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A critical discussion of how psychological and biological factors influence the development of anxiety disorders

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Abstract

Anxiety disorders are becoming a common symptom, with the number of people affected by them rapidly multiplying. Numerous studies try to explain their nature, yet there are no clear answer so far as to what exactly causes them. Up to date bibliography on psychological and biological factors possibly correlating with anxiety disorders, with a focus on genes, chromosomes, proteins, HPA axis, serotonin, the environment and even maternal care are critically discussed.

Keywords

anxiety disorders; chromosomes; HPA axis; methylation; serotonin; childhood trauma

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Anxiety, as a phenomenon, has been troubling humanity throughout its history and is rapidly increasing in importance [1]. Barlow (2002) [2] defines anxiety as 'an unpleasant inner state in which we are anticipating something dreadful happening that is not entirely predictable from our actual circumstances. It is a complex blend of physiological, behavioral, cognitive components'. Anxiety is not an abnormal phenomenon, since its main purpose is the preparation of the body for a potential danger, activating the 'fight or flight' response and therefore the sympathetic nervous system, which results, among others, to increased blood pressure and raised heartbeat [3]. However, it often affects people in the form of a disorder, in which case people experience those reactions in their body without the presence of a perceived or immediate danger, with the reason and magnitude to which the person experiences anxiety in such a state depending on the disorder [4]. Over the years, the number of people suffering from anxiety disorders is constantly increasing [5], with the pandemic of Covid-19 seemingly deteriorating this issue since, according to the American website of psychological health [6], in just a 10-month period in 2020, anxiety symptom reports had been increased by 634%. The same source [6] suggests that there is no clear answer on what causes these disorders, studies however indicate correlations with various psychological and biological variables. Hence, this paper will critically discuss, in regard to previous studies, biological and psychological factors involved in the development of anxiety disorders.

Genetics is a strong biological factor which seemingly correlates with anxiety. The background research regarding genetic factors that correlate with anxiety comes from studies in multiple species [7], mostly including mammals, and more specifically rodents, since they seem to use similar defensive behaviors with humans when it comes to perceived threats [8]. Most studies indicate a connection between genetic factors and anxiety phenotypes through individual differences and are using animals as their subjects born through family inbreeding [9, 10, 11, 12], in order to achieve higher homozygosity, which raises the chances for the descendants to inherit and be affected by deleterious genes and characteristics [13]. More specifically, anxious behaviors seem to be controlled by three autosomal regions: Area 'b' in chromosome 4 and area 'p' on chromosome 7 were studied on rats with high homozygosity by Clément et al. in 1994 [14], to whom it was observed that they spent an excessive amount of time in wide and exposed areas, a behavior usually interpreted as a sign of anxiety on these species [15, 16]. The same research team in 1995 [17] perceived that rats with a homozygous form in area 'se' of chromosome 9 spent more time grooming their fur, which also implicates stressful processes [18]. In a similar study, Mathis et al. in 1995 [17] observed that areas which associate more with anxiety mechanisms on rats are chromosome 1 and 10. Even though studies on the connection between inherited anxiety and chromosomes seem to include a large sporadic number of chromosomes, especially on studies which focus on humans, like the involvement of chromosome 13 [19] and chromosome 14 [20, 21, 22], most of these tend to support the findings of the first studies, and more importantly chromosome 4 [23, 24, 25]. All this research leads to the conclusion that genetic factors, engrossing in parts of multiple and not completely specified chromosomes, play a significant role in the development of an anxious behavior, leaving the existence of more affecting areas that have yet to be discovered in the realm of possibility. Contrastingly, Francis et al. in 1999 [26] disagree with the genetic transition of anxious behavior by noting in their articles some very carefully constructed studies, the findings of whom support that the anxiety which baby rats preserve from their parents is in fact a matter of development due to the influence of the environment, and not due to inheritance, since individual differences affect behavior and the way that the mother interacts with the infant, which on its own directly influences the child's environment. Through this process, the same research team explains the occurring changes in the HPA axis of the same experiments' baby rats, noting that these mutations are outcomes of methylation and were not co-existent as genotype characteristics. Studies on humans few years later still support that the same epigenetic markers can be inherited and expressed on the descendants [27, 28, 29].

HPA axis is probably the most important aspect in the development of anxiety disorders. It is an endocrine system, which consists of a complex nexus of influences and interactions between the hypothalamus, the gland pituitary and the adrenal glands [30]. When the hypothalamus is notified for an incoming stressful stimuli, a series of chain reactions leads to the activation of the pituitary gland and then to the adrenal cortex, where cortisol is produced [31], a stress-fighting glucocorticoid hormone [32]. This process is to be expected in short-term stress. In maladaptive however, which is of long duration and found in anxiety disorders, the body can reach the point of exhaustion, stop the production of cortisol and ultimately remain vulnerable and defenseless to stress [32]. HPA axis can be activated in multiple ways in long-term stress, which increases the way and amount that cortisol is produced [33], therefore the existence and the inheritance of genes that affect its function can transmit maladaptive stress to the descendants and consequently a predisposition for an anxiety disorder. There are numerous studies that support the existence of these genes. In particular, the NR3C1 gene is the one that encodes glucocorticoid receptors [34], gene FKB5 encodes the FK506 protein, which regulates the sensitivity of those receptors [35] the polymorphic nucleotides, like rs1360780 is associated with the inhibition of negative effects of the HPA axis, making it less effective [36], rc53576 on the oxytocin receptor gene which affects the axis function and leads to higher stress levels [37] and rs6295 in the region transcribing the serotonin receptor HTR1A gene, which has also been observed to correlate with anxiety [38]. In a study with human sample in 2020, Lindholm et al. [39] support the effect of polymorphic mononucleotides on stress levels, while also observing different effects between each sex. The drawback of all these studies is that they all report a very small effect size per variable/gene that measures stress formation. This can also explain why research on which biological factor causes anxiety disorders is progressing at such a slow pace

and has yet to provide an official answer to the question. In all likelihood, there are no few and specific genes that have a large and clear effect on the issue. It is therefore safe to assume that there are rather numerous genes with minor ramifications which, when clustered, can result in a high probability for the birth of an anxiety disorder [40].

Contrariwise. many theories and studies support that the development of an anxiety disorder resides in psychological causes, particularly at the influence of the environment on a person's development. Despite the fact that several studies, like the formerly mentioned, support the theory of a mainly biological cause for the development of these disorders, the standpoints on the subject diverge. More specifically, it is heavily substantiated that genes are not guaranteed to be expressed on the individual, but merely give a predisposition to the individual, making him/her more vulnerable to these disorders, while in reality the main predicament arrives from environmental factors who cause methylation, the process in which a gene can be activated and/or deactivated [41]. Most studies that try to divide a main cause, whether biological or environmental, are usually ran on homozygotic twins, a type of study considered to be 'the perfect physiological research' [42], since they share 100% of their DNA, bringing to light the effects of a different environment on two biologically identical humans [43]. Such studies indicate that the cortisol levels during the afternoon, as well as the volume of the amygdala, which also gives the information of stressful stimuli to the body [44], both receive significant effects from environmental factors [45, 46, 47]. In 2017, Alisch et al. [48] observed for a second time on a study which was conducted on homozygotic twins that the environment caused different methylation in 230 areas which correlate with 183 genes associated with anxiety. These results were also replicated on studies which used monkeys as their study group. In homozygotic twins, it is more likely that the largest impact on stress and anxiety is caused by the methylation of gene NR3C1, which also seems to be the most prone to have this change [49], since in a study by Hill et al. in 2019 [50] on women, methylation of NR3C1 is observed to have its roots mostly to the prenatal environment, while men are more susceptible to the postnatal environment. These results imply differences between each sex depending on how they are affected by each experience. On family studies with isolated anxiety disorders who also included twins, Hettema et al. in 2001 [51] observed that the environmental conditions which were not common between them had a significant effect on the anxiety levels of the participants. Looking further into these results, they were more dominant in panic disorder, especially when comparing with the results of homozygotic twins. In generalized anxiety disorder however, the impact of the environmental effects were less visible on homozygotic twins than other family members, indicating that genetics were dominant on that occasion. This magnifies the complexity of how anxiety disorders are born, since it is presumable that every anxiety disorder manifests in a separate way than the rest.

Over all the possible environmental factors which might affect the development of anxiety disorders, a few can be distinguished for how often they appear on studies and how much higher their effect levels are, comparing to the rest. Environmental adversities, especially childhood trauma, are considered the most accurate predictors of pathology and affect approximately 10% of western civilization [52, 53]. Dreadful experiences like abuse and neglect are considered by multiple studies as the main indicators for the potential development of many disorders, including anxiety [54, 55, 56, 57], especially when compared with other experiences, such as living in an authoritarian and demanding family environment [58, 59, 60]. Therefore, a child which growing in an environment flooded with negative emotions due to neglect, will likely shape and connect life with loss of hope and trust towards people, with possible isolative tendencies, an action that goes against human nature and deteriorates anxiety levels faster [61]. While these studies use childhood trauma as their area of investigation, other studies disagree on which way people are biologically affected by it, with some reporting increase [62, 63, 64] and some others decrease [65, 66] on the cortisol levels of the participants that reacted on stressful stimuli. Maternal care quality appears to have the greatest influence of other traumatic experiences on the spectrum of the development of anxiety disorders, with many studies on rats, like the previously mentioned by Francis et al. in 1999 [26] or Toki et al. in 2007 [67], Wöhr & Schwarting in 2008 [68], as well as Murgatroyd et al. in 2015 [69], all supporting this theory, but there is still lack of sufficient research on humans that study and support it. A deeper look on these studies shows that their focus is on environments that a person experiences from an early age, leading also to the possibility that these stages of life are also the most vulnerable in those stimuli for the development of anxiety disorders, a hypothesis which is further supported by the findings of McLaughlin et al. in 2010 [70]. However, studies that claim the development of an anxiety disorder from the adult stage of life are also present. For instance, the study by Pineda et al. in 2021 [71], in which healthy adult Japanese people exhibit signs of dysfunctional cerebral neurobiological aberrations and presented exacerbations in anxious symptomatology, were affected by the quality of their day-to-day life. In addition, the study of Hulting in 2005 [72] shows that an adult's diet also plays an important role mentioning theophylline, a substance which seemingly increases the vulnerability on anxiety and can be found in everyday food and beverages, like tea, coffee and chocolate. The most interesting studies, however, are those who research serotonin, a neurotransmitter known for its use on fighting anxiety [73], thanks to studies on humans who received agonists of serotonin's receptor 5-HT1A, along with SSRI's which are considered to be the best way of dealing with any anxiety disorder [74], even though other studies suggest that, under certain conditions, like high trait neuroticism levels, serotonin can also become anxiogenic [75, 76, 77]. The results of these studies however have not been recreated, indicating that there has to be some sort of environmental influence which explain the involvement of personality on how serotonin acts. A richer environment seems to increase the action of 5-HT1A receptor [78]. In adults, serotonin reuptake inhibitors work through the same receptor to

stimulate neurogenesis and reduce anxiety-like behaviors [79, 80, 81]. All these studies propose that the complexity of this neurotransmitter's system has various roles in configurating anxiety, both in development and adult life.

In conclusion, it is possible to give some hesitant explanations on what causes anxiety disorders. Looking at genetics, it seems that there are no powerful genes or chromosomes that ultimately decide the expression of maladaptive stress, their considerable number however can have an interactive effect with no clear outcomes, but they surely create a predisposition to the person, making it more susceptible to those disorders. Some of these genes, even if they get inherited, may never be expressed, making epigenetics an external factor on the subject. During a person's development, the environment may cause methylation and activate these genes, or even affect some others which are directly connected with anxiety, like the ones that determine the function of HPA axis, which manages by itself the normal treatment of stress by producing cortisol. Environmental conditions that show a higher effect and therefore cause higher percentages of methylation are mostly found in childhood and the traumatic experiences it may include, with great importance the quality and/or even neglect of the mother. However, as it has been stated from the beginning by the APA website, it seems that there is no clear answer on whether it is biological or psychological factors with the highest magnitude on the development of anxiety disorders, not with the current bibliography at least. There is enough supporting evidence however to provide a satisfying glimpse on what exactly occurs and which are the main causes of anxiety disorders.

Appendices

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