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The Current Concept of Anxiety: Implications from Darwin to the DSM-V for the Diagnosis of Generalized Anxiety Disorder

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Review Article for Expert Review of Neurotherapeutics

The Current Concept of Anxiety: Implications from Darwin to the DSM-V for the Diagnosis of Generalized Anxiety Disorder

Abstract

The article proposes a revision of the historical evolution of the concepts of generalized anxiety disorder (GAD). Currently, Darwin's evolutionary theory is the hegemonic paradigm for modern science and influences research on mental disorders. Over the twentieth century, the editions of the Diagnostic and Statistical Manual of Mental Disorders (DSM; American Psychiatric Association) have changed the diagnosing criteria for GAD, reflecting the prevailing psychiatric understanding of this disorder. The prevalence and symptoms of major depression and GAD show the fragility of the categorical conception of these conditions. Differences in cultural views towards anxiety disorders also suggest that anxiety cannot have a uniform definition. Besides, this article provides contributions for reflecting future guidelines concerning the diagnostic criteria for GAD in DSM-V.

Key words: History, classification, anxiety disorders, generalized anxiety disorder, diagnostic criteria, overanxious disorder, future diagnostic.

Introduction

Modern science views anxiety as a set of behavioral, endocrine and physiological responses, such as avoidance and arousal, which evolved to protect the individual from potential threats [1]. Although these responses convey clear adaptive value, experiencing them excessively or in the absence of the threatening stimuli might characterize serious illness, negatively interfering in the social and professional life of the individual.

Anxiety-related reports occur frequently in everyday life and, as a result, the concept of anxiety may appear to be a uniform construct that has been present throughout human history. While the behavioral responses currently associated with anxiety have been an enduring aspect of human psychology and behavior, they have not always been linked explicitly to anxiety. Rather, the concept of anxiety has evolved over time as it has both influenced and been modified by the prevailing view of anxiety disorders.

The subjective and objective feelings of anxiety have been universally experienced by humans, who have described anxiety in a number of contexts, including religious, anthropological, philosophical, medical, and psychological settings [2]. For example, Greek mythology provides the example of the god Pan, who was feared by all who needed to traverse the forest at night. Because the darkness and loneliness of crossing the forest produced feelings of sudden fear that did not have any apparent cause, the ancient Greeks attributed these unexplainable but extremely uncomfortable physical sensations to Pan, thereby resulting in the word *panic*.

During the eighteenth century, the term anxiety was used for the first time in the field of medicine to refer to a mentally ill state, which was then mostly understood in physical terms. From this medical perspective, anxiety was considered to be a somatic pathology, with the physical symptoms of anxiety primarily being taken into account when performing a medical evaluation. In the nineteenth century, the diagnosis of anxiety differed between authors, who employed vague and diverse criteria for identifying this mental disorder. However, Emil Kraepelin (1856-1926) performed some pivotal work in this period by classifying anxiety disorders. In 1899, Kraepelin comprehensively classified mental disorders by dividing them into thirteen groups according to their causes and symptoms. His theories dominated the field of psychology until the beginning of the twentieth century, when they were rejected by his follower, Adolf Meyer (1866-1950), who introduced a new system for classifying mental disorders. Meyer was inspired by Freud's ideas as well as by Darwin's theory of evolution through natural selection, which is now considered the most influential paradigm in western biological sciences. Meyer synthesized ideas laid forth by Kraepelin, Freud, and Darwin to propose that the functioning of the human mind depended on a combination of biological and psychological efforts to adapt to the world. Meyer communicated with other psychologists and also started to work with his patients from a more focused on the patient's life and personal perspective. In fact, at this time in America, psychologists were more concerned with understanding and treating mental disorders than they were with their classification, a practice that tended to be more prevalent amongst European psychologists [3].

During World War II, the environmental and psychological factors that contributed to mental disorders were highly emphasized by scientists. For example, William Menninger, who was chief of military psychiatry during World War II, became very well known for his

psychoanalytical approach to the diagnosis and treatment of mental disorders. During this time, the National Institute of Mental Health (NIMH) was also sponsoring important clinical research in modern psychology [3].

The first official American classification for mental disorders was issued in 1918 as the Statistical Manual for the Use of Institutions for the Insane, but various types of "psychoneuroses," including anxiety, did not appear in this manual until the tenth edition was published in 1942. Following this development, the Diagnostic and Statistical Manual of Mental Disorders (DSM) was published in 1952 and included three conditions for anxiety, which were termed anxiety reactions and were described in psychoanalytical terms. In the DSM-II, the terminology was revised such that anxiety disorders were now described as neuroses, although this condition was still based on psychoanalytical terms. With the intention of making the manual more neutral and accessible to students from different psychological backgrounds (e.g., cognitive, behavioral, interpersonal, family/systems, biological, and psychodynamic), the DSM-III was published in 1980 with extensive pragmatic changes, one of which was to lengthen the classification of anxiety disorders. In 1994, the DSM-IV was published with extensive revisions designed to make it more usable in clinical settings, such as hospitals, clinics, and private offices. In addition, the DSM-IV was also designed to be an instrument used by health professionals for calculating the prevalence of mental disorders in public health institutions. Currently, the American Psychiatric Association (APA) is attempting to revise the DSM-V in order to expand the scientific basis for diagnosing psychiatric conditions and to establish clearer definitions of mental disorders. So far, the APA has created the DSM-V Task Force and Work Groups, which are working with the World Health Organization (WHO) to provide a scientific basis for revising the International

Classification of Diseases. Hopefully, the diagnostic criteria in the DSM-V will be much improved as it has incorporated over a decade of work, including a comprehensive review of scientific developments, research analysis, and clinical experience. The DSM classification for anxiety disorders will be described in more detail later.

The Concept of Anxiety across History

Anxiety in the Eighteenth Century

The eighteenth century was a very important period for the development of a more modern view of anxiety because this was the first time that the medical field described anxiety as a mentally ill state. For instance, William Battie, a prominent British psychiatrist from the 1700's, defended anxiety as a disorder in his pioneering medical writings. Distinct from the modern psychological view that anxiety is derived from dysfunctional cognitive processes [4-6], Battie interpreted anxiety as primarily having a physical basis, which manifested itself as some type of excessive sensation [7]. On the other hand, James Vere (1778) believed that anxiety stemmed from more mental causes and possibly resulted from internal conflicts, a belief that could be considered one of the first roots for the Freudian psychodynamic model of the mind.

Nevertheless, in the eighteenth century, anxiety was mostly characterized by a strong emphasis on physical symptoms that produced anxiety profiles, that is, the emotion symptoms of anxiety. Indeed, it was very popular at that time to associate anxiety with some kind of nerve disease. For instance, Scottish physician William Cullen (1710-1790), who is

considered the father of the term neurosis, suggested in his writings that neurosis was an observably ill condition caused by some affliction of the nervous system.

Anxiety in the Nineteenth Century

Rather than explaining mental illnesses in terms of their underlying somatic pathologies, psychologists in the nineteenth century began to attribute psychological factors to the etiology and development of anxiety disorders.

By the end of the nineteenth century, there was not only more of a consensus that excessive anxiety should be placed within the realm of psychiatry, but also some acknowledgement that there were psychological contributions to anxiety. However, this latter idea deserves some additional consideration. At the end of the nineteenth century, Wilhelm Griesinger (1817-1868), a German psychiatrist and neurologist, defended the idea that mental illnesses and somatic symptoms were part of the same phenomena [7]. In his view, the etiology of anxiety was organic, i.e. anxiety was derived from abnormal neural functioning. However, he also believed that it arose at the level of affect, the strength of which could lead to serious anxiety symptoms. In this sense, Griesinger developed a conceptual model of mental illness that was based on a close relationship between the body and the mind. In his view, the body and mind formed a unified entity such that the brain was the organ and the psychological processes were the function of the brain. In this context, mental disorders could emerge as organopathological processes [8], a view that resembles that of modern neuroscience.

The biological orientation towards anxiety in the field of psychiatry persisted throughout the nineteenth century, as can be observed in the medical writings of Benedict Morel. Morel professed that psychopathology was an abnormality in human nature, a primitive trait that had been propagated throughout humankind by the principle of species continuity [9]. The biological interpretation of anxiety was also expressed by French psychiatrist Legrand du Salle (1830-1886), who made important contributions to the understanding of obsessive-compulsive disorder and suggested that adverse heritable traits, rather than psychological factors, may explain the etiology of anxiety [10]. One of the most important contributions during the nineteenth century to the modern concept of anxiety was the development of the term neurasthenia, by the American neurologist George Miller Beard (1881). This term was used to describe a set of symptoms similar to GAD and referred to some type of nervous exhaustion. Although this strict definition of neurasthenia may indicate that Beard subscribed to a biological understanding of mental disorders, it should be noted that he firmly acknowledged the importance of studying both the mental and physical aspects of psychiatric illnesses.

Freud published a theoretical paper that would be very popular at that moment. In it, Freud mentioned the “anxiety neurosis” and defined its symptoms, among them, general irritability, anxious awakening, anxiety attacks, and somatic equivalents such as cardiovascular and respiratory symptoms, sweating, tremor and nausea. The symptoms resulted from ‘hereditary taint’ or from somatic excitement originated from bad functioning of the nervous system and could be combined in various ways. Freud understood ‘anxiety neurosis’ as a form of ‘actual neurosis’ as a result of a reactive condition from childhood events [10-13]. Anyway the concept of the diagnosis of ‘anxiety neurosis’ had an impact on

the medical literature and a vast acceptance by psychiatrists for many decades. We can compare Freud's introduction of the 'anxiety neurosis' to the DSM-III introduction of the concept of GAD and panic disorder. Both, Freud and the DSM-III, presented a new paradigm that was quickly accepted by the scientific community and produced a vast literature about the theme.

Anxiety in the Nineteenth Century: Darwin and the Theory of Evolution

In the nineteenth century, one of the greatest influences on the biological understanding of human behavior came from ideas posited by Charles Darwin (1809-1882).

Darwin was a careful observer of the natural world, and his ideas greatly impacted many fields, including psychology and psychiatry, by providing compelling evidence that human beings were subject to the same natural laws as all other animals (Figure 1). His research also permitted humans to be studied in comparison to other animals and emphasized the role that natural selection has on influencing human psychological variability. In his seminal book, *The Origin of Species* (1859), Darwin proposed that behavioral and physical characteristics that tend to be more adaptive for an organism in terms of increasing the probability of reproduction and survival are selected for and spread throughout a species. This process, named natural selection, provided an important model for understanding why certain physiological, psychological and behavioral features may be prevalent within a specific species. In 1872, Darwin presented *The Expression of the Emotions in Man and Animals*, in which he highlighted the idea that human beings – as well as other animals – likely inherit some emotions and emotional expressions from their ancestors given that emotions are

important characteristics for promoting survival. Through this work, Darwin was able to explain how emotions – such as fear – may be interpreted as being adaptive within a functional framework. Although the theory of evolution was not yet adopted as the hegemonic paradigm for science at that time, these Darwinian concepts would later provide the basis for modern scientific thought, impacting not only biology but also psychology and psychiatry, as will be discussed later.

Anxiety in the Twentieth Century

The belief in the inheritability of emotions and a continuing emphasis on the biological aspects of anxiety influenced the academic and medical understanding of anxiety disorders at the beginning of twentieth century.

In this period, Ribot [8] greatly contributed to the concept of anxiety by identifying different types of anxiety disorders, such GAD and specific phobias. In addition, there was a shift from a biological to an environmental understanding of both normal and unhealthy characteristics in psychology during the middle of the twentieth century, which brought remarkable changes to how anxiety disorders were viewed. For example, in 1938 F.B. Skinner defined anxiety as a set of conditioned responses to aversive events. Given knowledge obtained from modern advances in genetics, neuroscience and cognitive psychology, it is doubtful that all cases of anxiety are manifestations of learned responses. However, such behaviorism likely played an important role in emphasizing that the environment contributes to the production of anxiety disorders. This novel understanding of anxiety helped provide the

rationale for treating anxiety with behavioral therapy, which utilizes exposure techniques that have proven effective for tackling symptoms of anxiety [14].

In the 20th century, the concept of anxiety as used in clinical psychiatry underwent an important historical moment when it was classified in the APA's *Diagnostic and Statistical Manual of Mental Disorders* (DSM) [15].

Anxiety Disorders' Classification in the DSM: Historical Facts

DSM-I (APA, 1952)

In the first DSM manual, anxiety disorders were defined using psychoanalytical terms as "disorders of psychogenic origin or without clearly defined physical cause or structural change in the brain" [15, p.5]. They were considered to be examples of psychoneurotic disorders and were precursors to the modern concept of anxiety disorders. They were classified as the following:

1) Anxiety reaction – A disorder that was referred to as "diffuse and not restricted to definite situations or objects" [15, p.32].

2) Phobia reaction – This disorder was said to occur when the individual "becomes detached from a specific idea, object or situation in the daily life and it is replaced by some symbolic idea or situation in the form of a specific neurotic fear… The patient attempts to control his anxiety by avoiding the phobic objects or situation" [15, p.33]

3) Obsessive-compulsive reaction – This condition was described as anxiety that is "associated with the persistence of unwanted ideas and of repetitive impulse to perform acts which may be considered morbid by the patient. The patient himself may regard his ideas and behaviors as unreasonable but nevertheless is compelled to carry out his rituals" [15, p.33].

Besides these anxiety-related disorders, the DSM included other syndromes that were part of the spectrum of "psychoneurotic disorders," including dissociative reaction, conversion reaction, and depressive reaction. It also made a brief reference to what is currently termed posttraumatic stress disorder. However, GAD was not included in the first edition of the DSM.

DSM-II (APA, 1968)

The DSM-II attempted to meet the needs of psychiatrists from different theoretical backgrounds and emphasized the need to integrate the DSM with the World Health Organization's International Classification of Diseases (ICD). During the developmental process for the DSM-II, communication with psychiatrists and a specialist encouraged the APA to emphasize the communicative function of the classification system, thereby partially neglecting the issues of reliability and validity.

Mental disorders continued to be described using psychoanalytic theory, and the term psychoneurotic disorder was replaced by the term neurosis. In this edition, there were three categories for anxiety disorders, including anxiety neurosis, obsessive-compulsive neurosis, and phobic neurosis. Anxiety neurosis referred to "anxious over-concern extending to panic

and frequently associated with somatic symptoms… not restricted to specific situations and objects" [16, p. 39], whereas phobic neurosis was "generally attributed to fears displaced to the phobic object or situation from some other object of which the patient is unaware" [16, p. 40].

Other anxiety syndromes described in the DSM-II included depressive, dissociative, hysterical, phobic, neurasthenic, depersonalization, and hypochondriacal disorders.

GAD was not included in the DSM-II.

DSM-III (APA, 1980)

Unlike in the DSM-I and DSM-II, the concepts in the DSM-III did not follow any particular theoretical approach. The criteria were much more explicit, and the disorders were subdivided into specific categories. For example, phobic disorder included agoraphobia with panic attacks, agoraphobia without panic attacks, social phobia, and simple phobia.

In the DSM-III [17], anxiety disorders included panic disorders, generalized disorders, obsessive-compulsive disorders, and posttraumatic stress disorder. Pharmacological studies greatly helped to redefine some categories of anxiety disorders.

In the DSM-III, generalized anxiety disorders were defined as uncontrollable and diffuse anxiety or worry accompanied by several related psychophysiological symptoms that persisted for 1 month or more.

This edition also included another category called atypical anxiety disorder, which was used when the patient's symptoms did not fit the diagnostic criteria for the other types of anxiety.

Heightened awareness about the importance of developing well-defined criteria for each mental disorder accelerated the refinement and revision of this manual, which culminated in the production of the DSM-III-R in 1987.

DSM-III-R (APA, 1987)

In the DSM-III, atypical anxiety disorders were renamed "anxiety disorder not otherwise specified." However, the general description of anxiety disorders remained relatively unchanged in the DSM-III-R [18]. The only notable difference was in the diagnostic criteria for specific disorders.

DSM-IV (APA, 1994)

The DSM-IV [19] represented the most important revision of the DSM to date. Because the ICD-10 had been published two years prior to the DSM-IV, there were serious concerns about coordinating information in the two manuals.

APA concentrated in the review drawn from scientific studies rather than simple professional consensus as was done previously.

In the DSM-IV, twelve anxiety disorder categories were described that are now part of formal nomenclature: panic disorder without agoraphobia, panic disorder with agoraphobia, agoraphobia without history of panic disorder, social phobia, specific phobia, generalized anxiety disorder, obsessive-compulsive disorder, posttraumatic stress disorder, acute stress disorder, anxiety disorder due to general medical condition, substance-induced anxiety disorder, and anxiety disorder not otherwise specified.

Among these disorders, there were three new categories of anxiety disorders that had been added to the DSM-IV, namely acute stress disorder, anxiety disorder due to general medical condition, and substance-induced anxiety disorder. The other categories had been through several revisions. For example, in panic disorders, severity specifications were eliminated, additional typology was included (unexpected, situationally bound, situationally predisposed), and there was an increased emphasis on cognitive features (i.e. worry about panic), along with other changes. In addition, GAD was modified in the DSM-IV so that the most important criterion for this disorder was the presence of uncontrollable worry. The list of associated physical symptoms was reduced from 18 to 6, primarily by eliminating autonomic symptoms.

DSM-IV-R (APA, 2000)

Although the diagnostic criteria for all disorders were not changed in the DSM-IV-R [20], the description of each disorder was updated to reflect current advances in knowledge about mental disorders.

DSM-V Overview: The Future Manual

The human brain is a very complex structure, making studying it highly challenging. Research in the fields of neuroscience, psychology, and psychiatry has been done to improve the diagnoses of mental illnesses and to develop more effective treatments for mental disorders. To make a more trustworthy and universal diagnostic assessment tool, the APA and WHO have been conducting research in several fields of mental health in order to formulate more objective criteria for the diagnoses and treatment of mental disorders.

Given recent advancements in the understanding of mental disorders, there are currently very high expectations surrounding the publication of the DSM-V and the ICD-11. There has also been much speculation about possible changes to the diagnostic criteria, particularly for some mental disorders. In the current literature, there has been some speculation regarding potential revisions to anxiety disorders. Several of these studies have raised issues related to nosologic validity. Some researchers believe that taking nosological issues into account will increase our understanding of the prevention, etiology, and progression of anxiety disorders and allow researchers to determine why some disorders are resistant to treatment [21].

As mentioned previously, GAD was first defined in the DSM-III. While the diagnostic criteria for GAD have undergone numerous changes in the various DSM publications, the validity of GAD is still under question, with some researchers suggesting that further investigation into GAD and its diagnostic criteria is warranted. When reviewing the scientific literature, suggested changes to GAD's diagnostic criteria include events generating anxiety, the duration and frequency of symptoms, the relationship of anxiety with other symptoms, and

specific behaviors. For example, the review article by Andrews et al. [22] suggested that various changes be made to the DSM-V, including changing GAD to "generalized worry disorder" based on the prevalence of excessive worry in patients with this disorder. Another area of controversy is accurately defining the end of a GAD episode. While some researchers argue that the end of a GAD episode is characterized by one month of symptom remission, others have suggested that it should be defined as one month with symptoms on less than fifteen days [23]. In addition, studies comparing the symptoms of GAD to the symptoms of major depressive disorder (MDD) indicate that more attention should be paid to differentiating between these two conditions. In clinics, depression, anxiety, and somatic symptoms occur together and share similar symptoms, indicating that further research is necessary to develop differential criterion for these conditions.

The diagnostic criteria for GAD in the DSM-III to the DSM-IV-R are listed in Table 1 along with the APA's suggestions for diagnostic criteria in the DSM-V. Please note that there was no GAD diagnosis in the DSM-I and II.

► Key points of change in the diagnostic criteria of GAD in the DSM

- GAD was not included in the DSM-I and DSM-II.
- In the DSM-I, the category anxiety reaction referred to a diffuse anxiety disorder.
- GAD appeared for the first time in the DSM-III as a residual diagnosis intended for individuals complaining about persistent anxiety of a nonspecific (i.e., generalized) nature. The diagnostic criteria were: generalized, persistent anxiety lasting at least one month in duration without symptoms of phobias, obsessive-compulsive disorders,

panic, or any other symptoms stemming from another mental disorder, such as depressive disorders or schizophrenia.

Symptoms also had to include three of the following four categories: motor tension, autonomic hyperactivity, apprehensive expectation (including anxiety, worry, and fear), and vigilance.

- In the DSM-III-R, the criteria changed to also include unrealistic or excessive worry about two or more life circumstances for six months duration.

  At least six symptoms had to be present from the following three symptom clusters: motor tension, automatic hyperactivity, and vigilance and scanning.

- In the DSM-IV, an additional criterion was added, namely that "the worry must be perceived by the individual as uncontrollable." The symptoms had to persist for at least six-month duration and the list of associated somatic symptoms was reduced from eighteen to six. Generally, it was thought necessary to have at least three of the following associated symptoms: restlessness or feeling keyed up or on edge; being easily fatigued, having difficulty concentrating or feeling like one's mind is going blank; irritability, muscle tension, or sleep disturbances.

- In the DSM-V (www.dsm5.org, site accessed on 09 March 2010), the duration of excessive worry and anxiety as well as the somatic symptoms necessary to be diagnosed with GAD will be reviewed.

Defining the conceptual boundaries of anxiety: the influence of depression

It would be incomplete to discuss the historical factors that have contributed to the modern concept of anxiety without mentioning the relationship between anxiety and

depression. The difficulty in establishing clear boundaries between anxiety and depression has been observed since the Medieval Ages and the Renaissance. During these periods, anxiety and melancholia frequently overlapped, so that it was common to find people who were both depressed and pathologically anxious. However, Brown and Leyfer [14] have reported that the psychological states currently diagnosed as anxiety disorders were not thought to require institutional care until the nineteenth century. Currently, there are many patients being treated for anxiety disorders, but the prevalence of depressive symptoms within this population highlights the ambiguity surrounding the concept of anxiety and the necessity for a better understanding of what differentiates anxiety from depression. For instance, the correlation between self-reports and scales of anxiety and depression have often been greater than 0.70 [21]. Hence, it is uncertain whether GAD as defined in the DSM-IV represents a distinct disorder from depression [22].

In addition, Brown and Leyfer [14] have suggested that GAD may be a variant or an early symptom of depression. These authors even point out that the ambiguous boundary between anxiety and depression is acknowledged in the DSM-IV, which stipulates not to diagnose a patient with GAD if GAD symptoms only occur during an episode of a mood disorder.

Genetic and environmental factors may account for both the similarities and differences between the two disorders. Hence, continuing to improve current neuroscience and biomolecular research techniques may prove important for unraveling the etiologies of anxiety and depression. Indeed, the high co-morbidity between anxiety and other mood disorders may stem from commonalities in their etiological roots. For instance, studies in female twins have

indicated that there may be a genetic correlation between the two disorders [23], which further support the hypothesis that in women, the same genetic factors may contribute to both major depression and GAD. It is worth noting that weak diagnosis boundaries also occur between GAD and other anxiety disorders, such as social phobia, as shown by a recent study on the prevalence of anxiety and mood disorders [28].

While such research has advanced our scientific understanding of anxiety, more extensive studies need to be done to examine the key components underlying both anxiety and mood disorders so that more valid and precise diagnoses and descriptions of these mental illnesses can be performed.

Evolutionary Psychology: Revisiting Darwin to build the current view of anxiety in psychiatry and neuroscience

For modern science, the Darwinian theory of evolution has become the most accepted explanation for how the brain functions. In the twenty-first century, the field of neuroscience and some schools of thought in psychiatry and psychology have acknowledged that the presence of universal features in human functioning is a legacy of natural selection.

Evolutionary psychology, which is one of the most prominent fields of psychology, applies evolutionary biology to psychology and conceives the human mind as a set of functionally specialized information-processing machines that were shaped by natural selection as our ancestors adapted to problems in their environment [29]. Evolutionary

psychology can be viewed as a way to think about psychology and can be applied to several topics, including emotions [30].

For evolutionary psychologists, emotions are thought to be adaptive processes that arose to help coordinate the mind's many subprograms. For instance, when facing a predator, emotional states are critical for helping the organism to initiate the flight or fight response rather than engaging in sleep or digestive behaviors. When the brain detects evolutionarily recognizable situations, the emotional centers can signal the appropriate subprograms to activate behaviors that are adaptive for that specific situation and deactivate other behaviors that may negatively interfere with the appropriate behavioral response.

While emotions such as fear and anxiety may appear to represent disorders in brain functioning, they may also be interpreted as representing well-designed mediators of perception and behavior [26]. However, this may not apply to individuals suffering from anxiety disorders. According to Cosmides and Tooby [30], emotions can fail to be adaptive because while they may be the best response to an environmental challenge from an evolutionary perspective, they may not be the best response in actuality. This idea is supported by one of the principles from evolutionary psychology that "*our modern skulls house a stone age mind"* [29].This phrase suggests that the expression of human emotions today merely reflects what used to be adaptive in our ancestors' environment. Hence, mismatches between our emotional responses and our modern environment may produce suboptimal outcomes [31]. Anxiety disorders could be seen as one of these dysfunctional outcomes.

In addition, Ness [32] has posited that adaptive fear responses often appear over-responsive in that some prey animals may express startle and flight responses that exceed the potential for danger in a certain situation. This over-expressed behavioral response may be seen as irrational, but it might also be considered an effective strategy from an evolutionary perspective. In other words, it would be more adaptive to over-react and survive rather than risking exposure to potential threats. In this context, emotional reactions may be incorrectly interpreted as the expression of a poorly-designed behavioral program [31]. However, it is important to note some additional factors in order to understand anxiety disorders. As previously mentioned, there are differences between the environmental pressures faced by modern human beings and those faced by our ancestors. Over-responding may have produced adaptive outcomes in the past when threats varied from wild animals to tribal rivalry. In contrast, the "predators" in our modern environment likely demand different behavioral responses. In other words, what may have been adaptive for our ancestors is not necessarily still adaptive in the modern age. Thus, constantly over-responding to the presence of threatening stimuli – such as giving presentations, the high demands of the marketplace, or loneliness – may contribute to anxiety disorders, such as GAD, given that these emotional responses may be quite maladaptative.

Currently, scientific thought considers emotions to be universal facets of human nature [33, 34]. Hence, if emotions correspond to an innate program designed to react to environmental cues, the evaluation of these cues may be highly modulated by cognitive processing. According to Cosmides and Tooby [30], when an emotional program is activated, specialized inference systems are also activated and are responsible for evaluating details of a threatening context (such as "*Did the lion see me?*" or, in modern terms, "*What if I lose my*

job?"). This probably happens on the basis of what Baron-Cohen [35] termed the "seeing-is-knowing" circuit, which is responsible for our ability to imagine and represent cues and states of mind held by us and others. As said previously, errors made in the frequency and magnitude of a behavioral response when activating this system may distort what was once a highly adaptive behavior, thereby producing errors in information processing. This cognitive distortion may be a core maladaptive characteristic of anxiety disorders, which may explain why anxiety disorders can be favorably addressed by cognitive-behavioral therapies [36, 37].

Undoubtedly, evolutionary psychology strongly contributes to the modern concept of anxiety and anxiety disorders. For a clear understanding of the historical changes that the concept of anxiety has gone through, important points in its history, including the valuable contributions from Darwinian Theory, are highlighted in figure 2.

Darwin and the Neurobiological Concept of Anxiety

While fear and anxiety have contributed to both current and evolutionarily ancient experiences in humans and animals, there is still no consensus on the definitions for these phenomena. There are several different definitions for anxiety in the scientific literature that have emphasized either the subjective, behavioral, and/or physiological aspects of anxiety. Hence, anxiety may be defined as a subjective state of apprehension and tension that is evoked by the anticipation of danger [38], or it may be seen as a diffuse and highly unpleasant feeling of apprehension that is often vague and accompanied by physical sensations, including fluttery stomach, chest tightness, palpitations, sweating, as well as other symptoms [39]. Alternatively, other authors have suggested that anxiety maybe a

motivational impulse that is critical for various behaviors and, as a result, has significant adaptive and evolutionary value [40].

The idea that anxiety-related behaviors have been evolutionarily selected for during the phylogenetic history of species for their adaptive/ protective function is recurrent across the different definitions of anxiety. In objective terms, anxiety may be a set of typical behavioral and physiological responses - including avoidance, vigilance, and arousal - that evolved to protect an individual from danger [41]. This definition includes the most current concept of anxiety in the field of neurobiology and profoundly takes the Darwinian paradigm into account.

The neurobiological view of anxiety suggests that anxiety may be a collection of somatic, perceptual, cognitive, and behavioral symptoms that are elicited by both the anticipation and presence of aversive stimuli [42]. Anticipating aversive stimuli may produce behavioral responses that resemble anxiety, such as a lower threshold to detect sensory cues and a higher rate of freezing [43]. Freezing is characterized by an immobile state in which all movements cease except respiratory movements and corresponds to periods during which an animal remains highly alert.

In the fields of neuroscience and evolutionary psychology, scientists have suggested that various behavioral and physiological modifications occur when an organism detects a threatening cue [30]. These responses include the following: (1) perception and attention are increased to enhance the animal's ability to hear and distinguish sounds; (2) motivational objectives and goals are redirected to make safety the absolute priority; (3) memory processes

are used to assess the present situation and recall strategies used in the past that were effective; (4) communication processes are modified; depending on the circumstances, the animal may either emit an alarm call or remain paralyzed without emitting any sound; (5) specialized learning systems are activated; and (6) following activation of the sympathetic nervous system and adrenaline release, important physiological responses occur, including increased heart rate, stress hormone secretion, hypoalgesia, and reflex potentiation [39]. Interestingly, although prominent and hegemonic, the Darwinian theory of evolution cannot explain all features of anxiety, presenting some gaps not yet filled out by experimental models. For instance, blushing is a common characteristic of social anxiety patients, and it appears to have no adaptive advantage associated to it. Additionally, no other animal than humans present this symptom.

The Neurobiology of Anxiety: Involvement of the GABAergic System

Several studies have demonstrated that different neurotransmitters are involved in the generation and modulation of responses to anxiety. However, few of these neurotransmitters are considered as central to the neurobiology of anxiety disorders as gamma-aminobutyric acid (GABA).

GABA is the main inhibitory neurotransmitter in the central nervous system and can be found in all areas of the human brain [40]. GABA receptors are classified as $GABA_A$, $GABA_B$, or $GABA_C$ receptors [46]. The involvement of GABA in the modulation of anxiety has been addressed in various studies [47], with evidence suggesting that activation of the $GABA_A$ receptors produces anxiolytic effects [48-50]. The participation of GABA in the

modulation of anxiety can be complex given its interaction with other neurotransmitters systems. For example, in area CA1 of the dorsal hippocampus in rats, GABA appears to interact with cholecystokinin [45], a gastric neuropeptide that is also found in the brain and acts as a neurotransmitter [51].

Studying the mechanisms and effects of the GABAergic system on anxiety is highly relevant from a clinical perspective given that benzodiazepines, the main class of drugs available for treating anxiety disorders, decrease anxiety by increasing synaptic transmission mediated by the $GABA_A$ receptor [52]. The $GABA_A$ receptor is composed of five different types of subunits, which can be five of the following subunit types: 6 α, 4 β and 3 γ. The most common combination of subunits is (α1)2(β2)2(γ1). When activated, the $GABA_A$ receptor permits chloride ions to influx into the neuron, thereby hyperpolarizing the post-synaptic membrane and producing neuronal inhibition [53]. Benzodiazepines bind to the γ subunit or to specific sites on the α subunit that are influenced by γ. By binding to the $GABA_A$ receptor, benzodiazepines facilitate the ability of the channel to open, which, in turn, amplifies the inhibitory effects of GABA.

Neuroimaging studies have suggested that GABA is involved in anxiety disorders based on evidence that patients with anxiety disorders exhibit decreases in both endogenous GABA levels and benzodiazepine binding profiles [54-55]. Studies on the genetics, physiology and neurochemistry of GAD have shown that the amygdala, the prefrontal cortex and the temporal areas are among the brain structures identified to participate in the responses to emotional processing and social behaviors [56], and therefore may count on abnormal GABAergic

transmission. However, these regions appear to abnormally function on other anxiety disorders [57], a feature that limits the specificity of the findings.

Neurotransmitters other than GABA also appear to play crucial roles on anxiety disorders, including GAD. In this sense, the effective clinical results of usage of selective serotonin reuptake inhibitors (SSRIs) among GAD patients [58] bring up evidence of unbalanced serotonergic mediation in this condition. A recent study showed that young GAD patients using fluoxetine, an important member of the SSRI class of medication, had increased activation of the ventral prefrontal cortex under visual stimulation of angry faces, which may be one of the mechanisms responsible for inhibiting neural correlates of anxiety, such as the amygdala [59]. Additionally, the endocannabinoid system, a neuromodulatory system that is believed to underlie the acquisition and/or extinction of aversive memories, can be pointed as another neurochemical substrate of anxiety disorders, including GAD [60].

Different ways to approach anxiety: cultural considerations

Anxiety disorders have always been studied with more interest in the west based on the great number of western publications on this disorder. This may stem from cultural differences in how anxiety has been understood. For example, in China, there has been a tremendous historical emphasis on the relationship between organs and emotions. As a result, traditional Chinese medicine currently treats mental disorders by paying special attention to particular parts of the body in alternative kinds. Similarly, in Korea, psychological problems like anxiety and depression are thought to be strongly associated with the organs [7].

However, medication and psychotherapy are more frequently used to treat anxiety disorders due to globalization.

With regard to GAD, there are some important differences in the observed duration of GAD in different cultures, which may stem from differences in cultural attitudes towards anxiety. In developing countries, there are fewer incidents of lifetime and one-year GAD [23], perhaps because people believe that worry and anxiety are normal parts of their personality rather than being a disorder. In concert with this, there are lower treatment rates for anxiety disorders in those countries.

Today more than ever, there appears to be a world-wide increase in strong feelings of fear, worry, and anxiety produced by disastrous events like terrorism, violence, and natural phenomena (tsunamis, typhoons). As a whole, the world population appears to have been affected by these traumatic incidents given the growing number of people with mental disorders, particularly psychological disorders such as GAD and posttraumatic stress disorder.

Key Issues

• The responses currently considered to be anxiety-related have not always been linked to anxiety, and the concept of anxiety has changing over time;

• The word anxiety was used in medicine to refer to a mental ill state for the first time in the eighteenth century;

• Anxiety was mostly understood in terms of its physical symptoms in the eighteenth century, whereas the psychological aspects of anxiety did not receive special attention until the nineteenth century;

• Biological science's most important personality, Charles Darwin, was highly influential in the nineteenth century;

• Evolutionary psychology, a Darwinian approach to understanding psychological processes, played an important role in producing the current concept of anxiety disorders. From this viewpoint, anxiety disorders result from suboptimal functioning of programs that had evolved to promote an individual's reproduction and survival;

• Among the expected changes in the DSM-V are revisions to GAD's diagnostic criteria and the duration and prevalence of this disorder;

• Cultural aspects can significantly contribution to the diagnosis, prevalence, and treatment of psychiatric disorders.

Conclusion

In many ways, anxiety has been considered a characteristic of modern society. From this medical perspective, anxiety was. However, reports indicate that feelings of anxiety were prevalent throughout history and have been studied over the years by researchers in different

fields. In the eighteenth century, the word *anxiety* was used for the first time in the medical field to refer to a mentally ill state. During the eighteenth and part of the nineteenth centuries, the medical field primarily focused on the physical features of anxiety disorders, viewing anxiety as mostly characterized by somatic symptoms. However, in the nineteenth century, the scientific community began to consider psychological factors as part of the etiology and development of anxiety disorders. One of biological science's most important personalities, Charles Darwin, importantly contributed to scientific thought in the nineteenth century. Darwin's Theory of Evolution states that adaptive responses are selected for because they promote an individual's reproduction and survival, thereby contributing to the continuity of the species. Evolutionary psychology, which employed a Darwinian approach to understanding psychological processes, played an important role in building the modern concept of anxiety. Evolutionary psychology interprets emotion as a program that evolved to enable organisms to adaptively respond to environmental challenges. However, this school of thought acknowledges that emotions may not be ideally designed for the modern world [30]. Hence, anxiety-related behaviors may have evolved to protect an organism and increase the probability of survival; however, anxiety may produce suboptimal psychological and behavioral reactions if this emotion is constantly activated or is activated in the absence of real threats.

In the recent history of medical advancements, the American Psychiatric Association (APA) published the first statistical manual for mental disorders (the DSM-I) in 1951, which was influenced by Adolf Meyer and his psychological view of mental disorders. The DSM-II, which was published in 1962, was similar to DSM-I, but it eliminated the term "reaction" from its description of anxiety. The DSM-III introduced many innovations to this manual and

developed a better basis for diagnosing mental disorders. In 1994, the APA published the DSM-IV, which introduced some considerable revisions to the DSM-III. The main changes to the DSM-IV-TR were to correct errors identified in DSM-IV. Ten years after publication of the DSM-IV-TR, the DSM-V is currently being prepared and is highly anticipated by scientists who study mental disorders and by clinicians working in this field. Extensive amounts of research are being conducted on mental disorders, including anxiety disorders; hence, the diagnostic criteria, prevalence, and comorbidity for these disorders should be reviewed when writing the DSM-V.

Expert Commentary

Studies about pharmacological therapies for GAD are still insufficient, although there are important studies still ongoing. The World Federation of Societies of Biological Psychiatry (WFSBP) published the first revision for the pharmacological treatment of GAD in 2008. In this update, the task force mentioned the selective serotonin reuptake inhibitors (SSRIs) like escitalopram, paroxetine, sertraline and fluvoxamine in double-blind placebo-controlled studies, which have demonstrated strong evidence of efficacy among this class of medication. Among selective serotonin-norepinephrine reuptake inhibitors (SNRIs), venlafaxine and duloxetine were studied. They turned out to be more effective than the placebo in a double-blind study [61]. Benzodiazepines are also effective, but in long term treatment for GAD, it is highlighted that escitalopram, paroxetine, venlafaxine, duloxetine, and pregabalin may be more effective in preventing relapses [61, 62]. This is important information as GAD is chronic and needs to have relapses prevented. It is consensual among clinical experts to recommend pharmacotherapy for at least twelve months [61, 63]. The risk of taking the medication for a year, although the patient might be feeling well, is a choice

which the patient needs to make. The choice between the risk of relapse and the side effects should be very thoughtful. Additionally, a study with escitalopram [64] showed that there is greater risk of relapse without it, and that using it compensated side effects. Combining pharmacotherapy and psychotherapy is common. In this sense, cognitive-behavior therapy has been often undertaken with GAD patients. Although substantial studies are still needed, in clinical practice medications help patients to motivate themselves to engage in exposure techniques [63], a context in which pharmacotherapy shows to be more effective.

Five-years Review

Multidisciplinary studies that have applied scientific methods to GAD have played an important role in this process. Both mental health professionals and patients suffering from psychological disorders are hoping that there will be more effective and agreed-upon ways to diagnose and treat these disorders in the near future.

One suggestion is to reproduce studies that have compared different cultural methods for treating patients with GAD, using neurological techniques to determine how the human brain may benefit from these treatments to give the patient a healthier life. Advanced studies can produce a better understanding of how cognitive, behavioral, and emotional dimensions influence one another, which will allow us to develop a more reliable basis for effective treatments.

During scientific research referring to the diagnosis and treatment of GAD, one can notice a highlight in anxiety with worry symptom as a key point for debates in the academic

field. Chronic worry is considered the central feature of GAD. It is important to point out that the term ´chronic´ used here highlights the time duration of this feature. Patients suffering from GAD, unlike those suffering from MDD, cannot state when they started worrying and they report it has been throughout their lives. Worry can have greater involvement with past issues, and they usually relate to "What if..." or to future issues. That does not mean that those patients do not get lost in daily problems, but they keep on thinking of these problems instead of trying to find the possible solutions, and if they ever do, they just can not make it work for the fear of not having made the right decision. It ends up triggering even more anxiety. There is a kind of anxiety related to being worried that, most of the times, paralyses them.

The subject of their worries is usually problems of our lives that disturb almost everybody. The difference seems to be in the associated symptoms and difficulties in changing the subject. Thinking of family matters (related to both relationships and health), work and finances, and school matters are the most common issues for the subjects. Other anxiety disorders also have worry as a complaint and, besides, the non-clinical population also experiences this condition even without being diagnosed for any particular pathology. Excessive and pathological worry means the one generating psychic suffering, impairing a person's daily life, associating physical symptoms like pain in the chest and migraine. This is the one feature that best describes patients with GAD. They know about the difficulty they find in controlling worry and many times they believe that it is able to protect them from all the suffering and, therefore, they do not search for medical help so easily, which makes early diagnosis hard, besides damaging statistics of prevalence of this disorder. Another point to be considered, still related to the statistics of prevalence of the disorder, is the time duration of the symptoms of GAD. Nowadays, in DSM-IV-R, the symptoms must occur for at least six

months and many times, what can be found are patients reporting excessive worry involving apprehensive expectation with a shorter duration, and because of that, they are not in the statistics nor benefit from appropriate treatment for their disorder. Being so, the suggestion is that both the way of approaching the components of disorder as well as the time duration should be revised for the next publication of DSM. Concerning clinical interview, matters related to the way and intensity of worry should be highlighted and well elaborated.

Figure captions

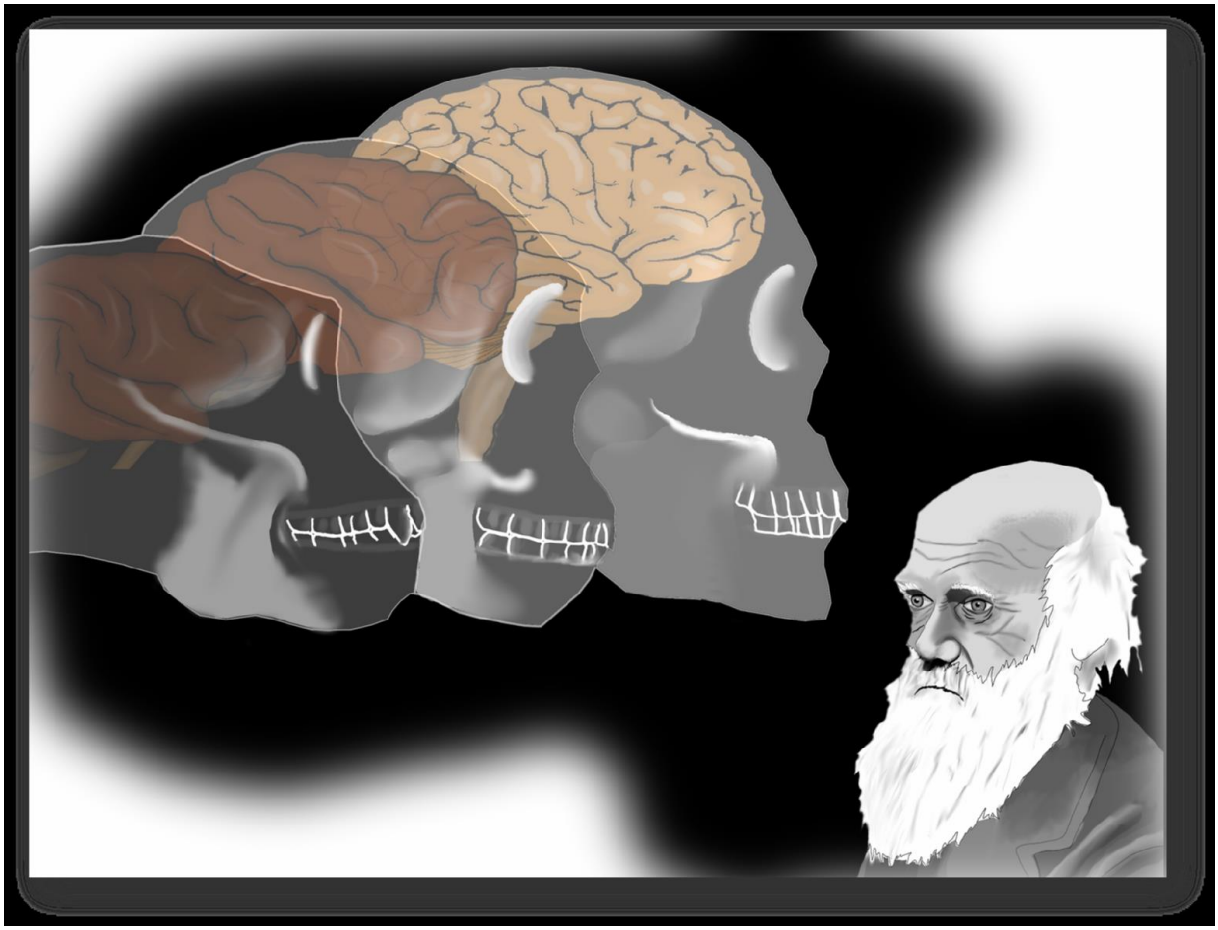

Figure 1: Charles Darwin (1809-1882) and his Evolutionary Theory. It was a start point to the neurobiologic concept of anxiety.

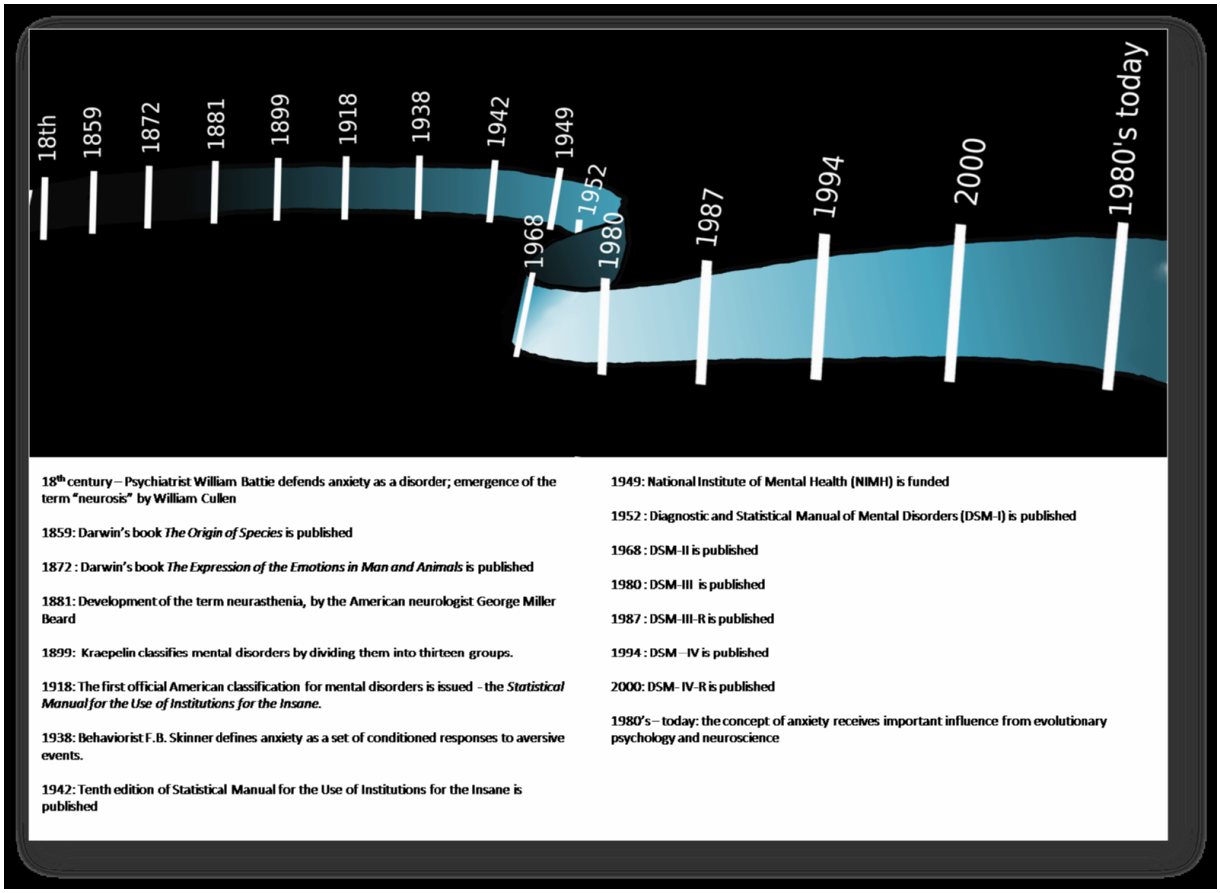

Figure 2: Timeline of key points in the history of the concept of anxiety. Some of the most important landmarks for the understanding of the concept of anxiety along history are chronologically displayed.

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