Obrela JOURNAL Dialogues in Clinical Neuroscience & Mental Health

e-ISSN: 2585-2795 • Printed-ISSN: 2654-1432
DOI: 10.26386/obrela.v4i2.157

A critical discussion of the development of anxiety disorders based on biological and psychological explanations

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Abstract

Anxiety disorders are early emerging and relatively common conditions, associated with a variety of genetic, psychosocial, developmental and psychopathological complications. The discussion around demographic variables, hereditary familial aggregation, neural interrelations, hormonal activity, parental influences, social learning mechanisms and simple exposure to life adversities as well as the in-between interaction of these factors, provided but a glimpse of the complex and often unanticipated biological and psychological implications, which seemingly promote the onset of anxiety disorders. Although, psychological factors such as parenting environment or adverse life events have a huge impact to subsequent anxious symptomatology, biological attributes such as familial genetics and neurohormonal activity, are typically leading predictors regarding the development of anxiety disorders. However, it remains relatively unclear to which degree these biological indications are a predictor or a consequence of psychological factors. Further research focusing on these reciprocal effects might provide better clinical guidance regarding early intervention

Key-words: Anxiety, life adversities, psychological factors, neural interrelations

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DOI: 10.26386/obrela.v4i2.157

Normative fears and anxieties are instinctive, survival-based and evolutionary predisposed manifestations of healthy development; however, excessive and persistent forms of anxiety are likely to escalate and generalize over time, leading to severe anxiety-oriented psychopathology, with lifelong detriments ([4]). Anxiety disorders are characterized by pronounced impairments in functioning and/or emotional distress, caused by significantly maladjusted cognitive systems underpinning fear responses and stress regulation ([39, 76, 81]). These disorders are the most common category of mental disorders ([19, 38]), have the earliest commencement age ([47]) and in any given year, affect about 18% of the population ([26, 50, 49]), while up to 29% of all people, develop some type of anxiety disorder throughout their lives ([48]). The timespan between early childhood and young adulthood, constitutes the typical high-risk period of onset, regarding the development of anxiety disorders ([10]), as behavioral, affective, neurocognitive and biological dysfunction, as well as environmental adversities during these sensitive developmental stages, are seen as an early predictor of subsequent psychopathology ([6]). The nature of pathological anxiety itself, expresses considerable complexity; as anxiety disorders usually share similar attributes, but also differ from each other in terms of risk factors, onset age, course and symptomatology ([21]), have distinct characteristics which differentiates them from other categories of mental disorders (e.g., depression or personality disorders; [17]), and possess the capacity to comorbid with other physiological or/and psychological conditions ([11, 83]). In this paper, the discussion will be revolved around the development of anxiety disorders and the numerous psychological and biological contributors involved.

Prospective-longitudinal studies produce relatively consistent findings; indicating that, frequently overlooked demographic variables, may in fact provide eminent considerations regarding the development of anxiety disorders ([8]). For instance, sex difference research indicates that, although females are neurobiologically more resistant than males ([31]) and do not show impairments in recognition or spatial memory, when exposed to the effects of acute stress ([57]); they are approximately twice as likely than males to develop any type of anxiety disorder ([23, 25, 54]). The possible reconciliation to these somewhat contradictory arguments is twofold; firstly, women, more often than men, undergo a constant barrage of evolutionary (e.g., fear of or actual compromised pregnancy) and societal (e.g., social media's portrayal of the ideal body image, economic status etc.) stressors which may eventually influence susceptibility to anxious symptomatology ([66]) and secondly, men's reduced neurobiological resistance and relatively impaired memory, is seen as adaptive, potentially by enabling them to indirectly "forget" the impact of acute stress and its associations quicker than females ([3]). In addition, lower financial and educational status is consistently associated with anxiety disorders ([96]), as unsatisfactory economic income significantly increases life adversities and lower educational background usually do not prepare nor provide the means to tackle those hardships ([22]). However, satisfactory educational background of individuals within the below-average financial spectrum, is not significantly correlated with anxiety disorders; implying that education, may even reduce the brunt of stressful life adversities, and consequently, anxious symptomatology itself ([14]). These results are in line with data suggesting that, education, is seen as a beneficial and self-protective factor ([58]). Lastly, urbanization; with certain exceptions ([67]), is also seen as a correlate to the development of anxiety disorders ([14]).

Familial aggregation studies have also shown substantial results, indicating that hereditary genetic pathophysiology is a leading predictor of anxiety disorders ([34, 56]). Offspring of parents suffering from at least one anxiety disorder, have an increased risk of developing one ([95]); and this risk is significantly elevated when the form of the parent's disorder is severe, multiple ([84]) or afflicts both parents ([40]). Linkage research, by investigating chromosomal loci (positions), likely to prompt genetic influence regarding biological traits or conditions, support these claims, and suggests that, major anxiety disorders such as panic disorder, specific phobia and generalized anxiety disorder, share common underlying genomes, likely to be inherited through reproduction ([45]). In fact, evidence for specificity, indicate that variations in chromosomes 1, 2, 15, and 16 may be broad contributors

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to anxiety susceptibility ([94]). These data provide a genetic insight on the estimates which suggest that up to 60% of the individuals affected by a specific anxiety disorder, are also likely to develop at least another one ([41]). Furthermore, gene-association studies, by examining genetic contribution to a specific phenotype, indicate that neural abnormality; such as inflated (or inhibited) neurotransmission across synapses, is correlated to aberrations of genes involved in glutamate, serotonin, dopamine and norepinephrine neurotransmitter structures ([60]). In fact, these neural anomalies, may even constitute the genetic basis of, often overlapping, yet systematically associated temperamental and personality trait vulnerabilities to anxiety disorders; such as elevated neuroticism (emotional instability and disposition tendencies towards adverse emotional states; [36]) and behavioral inhibition (tendency to display fear, reticence and withdrawal towards unfamiliar situations; [88]). In addition, genetic accountability occurs not only within, but also between mental disorders, as offspring generalized anxiety disorder is genetically associated with parental major depression; their severity and whether or not ought to be triggered however, is also susceptible to environmental factors ([43]). Regardless of these enticing outcomes, linkage and gene-association studies often yield false positive results, exhibit difficulties on producing consistent findings, and when they do, they present modest effect sizes ([86]). Genetic level heterogeneity, phenotypic assessment variations, individual's interpersonal differences and non-shared environment as well as the in-between interactions of these factors might be few of several interpretations to these tampering results ([64]).

Twin studies, often provide disentanglement of genetic from environmental predictors of anxiety disorders; as by using the fact that monozygotic twins share 100% of their genes, produce relatively more reliable condition resemblance comparisons. Results indicate an estimated heritability of anxiety disorders of up to 40% ([35, 34]); an immense percentage nonetheless, but significantly lower than other mental disorders such as bipolar disorder (85%; [65]) and schizophrenia (79%; [37]). Preceding studies however, by taking into consideration the gene-environment interaction (G^{x}E), that is, how twins' genotypes react to non-shared environmental variations, suggest that 40% represents an underestimation of true heritability, as they result to a genetic proportion of variance of up to 60% ([44]). These data suggest that, although the dominant source of familial aggregation regarding the pathogenesis of anxiety disorders remains genetic; environmental predictors should not be treated inconsequentially ([80]).

Neuroimaging research, indicates that the amygdala, which is associated with immediate processing of actual or perceived threats and the ventrolateral prefrontal cortex (vlPFC), which facilitates subsequent emotional governing (also other neighboring related structures, such as the hippocampus and the limbic system; [93]), constitute the basis of threat regulation response patterns and dysfunctional interactions between these threat regulatory neural circuits are correlated to anxiety susceptibility ([87, 73, 62, 72, 77]). Studies suggest an irregular upward tendency of amygdala-vlPFC activation during daunting face-viewing, among individuals with anxiety disorders ([92]). More specifically, adolescents affected from generalized anxiety disorder exhibit increased amygdala-vlPFC neural circuitry activation responses, to intimidating facial expressions, especially when the attentional stimuli (fearful faces) reflected participants' subjective degrees of internalized fear ([9]). These results underline the important role of attentional modulation toward emotional processing and suggest that attentional biases, such as constant observation or avoidance of fear-related environmental cues; possibly caused by preceding unresolved psychological trauma, predict atypical emotional responses, which consequently, form the ideal and typical ground for the development of several forms of anxiety disorders ([33, 79]).

Evidence indicates that these neural circuitry irregularities may in fact be prompted by hormonal imbalance ([13]). For instance, cortisol, the end product of the hypothalamic-pituitary adrenocortical (HPA) axis (a complex neuroendocrine system coordinating an abundance of physiological processes; [90]), exerts influence on nearly every live tissue in the body ([29]); and irregularities in this particular glucocorticoid steroid hormone have been systematically associated with the development of anxiety disorders ([15]). Data suggest, that even as early

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as the gestation period, prenatal intake of synthetic glucocorticoid drugs, usually prescribed for their anti-inflammatory, immunosuppressive and neural inhibitory actions regarding physiological (allergies, autoimmune disorders, adrenal insufficiency, cancer; [24, 5]) and psychological (anxiety disorders, bipolar disorders, depression; [75]) conditions, have the ability to elevate the already four-fold increased maternal cortisol levels and to inhibit certain placental enzymes responsible of oxidizing cortisol to its inactive form (cortisone; [28]). As a consequence, this hormonal dysregulation, may cause a portion of maternal cortisol to easily bypass the immature blood-brain barrier of the fetus and to target glucocorticoid receptors inside the central nervous system, affecting both cognitive and emotional development ([82]). Exposure to excess quantities of glucocorticoids this early, is frequently associated to increased fearful behaviors, poor emotional regulation, elevated stress reactivity and less social competence in the offspring ([27, 30]); followed by anxious symptomatology in childhood and adolescence ([55]). Interestingly enough however, these brain function abnormalities are declined via successful pharmacological treatment and/or cognitive-behavioral therapy ([61]). These results underline the various and often unforeseeable biological vulnerability considerations regarding the development of anxiety disorders ([76]).

Besides biological predictors, psychological factors based on certain environment circumstances, such as parental influences and adverse life events, are also seen as a correlate to the development of anxiety disorders ([76, 8]). Results suggest, that high levels of parental authoritarianism and coldness are significantly associated with increased risk of nearly every anxiety disorder in the offspring; yet, they present modest –at best– effect sizes ([42]). Studies focusing in the rejection-overprotection paradigm however, produce more consistent, and therefore, relatively more reliable results, indicating that, parental rejection is significantly associated with increased rates of separation anxiety ([85]) and social anxiety ([53]), whereas overprotection is significantly related with phobias, generalized anxiety disorder, and panic disorder ([10]). In line with these data, the cognitive-behavioral framework suggests that, parental rejecting behaviors formulate a caregiving environment which lacks of warmth and empathy. This, consequently, is likely to bolster the child's expectations that the world is unsupportive, hostile and unforgiving, thus, promoting emotional detachment from others and a self-centered view of life, in adolescence and adulthood ([12]); symptoms which are characteristically associated with a variety of anxiety disorders ([19]). Similarly, overprotection promotes overcontrol; followed by the concomitant discouragement of independence and autonomy. This is expected to restraint the child's sense of competence by reinforcing avoidance behaviors to potentially threating or challenging situations; this avoidance however, diminishes the resistance and resilience of the offspring towards stressful life events and consequently, may prompt environmental-based pathogenesis of anxious symptomatology ([16]). Well supported observational studies, suggest that, these associations can clearly reflect the quality of the caregiver-child attachment type ([18]); as attachment theory, has long hypothesized that parental rejecting behaviors and hindered autonomy granting, facilitates an anxiety-based type of attachment in the offspring ([1]). In fact, anxious attachment style is correlated to subsequent separation anxiety disorder and panic disorder, with chances of remission persistent enough to last of up to 30 years in a person's life ([59, 78]). These psychological implications, may even prompt biological-based stress regulation abnormalities, as recent cross-sectional studies suggest, that an anxious type of attachment predicts enhanced cortisol levels among young adults ([89]).

Attachment relationships, often reflect mediating learning mechanisms of the familial/social structure, as studies conducted under the theoretical premise of social learning theory; which suggest that behaviors are learned via observing and imitating the attitudes, behaviors and emotional reactions of others ([7]), indicate that, simple observation of anxiety in others may prompt anxious symptomatology on oneself ([70]). For instance, maternal fear modeling toward a non-fear inducing stimuli was associated with subsequent fear responses in the offspring, even after a period of 14 months ([74]). This, alongside with results suggesting that anxious mothers rarely express pleasant emotions during

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pleasurable situations and are more likely to exhibit catastrophizing comments regarding adverse incidents, links parental behavior to anxiety susceptibility among children ([71]). Parental inability to present appropriate behaviors towards stressful situations, fails to provide healthy and functional stress regulatory mechanisms and often promotes a caregiving environment which leaves the offspring misguided and confused ([76]). As a consequence, observation of imprudent parental models during childhood is seen as a correlate for the development of anxiety disorders in adolescence and early adulthood ([63]); characterized by symptoms which include, exaggerations of relatively mild environmental risks and/or overstatements concerning actual, fictional or perceived forthcoming threats ([76]).

Anxiety disorders are also a possible outcome of life adversities ([91, 32]). Occurrence of traumatic incidents throughout the lifespan, such as fear of ([20]) or actual loss of significant others (e.g., parent, husband etc.; [46]), physical, psychological or sexual abuse ([2]), parental psychopathology (e.g., parental depression or substance usage; [97]), and neglect, separation, danger or humiliation events, typically tend to precede subsequent onset of anxiety disorders ([51]). However, such results are called into question by literature indicating that pre-existing anxiety, predicts the occurrence of subsequent adverse life incidents ([76, 52]). An interesting view regarding these reciprocal and almost correlative influences, proposed by Miloyan and colleagues[69] (2018); suggests that, anxious individuals, often intentionally, signal the possibility of self-exposure to future adversity or perceive mildly challenging situations as adverse ones, in order to obtain an external verification of their coping capabilities. These consecutive actual or perceived hardships, act as a self-fulfilling prophecy, reducing one's competency to effectively cope with potential threats and therefore, produce a clear indication of vulnerability to the individual. The impulse to fixate on possible future detrimental circumstances is a characteristic feature of anxiety disorders and typically prolongs and inflates anxious symptomatology ([68]).

To summarize, anxiety disorders are early emerging and relatively common conditions, associated with a variety of genetic, psychosocial, developmental and psychopathological complications. The discussion around demographic variables, hereditary familial aggregation, neural interrelations, hormonal activity, parental influences, social learning mechanisms and simple exposure to life adversities as well as the in-between interaction of these factors, provided but a glimpse of the complex and often unanticipated biological and psychological implications, which seemingly promote the onset of anxiety disorders. Although, psychological factors such as parenting environment or adverse life events have a huge impact to subsequent anxious symptomatology, biological attributes such as familial genetics and neurohormonal activity, are typically leading predictors regarding the development of anxiety disorders. However, it remains relatively unclear to which degree these biological indications are a predictor or a consequence of psychological factors. Further research focusing on these reciprocal effects might provide better clinical guidance regarding early intervention.

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