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The Critical Roles of Early Development, Stress, and Environment in the Course of Psychosis

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Abstract

Psychotic disorders are highly debilitating with poor prognoses and courses of chronic illness. In recent decades, conceptual models have shaped understanding, informed treatment, and guided research questions. However, these models have classically focused on the adolescent and early adulthood stages immediately preceding onset while conceptualizing early infancy through all of childhood as a unitary premorbid period. In addition, models have paid limited attention to differential effects of types of stress; contextual factors such as local, regional, and country-level characteristics or sociocultural contexts; and the timing of the stressor or environmental risk. This review discusses emerging research suggesting that (*a*) considering effects specific to neurodevelopmental stages prior to adolescence is highly informative, (*b*) understanding specific stressors and levels of environmental exposures (i.e., systemic or contextual features) is necessary, and (*c*) exploring the dynamic interplay between development, levels and types of stressors, and environments can shed new light, informing a specified neurodevelopmental and multifaceted diathesis-stress model.

Keywords

psychosis; stress; neurodevelopment; systemic disparity; environment; contextual

INTRODUCTION

Psychosis is marked by acute episodes involving intense delusions, paranoia, and hallucinations as well as more chronic affective and cognitive symptoms. Psychotic disorders have a lifetime prevalence of 3% (Sullivan et al. 2020). They are typically diagnosed in early adulthood and are highly debilitating, with poor prognoses and courses of chronic illness. Traditionally, psychosis stages have been broken down into the prenatal period, the premorbid stage (spanning the period from birth until the onset of adolescence),

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the prodrome (the years immediately preceding onset, typically in adolescence), the first episode (including the years surrounding the onset of frank psychotic symptoms), and the chronic and late-stage periods (spanning the remainder of the lifetime). Etiological theories have long implicated stress as a pathogenic factor (Pruessner et al. 2017) and have understandably often focused on the most proximal risk periods leading up to onset. These theories have generated influential research and treatment development efforts for the adolescent and young adult years immediately before onset (Corcoran et al. 2003, Fowles 1992, Mittal & Walker 2019, Pruessner et al. 2017, Rosenthal 1970, Walker et al. 2008). Less attention has been paid to characterizing earlier developmental stages (i.e., it is common for these models to treat all of infancy and childhood as a uniform construct), teasing apart different types and levels of stressors (i.e., ecological and systemic factors), or considering the dynamic interactions of stress, environment, and development across the early life span. Recent advances in developmental neuroscience have provided key insights across each of these areas. The current review aims to apply these developments to psychosis.

First, as new methods and new types of data become available, the field is gaining a better understanding of the complex and significant interplay between brain development and environment. While psychosis classically has been labeled a disease of progressive deterioration, research is increasingly indicating that the primary determinants of psychosis onset and outcomes may instead be developmental in nature (Murray et al. 2022). The effect of a certain environment could vary depending on the developmental stage it is operating in (multifinality), or a variety of different initial environmental conditions could result in the same outcome (equifinality) (Cicchetti & Rogosch 1996). Second, existing models of psychosis have focused on stress as a uniform construct, frequently diving into stress sensitivity and individual-level stressors such as childhood trauma (Stanton et al. 2020). However, emerging research suggests that dimensions and types of stressors and environments could have both converging and distinct effects on neurodevelopment (Colich et al. 2020, Farrow et al. 2020, Ganzel et al. 2013, Gee et al. 2013, McLaughlin et al. 2014).

Further, research points toward the importance of distinguishing individual and contextual characteristics (Bronfenbrenner 1992, Hyde et al. 2020) for understanding systemic inequities impacting vulnerable communities. Systemic factors are not only impactful of their own accord but also likely interact with proximal factors to drive differing outcomes (Schofield et al. 2021). Similarly, assuming that what applies to individuals within a certain context (e.g., youth of the same race and socioeconomic status concentrated in a similar geographic region) also applies universally is misleading and compromises generalizability and interpretability. The current review aims to incorporate these points into an extended conceptual understanding of psychosis vulnerability. The focus is largely on neurobiological processes to build on existing diathesis-stress models and establish putative mechanisms of influence to inform etiological models and, ultimately, future downstream targets ranging from pharmacological treatment to behavioral interventions.

A NEURAL DIATHESIS-STRESS CONCEPTUALIZATION OF PSYCHOSIS

The diathesis-stress model is a foundational theory of psychosis etiology dating back to the 1960s (Rosenthal 1970). As schizophrenia research and its methods flourished, the model gained complexity, incorporating neural mechanisms and knowledge about adolescent development. Recent neural diathesis-stress models have expanded to (*a*) incorporate stages of psychotic illness progression (Walker et al. 2008); (*b*) include additional putative mechanisms, including epigenetic effects, neurotransmitter activity, neuroinflammatory processes, glucocorticoid receptor functioning, and cognitive deficits, on top of the original emphasis on hypothalamus-pituitary-adrenal (HPA) axis function; and, finally, (*c*) build on factors considered to confer vulnerability, including genetic predisposition, early life adversity, and chronic stress, as well as resilience factors (Pruessner et al. 2017).

Classically, the diathesis-stress model argued that a preexisting vulnerability for psychosis is present from the prenatal through late childhood periods (the premorbid period) and that subtle behavioral markers (e.g., developmental delays, minor physical anomalies, childhood trauma, parental instability, lower general cognitive function) reflect this vulnerability. The model argued that while indicative of a general vulnerability, the pluripotent nature of these signs and the wide range of what is considered normal meant they had limited predictive value relative to those in the prodromal adolescent period immediately preceding onset, which marked the emergence of attenuated symptomatology (e.g., hearing vague murmurs, seeing shadows, reading too much into coincidences, becoming increasingly suspicious) and other signs of psychosis-specific cognitive and functional deterioration (Corcoran et al. 2003). While the general nature of vulnerability markers during the premorbid period was distal and related to a host of different physical or mental disorders, the adolescent and young adult period marked an opportunity to unmask psychosis vulnerability and imminent risk. During this period of adolescence and early adulthood, a generalized premorbid susceptibility was posited to interact with exposure to stressors and both normative and pathological developmental processes (Insel 2010, McGlashan & Hoffman 2000), leading to the onset of formal psychosis (e.g., deeply distressing, impactful, fully formed hallucinations and delusions occurring frequently over a long period).

These models rightly posited that adolescence marks a critical period of neural plasticity and gray matter pruning, myelination, and hormonal development (Feinberg 1982, Insel 2010, McGlashan & Hoffman 2000, Pruessner et al. 2017, Walker et al. 2008). However, recent developments in developmental neuroscience have established that neural plasticity, pubertal development, and their precursors are also undergoing foundational changes in sensitive periods through infancy and childhood (Gilmore et al. 2018; Lyall et al. 2015; Mills et al. 2014, 2021; Saunders et al. 2019; Whittle et al. 2020). Further, a flourishing body of research has established that specific psychosis symptoms can emerge much earlier and be measured dimensionally across a spectrum of severity through methods including assessment of psychotic-like experiences (PLEs), which occur in up to 15% of the general population (Lee et al. 2016). Thus, delving into the premorbid period could inform psychosis etiology through several avenues (Farrow et al. 2020, Hastings et al. 2020, Mills et al. 2014, Nelson & Gabard-Durnam 2020) (Figure 1).

EARLY DEVELOPMENT IS NOT A UNIFORM CONSTRUCT

Many of the primary biological targets of adolescent-centric models (e.g., pruning, myelination, hormones), as well as environmental and social risk and resiliency factors (e.g., parental stability, socioeconomic support), begin to take shape in infancy through childhood. Infancy, from birth to 2 years of age, is marked by rapid and widespread neurodevelopment. Brain volume reaches 80% of adult size by the first 2 years, with cortical thickness reaching 97% of its adult measures (Knickmeyer et al. 2008). Gray matter–related sensorimotor and language functions have primary etiological links to psychosis (McGlashan & Hoffman 2000), and notably, regions of fast cortical thickness growth immediately after birth include areas serving primary sensorimotor and language functions (Lyall et al. 2015). Myelination also begins in the first year of life in areas critical for balance and sensorimotor function (Deoni et al. 2011). Similarly, primary functional networks develop first, including the sensorimotor, visual, and auditory networks (Khundrakpam et al. 2013).

Cortical thickness, peaking in infancy, begins to decrease linearly during early childhood (Gilmore et al. 2018). Subsequently, early childhood is marked by linear increases in global fractional anisotropy, indexing myelination, strengthening of structural networks, and communication (Krogsrud et al. 2016). It is noteworthy that white matter is central to the diathesis-stress model (Kelly et al. 2018). While some debate has focused on whether there is rapid degradation of white matter volume and connectivity during adolescence, it is important to consider that these alterations might begin much earlier. Further, childhood is a critical period for the maturation of prefrontal networks and connections, responsible for a host of higher-order processes (Krogsrud et al. 2016); this is crucial to consider in light of prefrontal dysfunction being a long-established psychosis marker putatively driving symptomatology, cognitive, and functional outcomes (Callicott et al. 2003).

Childhood also marks the beginning of adrenarche, which prepares the body for puberty, typically beginning at 5–7 years of age and marked by rapid increases in androgens (Remer et al. 2005). While diathesis-stress conceptualizations have focused on hormonal changes occurring during adolescence, hormonal abnormalities throughout this childhood period could mark early psychosis vulnerability, including in adrenarche-impacted prefrontal and limbic regions (Cunningham et al. 2002, Kesek et al. 2008, Saunders et al. 2019, Whittle et al. 2020). Further, dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEA-S) begin to increase at the start of adrenarche, stimulating neural growth and neurogenesis (Maninger et al. 2009). DHEA plays an important role in stimulating hippocampal neurogenesis and thus could be an influential player in psychosis risk and stress-driven interactions.

Finally, preadolescence (Bhana 2010) marks the period immediately prior to widespread gray matter volume decreases in adolescence (Marsh et al. 2008). While existing models of psychosis risk have focused on adolescent gray matter pruning, widespread pruning and specialization are also taking place during the preadolescence period, particularly in regions related to emotion processing and social functions (Mills et al. 2014). Critically, prefrontal gray matter density specifically peaks at 10–12 years of age, followed by extensive synaptic pruning and dendritic arborization (Hyde et al. 2020). As gray matter decline is a landmark

indicator of early psychotic disorder presentation, the preadolescence period could yield promising prevention targets (Dempster et al. 2017). In addition, gonadarche, marking the first gonadal changes of puberty and associated with rapid increases in estradiol and testosterone, begins at 10–11 years of age (Dorn 2006). Resulting developmental sequelae prepare the body for adolescence, impacting neural development and stress sensitivity, with key relevance for psychosis etiology (Blakemore et al. 2010). As such, the premorbid period of psychosis vulnerability is at the crux of multiple foundational developmental processes.

STRESSORS AND ENVIRONMENTS AS AGGREGATE, VARIED, AND SYSTEMIC FACTORS

While psychotic disorders have a substantial hereditary component, the sheer proportion of unexplained variance unaccounted for by genetic factors points toward meaningful environmental influence (Ripke et al. 2014). At the turn of the last decade, our increasing understanding of oxidative stress, an imbalance in antioxidants and prooxidants resulting in damage to an organism, heralded an era of insights. As a result, classical models of psychosis risk largely focused on chronic or acute stress, often envisioning stress as a subjective, unitary construct (Dauvermann & Donohoe 2019, Walker et al. 2008). However, the broader stress literature has started to go beyond these perspectives by incorporating different types of stressors and environments (Evans et al. 2013, McLaughlin et al. 2014). Further, while individual-level stressors such as exposure to trauma, home environment, and parental style have received a lot of support in the literature, we also exist within systems—neighborhoods, regions, cultures, and societies—that can and do impact individual development (Raizada & Kishiyama 2010) and, the literature suggests, psychosis vulnerability (Brito & Noble 2014). As such, the following sections discuss (*a*) aggregate exposures, (*b*) types of exposures, and (*c*) levels of exposures, with an emphasis on structural exposures occurring at the systems level.

Aggregate Stressors and Environmental Factors

It is well established that factors such as childhood trauma relate to increased vulnerability for developing a psychotic disorder (Fusar-Poli et al. 2017). It is also well established that an accumulation of stress can trigger a set of neural, developmental, and hormonal sequelae, ultimately driving psychotic disorder onset (Pruessner et al. 2017, Walker et al. 2008). Cumulative models counting the number of life events or stressors an individual has been exposed to have highlighted putative mechanisms implicated in the pathogenesis of schizophrenia and in the chronic stress response (Daskalakis et al. 2012, Vargas et al. 2019).

Within psychosis populations, landmark studies found that counting life events or life stressors missed a key part of the process. Assessing stress sensitivity, the degree to which an individual experiences an event as stressful, as well as the degree to which a certain event is impactful, offered key insights into psychosis vulnerability. Research showed that those vulnerable to developing psychosis endorse higher stress sensitivity and that stress sensitivity is itself predictive of symptoms over time (DeVylder et al. 2013, Lardinois et al. 2011, Ristanovic et al. 2020). The stress sensitivity literature solidified the notion that it is necessary to know not only the event itself but also how a specific individual reacts to

the event. In a parallel vein, emerging research incorporating both event and severity has taken an aggregate, or cumulative, perspective to exposure to events themselves. Similar to polygenic risk scores in genetics research, environmental exposome scores have been proposed, accounting for the magnitude of independent exposures while also weighing each exposure by its impact on the basis of preestablished reference samples (Pries et al. 2021). Through this aggregate approach researchers have been able to account for up to 13% of the variance in predicting a psychosis spectrum disorder diagnosis (Pries et al. 2019). This is largely consistent with the broader literature on cumulative risk exposure, which has leveraged powerful models with increased prospective prediction advantage for adverse outcomes (Evans et al. 2013).

Aggregate conceptualizations of early life stress have also allowed for a more mechanistic and integrative understanding of impacted neural systems. These include the HPA axis stress response, with key related regions including the hippocampus, medial prefrontal cortex, and amygdala as well as components of the brain's reward system such as the nucleus accumbens and orbitofrontal cortex (DeRosse & Barber 2021). There is ample evidence from animal and human studies that different types of stressors similarly trigger HPA axis function. In animal studies, chronic stress has been related to global changes in synaptic plasticity and dendritic branching throughout the prefrontal cortex, amygdala, and hippocampus (McEwen et al. 2016, Mondelli & Pariante 2008, Rodrigues et al. 2009). Changes in these regions, which are particularly sensitive to environmental influence, are often mediated by HPA axis–regulating agents such as glucocorticoids and corticotropin-releasing hormones, also implicating multifaceted inflammation processes (Aguilera 1998, Elenkov et al. 1999). In sum, aggregate and sensitivity models are insightful for predicting outcomes and understanding underlying mechanisms of the general stress response.

Types of Stressors and Environments

In recent decades, research emerged suggesting that distinguishing among types of stressors could uniquely aid in parsing heterogeneity in responses to childhood adversity. Early research in the field, for example, found that children experiencing physical abuse showed emotion-processing differences compared with children who had experienced physical neglect without direct physical threat (Pollak et al. 2000). Since then, a growing body of research has honed into ways of classifying types of experiences. Some studies have classified types of experiences using harshness (based on income-to-needs ratio), unpredictability (based on residential changes, paternal transitions, and parental job changes), and controllability (based on the degree of influence one can exert in one's environment), finding these factors predicted a variety of outcomes including socioemotional and academic functioning (Belsky et al. 2012, Chang et al. 2019, Cohodes et al. 2021, Li et al. 2018).

Other studies have differentiated between threats to one's physical integrity, putatively impacting fear learning, and deprivation exposures, including an absence of expected inputs and theoretically impacting neural proliferation and pruning (McLaughlin et al. 2014). Since then, a growing literature has emerged examining neural development along these dimensions. A meta-analytic synthesis found threat-related exposures related to cortical

thinning in the ventromedial prefrontal cortex, with deprivation exposures being associated with thinning in the frontoparietal, default, and visual networks (Colich et al. 2020). There are certainly challenges related to isolating general versus specific effects, especially when adopting categorical rather than dimensional models of exposure (Smith & Pollak 2021). Tackling these challenges by considering types of experiences dimensionally in the same sample while accounting for co-occurring experiences could aid in delineating distinct and converging underlying neural mechanisms.

Early research largely focused on individual-level exposures. Some studies have centered on youth at clinical high risk (CHR) for psychosis, who typically experience attenuated psychotic symptoms, or at genetic high risk due to a first-degree relative being diagnosed with a psychotic disorder along with decreases in day-to-day functioning (Fusar-Poli et al. 2016). A recent study examining a young adult CHR sample found reductions in cortical thickness in frontal and temporal regions for those with sexual trauma and physical abuse, with the middle temporal gyrus mediating the association between sexual abuse and transition to psychosis (Rapado-Castro et al. 2020); these associations did not extend to emotional neglect. Conversely, another recent study specifically delineated exposures into deprivation (poverty, neglect) and threat (abuse) dimensions in a young adult sample of CHR youth. In this sample, only the deprivation exposures were related to cortical volume and smaller right hippocampal volume (LoPilato et al. 2019). Though these studies were novel and theoretically driven, future studies are needed to establish replicability given broader concerns with the general reproducibility of imaging findings in smaller samples (Marek et al. 2022).

Psychotic disorders are known for their marked heterogeneity in symptom presentation, clinical course, and cognitive profiles, to the extent that many have hypothesized whether there are types of psychosis (Carpenter & Kirkpatrick 1988; Dickinson et al. 2004, 2018; Tsuang et al. 1990). As such, exploring types of stressors and environmental factors could represent a unique opportunity to parse heterogeneity. Exposures that activate neural systems engaged in threat processes could relate more strongly to positive symptoms intricately linked to dopaminergic systems function (Zhu & Grace 2021). Conversely, exposures relating to lack of resources or lack of exposure to developmentally appropriate resources could relate more to cognitive dysfunction while exposures related to social processing of belonging and exclusion could contribute to predicting negative symptomatology and function in glutamatergic systems (McCutcheon et al. 2020). Future studies hold promise for testing some of these questions and will benefit from including help-seeking comparison groups to establish vulnerability to psychosis risk versus transdiagnostic vulnerability.

Systemic and Ecological Stressors and Environmental Factors

Recently, attention has been called to the dearth of research on more contextual and systemic stressors and environments (Hyde et al. 2020, Nielsen et al. 2017). It is well established that developmental psychological research has an overrepresentation problem when it comes to Western, educated, industrialized, rich, and democratic populations (Nielsen et al. 2017). The need to increasingly consider population diversity in psychosis research has similarly been highlighted, including socioenvironmental, racial, cultural, and other contextual factors

(Burkhard et al. 2021). Measuring the individual while leaving out the contextual puts us in danger of both over- and undergeneralizing research findings while also jeopardizing our understanding of the mechanisms through which stressors and environmental exposures could impact neurodevelopment and vulnerability for psychopathology.

Research taking ecological factors into account from an epidemiological lens has already yielded key insights into psychosis vulnerability. Urbanicity is one example. Research conducted in Western samples has long theorized an association between living in urban areas and greater incidence of psychotic disorders (Haddad et al. 2015, Lederbogen et al. 2011, Vassos et al. 2012). In line with the discussion above on taking ecological context into account, recent research has shown that living in urban settings related differentially to PLEs depending on the country of exposure (DeVylder et al. 2018). While more urban areas related to higher PLEs in Laos, Mexico, Estonia, and Morocco, the opposite was the case for more urban regions in Nepal, Vietnam, Hungary, and South Africa (DeVylder et al. 2018).

Recently, a summary of types of systemic exposures was posed on the basis of the existing literature on types of exposures, contextual factors, and psychosis vulnerability. The stimulation, discrepancy, and deprivation model hypothesized three domains of contextual, systemic environmental exposures along with putative intermediary and biological mechanisms of influence (Vargas et al. 2020). The hypothesized stimulation domain comprised exposures conferring feelings of lack of safety and sensory overload, including neighborhood crime, population density, and urbanicity. The discrepancy domain, in turn, includes ecological factors conferring a sense of a lack of belonging, social exclusion, low social capital, and assimilation and acculturation stress (Vargas & Mittal 2021), including exposures such as low ethnic density, neighborhood income inequality, and high neighborhood social fragmentation. Finally, the deprivation domain includes exposures conferring a lack of exposure to neurodevelopmentally appropriate rich and complex environments with exposures such as neighborhood deprivation and regions with a lack of access to educational, employment, housing, or healthcare resources.

Notably, though these exposures may confer effects on neurodevelopment through inducing stress and activating stress response systems, this is not the only mechanism of action. Rather, these models take the view that environmental exposures can be impactful not only through engaging stress systems but also through altering the development of structural and functional neural architecture. For example, though high-deprivation environments could be considered stressful, they would not need to be considered stressful in order to alter neurodevelopment due to lack of developmentally appropriate environmental enrichment (Smith & Pollak 2021).

Recently, studies including children in the United States found support for the distinctness of the three domains of ecological exposures, along with evidence of their relation to psychosis vulnerability (Vargas et al. 2021) and neural structure (Vargas et al. 2022). Notably, a study of adolescents and adults in rural East England also found partial evidence of distinctness (finding exposures separated into racial and ethnic diversity, deprivation, urbanicity, and social isolation), as well as support for the three domains' value in predicting psychotic disorder incidence (Richardson et al. 2018). As many existing studies have focused on

singular exposures (e.g., focusing on neighborhood deprivation and treating other exposures as nuisance variables), future studies integrating multiple exposures, while being careful to account for co-occurrence of ecological risk factors, are needed. Future research could explore different cognitive and symptomatological dimensions, the interplay across types and levels, and underlying biological and neural mechanisms to parse heterogeneity in symptom presentation (Figure 2).

STRESS, ENVIRONMENT, EARLY DEVELOPMENT, AND PSYCHOSIS: A DYNAMIC INTERPLAY

Emerging research taking a developmental lens and informed by stress and environmental considerations at multiple levels (i.e., individual, contextual, or both) is promising and has begun to yield insights for general neurodevelopment and psychosis vulnerability.

Infancy

A large portion of the literature on infancy, the period between birth and 2 years of age, has focused on parental risk factors (Simcock et al. 2016). While exposure to prenatal stressors is beyond the scope of the current review, a subset of these studies is informative with regard to environmental factors. For example, children born to socioeconomically disadvantaged parents were found to be more likely to exhibit neurological abnormalities at 4 months, 1 year, and 7 years of age, even after accounting for pregnancy and delivery complications (Chin-Lun Hung et al. 2015). Of note, minimal associations have been found between parental education and brain volume at birth (Knickmeyer et al. 2017). When detected, infants from low-income families showed lower gray matter volume in frontal and parietal lobes, with no differences found in white matter volume (Hanson et al. 2013). Imaging studies of infants incorporating stress and environmental factors are emerging, though a smaller body of research has begun to examine stressors and environmental factors in infancy.

Electroencephalogram (EEG) studies in particular have shown compelling evidence, perhaps partially due to the methodological benefits of the EEG approach for this age group. A study of 6-to-9-month-old infants living in high socioeconomic deprivation in East London, for example, examined resting EEG activity (Tomalski et al. 2013). Researchers found significantly lower frontal gamma power in infants from low-income homes, accounting for maternal occupation, infant sleep, gestation length, birth weight, smoke exposure, and bilingualism (Tomalski et al. 2013). However, findings are not entirely consistent. Another EEG investigation of infants up to 2 years old did not find disparities in brain activity related to current socioeconomic status, though they did find relations between EEG power at birth and language and memory outcomes at 15 months (Brito et al. 2016).

Magnetic resonance imaging studies of resting-state connectivity have also given insight into possible relations of environmental factors. A recent infant study found lower socioeconomic status at birth to be related to differences in striatum and ventrolateral prefrontal cortex connectivity (Ramphal et al. 2020). Further, striatal and frontopolar connectivity mediated the relationship between socioeconomic status and externalizing

symptoms while striatal, frontopolar, and medial prefrontal cortex connectivity mediated the relationship between socioeconomic status and behavioral inhibition at age 2. Studies have also found household income and maternal education to relate to within-network connectivity of the default mode network as early as 6 months old (Gao et al. 2015). While samples were modest and replicability is yet to be established, early literature suggests there is more to uncover.

Infancy and Psychosis Vulnerability

The research on neural development during infancy and its relations to psychosis risk is growing and fruitful. There is evidence that socioeconomic status at birth relates to later risk of developing schizophrenia (Werner et al. 2007). A landmark study found that the offspring of individuals with a psychotic disorder adopted into another family during infancy were more likely to develop a psychotic disorder, possibly reflecting an interplay between genetic and environmental vulnerability (Tienari et al. 1985). Evidence has also been found for the specificity of the impact of environmental stressors occurring during infancy. For example, maternal postnatal bereavement stress was related to offspring psychosis incidence, with the risk being higher the earlier the mother's bereavement stress occurred in the offspring's life (i.e., infancy, childhood, or preadolescence) (Abel et al. 2014). Similarly, a robust body of research has related obstetric complications as a risk factor for psychotic episodes as early as childhood (Moreno et al. 2009). Hypoxia-related obstetric complications have been related to earlier-onset schizophrenia (Cannon et al. 2000). Though there are difficulties in imaging neurodevelopment in infants, researchers could learn more by collecting retrospective measures of childhood adversity and environmental factors across development, preferably across multiple responders to improve accuracy (Vargas et al. 2019).

Childhood, Including Early and Middle Childhood

Studies focusing on neural development during early and middle childhood, between 3 and 8 years old, are relatively plentiful with respect to stressors and environments (Bhana 2010). Some studies have illustrated benefits of examining interactions across levels of environmental exposures, from proximal (family level) (Fields et al. 2021) to distal (neighborhood and regional characteristics). For example, one study found that early childhood parental partner relationship quality related to positive social adjustment only in children with low levels of neighborhood disadvantage (Vanderbilt-Adriance & Shaw 2008). On the other hand, studies have begun to highlight the necessity of accounting for the timing of exposure. A recent investigation found that exposure to neighborhood disadvantage during early childhood, but not adolescence, uniquely related to greater amygdala reactivity to ambiguous neutral faces in adolescence and young adulthood (Gard et al. 2021). Consistent with another study (Lawson et al. 2017), associations remained after accounting for proximal, family-level adversities. In separate samples, the study found that neighbors' income and poverty status were predictive of participants' amygdala function, further supporting the need to incorporate contextual factors (Gard et al. 2021). Albeit in a smaller sample, experiencing poverty during early childhood was related to smaller white and cortical gray matter in hippocampal and amygdalar regions during adolescence (Luby et al. 2013). Further, caregiver support (right hemisphere) and stressful life events (left hemisphere) mediated the association. Though preliminary and in need of replication,

these studies lend further support for the relevance of examining types of adversities across different levels and different developmental periods.

Research has also sought to establish putative neural mechanisms for existing relations. A recent study found, for example, that conversational turns and language input (indexing access to neurodevelopmentally appropriate rich environments, in line with the deprivation domain) mediated a relation between parental education and left perisylvian cortical surface area (Merz et al. 2020). While the hippocampus has long been recognized as a region that is particularly sensitive to environmental influence, studies have also found that the association between childhood socioeconomic status and hippocampal volume survives adjustment for childhood mental ability, adult socioeconomic status, and education (Staff et al. 2012). There is evidence that socioeconomic factors relate more strongly to brain structure starting in early childhood (Hanson et al. 2013). Associations between socioeconomic status and white matter microstructure in children have been found (Ursache & Noble 2016), while findings with white matter volume have been less consistent (Mackey et al. 2015).

Childhood and Psychosis Vulnerability

From a stress sensitivity lens, relations between stress and psychosis vulnerability have been found to be stronger in individuals exposed to trauma during childhood (Pätzold et al. 2021). Beyond trauma, exposure to childhood adversity more broadly has been reliably linked to clinical and psychosocial outcomes in psychosis (Bell et al. 2019, Ramsay et al. 2011, Shah et al. 2014, Turner et al. 2020).

Specific individual-level stressors have been examined. For example, studies suggest that international migration is more strongly linked to psychotic disorder risk when occurring during childhood (Anderson & Edwards 2020). Recent studies have begun to undertake a longitudinal perspective, lending fresh insights. One, for example, found that childhood bullying assessed at age 7 predicted hallucinatory experiences assessed during preadolescence (Steenkamp et al. 2021). Notably, bullying exposure was not assessed during other developmental periods, limiting conclusions of specificity with respect to childhood developmental stage. While research has not often assessed exposure across ages with granularity, some has incorporated imaging modalities in an informative manner. A study assessing cumulative risk from childhood, adolescent stress, and adverse environmental conditions found relations with adult white matter microstructure (DeRosse et al. 2014). However, the literature is decidedly mixed, pointing to gaps in knowledge. For instance, research assessing adversities across the life span found that while mother-reported childhood adversity did indeed relate to PLEs experienced during preadolescence (age 10), adversities experienced prior to age 5 were similarly related when compared with those experienced after age 5 (Bolhuis et al. 2018). Modeling age of exposure continuously using mixed models in well-powered samples, as well as more richly assessing for and incorporating types and levels of exposures, will aid in understanding the dynamic interplay between environments and development.

In addition to individual-level exposures, some ecological factors have historically received attention. Change in family income during childhood has been established as a risk factor for psychosis (Björkenstam et al. 2017), as has living in urban environments during childhood

(Newbury et al. 2016). Other studies, including many recent ones, have further expanded into the interplay between proximal and distal exposures. Earlier cohort studies, for instance, found a dose–response relationship whereby experiencing an accumulation of environmental disadvantages during childhood predicted psychotic disorder incidence (Wicks et al. 2005), though, again, age and duration of exposure were not assessed. Similarly, another study found that the relation between psychotic symptoms and parental treatment in childhood was moderated by socioeconomic status (Akün et al. 2018). A recent study found that for youth exposed to neighborhood disadvantage during childhood, aggressive and withdrawn behaviors predicted higher risk for being diagnosed with a psychotic disorder (Hastings et al. 2020). Though current child neighborhood disadvantage was assessed at only one time point, the authors estimated worsening disadvantage over childhood by comparing it with parental neighborhood conditions 30 years prior, finding consistent relations across both measures (Hastings et al. 2020).

A marked limitation of the literature is lack of precision in defining the childhood developmental period. For example, many studies define childhood trauma as events occurring any time prior to the age of 16 (Stanton et al. 2020). Thus, incorporating multiple types of stressors and environmental exposures in the same sample and gathering detailed information on the timing and severity of exposure while tracking symptom trajectories over time will be particularly informative in this pursuit. In addition, the prevalence of premature adrenarche and accelerated adrenarche could be key to consider. Research has theorized that risk for mental illness can build throughout childhood as a result of premature or accelerated adrenarche (Belsky et al. 2015), though risk may not manifest until gonadarche (Mendle et al. 2010). Understanding early childhood adjustment in the context of gonadal and adrenal hormonal development of those that go on to develop a psychotic disorder could similarly aid in parsing psychosis risk (Horton et al. 2015, Walker & Bollini 2002). Though much is yet to be uncovered and studies are limited, the existing literature is promising.

In addition, DHEA and DHEA-S have been shown to index pubertal processes and reactivity to acute and chronic stress (Mendle et al. 2010, Whittle et al. 2015) while also driving neural interactions between the HPA and hypothalamic-pituitary-gonadal axes, which are crucial to psychosis vulnerability (Marceau et al. 2015). Given the hormonal increases during childhood across subcortical structures that are highly susceptible to experience-dependent plasticity (e.g., hippocampal regions), interactions with these processes could drive increased psychosis risk (Cohodes et al. 2021, Gee et al. 2012).

Preadolescence

Preadolescence, ages 9–14, marks the onset of the first biochemical phases of puberty (Bhana 2010). Research has recently related pituitary gland volume increases during preadolescence to the hormones of adrenarche (Whittle et al. 2020) and explored the possible impacts of proximal- and individual-level factors during this critical developmental period. A recent study related pituitary gland volume to types of early life stress (defined through exploratory factor analysis and including uninvolved parenting, negative affective parenting, neglect, trauma, and dysfunctional discipline). The study found childhood neglect (consistent with the deprivation domain) related to pituitary gland development, whereas

other types of early life stress did not (Farrow et al. 2020). Though the strength of association was not compared statistically, the study points to the necessity of incorporating different developmental periods of exposure, as results have been conflicting in different age ranges, pointing to a possible development-specific effect. Results were consistent with findings in children exposed to maternal deprivation and childhood maltreatment and could possibly be the result of HPA axis hyperactivation, consistent with the anterior pituitary containing adrenocorticotropic hormone (ACTH)-releasing corticotroph cells (Gee et al. 2013, Kaess et al. 2018). Given that the study did not assess for timing of exposure or exposure across the lifetime and given the modest sample size, future research is needed to enrich this line of research.

Studies in preadolescence have also examined white and gray matter in the context of different exposures. Though it did not statistically compare the strength of association between types, a recent study found higher neighborhood disadvantage (consistent with deprivation exposures) related to lower quantitative anisotropy (QA) of cingulum bundle, uncinate fasciculus, and stria terminalis/fornix tracts, while exposure to violence (consistent with stimulation and threat exposures) did not relate to QA in any tract (Bell et al. 2021). Another study found that low-socioeconomic-status preadolescents showed reduced gray matter volume within hippocampal, middle temporal, fusiform, and inferior occipitotemporal gyri; further, neural structure related to income and dual language use during adolescence but not earlier in childhood (Brito & Noble 2018). With regard to deprivation broadly, differences in gray matter have been found across the hippocampus, amygdala, superior temporal gyrus, and inferior frontal gyrus; evidence has also pointed toward differences due to socioeconomic factors increasing throughout childhood and preadolescence (Gilmore et al. 2018, Noble et al. 2012). While one of these studies modeled age by socioeconomic-status interactions, this was done cross-sectionally, and sample sizes were modest (Noble et al. 2012).

Preadolescence and Psychosis Vulnerability

Existing research on preadolescence has largely focused on individual-level stressors. For example, a recent study found preadolescent levels of daily individual-level stressors and elevations in diurnal cortisol increased risk for developing attenuated psychotic symptoms in adolescence and young adulthood (Cullen et al. 2021); only these two time points were examined, so further inquiry is needed to explore the contributions of other developmental stages. Another study in preadolescents found low family income, bullying, and theory of mind to be related to psychotic experiences, theorizing that these exposures could be particularly impactful during the preadolescent developmental period given ongoing maturation of socioemotional processes (Clemmensen et al. 2016). Some studies have incorporated both individual and systemic exposures. One study examined PLE trajectories starting at 10–11 years and assessed again 6 years afterward, finding ethnic minority status and childhood trauma to relate to the persistence of PLEs over adolescence (Wigman et al. 2011). With regard to systemic or ecological factors, a study examined trajectories of mother-reported discrepancy domain neighborhood cohesion, discord, and stress in childhood and preadolescence longitudinally. Highlighting the strengths of collecting data on exposure across multiple developmental periods, the authors found that neighborhood

stress predicted PLEs during preadolescence, and neighborhood cohesion predicted PLEs during early adulthood (18 years old) (Solmi et al. 2017). Focusing in on preadolescence, another study found urbanicity (stimulation domain), area deprivation index and poverty (deprivation domain), and lead exposure risk related to PLEs, with brain volume mediating 11–25% of the associations with poverty (deprivation domain), neighborhood safety (stimulation domain), and lead exposure (Karcher et al. 2021).

A study by our group found that in preadolescents, deprivation exposures measured through self-report showed the strongest association with PLEs (though stimulation and discrepancy domain exposures also related to PLEs) (Vargas et al. 2021). Consistent with this notion, outside of research on humans, recent research utilizing the methylazoxymethanol acetate (MAM) rat model of schizophrenia found that prepubertal environmental enrichment prevented dopamine hyper-responsivity, which may have a protective or preventive effect on developing psychotic symptoms (Zhu & Grace 2021). This promising research points toward the importance of the preadolescent developmental stage for understanding psychosis etiology and targeting prevention and intervention efforts. Though deprivation domain exposures, which are often operationalized as socioeconomic status and lack of resources, are more frequently covered in the literature, expanding across other exposures will be key in further clarifying links between environment and psychosis vulnerability.

In addition, pituitary gland volume has commonly been related to early life stress, and individuals with a psychotic disorder often exhibit significantly larger pituitary gland volumes; the anterior section, which contains ACTH-releasing corticotroph cells, relates to cortisol release and could be particularly relevant to environmental factors and stressors (Saunders et al. 2019, Whittle et al. 2020). Hormonal processes, such as female sex at birth and estrogen increases, have also been considered as putatively protective against psychotic disorder onset (Damme et al. 2020, Trotman et al. 2013) (Figure 3).

CONCLUSION, LIMITATIONS, AND FUTURE DIRECTIONS

The literature supports an unfolding neurodevelopmental (taking earlier stages into account), multifaceted (taking aggregate, types, and levels of stressors and environments into account), and dynamic (incorporating the interplay of stressors, environments, and early development) diathesis-stress model of psychosis. However, it is worth taking a step back to ask: Why psychosis? Are neurodevelopmental considerations and types and levels of stressors and environments not critical to psychopathology more broadly? The answer here is, of course, yes. Developmental stages and types and levels of stressors absolutely hold immense potential to inform transdiagnostic conceptualizations of risk and resilience and ought to be marshalled toward these pursuits. However, as reviewed above, there are several components of psychotic disorders that make these considerations likely to be immensely informative for psychosis vulnerability specifically.

First, the marked heterogeneity of psychotic disorders means that a group of individuals with the same diagnosis can act completely differently and have vast variation in symptom presentation and levels of functioning. Symptoms are wide ranging, resulting in complex and seemingly nonoverlapping presentations. Research on types of stressors

and environments could be particularly fruitful in parsing symptom heterogeneity and trajectories and indeed has already begun to inform these questions. Parsing this heterogeneity could be particularly fruitful in targeted treatment and prevention pursuits. Second, psychosis has been conceptualized as a neurodevelopmental disorder, and, truly, an overwhelming majority of psychosis diagnoses emerge during adolescence and young adulthood. This fact denotes the immense potential of incorporating earlier development into disorder conceptualizations. Third, with the immense toll that psychotic disorders take at the population level, early prevention and intervention health policy efforts facilitated by the expanded model are paramount. Fourth, there is a reasonable chance that stressors and environments are uniquely relevant for psychosis vulnerability. As discussed, youth that go on to develop a psychotic disorder often exhibit heightened stress sensitivity, and given certain symptom clusters, some types of stressors or environments could be particularly conducive to psychosis vulnerability—at this point, this is an open question.

To implement this expanded, multifaceted, and dynamic neurodevelopmental diathesis-stress model into research practice, several steps would be useful. It will be essential to differentiate transdiagnostic vulnerability from psychosis vulnerability more specifically. A majority of the reviewed studies either did not have nonpsychiatric control groups or employed comparison groups without a help-seeking or psychopathology history. If we hope to dissect psychosis vulnerability, it will then be crucial for future literature to distinguish it from transdiagnostic or general vulnerability by employing help-seeking comparison groups (Millman et al. 2022). Collecting more information on the exact timing of exposures to different environments and experiences will allow for a clearer understanding of putative environmental influences. While the accuracy of retrospective recall is a concern, these limitations can be attenuated by using multiple informants where possible as well as by using anchoring strategies to aid accurate recall (Vargas & Mittal 2018). While many studies have emphasized risk factors, more fully characterizing both protective and vulnerability-conferring environmental contexts and experiences will be informative.

Ideally, researchers would harness longitudinal samples and collect information across multiple time points to increase the likelihood of accurate recall. Measures capitalizing on the widespread use of technology and smartphones could also aid in measuring subjective experiences of stress and the environment in the moment (Bell et al. 2017). Self-report measures could be strengthened by more objective measures of the environment and contextual factors, such as geocoding (Finch et al. 2010, Morland et al. 2002).

Cross-site collaborations could aid replicability, improve the representativeness of study samples, and provide the power needed for more complex modeling. Finally, it is of utmost need to account for high levels of coexposure. An overwhelming majority of children exposed to one type of trauma, stress, or disadvantageous environment are likely also exposed to other types (Debowska et al. 2017), which is compounded by systemic disadvantage (Evans et al. 2013). As such, modeling for co-occurrence while addressing modeling complexities (e.g., collinearity) is a necessity, as is considering both converging effects (i.e., the broader effects on stress systems) and effects specific to certain dimensions of exposures. In tandem, research modeling the intensity and duration of dimensions of exposure will enrich these efforts (Ganzel et al. 2013).

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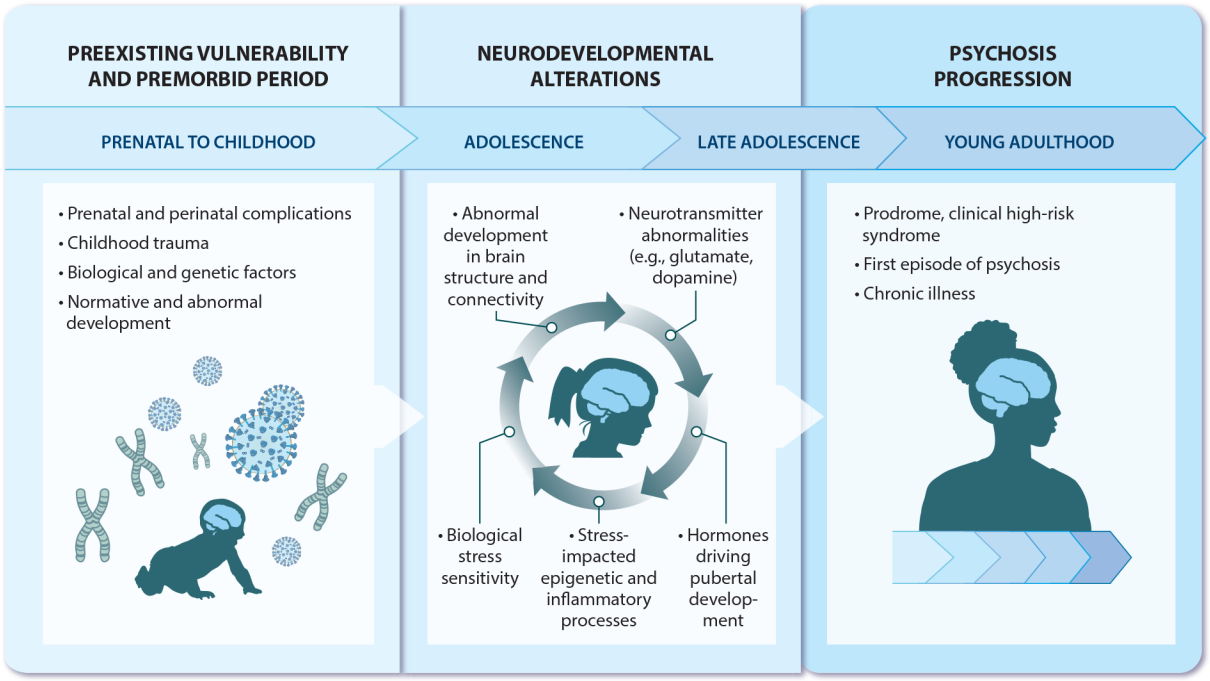

Figure 1.

A diathesis-stress model of psychosis, including a premorbid stage spanning the prenatal through childhood periods and a dynamic stage in adolescence and early adulthood, during which neurodevelopmental alterations interact with preexisting vulnerability, leading to psychosis progression, typically in late adolescence to young adulthood. Figure adapted from Vargas (2022).

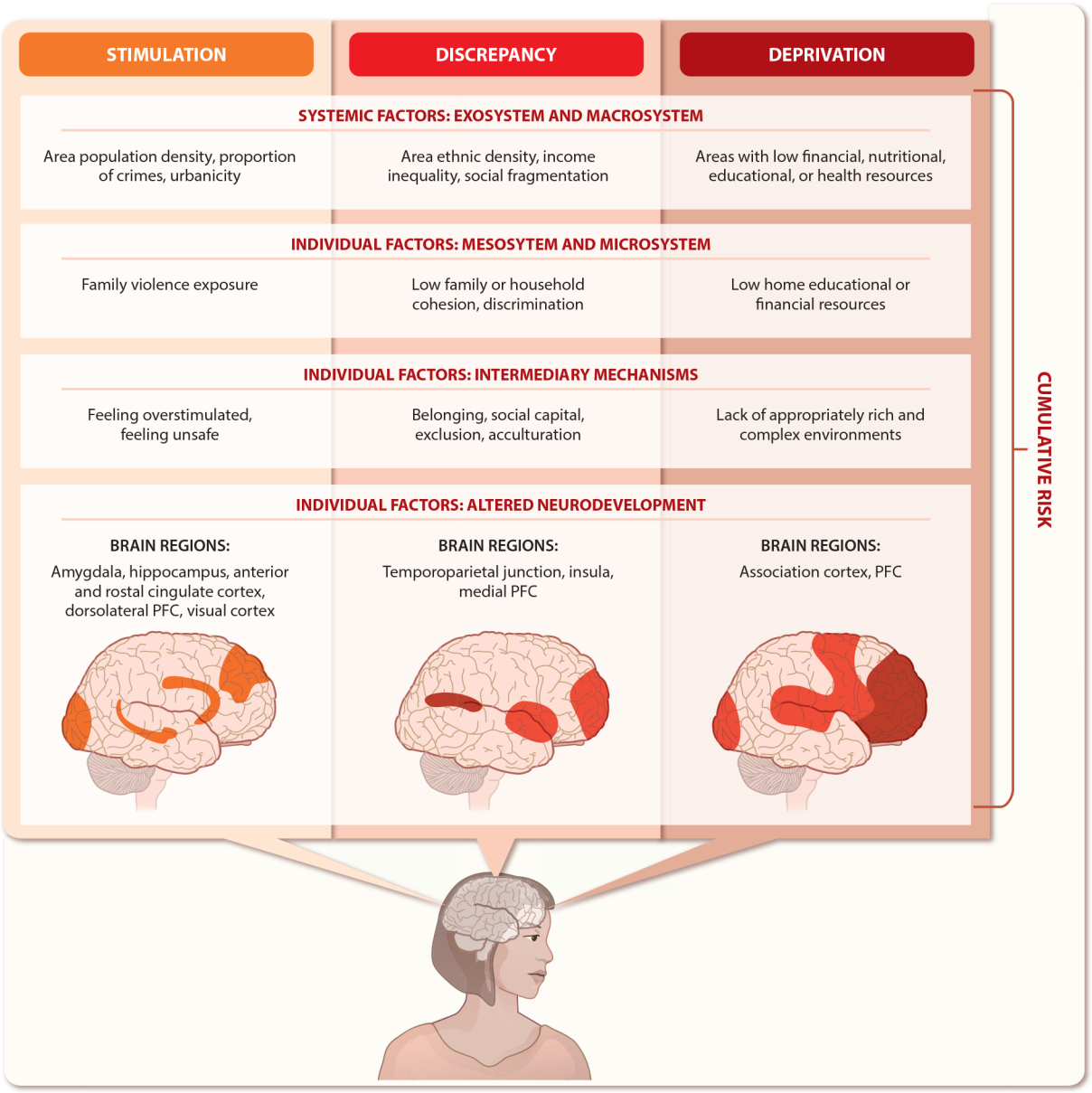

Figure 2.

The stimulation, discrepancy, and deprivation ecological model, including exposures (i.e., area population density, number of crimes, and urbanicity for stimulation; area ethnic density, income inequality and social fragmentation for discrepancy; and areas with low financial, nutritional, educational, or health resources for deprivation), intermediary mechanisms of influence (e.g., feeling overstimulated or unsafe for stimulation; low belonging, social capital, and acculturation for discrepancy; and lack of appropriately rich and complex environments for deprivation), and theorized impacted neural regions per domain. Abbreviation: PFC, prefrontal cortex. Figure adapted from Vargas (2022).

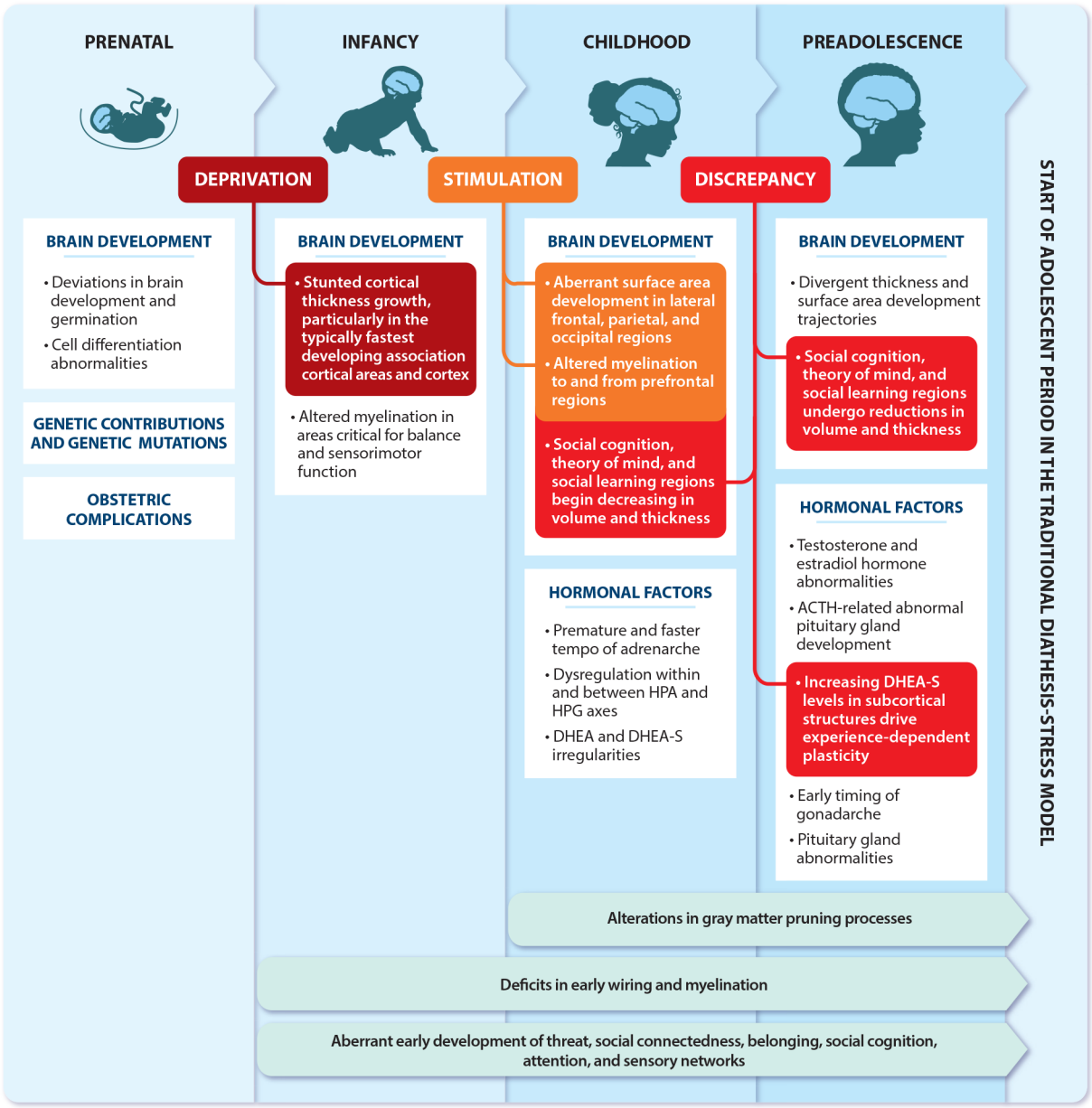

Figure 3.

Expanding the diathesis-stress model (see Figure 1) to consider early development as well as dynamic and multifaceted environments, stressors, and systemic factors. Abbreviations: ACTH, adrenocorticotropic hormone; DHEA, dehydroepiandrosterone; DHEA-S, dehydroepiandrosterone sulfate; HPA, hypothalamus-pituitary-adrenal; HPG, hypothalamic-pituitary-gonadal. Figure adapted from Vargas (2022).