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Biological, Psychological, and Sociocultural Processes in Emerging Mental Disorders in Youth

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Abstract

Vulnerability for the development of major mental health conditions during the transition from adolescence to adulthood is highly influenced by social and cultural contexts, yet our understanding of the way these contexts interact with individual differences (such as genetic variation) to generate or moderate psychopathology is limited. Such contextual interactions are likely to be nonlinear, bidirectional, and potentially age sensitive, requiring complex modeling to disentangle the most significant factors that contribute to the onset of mental illness in youth. Combined with known transcultural variation in these contexts (and psychopathology itself), there is a critical need to better understand the general applicability of models of youth mental health if we are to develop appropriate interventions. This chapter identifies gaps in current understanding in terms of how an individual's interaction with the environment shapes the risks and vulnerabilities to develop major mental disorders, or their behavioral precursors, thus resulting in functional impairments and increasing the high global burden of disease.

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Introduction and Setting the Framework

The Youth Mental Health Burden

The dynamic and differential influences that the environment exerts on a developing individual, at multiple levels of confluence, can lead to the emergence of major mental disorders (e.g., psychotic, mood and anxiety, and substance use disorders) in youth and adulthood. Such disorders, which are often chronic, contribute substantially to disease burden, both directly and indirectly, through a high population attributable risk (Table 6.1). In 2010, the Global Burden of Disease Study found mental and substance use disorders to be the leading cause of disability in children and youth under the age of 25 yr globally, despite high probabilities of underestimating the full extent of the burden (Erskine et al. 2015). Although greater in high-income countries, burden estimates in low- and middle-income countries are likely to grow with the possible control of morbidity due to infectious disorders in the near future (Lozano et al. 2012). While identification and treatment of these disorders during childhood and adolescence is certainly desirable, effective prevention strategies most likely have the greatest capacity to reduce the burden (Erskine et al. 2015).

To develop, test, and implement effective preventive and early intervention strategies, a scientifically robust understanding of the etiology of these disorders is necessary. A range of etiopathogenic processes have been identified as risk factors for youth mental health problems, yet their complex nature and the interdependent relationships involved (e.g., genetics, parental mental illness, poverty, and childhood adversity) are not easy to modify and quantify.

Table 6.1 Population attributable risk (PAR) of adult disorders, having been diagnosed with other disorders during adolescence, based on a national survey of U.S. adolescents. Note: PAR is the proportion of the disease incidence in a population (exposed and unexposed) due to exposure. It is the incidence of a disease in the population that would be eliminated if exposure were eliminated (Kirch 2008).

Adolescent Disorders	Adult Disorders	PAR (%)
Anxiety disorder	Depression	17.95
	Schizophrenia	26.71
Depression	Depression	21.20
	Bipolar disorder	21.20
	Schizophrenia	42.82
Attention deficit hyperactivity disorder	Schizophrenia	23.34
Conduct disorder	Depression	20.96
Oppositional defiant disorder	Depression	32.38
Conduct/oppositional defiant disorder	Bipolar disorder	22.54
	Schizophrenia	25.88
Substance use disorder	Depression	15.51

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Understanding these influences is necessary to identify key processes (as well as that which moderates and mediates specific outcomes), which in turn is needed to enable the early identification of vulnerable youth and the evaluation and initiation of scientifically informed corrective interventions in a scalable and sustainable manner.

A Conceptual Framework to Understand the Etiology of Youth Mental Disorders

Development encompasses various levels of biological (e.g., infancy, growth spurts, juvenility, puberty) and social (e.g., roles, responsibilities, interpersonal relationships) transitions—encountered and experienced by individuals within their unique environment—as well as neurobiological (brain size, white matter expansion, dendritic branching, myelination) and psychological (cognitive control and emotion regulation) changes. The developing child, with his/her own genetic endowment, progresses through these rapidly evolving phases of physiology and encounters along the way a range of environmental influences. The etiology and pathogenesis of major mental disorders in youth and adulthood cannot be comprehended without considering the various levels of milieus in which a developing child lives, and with which they transact (e.g., family, peers, school, and society), and the associated ethnocultural systems.

It is within this context that a life-course epidemiological perspective—one that focuses on the complex interplay of social and biological factors during gestation, childhood, adolescence, early adult life, or across generations in the production of mental disorders (Koenen et al. 2013)—appears to be an essential organizing paradigm to study the determinants of youth mental health (and disease). The population neuroscience approach is well suited to apply a life-course epidemiology paradigm to mental disorders as it acknowledges the complexity in time and space of *environmental* and *genomic* factors that shape the structure and functions of the human brain, best addressed at a population level (Paus 2010). Here, it is important to understand and apply the concept of *developmental cascades*, which is integral to population neuroscience approaches in appreciating how transactions at different timescales (e.g., perinatal, infancy, adolescence, early adulthood), constructs (cognition, mood, behavior), and levels (molecular, physiology, individual, and social) have a domino effect on subsequent development. Developmental cascades refer to the cumulative consequences of the many interactions and transactions which occur in developing children that result in spreading aftereffects across levels, among domains at the same level, and across different systems or generations (Masten and Cicchetti 2010). Therefore, efficient management of youth mental disorders and strategies to prevent them must consider this context to address the needs of children and families throughout the developmental trajectory. Effects of specific environmental exposures on the outcomes of mental disorders and their behavioral precursors can be potentially mediated or moderated

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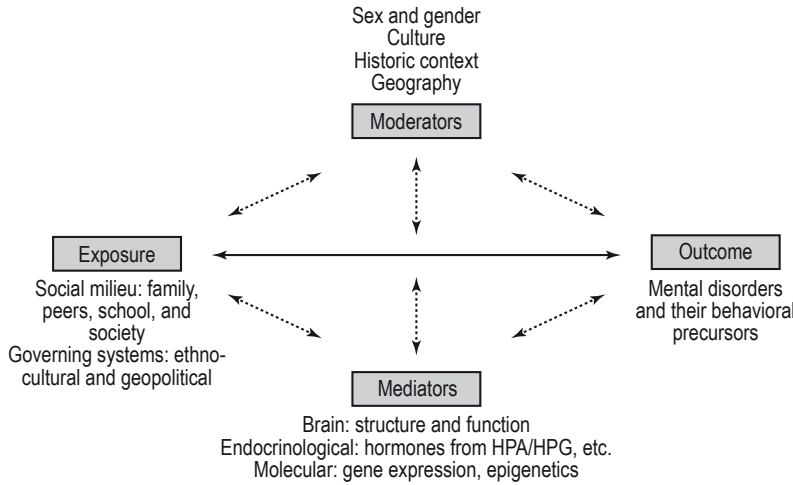

Figure 6.1 An illustrative model depicting how environmental exposures can impact behaviors across developmental cascades. Across exposures, mediators, moderators, and outcomes there is a dynamic fluid interchange, depending on where in the developmental cascade one is. HPA/HPG = hypothalamic pituitary adrenal/gonadal axes.

by a broad range of contextual, cultural, and biological factors, depending on the particular developmental epochs (e.g., periconceptional, perinatal, or peripubertal) during which the exposures occur (see Figure 6.1). A nuanced understanding of these developmental epoch-sensitive exposures and their mediators or moderators will reveal time-sensitive windows for therapeutic interventions that target remediation of the exposure, mediating, or moderating factors. This framework can elucidate the risks of environmental exposures in determining adverse mental health outcomes (Patterson et al. 1989) and may help identify protective factors (e.g., academic competency or sociability) during childhood that predict well-adjusted adult functioning, which can be harnessed during targeted interventions (Rutter 1999).

Environmental Adversities as Exposures

All complex human traits manifesting as personality, cognition, and psychopathology share varying causal contributions from the individual's genome as well as the shared and nonshared environment (Burt 2009; Plomin and Daniels 1987; Polderman et al. 2015). Emerging evidence from large-scale genomic initiatives reveal a finely distributed genetic influence of small effect sizes and low penetrance, spread across thousands of genetic variants (high prevalence), that are contingent on the environment and not specific to any single form of psychopathology (Brainstorm Consortium et al. 2018; Uher and Zwicker 2017). Similarly, several environmental exposures have now emerged that

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reveal low penetrance, high prevalence, and nonspecificity, resulting in ill-defined exposure-disease associations. Given the rapid advances in accurate and comprehensive measurement of variation across the entire genome, there is a pressing need to match similar progress in large-scale capture of potential environmental exposures as well as outcomes (Ioannidis et al. 2009). Concurrent measurement of such massive, large-scale data has the potential to yield novel etiologies and targets for intervention. This raises the following questions: How best can we characterize our environment? How can we improve measurement accuracy to account for the dynamicity, multiplicity, and collinearity of environmental exposures? Yet another challenge is to account for the cross-cultural variability involved in defining and measuring exposures. There have been strong proposals to improve the holistic measurement of environmental exposures within a developmental cascades framework in line with the exposome paradigm (Guloksuz et al. 2018; Wild 2005). When applied within a life-course population neuroscience framework, this will provide dynamic information about the total nongenetic component of psychiatric etiology as well as enable the study of interactions within and between the genome and exposome and lead to expression of the "phenome," the full set of phenotypes of an individual (Houle et al. 2010).

One step in improving the comprehensive and accurate measurement of the environment is to understand the levels at which it acts upon an individual. A developing child is not a mere solitary entity, but a social being that lives in and interacts with the environment (Hinde 1987). It is therefore important to identify the network of interpersonal relationships surrounding a child, as this dynamic network is a critical part of the environment that shapes the child's psychological and biological development. This context of social environment or ecological systems for the developing child ranges from a micro-level milieu of frequent direct interactions (e.g., with family, peers, and at school) to macro-level aspects of their broader milieu (e.g., available resources, infrastructure of their towns and cities, recreational and residential facilities, social support buffers, cultural practices), shaped and regulated by economic, geopolitical, and ethnocultural governing systems (Bronfenbrenner 1996). As depicted in Table 6.2, environmental exposures at micro- or macro-level ecological systems across critical developmental stages can trigger key processes with a potential cascading impact on subsequent development and psychopathology.

Influences of Micro-Level Environment Exposures

Peer–peer, peer–parent, or peer–teacher dyads are important contexts in which interpersonal relationships manifest in developing children. Secure attachment with a significant caregiver in childhood is linked to a reduced engagement in high-risk behaviors, higher prosocial behaviors, and healthy coping styles (Moretti and Peled 2004). In contrast, an ambivalent attachment has been associated with childhood anxiety (Colonnesi et al. 2011). Adverse

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Table 6.2 Environmental exposures during crucial stages of development can trigger processes that compromise mental health. Built environment refers to natural and modified elements of the physical environment. After Uher and Zwicker (2017).

Environment	Domain
Periconceptional	Infections
	Malnutrition
	Environmental toxins
Perinatal	Preterm birth
	Season of birth
	Birth complications
Child developmental	Family
Social	Childcare and parenting
	Adolescence and peers
	Workplace
	Neighborhood
	Community and culture
	Poverty and violence
	Neighborhood amenities: housing, activity and recreational spaces, and measures of community design
Built environment	Lighting, parks, roads, sidewalks
Physical environment	Noise
	Water and air quality, pollutants

experiences encountered at various developmental stages are indeed one of the most compelling determinants of mental health problems throughout the life span (Garner et al. 2012; McLaughlin et al. 2012). Nevertheless, despite these observations, very little is understood about the dose-response relationship, specificity of these adversities to psychopathology outcomes, their mediators, the influence of culture and other moderators, as well as the role of timing paired to critical developmental epochs. Recent studies have begun to answer some of these questions by applying a life-course epidemiological framework. For instance, longitudinal data from the Avon Longitudinal Study of Parents and Children (ALSPAC; n = 7476) were tested for three potential theoretical models of how early childhood adversity (abuse and stress) predicted emotional and behavioral problems (Strengths and Difficulties Questionnaire) at the age of 8 yr. Recency (temporal proximity) and accumulation (cumulative repeated exposures) of childhood adversities predicted psychopathology better than sensitive-period (specific timing of exposure) effects (Dunn et al. 2018). Similarly, analysis of cross-sectional data from the National Comorbidity Survey Replication (Adolescent Supplement) revealed an association between

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exposure to childhood adversity (interpersonal violence) and adolescent psychiatric diagnoses, irrespective of the age at first exposure to violence (Dunn et al. 2017). This suggests that there was no particular sensitive period for the exposure to result in the outcome studied. In contrast, provision of a caregiving environment early (18–24 months of age) in the course of a deprived nurturing environmental exposure (raised from early infancy in institutions in Bucharest) resulted in normalization of the physiological reactivity to stress (cortisol and autonomic functions), thus highlighting the presence of a sensitive period during which the developing stress response system is strongly influenced by environmental inputs (McLaughlin et al. 2015).

The potential effects of global sociocultural variations on the relationship between childhood adversity in the family context and first-onset psychiatric disorders during adulthood revealed a striking similarity in associations across nationalities (21 countries) assessed during the WHO World Mental Health survey. This cross-sectional survey also highlighted the nonspecificity of the relationship between childhood adversity and mental health outcomes (Kessler et al. 2010). When studying the impact of childhood adversity on subsequent psychopathology, it is important to understand the context in which adversity manifests. For a developing child, these include the transactional relationships shared with parents and peers in family and school contexts (Aldridge and McChesney 2018; Darling and Steinberg 1993). Parenting styles (e.g., control) determine cognitive and behavioral outcomes in developing children as a function of "household chaos" (i.e., lack of structure and unpredictability in everyday activities), as demonstrated in longitudinal studies (Kim-Spoon et al. 2017). However, parenting styles and their subsequent determination of child behavior vary according to the culture in which they are manifest. For instance, while Japanese mothers focus on early mastery of emotional maturity and social courtesy in their children, American mothers promote early mastery of verbal competence and self-actualization (Bornstein 2013; Caudill 1973). Similarly, authoritative parenting styles in European American and African American children leads to positive mental health outcomes (Brody et al. 2008; Damon 1989). The peer environment is again shaped by the transactional relationship of the developing child with friends and manifests most commonly in the school context. Prospective studies reveal that adolescent friendship, but not family support, determines subsequent resilient psychosocial functioning one year later (van Harmelen et al. 2017). Similarly, a positive school climate determines better prosocial behaviors one year later in Colombian adolescents (Luengo Kanacri et al. 2017).

An additional approach to improve the measurement of environmental exposures is to identify distinct dimensions of the adverse experience and trace the differential brain pathways through which its outcomes are mediated. Drawing from animal experiments, one approach proposes that adverse experiences within the immediate family can have two dimensions: threat (e.g., physical, sexual abuse, domestic violence) and deprivation (e.g., lack of cognitive,

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social input). Adversities within the realm of threat may alter neural circuits underlying fear learning (e.g., amygdala and hippocampus), whereas those associated with deprivation may act via effects on the association cortices responsible for executive and social cognition abilities (e.g., prefrontal, inferior parietal, and superior temporal cortices) (Sheridan and McLaughlin 2014). A third dimension is that of rejection. Adolescents with adverse peer interactions (e.g., repeated rejections by peers) demonstrate exaggerated activity in the dorsal anterior cingulate, during a social exclusion (Cyberball) task, when compared to adolescents who do not experience adverse peer interactions (Will et al. 2016). These exaggerated neural responses are likely to mediate depression and social anxiety symptoms (Rudolph et al. 2016).

In summary, parenting and school climate provide a rich opportunity to study the influence of environmental exposures on psychopathology via engagement of specific neural systems. They also offer significant opportunities to intervene and remediate the exposures and their moderators early during the course of development (Aldridge and McChesney 2018; Ryan et al. 2017).

Influences of Micro-Level Environment Exposures (Virtual or Online)

To study these processes, we must address real-world as well as virtual or online interpersonal relationships. To date, however, the impact of this latter on emerging psychopathology is poorly understood. While some longitudinal studies report a strong negative relationship between virtual or online activities and adolescent mental health (Kim 2017), others hint at beneficial effects (Adachi and Willoughby 2013). Clearly, there is a gap in our understanding of how individual-, family-, and social-level factors influence the relationship between online social behaviors and psychological health. Fundamental questions are now beginning to be addressed, such as process-level differences in social interactions performed in the real and virtual worlds, and their impact on cognitive and behavioral functioning. For instance, the online environment permits interactions with audiences that are practically limitless by virtue of their sheer reach across spatial, temporal, and social distances (McFarland and Ployhart 2015). In contrast, real-world social interactions require moment-to-moment appraisals of social cues, which guide reciprocity during face-to-face interactions under certain sociocultural environmental constraints (Vlahovic et al. 2012). With increasing social media use, it is critical to examine this behavior as a potential psychopathological manifestation of an underlying diathesis (Bányai et al. 2017) as well as a potential environmental exposure that can have long-range effects on neural networks and behavior. The mechanistic basis of such positive or negative impact is also poorly understood and could operate in different ways:

- At a biological level, where frequency of use sensitizes specific social cognition and reward pathways (Meshi et al. 2015).

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- At a psychological level, where newer anticipatory anxieties are an effect of maladaptive learning processes triggered by the immediacy and high expectancies of responses between peers.
- At a social level, where there is a false sense of secure virtual relationships at the cost of maintaining real relationships with peers and parents, as well as a negative affect secondary to having a constant external template of comparison and revising expectations based on fragile online peer relationships.

In contrast, online social networking, associated with psychological well-being, is perhaps mediated by a sense of greater "bridging" social capital. It enables "loose" connections between individuals, who may provide useful information or new perspectives to each other (Ellison et al. 2007).

Influences of Macro-Level Environment Exposures

Global variations in macro-level exposure to social phenomena can potentially elucidate the increasing rates of precise behavioral outcomes within specific cultural and geographical populations. Such complex social phenomena, with diverse underlying processes, include (but are not restricted to) migration (Cantor-Graae and Selten 2005), social and economic disparities (Weich and Lewis 1998), and population density (Colodro-Conde et al. 2018; Schweitzer and Su 1977). The concept of urbanization—a nonlinear process of population replacement or the global-scale reorientation of the social and environmental landscape across continents that results from population migration and natural demographic growth (Knox and McCarthy 2005)—encompasses these macro-level social phenomena and has been found to have varying associations with mental health morbidity (Dekker et al. 2008; Krabbendam 2005). These variations are likely to be a function of (a) the mental health outcome (e.g., psychotic vs. other disorders) being studied (Schifano 2008; Vassos et al. 2012), (b) the sociocultural variations and economic context (e.g., developed vs. developing societies) of the population being examined (de Vries et al. 2018; Paksarian et al. 2018; Wang et al. 2018), (c) the nature of urban exposure, such as green spaces, exposure to pollutants/toxins, built environment, dietary variations, population density, social capital (Bratman et al. 2015; Galea 2005; Wang et al. 2018), and (d) the study designs being implemented that determine the timing of exposure (Dekker et al. 2008; Paksarian et al. 2018). Moreover, specific aspects inherent to urban living can have disorder-specific associations, as in eating disorders, where a greater incidence of bulimia nervosa (but not anorexia) has been consistently tied to increased urbanization (Hoek et al. 1995; Van Son et al. 2006).

While urban living might confer potential causative influences on adverse mental health outcomes in a developing child, it also provides important benefits: greater employment and education opportunities, improved health-related

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knowledge, and better access to health-care facilities (Chen et al. 2017; Liu et al. 1999). Data are lacking, however, to determine if urban living yields greater overall health benefits or risks. It is thought that the strongest moderator of the effects of urban living on health outcomes is the economic disparity inherent to the urbanization process, which favors the rich over the poor (Dye 2008). Nevertheless, better observational data are required to understand risk processes across the life course, since we currently do not have definitive information about specific risk processes where we can intervene. One way forward is to have comprehensive cross-cutting quantification of environmental exposures based on existing risk ratios of specific exposures, as performed via polyenviromic risk scores (similar to the polygenic risk scores in quantifying genetic risk); this is likely to inform us about cumulative proportions of variance explained in the desired outcomes (Padmanabhan et al. 2017). In parallel, a more nuanced analysis of socially distributed exposures by age is needed to disentangle the complex interdependent effects of culture, ethnicity, and social class on specific environmental exposures and their predicted outcomes unique to specific developmental epochs; this will likely provide information about sensitive periods that may be targeted by appropriate interventions. Functional and morphometric brain changes (e.g., in the perigenual anterior cingulate and lateral prefrontal cortices), which mediate the impact of urban living and upbringing on the risk for youth mental disorders across the developmental cascades (Haddad et al. 2015), highlight the shared neurobiological mediators of micro- and macro-level environmental exposures. The translational utility of understanding such macro-level risk factors of youth mental health disorders is also illustrated in a novel prediction model that is applicable at the population level. Recently used to predict the annual number of new cases of psychotic disorders based on age, sex, ethnicity, population density, and socioeconomic deprivation, the PsyMaptic tool has potential in guiding us toward the appropriate allocation of resources (Kirkbride 2015).

Mediators and Moderators of Exposure–Outcome Interactions

A host of mediating factors can potentially drive the impact of environmental exposures on behavioral outcomes. These could be biological substrates that are engaged by environmental exposures in the process of generating adverse mental health outcomes: brain structure, function, and maturation; the endocrinological flux triggered by the hypothalamic-pituitary-gonadal/adrenal systems underlying the hormonal changes that drive puberty; immune and metabolic changes; the molecular-level gene expression changes and epigenetic factors that shape environment-related changes during sensitive periods of development. Yet, there are vast gaps in knowledge about this confluence of biological and environmental systems or "biological embedding," best understood as a process of experience getting "under the skin" and producing stable alterations

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in those biological and developmental processes that determine subsequent health and development (Hertzman 1999, 2012). The biological embedding of environmental exposures can provide us with a critical and mechanistic understanding about the pathogenesis of youth mental disorders. This, in turn, can provide targets that inform policy-making and preventive strategies and guide early and sustained interventions over the life course. Early life exposures are likely to be preferentially embedded due to a preponderance of sensitive developmental epochs that result in heightened brain plasticity (Berens et al. 2017).

Epigenetic alterations involve stable modifications of gene expression through attachment of chemical residues (e.g., methyl groups) to DNA or histones. These alterations may represent a biological vestige of early life environmental exposures, potentially transforming gene expression and thus, in principle, changing individual development trajectories. Emerging evidence suggests developmental epoch (e.g., infancy vs. preschool period) and gender-sensitive changes in DNA methylation of adolescents are triggered by maternal and paternal stress (Essex et al. 2013). Interestingly, epigenetic variations of neurodevelopmental genes at birth mediated the effects of prenatal maternal tobacco smoking on subsequent substance use behaviors during adolescence in a sample of 244 youth from the ALSPAC cohort (Cecil et al. 2016). These gene expression changes are likely to impact psychopathology via their effects on neural systems, as demonstrated in animal experiments (Jung et al. 2016). Novel efforts are underway to examine the impact of childhood adversity on behavioral outcomes and their epigenetic and neuroimaging mediators. One study on children and their families from an urban slum of Bangladesh reports preliminary data to suggest that adversity impacts neural systems, as measured using functional infrared spectroscopy and electroencephalography (Nelson 2017)—an impact seen at 36 months but not as early as 6 months of age. This suggests a potential window of opportunity for early interventions and reflects the benefits of intervening early (i.e., before the age of 2 yr) in deprived children (McLaughlin et al. 2015) highlighted earlier in this chapter.

Another promising model that can be examined using this approach is to examine the effects of urbanization on adverse mental and physical health outcomes as a function of exposure to artificial nighttime light (Cho et al. 2015). At an individual level, excessive artificial nighttime light exposure can trigger (a) circadian phase disruptions (Cho et al. 2015), (b) altered movement and activity patterns (Kurvers and Holker 2015), and (c) disruption of mood regulatory brain regions (e.g., medial amygdala and lateral habenula) via direct (stimulation of photosensitive retinal ganglion cells) and indirect (altered melatonin secretion and gene expression) effects on cortical physiology (Bedrosian and Nelson 2017). At a social level, this affects the frequency and duration of social interactions as well as the formation, maintenance, and size of social networks and social communication patterns (Kurvers and Holker 2015). In turn, this can have reciprocal influences on the individual's social brain, thus potentially increasing the risk for mood disorders (Bedrosian and

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Nelson 2017). This hypothesis is partly supported by observations of a higher (dose-dependent) prevalence of major depression in individuals who work night shifts, which predisposes the individual to greater exposure to artificial night light as well as disturbed circadian rhythms (Scott et al. 1997). Animal studies reveal a more nuanced understanding: a wavelength-dependent effect of nighttime blue-light is mediated by alterations in circadian rhythm (Bedrosian et al. 2013), and directly effects depressive behaviors via stimulation of the intrinsically photosensitive retinal ganglion cells, independent of circadian rhythms and sleep architecture (LeGates et al. 2012). If the latter is true for humans, then redesigning our nighttime light environment using a different wavelength (e.g., red light) could be an effective preventive strategy (Bedrosian and Nelson 2013).

The process of biological embedding socioenvironmental exposures must also account for changes in brain architecture throughout specific developmental epochs (e.g., juvenility and puberty). We do not yet understand if, and how, environmental risks operate differently before, during, and after the pubertal transition, information that is crucial for development of interventions across this period. Adult health outcomes in later life (e.g., general mortality, obesity, type 2 diabetes mellitus, cardiovascular disease, low bone mineral density, and major depression) have been linked to early puberty (Charalampopoulos et al. 2014; Day et al. 2015). In late childhood and early adolescence, more advanced pubertal stage has been associated (independently of age and school grade) with depression, anxiety, eating disorders in females, pain syndromes, self-harm, and substance use; this suggests that puberty marks the point of transition in risk for many early-onset mental disorders (Patton and Viner 2007). There is interest in knowing whether early pubertal timing may be associated with higher rates of emotional and behavioral problems, particularly in girls (Copeland et al. 2010). Puberty can be considered a sensitive phase, especially for LGBTQ (lesbian, gay, bisexual, transgender, queer) children and adolescents for whom the pubertal transition presents a higher risk for psychopathology. It appears to be a period when socioemotional strategies adapt to the prevailing social environment. Emerging research suggests that pubertal development is a sensitive phase and that interventions during this stage may have the ability to change the trajectories of health risks, and perhaps also mental disorders (Del Giudice et al. 2009). More research is needed, however, to characterize juvenility and measure the social environment during this life phase, as pubertal transition might provide a second chance for social and emotional development in children who have suffered early life psychopathology. Timely, effective interventions could modify the developmental trajectory and mitigate adverse behavioral outcomes.

Additional factors to consider include gender differences, the prevailing culture, dynamicity of social roles with development, and the vicarious transferability of behavior based on social learning and modeling. The latter includes positive (aspirations, self-identity, coping with adversity) as well as

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negative (substance abuse, restrictive eating, self-harm, and maladaptive coping) behaviors that can potentially be transferred, peer–peer, parent–peer, and teacher–peer. While gender norms that determine peer–peer affiliations are not well defined, the type and impact of negative interactions (e.g., bullying) is different in boys (shorter lasting physical bullying) than it is in girls (longer lasting social bullying) (Björkqvist et al. 1992; Carrera Fernández et al. 2013; Iossi Silva et al. 2013). The translation of these effects in the context of cyberbullying is poorly characterized (Wolke and Lereya 2015).

Cultural processes—the symbolic apparatus of meaning-making, representation, and transmission—are dynamic and grounded in local contexts; they diverge significantly from the experiences of other groups and result in the cultivation of collective and individual identity (Kleinman 1999; Kleinman and Benson 2006). Culture also influences how risk factors interact with social support and protective psychological factors that determine youth mental health outcomes (Kleinman 2004). Directly or indirectly, culture may even provide unique milieus for gene expression and physiological reactions that are reflected in regional secular trends of youth mental health disorders and their behavioral and pathogenic precursors (Thirthalli and Jain 2009). Cultural norms and expectations may also have transformative influences on the enactment of social roles in developing children and adolescents. For instance, cultural norms that define social responses to puberty shape the rate of social role transition (e.g., early marriages and early parenthood in developing countries) and hence impact psychological well-being. Cultural differences may also exist in the dynamics of peer–parent relationships (e.g., degree of affection being displayed, parenting style). Cultural processes and contexts also influence migration, especially from underdeveloped and developing to developed societies (Ali 2007; Caira 2008). Migration and the associated cultural bereavement and cultural identity confusion are significant risk factors for a broad range of mental health outcomes (Bhugra and Becker 2005). Cultural contexts are therefore important and complex dynamic moderators of environmental exposures on mental health outcomes, from a risk as well as a resilience perspective. There is, in fact, scant empirical data on the impact of different child-rearing beliefs and practices that are culturally grounded on early brain development. There is also limited data to determine which interventions have a significant impact on child well-being across a variety of political and cultural contexts, thus limiting policy reforms (Shonkoff 2010).

In the process of determining appropriate mediators and moderators of the effects of environmental exposures on disease outcomes, it is critical to acknowledge that these relationships are by no means unidirectional. In fact, there is a dynamic fluid interchange across exposures, mediators, moderators and outcomes depending on one's genetic endowment and where in the developmental cascade one is. At the macrolevel, secular time trends in global variations of exposures, mediating influences, and outcomes should be studied as moderating factors which are likely to shed light on increasing rates

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of particular behavioral outcomes within specific cultural and geographical populations. The changing megatrends in adolescent development, nutrition, inequality, economic globalization, migration, and urbanization are examples of such processes in need of future research.

Social Cognition as an Exemplar of Key Processes

Social cognition is the application of mental operations in social interactions (Brothers 1990). This broadly includes domains of mentalizing or theory of mind, emotion processing, social cue identification, and attributional styles (Green et al. 2008) that subserve a whole range of complex higher-order cognitive abilities (e.g., perspective taking, deception detection, empathy, trust). Illustrations from clinical vignettes (Penn et al. 2008) and extensive factor analytical studies demonstrate that the latent variable which best supports social cognitive processing is one related to (but significantly differs from) general cognitive processes (e.g., attention, concentration, and memory), which are utilized in both nonsocial (e.g., remembering a shopping list) and social (e.g., responding to an arrogant colleague) situations; further, it is relatively affect neutral (Mehta et al. 2013). In contrast, social cognition represents the interface between emotional and cognitive processing; it has an intersubjective quality, requiring reflective (metacognitive) and social inferential abilities (Dimaggio et al. 2008). The brain networks that support these diverse streams of cognition and behavior are also, understandably, overlapping yet distinct. The social brain network overlaps the mentalizing network (medial prefrontal and temporoparietal cortex), the affect-sharing and motor-resonance networks (premotor, inferior frontal, inferior parietal, and insular cortices), as well as the social cue detection network (fusiform gyrus, amygdala, and superior temporal gyrus) (Green et al. 2015).

Social cognitive processes follow a typical ontogeny during development, are key elements required for successful social functioning, and map on to the development of distinct structural and functional brain networks (Kilford et al. 2016). The development of these social brain networks happens distinctly from the development of motivational affective and cognitive control processes. Since the developing child socially transacts with most of his/her environment, there is a constant experience-based reciprocal shaping of the processes involved in this triangulation of social cognition and behaviors, their underlying social brain network structure and function, and the social environment (family, school, society). Social brain network structure (e.g., amygdala volumes) and function (e.g., intrinsic amygdala-cortical connectivity) are found to relate to social network size as measured using the social network index (Bickart et al. 2011, 2012). In addition, there is a bidirectional, probably causal, relationship between mental disorders and social network size in adolescents (Hill et al. 2015; Rosenquist et al. 2011). General intelligence, the prevailing school

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climate, cultural influences, environmental stimulation and enrichment, recreational opportunities, pubertal stage, parenting, mental ill-health in parents, and chronological age can all moderate how environmental exposures engage the social brain in driving specific social-behavioral outcomes during adolescence. The successful transition to adulthood requires a rapid refinement and integration of these processes. In the transition of childhood to adolescence types of behavior, dynamic interactions (e.g., peer influence, sensitivity to social exclusion) take place between these systems. The environmental factors that can alter these brain and cognitive processes include adverse social experiences (in the context of family and school transitions) as well as migration and urbanization, which bring about critical social role transitions for developing youth. These environmental factors, as discussed earlier, are not uniform; they vary across cultures.

Culture also has a substantial scaffolding impact on shaping social brain processes and their behavioral outcomes. For instance, perceiving and expressing emotions seem to be governed by prevailing cultural folk schemata (Uchida and Kitayama 2009); emotion recognition abilities are better between members of the same (rather than different) national, ethnic, or regional group (Elfenbein 2002). Developmental studies have demonstrated that while there is synchrony in the age at onset of social cognition abilities across cultures (Callaghan et al. 2005), culture-specific principles strongly influence the subsequent shaping of these abilities across the life span (Lillard 1998). Developmental plasticity is responsible for this, mediated through immediate and delayed probabilistic-epigenetic processes, with an emphasis on bidirectional interactions among genes, neuronal activity, behavior, and environment across developmental epochs and generations (Li 2003). Indeed, neuroimaging studies demonstrate how culture influences differential neural responses in the amygdala to fearful faces and gaze direction in the processing of fear (Adams et al. 2010; Chiao et al. 2008). Neural correlates of theory of mind abilities may also differ depending upon cultural background (Kobayashi et al. 2007). Some researchers propose different levels of processing socially relevant information. The immediate responses of premotor mirror neurons may be independent of culture, but the inferential responses of the medial prefrontal cortex are culture dependent (Vogeley and Roepstorff 2009).

In summary, social cognition and social connectedness (which themselves are influenced by genetic, epigenetic, brain maturational, and sociocultural factors) foster resilience or amplify the risk (from multilevel social environmental exposures) for mental health outcomes during adolescence (Lamblin et al. 2017). Within the developmental cascades framework, social cognition includes processes that (a) are related to specific social brain networks, (b) drive an individual's multilevel social interactions that form a major component of the environment and (c) are mediated by the developmental stage, gender, and culture. These key processes can be studied in laboratory as well as within population-level epidemiological settings, thus enabling large-scale

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measurements and identification of specific intervention targets to be delivered at specific points in time.

Measurements and Study Designs

As we pursue the expansion of our knowledge of these multilevel contexts in which the environment can shape emerging psychopathology, we face significant gaps in defining and measuring the exposures and outcomes, especially at a larger scale (comprehensive coverage at a population level of a broad range of exposures/outcomes), with sufficient accuracy and at a critically dense time frequency. How does one measure, for instance, the robustness of a social network? A healthy social network could be defined by the *number* of individuals (MacCarron et al. 2016) that are part of one's social network (e.g., the Dunbar number or layers) or by a "happy medium" that characterizes the peer–peer interaction quality as assessed using ethnographic methods (Morgan-Trimmer and Wood 2016). Modeling of social networks in the real and virtual worlds by implementing *graph theory approaches*, traditionally used by social scientists (Wasserman and Faust 1994), is already being implemented in health sciences (Hogan et al. 2016). When used in conjunction with digital technology, such a framework promises the acquisition of important social engagement data, at a much larger scale and better frequency than can be collected using traditional assessments (Zhang et al. 2015). *Experience sampling methodology* (ESM), or ecological momentary assessment, is a structured self-report diary technique used to assess moment-to-moment variation in cognition, emotion, and behavior in the real world and in real time, outside the laboratory (Myin-Germeys et al. 2018; Shiffman 2009). ESM typically requires participants to complete a momentary assessment questionnaire several times a day over a number of days. Given its superior veridicality, ESM lends itself to more accurate investigations of the effects of social contexts (e.g., family, peers, school, work) on individuals and their interaction with these contexts at the micro level. The informed pairing of ESM with (a) *digital data streams* (Giles 2012; Insel 2017), mapping individual and group behavior via sensor, keyboard, location, voice, and speech data from smartphones, and (b) *novel artificial intelligence guided language and behavior processing algorithms* (Bedi et al. 2015) can provide a template for acquiring ecologically accurate social behavioral data at unprecedented scales, measurement densities, and levels of detail. Another method of improving accuracy in the measurements is to examine collaborative behaviors under specific conditions in the laboratory by focusing on dyadic stranger interactions (Weinstein et al. 2010); this permits process-related outcomes not influenced by past

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experience to be identified, independent of social interaction quality (partner closeness and responsiveness). These innovative but more definitive approaches can be further modified for application in large-sample population studies and combined with other deep phenotyping assessments in longitudinal designs.

Holistic capture of puberty during adolescence presents another gap in contemporary knowledge and measurement practice. Existing studies have done little to examine the speed of transition through puberty or the relationships between the different elements in pubertal development (Dorn 2015). Moving beyond the timing of pubertal completion and focusing on the critical pubertal transition stages of adrenal and gonadal maturation, as well as the pubertal growth spurt, are likely to yield clues to sensitive periods during which environmental exposures can manifest as adaptive or maladaptive outcomes.

Similarly, recent studies have begun to better characterize and define components of urban living that play a role in influencing mental health. Green spaces, artificial nighttime light, and built space, for example, can now be accurately mapped using geographical information systems. An illustration of its application is the demonstration that exposure to natural environments (e.g., greenery) might have a role in reducing suicide mortality (Helbich et al. 2018). A related novel method is to use satellite imagery in conjunction with convolutional neural networks, a deep learning technique used to extract features of the built environment and examine their influence on health outcomes, as was carried out for obesity prevalence rates (Maharana and Nsoesie 2018). These methods can be similarly applied to mental health outcomes across massive population samples and geographical boundaries, and offers the potential to guide region-specific environmental modification policies which, in turn, could affect mental health outcomes.

A combination of dense time series assessments at critically defined intervals (sufficient time for effects of exposure to manifest) throughout the developmental trajectory will reveal necessary data which can then be modeled using complex computational approaches. To harness the naturalistic course of adolescent development, study designs need to be both flexible and creative to yield sufficient data points and data depth in studying these influences. To help minimize costs and increase the yield of potentially new information needed to disentangle the complexities of developmental cascades across large population-based samples, we recommended (a) using samples from ongoing prospective birth-cohort studies and (b) performing nested randomized trials that incorporate some of the collection methods described here (e.g., ESM and digital phenotyping) within a collaborative framework. This will certainly help us overcome the limited length and breadth of measurement and shed more light on how early developmental factors relate to child psychopathology.

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Using Newer Computational Approaches in Modeling Complex Systems

Given the tremendous amount of information that is likely to emerge from an in-depth acquisition of genomic, environmental, and brain connectomics data, parallel advances in statistical methods and data science techniques are imperative. In our efforts to tease out the effects of environmental exposures and behavioral health outcomes relevant to the developmental cascading context, we are likely to encounter not only direct and indirect linear relationships that can be understood using mediation models, but also more complex *nonlinear dynamic systems*, which encompass a more holistic rather than reductionist approach without sacrificing scientific and mathematical rigor. These models take into account the nonproportional exposure-outcome relationship, whereby "minimal" initial variations in exposure may produce "massive" unanticipated outcomes later, thereby being amenable to explore the dynamic environmental exposures on youth behavioral outcomes within the developmental cascading framework (Crutchfield et al. 1986). One important unanswered question concerns the timing of risk exposures in the development of behavioral and mental health problems. One possibility is that exposure to adversity in critical or sensitive periods is more likely to be followed by disorder. Alternatively, cumulative exposure over a longer period is the major determinant of risk. The adoption of sophisticated modeling techniques paired with appropriate measurements and study designs should provide more definitive answers to a question that is crucially important in designing prevention strategies.

Several efforts are already underway using advanced computational and analytical tools to identify hidden patterns in physiological (Drysdale et al. 2017), behavioral, phenomenological (Bedi et al. 2015; Clementz et al. 2016), real-world (Lee 2008), and virtual-world (Lazer et al. 2009) interpersonal exchanges, underwritten by both behavioral and neural responses and a broad range of macro-level environmental exposures (Maharana and Nsoesie 2018). Once identified, generative models of mental health outcomes can be tested by integrating these interactive levels of description (Huys et al. 2016; Stephan and Mathys 2014). Such models, when examined in prospective studies with dense time series data acquisitions, help to capture more accurately the relations between latent factors and observations, thereby facilitating theory building and empirical testing. This, in turn, can enable a more nuanced mechanistic interpretation of the data, ultimately permitting the identification of patient-specific combinations of various model parameters and model evidences for genetic and environmental disease mechanisms, as well as their mediators and moderators (Reiter et al. 2017).

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Interventions

Despite the importance of the early childhood and adolescent periods as watershed developmental epochs in the manifestation of major psychiatric disorders of young adulthood, the availability of preventive and treatment services during these developmental phases is limited (Bailey and Dolan 2004). Based on the developmental cascades framework, strategies aimed at primary prevention and early intervention can be targeted at specific timescales (sensitive developmental epochs) and at specific levels of exposure, mediation, or moderation.

At the developmental timescale level, a valid example of a time-sensitive intervention that can inform potential translations to the field of mental health is borrowed from studies in youth to prevent polycystic ovarian syndrome—a complex endocrinological disorder of genetic origins prevalent in ~7% of women of reproductive age (Dunaif 2012) that has significant associations with anxiety and depressive disorders (Blay et al. 2016) —as well as neurodevelopmental disorders such as autism spectrum syndrome (Cesta et al. 2016; Cherskov et al. 2018). It has been demonstrated that if girls vulnerable to develop polycystic ovarian syndrome (low birth weight and precocious puberty) were administered metformin early (8–12 yr) as opposed to later (13–14 yr) in life, a distinct change in their phenotypes (e.g., taller, low central fat) occurred at age 15 yr. In addition, the early-treated girls had a two- to eightfold lower risk of developing polycystic ovarian syndrome than later-treated girls (Ibáñez et al. 2011). These are certainly encouraging examples of time-sensitive interventions that can potentially alter the developmental cascade.

At the micro, social, and environmental level, schools are ideal for intervening across diverse developmental timescales, as large populations of children can be targeted who spend significant amounts of time in a controlled setting, learning as well as interacting with peers and teachers. Primary or secondary prevention school-based interventions also offer scalability across regions and sustainability over time if found to be effective. HealthWise is one such comprehensive life skills program. Developed for use in South Africa to encourage positive free-time behavior and reduce the prevalence of unhealthy or risky behaviors (Wegner et al. 2007), HealthWise has shown promise in preventing substance use in school children (Smith et al. 2008). In this context, it is also important to consider who provides the intervention. Although teachers may be an ideal choice because of their availability in schools, lay counselor-guided interventions may have a more far-reaching impact, due to responsibility and time constraints in both professions. This was recently demonstrated in a recent pilot skills training intervention in the state of Bihar, India (Shinde et al. 2017). Given the impact of peer group influences on an individual during early adolescence (Sawyer et al. 2012), peer-driven interventions need to be explored for acceptability and effectiveness in promoting youth mental health.

One youth-friendly way to disseminate an intervention on a large scale to targeted populations is through the use of digital technology and online social

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networks (Biagianti et al. 2017). Both can complement existing youth mental health support systems and, if found to be feasible and effective, can be used as separate interventions. Apart from providing platforms for educative discourse, digital technologies can integrate individuals into online networks to increase levels of perceived support and belonging. It is crucial that general practitioners and other primary care workers be trained to not simply recognize mental and substance use disorders, but to deliver simple treatments as well, including supportive counseling, cognitive behavioral therapy, and psychotropic medications (Patel et al. 2007). Digital technology can facilitate this through skill development modules and "on-consultation" training provided through collaborative video consultation modules (Manjunatha et al. 2018).

Conclusion

Understanding how the environment interacts with genetically shaped human behavior along the developmental cascades over time, systems, and levels in the presence of several moderating and mediating mechanisms, to determine precursor symptoms that lead to severe mental illness in later life, requires a complex framework. Several micro- and macro-level influences—ranging from interpersonal relationships with parents, peers, and teachers to the rapidly changing social, economic, political, and environmental landscapes of our larger environment (e.g., urbanization)—have a dynamic interplay within the prevailing cultural and developmental (e.g., early brain development, puberty) contexts. This can lead to possible changes in epigenetic regulation of gene expression, neuronal circuits, and, through an iterative process, the generation of protective and risk states that determine mental health later in life. Here, we have highlighted several challenges and gaps that exist in piecing together this complex jigsaw puzzle and offered ways to address them:

- Definitions and measurements of key dynamic processes need to be improved.
- Study designs require refinement.
- Novel computational approaches need to be implemented to enable the identification of hidden (perhaps nonlinear) patterns across various levels of analyses, and to model these patterns more accurately and efficiently.

Advances in the field of genomic sequencing and gene expression studies, nuanced and comprehensive characterization of the *envirome*, untangling of the structural and functional brain connectome, and the applications of novel computational tools that integrate clinical, social, and basic neurosciences suggest that we are at the threshold of being able to make the leap toward creating specific maps of symptoms, vulnerability, and resilience with respect to environmental risks. Hence, we should soon have an outline of sensitive phases

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during development where targeted interventions can work. This confluence of multidisciplinary scientific questioning of human development has implications for our ability to enhance the life prospects of children and to strengthen the social, intellectual and economic fabric of society.

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