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The urban environment and mental disorders

Epigenetic links

Sandro Galea,[1,*] Monica Uddin[2] and Karestan Koenen[1,3,4]

[1]Mailman School of Public Health; Columbia University; New York, NY USA; [2]University of Michigan School of Public Health; Ann Arbor, MI USA; [3]Harvard School of Public Health; [4]Center on the Developing Child; Harvard University; Boston, MA USA

For the first time in human history, more than half of the world's population lives in urban areas and this is projected to increase to two-thirds by 2030. This increased urbanity of the world's population has substantial public health implications. Nearly a century of research has shown higher risk of mental disorder among persons living in urban versus rural areas. Epidemiologic research has documented that associations between particular features of the urban environment, such as concentrated disadvantage, residential segregation and social norms, contribute to the risk of mental illness. We propose that changes in DNA methylation may be one potential mechanism through which features of the urban environment contribute to psychopathology. Recent advances in animal models and human correlation studies suggest DNA methylation as a promising mechanism that can explain how the environment "gets under the skin." Aberrant DNA methylation signatures characterize mental disorders in community settings. Emerging evidence of associations between exposure to features of the environment and methylation patterns may lead toward the identification of mechanisms that explain the link between urban environments and mental disorders. Importantly, evidence that epigenetic changes are reversible offers new opportunities for ameliorating the impact of adverse urban environments on human health.

Key words: urban environment, mental disorders, DNA methylation, epigenetics, posttraumatic stress disorder, depression

Abbreviations: *SLC6A4*, serotonin transporter gene; PTSD, posttraumatic stress disorder; IL-6, interleukin-6; CRP, c-reactive protein; DNHS, Detroit Neighborhood Health Study

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*Correspondence to: Sandro Galea; Email: sg822@columbia.edu

The 20th century has been characterized by the world-wide movement of populations from rural to urban areas. For the first time in human history, more than half of the world's population lives in urban areas and this is projected to increase to two-thirds by 2030. The movement of populations to urban environments is probably the most important demographic shift in the past century. In particular, the increased urbanity of the world's population has substantial public health implications. A body of research has long shown that there are different burdens of disease and disability in urban vs. non-urban areas and more recent work has linked specific features of the urban environment to particular health indicators (for reviews of the literature about urban health see refs. 1 and 2).

Some of the more promising work in this area concerns research that has shown relations between urbanity and mental disorders. There is more than a century of work that has shown higher risk of most mental disorders among persons living in urban versus rural areas.[3-8] Early research proposed several factors that may explain this association including selective migration and social disorganization.[3] For example, it has been proposed that persons within disadvantaged areas may have a more difficult time building and sustaining supportive social relationships, therefore increasing susceptibility to mental illness. Subsequent work has shown associations between particular features of the urban environment and risk of mental illness. Living in poorer urban neighborhoods is associated with greater risk of new episodes of depression compared to living in richer neighborhoods, even

when accounting for individual income or exposure to stressful or adverse circumstances.[6,9,10] Living in neighborhoods characterized by residential racial segregation is associated with a greater risk of depression and anxiety, compared to living in less segregated neighborhoods.[11] Other evidence suggests that neighborhood collective efficacy and norms are associated with the risk of substance use disorders[12] and suicide attempts,[13] again when taking into account individual experiences.

Coincident with the growing number of studies that have demonstrated links between features of the urban environment and mental health, there has been an increase in work that has sought to understand the mechanisms underlying these epidemiologic observations. In particular, there is an emerging interest in identifying biologic explanations that may clarify the link between features of the urban environment and individual mental health. Existing research has documented a role for changes in immune function,[14] gene-environment interactions[15] and psychological mechanisms,[16] among others, that may explain the links between the urban environment and mental health. This paper adds to this growing field and proposes that changes in DNA methylation may be one potential mechanism through which features of the urban environment contribute to psychopathology.

DNA Methylation is a Promising Mechanism that Can Explain How the Environment "Gets Under the Skin"

Adverse urban environments are characterized by factors such as concentrated disadvantage, racial segregation, dilapidated built environment and crime, all of which are associated with chronic psychological and physiological stress.[2,17] The relation between exposure to stressful circumstances and risk of psychopathology is well-documented.[18-22] More recently, epigenetic research has begun to address the central question raised by these observed associations: Mechanistically, how does stress "get under the skin"? Specifically, animal models have shown that variations in individual-level experiences, such as maternal care, shape neurobiology and behavior via epigenetic mechanisms. For example, the work of Meaney and colleagues has documented that natural variations in levels of licking and grooming in rodents are associated with differences in stress response and behavior among pups. Moreover, "better" maternal care, operationalized as more licking and grooming, is correlated with decreased methylation of the glucocorticoid promoter region in the hippocampus, increased glucocorticoid expression and a decreased stress response that persists into adulthood.[23-26] These findings have been extended to post-mortem brain samples from suicide victims with a history of childhood abuse.[27]

Human studies have shown an association between childhood abuse and differential methylation of genes implicated in mental disorders. For example, the serotonin transporter gene (*SLC6A4*) has been implicated in depression and posttraumatic stress disorder (PTSD).[28-31] Work by Philbert et al. using samples from the Iowa Adoption Studies cohort provided initial evidence that increased methylation levels in the CpG island overlapping with the transcriptional start site of *SLC6A4* was associated with decreased levels of *SLC6A4* mRNA and that those with the 5-HTTLPR s allele showed a trend toward higher methylation levels across CpG sites located in this upstream island.[32,33] The same research group showed that child abuse was associated with significantly elevated methylation levels across multiple CpG sites and, among females, at specific CpG sites as well.[34] Taken together, the Iowa Adoption study results are suggestive of a relation between childhood abuse, *SLC6A4* methylation and stress-related outcomes.

Aberrant DNA Methylation Signatures Characterize Mental Disorders in Community Settings

Our own work has focused on showing both that features of the urban environment are associated with greater risk of mental disorders and that specific epigenetic patterns are associated with depression and PTSD, potentially explaining some of the observed associations between the urban environment and mental health.[35-37]

The Detroit Neighborhood Health Study (DNHS) is an ongoing epidemiologic study of individual- and neighborhood-level determinants of mental health among Detroit residents. In analyses using the full baseline of the DNHS cohort, we found that lifetime prevalence of any traumatic event experience was 86.8% [more than half of the sample (50.8%) had experienced an event related to assaultive violence]. Of those who had experienced at least one traumatic event, 16.6% met criteria for lifetime PTSD and 11.6% had PTSD symptoms in the past year. Participants were more likely to develop PTSD from assaultive violence (18.0%) than from other types of traumatic events (8.6% on average for the other traumatic event types) (Goldmann et al, under review). The lifetime and 12-month prevalence of PTSD are more than twice the previously reported prevalence from other epidemiologic studies,[26,38] a finding that is due to greater exposure to violence in Detroit.[39] We also found that individuals with lower household income were more likely to develop PTSD after a traumatic event than those with higher income, but that this relationship was likely mediated by a greater burden of lifetime traumatic events among those with lower income. Collectively, these findings suggest that the exposure to adverse life circumstances is heterogeneous in a large, diverse urban environment and that these life circumstances contribute to poor mental health in this context.

Using samples obtained from the same study we have identified microarray-based methylation profiles that distinguish between those with and without lifetime depression and those with and without lifetime PTSD. With respect to depression, we found that unmethylated genes showed evidence for the involvement of inflammatory-related pathways and processes previously implicated in this disorder and confirmed the functional significance of these results by demonstrating elevated serum levels of two inflammatory markers—interleukin 6 (IL-6) and C-reactive protein (CRP)—among those with lifetime depression.[25] This functional relationship was further corroborated by the finding of an inverse correlation between methylation of IL-6, CpG and

circulating IL-6 and CRP levels among those with lifetime depression.[25] With respect to PTSD, we found that those with lifetime PTSD were characterized by a preponderance of immune-related gene clusters in their unmethylated gene sets and further corroborated these findings by demonstrating significantly higher levels of antibodies to cytomegalovirus, a typically latent herpes virus, in the PTSD affected group.[26] Importantly, this signature of apparent immune dysregulation was also observed in pathways associated with genes showing a significant negative correlation between methylation level and number of traumatic events experienced by those with lifetime PTSD,[26] suggesting the possibility that cumulative traumatic burden may leave a molecular footprint in those with the disorder. Most recently, our focused analysis of genes previously associated with gene expression differences in whole blood among those with PTSD has shown that methylation levels of one gene, *MAN2C1*, is associated with increased risk of lifetime PTSD, but that this effect is modified by the number of traumatic events individuals have experienced.[37] These results strongly suggest that there are distinctive biologic signatures of mental illness among community-dwelling urban residents. We are now extending this work to examine whether epigenetic signatures explain the relations observed in correlational studies among features of the urban environment and mental disorders.

DNA Methylation May Plausibly Explain the Links between Exposure to the Urban Environment and Mental Disorders

How do social environmental stressors or features of the urban environment that may be determinants of mental health, independently of individual stressful experiences, get under the skin? The emerging evidence, summarized here, suggests that DNA methylation may indeed explain the link between individual exposure to adversity and development of mental illness. Moreover, the epidemiologic data provides evidence for the effect of macrosocial features of the urban environment on mental illness over and above the effect of individual-level adversity. However, how does exposure to social environmental stressors, such as concentrated disadvantage, experienced by all individuals living in that particular urban environment, manifest as individual-level psychopathology? There is little doubt that some neurobiological processes must ultimately mediate this relation. However, relatively little attention has been paid in the urban health or in the psychiatric epidemiology literature to identifying potential neurobiological mechanisms.

Animal models mimicking human social environmental exposures exist and findings converge with epidemiologic studies to provide strong evidence that adverse social conditions affect mental health. One example of such evidence comes from the literature on variable foraging demand (VFD). Under the VFD model, the experimenter manipulates "ecologic settings" of infant-mother dyads by, for example, varying the amount of work required by each mother to obtain daily food rations. Under all conditions, adequate nutrition is available and accessed; infant weight gain and separation from mother does not vary by condition.[40] However, as noted by Rosenblum and Paully in their seminal study, "the imposition of unsignaled fluctuations in foraging requirements produced group instability, altered maternal patterns and disturbed development of infant independence."[40] Extant research has documented numerous adverse behavioral and physiological effects of VFD conditions on both the mother and child that parallel disruptions in biological systems observed in mental disorders.[41] We could not, however, at this time locate any published studies documenting methylation changes in maternal or offspring DNA using the VFD model. Correspondence with researchers in the VFD area suggests such studies may be forthcoming (Coplan, personal communication).

In considering the etiology of mental disorder, we ultimately need to ask ourselves whether features of the urban environment affect the human brain. Environmental epidemiology points to features of the urban environment that may affect brain development and thereby increase the risk for mental disorders. For example, certain environmental toxins such as community violence,[42] secondhand smoke[43] and air pollution,[44,45] known to be more prevalent in the urban environment, have been shown to affect cognitive functioning, particularly in childhood. Lower cognitive functioning in childhood predicts risk and severity of a range of adult mental disorders.[46] Thus, one way in which the urban environment might increase the risk for mental disorders is through effects on the developing brain. Recent neuroimaging studies also provide some clues about how the urban environment adversely affects adult brain functioning.[48,49] Exposure to rural versus urban images activates different brain regions. Notably, urban images were associated with greater activation of the "emotional brain" including the hippocampus and amygdala;[50,51] abnormalities in these brain regions have been commonly associated with mental disorders such as PTSD.[52-56]

Challenges in Integrating Epigenetics into Urban Mental Health Research

Our increasing capacity to conduct population-based epigenetic studies opens new opportunities for epidemiologists and population health scientists interested in understanding the biological mechanisms by which urban environments affect mental health. However, there are numerous challenges associated with conducting such research.

The first challenge is intellectual. Such studies require a truly multi-disciplinary team of investigators who can provide expertise in the practical assessment of urban environment, diagnosis of individual-level mental disorders, collection and analysis of biological specimens and complex statistical analysis of data from multiple-levels (neighborhood, individual, gene) and across time.

The second challenge is the need to use peripheral tissues in epidemiologic research. As researchers interested in mental disorders, we ultimately want to identify epigenetic changes in the human brain. Most animal-based evidence in the area and early work in humans have

relied on assessments of DNA methylation in central nervous system tissues. This is not feasible in large population-based samples. The use of blood-derived tissues for use in assessing psychiatric disorders is increasingly being recognized[57] and a growing body of research is documenting correspondence between brain- and blood-derived gene expression signals.[58,59] Furthermore, recent work in non-human primates confirms that *SLC6A4* shows concordant methylation levels in the blood and brain.[60] The use of buccal cell DNA also shows promise.[61] We would expect this work to lead to increased simplicity in the conduct of population-based studies leading us to substantial leaps forward in this area.

A third challenge has been the dearth of model organisms that have been exposed to group-level factors that may influence individual pathology. Animal models have focused largely on exposures that operate at the individual-level and not at the level of the social environment.

Fourth, disciplinary differences in how terms such as social environment are understood add to confusion in this area. For example, in studies that have been concerned with gene x environment interactions, social environment is typically defined in terms of maternal care or abuse,[62] while in social epidemiologic studies, social environment typically refers to shared features of the environment, over and above individual-level exposures.[63]

Fifth, work that bridges disciplinary levels, incorporating both epidemiologic assessments and biologic assessment, faces multiple levels of analytic challenges. While multilevel modeling approaches are now commonplace in epidemiology, very few analyses remain that have incorporated biologic and social environmental assessments in the same model. We have argued that the paucity of analysis in this area has substantially limited our ability to understand how environments modify genotype-phenotype relations.[64,65] Measurement issues in such analyses are also compounded, including well-documented challenges in social environmental measurement.[6] Ultimately, any consideration of determination over multiple levels must contend with challenges around the complexity of causation and the limitations of our dominant and deterministic models in dealing with these challenges.[66]

Sixth, while this work remains in its infancy, an expanded scope of inquiry must also take into account the added complexity of determination over the life course. The influence of exposures and the temporal link between exposures and pathology are likely to change over an individual's life. The change of methylation patterns with age is well-documented.[67-69] A life course perspective suggests that the ultimate impact of the social environment is likely to be a complicated function of exposure over the life course, which cannot simply be understood using narrow analytic windows and one-dimensional linear models.

Conclusion

The application of epigenetics to urban health offers new promise and direction for population mental health research. Challenges are rife, but the field also holds substantial promise. This work stands to help us extend our understanding of the links between features of the urban environment and the risk of psychopathology. However, even beyond explanation, the emerging evidence about the reversibility of DNA methylation[70,71] offers particular promise in the area. Population health science must contend with the challenge of how we may translate observations about the social environmental determination of health into tractable interventions. Demonstrating intervening mechanisms that are reversible, and potentially malleable, offers a promising direction in this area. Clearly, the gap between observational and interventional work is large. Thus far, work in the field, summarized here, suggests that this area holds tremendous promise to help us understand how urban environment may produce mental health in populations.

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