Review

From Genes to Regulatory Logic: Redefining Mechanisms and Therapeutic Strategies in Brain Disorders

Lin Wang , Yi Wang , Liming Tan *

Posted Date: 22 October 2025

doi: 10.20944/preprints202510.1749.v1

Keywords: brain disorders; critical periods; cis-regulatory element; regulatory topologies; preventive treatment

 doi:10.20944/preprints202510.1749.v1

Review

From Genes to Regulatory Logic: Redefining Mechanisms and Therapeutic Strategies in Brain Disorders

Lin Wang [1,2], Yi Wang [3,*] and Liming Tan [1,2,*]

[1] Shenzhen Key Laboratory of Neuropsychiatric Modulation, Shenzhen-Hong Kong Institute of Brain Science, Shenzhen Institutes of Advanced Technology, Chinese Academy of Sciences, Shenzhen 518055, China

[2] Guangdong Provincial Key Laboratory of Brain Connectome and Behavior, the Brain Cognition and Brain Disease Institute, Shenzhen Institutes of Advanced Technology, Chinese Academy of Sciences, Shenzhen 518055, China

[3] Department of Stomatology, First Medical Center, Chinese PLA General Hospital, Beijing, China

* Correspondence: wangyi1@301hospital.com.cn; lm.tan@siat.ac.cn

Abstract

Brain disorders—including psychiatric, neurodevelopmental, and neurodegenerative conditions—arise from complex interactions between genetic architecture, environmental exposure, and developmental timing. Rather than isolated molecular lesions, these disorders reflect hierarchical misalignments in regulatory systems that coordinate gene expression, chromatin state, and neural network dynamics. Genes establish potential boundaries of regulation, while early environmental conditions and experiences reshape cis-regulatory element (CRE) accessibility, thereby redefining the brain's transcriptional and circuit landscape. During sensitive developmental periods, transient external signals can become biologically encoded through stable regulatory modifications, creating enduring trajectories of vulnerability or resilience. Distinct disorders emerge when the same molecular components operate within divergent regulatory topologies—such as enhancer overactivation, promoter silencing, or insulation loss—producing disease-specific phenotypes. Advances in single-cell multi-omics data, clinical data and AI-based modeling now allow reconstruction of these hierarchical networks, enabling the prediction of regulatory vulnerability and identification of intervention points. This regulation-centric framework reframes brain disorders as dynamic failures of gene–environment coordination, highlighting early regulatory plasticity as both the origin of pathology and a window for preventive treatment.

Keywords: brain disorders; critical periods; cis-regulatory element; regulatory topologies; preventive treatment

Introduction

Brain disorders—including psychiatric, neurodevelopmental, and neurodegenerative conditions—represent a major global health burden(Paus et al., 2008; Steinmetz et al., 2024). Despite decades of research, the mechanisms underlying their onset and progression remain only partially understood(Sun et al., 2024; Crouse, 2025; Gao et al., 2025b; Öngür and Paulus, 2025). A growing body of evidence demonstrates that genetic predisposition alone is insufficient to explain disease risk, and that genes and lived experiences play decisive roles in shaping brain health across the lifespan(Lida-Alkisti et al., 2024; Gao et al., 2025b). Because the human brain undergoes prolonged structural and functional maturation, particularly during prenatal and early postnatal periods, it is uniquely sensitive to both biological and experiential influences(Hensch, 2004; Silbereis et al., 2016; Monk et al., 2019; Nelson and Gabard-Durnam, 2020; Peña, 2025). Understanding how these internal

 doi:10.20944/preprints202510.1749.v1

and external factors interact to shape neural development is essential for elucidating disease mechanisms.

Genetic programs provide the temporal and spatial scaffolding for brain development. During neurulation, neurogenesis, neuronal migration, and synaptogenesis, a hierarchy of transcriptional networks defines the potential range of neural differentiation and circuit formation(Lein et al., 2017). These networks establish potential regulatory boundaries—windows within which environmental signals can modulate developmental trajectories without disrupting the fundamental organization of the brain. Disruption of these genetic boundaries by mutation or stress can lead to early vulnerability and aberrant connectivity, setting the stage for later psychiatric and neurological disease(Nelson and Gabard-Durnam, 2020).

Environmental and experiential inputs influence these genetic programs through conserved molecular signaling pathways. Prenatal factors such as maternal infection, hypoxia, nutritional deficiency, and toxin exposure alter neurodevelopment via inflammatory, HIF, and Wnt/FGF pathways(Estes and McAllister, 2016; Szabó et al., 2025). Postnatal experiences—including sensory stimulation, social interaction, and stress—affect synaptic maturation through CREB–BDNF, glucocorticoid receptor, and calcium-dependent signaling cascades (Singh-Taylor et al., 2015; Mclaughlin et al., 2019; West, 2025). In normal development, these pathways ensure experience-dependent plasticity; when mistimed or chronically activated, they distort transcriptional timing and circuit refinement, increasing risk for disorders such as autism spectrum disorder (ASD), depression, and schizophrenia (Short and Baram, 2019; Huang et al., 2023; Nelson et al., 2025b).

While these findings highlight the interplay between genes and environment, the underlying regulatory architecture that mediates this interaction remains insufficiently defined. Accumulating evidence suggests that gene–environment interplay operates through a hierarchical regulatory system, where chromatin states and cis-regulatory elements (CREs)—including enhancers, promoters, silencers, and insulators—govern gene accessibility and responsiveness(Andersson and Sandelin, 2020; Kim and Wysocka, 2023). Genome-wide association studies reveal that most disease-associated variants reside in noncoding regions enriched for CREs (Guo et al., 2023; Zhu et al., 2024), while single-cell and spatial omics studies show that CRE activity is both cell-type- and region-specific (Li et al., 2023; Mannens et al., 2024). These insights point toward a regulatory logic in which environmental experiences shape disease vulnerability by dynamically reconfiguring the genome's control landscape.

In this review, we reframe the study of brain disorders within this regulatory perspective. We first describe how genetic programs establish developmental boundaries that define the context for environmental modulation. We then examine how environmental conditions and early experiences act through signaling pathways to influence neural development and disease susceptibility. Finally, we explore how emerging evidence places CREs and epigenomic plasticity at the center of this integration, and how combining clinical data and artificial intelligence approaches could enable predictive models of disease mechanisms and therapeutic reprogramming.

Genes and Environment as Hierarchical Partners in Brain Development and Disorders

Genes provide potential regulatory boundaries

Human brain development proceeds through a precisely timed and hierarchically organized sequence of genetic programs, beginning in early embryogenesis and extending well into early adulthood(Stiles and Jernigan, 2010; Silbereis et al., 2016). These processes include neurulation, neurogenesis, neuronal migration, axon guidance and neuritogenesis, synaptogenesis, synaptic pruning and circuit refinement, as well as gliogenesis and myelination(Zhou et al., 2024), each of which establishes the structural and functional foundation for subsequent stages. Rather than acting as an immutable script, genetic activity at each stage defines a potential regulatory boundary: a

 doi:10.20944/preprints202510.1749.v1

temporally and spatially constrained window in which transcriptional networks can respond to developmental signals while maintaining overall program integrity. These boundaries delineate when and where environmental modulation can occur, shaping both normal developmental trajectories and susceptibility to later disease.

Early embryonic and prenatal boundaries

The earliest genetic programs establish the architectural blueprint of the nervous system. During neurulation (3–4 gestational weeks), transcription factors such as PAX6, SOX2, and OTX2 orchestrate neural tube formation and dorsal–ventral patterning, while SHH and BMP gradients define progenitor domains(Libé-Philippot and Vanderhaeghen, 2021; Ypsilanti and Rubenstein, 2023). Between the fifth and twentieth weeks, neurogenesis generates most cortical and subcortical neurons, guided by temporally restricted expression of regulators such as FEZF2, EMX2, and NEUROD1(Telley et al., 2019; Molnár and Kwan, 2024). From 12 to 24 gestational weeks, neuronal migration organizes cortical lamination through transcriptional cascades involving DCX, RELN, and LIS1(Silva et al., 2019). Disruptions during these stages—such as folate deficiency, maternal infection, or hypoxia—can breach these structural boundaries, leading to neural tube defects, microcephaly, or cortical malformations (Demirtaş, 2020; Beke et al., 2022; Leibovitz et al., 2022). These early processes are largely experience-independent but represent critical windows of molecular vulnerability, where small perturbations in gene expression yield lifelong architectural consequences (Kostović et al., 2021; Russ et al., 2025).

Late gestation: establishing connectivity and network scaffolds

From late gestation through early infancy, the brain transitions from neurogenesis to circuit formation. Axon guidance and neuritogenesis, driven by genes such as ROBO1, EphA4, and SEMA3A, establish the scaffold for emerging networks (Engle, 2010; Polleux and Snider, 2010). These processes depend on temporally restricted expression of cytoskeletal and adhesion molecules, defining a developmental boundary for axonal growth and pathfinding (Barnes and Polleux, 2009; Kolasinski et al., 2013). Genetic disruptions or environmental insults hypoxia ischemia, preterm birth, infection, or nutritional deficiency can interfere with callosal development, producing miswired interhemispheric connections such as agenesis of the corpus callosum or impaired communication (Paul et al., 2007; Yuan et al., 2020; Bartha-Doering et al., 2021; Shi et al., 2021). These findings illustrate that even before sensory experience, gene-regulated timing defines how the brain can or cannot respond to perinatal environmental changes.

Infancy: genetic boundaries meet experience-dependent processes

Beginning in the third trimester and accelerating after birth, synaptogenesis produces exuberant neural connections, particularly in primary sensory cortices (Kostović et al., 2021; Luu and Tucker, 2023). During this stage, genes such as BDNF, NRXN1, SHANK3, and NLGN3 regulate synaptic formation and stabilization, but their activity depends on neuronal activity and sensory input (Hensch, 2004; Takesian and Hensch, 2013). The coincidence of high synaptic turnover and activity-dependent gene regulation defines a second type of regulatory boundary—the transition between intrinsic and experience-driven control. For instance, the visual system's critical period for ocular dominance (6–12 months) and the auditory system's phonemic sensitivity window (0–3 years) rely on gene programs that are temporarily open to modulation by environmental input (Werker and Hensch, 2015; Mitchell and Maurer, 2022; Hegde et al., 2024). When sensory input is absent or mistimed—such as congenital cataract or early deprivation—these windows close prematurely, leaving persistent functional deficits (Kiorpes, 2015; Mitchell et al., 2023).

Childhood and adolescence: long-range maturation and higher-order boundaries

From childhood through adolescence, genetic programs coordinate synaptic pruning, gliogenesis, and myelination to refine neural circuits and support higher cognitive functions (Spear, 2013; Baker et al., 2025; Nishio et al., 2025). Genes regulating oligodendrocyte differentiation (OLIG1, SOX10), axon insulation (MBP), and synaptic pruning (C4A, TREM2) are expressed in tightly controlled developmental waves(Nishio et al., 2025). These molecular boundaries coincide with sensitive periods for language acquisition, socio-emotional regulation, and executive function (Kidd

 doi:10.20944/preprints202510.1749.v1

et al., 2018; Pfeifer and Allen, 2021; Xu et al., 2022). Perturbations in these networks—through chronic stress, inflammation, or genetic risk variants—can desynchronize the timing of pruning and myelination, producing vulnerabilities to disorders such as schizophrenia, depression, and anxiety (Nelson and Gabard-Durnam, 2020; Sydnor et al., 2021; Friedman and Robbins, 2022). Thus, even higher-order functions emerge within genetically defined temporal limits that determine how long experience can shape the developing brain.

Integrative perspective: developmental boundaries as scaffolds for vulnerability

Across these stages, brain development reflects a nested hierarchy of regulatory boundaries: early genetic programs establish the brain's structure; later ones modulate connectivity and plasticity. These boundaries are not fixed—they define the permissible range of developmental plasticity. Environmental influences act within or against these limits, determining whether adaptation or pathology ensues. When the timing or coordination of these boundaries is disrupted, transient experiences can become embedded as lasting changes in circuit organization, predisposing the brain to future disorders (Kostović et al., 2019; Gabard-Durnam and McLaughlin, 2020; Pfeifer and Allen, 2021). This dynamic interplay between genetic constraints and developmental timing provides the biological foundation for the concept of hierarchical partnership between genes and environment in brain development.

Environment as a dynamic modulator across development

Environmental exposures and early-life experiences exert profound and often lasting effects on brain development by interacting with neurodevelopmental processes(Smith and Pollak, 2020; Gee and Cohodes, 2021; Torres-Berrío et al., 2025). These interactions are particularly potent during sensitive or critical periods, when genetic programs temporarily relax their structural constraints, allowing experience-dependent activity to shape neural circuits (Ribic, 2020; Röder and Kekunnaya, 2021; Wang et al., 2021). While such plasticity enables adaptive tuning to environmental contexts, it also introduces vulnerability: adverse or aberrant inputs can derail normative trajectories, inducing structural and functional alterations in neural architecture (Zhu et al., 2022; Milbocker et al., 2024; Birnie and Baram, 2025; Nelson et al., 2025a). The consequences of such perturbations depend critically on timing, duration, and intensity of exposure, as well as on the developmental processes active at that moment (Reh et al., 2020; Telzer et al., 2025).

Nutritional deprivation and metabolic imbalance: disruption of structural boundaries

Nutritional deprivation during early development is among the most thoroughly studied environmental insults, primarily affecting structural processes such as neurulation, neurogenesis, and myelination (Hart et al., 2025; Liu et al., 2025b; Perumal and Gernand, 2025). Folate deficiency in the periconceptional and early gestational period—corresponding to the first structural critical window—impairs neural tube closure, predisposing to severe malformations including anencephaly and spina bifida (Li et al., 2019; Beke et al., 2022). More broadly, prenatal protein-energy malnutrition and deficiencies in micronutrients such as iron, zinc, and omega-3 fatty acids interfere with neuronal proliferation, dendritic arborization, and myelin synthesis (Jarvie et al., 2025; Villalba et al., 2025). Iron deficiency in particular compromises hippocampal neurogenesis and dopaminergic signaling, resulting in enduring cognitive deficits (Bastian et al., 2020; Gao et al., 2025a; Zhao et al., 2025). These nutritional perturbations affect the first wave of developmental boundaries, when genetic control of structural assembly is dominant but still modifiable, thereby increasing the risk for neurodevelopmental disorders such as microcephaly, intellectual disability, and attention-deficit/hyperactivity disorder(Veena et al., 2016; Bennett et al., 2025).

Prenatal stress and early caregiving adversity: modulation of socio-emotional boundaries

In contrast, early-life stress (ELS)—including maternal stress during pregnancy and postnatal caregiving adversity—primarily impacts psychiatric domains, particularly anxiety, depression, and post-traumatic stress disorder (PTSD). These influences converge on the second wave of critical periods, when limbic-prefrontal networks undergo refinement and socio-emotional functions emerge (Jaffer, 2025; Khan et al., 2025). Elevated maternal glucocorticoids during gestation alter the maturation of limbic and hypothalamic–pituitary–adrenal (HPA) axis circuits, recalibrating

 doi:10.20944/preprints202510.1749.v1

emotional reactivity and stress responsivity (Krontira et al., 2020; Álvarez-Mejía et al., 2025). These changes are mediated through persistent epigenetic and transcriptional effects on genes regulating glucocorticoid receptors (NR3C1), synaptic plasticity (BDNF), and stress adaptation (FKBP5)(Khan et al., 2025). Postnatal stress, in forms such as neglect or inconsistent attachment, further disrupts the coordination between the prefrontal cortex and amygdala, contributing to affective dysregulation and impaired social cognition (Tomoda et al., 2024; Leisman et al., 2025; Nelson et al., 2025a). The cumulative outcome of ELS is a sustained reduction in stress-buffering capacity, predisposing individuals to major depressive disorder, generalized anxiety disorder, and PTSD (Fantasia et al., 2025; Wu et al., 2025), and in genetically susceptible individuals, it may lower the threshold for psychosis and bipolar disorder(Aas et al., 2016; Radua et al., 2018; Woolway et al., 2022). Thus, stress exposure during sensitive socio-emotional periods exemplifies how environmental signals modulate the plasticity boundaries defined by genetic programs.

Prenatal infection and immune activation: inflammatory remodeling of developmental timing

Another major environmental perturbation arises from maternal infection and immune activation (MIA), especially during mid-gestation. These exposures disrupt neurogenesis, neuronal migration, and microglial-mediated synaptic sculpting(Yockey et al., 2020; Vasistha and Sawa, 2025). Viral (influenza, CMV, Zika) and bacterial infections induce cytokine surges (IL-6, IL-17, TNF-α) that alter fetal immune profiles, impairing cortical lamination and subcortical connectivity(Otero et al., 2025; Suleri et al., 2025). The consequences extend beyond transient inflammation: they permanently shift developmental timing by altering the closure and reopening of molecular boundaries regulating neuronal proliferation and differentiation (Kostović et al., 2021; ten Donkelaar et al., 2023). MIA is robustly associated with autism spectrum disorder (ASD) and schizophrenia, disorders that differ in age of onset but share early circuit abnormalities (Estes and McAllister, 2016; Szabó et al., 2025). Schizophrenia, while manifesting in adolescence, may originate from prenatal immune disruptions that bias neuronal migration or synaptic pruning (Reisinger and Hannan, 2025). This illustrates how transient perturbations during early gestational windows can seed vulnerabilities for later psychiatric phenotypes—a process sometimes termed "developmental mis-timing."

Sensory deprivation: experience-dependent collapse of plasticity boundaries

Sensory deprivation represents a distinct category of environmental influence, operating during the highly time-locked sensory critical periods of infancy. Deprivation of visual input—such as untreated congenital cataract during the first 6 months—irreversibly disrupts ocular dominance columns and binocular vision(Mitchell and Maurer, 2022; Röder and Kekunnaya, 2022; Czarnek-Chudzik et al., 2024). Similarly, lack of auditory input during the sensitive window for phoneme discrimination (birth–3 years) impairs speech perception and language fluency (Ji et al., 2023; Foo et al., 2024). These experiences are exemplary of boundary-dependent plasticity, where experience-dependent remodeling is only possible within a narrow temporal window. Once this window closes, structural stabilization renders further compensation ineffective(Napoli et al., 2020; Prosper et al., 2025). As a result, early deprivation can propagate deficits from sensory to communicative and cognitive domains, contributing to disorders such as language delay, developmental coordination disorder (DCD), and in severe multisensory deprivation, ASD-like features (Mueller and Tronick, 2020; Wallace et al., 2020; Shen et al., 2025).

Environmental toxins: broad-spectrum perturbation of neural maturation

Environmental toxins, including heavy metals (lead, mercury) and air pollutants, act across multiple stages of development by interfering with neuronal differentiation, synaptogenesis, and myelination (Błażewicz and Grabrucker, 2022; Dierichs et al., 2025; Merced-Nieves et al., 2025). Lead exposure in early life impairs dopaminergic signaling and synaptic pruning, disproportionately affecting attention, impulse control, and learning capacity (Chandra et al., 2025; İçen, 2025). These effects predominantly occur during the first and second waves of sensitivity, producing ADHD and learning disabilities (Nikanfar et al., 2025). Chronic exposure, however, may induce oxidative stress and inflammatory cascades that later contribute to neurodegenerative disorders, including Parkinson's and Alzheimer's disease(Ramírez-Mendoza et al., 2024; Jones et al., 2025). Thus, toxins

 doi:10.20944/preprints202510.1749.v1

provide a molecular continuum linking early developmental vulnerabilities with late-life degenerative trajectories (Cory-Slechta et al., 2023; Calderón-Garcidueñas et al., 2024; Gong and Zaninotto, 2025).

Social and cognitive deprivation: experience scarcity during complex functional maturation

Social and cognitive deprivation, as observed in institutional rearing or extreme neglect, alters cortical and subcortical development, particularly during the second wave of critical periods (Mackes et al., 2020; Lyons-Ruth, 2025; Yang et al., 2025). The absence of enriched linguistic and interactive environments reduces cortical thickness and connectivity, especially in the prefrontal cortex and language-related regions (Joffe and Robertson, 2025). These disruptions compromise higher-order processes—language acquisition, social bonding, and executive control—contributing to reactive attachment disorder, language delay, and intellectual disability (Harden and Zeanah, 2025). Longitudinal studies further suggest that such deprivation perpetuates social and cognitive disadvantages, increasing vulnerability to mood and anxiety disorders in adulthood (Tomeny et al., 2023; Klass et al., 2024).

Integrative perspective

Across these examples, environmental and experiential inputs act within genetically established developmental boundaries, reshaping trajectories through distinct molecular, structural, and functional mechanisms. The specificity of outcomes—whether structural (as in malnutrition or infection), emotional (as in stress), or sensory-cognitive (as in deprivation)—reflects the alignment between environmental timing and active developmental processes. These boundaries not only define vulnerability windows but also determine the long-term persistence of experience-induced changes. When environmental modulation coincides with open developmental boundaries, neural systems can adapt; when perturbations occur at their edges or beyond closure, they instead leave enduring scars in neural architecture, establishing latent risk for psychiatric, neurodevelopmental, or neurodegenerative disease.

CREs as molecular translators linking development and disease

During brain development, environmental conditions and early-life experiences interact with genetic programs not by directly altering gene sequences, but by engaging CREs—the molecular interfaces where external cues are translated into transcriptional responses (Nord and West, 2020; Mitschka and Mayr, 2022; Song and Ovcharenko, 2025). CREs—including enhancers, promoters, insulators, and silencers—constitute a hierarchical regulatory architecture that determines when, where, and to what extent genes respond to developmental and experiential inputs. In this framework, CREs function as molecular translators, bridging environmental signals with the transcriptional and epigenetic landscapes that shape neural trajectory and disease vulnerability.

CRE types and their developmental functions

Each CRE class operates as a distinct regulatory node linking experience to gene activity.

Enhancers integrate sensory, metabolic, and hormonal signals to modulate gene transcription in an activity-dependent manner (Andersson and Sandelin, 2020; Preissl et al., 2023). In developing sensory cortices, enhancer accessibility is dynamically tuned by neuronal firing and calcium influx, enabling environmental input to reinforce specific circuit configurations(Griffith et al., 2024).

Promoters act as developmental checkpoints, responding to intrinsic timing cues such as transcription factor cascades and metabolic state, thereby ensuring sequential gene activation during neuronal differentiation (Pahl et al., 2021; Li et al., 2025).

Insulators define regulatory boundaries, ensuring that enhancer-promoter communication remains circuit-specific and preventing cross-activation between unrelated gene networks (Gaszner and Felsenfeld, 2006; Tang et al., 2015; Chen et al., 2023).

Silencers operate as developmental brakes, suppressing genes that should remain inactive in a given cell type or stage (Li et al., 2025). Their timely repression of inappropriate pathways safeguards cellular identity and prevents ectopic signaling.

 doi:10.20944/preprints202510.1749.v1

Collectively, these CREs establish a layered regulatory landscape, within which environmental signals can modify, but not overwrite, genetically preconfigured programs—thus defining the "permissive boundaries" of developmental plasticity.

Environmental modulation of CRE accessibility during sensitive periods

During sensitive and critical periods, environmental and experiential inputs can alter CRE accessibility, reconfiguring chromatin topology and leaving long-term molecular imprints. These changes are often stable across the lifespan, thereby converting transient experiences into enduring regulatory memory (Roberts et al., 2024).

In prenatal environments, maternal immune activation increases enhancer accessibility at cytokine-responsive loci within microglia and radial glia (Han et al., 2021; Hayes et al., 2022), reprogramming immune–synaptic crosstalk in cortical development. Similarly, nutritional deprivation—particularly folate or iron deficiency—reduces promoter activation of neurogenesis-related genes (SHH, FGF8), delaying neuronal differentiation and myelination (Wang et al., 2022; Liu et al., 2025a). Prenatal hypoxia modifies enhancer–promoter looping at mitochondrial and oxidative phosphorylation genes (ND1, COX6B2), compromising energy metabolism in developing neurons (Chevalier, 2020; Kremsky et al., 2023).

In early postnatal experiences, maternal separation and chronic stress induce glucocorticoid receptor–binding silencers near FKBP5 and CRHR1 in the hippocampus and amygdala (Bolton et al., 2020; Plank et al., 2021), creating persistent epigenetic desensitization of stress-regulatory circuits. Conversely, enriched environments and sensory stimulation reopen activity-dependent enhancers at BDNF and ARC, reinforcing synaptic plasticity in visual and auditory cortices (Reh et al., 2020; Eckert et al., 2021; Carter et al., 2025). These findings underscore that experience acts through CRE remodeling, determining whether developmental plasticity results in adaptive tuning or maladaptive vulnerability.

CRE dysregulation as a shared mechanism across brain disorders

Distinct patterns of CRE dysregulation correspond to specific classes of brain disorders, reflecting how different regulatory layers—enhancers, promoters, insulators, and silencers—fail to maintain proper boundaries of gene control.

Autism spectrum disorder (ASD): enhancer dysregulation of synaptic genes

Multiple studies have identified enhancer malfunction in cortical progenitors and excitatory neurons of ASD models (Cotney et al., 2015). CHD8 and SHANK3 enhancers show aberrant histone acetylation (H3K27ac) and altered 3D chromatin looping, leading to dysregulated synaptic gene expression (Gompers et al., 2017; Fazel Darbandi et al., 2024). This enhancer overactivity disrupts the timing of excitatory–inhibitory balance formation, producing core social and communication deficits characteristic of ASD.

Major depressive disorder (MDD): promoter dysfunction in stress-responsive networks

In MDD, environmental stress interacts with genetic predisposition to alter promoter accessibility in limbic circuits. Promoters of FKBP5, NR3C1, and BDNF exhibit hypermethylation or histone deacetylation in hippocampal and prefrontal neurons(Zhang et al., 2024). These changes blunt transcriptional responsiveness to glucocorticoids, impair synaptic resilience, and perpetuate maladaptive stress signaling (Peña, 2025). The promoter thus acts as the locus where chronic stress "reprograms" transcriptional sensitivity, converting transient adversity into enduring affective vulnerability.

Alzheimer's disease (AD): loss of insulation and ectopic enhancer–promoter interactions

In AD, chromatin insulation is weakened in microglia and cortical neurons, leading to enhancer spillover and hyperactivation of inflammatory and immune genes (Nott et al., 2019; Sudwarts and Thinakaran, 2023; Winfree et al., 2023). Disrupted topologically associating domains (TADs) around TREM2 and APOE permit enhancers that normally regulate neuronal genes to aberrantly activate immune loci, contributing to chronic neuroinflammation (Balusu et al., 2023). Such insulation loss effectively "breaks" regulatory boundaries, allowing pathological cross-talk between metabolic and inflammatory programs.

 doi:10.20944/preprints202510.1749.v1

Developmental timing and the persistence of CRE reprogramming

A central insight from recent epigenomic studies is that the timing of CRE remodeling determines its permanence and pathological consequence (Nott and Holtman, 2023). During early sensitive periods, chromatin is highly accessible, and external cues can establish new enhancer-promoter configurations that persist through mitotic inheritance. Once developmental boundaries close, similar stimuli evoke transient responses without lasting genomic memory. This temporal asymmetry explains why prenatal or early postnatal exposures—such as infection, malnutrition, or stress—produce life-long vulnerability, whereas equivalent adult exposures often do not (Ribic, 2020; Reisinger and Hannan, 2025).

Moreover, cell-type–specific CRE maps reveal that different brain regions exhibit distinct "regulatory openness" profiles, aligning with regional selectivity of disease. For instance, stress-responsive enhancers are concentrated in limbic neurons, while metabolic and inflammatory enhancers are enriched in microglia of the temporal cortex (Preissl et al., 2023; Mannens et al., 2024). This organization creates an intrinsic gradient of susceptibility across the brain, modulated by both genetic predisposition and experiential context.

In each case, the pathology arises not from isolated mutations or transient environmental insults, but from the failure to preserve the hierarchical order of regulation that normally constrains neural plasticity. CREs, by integrating external signals into this regulatory hierarchy, serve as both recorders of developmental history and architects of disease susceptibility. Understanding their temporal dynamics and network connectivity may thus redefine how we conceptualize and eventually target brain disorders—shifting from a focus on altered gene expression to a broader view of regulatory logic and boundary integrity that governs brain health across the lifespan.

The Regulatory Logic of Brain Disorders

Hierarchical regulation of vulnerability

Brain disorders emerge from multilevel interactions that integrate genetic architecture, environmental input, and regulatory organization(Nord and West, 2020; Mitschka and Mayr, 2022; Song and Ovcharenko, 2025). These layers form a hierarchical regulatory system rather than a linear cascade: genes define potential boundaries of regulation, environments shape their dynamic states, and network activity stabilizes or disrupts communication between regulatory modules.

At the genetic layer, risk variants often localize to noncoding domains that influence the structure and connectivity of CREs, determining which genes are permissive to modulation(Dong et al., 2022b; Zhu et al., 2024). At the environmental layer, stress, infection, or metabolic imbalance modify CRE accessibility through signaling pathways such as glucocorticoid, cytokine, and neurotrophin cascades(Bolton et al., 2020; Boyce et al., 2020; Han et al., 2021; Hayes et al., 2022), thereby tuning transcriptional responsiveness. Finally, at the network layer, neuronal and glial communication constrains how these molecular perturbations propagate across circuits(Preissl et al., 2023; Mannens et al., 2024; Carter et al., 2025), creating emergent system-level behaviors.

Disease specificity thus depends not solely on the presence of mutations or exposures, but on the topology of imbalance across layers—whether the disruption originates in genetic scaffolds, regulatory states, or network communication(Gandal et al., 2018; Virolainen et al., 2022). ASD, for instance, reflects enhancer network overactivation within cortical progenitors(Cotney et al., 2015; Dong et al., 2022a), while MDD arises from promoter desensitization in stress circuits(Zhang et al., 2024), and AD from insulation loss in chromatin–network coupling(Nott et al., 2019; Winfree et al., 2023). These examples illustrate that distinct diseases correspond to distinct patterns of regulatory topological collapse(Balusu et al., 2023; Sudwarts and Thinakaran, 2023).

Encoding experience into biology

Environmental experiences, both adverse and enriching, are not transient events in brain development—they are biologically encoded through CRE-mediated transcriptional and epigenetic remodeling(Dsilva and Galande, 2024; Roberts et al., 2024). External inputs act through canonical signaling pathways (e.g., CREB, glucocorticoid receptor, MAPK, and NF-κB), which converge on

 doi:10.20944/preprints202510.1749.v1

chromatin to modify the accessibility and histone status of specific regulatory loci(Khan et al., 2025). Once engaged, these changes can transform short-lived experiences into persistent regulatory memories, stored in the epigenome and reflected in stable changes in gene expression and circuit dynamics(Peña, 2025).

For example, early social deprivation during infancy reduces prefrontal enhancer accessibility at BDNF and NR3C1, leading to long-term suppression of stress-adaptive transcriptional programs(Tomoda et al., 2024; Leisman et al., 2025) and heightened emotional reactivity in adulthood. Conversely, positive social enrichment reopens these CREs, enhancing neuronal plasticity and resilience(Eckert et al., 2021; Carter et al., 2025). This bidirectionality illustrates that regulatory plasticity functions as a biological memory system, encoding both risk and protection.

We propose the concept of biological encoding: experience → regulatory memory → behavioral phenotype. This principle reframes how experience sculpts vulnerability—not by directly altering neuronal structure, but by reconfiguring the rules that govern gene expression. The persistence of such regulatory memory explains why early environmental perturbations have life-long behavioral and emotional consequences, even after the original stimuli have ceased.

Plasticity and reversibility of regulatory states

Despite their stability, regulatory states encoded in CREs remain partially plastic, particularly in circuits that retain chromatin flexibility into adolescence and adulthood(Mannens et al., 2024). This plasticity offers a theoretical basis for therapeutic intervention. The reversibility of disease-associated regulatory programs depends on two key properties: chromatin accessibility and CRE responsiveness to new signaling contexts(Hwang et al., 2025). When these properties remain intact, pharmacological or behavioral inputs can reprogram transcriptional networks toward health.

Epigenetic drugs targeting histone deacetylases or methyltransferases can reactivate silent promoters and enhancers, restoring expression of plasticity genes such as BDNF and ARC(Autry and Monteggia, 2012). Likewise, behavioral interventions—including sensory retraining, enriched environments, and cognitive therapy—can induce CRE reactivation via neuronal activity–dependent signaling. These combined approaches represent a programmable therapeutic logic, wherein interventions are designed not to replace genes or block pathways, but to rewrite the regulatory instructions governing them.

Such strategies suggest that even complex psychiatric and neurodegenerative disorders may be amenable to re-regulation rather than irreversible degeneration(Kampmann, 2024). By targeting the intermediate layer of control—the chromatin-level logic that links genes, environment, and experience—future therapies could move from symptom suppression toward true restoration of regulatory homeostasis.

In summary, brain disorders can be understood as diseases of disrupted regulation: genes provide the architecture, experience encodes lasting molecular memory, and the balance between flexibility and constraint determines both vulnerability and recovery. The emerging challenge is to map this multilayered logic—to identify where, when, and how the brain's regulatory boundaries can be safely reprogrammed.

Mechanistic and Theoretical Implications of the Regulatory Logic Model

From gene-centric to regulation-centric pathology

Traditional models of brain disorders emphasized gene-centric pathology, seeking causal variants or differentially expressed genes (DEGs) responsible for disease risk(Gandal et al., 2018; Virolainen et al., 2022). However, growing evidence demonstrates that genetic changes alone cannot explain disease onset or specificity. What defines pathology is not which genes are altered, but how their regulatory networks are rewritten (Nord and West, 2020; Song and Ovcharenko, 2025).

In this regulation-centric framework, CREs—enhancers, promoters, insulators, and silencers—serve as the organizing logic that determines a gene's responsiveness to internal and external cues. CREs provide the "regulatory grammar" by which identical genes can exhibit divergent behaviors across developmental stages, cell types, or environmental contexts. A mutation in a CRE, or an

 doi:10.20944/preprints202510.1749.v1

environmentally induced change in its accessibility, may thus redirect the gene's transcriptional trajectory without altering its sequence.

Disease vulnerability reflects contextual misregulation: a gene may remain structurally intact but becomes inappropriately activated, silenced, or disconnected from its normal regulatory neighborhood. Individual differences in CRE topology, developmental timing, and environmental exposure create distinct trajectories even among individuals sharing similar genetic variants(Bolton et al., 2020; Boyce et al., 2020; Hayes et al., 2022). This perspective reframes brain disorders as disruptions of regulatory architecture rather than static gene lesions.

The same gene produces disease-specific outcomes through distinct regulatory topologies

A striking implication of the regulatory logic model is that the same gene can produce opposite phenotypic effects across disorders, depending on its regulatory topology. Genes such as BDNF, IL6, and NRXN1 exemplify this principle.

BDNF, which supports neuronal survival and synaptic plasticity, operates under multiple enhancer networks that respond to both activity-dependent and stress-related cues. In ASD, hyperactive enhancer loops amplify BDNF transcription, driving excessive synaptic connectivity and hyperplastic circuits(Gompers et al., 2017). Conversely, in MDD, promoter silencing through DNA methylation and histone deacetylation reduces BDNF expression in prefrontal and hippocampal neurons, leading to emotional dysregulation and cognitive rigidity.

IL6, a pleiotropic cytokine, exhibits region-specific regulatory rewiring across neuroinflammatory disorders. In Alzheimer's disease (AD), loss of insulator integrity in temporal cortex microglia allows ectopic enhancer activation, sustaining chronic inflammation (Nott et al., 2019). In MDD, promoter demethylation and NF-κB signaling in prefrontal neurons enhance IL6 transcription transiently, linking peripheral inflammation to mood regulation (Miller and Raison, 2016; İş et al., 2025).

NRXN1, a synaptic adhesion molecule, displays developmental topology shifts that determine disease outcome. In schizophrenia, prefrontal cortical enhancers are selectively silenced, weakening inhibitory circuitry and executive function (Fromer et al., 2014; Sekar et al., 2016). In ASD, alternative enhancer networks in auditory cortex increase excitatory–inhibitory imbalance and sensory hyperreactivity(Südhof, 2008; Werling et al., 2018).

These examples highlight that disease specificity arises from distinct CRE network configurations, not from the gene identity itself. Each disorder represents a unique topological failure in regulatory communication—whether through enhancer overactivation, promoter desensitization, or insulation collapse. Understanding this topology-dependent logic enables a shift from cataloging DEGs to reconstructing regulatory network states that govern transcriptional behavior.

Predicting the full regulatory logic through single-cell multi-omics and computational modeling

To translate the regulatory logic model into predictive frameworks, advances in single-cell multi-omics now enable direct observation of the molecular hierarchy linking genes, CREs, and cell identity. Integration of scRNA-seq, scATAC-seq, and single-cell methylome data reveals how chromatin accessibility, transcription, and epigenetic memory interact at the cell-type level (Zhu et al., 2024; Chawla et al., 2025; Hwang et al., 2025).

By mapping these features across development and disease, researchers can construct regulatory state maps that capture how environmental inputs reshape network topology over time. These maps can then feed into computational regulatory network models, which infer causal relationships among transcription factors, CRE clusters, and downstream pathways (Gao et al., 2025b). Such models integrate temporal and spatial information to predict which regulatory boundaries are most susceptible to disruption and which can be therapeutically reprogrammed.

Ultimately, this approach aims to reconstruct the complete regulatory hierarchy—from genetic architecture through chromatin topology to network behavior—thereby linking molecular states to clinical phenotypes. By uniting biological data and computational inference, it becomes possible to

 doi:10.20944/preprints202510.1749.v1

forecast individual vulnerability, identify early molecular inflection points, and design targeted interventions that restore regulatory equilibrium (Kampmann, 2024; West, 2025).

In this vision, brain disorders are no longer defined by static gene lists but by dynamic regulatory topologies—a shift that aligns molecular neuroscience with systems-level logic and opens the door to truly mechanistic predictions of disease and recovery.

Outlook and Conclusion: Toward Predictive and Interventional Regulatory Logic

Reframing disease as regulatory misalignment

Across the evidence presented, brain disorders emerge not from isolated molecular lesions but from hierarchical misalignments in regulatory systems that coordinate genes, chromatin states, and neural networks. Genetic predispositions provide the architectural scaffold, but environmental inputs—ranging from prenatal stress and infection to sensory deprivation—reshape the regulatory landscape through CRE-mediated mechanisms. This remodeling redefines gene expression potential and determines network resilience or fragility.

Rather than viewing pathology as the failure of a single pathway, this framework conceptualizes disease as a disturbance in regulatory equilibrium, where feedback loops between molecular and circuit levels lose synchronization. The same molecular components may support adaptation in one developmental window but trigger dysfunction when regulation collapses.

Restoring regulation rather than repairing genes

Translational neuroscience is now shifting from targeting individual molecules to reconstructing regulatory logic. Epigenetic and activity-dependent therapies exemplify this transition. Pharmacological agents—such as HDAC inhibitors, DNMT modulators, and BET bromodomain blockers—can reopen silent CREs or restore chromatin flexibility. When paired with behavioral or sensory interventions that re-engage plastic circuits, these compounds act synergistically to re-establish appropriate gene–environment coupling.

This dual strategy—epigenetic modulation plus experience induction—represents a form of "biological reprogramming." Rather than suppressing symptoms, it aims to reinstate the original developmental regulatory logic that underpins circuit balance and emotional stability. As regulatory plasticity extends into adolescence and adulthood, these approaches open the door to interventions that are restorative rather than compensatory, repositioning therapeutic neuroscience around the reconfiguration of chromatin–network interactions.

Building predictive frameworks for early vulnerability

A major next step is to move from retrospective understanding to predictive prevention. The combination of single-cell multi-omics, clinical data and AI-driven modeling enables reconstruction of full regulatory hierarchies across development and disease.

By integrating chromatin accessibility, transcriptional output, and epigenetic marks with longitudinal environmental data, clinical reports, computational systems can generate regulatory vulnerability atlases—maps that identify which cell types, CREs, and signaling pathways are most susceptible to disruption at specific developmental windows.

Ultimately, computational biology may reconstruct the entire causal chain from environment → regulation → network → behavior, allowing early interventions that preempt maladaptive developmental trajectories rather than treating established disorders.

This predictive turn represents a paradigm shift: understanding vulnerability becomes the cornerstone of therapy, and prevention—grounded in regulatory insight—supersedes reactionary treatment.

Early regulation as both risk and opportunity

The dynamic plasticity of early regulatory systems is a double-edged sword: it confers extraordinary capacity for adaptation but also heightened vulnerability to adverse input. Yet this same flexibility offers the most powerful leverage point for prevention. By identifying early regulatory inflection points—periods when environmental experience can durably reconfigure CRE

 doi:10.20944/preprints202510.1749.v1

accessibility and circuit tuning—researchers can design targeted strategies that stabilize trajectories before pathology emerges.

Future work must therefore integrate longitudinal developmental studies, in vivo chromatin imaging, and AI-guided causal modeling to define how early experiences encode regulatory memory. Through such efforts, the field can move toward a comprehensive model where environment and genome interact dynamically to shape the regulatory logic of the brain—a framework that unites mechanism, prediction, and intervention into a single continuum.

Acknowledgement: This work is supported by the Shenzhen Medical Research Fund B2402005; National Key R&D Program of China 2022YFA1105503; National Natural Science Foundation of China (NSFC) 32371019; Shenzhen Science and Technology Program (Grant No. SYSPG20241211173950073); Guangdong Provincial Key Laboratory of Brain Connectome and Behavior 2023B1212060055.

Reference

Aas M, Henry C, Andreassen OA, Bellivier F, Melle I, Etain B (2016) The role of childhood trauma in bipolar disorders. International journal of bipolar disorders 4:2.

Álvarez-Mejía D, Rodas JA, Leon-Rojas JE (2025) From Womb to Mind: Prenatal Epigenetic Influences on Mental Health Disorders. International Journal of Molecular Sciences 26:6096.

Andersson R, Sandelin A (2020) Determinants of enhancer and promoter activities of regulatory elements. Nature Reviews Genetics 21:71–87.

Autry AE, Monteggia LM (2012) Brain-derived neurotrophic factor and neuropsychiatric disorders. Pharmacol Rev 64:238–258.

Baker AE, Galván A, Fuligni AJ (2025) The connecting brain in context: How adolescent plasticity supports learning and development. Developmental Cognitive Neuroscience 71:101486.

Balusu S, Praschberger R, Lauwers E, De Strooper B, Verstreken P (2023) Neurodegeneration cell per cell. Neuron 111:767–786.

Barnes AP, Polleux F (2009) Establishment of Axon-Dendrite Polarity in Developing Neurons. Annual Review of Neuroscience 32:347–381.

Bartha-Doering L, Schwartz E, Kollndorfer K, Fischmeister FPS, Novak A, Langs G, Werneck H, Prayer D, Seidl R, Kasprian G (2021) Effect of corpus callosum agenesis on the language network in children and adolescents. Brain Structure and Function 226:701–713.

Bastian TW, Rao R, Tran PV, Georgieff MK (2020) The Effects of Early-Life Iron Deficiency on Brain Energy Metabolism. Neuroscience Insights 15:2633105520935104.

Beke A, Bartek V, Simonyi A (2022) Fetal Craniospinal Malformations: Aetiology and Diagnosis. In: Ectopic Pregnancy and Prenatal Diagnosis: IntechOpen.

Bennett RG, Tibaudo ME, Mazel EC, Y. N (2025) Implications of cerebral/cortical visual impairment on life and learning: insights and strategies from lived experiences. Frontiers in Human Neuroscience 18.

Birnie MT, Baram TZ (2025) The evolving neurobiology of early-life stress. Neuron 113:1474–1490.

Błażewicz A, Grabrucker AM (2022) Metal Profiles in Autism Spectrum Disorders: A Crosstalk between Toxic and Essential Metals. Int J Mol Sci 24.

Bolton JL, Schulmann A, Garcia-Curran MM, Regev L, Chen Y, Kamei N, Shao M, Singh-Taylor A, Jiang S, Noam Y, Molet J, Mortazavi A, Baram TZ (2020) Unexpected Transcriptional Programs Contribute to Hippocampal Memory Deficits and Neuronal Stunting after Early-Life Adversity. Cell Rep 33:108511.

Boyce WT, Sokolowski MB, Robinson GE (2020) Genes and environments, development and time. Proceedings of the National Academy of Sciences 117:23235–23241.

Calderón-Garcidueñas L, Ayala A, Mukherjee PS (2024) 2024 United States Elections: Air Pollution, Neurodegeneration, Neuropsychiatric, and Neurodevelopmental Disorders. Who Cares? J Alzheimers Dis 98:1277–1282.

Carter AC, Koreman GT, Petrocelli JE, Robb JE, Bushinsky EM, Trowbridge SK, Kingsley DM, Walsh CA, Song JHT, Greenberg ME (2025) FOS binding sites are a hub for the evolution of activity-dependent gene regulatory programs in human neurons. bioRxiv.

 doi:10.20944/preprints202510.1749.v1

Chandra N, Karimi B, Bhobe A, Pagadala S, Pandey S, Sanchez SS, Yeung-Luk B, Rivera E, Kohr MJ, Riess B, Nachman KE, Biswal S, Sillé FCM, Graves AR (2025) Perinatal Exposure to Metal Mixtures Disrupts Neuronal Function and Behavior. bioRxiv.

Chawla A et al. (2025) Single-nucleus chromatin accessibility profiling identifies cell types and functional variants contributing to major depression. Nature Genetics 57:1890–1904.

Chen Y, Dai J, Tang L, Mikhailova T, Liang Q, Li M, Zhou J, Kopp RF, Weickert C, Chen C, Liu C (2023) Neuroimmune transcriptome changes in patient brains of psychiatric and neurological disorders. Molecular Psychiatry 28:710–721.

Chevalier RL (2020) Bioenergetic Evolution Explains Prevalence of Low Nephron Number at Birth: Risk Factor for CKD. Kidney360 1:863–879.

Cory-Slechta DA, Merrill A, Sobolewski M (2023) Air Pollution-Related Neurotoxicity Across the Life Span. Annu Rev Pharmacol Toxicol 63:143–163.

Cotney J, Muhle RA, Sanders SJ, Liu L, Willsey AJ, Niu W, Liu W, Klei L, Lei J, Yin J, Reilly SK, Tebbenkamp AT, Bichsel C, Pletikos M, Sestan N, Roeder K, State MW, Devlin B, Noonan JP (2015) The autism-associated chromatin modifier CHD8 regulates other autism risk genes during human neurodevelopment. Nat Commun 6:6404.

Crouse JJ (2025) Embracing complexity in the science of mental disorders. Nature Reviews Psychology 4:247–247.

Czarnek-Chudzik A, Toro MD, Rejdak R, Nowomiejska K (2024) Anatomical and Functional Impacts of Congenital Bilateral Visual Deprivation on the Visual Pathway—A Comprehensive Review. Journal of Clinical Medicine 13:1775.

Demirtaş MS (2020) The Pathogenesis of Congenital Anomalies: Roles of Teratogens and Infections. In: Congenital Anomalies in Newborn Infants - Clinical and Etiopathological Perspectives (Verma RP, ed). London: IntechOpen.

Dierichs N, Piersma AH, Peeters RP, Visser WE, Meima ME, Hessel EVS (2025) Mechanisms of developmental neurotoxicity mediated by perturbed thyroid hormone homeostasis in the brain: an adverse outcome pathway network. Crit Rev Toxicol 55:304–320.

Dong C, Zhao C, Chen X, Berry K, Wang J, Zhang F, Liao Y, Han R, Ogurek S, Xu L, Zhang L, Lin Y, Zhou W, Xin M, Lim DA, Campbell K, Nakafuku M, Waclaw RR, Lu QR (2022a) Conserved and Distinct Functions of the Autism-Related Chromatin Remodeler CHD8 in Embryonic and Adult Forebrain Neurogenesis. J Neurosci 42:8373–8392.

Dong P et al. (2022b) Population-level variation in enhancer expression identifies disease mechanisms in the human brain. Nature Genetics 54:1493–1503.

Dsilva GJ, Galande S (2024) From sequence to consequence: Deciphering the complex cis-regulatory landscape. Journal of Biosciences 49.

Eckert P, Marchetta P, Manthey MK, Walter MH, Jovanovic S, Savitska D, Singer W, Jacob MH, Rüttiger L, Schimmang T, Milenkovic I, Pilz PKD, Knipper M (2021) Deletion of BDNF in Pax2 Lineage-Derived Interneuron Precursors in the Hindbrain Hampers the Proportion of Excitation/Inhibition, Learning, and Behavior. Front Mol Neurosci 14:642679.

Engle EC (2010) Human Genetic Disorders of Axon Guidance. Cold Spring Harbor Perspectives in Biology 2:a001784–a001784.

Estes ML, McAllister AK (2016) Maternal immune activation: Implications for neuropsychiatric disorders. Science 353:772–777.

Fantasia S, Conti L, Andreoli D, Bordacchini A, Rimoldi B, Dell'Oste V, Pedrinelli V, Carmassi C (2025) Early or recent trauma in treatment-resistant depression: A systematic review. CNS spectrums:1–24.

Fazel Darbandi S, An JY, Lim K, Page NF, Liang L, Young DM, Ypsilanti AR, State MW, Nord AS, Sanders SJ, Rubenstein JLR (2024) Five autism-associated transcriptional regulators target shared loci proximal to brain-expressed genes. Cell Rep 43:114329.

Foo HC, Tang C, Kao Y, Wu H, Chang C, Wu M, Lo Y, Weng S (2024) The Latency of Auditory Event-Related Potential P300 Prolonged in School-Age Students with Unilateral Hearing Loss in a Mandarin Learning Environment. Am Ann Deaf 168:241–257.

 doi:10.20944/preprints202510.1749.v1

Friedman NP, Robbins TW (2022) The role of prefrontal cortex in cognitive control and executive function. Neuropsychopharmacology 47:72–89.

Fromer M et al. (2014) De novo mutations in schizophrenia implicate synaptic networks. Nature 506:179–184.

Gabard-Durnam L, McLaughlin KA (2020) Sensitive periods in human development: charting a course for the future. Current Opinion in Behavioral Sciences 36:120–128.

Gandal MJ et al. (2018) Shared molecular neuropathology across major psychiatric disorders parallels polygenic overlap. Science 359:693–697.

Gao Q, Zhou Y, Chen Y, Hu W, Jin W, Zhou C, Yuan H, Li J, Lin Z, Lin W (2025a) Role of iron in brain development, aging, and neurodegenerative diseases. Annals of Medicine 57:2472871.

Gao W, Jing S, He C, Saberi H, Sharma HS, Han F, Chen L (2025b) Advancements in neurodegenerative diseases: Pathogenesis and novel neurorestorative interventions. Journal of Neurorestoratology 13:100176.

Gaszner M, Felsenfeld G (2006) Insulators: exploiting transcriptional and epigenetic mechanisms. Nat Rev Genet 7:703–713.

Gee DG, Cohodes EM (2021) Influences of Caregiving on Development: A Sensitive Period for Biological Embedding of Predictability and Safety Cues. Current Directions in Psychological Science 30:376–383.

Gompers AL et al. (2017) Germline Chd8 haploinsufficiency alters brain development in mouse. Nat Neurosci 20:1062–1073.

Gong J, Zaninotto P (2025) Integrating Exposome into Lifecourse Understanding of Cognitive Ageing and Dementia: Current Evidence, Methodological Challenges, and Future Directions. Int J Environ Res Public Health 22.

Griffith EC, West AE, Greenberg ME (2024) Neuronal enhancers fine-tune adaptive circuit plasticity. Neuron 112:3043–3057.

Guo MG et al. (2023) Integrative analyses highlight functional regulatory variants associated with neuropsychiatric diseases. Nature Genetics 55:1876–1891.

Han VX, Patel S, Jones HF, Dale RC (2021) Maternal immune activation and neuroinflammation in human neurodevelopmental disorders. Nat Rev Neurol 17:564–579.

Harden BJ, Zeanah CH (2025) Centering the Young Child: A Developmental Case for Child Welfare Reform. Families in Society 106:292–322.

Hart KH, Hill AJ, Gonzalez JT, de la Hunty A, Gallagher AM, Stanner SA (2025) Diet in Pregnancy: A Review of Current Challenges and Recommendations. A British Nutrition Foundation Briefing Paper. Nutrition Bulletin 50:365–410.

Hayes LN, An K, Carloni E, Li F, Vincent E, Trippaers C, Paranjpe M, Dölen G, Goff LA, Ramos A, Kano SI, Sawa A (2022) Prenatal immune stress blunts microglia reactivity, impairing neurocircuitry. Nature 610:327–334.

Hegde M, Nazzi T, Cabrera L (2024) An auditory perspective on phonological development in infancy. Frontiers in Psychology 14.

Hensch TK (2004) CRITICAL PERIOD REGULATION. Annual Review of Neuroscience 27:549–579.

Huang Z, Jordan JD, Zhang Q (2023) Early life adversity as a risk factor for cognitive impairment and Alzheimer's disease. Translational Neurodegeneration 12.

Hwang A et al. (2025) Single-cell transcriptomic and chromatin dynamics of the human brain in PTSD. Nature 643:744–754.

İçen S (2025) Implications for the Prevention of Poverty-Related Environmental Risks for Childhood ADHD: A Narrative Review. Child Psychiatry Hum Dev.

İş Ö, Min Y, Wang X, Oatman SR, Abraham Daniel A, Ertekin-Taner N (2025) Multi Layered Omics Approaches Reveal Glia Specific Alterations in Alzheimer's Disease: A Systematic Review and Future Prospects. Glia 73:539–573.

Jaffer A (2025) Perinatal Psychological Distress and Child Brain Function and Behaviour Across Early Childhood.

Jarvie EM, Lovegrove JA, Weech M, Freeman DJ, Meyer BJ (2025) Dietary Micronutrient Intake During Pregnancy Is Suboptimal in a Group of Healthy Scottish Women, Irrespective of Maternal Body Mass Index. Nutrients 17:550.

 doi:10.20944/preprints202510.1749.v1

Ji H, Yu X, Xiao Z, Zhu H, Liu P, Lin H, Chen R, Hong Q (2023) Features of Cognitive Ability and Central Auditory Processing of Preschool Children With Minimal and Mild Hearing Loss. Journal of Speech, Language, and Hearing Research 66:1867–1888.

Joffe AR, Robertson CMT (2025) Developmental Care in the Early Years in Pediatric Intensive Care Patients as a Strategy to Mitigate Pediatric Post-Intensive-Care Syndrome: A Narrative Review. J Intensive Care Med:8850666251340646.

Jones A, Ali MU, Mayhew A, Aryal K, Correia RH, Dash D, Manis DR, Rehman A, O'Connell ME, Taler V, Costa AP, Hogan DB, Wolfson C, Raina P, Griffith L (2025) Environmental risk factors for all-cause dementia, Alzheimer's disease dementia, vascular dementia, and mild cognitive impairment: An umbrella review and meta-analysis. Environ Res 270:121007.

Kampmann M (2024) Molecular and cellular mechanisms of selective vulnerability in neurodegenerative diseases. Nature Reviews Neuroscience 25:351–371.

Khan Z, Messiri NE, Iqbal E, Hassan H, Tanweer MS, Sadia SR, Taj M, Zaidi U, Yusuf K, Syed NI (2025) On the role of epigenetic modifications of HPA axis in posttraumatic stress disorder and resilience. Journal of neurophysiology 133:742–759.

Kidd E, Donnelly S, Christiansen MH (2018) Individual Differences in Language Acquisition and Processing. Trends in Cognitive Sciences 22:154–169.

Kim S, Wysocka J (2023) Deciphering the multi-scale, quantitative cis-regulatory code. Molecular Cell 83:373–392.

Kiorpes L (2015) Visual development in primates: Neural mechanisms and critical periods. Developmental Neurobiology 75:1080–1090.

Klass P, Mendelsohn AL, Hutton JS, Dunlap M, Anderson AT, High PC, Navsaria D (2024) Literacy Promotion: An Essential Component of Primary Care Pediatric Practice: Technical Report. Pediatrics 154.

Kolasinski J, Takahashi E, Stevens AA, Benner T, Fischl B, Zöllei L, Grant PE (2013) Radial and tangential neuronal migration pathways in the human fetal brain: Anatomically distinct patterns of diffusion MRI coherence. NeuroImage 79:412–422.

Kostović I, Sedmak G, Judaš M (2019) Neural histology and neurogenesis of the human fetal and infant brain. NeuroImage 188:743–773.

Kostović I, Radoš M, Kostović-Srzentić M, Krsnik Ž (2021) Fundamentals of the Development of Connectivity in the Human Fetal Brain in Late Gestation: From 24 Weeks Gestational Age to Term. Journal of Neuropathology & Experimental Neurology 80:393–414.

Kremsky I, Ma Q, Li B, Dasgupta C, Chen X, Ali S, Angeloni S, Wang C, Zhang L (2023) Fetal hypoxia results in sex- and cell type-specific alterations in neonatal transcription in rat oligodendrocyte precursor cells, microglia, neurons, and oligodendrocytes. Cell Biosci 13:58.

Krontira AC, Cruceanu C, Binder EB (2020) Glucocorticoids as mediators of adverse outcomes of prenatal stress. Trends in neurosciences 43:394–405.

Leibovitz Z, Lerman-Sagie T, Haddad L (2022) Fetal Brain Development: Regulating Processes and Related Malformations. Life 12:809.

Lein ES, Belgard TG, Hawrylycz M, Molnár Z (2017) Transcriptomic perspectives on neocortical structure, development, evolution, and disease. Annual Review of Neuroscience 40:629–652.

Leisman G, Alfasi R, D'Angiulli A (2025) Emotional Brain Development: Neurobiological Indicators from Fetus Through Toddlerhood. Brain Sciences 15:846.

Li M, Francis E, Hinkle SN, Ajjarapu AS, Zhang C (2019) Preconception and Prenatal Nutrition and Neurodevelopmental Disorders: A Systematic Review and Meta-Analysis. Nutrients 11:1628.

Li Y, Chen L, Xue S, Song Z, Liu H, Li H, Shen W, Zhang C, Wu H (2025) Alternative spliceosomal protein Eftud2 mediated Kif3a exon skipping promotes SHH-subgroup medulloblastoma progression. Cell Death Differ.

Li YE et al. (2023) A comparative atlas of single-cell chromatin accessibility in the human brain. Science 382:eadf7044.

Libé-Philippot B, Vanderhaeghen P (2021) Cellular and Molecular Mechanisms Linking Human Cortical Development and Evolution. Annual Review of Genetics 55:555–581.

 doi:10.20944/preprints202510.1749.v1

Lida-Alkisti X, Stefanos D, Mirjana S, Nikos S (2024) Stress, Environment and Early Psychosis. Current Neuropharmacology 22:437–460.

Liu J, Mantantzis K, Kaufmann L, Campos Goenaga Z, Gromova O, Kuroda K, Qi H, Tetruashvili N, Di Renzo GC (2025a) Clinical Benefits and Safety of Multiple Micronutrient Supplementation During Preconception, Pregnancy, and Lactation: A Review. Nutrition Reviews.

Liu Z et al. (2025b) Single-cell multiregion epigenomic rewiring in Alzheimer's disease progression and cognitive resilience. Cell 188:4980–5002.e4929.

Luu P, Tucker DM (2023) Continuity and change in neural plasticity through embryonic morphogenesis, fetal activity-dependent synaptogenesis, and infant memory consolidation. Developmental Psychobiology 65:e22439.

Lyons-Ruth K (2025) Is neglect the first form of threat? Attach Hum Dev 27:511–538.

Mackes NK, Golm D, Sarkar S, Kumsta R, Rutter M, Fairchild G, Mehta MA, Sonuga-Barke EJS (2020) Early childhood deprivation is associated with alterations in adult brain structure despite subsequent environmental enrichment. Proc Natl Acad Sci U S A 117:641–649.

Mannens CCA, Hu L, Lönnerberg P, Schipper M, Reagor CC, Li X, He X, Barker RA, Sundström E, Posthuma D, Linnarsson S (2024) Chromatin accessibility during human first-trimester neurodevelopment. Nature.

Mclaughlin KA, Weissman D, Bitrán D (2019) Childhood Adversity and Neural Development: A Systematic Review. Annual Review of Developmental Psychology 1:277–312.

Merced-Nieves FM, Colicino E, Coull B, Bose S, Redline S, Wright RO, Wright RJ (2025) Prenatal exposure to manganese and objectively measured sleep disturbances in early childhood. Environ Res 279:121707.

Milbocker KA, Smith IF, Klintsova AY (2024) Maintaining a Dynamic Brain: A Review of Empirical Findings Describing the Roles of Exercise, Learning, and Environmental Enrichment in Neuroplasticity from 2017-2023. Brain Plasticity 9:75–95.

Miller AH, Raison CL (2016) The role of inflammation in depression: from evolutionary imperative to modern treatment target. Nat Rev Immunol 16:22–34.

Mitchell BA, Carlson BM, Westerberg JA, Cox MA, Maier A (2023) A role for ocular dominance in binocular integration. Current Biology 33:3884–3895.e3885.

Mitchell DE, Maurer D (2022) Critical Periods in Vision Revisited. Annual Review of Vision Science 8:291–321.

Mitschka S, Mayr C (2022) Context-specific regulation and function of mRNA alternative polyadenylation. Nat Rev Mol Cell Biol 23:779–796.

Molnár Z, Kwan KY (2024) Development and evolution of thalamocortical connectivity. Cold Spring Harbor Perspectives in Biology 16:a041503.

Monk C, Lugo-Candelas C, Trumpff C (2019) Prenatal Developmental Origins of Future Psychopathology: Mechanisms and Pathways. Annual Review of Clinical Psychology 15:317–344.

Mueller I, Tronick E (2020) Chapter 14 - Sensory processing and meaning making in autism spectrum disorder. In: Autism 360° (Das U, Papaneophytou N, El-Kour T, eds), pp 255–267: Academic Press.

Napoli D, Lupori L, Mazziotti R, Sagona G, Bagnoli S, Samad M, Sacramento EK, Kirkpartick J, Putignano E, Chen S, Terzibasi Tozzini E, Tognini P, Baldi P, Kwok JC, Cellerino A, Pizzorusso T (2020) MiR-29 coordinates age-dependent plasticity brakes in the adult visual cortex. EMBO Rep 21:e50431.

Nelson CA, Sullivan EF, Valdes V (2025a) Early adversity alters brain architecture and increases susceptibility to mental health disorders. Nature Reviews Neuroscience 26:642–656.

Nelson CA, Sullivan EF, Valdes V (2025b) Early adversity alters brain architecture and increases susceptibility to mental health disorders. Nature Reviews Neuroscience:1–15.

Nelson CA, III, Gabard-Durnam LJ (2020) Early Adversity and Critical Periods: Neurodevelopmental Consequences of Violating the Expectable Environment. Trends in Neurosciences 43:133–143.

Nikanfar M, Avci CB, Khalilnezhad A, Shahriyari E, Nourazarian A (2025) Brain-Derived Exosomes in Neurodevelopmental and Neuropsychiatric Disorders: Molecular Insights, Therapeutic Potential, and Translational Challenges. Mol Neurobiol.

Nishio M, Liu X, Mackey AP, Arcaro MJ (2025) Myelination across cortical hierarchies and depths in humans and macaques. bioRxiv:2025.2002.2006.636851.

Nord AS, West AE (2020) Neurobiological functions of transcriptional enhancers. Nat Neurosci 23:5–14.

 doi:10.20944/preprints202510.1749.v1

Nott A, Holtman IR (2023) Genetic insights into immune mechanisms of Alzheimer's and Parkinson's disease. Front Immunol 14:1168539.

Nott A et al. (2019) Brain cell type-specific enhancer-promoter interactome maps and disease-risk association. Science 366:1134–1139.

Öngür D, Paulus MP (2025) Embracing complexity in psychiatry-from reductionistic to systems approaches. The Lancet Psychiatry 12:220–227.

Otero AM, Connolly MG, Gonzalez-Ricon RJ, Wang SS, Allen JM, Antonson AM (2025) Influenza A virus during pregnancy disrupts maternal intestinal immunity and fetal cortical development in a dose-and time-dependent manner. Molecular Psychiatry 30:13–28.

Pahl MC et al. (2021) Cis-regulatory architecture of human ESC-derived hypothalamic neuron differentiation aids in variant-to-gene mapping of relevant complex traits. Nat Commun 12:6749.

Paul LK, Brown WS, Adolphs R, Tyszka JM, Richards LJ, Mukherjee P, Sherr EH (2007) Agenesis of the corpus callosum: genetic, developmental and functional aspects of connectivity. Nature Reviews Neuroscience 8:287–299.

Paus T, Keshavan M, Giedd JN (2008) Why do many psychiatric disorders emerge during adolescence? Nature Reviews Neuroscience 9:947–957.

Peña CJ (2025) Epigenetic regulation of brain development, plasticity, and response to early-life stress. Neuropsychopharmacology.

Perumal N, Gernand AD (2025) Nutrition during Pregnancy and Birth Outcomes. Annals of Nutrition and Metabolism 81:19–32.

Pfeifer JH, Allen NB (2021) Puberty Initiates Cascading Relationships Between Neurodevelopmental, Social, and Internalizing Processes Across Adolescence. Biological Psychiatry 89:99–108.

Plank AC, Frey S, Basedow LA, Solati J, Canneva F, von Hörsten S, Kratz O, Moll GH, Golub Y (2021) Prenatally traumatized mice reveal hippocampal methylation and expression changes of the stress-related genes Crhr1 and Fkbp5. Transl Psychiatry 11:183.

Polleux F, Snider W (2010) Initiating and Growing an Axon. Cold Spring Harbor Perspectives in Biology 2:a001925–a001925.

Preissl S, Gaulton KJ, Ren B (2023) Characterizing cis-regulatory elements using single-cell epigenomics. Nature Reviews Genetics 24:21–43.

Prosper A, Blanchard T, Lunghi C (2025) The interplay between Hebbian and homeostatic plasticity in the adult visual cortex. J Physiol 603:1521–1540.

Radua J, Ramella-Cravaro V, Ioannidis JP, Reichenberg A, Phiphopthatsanee N, Amir T, Yenn Thoo H, Oliver D, Davies C, Morgan C (2018) What causes psychosis? An umbrella review of risk and protective factors. World psychiatry 17:49–66.

Ramírez-Mendoza AA, Mendoza-Magaña ML, Ramírez-Herrera MA, Hernández-Nazara ZH, Domínguez-Rosales JA (2024) Nitrooxidative Stress and Neuroinflammation Caused by Air Pollutants Are Associated with the Biological Markers of Neurodegenerative Diseases. Antioxidants (Basel) 13.

Reh RK, Dias BG, Nelson CA, Kaufer D, Werker JF, Kolb B, Levine JD, Hensch TK (2020) Critical period regulation across multiple timescales. Proceedings of the National Academy of Sciences 117:23242–23251.

Reisinger SN, Hannan AJ (2025) Developmental origins of mental health and disorders (DOMHaD): an approach to understanding, preventing and treating psychiatric disorders. Nature Mental Health.

Ribic A (2020) Stability in the Face of Change: Lifelong Experience-Dependent Plasticity in the Sensory Cortex. Frontiers in Cellular Neuroscience 14.

Roberts BS, Anderson AG, Partridge EC, Cooper GM, Myers RM (2024) Probabilistic association of differentially expressed genes with cis-regulatory elements. Genome Research:gr.278598.278123.

Röder B, Kekunnaya R (2021) Visual experience dependent plasticity in humans. Current Opinion in Neurobiology 67:155–162.

Röder B, Kekunnaya R (2022) Effects of Early Visual Deprivation. In: Oxford University Press.

Russ JB, Agarwal S, Venkatesan C, Scelsa B, Vollmer B, Tarui T, Pardo AC, Lemmon ME, Mulkey SB, Hart AR, Nagaraj UD, Kuller JA, Whitehead MT, Cohen JL, Gebb JS, Glenn OA, Norton ME, Gano D (2025) Fetal malformations of cortical development: review and clinical guidance. Brain 148:1888–1903.

 doi:10.20944/preprints202510.1749.v1

Sekar A, Bialas AR, de Rivera H, Davis A, Hammond TR, Kamitaki N, Tooley K, Presumey J, Baum M, Van Doren V, Genovese G, Rose SA, Handsaker RE, Daly MJ, Carroll MC, Stevens B, McCarroll SA (2016) Schizophrenia risk from complex variation of complement component 4. Nature 530:177–183.

Shen J, Wang Y, Liu Y, Lan J, Long S, Li Y, Chen D, Yu P, Zhao J, Wang Y, Wang S, Yang F (2025) Behavioral Abnormalities, Cognitive Impairments, Synaptic Deficits, and Gene Replacement Therapy in a CRISPR Engineered Rat Model of 5p15.2 Deletion Associated With Cri du Chat Syndrome. Adv Sci (Weinh) 12:e2415224.

Shi M, Freitas LGA, Spencer-Smith MM, Kebets V, Anderson V, McIlroy A, Wood AG, Leventer RJ, Van De Ville D, Siffredi V (2021) Intra- and inter-hemispheric structural connectome in agenesis of the corpus callosum. NeuroImage: Clinical 31:102709.

Short AK, Baram TZ (2019) Early-life adversity and neurological disease: age-old questions and novel answers. Nature Reviews Neurology 15:657–669.

Silbereis John C, Pochareddy S, Zhu Y, Li M, Sestan N (2016) The Cellular and Molecular Landscapes of the Developing Human Central Nervous System. Neuron 89:248–268.

Silva CG, Peyre E, Nguyen L (2019) Cell migration promotes dynamic cellular interactions to control cerebral cortex morphogenesis. Nature Reviews Neuroscience 20:318–329.

Singh-Taylor A, Korosi A, Molet J, Gunn BG, Baram TZ (2015) Synaptic rewiring of stress-sensitive neurons by early-life experience: A mechanism for resilience? Neurobiology of Stress 1:109–115.

Smith KE, Pollak SD (2020) Early life stress and development: potential mechanisms for adverse outcomes. Journal of Neurodevelopmental Disorders 12.

Song W, Ovcharenko I (2025) Abundant repressor binding sites in human enhancers are associated with the fine-tuning of gene regulation. iScience 28:111658.

Spear LP (2013) Adolescent neurodevelopment. Journal of adolescent health 52:S7–S13.

Steinmetz JD et al. (2024) Global, regional, and national burden of disorders affecting the nervous system, 1990-2021: a systematic analysis for the Global Burden of Disease Study 2021. The Lancet Neurology 23:344–381.

Stiles J, Jernigan TL (2010) The Basics of Brain Development. Neuropsychology Review 20:327–348.

Südhof TC (2008) Neuroligins and neurexins link synaptic function to cognitive disease. Nature 455:903–911.

Sudwarts A, Thinakaran G (2023) Alzheimer's genes in microglia: a risk worth investigating. Mol Neurodegener 18:90.

Suleri A, Rommel A-S, Dmitrichenko O, Muetzel RL, Cecil CA, de Witte L, Bergink V (2025) The association between maternal immune activation and brain structure and function in human offspring: a systematic review. Molecular Psychiatry 30:722–735.

Sun J, Noss S, Banerjee D, Das M, Girirajan S (2024) Strategies for dissecting the complexity of neurodevelopmental disorders. Trends in Genetics 40:187–202.

Sydnor VJ, Larsen B, Bassett DS, Alexander-Bloch A, Fair DA, Liston C, Mackey AP, Milham MP, Pines A, Roalf DR, Seidlitz J, Xu T, Raznahan A, Satterthwaite TD (2021) Neurodevelopment of the association cortices: Patterns, mechanisms, and implications for psychopathology. Neuron 109:2820–2846.

Szabó D, Otrokocsi L, Sperlágh B (2025) The role of maternal infections in neurodevelopmental psychiatric disorders: focus on the P2X7/NLRP3/IL-1β signalling pathway. Journal of Neuroinflammation 22.

Takesian AE, Hensch TK (2013) Chapter 1 - Balancing Plasticity/Stability Across Brain Development. In: Progress in Brain Research (Merzenich MM, Nahum M, Van Vleet TM, eds), pp 3–34: Elsevier.

Tang Z et al. (2015) CTCF-Mediated Human 3D Genome Architecture Reveals Chromatin Topology for Transcription. Cell 163:1611–1627.

Telley L, Agirman G, Prados J, Amberg N, Fièvre S, Oberst P, Bartolini G, Vitali I, Cadilhac C, Hippenmeyer S (2019) Temporal patterning of apical progenitors and their daughter neurons in the developing neocortex. Science 364:eaav2522.

Telzer EH, Escalante E, Jack DB, Tsai RY-H (2025) How Social and Cultural Processes Shape Adolescents: An Ecocultural Transactional Framework of Adolescent Brain Development. Annual Review of Developmental Psychology.

 doi:10.20944/preprints202510.1749.v1

ten Donkelaar HJ, Vasung L, Molnár Z, Aronica E, Lammens M, van Bokhoven H, Ulzen KK-v, Hori A (2023) Development and developmental disorders of the cerebral cortex. In: Clinical neuroembryology: development and developmental disorders of the human central nervous system, pp 725–891: Springer.

Tomeny TS, Hudac CM, Malaia EA, Morett LM, Tomeny KR, Watkins L, Kana RK (2023) Serving Individuals With Autism Spectrum Disorder in the Age of COVID-19: Special Considerations for Rural Families. Rural Spec Educ Q 42:105–118.

Tomoda A, Nishitani S, Takiguchi S, Fujisawa TX, Sugiyama T, Teicher MH (2024) The neurobiological effects of childhood maltreatment on brain structure, function, and attachment. European archives of psychiatry and clinical neuroscience:1–20.

Torres-Berrío A, Bortolami A, Peña CJ, Nestler EJ (2025) Neurobiology of resilience to early life stress. Neuropsychopharmacology.

Vasistha NA, Sawa A (2025) Prenatal Immune Stress: Its Impact on Brain Development and Neuropsychiatric Disorders. Annual Review of Neuroscience 48.

Veena SR, Gale CR, Krishnaveni GV, Kehoe SH, Srinivasan K, Fall CH (2016) Association between maternal nutritional status in pregnancy and offspring cognitive function during childhood and adolescence; a systematic review. BMC Pregnancy and Childbirth 16.

Villalba N, Byrne K, Abdelmageed S, Votoupal M, Lam SK, Garcia RM (2025) Consumption of folic acid fortified foods among Hispanic women of reproductive age in the US: a systematic review. BMC Public Health 25.

Virolainen SJ, Vonhandorf A, Viel KCMF, Weirauch MT, Kottyan LC (2022) Gene–environment interactions and their impact on human health. Genes & Immunity 24:1–11.

Wallace MT, Woynaroski TG, Stevenson RA (2020) Multisensory Integration as a Window into Orderly and Disrupted Cognition and Communication. Annu Rev Psychol 71:193–219.

Wang L, Caras ML, Karayannis T, Froemke RC (2021) Editorial: Mechanisms Underlying Experience-Dependent Plasticity of Cortical Circuits. Frontiers in Cellular Neuroscience 15.

Wang S, Zeng Y, Pei P, He X, Liu F, Zhang T (2022) Abnormal transcriptome-wide DNA demethylation induced by folate deficiency causes neural tube defects. Front Genet 13:987210.

Werker JF, Hensch TK (2015) Critical Periods in Speech Perception: New Directions. Annual Review of Psychology 66:173–196.

Werling DM et al. (2018) An analytical framework for whole-genome sequence association studies and its implications for autism spectrum disorder. Nat Genet 50:727–736.

West AE (2025) Genetic Mechanisms of Experience-Dependent Neuronal Plasticity. Annual Review of Genetics.

Winfree RL, Seto M, Dumitrescu L, Menon V, De Jager P, Wang Y, Schneider J, Bennett DA, Jefferson AL, Hohman TJ (2023) TREM2 gene expression associations with Alzheimer's disease neuropathology are region-specific: implications for cortical versus subcortical microglia. Acta Neuropathol 145:733–747.

Woolway GE, Smart SE, Lynham AJ, Lloyd JL, Owen MJ, Jones IR, Walters JT, Legge SE (2022) Schizophrenia polygenic risk and experiences of childhood adversity: a systematic review and meta-analysis. Schizophrenia Bulletin 48:967–980.

Wu C, Tong S, You Y, Li Y, Cai R, Fang J, Fang X, Zhang X (2025) The causal and mediated relationships between major depressive disorder (MDD), post-traumatic stress disorder (PTSD), anxiety disorders and premature mortality: Evidence from genome-wide association study. Journal of Affective Disorders:119781.

Xu X, Liu Z, Gong S, Wu Y (2022) The Relationship between Empathy and Attachment in Children and Adolescents: Three-Level Meta-Analyses. International Journal of Environmental Research and Public Health 19:1391.

Yang Z, Luo Y, Yang Z, Liu Z, Li M, Wu X, Chen L, Xin W (2025) Mitochondrial dynamics dysfunction and neurodevelopmental disorders: From pathological mechanisms to clinical translation. Neural Regen Res.

Yockey LJ, Lucas C, Iwasaki A (2020) Contributions of maternal and fetal antiviral immunity in congenital disease. Science 368:608–612.

Ypsilanti AR, Rubenstein JL (2023) Mammalian Cortical Regional Specification. Neocortical Neurogenesis in Development and Evolution:443–475.

 doi:10.20944/preprints202510.1749.v1

Yuan J, Song X, Kuan E, Wang S, Zuo L, Ongur D, Hu W, Du F (2020) The structural basis for interhemispheric functional connectivity: Evidence from individuals with agenesis of the corpus callosum. NeuroImage: Clinical 28:102425.

Zhang X, Valeri J, Eladawi MA, Gisabella B, Garrett MR, Vallender EJ, McCullumsmith R, Pantazopoulos H, O'Donovan SM (2024) Transcriptomic Analysis of the Amygdala in Subjects with Schizophrenia, Bipolar Disorder and Major Depressive Disorder Reveals Differentially Altered Metabolic Pathways. Schizophrenia Bulletin.

Zhao Z, Shi Y, Sun M, Wang B (2025) Effects of prenatal iron deficiency on neurological development and related disorders in offspring. Frontiers in Nutrition 12.

Zhou Y, Song H, Ming G-L (2024) Genetics of human brain development. Nature Reviews Genetics 25:26–45.

Zhu X, Ma S, Wong WH (2024) Genetic effects of sequence-conserved enhancer-like elements on human complex traits. Genome Biology 25.

Zhu Y, Wang M-J, Crawford KM, Ramírez-Tapia JC, Lussier AA, Davis KA, De Leeuw C, Takesian AE, Hensch TK, Smoller JW, Dunn EC (2022) Sensitive period-regulating genetic pathways and exposure to adversity shape risk for depression. Neuropsychopharmacology 47:497–506.