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Urban environment and psychiatric disorders: a review of the neuroscience and biology

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ABSTRACT

Most of the world's population now lives in cities. While living in cities have both health risks and benefits, mental health has been usually considered to be negatively affected by urbanicity. While mental health disorders have complex etiology and multiple causes, it has been shown in multiple observational studies that mood and anxiety disorders are more prevalent in urban centers and incidence has been increasing. In addition, the incidence of schizophrenia is strongly increased in people born and raised in cities. Studies on the effects of urbanicity on the brain, however, are more challenging to conduct, since individual and environmental factors are hard to distinguish. The main objective of this article is to review studies on how specific neural processes mediate those associations between urbanicity and psychiatric disorders and how environmental factors affect genetic regulation (epigenetics). Neuroimaging studies have shown how urban stressors might affect the brain by conducting experiments using functional magnetic resonance imaging (fMRI). There have been demonstrations that urban upbringing and city living have dissociable impacts on social evaluative stress processing in humans. City living was associated with increased amygdala activity and the urban upbringing has been shown to affect the perigenual anterior cingulate cortex, a key region for regulation of amygdala activity, negative affect and stress. In addition, studies on epigenetics have shown associations between exposure to features of the environment and methylation patterns. The goal of understanding how urban environments act as a risk factor for mental disorders may be pursued on several levels. It can be approached by measuring the effects of economic factors (unemployment, socioeconomic status), social condition (social network support), environmental exposures (toxins, air pollution, noise, light), that must be weighed to identify how it contributes to mental disorders.

1. Introduction

Today, >50% of the world's population now lives in cities. It is expected that by 2050, this figure will increase to 70%, with >50% living in cities with a population of 500,000 or more [1]. While living in cities has benefits, like more access to better health care, employment and education [2], it also leads to increase exposure to risk factors originating from the urban social or physical environment (e.g. poverty, traffic noise, pollution), contributing to increased stress and negative mental health outcomes. It has been shown that mood and anxiety disorders are more prevalent in urban centers and its incidence has been increasing [3]. Meta-analyses of studies on the prevalence of mental illness among individuals living in urban setting have shown that for psychiatric disorders in general, the prevalence is increased by 38%. For anxiety disorders, there is increase of 21% and for mood disorders, it is greater by 39% [4]. Since they are results from observational longitudinal studies, the adjustment of cofounders is one of their limitations, but even when controlled for known factors such as age, social class, economic status, gender, ethnicity, the disparities in prevalence between urban and rural settings lingers.

While several observational studies have shown that the risk of developing mental illness generally higher in urban settings [4–10], the most striking example has been in the risk of developing schizophrenia [11]. One of the first reports linking urban living with mental disorder was the increased incidence in schizophrenia in the inner city arears of Chicago when compared to the city's periphery [12]. The link between schizophrenia and urban setting has been demonstrated in several studies, from European countries to China [9,10]. In a study performed in Denmark, for example, the risk of developing schizophrenia was more than two times than greater if the person had lived their first 15 years in a large urban center, as compared to rural areas [13]. Other observational studies have also corroborated the higher risk, with demonstrations of a dose-response relationship between the risk for schizophrenia and living in urban setting [8].

Although there are several epidemiological studies showing a clear link between urban upbringing and increase the risk of mental illness,

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they mostly focus on risk factors and are not designed to explain these epidemiological observations, but only to demonstrate the association. Recently, there has been increased interest in trying to understand the mechanisms underlying these observations, particularly through the identification of biological explanations linking features of the urban environment and mental health. There has been research documenting the role of changes in immune function, epigenetic modifications and changes in brain function. Advances in neuroimaging studies, combining functional magnetic resonance imaging (fMRI) techniques and stress research tools, have begun to show the effects of how urban living affects specific brain mechanisms and the processing of social stress.

This paper reviews the neuroscience and epigenetics of how urban living leads mental illness, focusing particularly on functional neuroimaging and epigenetic modification studies.

1.1. Neuroscience studies on effects of urbanicity and mental illness

Lederbogen and colleagues have shown how city living and urban upbringing are associated with how the brain responds to stressors [14]. They have postulated a possible mechanism by which urbanicity contributes to how individuals respond to acute social stress. The study, based on performing a stress task while undergoing a fMRI scan, exposed 32 healthy people - from rural and urban upbringings - to the Montreal Imaging Stress Task. The task is a social stress paradigm that involves solving arithmetic problems under time pressure.

The study found that urban living was associated with increased activity in the amygdala while performing the social stress task. The response from the city dweller, defined as individuals living in a place with >100,000 inhabitants, showed higher activity in the amygdala than people living in towns, defined as >10,000 inhabitants, which in turn had a higher amygdala activity than individuals in rural areas. Another result of the study involved the association urbanicity and activation of the perigenual anterior cingulate cortex (pACC), a brain region possibly involved in the development of schizophrenia, during this task, and the highest activity was observed in individuals brought up exclusively in cities.

Another area of intense study using fMRI has been on the assessment of interregional connectivity in specific neural networks, such as the default mode network (DMN). The default mode network (DMN) is a pattern of activation of brain regions that is active during rest and is deactivated when any task-oriented behavior is performed. Initial studies have associated the DMN with the appraisal of external and internal stimuli, self-referential and reflective processes [15].

The default mode network is usually divided into three major subdivisions: the ventral medial prefrontal cortex; the dorsal medial prefrontal cortex; and the posterior cingulate cortex and adjacent precuneus plus the lateral parietal cortex [16]. Although structural and functional alterations in these regions have been associated with schizophrenia and other mental illness, the direction of associations have shown conflicting results in different studies [17]. Regarding city living, it has been postulated that urbanicity can have negative effects on cognitive functions such as social cognition [18] and working memory capacities [19]. Since DMN activity is suppressed during any goal-oriented task, altered connectivity in rest may lead to compromised suppression and, therefore, diminished performance. Indeed, studies have shown that DMN hyperconnectivity in patients with schizophrenia was associated with reduced working memory performance [20]. It has been hypothesized, therefore, that altered DMN connectivity may not only be conditional on genetic risk for psychotic disorder, but also on established environmental risk factors for schizophrenia, such urban upbringing. One study [21] in particular examined the hypothesis of whether DMN functional connectivity reflects a cerebral phenotype that is the outcome of gene-environment interaction, particularly urbanicity, in psychotic disorders, but the study did not find evidence of a differential impact of environmental exposures on DMN functional connectivity. The authors suggest that that DMN functional connectivity may not be a sensitive enough outcome measure to investigate this specific environmental effect, and studies focusing on the functional connectivity of mesocorticolimbic circuits may be a better candidate for future research examining this type of interactions [11].

Another area of intense research interest has been on the biological effects mediating the interaction between environmental factors and genetic regulations: the field of epigenetics.

1.2. The association of environmental factors and epigenetic regulation

While the higher risk most mental disorders among persons living in urban versus rural areas has been well established, only recently studies on epigenetic regulation have begun to address questions raised by these observed associations. Originally, the term “epigenetics” was coined to describe the complex and dynamic interactions between genes and the environment, leading to wide phenotypic variations [22]. Today, it refers to variations in phenotype that are not mediated by changes in the genetic code, but to molecular mechanisms that modify gene expression. There are several mechanisms through which this regulation occurs, but the most widely studied involves histone methylation, acetylation and ubiquitination patterns. Since gene expression is dependent on how accessible DNA is to RNA polymerase and other gene transcription factors, changes in the densely packed chromatin alter how the gene is ultimately expressed [23]. In general terms, histone acetylation is associated with increased transcriptional activity whereas deacetylation or methylation is associated with transcriptional repression. Since the epigenetic process of DNA methylation is a stable and enduring, it has been studied in several animal models of stress. Recently, there has been growing interest in genome-wide epigenetics (epigenomics), comparing populations of healthy controls with populations with specific mental illness. Most work has been based on animal models showing that epigenetic modifications are implicated in behavioral phenotypes related to mental illness.

One of these studies, done by Meaney and colleagues, have shown that differences in licking and grooming in rodents, a proxy for changes in maternal care, are associated with differences in stress response and behavior among their offspring [24]. They found that better maternal care (or more licking and grooming) are associated with decreased methylation patterns of the glucocorticoid promoter region in the hippocampus, leading to increased glucocorticoid expression and a persistently decreased stress response [25]. In humans, comparison of samples from different populations using microarray-based methylation profiles, had demonstrated changes in methylation patterns of serotonin transporter gene (SLC6A4) in individuals with depression and posttraumatic stress disorder. Increased methylation of SLC6A4, leading to lower levels of SLC6A4 mRNA, may mediate this effect. Regarding major depressive disorder, unmethylated genes involved in inflammatory-related pathways and elevated serum levels of two inflammatory markers—interleukin 6 (IL-6) and C-reactive protein (CRP), have also been found [26].

Another study has demonstrated differential DNA methylation patterns in gene promoter regions throughout the genome in the hippocampus of suicide completers. These changes in methylation levels were seen in genes associated with regulation of behavioral and cognitive processes altered in individuals with suicidal behaviors [27].

2. Conclusions

The discoveries about the epigenome and its lifelong effects are relatively recent. The emerging evidence suggests that epigenetic modifications provides the mechanisms through which lifelong experiences can have sustained effects on an individual's phenotype. Here, we focused on the broad exposure to urban living, which in itself may be subdivided into higher exposure to several other factors, such as increased population density, poverty, air pollution and traffic noise. The converging evidence for the role of DNA methylation and histone modifications in

mediating the effects of early life and social experiences may also provide insights into possible therapeutic approaches, although it is still early to determine its feasibility. In addition, the idea these epigenetic modifications can have a transgenerational impact is gaining considerable empirical support and there is now clear evidence that environmentally induced changes in brain and behavior can influence future generations, with implications for research perspectives on the inheritance of epigenetic modifications in response to environmental risk factors.

Author contributions

The authors contributed equally.

Declaration of Competing Interest

The authors declare no conflicts of interest. JACS is a member of the Collège International de Recherche Servier (CIRS).

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