala, and brain stem and is part of a system that orchestrates the autonomic, neuroendocrine, visceral, and behavioral expression of emotion (van der Kolk, 2006). Activity in the ACC has been shown to be modulated by incoming sensory information from the thalamus as well as feedback from defensive responses produced by the brainstem that seek to change the condition of the environment (Fuchs & Flügge, 2003).

Connections from rostral and ventral areas of the ACC to the amygdala are proposed to serve emotional functions (Fuchs & Flügge, 2003). Damage to the ACC has been found to result in emotional disturbances including apathy and emotional instability (Phan et al., 2004). Dorsal

areas of the ACC appear to serve cognitive functions as evidenced by widespread connections with the prefrontal corticies. These subcortical and cortical links make it a central station for processing top-down and bottom-up stimuli and assigning appropriate control to other areas in the brain (Phan et al., 2004).

Neocortical structures. To review, the neocortex is the outermost layer of the triune brain that assumed prominence in primates and humans. In humans, the development of language, abstract and conscious thought, and imagination are believed to have emerged with the rise of the neocortex. The neocortex is considered to be flexible and possesses infinite learning abilities. Functions of the neocortex include learning motor sequences and generation of motor commands. In fear and anxiety, several key structures in the frontal regions of the neocortex are involved in emotional inhibition. Working in tandem with key limbic, these frontal areas are involved in different elements of conscious processing: integrating and organizing sensory and temporal experience, spatial reasoning, organizing working memory, directing attention, and memory for the future. The addition of conscious processing provides context in the interpretation of fear stimuli, inhibits limbic expression of fear and anxiety responses, and organizes and guides behavioral responses.

Orbitomedial prefrontal cortex. The orbitomedial prefrontal cortex (OMPFC) is a broad designation for the orbital and the medial prefrontal cortices that evolve during childhood (Cozolino, 2010). Animal models reveal that the OMPFC plays a role in emotional inhibition by serving as a modulator of intense emotional responses, especially conditioned fear responses generated by the amygdala (Phan et al., 2004). Electrical stimulation of mPFC has been found to reduce conditioned fear in a temporally specific manner in rats (Quirk, Garcia, & González-Lima, 2006). The mPFC plays a role in the extinction of conditioned fear responses by

inhibiting the limbic system, thereby regulating the generalization of fearful behavior (by attenuating sympathetic and hormonal responses to stress) and the stress hormone cortisol (by suppressing the stress response mediated by the HPA axis; van der Kolk, 2006).

The infralimbic cortex (IL) is a cortical region in the ventromedial prefrontal cortex which is important in tonic inhibition of subcortical structures and emotional responses, such as fear. Emotional arousal, particularly fear, strengthens memory for the threating context. Mueller, Porter, and Quirk (2008) suggested that NE released in IL during the extinction of a fear response activates a molecular cascade that strengthens extinction memory. The emotional arousal evoked by conditioned fear paradoxically promotes the subsequent extinction of that fear, thereby ensuring behavioral flexibility (also see Fear Extinction Pathway).

The OMPFC, along with the hippocampus, however, is also involved in the spontaneous recovery of previously extinguished fear stimuli. During extinction recall in human subjects, functional connectivity analysis revealed significant activations in the ventral OMPFC and hippocampus in response to extinguished versus unextinguished fearful stimuli. Activation in these brain regions was positively correlated with the magnitude of extinction memory (Milad et al., 2007).

Dorsolateral prefrontal cortex. The dorsolateral prefrontal cortex (DLPFC) is involved with directing attention, organizing working memory, learning motor sequences and organizing temporal experience, memory for the future, and integration of senses, the body, and memory to organize and guide behavior (Cozolino, 2010). Banich (2009) proposed the Cascade of Control model that involves a sequence of brain regions that maintain attention in order to arrive at a goal. The model assumes the top-down involvement of the posterior DLPFC, the mid-DLPFC,

and the posterior and anterior dorsal ACC. The activity of any of the areas involved in this model depends on the efficiency of the areas that came before it.

1. The posterior DLPFC creates an appropriate attentional set of rules for the brain to accomplish the current goal.
2. The mid-DLPFC selects the representation that will fulfill the goal. The task-relevant information must be separated from other sources of information in the task.
3. The posterior dorsal ACC is responsible for response selection.
4. Following the response, the anterior dorsal ACC is involved in response evaluation, deciding whether one was correct or incorrect. Activity in the ACC increases when the probability of an error is higher. If the DLPFC imposes a great deal of control on the response, the ACC will require less activity (Banich, 2009).

Parietal lobe. The parietal lobe is thought to be involved in awareness of self through time and space (Cozolino, 2010). The regions of the parietal lobes access information from the sensory cortex, an umbrella term for the primary and secondary cortices of the different senses: the visual cortex on the occipital lobes, the auditory cortex on the temporal lobes, the primary olfactory cortex on the temporal lobes, the gustatory cortex on the insular lobe, and the primary somatosensory cortex on the anterior parietal lobes. Within the anterior parietal lobe lies the primary somatosensory cortex, which is involved in somatic sensation, visual stimuli, and movement planning. Posterior to the primary somatosensory cortex lies the somatosensory association cortex, which integrates sensory information from the primary somatosensory cortex to construct an understanding of the object being felt (van der Kolk, 2006).

The paralimbic cortex. The paralimbic cortex, or basal forebrain, is interposed between the neocortex and the region encompassing the hippocampus and olfactory system, or the

allocortex. The paralimbic cortex lies close to, and is directly connected with, the structures of the limbic system, including the amygdala, the hippocampus, anterior superior temporal gyrus, and the cingulate cortex. At the apex of the paralimbic cortex sits the OMPFC. Extensive connections link the OMPFC to core limbic structures, particularly the amygdala, and provide a gradual transition from primary limbic regions to higher neocortical regions. Many structures within the paralimbic system contain receptors for CRH and glucocorticoids and are implicated in regulating the HPA axis response to environmental and psychogenic stressors, and are also subject to regulation by an activated HPA (Woody & Szechtman, 2011).

The paralimbic cortex is an interactive zone between affective and cognitive processing. It is believed to be involved in emotional aspects of goal-directed behavior, motivation, and self-control. It is thought that the emotional experiences that humans perceive such as fear, anger, and pleasure reflect an interplay between the specific subcortical limbic regions and the higher brain centers that make up the paralimbic cortex (Fuchs & Flügge, 2003).

Fear and Anxiety Circuitry

Merriam-Webster's Medical Dictionary defines circuitry as "the network of interconnected neurons in the nervous system and especially the brain" or "the neuronal pathways of the brain along which electrical and chemical signals travel" ("Circuitry," n.d., para. 6). Generation and modulation of emotions may be broadly characterzied as being top-down or bottom-up. Bottom up-processes stem from our sensory perceptions of the environment, or in response to inherently emotional perceptual properties of a stimulus. Top-down processes are driven by cognitive appraisals of an event, and modulate our emotional responses such as fear and anxiety (McRae, Misra, Prasad, Pereira, & Gross, 2012).

An fMRI study on 20 human female subjects revealed that bottom-up responses activated systems for attending to and encoding perceptual and affective stimulus properties, whereas top-down responses activated prefrontal regions that facilitate high-level cognitive interpretations. Self-reported affect also correlated with activity in the amygdala during bottom-up responding and with activity in the medial prefrontal cortex during top-down responding. Athough bottom-up and top-down responses activated the amygdala, bottom-up responses did so more strongly (Ochsner et al., 2009).

The high road and the low road: LeDoux. LeDoux (1996) outlined a pathway from the acquisition of a stimulus to emotional response and highlighted the prominent role of the amygdala in the fear conditioning. He described two amygdala pathways in rodent brains that lead to the expression of fear and anxiety: the *high road* and *low road*. The low road is a fast pathway in which a signal from a threat stimulus (perceived as life-threatening) is transmitted to the thalamus and then to the amygdala, which then activates a fear response. The low road is regarded as a more primitive mechanism of defense, evolving from lesser-developed animals that have not evolved a more complex part of the brain. It only involves the subcortical part of the brain and is believed to work without conscious experience of the stimulus. The high road is a slower road that is includes the cortical parts of the brain and is dedicated to non-life-threatening stimuli. Threat signals from a host of senses are integrated in the thalamus and relayed to the sensory cortex, which creates a conscious impression of the stimulus. Impressions made by the sensory cortex are then routed to the amygdala, where appropriate fear and anxiety responses are determined. In more developed animals, the high road and the low road work simultaneously to provide both the fear response and perceptual feedback (see Figure 2; LeDoux, 1996).

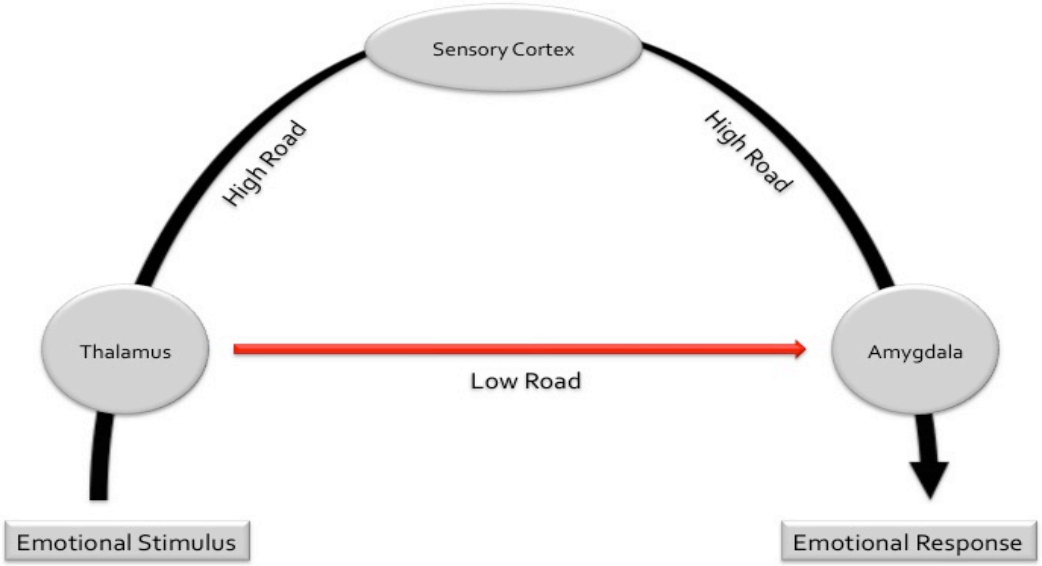

Figure 2. LeDoux (1996) – The high road vs. the low road.

Differential involvement of the CeA and BNST. For many years in the clinical literature, it was widely accepted that the amygdala was the most important structure in fear and anxiety. The work of Joseph LeDoux suggested that in the brain, fear and anxiety responses are relayed by neuroendocrine and autonomic centers that comprise largely the same pathways as those activated by anxiety, resulting in wide phenotypic overlap (Pêgo et al., 2009).

The work of Michael Davis and his colleagues, however, has shed some light on where fear and anxiety diverge in the brain. Davis (1997) posited that although the mechanisms of fear and anxiety are intricately linked phenotypically and have some overlap in neural pathways, they are indeed separate (Davis et al., 1997). Mapping studies implicated both the CeA and the BNST, and suggested that fear and anxiety:

- Are activated in response to particular stimuli: Davis and his colleagues found that the within the amygdala, the CeA is activated by stimulus specific threat (i.e., shock). In contrast, contextual threat cues (e.g., rats being exposed to a light for several minutes)

activate the BNST, which in turn activates the hypothalamic and brainstem areas involved in specific signs of anxiety (Pêgo et al., 2009).

- Are activated over different timeframes: The BNST was found to be involved in elevations of the startle response that lasted longer than the startle response observed in the CeA during explicit cue conditioning (Davis et al., 1997; Walker & Davis, 1997b).
- Resulted in the activation of distinct centers in the brain: Lesions to the rat BNST did not block fear-potentiated startle, whereas lesions to the CeA did not block light-enhanced startle, a paradigm used to measure anxiety (See review of CeA and BNST lesion and CRH studies; Walker, Miles, & Davis, 2009).

Davis proposed that the BNST may be a system that responds to threat signals more similar to anxiety than to fear, whereas the CeA is clearly involved in fear and not as much in anxiety. Assuming that phasic activation is like fear, whereas sustained activation of similar structures is like anxiety, this would suggest differential roles of the amygdala and the BNST in fear and anxiety, respectively (Davis, 1998b; Davis et al., 1997). The authors summarized:

> Fear and anxiety appear as two phenomenologically and anatomically dissociable response systems. One, which includes as an integral component the bed nucleus of the stria terminalis, can be characterized as a sluggish response system that once activated continues to influence behavior long after the initiating stimulus has been terminated. The other system, which includes the central nucleus of the amygdala, can be characterized as a rapid response system that mediates short-term responses to specific threat cues (i.e., stimulus-specific fear responses). We refer to the former, sustained type of response as anxiety, and to the latter stimulus-specific, short-lasting type of response as fear. (Walker, Toufexis, & Davis, 2003, p. 204)

Other studies appear to support Davis's theory. In response to exposure to chronic unpredictable stress, the morphology of the amygdala was preserved in contrast to significant level of plasticity in the BNST, suggesting chronic stress does not produce changes in fear-acquisition (Pêgo et al., 2008). In a review of imaging studies on specific anxiety disorders, Engel revealed a brain-based distinction between two classes of anxiety disorders – those involving intense fear and panic, and those involving excessive worry and rumination (Engel, Bandelow, Gruber, & Wedekind, 2008). Graeff (2007) also acknowledged that anxiety and panic seem to be qualitatively different emotional states that are related to two types of defense reaction to potential and proximal threat, respectively. Their related pathologies, GAD and panic disorder were found to promote differential mobilization of the HPA and sympathetic nervous system. Specifically while anxiety activated both the HPA and the sympatho-adrenal axes, panic attacks cause major sympathetic activation, but have little effect on the HPA axis (Graeff, 2007).

Fear pathway. Based on the findings of the differential involvement of the CeA and BNST in fear and anxiety, coupled with his own mapping studies, Davis (2001) proposed that the basolateral amygdala to CeA connection, along with the efferent projections of the CeA to brainstem and hypothalamic targets, appear to represent a system involved specifically in the acquisition and expression of conditioned fear (see Appendix: Mapping the Neural Pathway of Fear).

In the processing of fear, signals from a host of sensory modalities mediated by cortical, forebrain, thalamic, and brainstem regions converge in the basolateral amygdala. Signals are then sent to CeA, where determinations of appropriate response are made, and relayed to brainstem targets and hypothalamic targets (Davis & Whalen, 2001). Choi, Furay, et al. (2007) found that the CeA has limited connectivity and influence on hypothalamic targets, and more

profound influence on the brainstem, highlighting its greater involvement in sympathetic activation (Choi, Furay, et al., 2007; Graeff, 2007).

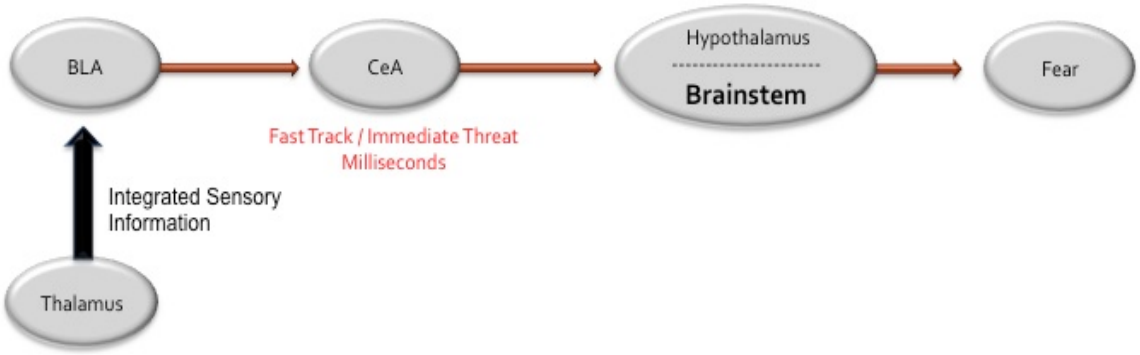

Figure 3. Fear pathway.

Anxiety pathway. In contrast to the pathway of fear responses, Davis's (2001) theory suggests that the basolateral amygdala to BNST connection, along with the BNST efferent projections to predominantly hypothalamic targets appear to represent a system involved in the anxiety. Because the CeA includes CRH-enriched neurons that project to BNST, phasic activation of the CeA (specifically the lateral division) by diffuse, unspecific stressors could lead to long-term activation of the BNST through CRH, which is released during periods of stress and preferentially activates the BNST (Davis & Whalen, 2001; Walker et al., 2009).

This assertion that CRH from the amygdala feeds into the BNST was substantiated by the work of Shepard, Schulkin, and Myers (2006), who found that when rats were exposed to an elevated plus maze (a measure of anxiety-like behavior), elevated corticosterone in the amygdalae of rats increased CRH levels in the dorsolateral BNST. Chronically elevated corticosterone in the dorsolateral BNST led to reduced exploratory behavior on the elevated plus maze, indicating an increase in anxiety-like behavior (Shepard, Chambers, Busch, Mount, & Schulkin, 2009).

To review and highlight the difference between the pathways proposed by Davis and his colleagues, characteristics of the fear response are similar to the quick responding of the sympathetic nervous system functioning, in that threat is processed very quickly, and responses are generally short lived. In contrast, the protracted nature of anxiety is similar to that of neuroendocrine functioning. Both are slow to initiate and prolonged in their response, which last anywhere from minutes to hours. As mentioned previously, the BNST has much more robust projections to the HPA as compared to the CeA. In contrast, as compared to the BNST, the CeA has much more robust projections to the brainstem.

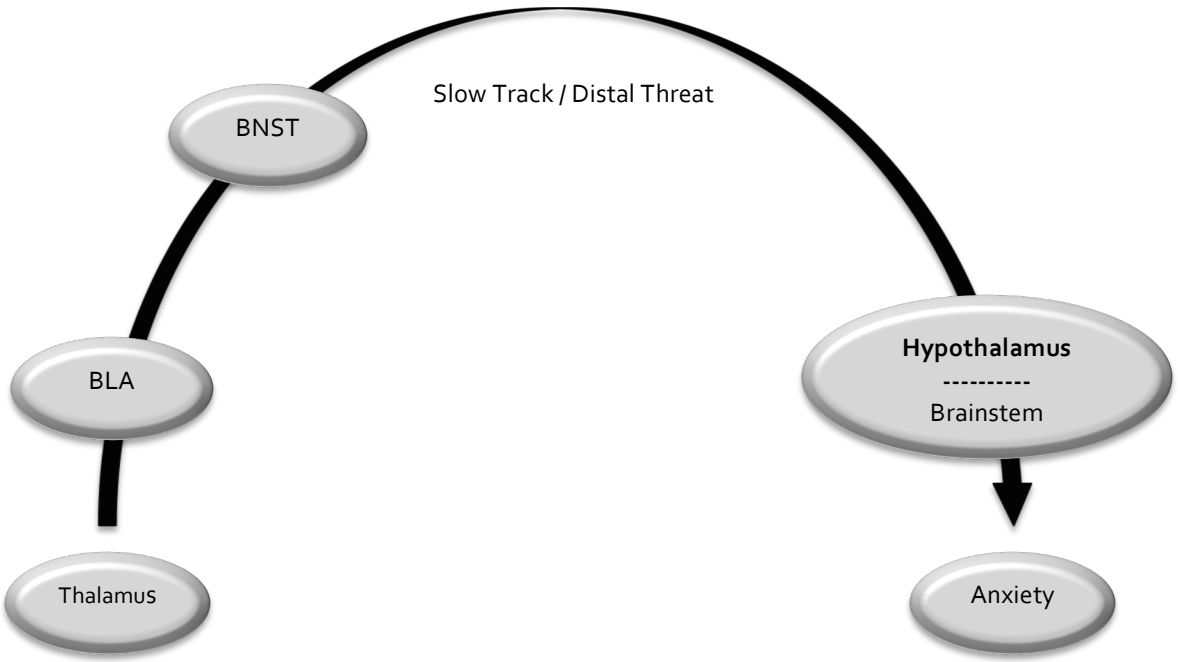

Figure 4. Anxiety pathway.

Development of Fear and Anxiety Disorders

Effective coping to stress implies the triggering of necessary responses and the termination of these responses when they are no longer needed. In contrast, pathologies of fear and anxiety imply that these typically adaptive responses outlast their exposure to threat and

result in prolonged activation of the neural substrates and processes that regulate them. The exaggeration or protraction of stress responses can lead to changes in the brain and immune system that may ultimately result in disease (Pêgo et al., 2009). From the perspective of homeostasis, prolonged and/or uncontrollable stress can devastate an organism, leading to the suppression of anabolic processes, depletion of energy stores, immunno-suppression, and exhaustion (Sapolsky, 1992). McEwen describes this as *allostatic load* (McEwen & Gianaros, 2010), which refers to "the price the tissue or organ pays for an inefficiently managed allostatic response" or the 'cost of adaptation'" (Darnaudéry & Maccari, 2008)(p. 573).

Family inheritance of anxiety disorders have shown a strong influence of genetic background and familial aggregation for specific phobias and unspecific anxiety disorders. Despite a strong genetic contribution, part of the variability could be explained by family and other environmental factors. Both animal and humans studies reveal that traumatic events or emotional stressors in early life constitute a developmental risk factor for pathologies of anxiety and fear in adulthood (Pêgo et al., 2009).

A number of studies have highlighted the consequential biological impacts of environmental adversities due to prolonged stress responses. These studies center on developmental and lifespan risk factors including the effects of prenatal stress, adverse early-life experience, and lifespan issues that lead to HPA dysregulation, genetic modification, as well as remodeling of brain structures that correlate with fear and anxiety disorders (Pêgo et al., 2009).

Environmental adversity and HPA dysregulation. Anxiety patients show a wide spectrum of patterns of HPA activity which reflects the heterogeneous nature of anxiety disorders. The effects of chronic stress have been modeled extensively in animals and has been found to be a powerful modulator of emotional behavior. These studies indicate that substantial

stress exposure can produce changes in responsiveness of the HPA axis. Animal studies have demonstrated altered reactivity of the HPA axis in gestation, early childhood, and throughout the lifespan due to adverse early-life experiences (Pêgo et al., 2009). These changes appear to reflect increased reactivity to potential threat as well as HPA dysfunctions in later life that may predispose an individual toward the development of certain kinds of psychopathology (Woody & Szechtman, 2011).

Gestational stress in rats has been found to have long-lasting effects on the HPA axis, with chronic hyperactivation of the HPA response associated with an altered circadian rhythm of corticosterone secretion in rats. Female rats exposed to prenatal restraint stress exhibited blunted corticosterone secretion response to stress following an inescapable foot shock. In male rats, sleep disturbances and HPA dysfunctions were observed in infant, young, adult and aged animals, suggesting a permanent effect of early stress. Both male and female offspring later exhibited behavioral disturbances including high levels of anxiety and depression-like behavior during adulthood, as well as cognitive deficits including memory impairments (Darnaudéry & Maccari, 2008). Life events occurring during the perinatal period (i.e., the period immediately before and immediately after birth) as well as maternal separation stress have also been linked to profound, long-term dysregulation of the HPA axis and increased anxiety-like behavior that appears to be established during restricted windows of time when the HPA axis seems particularly vulnerable to stress (Darnaudéry & Maccari, 2008; Pêgo et al., 2009).

Despite the permanent imprinting induced by early stress, HPA dysfunctions can be reversed by environmental enrichment or pharmacology (Darnaudéry & Maccari, 2008). An established example of the consequences of early-life experience-induced programming includes the effects of maternal care, where patterns of augmented maternal care result in decreased

neuroendocrine stress responses, improved cognition and resilience to depression in the recipients of this care (Korosi & Baram, 2010). Alterations in maternal behavior make a strong contribution to the long-term effects of prenatal restraint stress in rats, through epigenetic mechanisms (Darnaudéry & Maccari, 2008).

Early-life experience including maternal care profoundly influences hormonal stress responses during adulthood(Fenoglio, 2004). Fenoglio (2004) found when rat pups were stressed by daily handling, as compared to undisturbed pups, increased CRH expression was apparent in the CeA and BNSTs of handled pups. Upon return to their cages, handling-evoked augmentation of maternal care of pups induced long-lasting reduction of hypothalamic CRH expression. These changes promote a lifelong attenuation of hormonal stress responses (Fenoglio, 2006). Alterations in mRNA expression in CeA, BNST as well as PVN may contribute to the molecular cascade by which handling (and increased maternal care) influences the stress response long-term (Fenoglio, 2006). Neuroplasticity of the HPA in early life requires the recurrent recruitment of CeA and BNST (Fenoglio, 2006).

Environmental adversity and altered gene expression. Genetic programming governs many behavioral and physiological phenotypes and promotes susceptibility or resilience to disease by determining the sequence and expression of specific neuronal genes. These genetic programs, however, can be modified enduringly as a result of experience taking place during critical developmental periods. Epigenetic changes include modification of the genetic material due to methylation and other chemical alteration, as well as non-programmed remolding of an organism by physical and other environmental effects due to the inherent plasticity of developmental mechanisms (Korosi & Baram, 2010).

Animal models suggest that environmental adversity results in parent–offspring interactions that increase stress reactivity, and sustain effects on gene expression in brain regions known to regulate behavioral, endocrine, and autonomic responses to stress (Parent et al., 2005). Roth, Lubin, Funk, and Sweatt (2009) proposed that adverse parental care may contribute to familial transmission of mental illness. In rats, infant maltreatment resulted in methylation of brain-derived neurotropic factor (BDNF) DNA through the lifespan to adulthood that corresponds with reduced BDNF gene expression in the adult PFC. Altered methylation are passed from one generation to the next, with transmission of phenotype and particularly of maternal behavior. Further, rodents that have experienced abuse not only grow up and mistreat their own offspring, but that their offspring also have significant DNA methylation. Despite this, altered epigenetic marks and gene expression in adult rats can be reversed with a DNA methylation inhibitor.

Structural remodeling in chronic stress. Neuroplasticity refers to modifications of the living brain that include chemical exchanges between neurons, changes in cellular excitability (Centonze, Siracusano, Calabresi, & Bernardi, 2004), neuronal replacement, dendritic remodeling, and synapse turnover (McEwen et al., 2012). For most of the 20th century, it was believed that the brain was shaped by sensitive (or critical) periods of rapid growth during early life, and remained static after that. However, in recent decades, the idea that the brain, nervous system, genetic makeup change in response to experience has garnered increased support. Contemporary neuroscience now fosters the idea that the brain changes in response to experience throughout the lifespan, highlighting the continuing impact of challenging environments in sculpting the brain through its development (Cozolino, 2010).

Studies have shed light on the deleterious effects of stress hormones on brain architecture related to systems of memory, learning, and executive functioning resulting in the reduction or enlargement of brain structures in humans, as well as dysregulation of cortical and limbic systems that modulate strong emotions (Bremner, 1999). The amygdala and the prefrontal cortex, brain regions involved in anxiety and fear, mood, cognitive function and behavioral control, show structural plasticity. Acute and chronic stress cause an imbalance of neural circuitry implicated in cognition, decision making, anxiety and mood that can increase or decrease expression of those behaviors and behavioral states (McEwen et al., 2012). In the developing brain through adulthood, there also appears to be a remarkable ability to show reversible structural and functional plasticity in response to stressful and other experiences (McEwen et al., 2012).

Atrophy of higher systems. The hippocampus and prefrontal cortex are important for coordinating the adaptive response to stress; their functions are complemented by the amygdala and the BNST, both of which display a rich population of corticosteroid receptors that are activated during stress (Pêgo et al., 2008). Plasticity is particularly evident in the hippocampus (McEwen et al., 2012). In severe cases of anxiety, PTSD has been found to result in atrophy of the prefrontal cortices (Bremner, 1999). Panic disorder and specific phobias were characterized by hypoactivity of prefrontal cortex areas that play a role in disinhibiting the amygdala (Engel et al., 2008).

Early stress research (circa 1990) revealed that individuals with post-traumatic stress disorder and victims of childhood abuse showed deficits in declarative memory per neuropsychological testing. Further, MRI studies of those with PTSD showed reductions in hippocampal volume in these individuals. Cortisol levels were related to memory function, with

evidence increased memory problems with stress-induced cortisol elevations, and improvement of memory function with reduction of cortisol levels (Bremner, 1999).

Enlargement of limbic structures. Chronic stress models have been have revealed hyperactivity of the amygdala and the BNST. GAD or social anxiety were characterized by hyperactivity of both the amygdala and right prefrontal cortex in adults (Engel et al., 2008). Schumann (2011), noted that amygdala enlargement In an fMRI study of children ages 7-9, high levels of childhood anxiety was associated with enlargement of the amygdala, particularly in the basolateral amygdala (Qin et al., 2014). Fearfulness was correlated with higher amygdala volumes in a sample of normal healthy females ages 7-17 (van der Plas, Boes, Wemmie, Tranel, & Nopoulos, 2010).

Using volumetric MRI analysis, De Bellis et al. (2000) demonstrated that children and adolescents with GAD (mean age 12.7 years) had larger right and total amygdala volume as compared to age-matched controls. A similar pattern of amygdala enlargement has recently been reported in adolescents (average age 14.7 years) who showed characteristics of behavioral inhibition earlier in childhood (Hill, Tessner, Wang, Carter, & McDermott, 2010). However, not all studies have reported increases in amygdala volume in individuals with pediatric anxiety or behavioral inhibition. One morphometry analysis that included children with separation anxiety, social phobia or GAD (mean age 12.9 years) reported a significant grey matter volume reduction within the left amygdala of children with a pediatric anxiety disorder compared to healthy controls (Milham et al., 2005). The authors highlighted the fact that pediatric anxiety disorders are heterogeneous conditions, and although changes in amygdala structure may be present, the changes depend on the specific diagnoses of the participants (Schumann et al., 2011)

Pego et al. (2008) found that chronic unpredictable stress induces hyperanxiety without influencing fear conditioning. Stress-induced hyperanxiety was correlated with increased volumes of the BNST but not of the amygdala. These changes were primarily seen in the anteromedial BNST, an area strongly implicated in the neuroendocrine control of the stress response (Pêgo et al., 2008). Chronic uncontrollable stress affect peptides that affect neuroplasticity of the BNST and maladaptive remodeling of the BNST associated with anxiety-like behavior (Hammack et al., 2009). The behavioral effects of uncontrollable stress can be blocked by lesion to the BNST (Hammack, Richey, Watkins, & Maier, 2004).

As mentioned previously, deleterious effects of stress are thought to be mediated in part by dysregulation (e.g., overactivation) of the HPA axis. Structural changes in the BNST observed after chronic stress correlate with the behavioral responses to stress (Pêgo et al., 2009). Because regulation of the HPA axis by the hippocampus and other limbic structures is mediated in part by synaptic relays in the BNST , the BNST is in a key position to regulate not only anxiety, but also stress responses implicated in neuropathology and precipitation of other neuropsychological disturbances (Walker et al., 2003).

To review, the BNST appears to act as a relay point into the HPA axis via the PVN. Findings on the structural modification of the BNST pertain to the modulation of emotional behavior and the maladaptive response to stress. Specifically, enlargement of the BNST bears on our understanding of stress-induced hyperactivity of the HPA axis, providing an anatomical basis for dysregulated closure of this neuroendocrine loop under conditions of chronic stress (Pêgo et al., 2008).

Changes in connectivity. In those with general anxiety disorder, the amygdala areas have (a) decreased connectivity with the insula and cingulate areas that control general stimulus

salience and (b) greater connectivity with the parietal cortex and prefrontal cortex circuits that underlie executive functions (Etkin, Prater, Schatzberg, Menon, & Greicius, 2009).

Neuroscience of Unlearning Fear

Research using emerging neuroimaging techniques seek to explore a broad range of psychotherapies, and to guide interventions by specifying what brain regions may be stimulated in anxiety patients to normalize deficient neural activities (Peres & Nasello, 2008), with the ultimate goal of improving clinical decision-making and treatment (Roffman, Marci, Glick, Dougherty, & Rauch, 2005). Reviewing 21 studies using photon emission tomography, positron emission tomography, and functional magnetic resonance imaging, Peres and Nasello (2008) found that behavioral and cognitive-behavioral psychotherapies have the potential to modify dysfunctional neural circuits associated with disorders such as obsessive-compulsive disorder, major depression, social phobia, specific phobia, and post-traumatic disorder.

In an review of 14 neuroimaging studies on the effects of psychotherapy on anxiety disorders, Roffmann and colleagues (2005) found reduced abnormalities in brain regions linked to anxiety disorders, and increased activation of brain regions related to reappraisal of anxiety-provoking stimuli. In addition, van der Kolk (2006) states that changes in the brain in response to psychotherapeutic intervention appear to be unique from those of pharmacological interventions. For any given psychiatric disorder, only a partial overlap between the brain changes associated with pharmacotherapy and those associated with psychotherapy were evident (Roffman et al., 2005).

Cozolino (2010) states that, "Various psychotherapies are built in the premise that consciously experienced anxiety provides the opportunity to face and work through fears" (Cozolino, 2010). This is consistent with Yerkes Dodson Law which posits that optimal learning

occurs when there is moderate levels of anxiety present (Diamond, Campbell, Park, Halonen, & Zoladz, 2007). As mentioned previously, emotional arousal evoked by conditioned fear paradoxically promotes the subsequent extinction of that fear, thereby insuring behavioral flexibility (Mueller et al., 2008).

Fear extinction pathway. The neurobiological processes that underlie the regulation of fear and anxiety go hand in hand with the extinction of fear memories inhuman subjects (Schiller et al., 2008). During reconsolidation, stored information is rendered labile after being retrieved. Reconsolidation is an adaptive mechanism by which new information is incorporated into old memories. By introducing new information during the reconsolidation period, it may be possible to permanently change the fear memory. Schiller (2009) provides evidence in humans that old fear memories can be updated with non-fearful information provided during the reconsolidation window in humans. As a consequence, fear responses are no longer expressed (Schiller et al., 2009).

Recent studies suggest that top-down cognitive processes can attenuate the amydala response, resulting in down-regulation of fear and anxiety responses. The activation of the OMPFC is inversely related to that in the amygdala during an emotional experience. Rates of glucose metabolism in the OMPFC and amygdala are negatively correlated. Tasks requiring increased cognitive effort (e.g., appraising stimulus content for personal relatedness) that does not necessarily redirect attention away from emotional content result in attenuation of the amygdala. Human studies indicate that cognitive appraisal of visual threat activates the OMPFC and in turn attenuates activity in the amygdala. Amygdaloid activity is attenuated while the OMPFC and cingulate sulcus (ACC) are activated during a cognitive appraisal condition of aversive visual stimuli (Phan et al., 2004). Labeling the emotional content reduced activation in

the amygdala relative to a simple stimulus matching or emotional perception task. In humans, when subjects turn their attention inward toward themselves, mpfc activity is increased (Hariri, Mattay, Tessitore, Fera, & Weinberger, 2003).

At the level of the limbic system, active coping prevents the establishment of conditioned endocrine and behavioral responses. LeDoux and Gorman (2001) showed that in rats, the fear conditioned pathway responsible for initiating autonomic, endocrine, and behavioral immobilization reactions may be redirected. When given the option of physically escaping from an adverse stimulus, subjects lost their conditioning even after a conditioned fear response was well established. This work suggests that active coping diverts the flow of information from the lateral nucleus of the amygdala away from the central nucleus to the basal nucleus of the amygdala, which, in turn projects on motor circuits in the ventral striatum (LeDoux & Gorman, 2001). Van der Kolk (2006) states that:

> By engaging these alternative pathways, passive fear responding is replaced with an active coping strategy. Learning that takes place, does not occur if the rat remains passive. It requires that the rat take action. It is "learning by doing," a process in which the success in terminating the conditioned stimulus reinforces the action taken. (p. 7)

However, the process of extinguishing fear is slow. Although pathways that connect the amygdala with the cortex provide a channel of communication between cognition and emotion, these connections are not symmetrical. Projections from the cortex to the amygdala are considerably weaker than those from the amygdala to the cortex and may explain why strong emotions are difficult to deactivate (LeDoux, 1995).

HPA regulation. The dorsal mPFC attenuated the expression of CRH in the secretory region of PVN, and in turn, HPA secretory responses (Radley et al., 2008). Because mPFC

projections do not target the HPA (via the PVN) directly, intermediary forebrain regions implicated in inhibitory PVN control were explored. Anatomical tracing and selective immunotoxin-mediated ablation of anterior BNST experiments implicated BNST cell groups which project to the PVN in acute stress-induced activation of HPA output. The identification of the BNST as a mediator of HPA-inhibitory limbic influences contributes to the understanding of the integration of inhibitory controls of HPA output, adaptations of the HPA to chronic stress, and how endocrine abnormalities may contribute to stress-related psychiatric illnesses in which mPFC dysfunction is involved (Radley, Gosselink, & Sawchenko, 2009).

Statement of the Problem and Research Proposal

Two camps that have historical vested interests in fear and anxiety clinical psychology and neuroscience. Clinical psychology deals largely in examining psychopathology, which focuses on symptoms of anxiety or panic and classifying symptoms. However, the emphasis on the pathological features of fear and anxiety without an understanding of their normative states can be problematic. Van der Kolk (2006) identified lack of appreciation by the insight-oriented, main staples of psychotherapy, CBT and psychodynamic therapy, for the pre-programmed physical processes of fear and anxiety. He suggests psychotherapy may be placing biology of fear and anxiety out of its context in survival, and have instead focused primarily on the structural and chemical elements of as the main causes of psychopathology (e.g., a lack of serotonin in depressed individuals, increased dopamine in schizophrenic patients). According to Van der Kolk,

> Psychiatry and psychology may have lost sight of the forest for the trees. It is not the presence of chemicals that causes fear and anxiety, both neurochemistry and emotions are activated in order to bring about action: either to engage in physical movements to

protect, engage, or defend or displaying bodily postures denoting fear, anger, or depression that invite others to change their behavior. (p. 5)

Psychology and psychiatry focus primarily on the presence of chemical or structural brain abnormalities that produce emotional states (e.g., a lack of serotonin in depressed individuals, increased dopamine in schizophrenic patients, excess cortisol in anxiety and panic disorders). This focus presents a picture of control of these chemicals to reduce symptoms of these disorders. This suggests that the patient is a passive agent, that there is little they can do about brain abnormalities they have. It may further suggests the patient as a passive agent, predisposed to biological markers, with little control over *brain abnormalities* present since birth, and less on the effects of the environment in producing these abnormalities.

Further it impinges on one of the most important roles where psychotherapy can focus its efforts, which is to understand how environment can impact the brain. By drawing awareness to environment and the activation of these biological processes that counter the development of psychopathology. An understanding of the process of fear and anxiety, from its acquisition to expression, may be more naturalistic in that it allows consideration of the individual sensitivities and experiences of a person and in forming who they have become.

Problems with integration. Although exciting prospects exist for their synthesis, neuroscience has yet to find a comfortable place in the therapy room. Despite seemingly high interest among clinicians, digesting and integrating neuroscience in clinical practice remains a difficult task. Several reasons are enumerated, pertaining to conceptual and practical differences between neuroscience and psychology.

1. The lack of integration with adequate, neurobiological models may have contributed to a classification system in clinical psychology that was devoted largely to clustering their overt expressions.
2. The language of neuroscience may be daunting to practitioners whose training provides them with only minimal exposure to neuroscience, and what is offered to them mostly are textbooks devoted to neuroscience. Language differences aside, other problems may be at hand, possibly owing to the historical biases of these separate fields that study the same constructs.

These disparities may pose continued challenges to the symbiosis between the two fields, and may have wider implications as to how neuroscience is being understood and implemented in psychology. The gap between how clinical psychology and neuroscience understand and mechanisms of fear and anxiety have possibly led to some consequences that may affect how ideas from one field are being interpreted and used in another. Van der Kolk (2006) argued for greater inclusion of the normative framework in considering pathological models (van der Kolk, 2006).

Research proposal. Although these ideas from neuroscience hold direct implications for psychotherapy, how can the neuroscience be better presented so it can be integrated meaningfully in clinical practice? This project seeks to address the problem of how the neuroscience information is disseminated to clinicians and their patients. Keeping in mind the historical biases of both neuroscience and clinical psychology, this endeavor seeks to address the problem of integration by merging the translational gap between basic neuroscience research and clinical practice. We propose the construction of a concise reference manual on the neuroscience

of fear and anxiety that is both data-driven and accounts for the practical and conceptual issues mentioned above.

This project may yield certain benefits.

1. A concise manual may offer explanations that validate psychotherapeutic technique employed by therapists of what they are targeting in the brain. This may help therapists transcend theoretical orientation and establish a common language focused on targeting brain structures.
2. A concise manual may serve to bridge linguistic barriers, and may offer explanations that validate psychotherapeutic technique employed by therapists by revealing what they are targeting in the brain.
3. This framework can be helpful in explaining to our clients tell what is normal vs. abnormal, as well as elucidate the processes in which their pathological symptoms emerge. Patients may benefit from an understanding of the brain basis of anxiety and fear to give another explanation of their disability, one that is less about inadequacy and self-blame, and more about common experience. Further, they would gain knowledge about the experience- and social-dependence on neuroplasticity of the brain. From a cultural standpoint, societies utilize different therapeutic methods to help people cope with the anxieties of life. An accessible, neuroscience-based explanation as to how these methods work may provide a unified way of describing and treating these complex emotions.
4. How this gap is addressed may be pertinent to the goal of retooling psychologists' understanding of neuroscience from simply focusing on psychopathology to a more

comprehensive view: that is, the development of disorders from adaptive neurobiological processes to the protraction of these processes leading disorders of anxiety and fear.

Chapter 2. Methodology

Neuroanatomical studies on brain mechanisms involved in fear and anxiety have revealed differential pathways that are not commonly known in the field. In their pathologies, consistent abnormalities in the limbic areas, HPA axis, and cortical regions have been documented. Of note, these brain regions are interconnected to one another suggesting the disorders of fear and anxiety involve dysfunction within HPA. Therefore, the purpose of this investigation were twofold: 1) to look at the functional circuitry of fear and anxiety and 2) factors that lead to impairment in this circuitry. To accomplish this, a qualitative inquiry was conducted pertaining to the functional development and structural/systemic dysfunction of this circuitry in view of behavioral characteristics of fear and anxiety. Detailed information with reference to areas of research, databases used along with dates of publication, keywords searched, inclusion/exclusion criteria, and the primary methods of research used in the present journal article are discussed below.

Databases and Dates of Publication

The following databases were used to locate journal articles and textbooks relating to the stated areas of research: PubMed (mid 1950s-2015), Pubget (up to 2015), Medline (mid-1950s-2015), PsychInfo (1887-2015), Google Scholar (up to 2015), ScienceDirect (1823-2010), Scopus (1960-2015), and Wiley Interscience (1799-2015). Textbooks on human/primate evolution, functional brain development, neural circuitry, and neural dysfunction were also examined.

Key Search Words

The following key words were used: amygdala, anterior cingulate, anxiety and anxiety disorders, bed nucleus of the stria terminalis, brainstem, cerebral cortex, cingulate, circuitry, correlates, corticosterone, cortisol, damage, development, differential involvement, dorsalmedial

prefrontal cortex, dysfunction, emotional regulation, epigenetic, evolution, extinction, fear-conditioning, functions, glucocorticoids, hippocampus, hypothalamic-pituitary-adrenal axis, inferior parietal lobe, insula, learning, lesion, limbic region, memory, neurochemistry, neuroplasticity, orbital medial prefrontal cortex, panic and panic disorders, phylogeny, primates, sensory cortex, sensory association cortex, stress, and volumetric studies.

Inclusion/Exclusion Criteria of Studies

Scholarly journals and publications were investigated. Literature including rodent, primate, and human subjects were reviewed pertaining to functional brain development and structural/systemic brain dysfunction. Subjects in the reviewed literature ranged in age from gestation to adulthood and were predominantly from animal and human populations.

Consultation

Experts were consulted on topics related to the evolution of fear and anxiety mechanisms and the state of our current understanding of them. Email correspondence with Michael Davis and David Walker were instrumental clarification on topics related to the amygdala and bed nucleus of the stria terminalis. George Alheid and Joel Price were consulted on the evolution of the extended amygdala.

Primary Methods of Research

The literature included studies that used three primary methods to examine the functional development of brain structures and circuitry extending from the brainstem, the limbic system, and cortical regions. These methods included electrophysiological stimulation techniques, imaging techniques, and microscopy with staining, and both anterograde and retrograde tracing.

Structural and functional brain imaging techniques detect the location and the neural circuits involved through measuring the change in blood flow in the brain. This measurement

often allows for the association of neural activity with specific mental functions. Microscopy allows for the observation of biological tissues, structures, and neural connectivity. This is often paired with a variety of staining techniques that concentrate in different parts of the cells and tissues, further highlighting specific areas for observation.

Mapping was conducted through retro- and anterograde tracing methods. Anterograde tracing is a method used to chemically trace axonal projections from their source (the cell body) to their point of termination (the synapse). In contrast, retrograde tracing is used to trace axonal projections from the point of termination to the source. Much of what is currently known about the connectivity of different brain regions was achieved through anterograde and retrograde tracing techniques. Both of these methods allow the detailed descriptions of neuronal projections from a single population of neurons to their various targets throughout the nervous system. These techniques allow the mapping of connections between neurons in a particular structure and the target neurons in the brain.

Further, examination of dysfunctional brain regions was accomplished through both intentional lesions to specific brain regions in animal models, and measurement of subsequent impairments in ability-specific tasks. With regard to examination of damage to regions within this circuitry, lesions were mechanically or chemically created in animal subjects. Furthermore, ability-specific task-performance was also used to determine the quality and severity of impairment resulting from the lesion.

Analysis of Data and Integration of Findings

The initial focus of this project was to uncover and confirm a possible dichotomy in the way fear and anxiety are processed. This idea for this project was spawned by my advisor, who asked me to "look into a structure called the 'bed nucleus of the stria terminalis,' and find out

everything about it." The dichotomy was confirmed through the work of Michael Davis and his colleagues, as well as other investigators involvment the BNST in while sparing the amygdala. This led us to want explore the of the amygdala and BNST in relation to anxiety and panic disorders to attempt to differentiate possible impairments or volumetric differences between these two structures. Owing to the paucity of studies on the BNST and specific anxiety disorders, in contrast to an abundance of studies showing amygdala enlargement in an array of anxiety and panic disorders, it was concluded that were not able to continue this particular endeavour.

We decided to shift our focus onto examining other aspects of the dichotomy between the BNST and CeA, paying particular attention to connectivity. Examination into associated brainstem, limbic, and neocortical structures was conducted to determine their roles in supporting or regulating anxiety and fear responses via the BNST and CeA. Studies by Dong and Swanson, detailing the extensive connectivity of the BNST to the HPA axis, suggested its role as the prime intermediate structure, through which both limbic and neocortical information is funneled, in modulating the HPA axis and the production of cortisol.

In addition, focus on connectivity issues revealed that the BNST and CeA were influenced by different memory systems (the hippocampus vs. the LA+lCeA circuit, respectively). The idea that conditioned fear memory lies within the amygdala itself challenges existing notions in clinical psychology that the hippocampus is the primary informer and regulator of strong emotional responses from amygdala, and provides a possible, new narrative of the involvement of unconscious memory in fear vs. conscious memory in anxiety.

Recent literature in neuroscience has provided greater clarity and enhanced specificity in detailing structure-to-function and pathways involved in fear and anxiety. Emerging out of this

investigation, it became evident the neuroscience involved in fear and anxiety was more complex than what is commonly known in clinical psychology. Integration of the above findings contributes to an updated model of the neuroscience of fear and anxiety that will best be presented in a concise manual that is accessible to mental health clinicians.

Chapter 3. The Neuroscience Of Fear Vs. Anxiety: A Primer

With myriad expressions from panic, to lingering feelings of apprehension and tension, to intense flashbacks experienced in post-traumatic stress, fear and anxiety are an undeniable aspect of most living organisms. While we know what they feel and look like in our everyday lives, our common tendency is to dwell on the burdens they create and aspire to rid our lives of them entirely. But rather than take this view, we might want to look at why these emotions evolved to take a purposeful place in our lives.

Since the mid-1990s, a confluence of studies in neuroscience and comparative neuroanatomy has advanced our understanding of how fear and anxiety work in the brain. From this research, clues emerged as to how these emotions evolved as defenses that have been advantageous to the survival of many species. And though they evolved to serve critically important purposes, we also have learned how fear and anxiety can shape into forms that no longer serve us, instead interfering with how we live our lives.

But how might an exploration of the neuroscience underlying these emotional phenomena help us? One important reason is to cultivate an appreciation for how the interactions between biology and environment leave indelible imprints on our brains. Additionally, an exploration of this aspect of the brain helps us to understand how fear and anxiety allow us to adapt to challenges, as well as document how what we take and make of our world affect our brains. Finally, and perhaps most importantly, this investigation may help us to become more aware of our true place between extremes on opposite sides of a spectrum: on one end, the unrealistic perception of fearlessness, and on the other, the state of being endlessly consumed by our fears.

Stress, Fear, and Anxiety: An Adaptive Relationship

From the earliest invertebrates to humans, living organisms have strived to maintain *homeostasis,* a complex and dynamic balance of one's internal environment. This balance is challenged constantly by external and internal demands, creating the *stress*, or the non-specific response to any demand for change, we feel in our bodies (Habib, Gold, & Chrousos, 2001; Selye, 1949). To return to a state of homeostasis, the ability of an organism to adapt to stress is vital to preserve its viability (Gunnar & Quevedo, 2007; McEwen, 1999). Adaptation, or the stress response, allows the organism to maintain stability through change (Sterling & Eyer, 1988).

Fear and anxiety are stress responses to external or internal threat that allow an organism to return to a state of homeostasis (see Figure 5). They share a common goal of seeking to change the condition that a threat presents, allowing the body to recuperate and return to homeostasis.

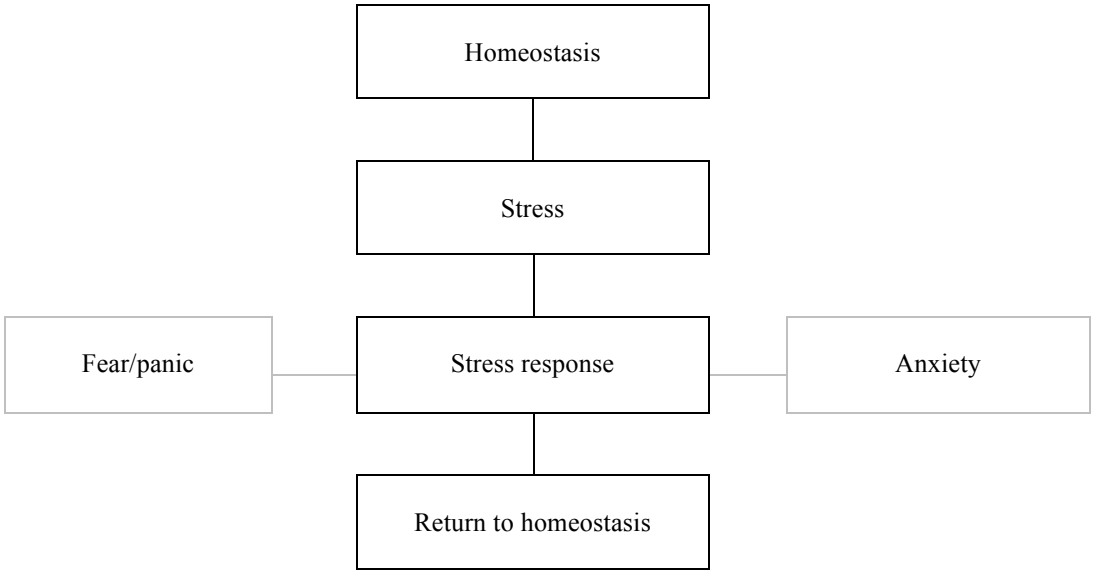

Figure 5. Fear and anxiety as stress responses.

While intricately related and often used interchangeably, fear and anxiety are easily felt, but not so easily understood, defined, nor teased apart. In part, this may be because their multitude expressions overlap widely and simultaneously engage our emotions, thoughts, and behaviors. We may experience a range of distress and alarm. Our attention may be deeply focused on a threat and we may also associate its surrounding circumstances with harm, forming memories to help us prevent future occurrences of danger (LeDoux, 2012). We may display fear, anger, or depression, all of which invite others to help us manage our behavior. And ultimately, we may be motivated to take action: to escape, to defend ourselves by engaging a threat, or by succumbing to it altogether. (van der Kolk, 2006).

We may also be bewildered by what triggers them. Threats can be very specific. Or they can be diffuse cues that we associated with a previous danger. They can vary along dimensions of their proximity to us, as well as how long they last. Threats can also be representations of danger that exist in our memories, both those that we can recall easily and those out of our immediate awareness but nevertheless, have significant impacts on our lives. While it may be impossible to list the combinations origin, proximity, and duration, these different characteristics of threat can trigger either fear or anxiety and have differential impacts on how we attend to, how we remember and interpret, and how we deal with threats that present themselves (see Table 7).

Table 7

Fear versus Anxiety

	Fear (or Panic)	Anxiety
Triggers	Threats perceived as life-threatening (Davis, 1997; Barlow, Brown, & Craske, 1994).	Potential danger, distal, and contextual or symbolic threats.
Temporal Profile	Short in duration, lasting milliseconds to seconds, and resolves upon the termination of a threat (Pego et al., 2010).	Long-term state (Rennie, 1948), lasting from minutes to hours.

(continued)

	Fear (or Panic)	Anxiety
Emotions	An emotional alarm characterized by intense apprehension, terror, and feelings of impending doom	Worry, apprehensive expectation, tension, and feelings of unpredictability and uncontrollability.
Behaviors	A fight response taken to alter the impact of a threat, a flight response representing escape or changing course, or a freezing/immobilization response.	Risk assessment and avoidance.
Learning	Previous or innate learning that specific contexts predict imminent harm (Grillon, 2008).	Previous learning that certain contexts surrounding a specific threat may also be associated with adversity. These associations have been generalized (Grillon, 2007).
Attention	Attention is drawn toward a threat (attentional bias) and inhibits competing responses, making it more difficult to contextualize a situation.	Attention is drawn not only to the threat, but a number of associated stimuli in the environment may represent danger.
Awareness	Fear is believed to function without conscious awareness. In fear, conscious, cognitive appraisal of the threat is absent.	Conscious cognitive appraisal of a threat is prerequisite of anxiety (Lazarus, 1991). The thought process involved in anxiety is conscious.
Memory	Implicit/unconscious memory.	Explicit/conscious memory.
Purpose	Addresses the immediate physical survival of an organism. Fear is adaptive when one is confronted with a real, actual threat (Barlow, Brown, & Craske, 1994). However, fear responses become maladaptive when they last longer than the presence of a threat, or when it becomes activated when the threat is not present.	Prepares an organism for a second stressor or a chronic stressor (Woody & Szechtman, 2011)

Immediate and Preparatory Response Systems

When we are faced with a threat, a cascade of electrical, hormonal, and neuro-immune activity takes place within the brain, all aimed at preparing us to adapt to or reduce its impact. Adapting to stress involves activation of biological systems that detect not only environmental challenges, but also opportunities to bring closure to a situation and achieve internal physiological adjustment (LeDoux, 2012).

As defensive responses, fear and anxiety are organized hierarchically along a spectrum of safety to dangerousness. In an environment safe from dangers, a minimal threat level is

supported by neural mechanisms that facilitate responses for social interactions. On the other hand, an organism attends more keenly to the environment because of novelty or potential threat. Fear occurs when danger is imminent, mobilizing fight-or-flight responses, or triggering immobilization or freezing when fight-or-flight responses are not an option (Porges, 2001).

By viewing these differences of why they are employed, we get a picture that these adaptive responses evolved to address imminent and preparatory defensive needs of an organism. Within all complex animals, systems in the brain and body evolved to execute defensive responses to help maintain internal balance.

Autonomic nervous system. The autonomic nervous system (ANS) regulates processes that allow us to maintain homeostasis. It consists of a series of hierarchical levels encompassing neocortical, limbic, and brainstem structures, with the higher levels being responsible for more widespread and general functions. These functions—such as heart rate, digestion, smooth muscle function, glandular activity, and the control of stress hormones—do not require consciousness. The ANS is comprised of systems involved in adaptation to stressors that pose an immediate threat, potential threat, as well as mechanisms that calm us after a threat is over.

Sympathetic nervous system. When confronted with immediate danger, we experience an initial surge of alarm and arousal and are flooded with fear. This state represents the sympathetic nervous system, which supports a number of biological systems that are activated to mobilize energy, such as increasing heart and lung functions to facilitate delivery of oxygen and glucose to tissue. Energy storage is halted by suppressing digestion, growth, reproduction, inflammatory, and immune responses.

These processes work to support fight-flight-freeze responses, act quickly (milliseconds to seconds), and persist until the acute emergency has been survived. The sympathetic nervous

system is composed of fibers from thoracic and upper lumbar levels of the spinal cord that connect directly to internal organs in the main cavities of the body and blood vessels of the limbs, or return to spinal nerves.

Hypothalamic-pituitary-adrenal axis. The hypothalamic-pituitary-adrenal (HPA) axis refers to a complex set of interactions between the hypothalamus, pituitary glands in the brain, and the adrenal glands perched on top of the kidneys. It is part of a system that guides autonomic and energy homeostasis and can be found in the earliest vertebrates (Dong & Swanson, 2004a; Denver, 2009).

In the stress response, the HPA axis is primarily involved the production of the stress hormone *cortisol* in humans. These hormones affect the storage and expenditure of energy during stress (Choi, Evanson, et al., 2007; Dong & Swanson, 2004b). After the initial surge of sympathetic activity subsides, the HPA axis prepares the organism for subsequent danger: a process that acts slowly from minutes to hours in preparation for another threat to materialize. But because not all stressors present as life-threatening emergencies, the HPA axis can also be triggered without activating the sympathetic nervous system (Woody, 2011).

Parasympathetic nervous system. The parasympathetic nervous system is made up of fibers that issue from the brainstem and sacral part of the spinal cord and is concerned with functions, such as digestion, metabolism, excretion, and lowering of heart rate (Davis, 1997). When we respond adaptively to a threat by engaging with or avoiding it, conditions change in the environment, and the body respond in kind. The parasympathetic nervous system helps to calm us after an emergency is over. When a threat subsides, the parasympathetic nervous system is activated to inhibit sympathetic and HPA effects on tissue and organs, allowing the body to recuperate and reinstate homeostasis (Porges, 2001).

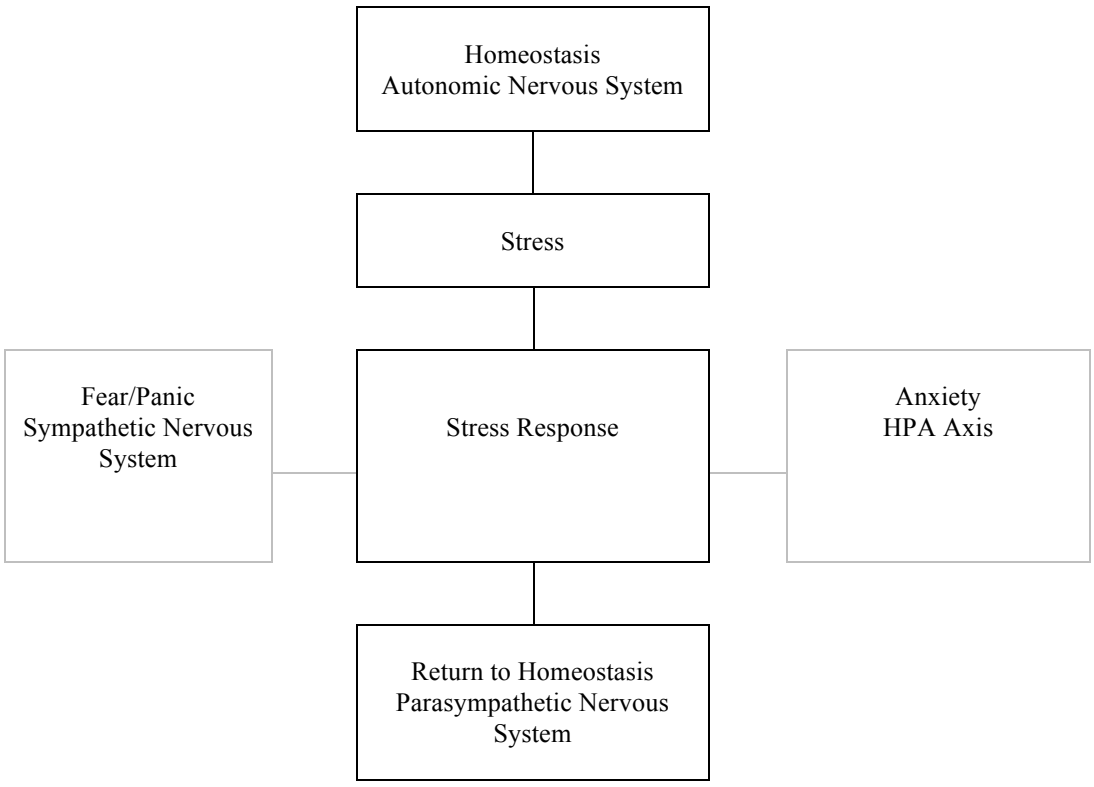

Figure 6. Sympathetic and HPA axis activation in the stress response.

Neuroanatomy of Fear and Anxiety

From the moment we are born, the brain circuitry involved in fear and anxiety are online. Evolving from what originated as an ancient system dedicated to physical survival, these circuits are part of an inherited legacy present in all complex animals (invertebrates and vertebrates), having been shaped over billions of years of evolution and through billions of brains (LeDoux, 2012). Over the evolution from reptiles to humans, three layers of the brain evolved in part to address threats to survival. From this common ancestry, key defensive functions and associated brain structures in lower animals expanded to newer areas in in higher animals.

The *reptilian brain* represents the innermost and the most primitive layer of the triune brain that facilitates motor responses to escape imminent physical threat in the form of predators. The *limbic system* is the middle layer of the triune brain that gained prominence in the brains of

mammals. As adaptivity depended on the ability to detect a threat rapidly, alert the organism, and appraise life-threatening events (LeDoux, 1996), limbic structures facilitated emotional to motor responses to increase physical and temporal space between the self and the source of the threat across environmental landscapes. Limbic structures also helped to preserve this space between oneself and a threat through continual learning and monitoring of the environment.

The *neocortex* is the outermost layer of the triune brain that assumed prominence in primates and reached its peak size and evolution in the human brain. Abstract thought, imagination, and development of language are believed to have emerged with the rise of the neocortex. Its size in mammals correlates positively with social group size and is believed to have evolved in part to increase the chances of survival in social landscapes by navigate the cognitive demands of competitive and cooperative relationships (Barton & Aggleton, 2000). The ability to recognize interpersonal threats suggests that fear and anxiety may have developed to appraise dominant or submissive group members (Öhman & Mineka, 2001).

On the other hand, the evolution of culture and social norms may have served to attenuate fear and anxiety by enhancing the control and predictability of environmental and social landscapes. Beyond the advent of tools and weapons by humans that helped to procure resources and defend against physical threat, behavioral scripts, language, and communal activities fostered cooperation. Art and storytelling served to pass on knowledge, thereby enhancing the predictability of the world for generations to come (Bronowski, 1973).

With the addition of layers and increased neural complexity, the behavioral and affective repertoire of higher animals became enriched (Porges, 2007). In the mammalian brain, phylogenetically newer layers exercised greater control over/inhibit more primitive layers (Jackson, 1958; Porges, 2007). Among other functions, the interaction between these layers

helped coordinate responses of approach or avoidance depending on the nature of a presenting threat, facilitated learning to enhance predictability and control over the environment, and provided awareness of oneself through space and time to keep threats at bay (Öhman & Mineka, 2001). Despite this expansion, core components of these circuits were kept (or conserved) if they proved useful, as reflected in some neuroanatomical similarities among reptiles, lower mammals, primates, and humans (LeDoux, 2012). These anatomical artifacts reflect the importance of retaining this circuitry and lasting functions that are built for survival.

Reptilian brain structures. Within the reptilian brain lies a collection of structures known as the brainstem that serves as a relay center of sensory and motor information between the brain and the spinal cord. The role of the brainstem is complex, controlling basic functions such as heart rate, breathing, body temperature, circulation, and balance. Brainstem structures respond to immediate threat by activating the sympathetic nervous system that produces fight, flight, and freezing responses and the mechanisms that support them. These include:

- Production of the stress hormone norepinephrine in the locus coeruleus
- A surge of arousal and increased vigilance
- Startle and facial expressions of fear
- Impaired social interactions
- Decreased sensitivity to pain
- Panting and respiratory distress to increase oxygen supply (Davis, 1997, Davis, 1998; LeDoux, 1996; Ohman & Mineka, 2001; Porges 2001).

Limbic structures. The limbic system is believed to be the center of emotional processing and is also the seat of unconscious values that exert a strong influence on behavior. Limbic structures attach emotional salience to incoming sensory information, and facilitate

perception and memory for emotionally meaningful material. In fear and anxiety, they are critical for motivation and coordination of approach-or-avoid responses (Phan, Wager, Taylor, & Liberzon, 2004).

The thalamus. The thalamus receives information from nearly every sensory organ in the body. This information is relayed to the somatosensory association cortex in the parietal lobe of the brain that integrates the sights, sounds, smells, and tactile sensations of a threat. This allows us to construct an understanding of the object being felt and helps in planning movement (van der Kolk, 2006).

The amygdala. The amygdala is almond-shaped structure is involved in both reward- and stress-related emotions that comes online immediately before birth (Cozolino, 2006). In humans, the activation of the amygdala has been observed in the perception and processing of direct and indirect threats such as fearful faces, threats in complex visual situations (Ohnman & Mineka, 2001), outgroup versus ingroup faces, and threatening words and vocalizations (Adolphs & Tranel, 1999). In anxiety and other psychiatric disorders where chronic stress is a risk factor, the amygdala is known to be enlarged owing to over-activity.

The amygdala is highly connected to many parts of the brain, highlighting its widespread influence. Three of its approximately 15 known regions have been associated with specific roles in fear and anxiety:

- The *basolateral amygdala (BLA)* attaches an emotional value to incoming or perceived stimuli. In both fear and anxiety, the BLA assesses the salience of a threat and determines whether a fear or anxiety response is appropriate to a situation.
- The *lateral nucleus of the amygdala* has been implicated in consolidation of conditioned fear memories or implicit memories. These memories are difficult to

access consciously and activate reflexive responses (LeDoux, 1995; Schafe & LeDoux, 2000).

- The *central nucleus of the amygdala (CeA)* plays a key role in executing a fear response to a specific threat (Davis, 1997). The CeA has been linked to the expression of fear, and not as much to anxiety, given its robust connections to brainstem areas that control rapid sympathetic effects including fight, flight, and freezing. Its limited connectivity to the HPA axis gives it minimal control of neuroendocrine responses to stress (Choi, Evanson, et al., 2007; Graeff, 2007).

The bed nucleus of the stria terminalis. The bed nucleus of the stria terminalis (BNST) is a cell mass in the basal or non-cortical division of the brain. Its neurons are among the earliest formed in the cerebral hemispheres (Dong, Petrovich, Watts, & Swanson, 2001). The BNST lies close to the amygdala, but on the opposite side of the stria terminalis (Fudge & Haber, 2001).

Like the amygdala, the BNST is highly connected to different parts of the brain, responds to both stress- and reward-related stimuli, and links to both the brainstem and HPA axis (Fudge & Haber, 2001; Shin, Geerling, & Loewy, 2008). It shares a particularly close resemblance to the CeA in terms of the shape of its cells and neurotransmitter content. Unlike the CeA, however, the BNST is strongly implicated in stress responses triggered by diffuse or contextual threat stimuli. Further, its effects appear to last longer in duration than those produced by the CeA. These characteristics suggest that the role of the BNST is more akin to anxiety, whereas the CeA's role is more similar to fear (Casada & Dafny, 2010; Davis et al., 1997; Pêgo et al., 2008).

Its position allows it to relay both limbic and neocortical information to the HPA axis to modulate neuroendocrine responses (Choi, Furay, et al., 2007; Radley, Gosselink, & Sawchenko, 2009).. The dorsalmedial division of the BNST generates the densest known inputs to the HPA

axis of any part of the cerebral hemispheres (Dong & Swanson, 2005; Pêgo, Sousa, Almeida, & Sousa, 2009). Further, other BNST regions are known to both excite as well as inhibit the HPA axis (Choi, Furay, et al., 2007).

Although the BNST and HPA axis are susceptible to chronic stress, this is a not one-dimensional relationship. Often, if we are exposed to the same stressor multiple times, we habituate to it, making it predictable and easier to tolerate which eases our anxiety (Pego, 2009; Woody & Szechtman, 2011). Exposure to these invariant stressors decreases the size of the BNST (Pego et al., 2008), which in turn produces rapid and enduring depression of HPA responses (Tartar, King, & Devine, 2006). In contrast, chronic, unpredictable stress can increase our sensitivity to subsequent stressors, resulting enlargement of the BNST owing to its over-activation and prolonged HPA activation (Pego et al., 2008; Pego 2010).

The hypothalamus. Located at the base of the brain, the hypothalamus is a production center for hormones that control various organs in the autonomic nervous system. In the stress response, the paraventricular nucleus (PVN) of the hypothalamus acts as the gateway to the HPA axis. The hypothalamus connects to and influences the pituitary gland, which in turn influences the adrenal gland in the production of the stress hormone, cortisol.

The hippocampus. The hippocampus plays a central role in the learning and memory. In adapting to a threat, the hippocampus helps to provide information of past threats to help guide behavior in current threatening situations (Barton & Aggleton, 2000; Walker, Toufexis, & Davis, 2003). It may also be involved in probing for possible danger and creating mental scenarios in which vague signs materialize as real threat to facilitate predictions about upcoming events (Woody & Szechtman, 2011).

The hippocampus is rich with receptors for stress hormones that modulate the strength of declarative memories (LeDoux & Phelps, 2008; Woody & Szechtman, 2011). Its close proximity and dense ties to the amygdala make the hippocampus susceptible to the influence of strong emotional responses.

In intense fear reactions, formation of conscious memories is impaired. The ability to form unconscious, fear-conditioned memories remains intact, however, because these memories are housed within the amygdala itself (LeDoux & Phelps, 2011; Penzo, Robert, & Li, 2014). In a number of psychiatric disorders, atrophy of the hippocampus has been observed, highlighting its vulnerability to prolonged stress responses.

The insula. The insula is a limbic structure believed to process emotionally relevant information between somatic internal feelings and external cues to guide behavioral responses (Phan, Wager, Taylor, & Liberzon, 2004). In fear and anxiety, the insula serves as an alarm center for internally sensed dangers to changes in the environment. The insula receives integrated sensory information from regions of the thalamus and the somatosensory cortex.

Through widespread, reciprocal connections the insula relays this fluid information about the environment to the amygdala (and in particular, to the CeA) where appropriate responses to danger are determined (Phan et al., 2004). The insula also works in tandem with the BNST to track threat proximity and maintain hypervigilance, a key symptom underlying many anxiety disorders, in highly anxious people (Somerville, Whalen, & Kelley, 2010; Alvarez, Chen, Bodurka, Kaplan, & Grillon, 2011).

The anterior cingulate. The anterior cingulate cortex (ACC) is a central station for processing cognitive, emotional, and behavioral information, assigning control between neocortical, limbic, and brainstem areas (Fuchs & Flügge, 2003; Phan et al., 2004). It is part of a

system that orchestrates the autonomic, neuroendocrine, and behavioral expression of emotion (van der Kolk, 2006). Its involvement is critical in maintaining emotional stability (Phan et al., 2004).

The ACC is constantly influenced by fluid threat information from incoming sensory information as well as feedback from defensive responses that seek to change conditions in the environment (Fuchs & Flügge, 2003). In responding to threat, the ACC is involved in a sequence of actions that include response selection, determining reaction speed and producing gut reactions (Fuchs & Flügge, 2003; Cozolino, 2010). Along with higher cortical centers, it is also involved evaluating whether a response to a situation is correct or not (Banich, 2009).

The neocortex. The neocortex is the rational or thinking brain that is considered to be flexible and possesses almost infinite learning abilities. Structures of the neocortex are involved in managing cognitive processes that influence sensory perception, guides behavioral responses and help to regulate strong emotions. When fear and/or anxiety are activated, prefrontal regions of the neocortex work with key limbic areas to inhibit strong emotions.

The orbitalmedial prefrontal cortex. The orbitomedial prefrontal cortex (OMPFC) is a prefrontal area that evolves during childhood (Cozolino, 2010). The OMPFC prevents the generalization of fearful behavior by attenuating sympathetic and hormonal responses to stress (van der Kolk, 2006) through the inhibition of subcortical limbic structures. The OMPFC plays a role in the inhibition of fear responses generated by the amygdala (Phan et al., 2004; Milad, Vidal-Gonzalez, & Quirk, 2004). In addition, it is also involved in reductions in anxiety by regulating HPA activity via the BNST (Radley et al., 2009).

The OMPFC is activated via increased effort on tasks, such as cognitive appraisal of a threat or labeling emotions, that do not redirect attention away our emotions (Phan et al., 2004).

Under the right level of emotional arousal, and OMPFC involvement helps to strengthen memories for fears that we have unlearned and promote behavioral flexibility (Mueller, Porter, & Quirk, 2008). These inhibitory processes are slow, however. Because projections from the cortex to the amygdala are considerably weaker than those from the amygdala to the cortex, strong emotions are difficult to deactivate (LeDoux, 1995).

For better or worse, however, inhibitory functions of the OMPFC can be overridden easily when fear takes over. The OMPFC, along with the hippocampus, is also involved in the spontaneous recovery of previously extinguished fear memory (Milad et al., 2007). In severe anxiety disorders, such as PTSD, and certain such panic disorders, the OMPFC is known to show morphological and functional abnormalities, suggesting that extinction circuits are compromised (Quirk, Garcia, & González-Lima, 2006; Shin Rauch Pitman, 2006).

The dorsolateral prefrontal cortex. The dorsolateral prefrontal cortex (DLPFC) is involved with the management of a number of cognitive processes including directing attention, organizing memory and integration of senses and temporal experience and motor sequences to guide behavior (Cozolino, 2010). Reasoning abilities improved strategizing in threatening situations to guide and assess decisions whether to approach or avoid. One hypothesis suggests that the DLPFC creates an appropriate attentional set of rules to accomplish a goal and selects the representation that will fulfill the goal. The ACC is responsible for response selection and evaluates the response, deciding whether one was correct or incorrect. Activity increases in the ACC when the probability of an error is higher. If the DLPFC imposes a great deal of control on the response, the ACC will require less activity (Banich, 2009).

Neurochemistry of Fear and Anxiety

Neurochemicals include neurotransmitters, hormones, and peptides that help to facilitate communication between neurons. In the face of threat, they facilitate behavioral and neuroendocrine effects seen in fear and anxiety (Davis, 1998; Muller et al., 2003; Sajdyk et al., 1999; Szechtman & Woody, 2004). These chemicals potentiate brain mechanisms involved in heart rate, blood pressure, respiration, and gastrointestinal responses. Behaviorally, we see increased motor activity in a familiar environment, and decreased motor activity in unfamiliar environment. (Woody & Szechtman, 2011).

Norepinephrine. Norepinephrine is a stress hormone and neurotransmitter produced in the brainstem. Its release increases sympathetic activity while inhibiting parasympathetic activity (Ramos, 2007). It supports the fight-or-flight response by increasing heart rate, triggering the release of glucose from energy stores, increasing blood flow to skeletal muscle, and increasing the brain's oxygen supply. Emotionally, it increases feelings of fear and anxiety by acting on the limbic system. Norepinepherine alters cognitive functions by shifting one's focus towards a potential threat. It also heightens vigilance and detection and analysis of threat by optimizing scanning and sampling of the environment (Woody, 2011). Norepinephrine can increase working memory, but an excess may decrease working memory (Ramos, 2007).

Corticotropin-releasing hormone (CRH). CRH is a peptide produced in the brain within the paraventricular nucleus of the hypothalamus. CRH innervates the brain and spine during times of stress. In intense stress, norepinephrine stimulates CRH secretion from the hypothalamus (Ramos, 2007). It acts on limbic system, which induces ACTH release from the anterior pituitary and subsequent cortisol release in the adrenal glands (Ramos, 2007). CRH also feeds back to modulate the production of norepinephrine and cortisol (Benarroch, 2009).

Glucocorticoids. Glucocorticoids (a.k.a. cortisol in humans and corticosterone in rats) are produced in the adrenal glands in the kidneys as part of the HPA axis (Dunn, 1987). In the stress response, glucocorticoids target organ systems that will help an organism address immediate and diffuse or distal stressors (Woody, 2011). Glucocorticoids support the immediate needs by enhance energy availability; that is, by increasing circulating glucose (the fuel needed in cells) and inhibiting glucose storage (Sapolsky et al., 2000).

Glucocorticoids also prime mechanisms that help an organism adapt to a subsequent stressor and/or to a chronic stressor by potentiating sympathetic effects on the cardiovascular system without producing an actual sympathetic activation in case potential danger turns into an actual threat. These hormones exert their effects for prolonged periods and involve changes in gene transcription (Sapolsky et al., 2000; Woody, 2011). In the recovery stage, glucocorticoids exert negative feedback on the HPA axis, thereby limiting its activation (Choi, Evanson, et al., 2007; Choi, Furay, et al., 2007; Choi et al., 2008).

Fear and Anxiety Circuitry

The pathways run through an interactive zone between cognition and emotion, and are the roadways along which electrical and chemical signals travel. Goal-directed behavior, motivation, and self-control involved in fear, anxiety, and other emotional experiences, are born from the interplay between limbic and neocortical areas (Fuchs & Flügge, 2003).

While genetics may exert a strong influence on the development of these circuits, our environments matter deeply in shaping how these circuits develop, particularly during periods of rapid brain development in early childhood (Gunnar & Quevedo, 2007). Nurturing environments promote adaptive coping. Here, fear and anxiety pathways are triggered when needed and shut off quickly once an emergency is over.

Fear pathway: Activating the brainstem. Some emotions are generated from our sensory perceptions of the environment. In fear, a threat that is deemed to be immediate is processed quickly and unconsciously. This process only involves the subcortical part of the brain and is believed to work without conscious experience of the stimulus, overriding higher cortical processes. It is regarded as a more primitive mechanism of defense, evolving from lesser-developed animals that have not evolved a more complex part of the brain (see Figure 7).

1. In the processing of fear, signals from our sensory organs are collected in the thalamus (LeDoux, 1996; Davis, 1997). These integrated signals converge in the basolateral amygdala, where the seriousness of a threat is determined, after accessing the lateral amygdala where conditioned fear memories are stored. In this appraisal phase, dense neural ties and close proximity between regions of the amygdala allow for rapid and efficient transmission of threat-related information (Barton & Aggleton, 2000; Pego et al., 2010).
2. When the threat is determined to be immediate, these signals are then sent to CeA, where determinations of appropriate response are made (Davis, 2001).
3. Signals are relayed to brainstem and hypothalamic targets (Davis, 2001). Because the CeA has a profound influence on the brainstem, and limited influence on hypothalamic targets, greater sympathetic activation is observed (Choi, 2007; Graeff, 2007).
4. The activation of the sympathetic nervous system (via the brainstem) results in rapid, automatic responses to danger and produces fear behaviors fight, fight, or freezing responses (Davis, 1997). These responses are processed very quickly, and are generally short lived.

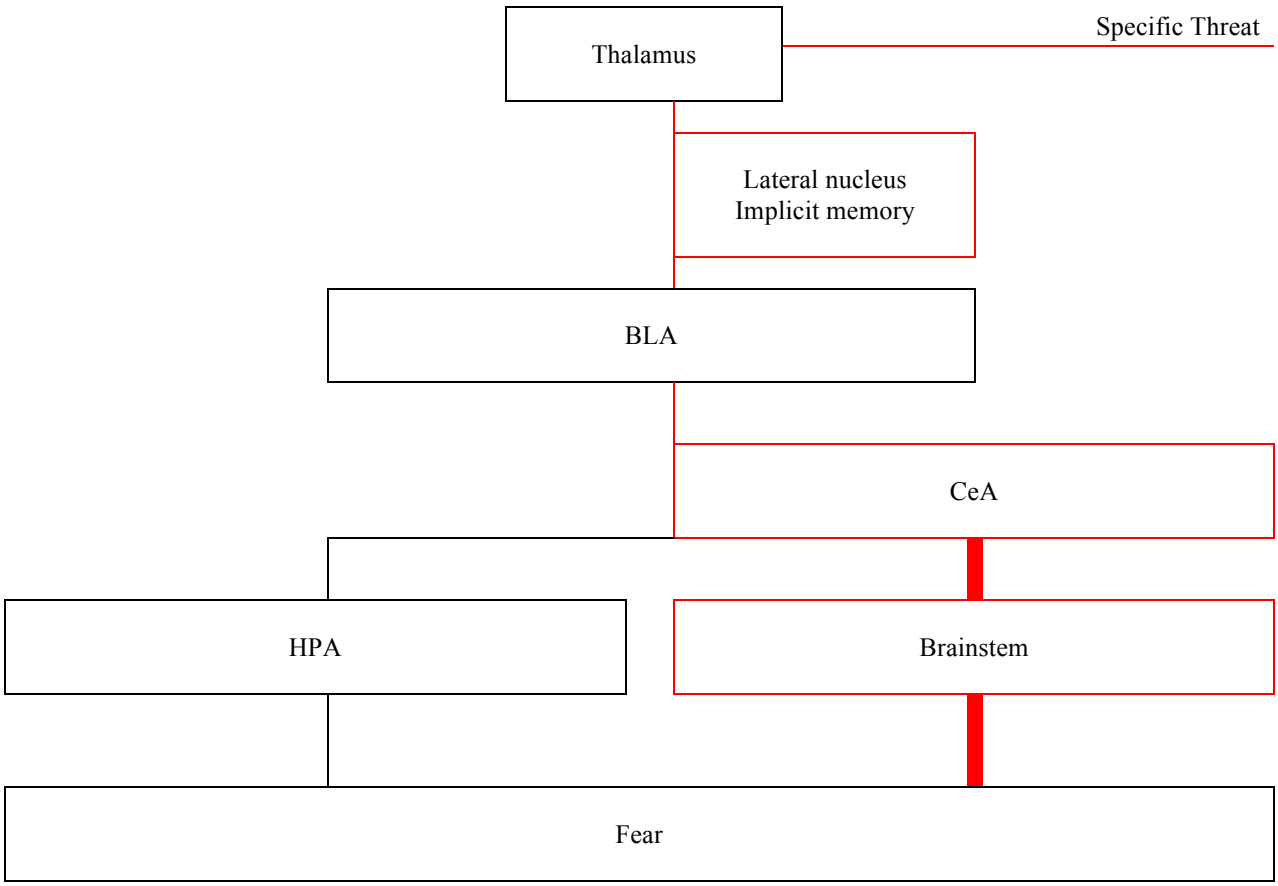

Figure 7. Fear pathway stage 1.

Anxiety accompanies the initial surge of fear. When a threat no longer presents as immediate due to defensive actions, anxiety is activated to keep the individual attentive to recurrences of an adverse situation (Pego et al., 2010). In more developed animals, anxiety will always accompany fear to prepare an organism for a second stressor or to adapt to a chronic stressor. These two pathways work simultaneously (see Figure 8).

1. Attention is tuned to potential or diffuse stimuli surrounding the initial threat. Here, signals from a host of sensory modalities from the thalamus, sensory cortex, multiple and limbic structures are integrated (LeDoux, 1996; Davis, 1997).
2. These sensory signals converge on the BLA, where determinations of appropriate response are made.

3. Signals are then sent to the BNST (Davis, 1998).
4. Signals are relayed to hypothalamic and limited brainstem targets (Davis & Whalen, 2001). Robust connections between the BNST and the HPA axis highlight the BNST in modulating neuroendocrine responses to stress.
5. The protracted nature of anxiety is similar neuroendocrine functioning in that both are slow to initiate and prolonged in their response, which last anywhere from minutes to hours (Walker, Toufexis, & Davis, 2003).

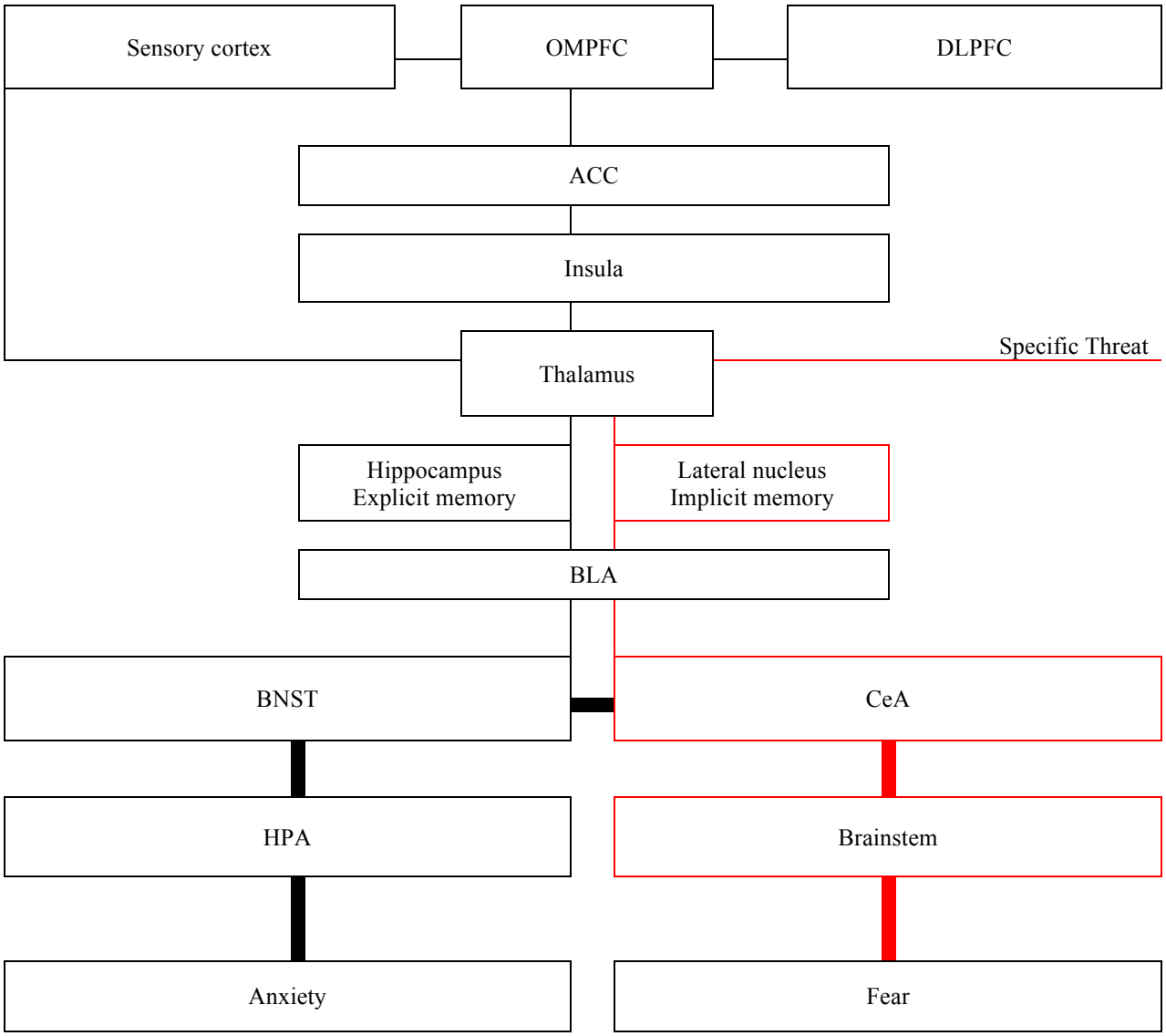

Figure 7. Fear pathway stage 2: Activation of anxiety and the HPA axis.

Anxiety (alone) pathway. Although fear begets anxiety, anxiety does not necessarily beget fear. In contrast to the route taken by fear, the processing of sensory information related to non-life-threatening, distal, diffuse, or potential threat takes a slower route. This route includes the cortical parts of the brain which, in turn, can prohibit intense fear responses generated by the amygdala (McRae et al., 2012; see Figure 8).

1. In the processing of diffuse threat, signals from a host of sensory modalities from the thalamus, sensory cortex, multiple and limbic structures are integrated (LeDoux, 1996; Davis, 1997).
2. When the threat is determined to be diffuse or distant, signals converge on the BLA, where determinations of appropriate response are made.
3. Signals are then sent to the BNST (Davis, 1998).
4. Signals are relayed to hypothalamic and limited brainstem targets (Davis & Whalen, 2001). Robust connections between the BNST and the HPA axis highlight the BNST in modulating neuroendocrine responses to stress.
5. The protracted nature of anxiety is similar neuroendocrine functioning in that both are slow to initiate and prolonged in their response, which last anywhere from minutes to hours (Walker, Toufexis, & Davis, 2003).

When fear and anxiety take over. In contrast to the pathway of an adaptive stress response, if fear and anxiety circuits are prolonged or exaggerated, they can result in disease. And when taken to an extreme, they can have deleterious effects on the architecture of the brain and impacting systems of memory, learning, emotion, and executive functioning, all of which are critical in helping us cope (Pego et al., 2010).

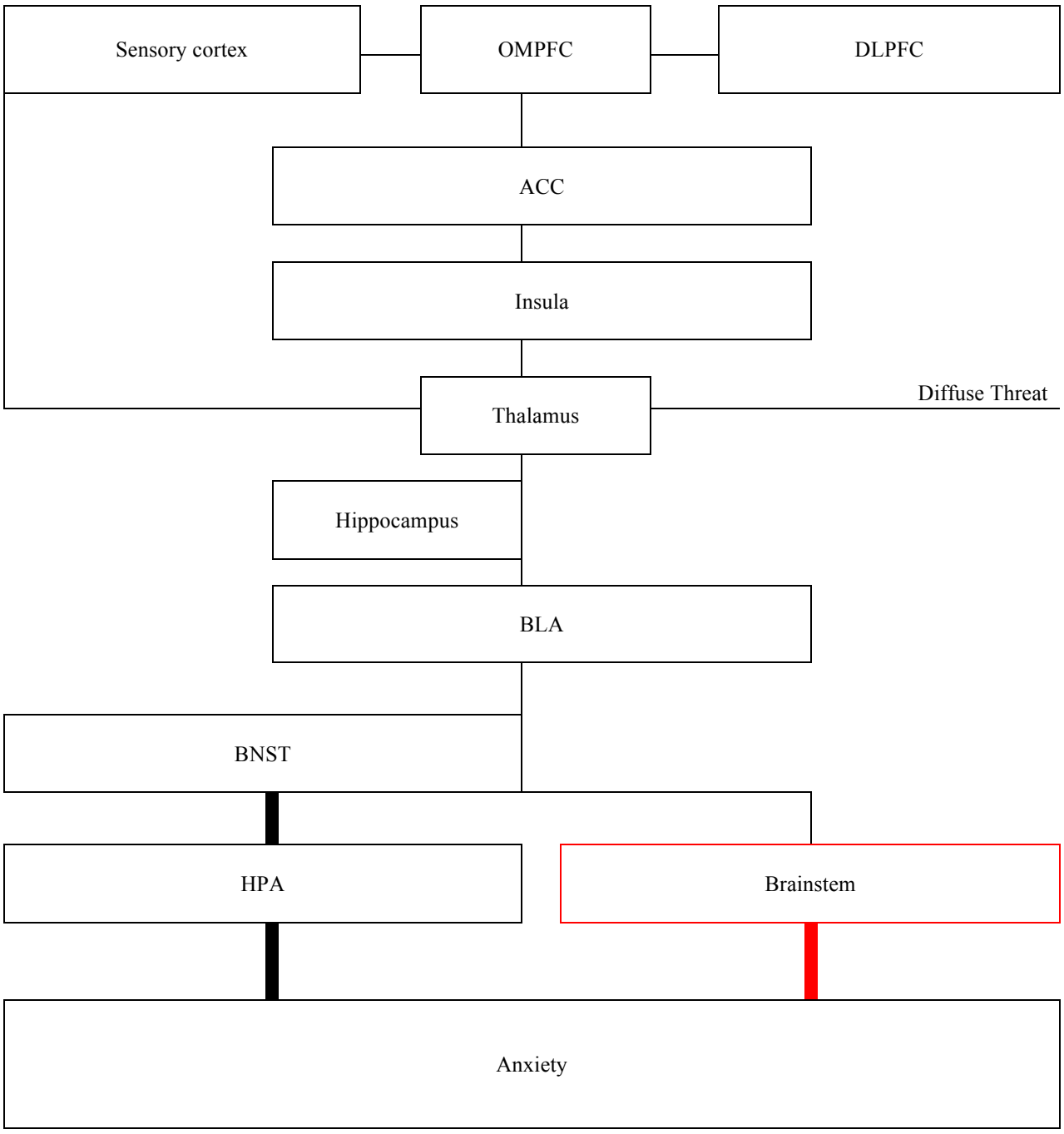

Figure 8. Anxiety alone pathway.

Adverse, and usually chronic and unpredictable stressors, can shape fear and anxiety circuits at any point in the lifespan from our prenatal existence through adulthood. Prenatal stress in mothers, as well as adverse experiences such as maternal separation, and emotional and/or physical abuse, can lead to increased stress responding in children. Beyond childhood, frequent

neurobiological stress responses can lead to hyperactivity of these circuits and enlargement of the amygdala and BNST, prolonged HPA axis responses, as well as atrophy and disenabling of higher cortical centers that help us regulate our emotions.

Sustained effects of fear and anxiety also impact how genes express in brain regions that regulate behavioral, endocrine, and autonomic responses to stress, and can also shape how genes get passed on from one generation to the next. The combination of our genes and adverse environmental challenges can increase our risk for anxiety disorders and other mental health disorders, as well as stress-related and other physical illness through adulthood (Darnaudéry & Maccari, 2008).

Chapter 4. Discussion

Case Study

For therapists, understanding how predisposing, genetic factors for fear and anxiety disorders and their interaction with the characteristics of stressors in the lives of their patients can help identify potential therapeutic targets in the brain. The following case study illustrates how information about the structures and pathways involved in fear and anxiety may be used in the therapy room.

Background

At the time he was under my care, Mark was 62-year old, Latino gentleman, a veteran of the conflict in Vietnam. Mark was diagnosed with severe PTSD and a history of major depression. Prior to coming to the VA, he had lived with intense flashbacks for nearly two decades without seeking treatment. Over that time, he felt increasingly isolated and misunderstood, expressing that his family would become disinterested when he talked about his experiences during the war. He remarked that it was it was "chicken-shit" to go to the VA for many years. But when it started to affect his family, he sought treatment and had been going every day since.

Mark was born in an agricultural community in the Central Valley of California, the son of migrant farm workers. He stated that his family was poor, and he rarely saw his parents because they were working in the fields for long hours. While Mark was in junior high school, he and his family moved to Los Angeles where his home life was dominated by masculine pride or "machismo." During and beyond high school, Mark used dealt cocaine and marijuana to fellow students and people in his neighborhood because few opportunities for upward mobility existed for Mexican Americans. He reported multiple encounters with the police, and felt that he was

targeted for no compelling reasons. When he almost got in trouble with the law, he joined the Marines.

In The Therapy Situation

In our initial sessions, Mark would appear aloof, and avoid eye contact while talking about himself. He would often call me "Doc" and stated that he was used to interns "coming and going" when they finished their training rotations. I assured him that my rotation was for a year, so we had time. During sessions, he would often complain about "The Man," and suspected that I, also being a minority, could relate to this by expressing, "You know how it is."

As our rapport grew, Mark related to me that he had the sense that he was "corrupted morally," and described himself as a "miserable father and bad husband." He described instances of becoming physically and verbally abusive towards his wife, and admitted that she went through "a hell of a lot," and that he is "one lucky bastard." One of his goals in therapy was to work on their relationship and to let her to know how much he appreciated her.

Despite his abusive behavior towards his wife, Mark reported that he was never abusive toward his children. Realizing that his violent behavior and drug use might affect his children, he worked as a truck driver and took jobs that would often transport him far away from his family. Mark became tearful when he talked about his children, particularly his feelings about denying them a good childhood. He stated that his children, however, saw him as a good father, and I validated what they said. He had taken them from harms way by taking far away jobs to shield them from his drug use and violent behavior.

Discussing War Experiences

When I would ask him about his experiences in combat, in the early phase of treatment, Mark would say abruptly, "I did my time. I saw people die. Case closed." He would then talk

about his week. The was first time I realized that he was beginning to open up about his combat experiences, Mark brought in medals and awards that he had earned while in the Marine Corps. In a subsequent session, he brought in his dog tags and pictures he drew of soldiers – simply-drawn stick figures lined up in formation. To me, this was his way of approaching slowly toward some of the challenges that he faced in combat and possibly a progression towards a past trauma.

I encouraged him to bring in more, my thought being to engage him in the therapy room, creating the expectation that this was a place where he might experience anxiety (albeit safely) from bringing up past traumas. But more importantly, I wanted him to feel like he had control over this process, at his own pace and on his own terms. My goal was to evoke a level of anxiety that was tolerable for him, still allowing for cognitive processing and new learning to occur.

Over subsequent sessions, he brought in comicstrip or storyboard-like drawings depicting combat scenes. These initially had successful endings, with dead enemy soldiers and smiling American soldiers with their arms raised. After commenting on how well-drawn they were, I took out some paper and asked him to draw more. I also let him know that I was there to draw with him if he wanted. Our drawing sessions together eventually produced scenes with depictions of American soldiers losing limbs or being killed. I also noticed that the enthusiasm that he possessed when he brought in his medals and initial drawings began to wane.

Fear at Inappropriate Times

During one session, Mark related a story that happened earlier in the week. While he was gardening in his backyard, a police helicopter flew overhead. He indicated that he froze, breathing heavily, and cowered with his arms folded over his head in his garden for 30 minutes. After he related the story, he stared blankly at the sterile, white wall behind me, and was speechless for several minutes. He said he felt ashamed that this response, and numerous others

like it in the past, was beyond his control. Part of his shame stemmed from the fact that he knew logically that he was set off by something that posed no danger to him.

I relayed to him that his paralysis was a hallmark of extreme fear that looked different from fight-or flight. His response reflected the helplessness he felt. It also reflected his belief that confronting or avoiding the threat were not options. During these moments, our reasoning skills and memories that help us get a sense of where we are can become much more difficult to access. We can easily miss other things in the environment that tell us we are safe because we are so focused on the threat. I also let him know that the worry and tension from represented his body preparing for a second stressor. In his day-to-day anxiety, his senses are attuned to many things as if waiting and searching for a threat to manifest. In his body, these activated long-lasting, chemical responses. And although anxiety does not typically activate a fear response, it did for him and many others who suffer from PTSD and panic attacks. He had become very sensitized to threat and his stress response system was heavily primed. And therein lay the problem: although fear and anxiety evolved to promote survival, this was no longer the case for him and that it was time to rewire.

He had encountered numerous stressors in his life that stemmed not only from the war, but also from the racism, poverty, and long stretches of separation from his parents during childhood. I let him know that the chronicity and often unpredictable nature of these stressors had taken a heavy toll. Part of this was to learn about what was at stake for his brain and his body. Chronic anxiety, when left unchecked, it continues to burn fuel: fuel taken from the rest of the body in the form of immunosuppression and other physical problems. This depletion also wears out systems in our brain responsible for judgment, memory, and organizing how we perceive our environment.

Flashback

In a session after a Thanksgiving holiday, Mark came in visibly shaken. Slow to speak, he disclosed that he was unable to carve the turkey during dinner with his family after multiple attempts. He stated that he could not take his eyes off the turkey. When he would put the carving knife against it, his hands would shake violently. So finally, he stopped and let his son take over the task.

When I asked what was going through his mind, he said that he was reminded of an event during the war. A Viet Cong boy, probably no older than 15-years old, was surrounded by Mark's platoon. As Mark entered, his commanding officer ordered him to take the shot. With the rest of his platoon egging him on to take the shot, he responded. The boy collapsed with a trail of blood coming from his head. As celebratory cheers and back-slapping ensued, Mark recalled that he could not feel anything. As he told this story, his face looked as if he were stunned, completely unaware of his surroundings. I could finally see the trauma of a 19-year old Marine who just took a life of another child.

He paused for a while before sobbing, "They told me step on his brains! And so I did! That innocent kid! He didn't do anything wrong! He was just trying to take care of his family!" Mark burst into tears and said, "I've never told anyone that before." Fear had overtaken him and his limbic system was in overdrive, I thought. He could not think and so it was better to let his body recover. And there was nothing I could do but sit with him silently and thank him for the privilege to bear witness.

In the next session, when he was able to talk, we made an attemt to reconstruct the narrative of what really happened. That horrific, pressured situation that unfolded quickly. It tested his judgement, morality, but also the loss of his manhood and comraderie with his

So many things were beyond his control. the fact that he was under someone else's command and feeling compelled to follow orders. He stated that he feared the consequences if he disobeyed. What would you have done knowing what you know now? To hand him the control that he did not have during the horrifying situation.

Guidelines

In the last two months of our sessions, my plan shifted to giving Mark some tools he might be able to use after my rotation ended. I decided to give him a set of guidelines to help him return him to a place where fear and anxiety help might him, and not topple him. Within these guidelines, incorporating mindfulness and systemtatic desensitization, contained steps to create a place of centeredness that he could return to whenever he needed to recharge, education about how threats are processed in the brain, triggers and responses, and steps to taking action to confront the threats that counters passive responding.

Promoting calm. First, I wanted to create an awareness to a place of centeredness where he could always return in moments of stress to calm limbic and HPA activity and to recharge. Mark indicated that he learned meditation at the VA that focused on his breathing. He found it so helpful in centering him that he built a meditation room at his home. He was so proud of it, he invited me to his house to see it. Seeing an opportunity, I encouraged him to go further, beyond focusing on his breath.

I encouraged him to focus on the body, noticing any tension that might be present. Next, I asked him to focus on his emotions. I equated it to as catching ourselves in the emotional state, particularly the stressful moments. In these moments, return to back to the body to focus on breathing. Third, I encouraged him to focus on what his senses were taking in in the present moment, getting used to the sight, the smell, as best as he could, then to ask himself, "Are you

safe here?" Finally, I encouraged him to focus on his thoughts where he might ask himself "Is your mind wandering back to past?" The goal of this was to be aware of and centered on the present.

Basic fear and anxiety processing. Another part of these guidelines entailed discussing how responses to the threat follow a bottom up or top-down process. In a bottom-up process, we react to our environment and our senses dictate how we respond to a threat. In contrast, in a top-down process, we make choices. By doing so, we target thinking to activate higher brain centers that help us to contextualize where we are, here and now, and what we can do.

Confronting threat: Identifying triggers and responses. I also encouraged him to explore his responses to threats. This would be done in moments when he felt safe, but want to challenge himself. I let Mark know that it was important to think about how they applied to him without digressing from his emotions, and that this exercise could done with another person present if he felt safer doing so. Several of the questions I asked him to consider are below.

- *Identifying triggers*. What are things you consider to be anxiety-provoking, but non-life threatening? What are things you consider to be life-threatening?
- *Identifying perception of control*. What is your control over these things? Are they predictable or unpredictable?
- *Identifying his responses to specific or diffuse triggers*. Do you avoid or confront? Do you feel immobilized over the situation or event?

Confronting threat: Promoting habituation. During our sessions, we employed some desensitization techniques. I communicated to Mark that confronting some of the traumas in his past through habituation can help with living with them, and that he could do this with the help of another person. I also informed him that he may feel although he might feel frustrated about

the speed of the process, this could be tempered by keeping in mind the process of extinguishing fear is slow.

Using answers from his identified triggers, I asked him to bring up an image of a threat. When doing so, it was important to keep a balance between moderate anxiety, thinking, and knowing when to back down, and that this initiated the process of inhibiting the limbic system. I reminded him that in these moments of safety, he had control to take in sensory information of "what things are and what things are not," and that he could return to his center if things become too intense. If he could not bring himself to be in its presence, he could step back and take care of his body by focusing on breathing and drawing awareness to his environment.

The next step was to ask himself, "What would I have done differently?" while knowing that he has power to make choices in how to react to a situation: to run, to avoid, to confront, how much you want to confront. To gather more ideas about other ways of responding, he could talk to someone about how they might respond in a similar situation. Finally, I asked Mark to make a list of these alternative responses, and rehearse them so that he would be armed with knowledge and a plan about how to carry them out.

Limitations and Recommendations

Certain limitations of this study are noted forthright. The brain is a highly complex organ and focusing on just a few structures is a dramatic simplification of involved neural processes. Although many brain regions are involved in a variety of functions (e.g., stress and also reward), discussion centered largely on their relationships to fear and anxiety for the purposes of this study.

Despite rapid advances in neuroimaging that have allowed for a clearer understanding of human brain functioning, research in affective neuroscience is still considered to be in its nascent

stages. This is primarily due to limitations in anatomical resolution in neuroimaging that continue to obscure finer details of neurocircuitry. With this in mind, animal studies are still regarded as first-line evidence for detailing structure to function in the human brain, but continue to pose challenges to hypothesis testing and generalizability to human populations. Consequently, caution must be exercised when extrapolating and interpreting these data to humans. Further, many of these studies in both the animal and human literature have small sample sizes, further compromising generalizability.

From a cultural standpoint, can we assume that brain structures and pathways as the overarching conceptualization. Threat triggers and expressions of fear and anxiety vary across cultures, and assuming that the techniques used here will reduce clinical symptoms of anxiety and fear from one cultural group to another may be problematic. The risk is that the triggers of clinical fear and anxiety are often thought to be cognitive distortions, which may be stigmatizing, negate one person's experience over another's, and may be detrimental between cultural and generational contexts.

Despite these limitations, there is a certain urgency for mental health specialists to keep up with the growing neuroscience literature that continues to parse out structure-to-function issues in the brain with increasing specificity. But because this is daunting task, owing to a translational gap between these fields, discourse between neuroscientists and clinical psychologists is strongly encouraged. It is also recommended that teaching tools incorporate translational research to address the language barrier.

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APPENDIX A

Davis - Mapping Fear and Anxiety

Evolving from his research on the amygdala, Davis and his colleagues set out to map the neural pathway of potentiated fear as measured by acoustic startle. The short latency of fear-potentiated startle implied a simple pathway in the brain. To understand where this response was processed, Davis and his colleagues employed retrograde tracing to determine axonal projections from their point of termination to their source (i.e. synapse to cell body). By injecting chemical tracers within the acoustic startle reflex, the authors found corresponding efferents from different cell bodies in the CeA (Davis et al., 2010).

After failing to reconcile the ineffectiveness of anxiolytic compounds on expressions of fear, Davis shifted his attention to understanding the mechanisms for anxiety. Other research showed that benzodiazepines have an anxiolytic effect in rats on the elevated plus maze test, but lesions to the amygdala did not produce anxiolytic effects on this test, suggesting that mechanisms for anxiety differed from that of the fear pathway (Davis, 1998a; Davis et al., 1997).

To explore the possibility of differential involvement of the BNST, Davis phasic fear and anxiety (defined as sustained fear), Davis and his colleagues conducted a series of chemical and mechanical lesion studies on both structures. He found that lesions to the CeA blocked fear-potentiated startle, and that lesions to the BNST blocked light-enhanced startle.

Through a series of tracing studies, the implication of a neighboring structure, bed nucleus of the stria terminalis (BNST), emerged. an anterograde tracer - a method used to chemically trace axonal projections from their source (the cell body) to their point of termination (the synapse) - was infused into the posterior part of the basolateral nucleus of the amygdala. The brain was later sectioned so as to capture labeled terminals in both the CeA and the BNST. Davis found that many fibers terminate in the CeA, but many pass through the CeA to terminate in the BNST. He proposed that electrical stimulation or mechanical lesions of the CeA not only

disrupt cells in the CeA, but also disconnect the basolateral amygdala from the BNST (Davis & Shi, 1999).

Davis states, “Most of the literature on the amygdala involves an analysis of the role of the CeA using various measures of fear, primarily in rodents. However, many effects attributed to the CeA may actually result from disconnecting the basolateral nucleus from the BNST because the fibers that connect the BLA to the BNST pass right through the CeA.”

Davis concluded that electrical or chemical stimulation of the CeA not only can activate CeA cells that project to the hypothalamus and brainstem but also CeA cells that project to the BNST. Similarly, chemical, fiber-sparing lesions of the CeA also can block inputs from the CeA to the BNST. Hence, manipulations of the CeA potentially will always have these dual effects on the CeA and the BNST (Davis & Whalen, 2001). He concluded that the amygdala and BNST have differential roles – specifically, that the seat of fear lies within the amygdala, whereas anxiety stems from the BNST (Davis, 1998b; Walker & Davis, 1997b).

APPENDIX B

Implications of the Extended Amygdala

The amygdala was believed to be responsible for both fear and anxiety responses in much of the neuroscience literature and is the current knowledge in clinical psychology. This was obscured due to methodological issues in lesion studies. Namely, boundaries of the amygdala and where the lesions were being made within the amygdala obscured these findings. The implications are summarized below.

- The BNST has numerous similarities to the CeA in terms of anatomical properties, transmitter content, cell morphology, and efferent connections in primates and humans (Price, Martin, Powers, & Dellovade, 1991; Shammah-Lagnado et al., 2000).
- The CeA and BNST share a strong alliance tied through dense neural connections (Dong et al., 2001).
- A robust level of temporal coordination between the inputs and outputs of CeA and BNST neurons support the idea of that these structures share functions (Nagy & Pare, 2008).
- Both receive strong glutamatergic inputs from the basolateral amygdala (Davis et al., 2010).
- In addition, CeA and BNST neurons send robust projections to an overlapping set of autonomic and motor brainstem nuclei thought to generate components of fear and anxiety responses (Davis et al., 2010).
- The posterolateral division of the BNST has many of the same hypothalamic and brainstem projections as the CeA so that outputs from the basolateral nucleus of the amygdala to the BNST can eventually activate the same targets as the CeA does (Davis, 1998b).

- In addition, the CeA projects heavily to the lateral division of the BNST. Collectively this is known as the lateral extended amygdala (Davis, 1998b).

These similarities are so striking that anatomical debate continues to surround whether or not they are the same entity (Alheid, 2012; Holstege, Meiners, & Tan, 1985). The anatomist Lennart Heimer, who assumed that the CeA and BNST belonged to the same anatomical entity and termed this system the "extended amygdala" due to similarities in transmitter content, cell morphology, and overlapping connections (Davis & Whalen, 2001; Fudge & Haber, 2001). The term "extended amygdala" has been used to describe the neural continuum between the centromedial amygdala and the BNST (Alheid, 2012). Tracing studies provided evidence supporting the idea of the extended amygdala.

APPENDIX C

Davis – Paradigms for Measuring Fear and Anxiety

Measuring Fear – Fear-potentiated Startle Paradigm (Davis and Astrachan, 1978). Based on the notion that startle increases significantly when one is already afraid, Davis & Astrachan (1978) pioneered the fear-potentiated startle paradigm in rats. Conditioned fear is defined as elevated startle amplitude in the presence versus the absence of a conditioned, acoustic stimulus.

- Baseline startle is established by presenting small number of acoustic startle stimuli (i.e., loud noise) to an animal and allowing habituation to occur to achieve a stable level of amplitude.
- On the next day, train the animal to be afraid of light by pairing with shock. No startle test given on this day.
- Testing is conducted the after a period of time (1-30 days) by eliciting acoustic startle in absence or presence of a light (presented for 3-4 seconds).
- Difference in startle amplitude elicited in the presence vs. absence of light, and the original baseline level of startle is used to define the magnitude of conditioned fear (fear potentiated startle).

Through these experiments, startle amplitude was found to be significantly higher when elicited by the same auditory stimulus in presence of light. In addition, when startle was elicited at various times during testing, it increased almost immediately after light onset and returned to baseline shortly after the light went off (Davis & Whalen, 2001; Walker & Davis, 1997a). This suggests that fear-potentiated startle is time sensitive to the presence of emotionally significant stimulus, namely, that it acts in a phasic manner and recovers quickly.

Measuring Anxiety - Light Enhanced Startle Paradigm. Whereas fear acts in phasic manner and recovers quickly, anxiety is sustained. Coupled with research indicating that rats

find light to be anxiety provoking, the authors used a light-enhanced startle paradigm. Along with data from mechanical and chemical lesion studies, electrical stimulation and local infusion of various compounds to were employed to determine functions of the amygdala and BNST (Davis & Whalen, 2001; Walker et al., 2009).

- Rats are exposed to light for a long duration (5-20 minutes)
- They become anxious in the presence of light (and not dark, so this is species specific). There is no conditioned stimulus (e.g. foot shock) presented. Light enhanced startle does not depend on specific cue conditioning (Walker & Davis, 1997a).
- When the acoustic stimulus is presented, rats startle more significantly just to light (light enhanced startle)
- Startle amplitude was directly related to intensity of light

Differences between FPS and LES. Fear-potentiated startle reflects anticipatory fear of a specific and imminent threat (i.e., shock). In contrast, light-enhanced startle is a more diffuse response to a less certain threat. The temporal profile of startle increases in these two paradigms is also different: Fear-potentiated startle has a very rapid onset and offset, measured in milliseconds to seconds respectively. Light-enhanced (as well as CRF-enhanced) startle having a more gradual onset and offset. These characteristics have been used to distinguish between 'fear' and 'anxiety', respectively (Walker et al., 2009).

APPENDIX D

BNST Outputs

Source	Target	Responses	Reference
BNST	Parabrachial nuclei	Stress-elicited alterations in feeding behavior	(C.-S. Li & Cho, 2006)
Medial bed nucleus of the stria terminalis (BSTm)	Basal forebrain	Social approach/ aversion, motivational/behavioral differences between social/asocial species	(Goodson, 2006)
Juxtacapsular nucleus (BNSTju)	Vetromedial caudoputamen, anterior basolateral amygdalar nucleus	Visceromotor responses, autonomic responses with somatomotor activity in adaptive behaviors	(Dong, Petrovich, & Swanson, 2000)
	Caudal substantia innominate, mesencephalic reticular nucleus, retrorubral area	Somatomotor outflow	
	Prelimbic, infralimbic and ventral CA1 cortical areas; posterior basolateral, posterior basomedial, and lateral amygdalar nuclei; paraventricular and medial mediodorsal thalamic nuclei; subthalamic and parasubthalamic nuclei of hypothalamus; ventrolateral periqueductal gray		
Oval nuclei BSTov)	Caudal substantia innominata, adjacent central amygdalar nucleus, retrorubral area, and lateral parabrachial nucleus; caudal nucleus accumbens, parasubthalamic nucleus, and medial and ventrolateral divisions of the periaqueductal gray; anterior parvicellular part of the hypothalamic paraventricular nucleus and nucleus of the solitary tract	Autonomic, neuroendocrine, and ingestive behavioral responses during stress	(Dong, 2001b)
Fusiform nuclei (BSTfu)	Nucleus accumbens, caudal substantia innominata and central amygdalar nucleus, thalamic paraventricular nucleus, hypothalamic paraventricular and periventricular nuclei, hypothalamic dorsomedial nucleus, perifornical lateral hypothalamic area, and lateral tegmental nucleus; parastrial, tuberal, dorsal raphe, and parabrachial nuclei and in the retrorubral area, ventrolateral division of the periaqueductal gray, and pontine central gray; olfactory tubercle, lateral septal nucleus, posterior basolateral amygdalar nucleus, supramammillary nucleus, and nucleus of the solitary tract.	Autonomic, neuroendocrine, and ingestive behavioral responses during stress	(Dong, 2001b)

Posterior BNST			
Principal nucleus	Septal and hypothalamic regions	Reproductive and visceromotor responses	(Dong, 2004)
Interfascicular nucleus	Septal and hypothalamic regions	Defensive and reproductive behaviors	
Transverse nucleus	Midbrain parts of the behavior control column	Foraging/exploratory behavior	
All three nuclei	Medial amygdalar nucleus, lateral septal nucleus, nucleus accumbens and substantia innominata, hypothalamic parts of the behavior control column, hypothalamic periventricular region (patterned neuroendocrine and autonomic responses)		
Anterolateral area and BSTal and BSTsc	Somatomotor system: nucleus accumbens, substantia innominata, ventral tegmental area, and retrorubral area and adjacent midbrain reticular nucleus	Visceral and somatic motor responses, especially in response to noxious stimuli	(Dong, 2004)
	Central autonomic control system: central amygdalar nucleus, dorsal lateral hypothalamic area, ventrolateral periaqueductal gray, parabrachial nucleus, and nucleus of the solitary tract		
	Neuroendocrine system: paraventricular and supraoptic nuclei, hypothalamic visceromotor pattern generator network		
	Thalamocortical feedback loops: midline, medial, and intralaminar nuclei		
Anteromedial Area	Neuroendocrine system: regions containing magnocellular oxytocin neurons, parvicellular corticotropin-releasing hormone, thyrotropin-releasing hormone, somatostatin, and dopamine neurons	Neuroendocrine, autonomic, and behavioral or somatic responses associated with maintaining energy balance homeostasis	(Dong & Swanson, 2005a)
	Central autonomic control network: central amygdalar nucleus, descending paraventricular nucleus, and ventrolateral periaqueductal gray		
	Five of six known components of the hypothalamic visceromotor pattern generator network		
	Behavior control column: descending paraventricular nucleus and associated arcuate nucleus; ventral tegmental area and associated nucleus accumbens and		

	substantia innominata Behavioral state control: supramammillary and tuberomammillary nuclei		
Dorsomedial Nucleus	Humeral sensory-related (subfornical organ and median preoptic nucleus) Neuroendocrine system (magnocellular): oxytocin, vasopressin; parvicellular: gonadotropin-releasing hormone, somatostatin, thyrotropin-releasing hormone, corticotropin-releasing hormone Central autonomic control network: central amygdalar nucleus, BST anterolateral group, descending paraventricular hypothalamic nucleus, retrochiasmatic area, ventrolateral periaqueductal gray, Barrington's nucleus Hypothalamic visceromotor pattern-generator network (five of six known components)	Initiating drinking behavior and salt appetite, homeostatic and behavioral responses associated thirst and salt appetite.	(Dong & Swanson, 2005b)
	<u>Behavior control column</u> Descending paraventricular nucleus Lateral medial preoptic nucleus Anterior hypothalamic nucleus Ventral tegmental area, along with interconnected nucleus accumbens and substantia innominata Retrorubral area Paraventricular, central medial, intermediodorsal, and medial mediodorsal nuclei Nucleus reuniens Subparaventricular zone, ventrolateral preoptic nucleus, tuberomammillary nucleus, supramammillary nucleus, lateral habenula, and raphe nuclei	Ingestive Reproductive Defensive Foraging Orofacial motor control Thalamocortical feedback loops Behavioral state control	