Etiology of Fear and Anxiety

Michael Sweeney, Ph.D.

&

Daniel Pine, M.D.

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Introduction

The term "emotion" refers to a brain state associated with signs of reward or punishment, a stimulus for which an animal will extend effort to approach or avoid. The term "fear" refers to a specific emotion elicited by potentially dangerous stimuli. Fear provides organisms with an internal early warning system that issues a call to action. Fear warns the organism of perceived impending danger and readies the organism for potential flight. Anxiety typically refers to emotional states that are analogous to fear. Anxiety differs from fear, however, in that anxiety refers to fear-like states that are out of proportion, in terms of duration, degree of avoidance, or subjective distress, relative to the current level of danger provoked by potential fear stimuli.

Complications in developing a unified, comprehensive theory of fear or anxiety derive from the multiple factors that influence fear states. Genes, development, cognition, behavior, learning, physiology, and neuroanatomy interact to create the experience of fear (Taylor & Arnow, 1988). The situation is further confounded by the multifaceted manifestations of fear given its cognitive, affective, behavioral, and physiological dimensions. Speculation about the purpose and mechanisms of fear has been at the center of the major theories of human development: evolutionary, biological models, psychoanalytic, and behaviorist.

The current chapter is divided into two parts. The initial section presents an historical overview of four key theories as they apply to pathological anxiety: psychoanalysis,

behaviorism, cognitive theories, and neuroscience. In the second section, findings from current areas of research are reviewed, as they inform refinements in etiologic theories.

Theories on the Etiology of Anxiety

Psychodynamic Theories

Freud coined the term 'anxiety neurosis' in 1895. He viewed anxiety as the "fundamental phenomenon and the central problem of neurosis" (Freud, 1964). Freud's theory of anxiety evolved over time. The important aspects of early psychodynamic theory include the structural model of personality, the concept of psychosexual stages, and the notion that anxiety is a signal of underlying conflict. In 1903, Freud proposed psychosexual stages of development, e.g., oral, anal, oedipal, latent, and phallic. Unsuccessful navigation through these stages would result in a "fixation" that would manifest itself in a symptom of anxiety. Each stage, because of the different developmental tasks, was posited to relate to a different type of anxiety.

In 1926, Freud devised the structural model and revisited his conceptualization of anxiety. The structural model posits a personality comprised of an id, ego, and superego with anxiety resulting from conflict between these forces and the a need to inhibit unacceptable thoughts and feelings from emerging into conscious awareness. If this 'signal anxiety' does not adequately activate the ego's defensive resources then intense, more persistent anxiety or other neurotic symptoms are thought to result (Gabbard, 1992).

Consequently, anxiety is a signal of unconscious fantasies of imagined dangerous situations. These fantasies are provoked by instinctual wishes or by perceptions of

external situations (Michels et al., 1985). Anxiety becomes problematic when defense mechanisms are no longer able to inhibit its manifestation adequately and symptoms therefore surface.

Learning Theory

Initial learning-based theories of anxiety developed from data on classical conditioning, also known as respondent conditioning, generated by Pavlov (1927). In a classical conditioning experiment, an unconditioned stimulus (UCS), such as an electric shock, refers to a stimulus that can elicit an unconditioned response (UCR), such as fear. If a second, neutral stimulus, such as a tone or a light, is repeatedly paired with the UCS, the previously neutral stimulus (referred to as a conditioned stimulus (CS), can come to elicit a response similar to the one produced by the UCR. The effect the CS produces after conditioning is a conditioned response (CR).

Watson and Morgan (1917) argued that clinical anxiety is a conditioned response. Watson and Rayner (1920) tested this hypothesis in a now famous experiment with an 11-month-old child who has come to be known as 'little Albert.' In the experiment, Albert initially demonstrated no fear of rabbits. Through repeated pairings of a rabbit with a startling noise, however, Albert began to fear the rabbit.

The Little Albert experiment, and others, suggest that humans can learn to be anxious, though a number of both scientific and ethical questions arise concerning these early experiments. Nevertheless, theories based on classical conditioning motivated development of a number of treatment approaches, including flooding, implosion,

modeling and systematic desensitization. Moreover, recent data in the neurosciences has raised new questions on the role played by classical conditioning in clinical anxiety.

Systematic desensitization is the process of pairing relaxation with progressive approximations of the feared situation (Wolpe, 1958). While studying the development of anxiety in cats, Wolpe observed that a cat that had received a shock in an experimental cage would appear nervous and refuse to eat while in the cage. Wolpe wondered if feeding might inhibit the anxiety, a process he termed reciprocal inhibition. Wolpe had the cats eat in rooms that were progressively more like the cage in which they were shocked. Once an animal appeared calm eating in one setting, he was moved to the next room in the hierarchy until eventually the animal was comfortable in the cage where the fear was initiated. Such work relates to other research on instrumental conditioning, whereby an animal is trained to exert an active response to provoke one or another form of feedback, such as elicitation of a reward.

Classical conditioning was an important advancement in the understanding of the etiology and treatment development of anxiety disorders. However, classical conditioning alone could not account for how all fears are acquired. Mineka (1986) has outlined three shortcomings of classical conditioning. First, not every child exposed to the same classical conditioning paradigm will develop a fear reaction to the new stimuli. Second, many people demonstrate fears that have not been associated with any aversive event, such as people who fear dogs, though they have not had any negative contact with dogs. Third, anxiety problems do not develop in many people who have been repeatedly

exposed to fearful situations. Many of these concerns were addressed in the development of social learning theory.

Social learning theory posits that behavior in a given situation is the result of the interplay of interpersonal, environmental, and behavioral factors. Social learning theory builds on the principles of classical and instrumental conditioning by adding the concepts of modeling, regulatory control, and self-efficacy (Bandura, 1986). Modeling is learning by observing others. An individual can surmise what is adaptive by learning from his observed experiences of others. Consequently, a parent who demonstrates relief after engaging in anxious avoidance teaches the child that some situations are dangerous and that avoidance is an adaptive strategy. Modeling is one mechanism that may contribute to the familial transmission of anxiety disorders. Self-efficacy is an individual's estimate of his/her ability to produce an outcome. Individuals with low self-efficacy hold that control over situations lay outside of themselves. High self-efficacy individuals believe they can impact or manage a situation. Individuals have low-self efficacy for the situations in which they feel anxious. For example, people who fear public speaking often believe that no amount of preparation will allow them to avoid the inevitable failure that is beyond their control. A greater belief in one's abilities and a higher expectation of positive outcome would decrease the magnitude of the person's anxiety. Many aspects of social learning theory are incorporated into the cognitive model of anxiety.

Cognitive Theories

Behavioral theories of anxiety show strong overlap with cognitive theories, which place an emphasis on regulatory control, interactions of stimuli, thoughts, or cognition, and

available reinforcement. Stimuli provide information about a situation, facilitating prediction about the future. For example, a traffic light provides information about when an individual can safely cross the street. Cognition refers to the thoughts about a situation. Reinforcement control is the notion that individuals act in accordance with the likely consequences. Cognitive-behavioral theories suggest that anxiety disorders are perpetuated by an interaction among these factors.

In the cognitive model of anxiety the expectation and interpretation of events, and not simply events in themselves, govern one's experience. Cognition does not act alone. It functions synergistically with other primal systems, e.g., affective, behavioral, and physiological. Primacy is attributed to the role of cognition because the cognitive system is responsible for integrating input, selecting an appropriate plan, and activating the other subsystems (Beck et al., 1985). In the cognitive model, anxiety disorders result from a chronic tendency to overestimate the likelihood of threat (Beck, 1976). For example, the person who fears elevators greatly overestimates the likelihood of being stuck in one. These misestimates of threat result in heightened levels of anxiety, triggering a set of responses designed to protect the individual from harm (Beck, 1976). These responses include changes in autonomic arousal (fight or flight), inhibition of ongoing behavior, and selectively scanning the environment for possible sources of danger. The autonomic arousal further increases heart rate and lends evidence to the initial fear. In addition to inappropriate reactions to new situations, the anxious individual remains geared for defensive action long after the situation has passed.

Cognitive theory differentiates two levels of cognition: self-schemas and negative automatic thoughts. Self-schemas are general core assumptions or beliefs that people hold about themselves and the world. Dysfunctional assumptions make people prone to interpret situations in a maladaptive manner. For example, the adolescent who holds the belief that "everyone must like me" has tied his or her self-worth to social approval. As a result of this schema, the individual has heightened his or her anxiety about all social

contacts. There is likely a decrease in comfort and competency in social situations as well. Negative automatic thoughts function in the same manner but refer to certain thoughts and images that arise in a specific situation. For example, a child concerned about social evaluation may, during a lull in conversation, have a negative automatic thought, "This group thinks I'm boring."

Neuroscience

In general, the past 20 years has been marked by a resurgence of interest in the biological aspects of emotion, and much of this interest has followed from insights on neuroscientific aspects of fear. Advances in neuroscience follow from the strong cross-species parallels, from rodents through humans, in the phenomological, physiological, and neuroanatomical correlates of acute fear states (LeDoux, 1996; 1998). Much of this work extends insights into the instantiation of fear states through the fear conditioning experiment, as described in learning theory, above. Fear conditioning involves pairing of an aversive UCS with a neutral CS. Conditioning results from changes within a neural circuit centered on the amygdala, a structure that lies within the brain's medial temporal lobe. Following advances in research on fear conditioning, recent studies have begun to examine related fear states, such as the states elicited by innate fear-provoking stimuli (Davis & Shi, 1999). These states engage both the amygdala as well as a range of other brain structures described below.

Considerable diversity emerges in research relating particular neural circuits to distinct fear states (Davis & Shi, 1999). Despite such diversity, research on the neuroscientific aspects of fear states does provide some uniformity in the approach to fear as a normal adaptive construct and anxiety as a clinical problem. Namely, neuroscientific theories consistently explore the manner in which particular brain regions are engaged in specific fear states. Such a theoretical approach emphasizes the view that anxiety states represent outward manifestations of changes within brain systems. Nevertheless, such theories consider many factors, both socio-environmental and genetic, which ultimately influence the manner in which changes in brain states relate to overt symptomatic manifestations of an anxiety disorder (Meaney et al. 1999). As a result, a focus on brain states in such theories can equally lead to an emphasis in therapeutic research on both environmental or social treatments as well as pharmacological treatments.

Current Research

The previous section of this chapter provides a theoretical and historical framework for research on the etiology of anxiety. The current section reviews data in six areas that are likely to inform ongoing efforts to refine the available theories. These six areas comprise: genetics, temperament, longitudinal course, neurochemistry, psychophysiology, and cognitive-neuroscience.

Genetics

Anxiety disorders aggregate within families (Marks, 1986), and research has suggested that the development of childhood anxiety disorders may be genetically mediated

(Biederman et al., 1991; Last et al., 1991). Many studies document such familial associations. For example, Weissman et al. (1984) found children of panic disordered probands to be at increased risk for anxiety disorders. Last et al. (1991) found a higher prevalence of anxiety disorders in the first degree relatives of affected children as compared to controls. Family aggregation, however, does not necessarily imply heritability, as common genes are confounded with common environment (Legrand et al., 1999). Twin or adoption methods must be employed to disentangle these effects.

Twin studies have been the most common method to investigate the heritability of anxiety. Twin studies compare scores between monozygotic (MZ) twins and dizygotic (DZ) twins to estimate heritability. MZ twins are genetically identical whereas DZ twins share, on average, half their genes. Consequently, if a trait were due solely to genetics and measured without error, correlations between MZ twins in theory, should be 1.0, while correlations between DZ twins should be 0.5. However, MZ and DZ twins also share aspects of their environment. Therefore, if shared aspects of the environment, such as social class, exert a substantial influence on a trait such as anxiety, the within-pair correlations for MZ and DZ twins on an anxiety measure should be similar. Hence, an examination of the degree to which within-pair correlations for MZ and DZ twins differ provides a measure of heritability.

As reviewed by Klein and Pine (in press), twin studies in juveniles are only beginning to emerge. We briefly review the results from five twin studies below.

Warren et al. (1999) investigated the heritability of anxiety in a sample of seven year old twins. The sample was comprised of 174 monozygotic and 152 dizygotic twin pairs. Participants completed the Revised Children's Manifest Anxiety Scale (RCMAS). The RCMAS has a total score and subscales for physiological anxiety, worry, and social concerns. The investigators found that within-pair correlations were significantly higher for MZ than DZ twins on both the physiological and social subscales. This suggested a genetic component for the attributes tapped by these subscales. However, the within-pair correlations for both the worry scale and the total anxiety score were more similar in MZ and DZ twins than the correlations for the physiological or social subscales. This suggests the presence of shared environmental influences. Specifically, these data suggest that genetic factors influence approximately one third of the variance for the physiological and social anxiety scores.

Legrand et al. (1999) investigated heritability in a large sample of twins: 311 twin pairs age 11 (188 MZ pairs, 123 DZ pairs) and 236 twin pairs age 17 (155 MZ, 81 DZ). Participants completed the State-Trait Anxiety Inventory (STAI) and the State-Trait Anxiety Inventory for Children (STAIC). Based on the pattern of correlations for MZ as contrasted with DZ twins, the investigators concluded that trait, but not state, anxiety symptoms are moderately heritable, with additive genes accounting for 45% of the variance.

Thapar and McGuffin (1995) found that parents' and children's reports disagreed on the magnitude of anxiety that can be attributed to heritable factors. The investigators

obtained parental reports and adolescents' self-reports of anxiety on the RCMAS. Anxiety symptoms appeared highly heritable by parental report, with additive genes accounting for 59% of the variance. The adolescents' self-reports, however, provided very different results in that the shared environmental effects rather than genetic factors appeared to be of primary importance. This difference could be attributed to a variety of factors, and the findings raise major questions concerning the most appropriate interpretation of twin data. Anxiety is generally viewed as a unitary construct, reflective of some feature of the child. As a result, data documenting different heritability for parent- versus child-reported anxiety raise questions about which informant provides the most valid data from a family-genetic standpoint. Similarly, such divergence raises questions on the precise construct that is being modeled in twin studies of rating scales.

Attributes that are thought to be the precursor of anxiety disorders have also been the subject of investigation, though such studies typically have been conducted in adults. Anxiety sensitivity is the fear of anxiety-related sensations. Individuals with high anxiety sensitivity are more likely to experience anxiety symptoms as threatening, and high anxiety sensitivity has been found to be a risk factor for panic disorder. Stein et al. (1999) investigated the heritability of anxiety sensitivity in adults. The study group was comprised of 179 monozygotic twin pairs and 158 dizygotic twin pairs. The investigators found that anxiety sensitivity has a strong heritable component, accounting for nearly half the variance in total anxiety sensitivity scores. Similar conclusions have been generated in twin studies of other potential anxiety precursors, such as measures of respiratory dysfunction, as reviewed below.

Finally, in contrast to most reports, some studies have found an overwhelming environmental influence. Topolski et al. (1999) investigated heritability in a sample of 1412 twin pairs aged 8 to 16 years. As in Warren et al. (1999), participants completed the RCMAS. The investigators concluded that environmental influences accounted for 80 to 90% of the variance.

While findings from such genetic epidemiology studies generate consistent interest in genetic contributions of various complex behaviors, the sequencing of the human genome has accelerated interest in genetics research. Associations between several genes and various anxiety disorders have been reported. However, as in twin studies, inconsistencies or non-replication of findings have been common, and none of the associations between specific behaviors and one or another genetic factor have been clearly established (Smoller et al., 2000)

Temperament

The term "temperament" refers to a relatively stable pattern of behavioral tendencies that emerges early in life. Chess et al. (1960), in their seminal work on temperament, argued for the existence of an innate predisposition that renders some children more prone to problems with fear and anxiety. Work by Kagan and colleagues (1989, 1991, 1994, 1999) over the past 20 years extended this view, demonstrating a consistent association between early life temperament and later-life behavior, including anxiety symptoms. Kagan and colleagues conducted a series of prospective studies on the influence of

temperament, following a sample of 462 healthy children from infancy through middle childhood. At four months of age the children were presented with a variety of visual, auditory, and olfactory stimuli. Children were categorized as high or low reactive based on their responses. About 20% of the sample was categorized as high reactive. When presented with the stimuli they demonstrated a combination of frequent vigorous motor activity, fretting, and crying. About 40% of the sample demonstrated the opposite profile. These children, who had low activity and minimal distress to the same stimuli, were categorized as low reactive. Follow-up evaluations were conducted when the children were ages 14 and 21 months. The children were systematically exposed to a variety of unfamiliar social and non-social events. Unfamiliar stimuli included interacting with an examiner, placement of heart electrodes and a blood pressure cuff, an unfamiliar liquid placed on the child's tongue, and the appearance in different episodes of a stranger, a clown, and an odd looking robot. Children who were categorized as high reactive at age four months demonstrated significantly more fears at the both the 14 and 21 month assessments as compared to children who were initially categorized as low reactive. Children in the high reactive group were also found to smile less frequently.

Signs of shyness and inhibition were evaluated again when the children were 4.5 years of age. The children interacted one-on-one with an examiner with whom they were unfamiliar in a playroom with two other children, while the parents of all three children were present. Videotapes of these interactions were coded for the occurrence of spontaneous comments and smiles. The children who were high reactive infants were more likely to be classified as shy and demonstrated fewer spontaneous comments and

smiles as compared to the group that had been low reactive as infants. The high and low reactive children were again evaluated when they were 7.5 years old. The presence of anxiety symptoms was assessed through parent and teacher reports. Anxiety symptoms included nightmares and fear of the dark, thunder, and lightning. Anxiety symptoms were present in 45% of the children who were high reactive as infants but only in 15% of the children who were low reactive as infants. Additionally, children in the high reactive group demonstrated fewer spontaneous comments and smiles.

Kagan et al. (1999) concluded that temperament does not determine future behavior, but limits the range of possible outcomes. Namely, not every high reactive child was consistently rated as inhibited at every evaluation. Not a single high reactive child, however, was consistently rated as uninhibited at the follow-up assessments. Only 18% of high reactive children were rated as inhibited at every evaluation. Although some high reactive infants will have anxiety problems in childhood, it is important to note that most will not.

High reactivity in infancy does appear to increase the likelihood of inhibition in childhood. In turn, inhibited children may be more likely to develop anxiety disorders including simple phobia, social phobia, separation anxiety, and PTSD. In the samples followed by Schwartz, Snidman, and Kagan (1999), a specific association between inhibition and social anxiety disorder during adolescence was demonstrated. In terms of other anxiety disorders, a number of reports have demonstrated the influence of a preexisting inhibited style on risk for psychopathology. Pynoos et al. (1987) assessed all

of the children in a Los Angles school one month after a sniper had killed one and injured 13 of the students. Anxiety problems were found in only 38% of the children. A preexisting inhibited style differentiated children who did and did not have a problem with anxiety in response to the tragedy (Terr, 1979).

Longitudinal Course

A series of studies have examined the longitudinal outcome of children with various forms of anxiety disorders. In general, these studies document a moderate level of stability among anxiety disorders present during childhood, adolescence, and adulthood (Pine et al., 1999). Pine et al. (1998) prospectively studied the continuity of adolescent to adult anxiety disorders in 776 young people evaluated on three occasions across a span of nine years. For many, but not most, subjects, adolescent anxiety disorders persisted into adulthood. Most adult disorders, however, were preceded by adolescent disorders. The presence of an anxiety or depressive disorder in adolescence predicted a two to three fold increased risk for adult anxiety or depressive disorder. Particular questions have arisen in these studies on the differential longitudinal course of specific anxiety disorders. There is some evidence to suggest specific outcomes for fears, panic attacks, social anxiety, and generalized anxiety disorder.

With respect to specific childhood fears, Muris et al. (2000) investigated a sample of 290 children (ages 8 to13) who acknowledged current fears. The results indicated that childhood fears reflected an impairing anxiety disorder in a substantial minority (22.8%) of these children. For most children, fears cause transient upset and no enduring

impairment. For many children, however, fear and anxiety problems beginning in childhood continue into adulthood(Pine et al., 2001, 1998).and may predict adolescent and adult episodes of major depression (Weissman et al., 1997).

Childhood fears are modified by developmental, environmental, and familial factors. As children grow they enter new situations and acquire the ability to imagine future circumstances and new opportunities for fearful reactions. For example, fear of sleepovers becomes apparent when sleepovers become common in a child's peer group, and fear of death occurs when children are old enough to consider the notion of death.

With respect to other forms of anxiety, episodes of spontaneous panic in adolescents have been found to predict the onset of panic disorder in adulthood (Pine et al., 1998; Keyl & Eaton, 1990). Similarly, separation anxiety in childhood may also represent a precursor of panic disorder in adulthood. Adults with panic disorder, as compared to other psychiatric disorders, report higher rates of separation anxiety as children (Berg, Butler, & Pritchard, 1974; Klein et al., 1980; Klein et al., 1992). The offspring of adults with comorbid panic disorder and depression have been found to have higher rates of separation anxiety disorder than the offspring of adults with major depression without panic disorder (Capps et al., 1996; Weissman et al., 1984). Additional evidence comes from treatment trials finding that adults with panic and children with separation anxiety have a positive response to the same medication (Gittelman-Klein & Klein, 1971).

Finally, Pine et al. (1998) and Peterson et al. (2001) examined specificity in course for other anxiety disorders. Children and adolescents with social anxiety disorder faced an increased risk for social anxiety disorder but no other anxiety disorders as adults. Other anxiety disorders exhibited different longitudinal courses. For example, childhood or adolescent obsessive compulsive disorder exhibited a particularly strong tie with later generalized anxiety disorder. Similarly, broad associations among overanxious, generalized anxiety, panic, and major depressive disorders were found. Adolescents with overanxious disorder were about as likely as adolescents with major depressive disorder to have an episode of major depression in their adulthood. Adolescents with major depressive disorder were at a high likelihood to have generalized anxiety as adults.

In conclusion, anxiety disorders with an onset during childhood or adolescence persist into adulthood in many but not most cases. Most adult disorders, however, were preceded by adolescent disorders.

Neurochemistry

Rapid advances continue in our understanding of neurochemistry as it may apply to the causes and treatment of anxiety disorders. Research in this area may carry significant clinical insights by facilitating the development of effective pharmacological treatments. As a result, studies of neurochemistry are relevant to conceptualizations of both therapeutics and etiology.

Nerve cells communicate via chemical messengers know as neurotransmitters. At least three different groups of neurotransmitters have been implicated in anxiety. Recent studies have generated interest in a class of neurotransmitters known as neuropeptides. These substances include compounds such as substance-P and corticotropin releasing hormone that have parallel effects in both nerve cell communication and hormonal regulation. While research on neuropeptides remains at the forefront of ongoing basic science studies, this subject is not reviewed in the current chapter, since this research has yet to generate clinical insights relevant to childhood anxiety disorders. Perhaps some of the most consistent interest in neurochemical aspects of anxiety pertains to studies of gamma-hydroxybutyric acid (GABA). Studies on this widely distributed neurotransmitter consistently note relationships to anxiety. Benzodiazepines, which exert their effects through the GABA receptor complex, reduce acute anxiety both in animal models and in various forms of clinical anxiety among adults. Because available randomized controlled trials in children generally do not document such beneficial effects for anxiety, this area is also not reviewed. Finally, two specific monamine neurotransmitters have been implicated in anxiety, both in animals and humans. Monamines exert their effects by modulating activity in distributed neural circuits. Research on monamines and their effects on neural circuits implicated in anxiety may carry significant implications for childhood anxiety disorders. As a result, research in this is briefly reviewed.

The neurotransmitter serotonin appears particularly important to anxiety. Serotonin, as a monamine, is involved in the mediation of a range of behaviors by effecting neural

systems. These behaviors include emotional behaviors that relate to anxiety and related fear conditioning. Serotonergic neurons emerge from the raphe nuclei, with the median raphe providing innervation to the septo-hippocampal system, as well as the cortex, which may play an important role in emotional cognition (Melik et al., 2000).

Studies of genetically altered mice have been used successfully to investigate the influence of different neurotransmitter receptors on fear and anxiety. These are often referred to as knockout studies because a certain receptor site has been deleted or "knocked out." Mice with a genetic deletion of various serotonin-related proteins, including both receptors and the re-uptake transporter, have been shown to exhibit abnormal fear or anxiety responses in a number of behavioral conflict tests, confirming the important role of this receptor in modulating anxiety (Gross et al., 2000). Serotonin knockout mice, as compared to control mice, demonstrate increased anxiety to a variety of tasks, including tasks related to eating, locomotion, and heart rate. In response to a discrete aversive stimulus, e.g., foot shock, the knockout mice show increased freezing and increased tachycardia. Activation of the hypothalamic-pituitary-adrenal axis in response to stress appears to be slightly blunted in the knockout mice, however. Together, these data support the idea that serotonin modulates an important fear circuit in the brain. Serotonin is thought to serve a dual function as a presynaptic autoreceptor with the function of negatively regulating serotonin activity and as a postsynaptic heteroreceptor with the function of inhibiting the activity of nonserotonergic neurons in forebrain structures (Gross et al., 2000).

As noted above, the median raphe nucleus (MRN) provides key inputs to neural circuits within the brain that mediate fear and anxiety responses. Melik et al. (2000) investigated the role of the MRN in the development and maintenance of fear as measured by freezing behavior. A fear response was conditioned by pairing a foot shock with contextual cues. The contextual cues elicited the same fear response in MRN lesion rats and control rats directly following the conditioning. MRN lesioned rats, however, showed a marked deficit in freezing behavior 48 hours after the conditioning. Findings indicate that the MRN-serotonergic septo-hippocampal pathway is involved in the regulation of anxiety related to fear conditioning triggered by contextual cues, suggesting that short-term contextual fear is independent of the MRN while long-term contextual fear depends on the MRN.

Garpenstrand et al. (2001) investigated the role of serotonin and dopamine in the development and maintenance of fear in humans. A faster acquisition of fears was found among participants with a short serotonin transporter promoter allele or low monoamine oxidase activity in platelets as compared to participants with only long alleles or high monoamine oxidase activity. Concerning the maintenance of fears, participants with a long dopamine D4 receptor allele showed delayed extinction compared with those with only short alleles. The findings are consistent with animal studies and support the role of serotonin and dopamine in the development and maintenance of fears in humans.

Finally, perhaps the strongest evidence implicating serotonin in human forms of anxiety derives from research on psychopharmacology. Medications that alter functioning of the

serotonergic nervous system exert considerable beneficial effects on various forms of anxiety. Perhaps the strongest evidence of such effects derives from studies of serotonin reuptake inhibitors. These medications show benefits in both children and adults for virtually all forms of anxiety. (CITATION)

The neurotransmitter noradrenaline also appears important in anxiety. Noradrenergic neurons arise from a region of the brain known as the locus ceruleus. The locus coerulesus (LC) is thought to serve as a relay center for warning or alarm. The LC releases stores of noradrenaline directly into the brain. Noradrenergic neurons, like serotonergic neurons, innervate diverse regions of the brain, such that this brain system exerts a wide-spread modulatory influence. This serves to increase signal-to-noise in ongoing processes. In animals, electrical and pharmacological activation of the LC increases norepinephrine turnover and fear-associated behaviors, whereas lesions and pharmacologic inhibition of the LC decreases fear-associated behavior and NE turnover (Boulenger & Uhde, 1982). Furthermore, exposure of rats to uncontrollable stress produces behavioral symptoms characteristic of depression and anxiety and results in decreased levels of norepinephrine in the LC (Simson &Weiss, 1994). Finally, the LC interacts closely with another set of neurons that use CRF as a neurotransmitter to regulate fear-related behaviors. Much like for the serotongeric nervous system, the strongest data implicating the LC and noradrenaline in human anxiety derives from pharmacological studies. Among adults, agents that alter noradrenergic functioning are powerful anxiolytics. Similarly, agents, such as yohimbine, that increase firing of the locus ceruleus are potent anxiogenic compounds. Among children, available data less clearly document therapeutic effects of noradrenergic agents, though Sallee et al. (2000)

did replicate in children with separation anxiety disorder findings of enhanced anxiogenic response to yohimbine previously reported in adult panic disorder.

Psychophysiology

Considerable research examines the association between anxiety and various forms of autonomic regulation. For example, both adults and children with various forms of anxiety exhibit alterations in cardiovascular control. Despite the consistency of these findings, many questions remain. First, cardiovascular measures are regulated by a diverse array of neural structures and provide relatively indirect information concerning the state of brain systems presumably implicated in anxiety disorders. Second, abnormalities in cardiovascular control are not specific to anxiety disorders but also occur in a range of other conditions, including behavior disorders. Third, abnormalities in cardiovascular control can be heavily influenced by context and may be most apparent in anxiety provoking situations. This raises question as to the degree to which findings in this area represent epiphenomena. In contrast to data on cardiovascular control, data for respiratory indices address some of these limitations.

The relationship between anxiety and respiration has been supported by a wealth of research (McNally, 1994). The primary function of respiration is the exchange of oxygen (O2) and carbon dioxide (CO2) between the environment and the blood. This exchange requires effective movement of air into and out of the lungs. Minute ventilation is the amount of air breathed every minute and is determined by the size of each breath, known as tidal volume, multiplied by the number of breaths per minute, known as respiratory rate. Minute ventilation, tidal volume, and respiratory rate are regulated to ensure that

adequate gas exchange occurs. For example, in response to high levels of CO2 minute ventilation typically increases because of an increase in tidal volume, with respiratory rate remaining relatively unchanged. This response occurs reflexively and rapidly, as central chemoreceptors are extremely sensitive to chemical alterations produced by CO2 in the brain's extracellular fluid. From a physiological standpoint suffocation is associated with high levels of arterial CO2, known as hypercapnia, and low levels of arterial O2, known as hypoxia (McNally, 1994).

A leading theory holds that panic attacks are a suffocation alarm triggered by cues of impending suffocation (Klein, 1993). Studies utilizing CO2 have contributed greatly to the understanding of anxiety and panic. The designs of respiratory challenge studies vary, but in the most common design, individuals with either panic disorder, an anxiety disorder other than panic, and normal controls breathe air that has an increased concentration of CO2 (McNally, 1994). Numerous studies have found individuals with panic disorder, but not individuals with major depression, generalized anxiety, or non-anxious controls, experience high degrees of anxiety, panic attacks, and pronounced changes in respiratory parameters in response to CO2 exposure (Papp et al., 1993, 1997; Papp, Martinez, Klein, Coplan, & Gorman, 1995). See Table 1. Pine et al. (1998) extended this research to anxiety disordered children (ages 7-17) and obtained results that parallel those obtained in adults. Hypersensitivity to CO2 has not always been observed, however (Rapee et al., 1992; Woods & Charney, 1988).

Family studies have also supported the role of respiratory dysregulation and CO2 sensitivity in the transmission of panic disorder. A stronger family loading for panic disorder is found in patients with evidence of regulatory dysregulation (Perna et al., 1995). A hypersensitivity to CO2 is found among the asymptomatic adult relatives of panic disordered patients. Finally, respiratory indices linked to panic are heritable, raising the possibility of a shared genetic vulnerability for panic attacks and respiratory dysregulation (Coryell, 1997; Perna et al., 1995).

Cognitive models posit that CO2 sensitivity results not from a biological switch but from panic disordered individuals' hypersensitivity and catastrophic interpretation of internal sensations such as difficulty breathing (e.g., Barlow, 1988; Clark, 1986). In an examination of cognitive factors, McNally & Eke (1996) found that fears of bodily sensations are better predictors of response to CO2 challenge than either behavioral sensitivity to carbon dioxide or general trait anxiety.

Because the interplay between physiological and psychological processes during a panic attack is practically instantaneous, it is difficult to determine whether physiological factors are a cause or a consequence of psychological factors involved in panic. Nevertheless, this paradigm has proven informative in that it has demonstrated that physiological factors are a key component in panic disorder in a way that they are not for other anxiety disorders.

Neuroscience

Earlier neuroscientific approaches emphasized the role of the limbic system, which includes the hypothalamus, septum, hippocampus, amygdala, and cingulum, in anxiety. This view has lost favor in recent years, however, due to considerable imprecision in definitions of anatomical as well as functional aspects of the limbic system. Traditionally, the limbic system was thought to influence attentional processes, memory functions, affect, drive states, and olfaction (Lezak, 2000). Current research on fear conditioning and related fear states does emphasize a role for structures encompassed within older models of the limbic system (Dozier, 1998). The amygdala in particular plays a central role in fear and anxiety. Evidence also exists implicating the amygdala in anxiety disorders. Much of this knowledge is derived from extensions of animal-based research as opposed to studies conducted directly on humans (LeDoux, 1998). When the amygdala of patients having brain surgery is stimulated, they often experience realistic hallucinations, thoughts, or perceptions coupled with fear (Dozier, 1998). Damage to the amygdala can also effect fear states across a range of species, including humans, though such effects can appear relatively subtle or inconsistent (Lezak, 1995).

EEG Studies

While considerable research examines amygdala involvement in anxiety, other studies examine activity in other brain regions. For example, neural activity within the cortex can be monitored through qEEG. Children who are avoidant of or fearful of unfamiliar events show greater desynchronization of alpha frequencies over the right frontal area compared with the left frontal area under resting conditions (Davidson, 1992; Fox & Davidson, 1988). A subsequent study of frontal area activation was conducted with high

and low reactive infants, characterized by vigorous motor activity, fretting, and crying versus low activity and distress. This study demonstrated greater activation of the right frontal area in high reactives when they were 9 and 24 months old, whereas low reactives showed greater activation over the left frontal area (Fox, Calkins, & Bell, 1994). Because neural activity in the amygdala can effect frontal lobe activity via cholinergic fibers projecting from the basal nucleus of Meynert, desynchronization of alpha frequencies in the right frontal area may reflect greater activity in the right amygdala (Kapp et al, 1994; Lloyd & Kling, 1991). Kagan and Snidman (1999) evaluated children from a longitudinal sample at ten years of age and found that of 28 high reactives and 24 low reactives, the high reactives demonstrated greater EEG activation under resting conditions over the right frontal area (30% vs. 8%). The low reactives showed greater activation over the left frontal area (55% vs. 25%). Nevertheless, in two studies of both qEEG and behavioral laterality profiles, no evidence emerged of abnormal asymmetries in adolescents with anxiety disorders (Kentgen et al. 2000; Pine et al. 2000).

Imaging Studies

Recent developments with functional magnetic resonance (fMRI) have made it possible to examine the relationship between sensitivity for various danger cues in amygdala-based circuits and developmental changes in behaviors potentially related to anxiety disorders. This including behaviors possibly related to both social phobia and panic disorder (Pine, 1999). For example, in healthy adults, a selective response by the amygdala to facial displays of aversive emotions, even when presented below levels of conscious perception, has been demonstrated (Breiter et al., 1996; Whalen et al., 1998).

Other studies have shown adults with social phobia facial stimuli at a conscious level to demonstrate amygdala hypersensitivity in an fMRI paradigm (Birbaumer et al., 1998).

Beyond the amygdala and cortex, the hippocampal formation has been implicated in some aspects of anxiety as well as depression. Animal-based studies on anxiety-related processes have implicated the hippocampus through its connections with the amygdala in mediating an organism's response to contextual stimuli where fear cues are presented (Philips & LeDoux, 1992). Furthermore, the effects of anxiolytics show parallels with the effects of septo-hippocampal lesions in animal studies; both manipulations decrease bias towards aversive stimuli (Gray & McNaughton, 1996). Hence, neural circuits involved in aspects of anxiety may involve the hippocampal formation through interactions with fear-relevant systems in the amygdala.

The thalamus participates in most exchanges between higher and lower brain structures, between sensory and motor or regulatory components at the same structural level, and between centers at the highest level of processing. In particular, the thalamus may play a key role in focusing attention on the source of threat (Dozier, 1998). The thalamus is one termination site for the ascending reticular activating system (RAS). Stimulation of the medial thalamus or dorsolateral thalamic nucleus may evoke feelings typical of anxiety (Delgado, 1972).

Anxiety and Attention

Biases in information processing may play a role in the development and persistence of anxiety disorders (Beck & Emory, 1976; Dalgleish & Watts, 1990; Mineka & Sutton, 1992; McNally, et al. 1992; Daleiden &Vasey, 1997). Every day we are bombarded by stimuli. One would be overwhelmed by extraneous stimuli if it were not for selective attention. Selective attention is the automatic and ubiquitous process of allocating greater attentional resources to some stimuli and less to others (Pick, Frankel, & Hess, 1975). The nature of the selected stimuli will affect one's experience. Anxious individuals may have a bias to selectively attend to stimuli perceived as threatening, which facilitates the development and maintenance of anxiety (Beck & Emory, 1976; Dalgleish and Watts, 1990; Mineka & Sutton, 1992).

Investigators have attempted to identify biases in the allocation of attention in anxious individuals (Dalgleish and Watts, 1990; Mineka & Sutton, 1992; Mogg, et al., 1992; McNally, et al. 1992). Self-report has been a common method of investigation. The limits of self-perception for an automatic process and the problems of response bias, however, circumscribe the utility of self-report. Consequently, there has been a move to study information processing in emotional disorders using paradigms taken from cognitive neuroscience (see Dalgleish and Watts, 1990 for review). Paradigms from cognitive neuroscience offer a number of advantages over self-report. These paradigms vary but some features are common. Anxious individuals and controls are exposed to a variety of stimuli, including anxiogenic and neutral stimuli; the presentation of stimuli may be masked in some manner so that perception is thought to be more reliant on

automatic attentional processes. Often the outcome is an indirect measure of the attention to threat, such as speed to complete one or another task.

To investigate if anxious individuals allocate greater attention to threatening written words, investigators have employed an emotional Stroop task. In a Stroop task (Stroop, 1935), a participant is presented with a list of words and asked to name the color of the word while ignoring the meaning of the word. The color of a word can be named quicker in congruent (green ink used to print the word "green") than in incongruent (green ink used to write the word "blue") pairs. Attending to the meaning of a word is thought to be an automatic process and the delay for incongruent word pairs is thought to result from the unintended deployment of attention to the meaning of the word. More recently, the Stroop test has been used to examine cognitive processing of emotional words. Williams et al. (1996) present results from a meta-analysis examining the relationship between attention bias on emotional Stroop paradigms and clinical anxiety. This review convincingly documents an association between attention bias and clinical anxiety. For example, in one such study, Mogg et al., (1990) investigated allocation of attention differences in a sample of high and low anxious subjects. Subjects were presented with three sets of words: either general threat words (mutilated, lonely), achievement threat words (stupid, ignorant), or neutral words (cooking, staircase). The words were matched for length and frequency of use in common language. The words were colored red, yellow, green or blue. Subjects were instructed to name the color of the word as quickly as possible while ignoring the meaning of the word. Greater allocation of attention to threat words would result in slower completion of the threat word lists. Mogg et al.,

(1990) found that high anxious subjects were slower in color naming threat words as compared to neutral words. As noted above, longer response latencies for threat words over neutral words among individuals with anxiety has been replicated in numerous studies with varied populations, including: subjects with spider phobia (Watts, et al. 1986), GAD (Martin, et al. 1991; Mathews & MacLeod, 1985; Mogg, et al. 1989), posttraumatic stress disorder (Foa, et al. 1991; McNally, et al. 1992), panic disorder (Ehlers, et al. 1988; McNally, et al. 1990), and social phobia (Hope, et al. 1990; Mattia et al., 1993; Lundh & Ost, 1996).

More direct investigations of the allocation of attention have been conducted with a dot-probe task. A dot-probe task measures the allocation of attention by measuring participants' reaction time to the appearance of a dot. In this task two stimuli, such as words, are simultaneously flashed on a screen for milliseconds. A dot sometimes appears where a word had been. Faster reaction times to dots that follow threat words indicate a greater allocation of attention towards toward threat. This task eliminates the possibility of response bias interpretations by requiring a neutral response (pressing a key) to a neutral stimulus (a dot).

In one of the first uses of the dot-probe task, MacLeod et al., (1986) investigated differences in the allocation of attention in a sample of anxiety disordered and not-ill adults. Subjects were presented with 288 word pairs, 48 of these pairs contained one threat word. Example of threat words included criticized, humiliated, injury, fatal. The word pairs were presented briefly (500 milliseconds) and simultaneously on a computer

screen, one on the top and the second on the bottom half of the screen. Following some word pair presentations, a dot would appear where the word had been. Subjects were instructed to strike a key immediately upon seeing the dot. Greater attention allocation to threat words would result in both faster response times to dots that followed threat words and slower response times to dots that followed the neutral stimuli. MacLeod et al., (1986) found that anxiety disordered individuals shifted there attention in exactly this manner. These results have been replicated in numerous studies with varied populations, including: high and low anxious medical students (Mogg et al., 1990), and anxiety disordered individuals (Mogg, et al., 1992; Mogg et al., 2000; Mogg et al., 1995; Taghavi et al., 1999; Vesey et al, 1996).

Together, the above research indicates outlines a relationship between clinical anxiety and attention allocation. This allocation of attention may occur at a preconscious level with the allocation of attention occurring automatically, without the awareness of the individual (Mineka and Sutton, 1992). Attention to threat is adaptive in truly threatening situations. If, however, the mechanism for the identification of threat were set too low the result would be excessive and unnecessary anxiety. This could result in a sustained high level of arousal and maladaptive avoidance (Vasey et al., 1995).

Selective attention toward material perceived as threatening clearly plays a role in the etiology and maintenance of anxiety, however the nature of this role is unclear. It may be that biases in attention precede and provoke heightened arousal. Conversely, heightened arousal may result in greater vigilance for threatening material. A more complete view

may be a synergistic process with attentional bias increasing arousal and arousal increasing or maintaining a biased allocation of attention (Beck & Emory, 1976; Dalgleish & Watts, 1990; Mineka & Sutton, 1992; McNally, et al. 1992; Daleiden & Vasey, 1997).

Conclusions

Fear and anxiety facilitate the survival of a species. As such, these emotions have played a central role in evolution and natural selection. Fear provides a phylogenetic connection with our evolutionary ancestors and has been necessary for the propagation of a species. Fear represents an emotion that shows relatively strong cross-species parallels, from humans through lower mammals. These parallels have facilitated animal research providing a basis for biological models.

Despite its necessary and adaptive function, the pathological manifestations of fear have garnered the greatest attention. Psychoanalysis provided the earliest, and as such, highly influential theory for the development and maintenance of anxiety. Psychodynamic notions of anxiety have since lost favor to the more parsimonious and empirically grounded behavioral theories though. Behavioral theories have provided the basis for effective treatments but have been criticized as reductionistic. The criticisms of strict behavior theories include inadequate attention to the cognitive, social, and physiological aspects of human anxiety and the inability to explain all cases of anxiety. Social learning and cognitive theories evolved, in part, out of these concerns. Social learning theory

stressed the continual interaction between behavior and its controlling influences, including vicarious and symbolic learning. Cognitive theories introduced the notion that expectation and interpretation of events, and not simply events in themselves, govern one's experience. These latter theories were also more inclusive of the growing information on the biological basis of behavior.

Temperament research has documented the presence of constitutional factors that may provide a persistent and influential bias towards a certain style of life, including the propensity for anxiety problems. Perception researchers have contributed the notion of biases in memory and attention that may influence an organism's assessment of the environment. Recent advances in neuroanatomy, psychophysiology, and respiration have helped identify the physical structures, chemical messengers, and correlates of anxiety.

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Table 1. Rate of panic attacks during CO2 exposure.

	Author (year)	N	CO2 %	Panic Disordered Subjects	Not-ill Controls
1	Beck et al., 1999	28	5	29%	14%
2	Gorman et al., 1984	16	5	58%	0%
3	Gorman et al., 1988	56	5	39%	8%
4	Gorman et al., 1994	38	5	29%	0%
5	Gorman, 2001	115	5	52%	9%
6	Papp et al., 1997	98	5	54%	8%
7	Sasaki et al., 1996	28	5	38%	0%
8	Sinha et al., 1999	24	5	63%	0%
9	Papp et al., 1995	42	6	38%	5%
10	Bocola et al., 1998	19	7	89%	0%
11	Gorman et al., 1994	36	7	68%	12%
12	Gorman, 2001	115	7	67%	16%
13	Papp et al., 1997	98	7	58%	18%
14	Caldirola et al., 1997	68	35	69%	6%
15	Coryell, 1997	39	35	46%	0%
16	Coryell et al., 1999	46	35	42%	3%
17	Gorman et al., 1990	52	35	50%	21%
18	Perna et al., 1995	59	35	55%	1%
19	Perna et al., 1995	86	35	46%	2%
20	Perna et al., 1999	15	35	80%	25%
21	Van De Hout et al., 1987	21	35	93%	12.5%
					Ill Controls
22	Gorman et al., 1988	56	5	39%	0% (OAD)
23	Gorman, 2001	115	5	52%	50% (PMDD) 14% (MDD)
24	Gorman, 2001	115	7	67%	56% (PMDD) 35% (MDD)
25	Caldirola et al., 1997	68	35	69%	54% (PD+SP) 43% (SP)
26	Coryell, 1997	39	35	46%	0% (MDD)
27	Gorman et al., 1990	52	35	50%	36% (SP)
28	Perna et al., 1995	59	35	55%	1% (MDD)
29	Perna et al., 1996	238	35	77%	90% (GAD+PD) 8% (GAD)
30	Verberg et al., 1998	35	35	65%	100% (PD+MDD)

OAD = overanxious disorder; PMDD = Premenstrual dysphoric disorder; SP = social phobia; MDD = major depressive disorder; GAD = generalized anxiety disorder; PD = panic disorder