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From Risk to Disorder: How Biology and Early Experience Shape Psychopathology

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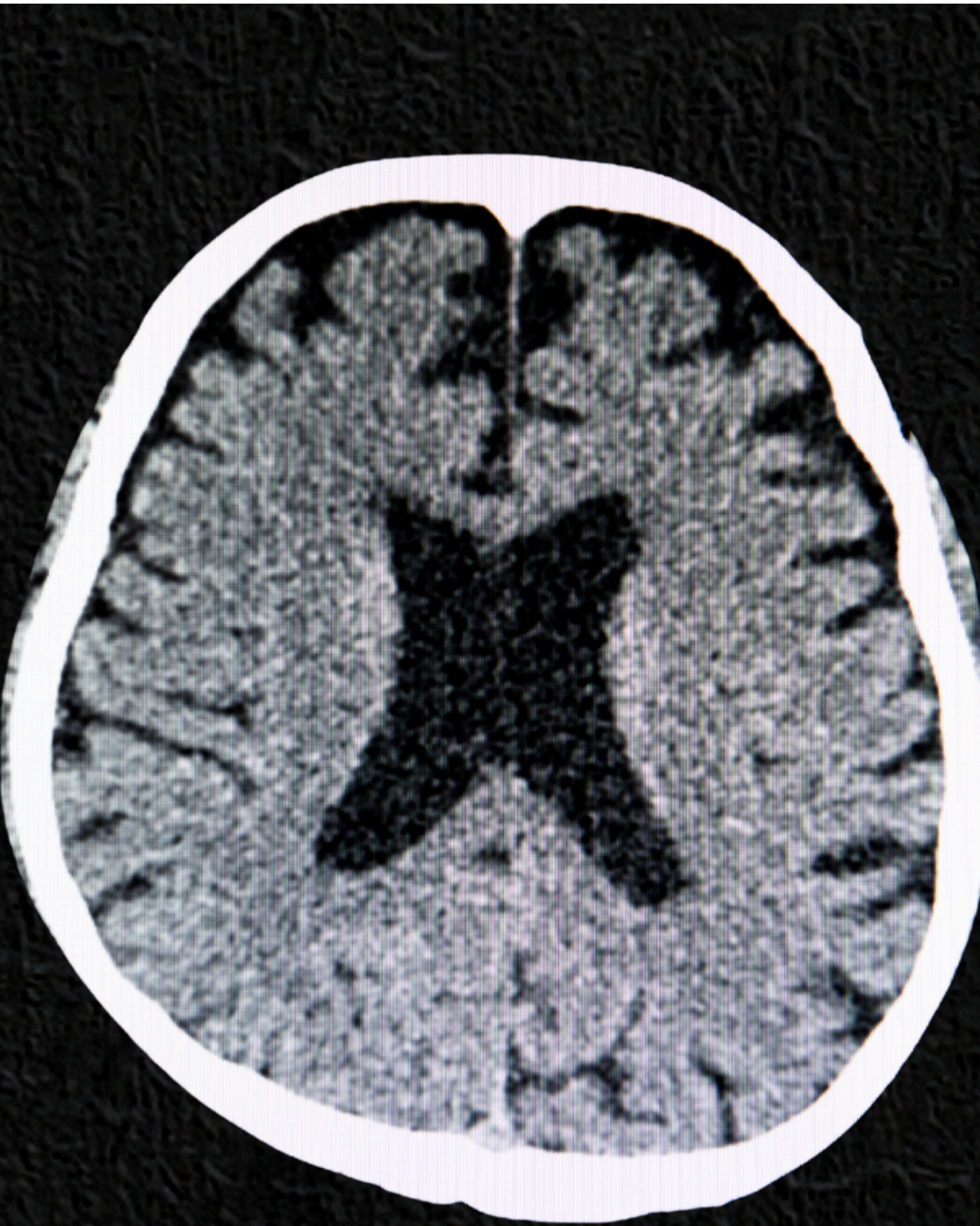

Mental disorders don't stem from a single origin; they arise from the dynamic interaction between biological vulnerability and environmental factors. This paper aims to explore how early life adversities activate an underlying genetic vulnerability through neurobiological pathways, and ultimately lead to psychopathology. The importance of understanding this etiology lies in early detection and prevention of mental disorders.

Psychological disorders are a significant global health burden, affecting individuals across different ages, sexes, backgrounds, and socioeconomic statuses. Understanding the roots behind these disorders is essential for advancing both clinical and psychotherapeutic approaches. Etiological knowledge helps screen patients at a higher risk of developing mental disorders, encouraging early intervention and treatment, ultimately preventing patients' distress and the worsening of the symptoms. Some researchers believe psychological disorders are shaped by one's environment: abandonment, neglect, toxic households, or severe trauma. Others emphasize that genetic predisposition, hormonal imbalance, and brain atrophy or abnormalities are what contribute to mental disorders. Contemporary research suggests that it's the dynamic interaction between both environmental and biological factors that underlies psychopathology.

The biopsychosocial model proposes that mental disorders arise from the combination of genetic predisposition, biological vulnerability, trauma, environmental stressors, and low socioeconomic status. No single etiological factor can lead to mental disorders alone. Similarly, the diathesis-stress model emphasizes that biological vulnerability and hormonal imbalance might increase the risk of developing mental disorders, but the symptoms do not manifest unless triggered by traumatic events. Together, these models show that biological predisposition does not lead to determinism; it's the gene-environment interactions that shape mental disorders.

Genetic machinery

Single-nucleotide polymorphisms (SNPs) are the most common form of genetic variation studied in psychiatric genomics (Smoller et al., 2018). While very common, one SNP rarely ever leads to the formation of a mental disorder (odds ratio of 1.1 or less); it's the accumulation of SNPs (polygenicity) that increases the risks of developing disorders like schizophrenia and depression (Wray et al., 2014).

Copy number variants (CNV), which are the deletion or duplication of large segments of DNA, are considerably rarer, occurring in less than 0.5% of cases (Smoller et al., 2018). However, they exert a greater risk impact, varying from 3.8% to 6.8%. 22q deletion syndrome is the most widely known example of a CNV that increases the risk of developing psychological disorders; individuals with a deletion of arm 11.2 on chromosome 22 were more prone to developing conditions like psychosis and schizophrenia (CNV Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2017).

Polygenic risk scores (PRS) are a single metric that accounts for the additive effects of multiple SNPs predicting the likelihood of an individual developing a certain mental disorder (Smoller et al., 2018).

PRS demonstrate that the same cluster of genes doesn't cause one specific disorder but rather increases the risks of many, showing why co-diagnosis might occur, i.e., schizophrenia PRS is not only associated with schizophrenia but also with bipolar disorder , and neurodevelopmental problems (Purcell et al., 2009). While PRS alone are not sufficient to fully diagnose an individual, they are valuable research tools for understanding genetic vulnerability, shared biological risk across disorders, and gene-environment interactions. Thus, genetic predisposition doesn't automatically lead to determinism but rather increases vulnerability.

Biological pathways

Studies indicate that schizophrenia symptoms don't show until later on; however, affected individuals show neurodevelopmental impairments early in childhood, suggesting that the disorder has early neurodevelopment origins. In addition, mutations linked to schizophrenia and autism have been mapped to fetal prefrontal cortical networks, further suggesting that these disorders have begun early in development.

The major histocompatibility complex (MHC) is a region in the genome commonly associated with schizophrenia. Complex fine mapping of the genetic material allowed the discovery that specific functional alleles of the C4 genes in the MHC increase the risk of developing schizophrenia. C4 protein's main function is to activate the immune system and help protect against pathogens. However, further studies demonstrate that C4 proteins are also involved in microglia-mediated synaptic pruning (Sekar et al., 2016).

Synaptic pruning is a naturally occurring process where the brain eliminates extra synapses to increase the efficiency of synaptic networks. C4 tags the synapses ready for pruning, helping microglia eliminate them. Synaptic pruning is most active during adolescent years, a developmental period that coincides with the onset of schizophrenia, suggesting that variation in C4-mediated pruning increases the vulnerability and risk of developing the disorder (Smoller et al., 2018).

Environment

Early life adversity (ELA) refers to negative childhood events that deviate from the healthy, expectable environment a child should grow up in and require significant adaptation (McLaughlin, 2016). When experienced during sensitive developmental periods where brain plasticity is particularly high, ELA increases the risk of developing socioemotional and behavioral difficulties in children and youth (Nelson & Gabard-Durnam, 2020). Studies have shown that more than 50% of children experience at least one ELA by the time they reach adulthood, which is concerning given the fact that psychiatric difficulties arising from ELA are chronic, persistent, and more resistant to treatment than difficulties not associated with ELA (McLaughlin et al., 2010).

To better understand the effects of environment on the development of mental disorders, ELA is divided into core dimensions, each with different developmental consequences.

- **Threat and harm**

The first dimension of ELA is threat and harm, referring to the exposure of youth to direct physical violence, sexual assault, emotional abuse, bullying by peers (Wade et al., 2022). Research shows that youth exposed to these types of threats early on have heightened sensitivity to threatening cues. While this sensitivity may be adaptive in dangerous environments, it can cause difficulties with emotional regulation in the long term. In addition, children and adolescents exposed to these threats are at a higher risk of developing disorders like PTSD, conduct disorder, depression, and self-harm behaviors (Danese et al., 2020).

- **Deprivation**

Deprivation is a type of ELA characterized by a developmental environment that lacks the expected cognitive, social, and emotional inputs that are necessary for healthy development. Children who experience severe forms of deprivation, like institutionalized rearing, were shown to have a higher risk of developing a psychiatric disorder than children who were never exposed to deprivation. (Humphreys et al. 2020)

However, studies indicate that when institutionally reared youth were adopted by healthy and stable families early on, the symptoms reduced in severity, which suggests that early interventions can reduce the effects of deprivation on mental health.

Impairments in cognitive functions, including reduced language and academic abilities, were also associated with other forms of deprivation, such as neglect, poverty, and low socioeconomic status. Furthermore, these cognitive deficits showed a link between deprivation and later psychopathology, including ADHD (attention-deficit/hyperactivity disorder) (Golm et al., 2020).

- **Unpredictability**

'Unpredictability' refers to early environments prone to inconsistency and instability, in which children are constantly being exposed to abrupt changes like inconsistent parenting, unstable residential areas, and frequent conflict (Belsky et al., 2012). Research has shown that unpredictability is not associated with a single mental disorder, but rather acts as a transdiagnostic risk factor, increasing the risk of developing a broad range of mental disorders. These findings suggest that children exposed to unpredictability exhibit increased vulnerability to later psychopathology (Hurst & Kavanagh, 2017).

Biology X Environment

Exposure to ELA, especially during developmental periods, has been shown to activate the body's stress response mechanisms, particularly the hypothalamic-pituitary-adrenal (HPA) axis. While this activation is necessary to maintain homeostasis in the body, long-term exposure to stress leads to prolonged activation in the HPA axis, causing dysregulation in cortisol secretion, the body's central stress hormone. This altered secretion of cortisol increases the risk of developing psychopathology (Zhou & Ryan, 2023).

Another mechanism through which early-life environment becomes embedded in human biology is through epigenetic modification, which alters the levels of gene expression without affecting the DNA itself. The most common form of epigenetic modification is DNA methylation, which is the addition of a methyl group to DNA, causing certain genes to turn “on” or shut “off.” Research has shown that ELA has been linked to changes in the methylation levels of stress-related genes like NR3C1 and FKBP5, causing cortisol dysregulation and an increased sensitivity to future stressors, increasing the vulnerability to psychopathology (Zhou & Ryan, 2023).

In conclusion, mental disorders do not stem from one etiological origin; it’s the interplay of genetic predisposition, biological pathways, and early developmental environments that shapes psychiatric disorders. While genetic predispositions like SNPs and CNVs, synaptic pruning, and activation of the HPA axis all increase the vulnerability of developing psychopathology, it’s the early life adversities and developmental environment that influences when and how this vulnerability manifests.

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