Commentary

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Introduction to the Special Issue on the Exposome—Understanding Environmental Impacts on Brain Development and Risk for Psychopathology

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There is robust evidence that a host of environmental features influence neurobiological factors that contribute to risk for mental health challenges. This compelling body of evidence indicates that children's experience of early social adversity in the form of lower family socioeconomic status (SES) in childhood is associated with a greater risk of impairment in behavioral (emotional and cognitive) development—a key risk factor for childhood psychopathology—as well as increased rates of childhood mental health challenges (1,2). In addition, exposure to social adversity early in life is related to a wide range of related disruptions in brain development, including reduced cortical and subcortical gray matter development, reduced white mater volume, and disruptions in both functional and structural connectivity, including altered white matter development and myelination (3–11). It has been hypothesized that these disruptions in brain development are part of the pathway mediating the relationship between early experience of poverty and subsequent risk for childhood psychopathology. Much of this research has focused on exposures centered in the home, such as adverse childhood experiences, family SES, abuse, and trauma. These are all highly important, but it is also important to consider additional "exposures" both inside and outside of the home, including toxins, air pollution, and neighborhood-level factors, such as poverty, crime, and greenspace, as well as the mechanisms or pathways by which such exposures contribute to mental health. This special issue of *Biological Psychiatry: Global Open Science* focuses on exposures to factors that might impact healthy child development, the full range of which is often referred to as the exposome. Such factors that may occur outside the home include environmental toxins and pollution (though children can also be exposed to toxins in the home), urbanicity and its correlates (greenspace), and neighborhood levels of poverty (over and above household income) and crime.

This special issue contains reviews/thought pieces and empirical pieces that help frame the broader literature on the exposome and its relationship to mental health challenges. A central component of the exposome is neighborhood SES, or what is often referred to as neighborhood disadvantage. It is critical to consider neighborhood SES factors separately from family SES, as they can be dissociable, especially when structural racism and classism reduce mobility of families based on their individual SES. Neighborhood disadvantage is often assessed using a measure called the Area Deprivation Index (ADI) (12) at the census block level, derived from 17 census variables that indicate SES attributes of that census block (e.g., median family income, percent of households living below the poverty line). In this special issue, Huggins *et al.* (13) show that higher ADI, even when controlling for individual family SES, was associated with less amygdala activation to negatively valenced pictures in school-age and early adolescent children. These data suggest that neighborhood levels of disadvantage may influence how children process potentially threatening information. Relatedly, Miller *et al.* (14) show that higher ADI was associated with reduced left hemisphere cortical thickness in adolescents even when controlling for family SES. In turn, reduced cortical thickness was associated with greater depression severity in adolescents. Together, these studies add to the literature demonstrating that neighborhood SES can relate to brain structure and function and the risk for mental health challenges independent of family-level SES. Of course, showing that neighborhood SES relates to brain development and mental health risk raises the question of the mechanisms by which this influence operates. There are likely many factors associated with lower neighborhood SES, including, as discussed below, exposures to toxins and features related to urbanicity. Intriguingly, Tomas *et al.* (15) illustrate the possibility that neighborhood SES may impact how people respond to predictability versus uncertainty, showing that brain responses to predictable versus unpredictable cues varied as a function of ADI among individuals with traumatic brain injuries. Further, Chat *et al.* (16) provide evidence that neighborhood features may moderate other factors associated with risk for mental illness. Specifically, Chat *et al.* (16) show that adolescents living in neighborhoods with higher crime rates demonstrate stronger relationships between inflammatory cytokines (interleukin 6 in particular) and brain activation in the nucleus accumbens to experiences of being socially accepted. Together, the Tomas *et al.* (15) and Chat *et al.* (16) studies suggest that experiences of living in neighborhoods with lower SES or higher crime rates may influence an individual's psychological processing in ways that could in theory mediate risk for a range of mental health challenges.

Barzilay *et al.* (17) broaden the perspective on environmental factors in relationship to mental health by providing a review of the exposome and the pathway to psychosis. This review and thought piece illustrates the many ways in which a variety of exposures, including living in urban environments, exposures to discrimination and other stressors that accompany having a minoritized status, as well as other forms of trauma and adversity, contribute to risk for psychosis. Using

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psychosis as an example is particularly compelling, as it is a form of mental illness that many people assume has strong or even primarily genetic origins. However, Barzilay *et al.* (17) make the strong case for the importance of early exposures in the genesis of risk for psychosis. Further, they point out the highly transdiagnostic nature of this risk, in that greater adversity in exposure to environmental factors increases risk for many forms of mental illness, raising important questions about both the shared components of the exposure that more generally increase risk for mental illness, and those factors that might be more specific to particular forms of mental illness. This review is accompanied by an empirical article by Pries *et al.* (18) using data from the Adolescent Brain Cognitive Development Study to document broad relationships of most features of the exposome including neighborhood disadvantage with the "p factor," the general psychopathology factor. Further, psychotic-like experiences in adolescents were particularly strongly associated with household adversity, pregnancy and birth complications, and day-to-day experiences including school-related factors. Neighborhood disadvantage was not significantly associated with psychotic-like experiences, but the effect was trend level and similar in magnitude to pregnancy/birth complications.

Tran *et al.* (19) provide a systematic review of the relationship between greenspace exposure and the risk for mental health challenges, as well as potential interactions with other features associated with living in an urban environment, such as population density or pollution. In this important review, Tran *et al.* (19) show that greater exposure to greenspace was in general associated with less severe rates of psychopathology of many forms, including attention-deficit/hyperactivity disorder, depression, suicidal ideation, and psychosis. A critical issue in this greenspace literature is the degree to which such effects might be a proxy for other features of more urban environments that have also been associated with higher rates of psychopathology, such as population density and pollution, (20,21), or even ways that these features might interact with greenspace. At this point, the literature is mixed, with few studies examining interactions, and variable findings in terms of whether greenspace remains associated with risk for mental health challenges when accounting for urbanicity-related features. This is clearly an area with a great need for future research, including potentially more intervention-type studies and longitudinal prospective studies that could better address aspects of causality.

Cardenas-Iniguez *et al.* (22) provide a thought-provoking review on the role on neurotoxicants in disrupted brain development and the risk pathway for mental health challenges. All too often, individuals living in lower SES areas are exposed to a range of toxins in the environment that might impact the healthy development of cognitive, affective, and socioemotional skills, which could put individuals at risk for developing psychopathology. While there are many such toxins, Cardenas-Iniguez *et al.* (22) focus on 3 major categories with the most empirical evidence of links to brain development and mental health: lead, outdoor particulate matter pollution, and endocrine-disrupting chemicals (e.g., phthalates). While all 3 of these categories of toxins may have different mechanistic pathways of impacting the brain, they do all seem to converge on a range of effects on brain development, including relations to both gray and white matter development. Further, all 3 have been associated with an increased risk for mental health challenges, including increased rates of attention-deficit/hyperactivity disorder in children associated with all 3 types of toxins, increased rates of anxiety, depression, and psychosis associated with pollution, and increased rates of anxiety and depression associated with endocrine-disrupting chemicals.

This review on neurotoxins is accompanied by several empirical pieces further documenting the links between toxin exposure and risk for psychopathology. Margolis *et al.* (23) show that exposure to polycyclic aromatic hydrocarbons, a form of air pollution, during pregnancy interacted with maternal experience of psychosocial distress to predict hippocampal brain volume. Examining this relationship is critical given the known role of the hippocampus in stress responsivity, memory, and special processing function, with disruptions in hippocampal structure and function linked to risk for depression, anxiety, and psychosis (24–27). Margolis *et al.* (23) show that among mothers experiencing stress, greater exposure to polycyclic aromatic hydrocarbons strengthened associations with reduced hippocampal volumes in their school-age offspring, suggesting a potentiation of the negative associations of maternal stress with offspring outcomes in the context of exposure to ambient pollution. Widom *et al.* (28) build on the review by Cardenas-Iniguez *et al.* (22) to show that ongoing exposure to lead in adulthood continues to have negative impacts on function, demonstrating that blood levels of lead in adulthood predict arrests after blood collection, and that the level of lead in blood was strongly related to neighborhood disadvantage measures. While this study could not assess neighborhood disadvantage and lead levels in these individuals in childhood to understand the unique predictive effects of lead levels in adulthood, the data do indicate that these important relationships continue to be apparent in adult behavior.

Luby *et al.* (29) provide a thought-provoking review and opinion piece that links disadvantage in the home and neighborhood to challenges in parenting that might mediate some of the impacts of adversity exposure on brain development and risk for the emergence of child psychopathology. These authors point out that living with poverty and exposure to neighborhood adversity may make it difficult for parents to provide the type of caregiving necessary for optimal child development, potentially owing to the demands of multiple jobs and the other stressors associated with adverse environments. They call for early supports for families facing such adversity as a potentially highly cost-effective intervention pathway that might help prevent the emergence of mental health challenges in children across development.

Together the reviews and empirical pieces in this special issue highlight the need to consider many features of a child's environment outside the home in understanding risk pathways to mental health challenges. At this point, the mounting evidence of such relationships points to the critical need for more research that can identify the pathways by which such adversity gets under the skin and into the brain so as to develop effective prevention or intervention approaches. As the articles in this special issue illustrate, it is highly unlikely that there is a single pathway, but rather there is a convergence of factors that modulate brain and behavioral development, including exposure to toxins, aspects of the built or unbuilt environment (greenspace, density, crowding, noise, light), feelings of safety and exposure to

threat, access to nutrition and health care, etc. We do not yet know if all of these factors converge on the same pathways to risk at some level or whether they are modulating multiple distinct neural mechanisms that might influence separable cognitive, affective, and social functions that put youth at risk for psychopathology. Further, we face the challenge of causal inference. A growing body of animal models mimicking impacts of environmental adversity help to address causality (30,31), but in the human literature, greater work using positive interventions is needed to help identify causal pathways (32,33). The urgency of this work is underscored by one of the critical points that Cardenas-Iniguez *et al.* (22) make in their review, which is that the distribution of exposure to such environmental adversities is likely a key contributor to health disparities, as individuals living in lower-income neighborhoods and/or neighborhoods with a higher percentage of individuals with minoritized identities are much more likely experience these negative environmental impacts. The time is now to ameliorate the key risk pathway for mental health challenges across the lifespan.

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