Review paper

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Before the First Synapse: Neurodevelopmental Origins of Mental Disorders

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Keywords

Neurodevelopmental disorders; mental disorders; epigenesis, genetic; embryonic development; gene-environment interaction

Abstract

Aim: This review examines how genetic vulnerability, epigenetic regulation, and early embryonic development contribute to neurodevelopmental trajectories that may increase susceptibility to psychiatric disorders later in life. **Materials and Methods:** A narrative review approach was used to synthesize current literature on the neurodevelopmental continuum, psychiatric genetics, epigenetic regulation, embryonic epigenome remodeling, and environmental influences during preimplantation and prenatal development. **Results:** Evidence increasingly challenges the strict separation between childhood neurodevelopmental disorders and adult psychiatric conditions. Intellectual disability, autism spectrum disorder, attention-deficit/hyperactivity disorder, schizophrenia, bipolar disorder, and depression share partly overlapping genetic and molecular risk architectures. Rare copy number variants, single-nucleotide variants, de novo mutations, and polygenic risk interact with epigenetic mechanisms, including DNA methylation, histone modifications, chromatin remodeling, and RNA methylation. Early embryogenesis represents a particularly sensitive developmental window because the parental epigenomes undergo extensive demethylation, remodeling, and re-establishment. Disturbances caused by parental age, stress, inflammation, metabolic imbalance, assisted reproductive procedures, or other environmental exposures may therefore influence neurodevelopmental programming and long-term psychiatric vulnerability. **Conclusion:** Mental disorders should increasingly be understood within a developmental framework in which genetic predisposition and epigenetic plasticity interact across sensitive periods of brain development. Greater attention to the preconceptional, embryonic, and prenatal environment may improve prevention strategies, early risk identification, and future biomarker development in psychiatry.

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Introduction

Neurodevelopmental disorders (NDDs) are traditionally defined as conditions that have their onset during early development and are associated with impairments in personal, social, academic, or occupational functioning. According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5-TR), they include intellectual disability (ID), communication disorders, autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD), developmental motor disorders, and specific learning disorders [1]. Historically, these conditions were considered mainly within child

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psychiatry and were often treated as separate diagnostic entities, with limited recognition of shared mechanisms across diagnostic boundaries [2]. In parallel, adult psychiatric disorders such as schizophrenia, bipolar disorder (BD), and major depressive disorder (MDD) were conceptualized as distinct clinical categories with later onset and separate etiologies [3].

This categorical separation is increasingly difficult to maintain. Clinical and epidemiological evidence shows that individuals with NDDs have an elevated risk of later psychiatric symptoms and disorders, including anxiety, depression, behavioral dysregulation, and personality-related difficulties [4]. Part of this association may reflect heightened emotional vulnerability and functional impairments in children with NDDs that increase the risk of behavioral and personality-related difficulties in adulthood [5]. However, these associations also point to deeper biological overlap between childhood neurodevelopmental conditions and adult mental illnesses.

Genetic research has substantially strengthened this developmental view of psychiatry. It is now evident that childhood neurodevelopmental conditions such as ID, ASD, and ADHD are linked to adult psychiatric disorders through shared genetic risk factors, such as rare copy number variants (CNVs) and single-nucleotide variations (SNVs) [6,7].

These findings suggest that many psychiatric disorders do not arise suddenly at the time of clinical presentation but may reflect earlier deviations in brain development that become clinically visible only when developmental, hormonal, cognitive, or environmental demands increase [8].

These insights have fostered the neurodevelopmental paradigm in psychiatry, which holds that mental disorders arise from disruptions in brain development—an intricate process that begins before birth and depends on tightly coordinated regulation of cell fate, neuronal migration, synaptogenesis, circuit formation, and later plasticity [9]. This perspective challenges the artificial historical divide between childhood NDDs and adult mental illnesses, recognizing a continuum where early perturbations establish risk or resilience for later neuropsychiatric conditions [10].

The aim of this narrative review is to discuss the neurodevelopmental origins of mental illness, with particular emphasis on genetic and epigenetic mechanisms operating during embryogenesis and early brain development. By integrating evidence from psychiatric genetics, epigenetics, developmental biology, and environmental neuroscience, this paper highlights how early biological perturbations may contribute to a continuum of outcomes ranging from NDDs in childhood to psychiatric disorders in adolescence and adulthood.

The Neurodevelopmental Continuum: From Embryogenesis to Psychopathology

The concept of a neurodevelopmental continuum marks a paradigm shift in psychiatric nosology, moving away from the DSM-5's rigid, discrete diagnostic categories toward a model of shared etiological and neurodevelopmental origins [11]. This perspective conceptualizes childhood NDDs, such as ID, ASD, and ADHD, alongside adult psychiatric conditions like schizophrenia and BD as a diverse range of outcomes resulting from disrupted or altered brain development [2]. Although the DSM-5 classifies childhood and adult psychiatric disorders separately, they are increasingly seen as diverse conditions with overlapping neurodevelopmental paths. These conditions represent different points along a spectrum of neurodevelopmental impairment, where severity and age at onset are linked to the extent to which development deviates from typical pathways [11,12]. Indeed, the emergence of psychiatric illnesses is critically dependent on the timing of developmental disruption, wherein early alterations often lead to severe developmental phenotypes such as ASD, while later alterations may predispose individuals to conditions like schizophrenia [13]. Genetic investigations reinforce this continuum by identifying shared rare risk factors, such as CNVs and damaging de novo mutations, that are enriched across NDDs including ID, ASD, ADHD, and schizophrenia. According to the neurodevelopmental gradient hypothesis, ID, ASD, and schizophrenia exist on a single neurodevelopmental spectrum, where the severity of cognitive impairment and the burden of rare genetic mutations decrease sequentially from one condition to the next [2,3].

From phenotype-first to genotype-first approaches

The shift to the neurodevelopmental paradigm underscores the importance of investigating neurodevelopmental origins of psychopathology, moving from phenotype-first approaches to genotype-first investigations [14]. This genomic emphasis allows for a more precise understanding of the underlying molecular mechanisms, moving beyond descriptive symptom clusters to identify specific genetic variants that confer risk across various disorders [15]. This refined understanding recognizes that a single disorder can arise from various genetic etiologies, while, conversely, a single genetic variant may contribute to the pathogenesis of multiple seemingly distinct psychiatric conditions [16]. Large genome-wide association studies (GWAS) have shown that there is no single "disease-gene" for psychiatric disorders, but thousands of genetic variants that act together and collectively influence the risk of illness [16]. Conversely, specific genetic variations, whether common or rare, have been

implicated in a spectrum of NDDs, encompassing ASD, schizophrenia, epilepsy, and ID. Interestingly, the genetic risks for several mental health conditions overlap significantly with positive, highly adaptive human traits such as exceptional cognitive performance, creativity, and openness. This phenomenon is driven by genetic pleiotropy, in which the same genetic variants influence multiple seemingly unrelated traits. For example, risk for ASD is genetically correlated with higher educational attainment and better cognitive performance, while the risk for BD and schizophrenia is genetically correlated with higher levels of the personality trait openness to experience and creativity [17-20].

The genetic heterogeneity and pleiotropy underscore the complexity of psychiatric genetics, necessitating a comprehensive analysis of both inherited and de novo mutations to fully elucidate disease pathogenesis. Mutations can occur in coding or regulatory DNA regions, leading to either reduced or increased expression of critical genes, thereby perturbing protein function and having consequential impacts on neurodevelopmental processes [21,22]. Beyond direct genetic alterations, epigenetic modifications - heritable changes in gene expression that do not alter the underlying DNA sequence - also play a critical role in neurodevelopmental trajectories and disease susceptibility.

Genetic mutations

The most common types of genetic mutations implicated in NDDs include SNVs, CNVs, and rare variants such as de novo or inherited loss-of-function mutations, insertions, deletions, and structural rearrangements [23]. De novo variants are particularly relevant in sporadic cases of NDDs without a family history, providing critical insights into their etiology [24,25]. They arise spontaneously in paternal germ cells or during early embryonic development [26]. The impact of de novo mutations is often more severe because they act immediately on critical developmental processes, particularly when they occur in genes essential for neurogenesis and nervous system development [27]. Both inherited and de novo mutations can lead to diverse clinical outcomes, ranging from subtle behavioral differences to severe developmental pathologies, depending on the affected gene and the nature of the mutation [28,29].

Genetic mutations have distinct implications for gene function depending on their precise location within the genome. For instance, mutations in coding regions can alter protein sequences, while those in regulatory regions, such as promoters and enhancers, can profoundly affect gene expression levels, even without changing the encoded protein [30]. Missense, nonsense, and frameshift mutations can lead to truncated or nonfunctional proteins, whereas synonymous mutations, though they do not alter the amino acid sequence, can still affect mRNA splicing or stability, thereby influencing protein abundance [31]. The diverse mutation types contribute to disease risk to varying degrees, depending on their frequency, effect size, and genomic location [16,21].

Recent advancements in sequencing technologies, including long-read sequencing, have significantly enhanced the diagnostic yield for NDDs by enabling the identification of rare variants and the detection of complex structural variants, such as tandem repeat expansions [32]. However, despite these advances, a substantial proportion of cases remain genetically unresolved. One contributing factor may be pathogenic variation in non-coding regulatory elements, such as promoters, enhancers, and untranslated regions, which can alter gene expression and developmental trajectories without affecting protein-coding sequences [30]. More broadly, understanding the pathophysiology of neurodevelopmental and psychiatric disorders requires integration of genetic findings with regulatory, developmental, and environmental mechanisms [33]. Regulatory genomic regions are subject to epigenetic modifications that influence chromatin dynamics and gene accessibility and may provide one mechanism linking genetic susceptibility with environmental influences during neurodevelopment [34-36]. Such epigenetic alterations can arise from various internal and external factors, ranging from parental gamete modifications to early embryonic environmental exposures, thereby influencing the vulnerability to mental illness throughout life.

Epigenetic Regulation

Epigenetic regulation enables the fine-tuning of gene expression in response to environmental cues. Environmental factors, including socio-economic status, early life stressors, childhood trauma, and even later adverse events, significantly impact the risk of psychiatric disorders via lifelong epigenetic modifications [34,35]. Interestingly, individuals exhibit considerable inter-individual differences in their responses to environmental stressors, partly reflecting differences in genetic architecture. Beyond directly contributing to disease susceptibility, genetic variation may also influence epigenetic responses to environmental stimuli [35]. Genes involved in establishing and maintaining epigenetic modifications—the so-called "epigenetic machinery"—have themselves been implicated in schizophrenia and neurodevelopmental disorders when disrupted by pathogenic genetic variation [35,36]. Thus, a complex landscape of risk and resilience emerges from the interplay of genetic predispositions and epigenetic modifications. Finally, evidence that genetic variation can influence epigenetic responses to early-life adversity highlights the complex interaction

between inherited susceptibility and environmental exposure [35].

Epigenetic modifications, which encompass DNA methylation, histone modifications, and non-coding RNA-mediated regulation, collectively modulate chromatin structure and gene accessibility without altering the primary DNA sequence. These modifications are tailored to developmental needs and are crucial for orchestrating gene expression patterns during critical periods of neurodevelopment. They govern neuronal differentiation, migration, and circuit formation, thereby influencing neuroplasticity and cognitive function throughout the lifespan [38]. Dysregulation of these epigenetic mechanisms may result in aberrant gene expression patterns, thereby contributing to the pathogenesis of various NDDs and mental illnesses [37]. For instance, disruptions in epigenetic programming lead to altered neuronal connectivity and impaired cognitive functions, resulting in conditions like ASD and schizophrenia [38].

A study on rats describes epigenetic modifications of brain-derived neurotrophic factor (BDNF), a molecule involved in neurodevelopment, neuronal regeneration, synaptic plasticity, and learning and memory [39]. Hypermethylation of the BDNF promoter and persistently reduced BDNF mRNA and protein levels have been consistently observed in the prefrontal cortex and hippocampus of rodents subjected to early adversity models, such as maternal maltreatment or limited bedding [40]. In humans, similar BDNF promoter hypermethylation correlates with a history of childhood trauma in postmortem brain tissue and peripheral blood from patients with MDD and borderline personality disorder [41-43]. Furthermore, analyses of hippocampal tissue from suicide victims with a history of childhood abuse revealed reduced glucocorticoid receptor (GR) expression and elevated methylation of the GR 1F promoter [44]. GR is a critical mediator that translates environmental and hormonal signals into structural changes in the developing brain [45,46]. Together, these findings illustrate how environmentally associated epigenetic modifications may influence molecular pathways involved in neurodevelopment, neuronal plasticity, and stress responsivity [45-47]. Beyond DNA methylation, histone modifications, including histone methylation and acetylation, have been implicated in the regulation of gene expression relevant to schizophrenia and depression [35].

In the context of NDDs and psychiatric conditions, investigation of molecular mechanisms increasingly extends beyond traditional DNA methylation, histone modifications, and non-coding RNAs to include additional biochemical and structural layers of epigenetic regulation. The oxidized cytosine derivative 5-hydroxymethylcytosine (5hmC), which is highly enriched in the mammalian brain and participates in active DNA demethylation, has been implicated in neurodevelopmental disorders through alterations in genes involved in neuronal development and function, including RELN and GAD1 [48]. Emerging evidence also implicates histone lactylation as a metabolically sensitive post-translational modification linking cellular metabolic states to transcriptional regulation and neuroinflammatory processes [49]. At the chromatin level, ATP-dependent remodeling complexes, particularly mammalian SWI/SNF (mSWI/SNF) complexes, regulate genomic accessibility and neural differentiation, and pathogenic variants affecting their components have been associated with neurodevelopmental disorders, including intellectual disability and ASD [50,51]. Post-transcriptional regulation represents an additional layer of gene-expression control, with N6-methyladenosine (m6A) modification influencing mRNA processing, stability, and translation in the nervous system. Experimental evidence suggests that alterations in m6A-related regulatory mechanisms may influence stress-related behavioral phenotypes, although their specific contribution to human psychiatric disorders remains to be established [52]. Together, these emerging regulatory mechanisms illustrate additional pathways through which genetic, metabolic, and environmental factors may interact to influence neurodevelopmental and neuropsychiatric vulnerability.

The Critical Window: Embryonic Development and Epigenome Remodeling

Studies have shown that, in addition to being induced by early-life experiences during sensitive developmental periods, some environmentally associated epigenetic alterations may also be detectable in parental germ cells and potentially influence offspring development [53-55]. Epigenetic modifications acquired by parents throughout life—through factors such as stress, nutrition, toxin exposure, infections, or other environmental influences—can persist in their gametes and serve as a form of biological "memory" of parental experiences. Older paternal age is associated with a heightened risk of NDDs in offspring. This association is attributed to increased methylation of genes implicated in NDDs, as well as numerous imprinted genes, resulting from greater susceptibility to epimutations in sperm with age [56]. Although epigenetic marks are transmitted to the zygote at fertilization, they are not passed on to the next generation because they undergo extensive epigenetic reprogramming during the preimplantation stage of early embryonic development, which is characterized by zygotic genome activation (ZGA) [57].

Proper embryonic development depends on the precise reprogramming and re-establishment of DNA methylation patterns that support early developmental potential, lineage specification, and, later, sex-specific

epigenetic regulation. Therefore, immediately after fertilization, the parental epigenomes undergo extensive remodeling before new embryonic epigenetic patterns are established.

Shortly after fertilization, the embryo undergoes extensive epigenetic reprogramming, including widespread erasure of pre-existing epigenetic marks, to establish developmental competence [57,58]. The paternal genome undergoes rapid active DNA demethylation involving the Ten-Eleven Translocation 3 enzyme (TET3), whereas the maternal genome undergoes predominantly passive demethylation across successive cleavage divisions, resulting in epigenetic asymmetry between the parental genomes in the early embryo [57,59]. At the same time, dynamic histone modifications and chromatin remodeling reshape genomic accessibility, enabling the activation of embryonic transcription during zygotic genome activation (ZGA) [57-59]. Genome-wide DNA methylation reaches low levels around the blastocyst stage, while imprinted regions and other protected loci largely escape extensive demethylation [57,58]. This is followed by de novo remethylation, supporting lineage specification after implantation and the establishment of increasingly cell- and tissue-specific epigenetic patterns [57-59]. These tightly regulated processes establish developmental gene-expression programs necessary for lineage specification and subsequent cellular differentiation [57-59].

Because of the intensity and precision of these processes, early embryogenesis represents a particularly sensitive developmental window. Environmental exposures during the periconceptional and early embryonic periods may interfere with developmental and epigenetic programming and thereby influence subsequent developmental trajectories [60-62]. Experimental evidence, including studies of preimplantation alcohol exposure, supports the possibility that environmental exposures during this period can induce persistent epigenetic alterations [61]. The importance of appropriate epigenetic regulation is further illustrated by TET3 deficiency, which is associated with a genome-wide DNA hypermethylation episignature and a neurodevelopmental phenotype that may include intellectual disability and behavioral or psychiatric manifestations [63].

Consequently, the intratubal and intrauterine environment functions as a critical mediator of this biological vulnerability, in which adverse maternal exposures—ranging from psychological stress to nutritional deficits—directly disturb these foundational epigenetic pathways [62]. Prenatal stressors, including maternal infections that trigger immune activation (e.g., influenza or viral mimetics such as polyinosinic-polycytidylic acid and hormonal imbalances from metabolic disorders or chronic stress, induce persistent epigenetic modifications in the fetal brain. These include DNA hypermethylation at promoters of glutamate decarboxylase 1 and 2 (GAD1 and GAD2) genes impairing gamma-aminobutyric acid (GABA) synthesis, hypomethylation of methyl-CpG-binding protein 2 (MeCP2) leading to dysregulated long interspersed nuclear element-1 (LINE1) expression and altered histone acetylation patterns, which disrupt neuronal differentiation, synaptic pruning, and circuit formation. These changes increase offspring's risk of ASD and schizophrenia [64-67]. Often observed in animal models of maternal immune activation, the described epigenetic changes persist into adolescence and adulthood, correlating with behavioral deficits like impaired social cognition and cognitive flexibility [65,68]. Human epidemiological studies have also associated maternal infection and fever during pregnancy with an increased risk of neurodevelopmental and psychiatric disorders in offspring, including ASD and schizophrenia, although the extent to which epigenetic mechanisms mediate these associations remains unclear [64,65].

The oviductal microenvironment plays an active role in fertilization and early embryonic development by providing a dynamic milieu of proteins, metabolites, and extracellular vesicles that supports embryo–maternal communication and developmental competence [69-71]. In contrast, embryo culture during assisted reproductive technology (ART) exposes the developing embryo to non-physiological conditions during a period of extensive epigenetic reprogramming, and experimental and clinical evidence suggests that such conditions may influence epigenetic regulation and gene expression [72,73]. Experimental studies have further shown that manipulation of culture conditions during early cleavage stages can affect brain epigenetic patterns and later phenotypes; for example, thermal manipulation during the first cleavage stage has been associated with alterations in offspring circadian rhythms, sleep, and brain epigenetics [74]. ART and specific procedures such as oocyte vitrification have therefore been investigated for their potential effects on epigenetic regulation and neurodevelopmental outcomes. Although some epidemiological studies have reported associations between medically assisted reproduction and ASD or other NDDs, the available evidence does not establish a direct causal relationship between individual ART procedures and these disorders [75-77]. Prenatal environmental and endocrine conditions may likewise influence fetal neurodevelopment through epigenetic mechanisms. In particular, alterations in maternal stress-related signaling and glucocorticoid exposure have been associated with epigenetic regulation of the hypothalamic-pituitary-adrenal axis and other pathways involved in fetal brain development [78-80]. Together, these findings suggest that environmental conditions during sensitive periods of embryonic and fetal development can interact with epigenetic regu-

latory mechanisms and potentially contribute to long-term variation in neurodevelopmental trajectories.

Clinical translation within a neurodevelopmental framework

Within the neurodevelopmental framework, genetic and epigenetic findings should be understood as complementary to, rather than replacements for, clinical diagnosis. Conventional diagnostic categories such as schizophrenia, BD, depression, and autism encompass substantial biological heterogeneity and may share genetic and neurodevelopmental mechanisms [81,82]. Molecular testing may therefore be particularly informative when it helps clarify etiology or identify an underlying neurodevelopmental or genetic condition, thereby contributing to clinical management and genetic counseling [83,84].

In clinical practice, genetic testing is particularly relevant when psychiatric symptoms occur in the context of developmental delay or ID, autism spectrum features, epilepsy, congenital anomalies, dysmorphic features, neurological abnormalities, developmental regression, or a suggestive family history [83,85,86]. Depending on the clinical phenotype, chromosomal microarray, exome sequencing, or genome sequencing may identify pathogenic copy-number, coding, or structural variants associated with neurodevelopmental disorders [83,87]. More targeted investigations may be appropriate when clinical findings suggest a specific genetic, metabolic, mitochondrial, or repeat-expansion disorder [86,87].

Epigenetic testing currently has a more restricted clinical role. DNA methylation-based assays can provide diagnostic information in selected Mendelian neurodevelopmental disorders characterized by recognizable epigenetic signatures ("episignatures") [88-90]. In contrast, epigenetic biomarkers associated with stress-related disorders, psychiatric vulnerability, or treatment response remain predominantly investigational [91,92]. Their translation into routine psychiatric practice is limited by tissue and cell-type specificity, environmental and medication-related influences, biological heterogeneity, and the difficulty of distinguishing causal alterations from changes secondary to illness or exposure.

Similarly, polygenic risk scores have substantially advanced research into the shared genetic architecture of psychiatric disorders, but their predictive performance, ancestry portability, and individual-level clinical utility remain insufficient for routine diagnosis or treatment planning [93-95]. Emerging genomic, transcriptomic, neuroimaging, and other high-dimensional approaches may further improve the biological characterization and stratification of neurodevelopmental and psychiatric phenotypes, although their clinical implementation will require robust validation and demonstration of meaningful clinical utility [96-98].

Overall, the neurodevelopmental perspective supports an integrated rather than molecularly deterministic approach to psychiatric disorders. Genetic and epigenetic findings should not be viewed as substitutes for clinical diagnosis, but as additional layers of information that may help define etiological subgroups and link early developmental mechanisms with later psychiatric phenotypes. Their greatest clinical value is likely to emerge when molecular findings are interpreted alongside developmental history, phenotype, family history, environmental exposures, and longitudinal clinical course.

Conclusion

In conclusion, genetic predisposition and environmental influences, mediated in part by epigenetic mechanisms, interact across development to shape neurodevelopmental trajectories and susceptibility to mental illness [35,40,54]. Future research should prioritize robust longitudinal epigenetic profiling to clarify gene–environment interactions and to identify reproducible biomarkers of vulnerability and resilience [35,54]. Integrating genetic, epigenetic, developmental, and environmental data through integrative approaches may provide a more comprehensive understanding of the etiology and heterogeneity of complex neuropsychiatric disorders [81,99]. As evidence develops, molecular profiling may eventually contribute to more refined biological stratification and developmental risk assessment, although its predictive and clinical utility at the individual level remains to be established [29, 84]. The broader social and ethical implications of epigenetic research should also be considered, particularly when translating associations between environmental exposures and later health outcomes into preventive strategies. The preimplantation and periconceptional periods warrant particular research attention because extensive epigenetic reprogramming occurs during early embryogenesis and may be sensitive to environmental conditions [57-59]. However, these associations should not be interpreted deterministically, and evidence linking specific periconceptional exposures to later neuropsychiatric outcomes should be evaluated cautiously [60,61].

Abbreviations:

ADHD	attention-deficit/hyperactivity disorder
ASD	autism spectrum disorder
BD	bipolar disorder
BDNF	brain-derived neurotrophic factor

CNVs	copy number variants
DSM-5-TR	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision
GR	glucocorticoid receptor
ID	intellectual disability
MDD	major depressive disorder
NDDs	neurodevelopmental disorders
SNVs	single-nucleotide variants
TET3	ten-eleven translocation methylcytosine dioxygenase 3
ZGA	zygotic genome activation

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Conflict of Interest

None to declare.

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