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Review Article

Transactional Nexus of Risk: The Interaction of Genetic Susceptibility and Environmental Stress in Adolescent Depression

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Abstract

Depression in adolescents has become a major social issue and, in most cases, leads to permanent functional impairment in adulthood. Since then, the discipline has successfully overcome the naive nature versus nurture controversy and embraced dynamic models of integration. This review contributes to a developmental-transactional model, which assumes that depressive outcomes are a result of the interaction of diffuse genetic vulnerabilities and powerful interpersonal stressors. In this case, genetic predisposition creates a risk gradient of probability, which often is manifested as increased sensitivity to the environment, especially the relationship landscapes of family and peers. Genetic factors can affect reactivity to adversity and determine the stressors people face in a systematic manner through gene-environment correlation and interaction mechanisms. A dual-pronged intervention approach is thus needed: to decrease the modifiable social risks and at the same time increase the environmental buffers to reduce the inherent biological vulnerability.

Keywords: Adolescent depression, gene-environment interaction, polygenic risk, differential susceptibility, transactional model.

INTRODUCTION

Depression with onset in adolescence is not a transient developmental phase. It is associated with an increased vulnerability to chronic diseases, suicide, and poor academic, social, and occupational performance (Clayborne *et al.,* 2019). The shocking increase in the rates of depression in adolescents has aroused a burning question: why is it this period of life that generates such vulnerability?

The quest to identify a simple root cause behind development has been abandoned by modern developmental psychology, which has adopted unified models that consider a myriad of risk factors as dynamic and interactive in nature. From this perspective, depression is the result of the constant exchange between the internal weaknesses of a person and his or her outside experiences (Cicchetti & Toth, 1998). Adolescence is marked by changes in the brain, hormonal changes, and swiftly changing social worlds, which form a situation where such interactions may trigger mental disorder (Pfeifer & Allen, 2021).

The review is a synthesis of existing evidence that proves the transactional relationship between genetic vulnerability and environmental stress. First, it outlines the genetic architecture of depression. Then, it looks at the proximal environmental risks, especially early adversity and important social settings during adolescence. Lastly, it outlines how these areas are interrelated concerning the concept of gene-environment interaction, which should highlight that nature and nurture are inseparable in human development

Genetic Susceptibility Polygenic Landscapes and Developmental Expression.

The twin and family studies are consistent in that genetics describes approximately 30–50 percent of the variance in depressive symptoms (Nivard *et al.,* 2015). The heritability increases between childhood and adolescence, a phenomenon known as genetic innovation. This deduction means that puberty and the development of the brain can turn on new genes that control our emotions and stress response.

Genome-wide association studies (GWAS) revealed that there are numerous genes that are related to depression: thousands of common variants that contribute a small effect each (Howard *et al.,* 2019). These can be summed up into a polygenic risk score (PRS). The PRS is not a destiny determinant; it just displays a risk gradient. Studies have now indicated that genetic risk not only predisposes to depression but also influences the depression pathway. Individuals who carry the polygenic loads tend to have earlier onset, worse symptoms, and prolonged episodes (Musliner *et al.,* 2019). However, PRS is not as predictive in individuals and less effective in other ancestries (Murray *et al.,* 2021). This result indicates that it does not have a predetermined genetic risk, but it functions within the environment.

However, PRS is not as predictive in individuals and less effective in other ancestries (Murray *et al.,* 2021). This result indicates that it does not have a predetermined genetic risk, but it functions within the environment. A polygenic risk score is not a deterministic template, but it is a probabilistic marker, which has clinical usefulness only in the context of an environment and is a latent vulnerability that can be activated, amplified, or buffered by life events.

Conditions in the environment The Salience of Interpersonal Stress.

The environment offers the dynamic conditions that create the vulnerability landscape drawn by genetics. Stress, particularly chronic, severe, or interpersonal, is one of the best predictors of depression.

Early Life Stress (ELS) incorporates abuse, neglect, and family problems. Meta-analysis demonstrates that such adversity increases the risk of depression two to three times, and the risk increases with the levels of stress (Gardner *et al.,* 2019). The rationale is that stress at a young age conditions the stress-response system, which causes the HPA axis to be hyper-reactive and encourages negative thinking patterns (Heim *et al.,* 2019). This latent weakness tends to manifest itself when adolescents face new challenges.

Peer bullying is one of the leading risks as social worlds increase. Longitudinal studies indicate that bullying leads to depressive symptoms in adulthood even when past mental health is taken into account (Schacter & Juvonen, 2020). In a period when identity and belonging are being formed, the sense of rejection, humiliation, and threat may destroy self-esteem and provoke depressive thoughts.

Family climate remains significant even when the teens become more independent. Despite the normal state of conflict, families with high levels of criticism, hostility, low levels of warmth, and emotional invalidation are always associated with depression (Yap *et al.,* 2014). This illustrates a fundamental transactional loop: a child with a genetically predetermined temperament (e.g., irritability) can be subjected to harsh parenting, which only advances the depressive symptoms of the child further, causing additional parental negativity and a vicious cycle of misery (Hammen, 2018).

Gene-Environment Interaction Transactional Mechanisms.

The relationship between genetics and the environment throughout time reveals the most important lessons. This association is explained in two primary ways, which are correlation and interaction.

Gene-environment correlation (rGE) implies that genetically influenced traits also shape the environments that people live in. It may occur passively when parents provide children with genes and the home; evocatively when the temperament of a child makes other people respond in a specific manner; and actively when individuals pursue environments to support their characteristics. As an example, a genetic predisposition to negative feelings may result in a clash with peers or even more parental aggression (Jami *et al.,* 2021). Genetic risk has the power to increase the likelihood of exposure to stressful circumstances.

Gene-environment interaction (GxE) occurs when the genetics of an individual influences the individual's response to the environment. Recent research based on polygenic risk scores provides more evidence in favor of GxE as compared to older approaches. Studies have indicated that adolescents who have a greater polygenic burden of depression have their symptoms escalate more in response to childhood adversity or family conflict than those who have a lower genetic risk (Peyrot *et al.,* 2020). This conclusion is aligned with the differential susceptibility theory, which indicates that neurobiological characteristics that increase vulnerability to adverse environments also increase the responsiveness of a person to positive, enriched environments, leading to worse or better outcomes (Pluess, 2015).

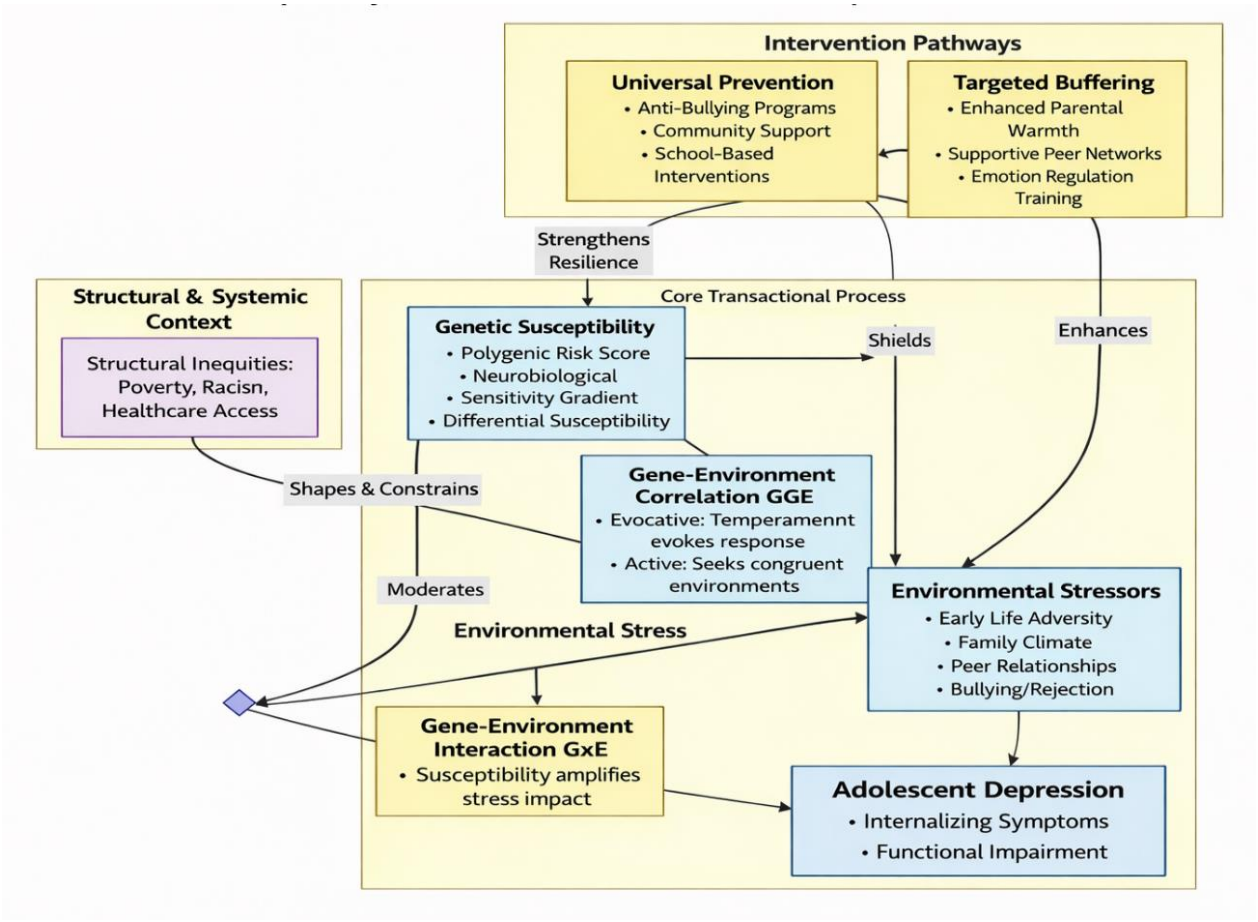

Figure 1: How genes and experience weave together to shape teen depression

This figure explains teen depression risk as an ongoing two-way interaction between a young person's genetic sensitivity and the stresses they face, such as family conflict, peer difficulties, bullying, or early adversity within a broader social context shaped by poverty, racism, and access to healthcare. It suggests that genetics can shape the kinds of environments teens encounter and can also affect how strongly they react to stress. As stress builds, it can trigger knock-on effects like more conflict or weaker support networks, which can worsen symptoms and day-to-day functioning. The model also points to what helps: broad prevention efforts and more targeted support can reduce stress and build resilience, particularly for teens who are most sensitive to their surroundings.

Considerations and Future Directions

Despite the usefulness of the transactional model in the study of adolescent depression, it should be reviewed with certain limitations in mind. Focusing on the concept of differential susceptibility in excess can cause one to overlook the major role of structural and systemic inequalities like poverty, racism, and insufficient healthcare, which create and maintain harmful environments regardless of genetic composition (Causadias, 2020; Pluess, 2015). As an example, the persistent, omnipresent stress of socioeconomic disadvantage can trigger depression even among people who have low polygenic risk, which cannot be completely explained by individual-based models of sensitivity. In addition, the application of this research into practice is associated with major ethical concerns. Biological sensitivity marker utilization is associated with stigma and genetic determinism and may worsen health disparities in case access to targeted interventions is uneven (Loughnan *et al.,* 2019; Martin *et al.,* 2019).

Further studies should examine the role of extended social determinants in transactional processes. Future, intensive, and highly phenotyped studies are required to trace the interaction of normative adolescent distress with individual genetic risks. More ancestrally diverse genetic samples are also urgently required to ensure that polygenic studies are relevant and applicable to all populations (Martin *et al.,* 2019). Finally, to increase effectiveness and avoid ethical pitfalls, intervention science should rigorously test the application of biologically specific interventions (Belsky & van Ijzendoorn, 2017).

CONCLUSION AND IMPLICATION

Depression in adolescence is a product of the constant interplay of nature and nurture and is not necessarily caused by either one. The evidence is drawn together around a single model where polygenic risk sets up a gradient of neurobiological susceptibility, usually as

heightened sensitivity to interpersonal situations, particularly threat, rejection, and invalidation. Experience is a factor that contributes to this vulnerability in both gene-environment correlation and interaction; genetics defines who is susceptible and the pattern of illness, while the environment plays an important role in determining when and whether a person develops depression.

This transactional perspective, however, should be implemented with care since excessive focus on the individual vulnerability may hide the contribution of structural inequity, including poverty, structural racism, and poor healthcare that perpetuate harmful environments irrespective of genetic composition. Ethical concerns are also associated with translating this model to practice: the application of biological markers can become a source of stigma and genetic determinism and can create inequities when targeted help is not evenly distributed.

Considering these warnings, the model recommends dual-focused intervention. Universal prevention should be used to minimize modifiable social hazards, including bullying, harsh parenting, and peer rejection with the help of evidence-based school and community interventions. An even more specific approach can be especially useful in the case of youth with high genetic risk. Since such individuals are more context sensitive, they might gain more as a result of interventions that increase environmental buffers, including increasing parental warmth, establishing supportive peer networks, and developing emotion regulation skills.

Finally, acknowledging the subtle, continuous conversation between genes and environment and combining scientific and ethical concern will enable us to develop more accurate, useful, and fair methods to alleviate the excessive burden of depression during adolescence.

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