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TEMPERAMENTAL CONTRIBUTIONS TO THE AFFECT FAMILY OF ANXIETY

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A large proportion of scientists and clinicians write about anxiety as if this concept referred to a unitary natural phenomenon and the intellectual challenge were to achieve consensus on the correct definition and discover the most valid measurements of this process. The continued reliance by investigators on familiar words, such as *anxiety*, presumes that the communities that invented this contextually unconstrained term eons ago possessed a profound insight into the nature of human emotions. The popular words for emotions were intended to communicate to another that an agent experienced consciously a change in body tone that could not be attributed to an organic need. Furthermore, the community of listeners understood that the agent was accommodating to the incentive and her accompanying thoughts when she selected a word to describe her feeling state.

The evidence used to infer the emotional state of anxiety in humans can include verbal report, observed behavior, and physiology. These three classes of information are not highly correlated and, therefore, the meaning of *anxiety* inferred from one source is not equivalent to the meaning inferred from another. That is, a verbal report of anxiety over one's economic position need not be correlated with the biological profile

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that scientists presume is the basis for that emotion. A serious problem with the current construct of anxiety is that investigators are prone to award the same term to four distinctly different phenomena.

CATEGORIES OF ANXIETY

A person's verbal judgment of being anxious without the presence of any accompanying change in bodily state or central physiology is one basis for ascribing anxiety to an individual. Many individuals will say that they are anxious over their child's high fever or a possible economic recession, but if scientists had measured their physiology at the time that they made this statement, they would not have detected any particular change in brain or bodily activity. The authors call this meaning *judged anxiety.*

A second category is a verbal report of anxiety that is accompanied by a physiologic profile; however, the physiologic pattern is not the one scientists assume is theoretically appropriate. An individual with a viral infection might feel tense and, in an attempt to understand the unexpected sensations, decide that she is worried about her job. The authors call this meaning *constructed anxiety.*

A third meaning is the one used by investigators who work with animals. A particular stimulus provokes activity in the brain structures believed to be relevant to fear; that is, activation of the amygdala and its projections.[8] But the person does not consciously detect any change in physiology. The authors call this meaning *physiologic anxiety.*

The fourth referent is the one scientists would like to believe occurs when anxiety is attributed to a person. In this case, an event—either a thought or an external provocation—has provoked the physiologic state believed to accompany anxiety, and the person detects the sensory consequences of the changed physiology and interprets them as reflecting an anxious state. The authors call this meaning *anxiety.*

It is important to distinguish between a change in physiology that is, or is not, detected by an agent and to differentiate between transient, acute anxiety provoked by a specific incentive and a chronic mood that is less clearly linked to an external event. An acute state of anxiety following a physician's diagnosis of cancer should be distinguished from the chronic anxiety of a melancholic, such as Sylvia Plath. Four different emotional constructs are created by crossing the distinction between consciously detected, compared with undetected, changes in physiology with the distinction between acute emotions and chronic moods.

TEMPERAMENT

Individual variation in vulnerability to states of uncertainty, fear, or worry are usually regarded as a diathesis for anxiety. This variation is probably influenced in part by heritable variation in neurochemistry of the central nervous system, and these profiles are regarded as temperamental categories.[10] A combination of a stable psychologic profile and a presumed physiologic foundation represents the idealized definition of *temperament.* This definition bias motivates the gathering of biological information to separate groups of children or adults who display similar behavioral phenotypes into those who probably do, or do not, possess the relevant temperament. Although future research will reveal a large number of human temperaments, the existing evidence suggests that one of them renders some individuals more ready than others to experience one of the anxious emotions.

Concept of Infant Reactivity and Child Inhibition

The authors' laboratory has been following up a large group of middle-class, healthy white children who were evaluated initially at 4 months of age.[10, 11] Twenty-two percent of this group of 462 infants, called *high reactive,* displayed high levels of motor activity and frequent distress to a standard battery consisting of visual, auditory, and olfactory stimuli. The visual episode consisted of a mobile of colorful toys that moved back and forth in front of the child's face; the auditory episode consisted of a human voice speaking short sentences or syllables of varied loudness. A contrasting group, composing 40% of the sample and classified as *low reactive,* displayed very little motor activity and no distress to the same set of episodes.

A great deal of research with animals reveals that the amygdala is responsive to unfamiliar events and, in addition, seems to be necessary for the acquisition of conditioned freezing reactions to the unconditioned stimulus of shock.[6, 7, 14] The basolateral area of the amygdala sends projections to the ventral striatum and ventral pallidum, and excitation of this structure induces limb movements in animals.[1] Furthermore, the amygdala is the origin of the amygdalofugal pathway, whose projections to the central gray and anterior cingulate modulate distress cries.[16] Thus, infants born with a neurochemistry that creates a low threshold in the amygdala and its projections should display vigorous limb movements and distress to unfamiliar stimuli. These are the characteristics of high-reactive infants. By contrast, infants born with a neurochemistry that raises the threshold of the amygdala and its projections should display minimal motor activity and little distress and behave like low-reactive infants. These presumed differences between high- and low-reactive infants imply that high-reactive infants should develop into avoidant, fearful children, whereas low-reactive infants should develop into relatively sociable, fearless children.

Derivatives of Infant Reactivity

Most of these children were brought back to the laboratory when they were 14 and 21 months and were exposed to unfamiliar people, objects, and procedures. These episodes included encounter with moving robots, unfamiliar adults, flashing lights, and the placement of electrodes on the body. Because less than one third of the children cried in fear to any one of the 17 episodes, the authors assumed that the children who displayed at least four fears—the top tercile—had a special susceptibility to becoming apprehensive to unfamiliar events. Thirty-five percent of the high reactives showed four or more fears at both 14 and 21 months (only 3% were minimally fearful), but only 4% of the low reactives were that fearful at 14 and 21 months of age.[10]

A sample of 193 of these children were evaluated again when they were 4.5 years old. The children who had been high-reactive infants were more subdued than were the low reactives as they interacted with an unfamiliar female examiner. Specifically, they displayed fewer spontaneous comments and fewer spontaneous smiles in the interaction. In addition, when these children were observed in a play session with two other unfamiliar children of the same age and gender, with parents present in the room, two thirds of those who had been low-reactive infants, but less than 10% of high reactives, were outgoing and sociable in their play with the other two other children. By contrast, 40% of the high reactives were shy and timid compared with only 10% of the low reactives.[11] Ten of the 74 children who had been high-reactive infants (13% of the sample) and highly fearful in the second year were extremely inhibited during both sessions at 4.5 years. It is probably not a coincidence that these 10 children had displayed unusually high levels of fear when they were seen in the laboratory at 14 and 21 months.

A sample of 164 children from this cohort were evaluated again when they were 7.5 years old. Initially, a questionnaire was sent to the mothers asking them about their child's shyness and fear of strangers, storms, animals, loud noises, and tendency to have nightmares. The mothers who described their children as fearful or shy were interviewed and asked to provide examples to support their descriptions of their child. On the basis of these interviews, some children were eliminated from the potentially anxious group. The teachers of the remaining children were also interviewed. The teacher, who had no knowledge of the child's prior behavior, first described and then ranked the child with respect to all children of the same gender in that classroom for the traits of shyness and fearfulness. The maternal and teacher information was discussed by a trio of investigators. If all three agreed that the evidence indicated that the child met criteria for anxious symptoms, then the child was categorized as belonging to an anxious group. A group of 42 children, or 26% of the sample met that criterion. This group of 42 children was compared with 107 control children from the longitudinal sample who did not meet criteria for any symptom. All children came to the laboratory, where they were administered a variety of procedures (the remaining 15 children had other symptoms).[13]

The children who had been high-reactive infants were most likely to have acquired anxious symptoms (45% of high reactives but only 15% of low reactives were classified as possessing anxious symptoms). The high-reactive children who developed anxious symptoms were most likely to have screamed in terror during the 21-month laboratory assessment when a person dressed in a clown costume unexpectedly entered the room where the child had been playing.

As at 4.5 years, the high reactives displayed fewer spontaneous comments and fewer smiles with the examiner compared with the low reactives and were more cautious and reflective on a cognitive test requiring the child to select the correct answer from a number of similar alternatives. It is also of interest that, among the high reactives, those who had anxious symptoms had higher sitting diastolic blood pressures than those who did not. These children also showed a second sign of sympathetic activity; they displayed a greater magnitude of cooling of the fingertips across a series of digit-recall problems. The cooling of the skin temperature reflects sympathetic activation of arteriovenous anastomoses in the fingertips.[12]

Although only 18% of the children who had been high-reactive infants were consistently inhibited at 14 months, 21 months, 4.5 years, and again at 7.5 years, not one high-reactive infant had become consistently uninhibited, fearless, and sociable across the four longitudinal evaluations.

These children were evaluated for the fifth time when they were between 10 and 11 years of age. A group of 55 children who had been high-reactive infants were more likely than were the 62 low reactives to show physiologic signs that are in theoretic accord with the assumption of greater amygdalar activity among the high reactives. The first sign is a decrease in low-frequency alpha activity and an increase in the higher-frequency beta activity in frontal areas because amygdalar projections to the prefrontal cortex desynchronize alpha frequencies. EEG activity was recorded while the child sat relaxed with eyes open, eyes closed, and during a minute when the child was asked to reflect on his or her thoughts on the way to the laboratory and to be prepared at the end of the minute to stand up and recite those thoughts. Significantly more high than low reactives showed more 14- to 30-Hz activity in frontal areas, especially during the minute when they were thinking about their speech.

A second sign was greater desynchronization of alpha frequencies on the right compared with the left frontal area. Considerable evidence supports the hypothesis that the right frontal region participates more fully in states linked to unpleasant or anxious feelings.[5, 9] The children who had been high-reactive infants and, in addition, highly fearful in the second year, were most likely to show greater activation in the right compared with the left frontal area. Furthermore, these children were emotionally subdued during the interview with the examiner, and they made significantly fewer comments while interacting with her.

A third physiologic sign involves the sympathetic nervous system. The amygdala sends projections to the autonomic nervous system, and therefore high reactives should show some signs of greater sympathetic lability or activity. The 10-year-olds who had been high-reactive infants were more likely than were the low reactives to show significant cooling of the tips of the index fingers while being administered a series of digits they were asked to remember. As noted earlier, the cooling of the fingertips is due to sympathetic constriction of anastomoses.[10, 12]

The fourth biological feature, which also implicates the amygdala, is a larger than normal wave 5 component in the brainstem auditory evoked potential, which is generated by the inferior colliculus. Activity in the amygdala influences the excitability of the inferior colliculus through projections to the central gray and locus ceruleus and, as a consequence, can enhance the magnitude of wave 5.[3, 15] Therefore, children who had a more excitable amygdala should have a larger wave 5 in the brainstem auditory evoked potential. As expected, the high reactives, as a group, had a significantly larger wave 5 component than did the low reactives, measured as a change in amplitude from the trough of wave 3 to the peak of wave 5 to a series of alternating clicks. In addition, the high reactives who had the highest fear scores in the second year had the largest wave 5 magnitudes.[21]

However, some high reactives who were not exceptionally shy or timid at 10 years of age showed greater than expected 14- to 30-Hz activity, right frontal activation, cooling of the fingertips, and a large wave 5 component. These facts mean that possession of some of the physiologic signs of an inhibited temperament need not be permanently linked to an inhibited profile. Experience can change an early behavioral profile of timidity and fearfulness owing, in part, to the excitability of the amygdala to a more normative profile without necessarily changing the excitability of the limbic structures that were the foundation of the infant classification. Jung would have agreed with this claim, for he believed that an individual with an introverted anima could acquire a persona of extroversion. This small group of children might fit the third meaning of *anxiety* described earlier, namely, a physiologic profile that is presumed to be part of the foundation of an anxious state but without the subjective feelings or behaviors that are assumed to accompany that state.

Children of Parents with Panic Disorder

In collaboration with Rosenbaum and Biederman, psychiatrists at Massachusetts General Hospital, the authors assessed children from 21 months to 6 years of age who had parents diagnosed with panic disorder ($n = 22$), panic disorder with depression ($n = 129$), depression only ($n = 49$), or control parents without psychiatric symptoms ($n = 84$).[19] Twenty-nine percent of the children with parents who had panic or panic with depression were inhibited in the laboratory, compared with only 12% of the controls. The children with parents who had both panic disorder and depression had higher rates of behavioral inhibition than did the controls (OR = 2.6; 95%CI = 1.2–5.6; $z = 2.44$; $P < 0.05$).

In addition, the children of parents with panic had a large temperature asymmetry between the pair of index fingers while they were watching a series of film clips.[13] Twice as many children with a parent with panic compared with those of controls had temperature asymmetry values greater than 0.5°C between the pair of index fingers. This variable implies a labile sympathetic nervous system. If one combines a subdued, inhibited profile with the examiner with a large temperature asymmetry, then 1 in 10 children with a parent with panic, but only 1 in 100 control children, combined an inhibited behavioral profile with this index of sympathetic lability. If inhibition were regarded as analogous to a physical illness, then the difference in risk between 1 in 10 and 1 in 100 would be a fact of clinical significance.

RISK FOR SOCIAL ANXIETY

The greater prevalence of anxious symptoms among the 7.5-year-old children who had been high-reactive infants suggests that this temperamental group is at higher risk than are most for the development of social anxiety. Support for this hypothesis comes from a study of 79 13-year-olds from an independent sample who had been classified in the second year of life as either inhibited or uninhibited based on their behavior in the laboratory. In addition to an extensive psychiatric interview, these children were assessed in the laboratory by an unfamiliar female examiner. There was a significant association between classification of a child as inhibited in the second year and a diagnosis of generalized social anxiety at adolescence but no association between earlier inhibition and the development of specific phobias or performance anxiety. Sixty-one percent of the adolescents who had been classified as inhibited in the second year had current social anxiety compared with only 27% of those who had been uninhibited in the second year. In addition, the adolescents who were diagnosed as having social anxiety made fewer spontaneous comments with the examiner than did other children. When the threshold was raised to require definite impairment in the adolescent's normal routine, academic functioning, or social activities, 44% of the female adolescents who had been inhibited earlier were impaired to a major degree by their social anxiety, compared with only 6% of the female adolescents who had been classified as uninhibited. The difference among the male adolescents was less striking; 22% of male adolescents who were inhibited as toddlers were impaired by their generalized social anxiety compared with 13% of the male adolescents who had been classified as uninhibited.[20]

The fact that inhibition in early childhood was a better predictor of generalized social anxiety in adolescence than of specific fears is in accord with research in animals. The neural circuits that mediate a fear reaction to a specific conditioned stimulus associated with electric shock are different from those circuits that mediate a fear reaction to the context in which shock was delivered. Generalized social anxiety might be thought of as reflecting a fear of an unfamiliar context rather than fear of a specific person or object.[17]

TEMPERAMENT AND INTERNAL TONE

The primary symptoms of the varied categories of anxiety disorder include reports of fears of animals, insects, heights, or the dark; panic attacks; chronic worry over illness, harm, failure, or social evaluation; or obsessions and compulsions. Because a majority of adults experience, temporarily, one or more of these symptoms at least once during a lifetime, a diagnosis of anxiety disorder is applied only if the symptoms are chronic or impair activity severely. Two facts must be explained.

Less than 20% of U.S. adults possess one or more of the anxiety disorders, and more women then men—10% versus 5%, respectively—are given this diagnosis.[18] If the causes of anxiety disorder were simply external stressors, many more adults should be assigned that category, for more than 20% of the population experiences job loss, chronic illness, death of a loved one, or failure to gain a desired goal. Moreover, these frustrations occur as often to men as to women. Because females of many animal species are more avoidant and defensive than are males,[2] it is likely that a proportion of patients with social anxiety possess a special biological diathesis that renders them vulnerable to developing these attributes.

One feature of this diathesis is a change in the person's conscious feeling tone. Sensory information from select body sites is relayed to the nucleus tractus solitarius in the medulla, where epinephrine and norepinephrine potentiate, but opioid receptors mute the intensity of these signals, which are sent first to the amygdala and from there to the ventromedial prefrontal cortex.[4] If these unexpected signals pierce consciousness, they are likely to be experienced as unpleasant and the person will be motivated to interpret the change in feeling tone. A small proportion of individuals are born with a temperament that renders them especially susceptible to more frequent or more intense changes in this unpleasant feeling tone. The person's culture and history, acting together, provide a foundation for the interpretation imposed on these perceptions.

Two interpretations come easily as individuals try to understand why they suddenly feel unpleasant. On the one hand, the individual may attribute the feeling to worry over a possible future threat. Some patients with social phobia attribute their sensations to worry over behaving inappropriately in a social situation. A second popular interpretation for the change in tone is an ethical lapse. Because a failure to honor one's standards for proper behavior is often followed by a feeling of shame or guilt, a person experiencing the onset of dysphoric feeling tone, but not knowing why, is biased to regard it as due to a failure to meet one of his or her ethical standards. Every individual can cite many occasions when his or her actions failed to meet his or her standards for civility, honesty, or virtue.

A diathesis that results in more intense or more frequent bouts of dysphoric tone explains why social anxiety is not more prevalent but does not explain why more women than men develop these symptoms. That fact could be explained if (1) the bodily signal arriving in the medulla were more intense in women than in men; (2) the female medulla was either more active or was less effective in muting the bodily signal; (3) the activation of the amygdala by information from the medulla was greater in women and, therefore, amygdalar projections to the ventromedial prefrontal cortex were stronger in women; or (4) the ventromedial surface of the prefrontal cortex was more responsive in females than males. Each of these four mechanisms relies on a different neurochemistry. Although the authors favor the second explanation, any one of the four could explain the sex difference.

Nineteenth-century women felt the moral imperative to be faithful wives and selfless mothers. Many contemporary US and European women, especially those who are well educated, are barraged with three standards that are especially difficult to meet: (1) be beautiful, (2) be loved, and (3) accomplish something important. It is easy to fail any one of these assignments. Thus, when dysphoric bodily information penetrates consciousness demanding an interpretation, a woman might decide, "I am not pretty enough," "I am not valued enough," or "I am not accomplished enough," and will be prone to avoid social situations. This is one reason why social class is a predictor of the prevalence of social anxiety. Many US women now pursue professional careers; hence, those who have not attended college or work in less skilled vocations are likely to be embarrassed about their lack of accomplishment and will be anxious over an undesirable evaluation by others.

PREOCCUPATION WITH ANXIETY IN MODERN LIFE

Fear and anxiety have come to be classified as less natural and more undesirable emotions over the past 150 years. The Greeks believed that envy, jealousy, and anger were more significant causes of mental illness than were fear or anxiety because the former states disrupt social harmony. Psychopathology had ethical implications in Plato's century, for it signified a failed morality. Aristotle naturalized the emotions and set the stage for a millennium of ethically neutral, more materialistic explanations of feelings.

Fear assumed prominence during the medieval centuries, when worry over God's wrath was a preoccupying concern. Augustine saw fear as adaptive because it helped humans to behave morally. John Bunyan, almost 1000 years later, reasserted that fear of God was a blessing, for it permitted one to love the Deity. Readers should reflect on the dramatic change in premise from the seventeenth-century claim that fear was a requisite for love to the contemporary belief that fear restricts the ability to love.

The twentieth century was marked by liberation from ethical restraints on sexuality, aggression, competitiveness, and narcissism. As the years passed, many individuals lost strong identifications with institutions and communities and felt freer to pursue personal desires. However, because many individuals were unsure as to what goals they should seek with their new freedom, Auden named our era "The Age of Anxiety." Although Kierkegaard was prescient in sensing, as early as the 1840s, the mood that would explode in Europe over the next century, Auden's diagnosis required special historical conditions, especially a working class demanding more autonomy, fragmentation of village life as a result of industrialization, and a middle class pushing to be free of the last restraints of medieval Christian ethics. These forces came together to permit some adults to realize that they had a choice in their life decisions. Freud argued that the uncertainty over sexual decisions was the fundamental cause of a neurosis.

Humans are capable of worrying about a great many things. A particular culture can promote one target to a dominant position, but only for a while and only in some places. The belief that humans can and should be free of anxiety is one of the distinguishing illusions in Western thought in this century.

SUMMARY

The discovery of pharmacologic interventions that mute the intensity of anxiety and guilt in some individuals has been a benevolent gift to those who suffer from these disabling states. Although some commentators have wondered about the social consequences of large numbers of asymptomatic persons taking these drugs, few have questioned the advantages for the smaller group of anguished patients. It is likely, however, that, during the next century, scientists will discover a drug that eliminates the feeling components of guilt and remorse while leaving intact the semantic knowledge that certain acts are ethically improper. An individual who took this drug regularly would continue to know that deceiving a friend, lying to a client, and stealing from an employer are morally wrong but would be protected from the uncomfortable feeling of guilt or remorse that accompanies a violation of a personal moral standard. It is reasonable to wonder, therefore, whether our society would be changed in a major way if many citizens were protected from guilt and remorse.

Most Western philosophers, especially Kant, made reason the bedrock of conscience. People acted properly, Kant believed, because they knew that the behavior was morally right. All individuals wish to regard the self as virtuous and try to avoid the uncertainty that follows detection of the inconsistency that is created when they behave in ways that are not in accord with their view of the self's desirable attributes.

Kant believed that, although the moral emotions restrain asocial acts, they were not necessary for the conduct of a moral life.

On the other hand, some philosophers, such as Peirce and Dewey, argued that anticipation of anxiety, shame, and guilt motivate a continued loyalty to one's ethical standards. A person who was certain that he or she was protected from these uncomfortable emotions would find it easier to ignore the moral imperatives acquired during childhood and adolescence. It is not obvious that a drug that blocks remorse also will eliminate the mutual social obligations that make a society habitable; nonetheless, a posture of vigilance that is appropriate for—unlike gorillas—humans can hold representations of envy, anger, and dislike toward people they have never met for a very long time. While we wait for future inquiry to resolve this issue, it is useful to acknowledge that a satisfying analysis of this problem will require a deeper appreciation of the differences between the representations of the biological events that are the foundation of an emotion and the representations that define the semantic networks for the concepts good and bad.

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