THE NEUROBIOLOGY OF ANXIETY DISORDERS

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Overview

Anxiety is a biological response that protects humans from harm. All human beings experience normal anxiety at some level; however, some individuals experience this emotion with sufficient intensity or duration to produce psychophysiological dysfunction. There is a broad range of normal anxiety that is considered to be healthy under normal circumstances. Pathological anxiety is characterized by excessiveness, pervasiveness and uncontrollability. Anxiety has three components: 1) identification of potential threat or harm, 2) the psychological features of alarm, dread, or fear, and 3) the physiological response that includes autonomic discharge and motor activity. Each component localizes to discrete brain regions including: 1) cortical interpretations of potentially dangerous sensory information, 2) subcortical recruitment of key brain regions, e.g., hypothalamus, to alert the person of impending harm, 3) brain stem responses to cortical and subcortical inputs, and 4) ascending catecholaminergic inputs to cortical and subcortical regions. Both excessive and inadequate anxiety can produce dysfunction. Excessive anxiety produces disorders while inadequate anxiety is seen in some antisocial personality disorders.

Although many types of anxiety disorders are listed in the DSM IVR, the five most common clinical syndromes include: 1) generalized anxiety disorder (GAD), 2) panic disorder, 3) post-traumatic stress disorder (PTSD), 4) social phobias, and 5) agoraphobia. Anxiety disorders are common in all age groups (5-10%), especially the elderly (10.2%). Many patients meet criteria for two or more conditions. Many, i.e., up to 62%, meet criteria for depression or dysthymia (40%). Many (13%) nursing home residents experience anxiety and a few (3%) have GAD.

The spectrum of anxiety experiences ranges from a normal mild sense of distress produced by the concern of danger to severe, paralyzing fear with a massive autonomic discharge, e.g., hyperventilation, with lowering of arterial CO₂, respiratory alkalosis, and carpal-pedal spasm. A typical hyperventilation episode commences with peri-oral and stocking-glove paraesthesias followed by involuntary muscle contractions and loss of alertness. In contrast, panic attacks are characterized by a massive impending sense of doom, sweating, tremulousness, and tachycardia. Some anxiety may also produce depersonalization experiences where the patient develops a subjective sense of not being real while de-realization experiences include a sense that the environment is unreal. These anxiety symptoms can mimic TIA’s, seizures, or pseudo seizures.
The Neurobiology Of Anxiety And Fear

Anxiety can be conceptualized as a spectrum that ranges from a normal sense of apprehension to severe, disabling symptoms associated with panic disorder. Some anxiety symptoms are acquired, e.g., PTSD, and others may result from subtle neurodevelopmental problems. For example, individuals with panic disorder may have subtle developmental abnormalities of the right cerebral hemisphere. The left cerebral hemispheric specializes in discrete functions like language, while the right hemisphere specializes in multimodal sensory function and emotions. Right hemispheric, i.e., mesial temporal cortex, lesions are more commonly associated with panic.

The neurobiology of fear includes pathways that process sensory information, associates sensory data, and activate circuits of arousal. Threatening sensory cues are received in the association cortex where they are projected into the thalamus and the amygdala. Information is then relayed to the frontal cortex for a measured reaction as well as to the paraventricular nucleus for activation of the pituitary gland and release of stress related hormones. Outputs from the hypothalamus and the amygdala project to the locus ceruleus where norepinephrine is released throughout the neocortex to precipitate generalized cortical arousal. Other limbic and brain stem structures are also involved including the hippocampus as well as the pontine nuclei that stimulate sensory arousal and defensive posturing. Post traumatic stress disorder, an acquired condition that produces anxiety, alters the hypothalamic pituitary adrenal axis. For example, individuals who survive natural disasters or motor vehicle accidents are found to have low levels of cortisol that predicted high risk of post traumatic PTSD.

Anxiety is linked to stress and other psychopathology. Stress may produce anxiety and the consequent disorder can then produce additional stress. The cause, duration, and features of psychological or physiological stress determine the CNS response to this event. The biological consequence of harmful stress depends on its nature as well as its timing in neurodevelopment.

Chronic, severe stress alters synaptogenesis, neuronogenesis, and neuron receptor densities. Neurons are hypothesized to reproduce throughout maturity in specific human brain regions, especially the hippocampus. Primates studies demonstrate that long-term stress of the hippocampus reduces the rate of neuronogenesis in the dentate gyrus. Human models of childhood stress, e.g., sexual abuse, document victims with overall reduced hippocampal volume. Studies with fMRI demonstrate abnormal activation of the mesial temporal cortices including amygdale; however, neuropathological studies have not been completed to assess possible hippocampal damage from prolonged stress.
The specific psychological triggers for many anxiety symptoms are mediated by past experience and cognitive processes. Phobic anxiety produced by specific items or objects, e.g., snakes, spiders, etc., are generally learned behaviors that then trigger a biological cascade. Generalized anxiety is often embedded in other psychological stressors that promote unrealistic expectations in the affected individual, e.g., unrealistic expectations of performance, fear of abandonment or isolation, etc. The precipitant psychological stressor then triggers the biological response. Specific life events can produce massive stress that provokes anxiety reactions in persons otherwise not predisposed to this clinical condition. Death of a loved one with bereavement, loss of a job, serious legal problems, etc., consistently produce substantial stress in normal individuals that may trigger the symptoms of anxiety in a person who is otherwise normal.

Few discrete human brain lesions produce fear or arousal in isolation from other symptoms, e.g., depression. Pre-ictal auras associated with temporal lobe seizures can produce fear and dread. Symptoms of generalized anxiety disorder can be produced by stroke, demyelinating disorder, e.g., multiple sclerosis, dementia, and Parkinson’s disease. Significant numbers of post-stroke patients, e.g., 29%, develop generalized anxiety disorder symptoms that persist over a three-year period and most (92%) are associated with clinical depression. Generalized anxiety disorders in multiple sclerosis and traumatic brain injury are also associated with depressive comorbidity. The symptoms of GAD are also common in Alzheimer’s patients and those with Parkinson’s disease, especially in the early or middle stages of the disorders.

Anxiety is a common symptom in other mental illnesses including schizophrenia, mental retardation, and ADHD, and mood disorders. Anxiety disorders are very common in depression (up to 70 %) and bipolar disorder (up to 40%). A shared neurobiology may reflect this high rate of comorbidity as both disorders alters noradrenergic and serotonergic systems.

Biomedical Psychosocial Aspects Of Anxiety Disorders

The biomedical, psychosocial aspects of anxiety disorders are complex and most patients with anxiety disorders will demonstrate problems in all four domains. The biological aspects include genetic vulnerability or neurological damage that produce these symptoms. Although the specific neurobiology of anxiety is unclear, many neurological and neurodegenerative disorders produce anxiety, including parkinsonism, Alzheimer’s disease, traumatic brain injury, etc. The co-occurrence of depression and anxiety suggests a link between neural mechanisms. The medical aspects of anxiety disorders centers on health conditions that mimic anxiety, e.g., supraventricular tachycardia, seizure disorder, drug toxicity, etc. Psychological aspects of anxiety include learned behaviors that trigger or worsen the symptoms of anxiety and psychological interventions.
to alter that behavior, e.g., cognitive behavioral therapy. The social aspects of anxiety disorders include disruption of social contacts and interpersonal relationships, as well as loss of employment due to paralysis from specific syndromes, e.g., agoraphobia. The psychosocial aftermath includes inability to marry (25%) and maintain employment (35%).

Many forms of mental illness produce the symptoms of anxiety, e.g., depression, schizophrenia, personality disorders, etc. The differential diagnosis of anxiety is extensive and age-dependent. Three distinct groups of individuals suffer from anxiety: 1) children, 2) adults, and 3) elders. The differential diagnosis of anxiety in each group must be interpreted according to the biomedical, psychosocial aspects of mental illness. For example, many anxiety disorders appear in childhood or early adulthood. Children may have symptoms of anxiety due to abuse, neglect, or family issues while elderly patients may suffer anxiety as a consequence of medical problems, neurological diseases, or neglect.

**Epidemiology Of Anxiety Disorder**

About 1/4 of all citizens in the United States will report at least one anxiety disorder during their lifetime. Anxiety disorders are more common among young with a peak prevalence between ages 25 and 44, especially those who are poorly educated, unmarried, childless, and female. The ECA data demonstrates that 6% of men and 13% of women in the United States will have symptoms of anxiety disorder in any six month period. Comorbidity studies demonstrate that 75% of these individuals also have at least one other comorbid psychiatric condition, e.g., depression, substance abuse. Anxiety disorders are also prevalent among other societies and cross ethnic boundaries.

Generalized anxiety disorders have a lifetime prevalence rate of between 4-6%, with 5% as the accepted norm. GAD is quite persistent and only 1/3 will describe spontaneous remission. The symptoms of generalized anxiety disorder increase with age and women over age 45 are most frequently affected. GAD is uncommon as a single disease but quite common as a comorbidity in major depression (38.6%), specific phobia (24.5%), panic disorder (22.6%), alcohol dependence (11.2%), and drug dependence (5.1%).

Panic disorder occurs in 1.5 to 3.5% of Americans. It is less common in the elderly. The age of onset usually occurs between the teenage years and the mid 30’s. It is frequently comorbid with social or specific phobias, agoraphobia, obsessive compulsive disorder, generalized anxiety disorder, major depression, and substance abuse.

Social phobia has a lifetime prevalence of between 4.8 and 13.3%. Social anxiety disorders differ across cultures and have less gender difference than other anxiety disorders.
disorders. Social phobia, a disorder with comorbidity of 69%–81%, is most frequently present with agoraphobia and this combination has increased risk of suicidality. Depression is common, i.e., up to 75% in persons with social phobias, and the comorbid mood disorder increases the risk for suicide attempt, i.e., 16%.

**Differential Diagnosis**

The onset of anxiety disorders in childhood or adolescents poses a significant, therapeutic challenge to the primary care physician or neurologist. Many individuals go undiagnosed with an average of 17 years between symptom onset and correct diagnosis. Many (37%) are misdiagnosed as unipolar depression. Anxiety symptoms are common in both children and teenagers, while most anxiety disorders commence during the first three decades of life. Anxiety can be produced by a wide range of psychological and psychiatric problems with symptoms that can mimic attention deficit disorder, oppositional disorder, etc. Teenagers with anxiety disorders have a substantial risk for comorbid substance abuse. Many forms of mental retardation have comorbid anxiety as a symptom component, e.g., autism, pervasive developmental disorder, etc. Children and adolescent with symptoms of anxiety should be referred to a psychiatrist with expertise in this age group to construct a specific comprehensive management program that includes pharmacological as well as psychological interventions. Symptoms of anxiety can disrupt learning or classroom behavior and the treatment team must coordinate with educators to assure that children and adolescents continue their academic achievement.

The treatment of comorbid anxiety and depression in children and adolescents is complex. Pharmacological interventions are rarely effective in the absence of other psychosocial treatment strategies, including individual therapy, family therapy, and coordination with the educational system to assure that children do not develop academic difficulties. Depression can masquerade as anxiety, attention deficit disorder, oppositional defiant disorder, or other common psychiatric disorders in children and adolescents. Depression in children and adolescents is best managed by psychiatrists with specific knowledge or expertise in child or adolescent psychiatry.

The clinical presentation of anxiety in the geriatric population differs from that of younger individuals. Most older patients have a longitudinal history of anxiety disorder that reoccur later in life and the new onset of anxiety symptoms should suggest some other diagnosis, such as depression. The rates of comorbid substance abuse, e.g., alcohol, stimulants, depressants, etc., is lower in older patients; however, the overuse of medication may be higher because the risk of psychological dependency is greater in older people. Older patients who receive long-term benzodiazepine may be at higher risks for withdrawal than younger individuals. The geriatric population is also more sensitive to medical and neurological complications produced by these medications.
Clinical Evaluation
The evaluation of any person with a primary anxiety disorder begins with a careful clinical history and medical evaluation. A variety of medical, neurological, and psychiatric diseases can produce the symptoms of anxiety as well as medications prescribed for those medical conditions. The clinician should quantitate the nature, frequency, and characteristics of each anxiety symptom, as generalized anxiety may be a manifestation of other problems such as agoraphobia. The clinician should determine whether specific clinical triggers produce the symptoms from the psychological standpoint and then search for physiological responses to the psychological triggers. Every evaluation should assess for comorbid depression, substance abuse, and risk for suicide. Some medical problems such as hyperthyroidism, hypoglycemia, and supraventricular tachycardia and parathyroidism may mimic the symptoms of anxiety. Some post-ictal events associated with partial complex seizures may also produce symptoms similar to anxiety. Careful clinical assessment can differentiate the symptoms of medical problems from a generalized anxiety disorder.

Therapy For Anxiety Disorders
The treatment of generalized disorder begins with treatment of any underlying medical or psychiatric disorder. The acute onset of anxiety symptoms may be treated with a brief course of benzodiazepines. Persistent GAD should be treated with an antidepressant such as SSRI’s, i.e., paroxetine or venlafaxine, which are approved for this disorder.

The treatment for panic disorders includes benzodiazepines, tricyclic antidepressants, and selective serotonin reuptake inhibitors. While the benzodiazepines demonstrate a marked rapid decrease in severity of panic attacks, these addictive medications have many potential side effects. The use of TCA’s and SSRI’s are approved for the treatment of panic disorder and paroxetine may be an easy medication to use in these individuals. SSRI-induced sexual dysfunction in younger individuals becomes a major issue that limits compliance for some patients. The use of antipsychotic medications in anxiety disorders is limited to severe disabling cases for which other interventions have failed. Anticonvulsants and other mood stabilizers have minimal benefit except in the setting of pre-existing comorbid mood disorders. The prescription of benzodiazepine should be carefully monitored; however, some individuals require long-term benzodiazepine therapy. A trial with Buspirone up to 60mgm for a period of several months should be tempted prior to the institution of chronic benzodiazepine therapy. Abrupt cessation of benzodiazepine therapy can produce an abstinence syndrome similar to that of alcohol and several instances of seizures have been reported. A prolonged delirium can result from abrupt cessation of Xanax and dose titration, both upward and downward, should be completed in a slow progressive manner. Addiction may occur after several months of continuous use. Patients should receive the lowest effective dose and short half-life medications, e.g., Xanax, Ativan, should be given at sufficient frequency to prevent mini-
withdrawal, e.g., every six hours. Long half-life medications, e.g., Valium, Librium, can produce sedation caused by slow accumulation of blood levels, especially in the elderly. Benzodiazepines can cause delirium in brain-damaged patients and these medications should be avoided in persons with neurodegenerative disorders.

All treatment for anxiety requires careful use of psychological interventions to allow the patient a better sense of self-control and internal monitoring. Specific psychological patterns, e.g., repetitive ruminations on stressful subject, will produce symptoms of generalized anxiety. Individuals can be treated with a range of psychological interventions, e.g., cognitive behavioral therapy, exposure therapy, etc., to reduce the psychological component that triggers the physiological response.

**PTSD**

Post traumatic stress disorder is a good model for understanding the neurobiology of stress. PTSD is produced by massive overwhelming psychological stress that manifests as a fairly reproducible clinical syndrome including psychological distress, autonomic arousal and neuropsychological dysfunction. Brain imaging studies, functional MRI, and PET studies demonstrate abnormalities in specific brain regions that are linked to emotion and stress response. Individuals with PTSD may have specific genetic or neurodevelopmental vulnerability that predisposes to this abnormal manifestation of normal stress reactions. The function of the hypothalamic pituitary adrenal axis is unique to PTSD. Individuals with this disorder manifest symptoms of depression; however, their HPA axis abnormality differs from those of depressed individuals. In contrast to depression, some individuals have sustained fixed output of cortisol that is refractory to negative feedback to the hypothalamus. Persons with PTSD have diminished ACTH secretion and diminished cortisol secretion. This observation suggests that some individuals may have a predisposition to developing PTSD, a model for anxiety disorder. The disruption of the cortisol modulation would affect areas where steroid sensitivity, including the orbitofrontal cortices and the hippocampus. These areas also correspond to those brain regions implicated in PTSD. The administration of exogenous steroids does not mimic this clinical syndrome and it is assumed that other conditions must exist to allow the manifestation of this abnormal stress reaction. The sustained long-term nature of PTSD suggests structural brain changes in response to the stressor. The absence of “spontaneous” PTSD indicates that a primary neuro-developmental abnormality is not sufficient to produce this syndrome. PTSD exemplifies the interaction between environment and neurobiology. PTSD is seen in a broad range of clinical settings and in persons with neurological disease or intellectual disability. The occurrence of PTSD in a broad range of clinical populations suggests that the stress-anxiety-neurobehavioral relationship is fundamental to the human brain. Since most of the clinical manifestations of PTSD are psychological, animal modeling is limited for this disorder.
Structural brain alterations identified via image analysis have some variability that may reflect the clinical heterogeneity of this disorder. Functional brain imaging also shows some differences across study groups. This heterogeneity probably reflects neurodevelopmental issues in specific patient populations as well as the heterogeneity of stressors.

**Conclusion**

Anxiety can be a challenging symptom in the neurologically damaged patient. Anxiety associated with stroke, dementia, multiple sclerosis, etc., can substantially lower quality of life or produce disruptive behaviors. For example, the anxious patient with parkinsonism or dementia, may exhibit behavioral problems such as pacing, yelling, irritability, etc. Patients with neurological damage and symptoms of anxiety should be assessed for other potential causes, e.g., side effects of medication, delirium, depression, etc. Anti-anxiety medication, e.g., benzodiazepines, are associated with increased risks of delirium or other neurological problems, e.g., falls.

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REFERENCES – ANXIETY


