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INVITED REVIEWS

The neurobiology of social environmental risk for schizophrenia: an evolving research field

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Abstract
Introduction Schizophrenia is a severe and complex brain disorder that usually manifests in early adulthood and disturbs a wide range of human functions. More than 100 years after its initial description, the pathophysiology of the disorder is still incompletely understood. Many epidemiological studies strongly suggest a complex interaction between genetic and environmental risk factors for the development of the disorder. While there is considerable evidence for a social environmental component of this risk, the links between adverse social factors and altered brain function have just come into focus.
Methods In the present review, we first summarize epidemiological evidence for the significance of social environmental risk factors, outline the role of altered social stress processing in mental illness, and review the latest experimental evidence for the neural correlates of social environmental risk for schizophrenia.
Conclusions The studies we have discussed in this review provide a selection of the current work in the field. We suggest that many of the social environmental risk factors may impact on perceived social stress and engage neural circuits in the brain whose functional and structural architecture undergoes detrimental change in response to prolonged exposure. We conclude that multidisciplinary approaches involving various fields and thoroughly constructed longitudinal designs are necessary to capture complex structure of social environmental risks.

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Introduction

The etiology of schizophrenia is genetically and environmentally complex and multifactorial in nature. Despite many years of research, the causally contributing factors to the disorder are incompletely understood [1, 2]. Epidemiology has substantially contributed to our understanding of the contributors and effects of schizophrenia within and across populations [3]. Schizophrenia incidence is around 0.2/1,000 per year but varies significantly within populations, with higher rates being typically observed in males, immigrants, and individuals brought up in larger cities [3–7]. Schizophrenia is highly heritable [8], and neuropsychiatric research has consequently initially focused on the neural effects of genetic risk factors in preceding decades. Here, evidence shows that both rare genetic variants with large effects and common variants with small effects contribute to the genetic and neural risk architecture [3–7, 9]. However, about 60 % of schizophrenic patients do not have an affected first-degree relative, and about 40 % of the monozygotic twins of schizophrenia patients remain healthy [10–12], leading to an estimated heritability of around 60–80 % demonstrating that genetic risk alone does not explain the full picture [10, 13]. The reported increase in risk ratios varies between risk factors and may range from <1.2 (for common single nucleotide polymorphisms), over 2–5 (for adverse environmental factors such as urbanicity and minority status) to up to 30 (for some rare events of copy number variation (CNV) deletions or duplications, such as deletions at *22q11*) [9, 14–16]. This may explain the renewed attention to environmental factors since within this

range the risk of environmental factors exceed that of all common single genetic risk variants by far [1, 2, 9, 17]. A rough classification of social environmental risks for schizophrenia proceeds from a life span and distinguishes between pre- and perinatal factors on the one hand, and postnatal factors on the other hand. The latter include childhood adversity, cannabis use during puberty, migration, and urban upbringing [4, 14, 18–20]. Furthermore, low socioeconomic status and social isolation have received significant support [18, 19, 21, 22].

Here, we will focus specifically on the discussion of postnatal social environmental risk factors that include an explicit social context, namely social status, social support, urbanicity, and migration. This area of schizophrenia research has unfortunately received comparatively little attention until recently, at least regarding the investigation of associated neurobiological alterations. In our review, we will gather existing scientific evidence on the effects of social environmental risk, discuss existing pathophysiological models on their operating mode while impacting mental health, and summarize recent evidence from social neuroscience on the neural regulatory circuits that seem to contribute to the translation of social risk factors into schizophrenia susceptibility. A particularly important concept in this context is that of social stress, since it is believed that many social environmental risk factors such as childhood adversity, ethnic minority status, urbanicity, low social support, and low perceived social status operate through shared psychological, neurobiological, and psychophysiological mechanisms that facilitate a lasting (and likely detrimental) reorganization of neural stress regulatory circuits [2, 11, 23].

Stress and mental health

Stress affects the psychological and physiological well-being of individuals and is a major environmental risk factor for the development of a number of health issues including major psychiatric disorders such as depression and schizophrenia [24–28]. In the classical framework of Lazarus [29], stress is the outcome of negative appraisal, i.e., the evaluation that the demands of a life event exceed the available strategies of an individual to cope with it. The physiological reactions to stress are rooted in evolutionarily conserved defense mechanisms that as such are beneficial for survival, at least when they are engaged infrequently and in response to imminent physical harm or threat [30]. Among others, stress activates the hypothalamic-pituitary-adrenocortical (HPA) axis and facilitates the release of adrenocorticotropin (in the pituitary) and cortisol (in the adrenal glands) [30, 31], hormones involved in the regulation of "fight-and-flight"-related adaptations in energy homeostasis, immune system activity, emotion, and cognition [32]. In cases where the cortisol response is relatively selective (i.e., limited to imminent physical threat) and dynamic (i.e., recovers in the absence of threat), the resulting physiological changes promote short-term survival [25, 30]. However, in the case of chronic stress, the resulting physiological and neurobiological changes can be detrimental to health [24, 25, 27, 33, 34].

Prolonged and repetitive activation of the human stress response system results in a chain of neurophysiological processes that may promote, in the long run, HPA axis suppression, immune dysfunction, cardiovascular and metabolic disturbances, and susceptibility to psychiatric illness [26, 27]. Here, McEwen's concept of "allostatic load" [27, 35] is vital for the understanding of the pathological dynamic, one of the most studied theories in psychology and medicine in this context [24, 27]. While the term allostasis describes the adaptive changes that reestablish the physiological and emotional balance of an individual in response to an acute challenge, allostatic (over)load describes the "wear and tear" on the body and psyche that results from the maintenance of allostasis in the context of chronic stress [35]. Similar to the "stress" definition of Lazarus [29], McEwen hereby underscores the importance of the person's perception of ability to cope with a situation in the context of allostatic overload [24].

To date, converging evidence suggests that complex social stressors contribute to HPA axis dysregulation and likely also allostatic overload. In psychology, the relationship between social stress and HPA reactivity was widely studied with paradigms such as the Trier Social Stress Test (TSST) or public speaking experiments [31, 34, 36–38]. The tests typically involve situations that combine two of the most powerful social stressors: social evaluative threat and perceived uncontrollability (or a situation facilitating negative appraisal). To date, it is generally accepted that in addition to actual physical threats, comparable HPA axis activation and cardiovascular responses are seen in response to complex social stressors such as the perceived threat to an individual's perceived status, self-esteem, and social self [34, 36, 37, 39–41]. Some of these observations motivated Jones and Fernyhough [39] to suggest that the human "social self-preservation system" [40, 41] operates through HPA axis regulation and might contribute to the development of schizophrenia [39]. However, it is clear that the HPA axis is not the only effector of stress and adaptation and is, in many aspects, perhaps best understood as a limited window into neural processing of stress and threat that can be more directly assessed using modern neuroimaging techniques. As discussed in more detail below, at the brain level, the acute social stress engages both evolutionarily conserved areas mediating survival-related defense functions (e.g., brain stem) and higher order control regions such as prefrontal cortex (PFC) and more specifically the anterior cingulate cortex (ACC) that integrate social cues

and conceptual knowledge to complex social experiences [42–45]. Similarly important, the brain is also a target organ of allostatic (mal)adaptation, and preclinical data show that chronic stress can induce extensive functional and architectural changes in the brain [46]. Various human studies showed that PFC function is impaired as a result of acute mild stress [46–48], while several animal studies repeatedly proved the negative relationship between stress (acute and chronic) and the PFC architecture (such as dendrite length and density) [49–52]. Therefore, similar effects in humans appear plausible in the context of chronic social stress, in particular when the exposure coincides with neurodevelopment.

In addition to the social stress, it is also essential to mention two other concepts in the field, namely social disadvantage and social defeat. These concepts are theoretically very broad and also popular in the mental health literature [53, 54]. Fundamentally, both seem to involve the perceptions of outsider position, failure and isolation; in other words they might require certain level of higher order cognitive processing (such as social comparison). Consequently, they result in negative emotions and eventually lead to increased stress [53–56]. A good example demonstrating the close link between social disadvantage, social defeat, and social stress might be the studies where unemployed individuals showed increased psychological and physiological stress [57, 58].

Evidently, chronic social stress and social defeat are risk factors not only for schizophrenia, but also for depression and addiction. Genetic predisposition, time window of the risk exposure during neurodevelopment, and interaction with other causal variables (such as personality traits) would determine the possible outcome [53, 55]. For instance, it has been proposed that the adaptive brain processes in response to "social allostatic overload" may facilitate the emergence of psychotic symptoms through dysregulation of downstream dopaminergic pathways, particularly in genetically vulnerable individuals [39] and push them to a psychiatric state where schizophrenia is more plausible than depression (see Fig. 1).

Combining this general framework with the epidemiological data, many researchers have favored the hypothesis that social environmental risk factors for schizophrenia, such as low social status, urban upbringing or ethnic minority status, are proxies for increased exposure to social stress [14, 39, 55]. Notably, similar to the basic characteristics of laboratory stress experiments, repeated exposure to a combination of social defeat, social evaluative threat, and uncontrollability have a propensity to trigger psychotic symptoms in vulnerable individuals [39, 40, 55]. These hypotheses are supported by observations linking chronic stress, social defeat, schizophrenia, and related neural alterations. For instance, healthy individuals with increased chronic stress

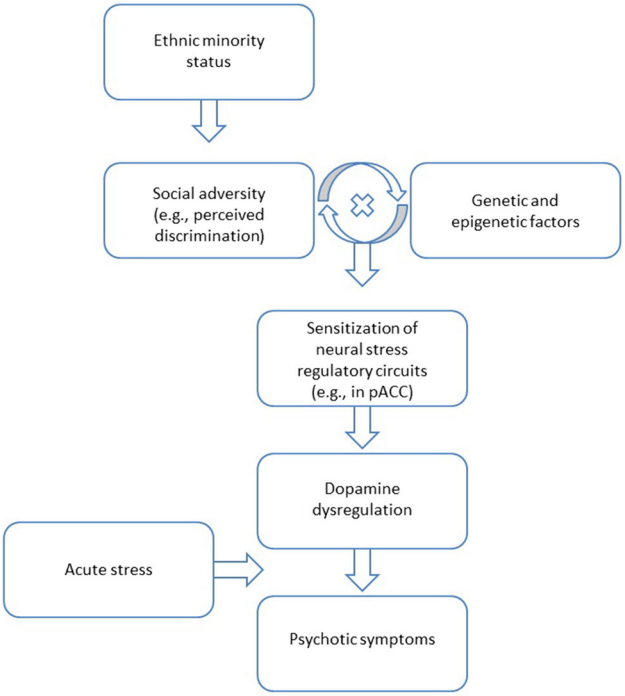

Fig. 1 A proposed theoretical framework for the development of psychosis in the context of ethnic minority status. The vulnerability-stress model for psychosis drawing on the example of ethnic minority status: In this theoretical framework, schizophrenia susceptibility results from an interaction of early social stress (e.g., perceived social adversity through discrimination) and (epi)genetic risk factors. The resulting sensitization for social stress coincides with functional alterations in pACC and a vulnerability of the downstream dopaminergic system for dysregulation. Acute social stress in adulthood may lead to an acute decompensation of the sensitized stress system and facilitate the development of psychotic symptoms

show decreased gray matter volume in hippocampus and frontal cortex [59], areas that have been repeatedly implicated in schizophrenia pathophysiology [60, 61]. Moreover, stress may disinhibit the release of dopamine [55, 62, 63], one of the core neurochemicals proposed to be dysbalanced in schizophrenia [64, 65]. Last but not least, stress tends to worsen schizophrenia symptoms, likely through indirect effects on dopaminergic neurotransmission [39, 55, 66].

Neural mechanisms: insights from social and cognitive neuroscience

Social neuroscience investigates the neural underpinnings of social behavior and its implications by combining methods from social psychology, medicine, and neuroscience [67, 68]. The following discussion of social environmental risk factors cannot provide a full representation of the topic. Instead, we will focus on the factors that have been proposed to involve an explicit social component and

have received substantial attention in recent neuroscience research. Specifically, we will discuss data on the effects of social (economic) status, social support, urbanicity, and migration. While the last two factors are more specifically linked to psychosis risk, social status and social support are among the environmental risk factors associated with a wider range of mental and physical disorders [14, 69–71].

Socioeconomic and social status

Socioeconomic status (SES) is a variably defined and multidimensional construct consisting of items such as an individual's education, income, wealth, occupation, and characteristics of the proximate social environment (family, neighborhood) [72, 73]. The inverse relationship between SES and mental health outcomes is one of the best established associations in the field to date [74, 75]. Even though a convincing causal link to schizophrenia is missing and likely bidirectional in nature [18, 21, 22, 69, 76], it is possible that socioeconomic status during childhood may have detrimental impact on mental health that is mediated, at least in parts, by adverse effects of low SES on brain structure and function [73].

A particularly important composite feature is that of the subjective social status, i.e., a person's own perception about his or her social standing in relationship to other individuals in society [77]. Specifically, perceived status is a good representative of the psychological aspect of SES since it is more strongly related to subjective stress and negative emotionality [78–80] and likely also health outcomes [81]. First evidence for the involvement of brain areas came from one of our own neuroimaging studies [82] examining the neural correlates of social status processing. Here, individuals exposed to unstable social hierarchies showed a specific activation of stress- and salience-related areas such as ACC, amygdala, and striatum [82]. Evidence from a structural study [78] suggests that individuals with a lower perceived social standing also have a decrease in gray matter volume in the perigenual anterior cingulate cortex (pACC), an area known for its regulatory involvement in emotion and stress processing [45, 83, 84] that is tightly linked to the limbic system [83]. Consistent with this, functional work demonstrates an association between lower perceived parental social standing, and increased amygdala reactivity during the processing of emotional social cues (angry faces) [85]. Last but not least, in children from low-income families, decreased gray matter has been detected in the hippocampus [86], a highly stress-sensitive sub-cortical structure critical for learning, memory, and the regulation of neuroendocrine activity implicated in both schizophrenia and depression [87–89]. Taken together, while these neuroimaging studies are cross-sectional, and thus of limited explanatory power with respect to causality, these data are well in line with the idea that perceived and experienced social disadvantage may facilitate lasting alterations in neural and cognitive systems that are mediated by social stress.

Social support and social networks

On the side of resilience, it is well known that social support has a positive impact on mental and physical health [90–92], with better outcomes in individuals with strong and positive relationships with their significant others, family, friends, and neighbors [91]. In sociology, the social capital of humans [93–95] is defined as the elements in the social environment that foster benefits such as increased well-being [96] through cooperation and other collective behaviors of individuals [96, 97], a key factor driving brain development in primates and humans during evolution [98]. Plausible psychological intermediates of social support are the facilitation of positive affect and higher self-esteem (e.g., through positive emotions related to perceived valuation and acceptance) and also the protective effects of the received support itself, which can function as a "stress buffer" [90, 99].

The neurobiology of social support and its relationship to neuroendocrine stress responses has received significant attention in the past decade. For example, a study by Eisenberger and colleagues [100] showed that social support involves dorsal ACC (dACC) [100, 101], a region that serves as a control area of pACC during emotion and stress [102–104]. According to these findings, individuals with lower social support show higher cortisol responses in a laboratory social stress task and increased dACC responses in an functional magnetic resonance imaging (fMRI) task challenging social exclusion [100]. These data suggest that the acute experience of a lack in social support engages a higher order area involved in the processing of cognitive conflict and pain, and elicits a stress reaction comparable to that of acute physical endangerment [105].

In addition to the acute experimental challenge of social support and the study of its functional consequences, further interest has been directed to the brain structural correlates of human social networks. For example, it has been shown that increased size and complexity of social networks correlate with increased amygdala and cingulate cortex volume [106]. The amygdala is a core structure of the limbic system, functions as a signaling system for environmental threat, and plays a critical role in the pathophysiology of depression and anxiety disorders [83]. Another core structure of the social brain is the temporoparietal junction (TPJ) in the posterior aspects of the superior temporal sulcus [107]. Here, it has been demonstrated that individuals with higher subjective feelings of loneliness and social isolation have less gray matter volume in the left TPJ [108]. Individuals with a higher number of friends on online social network sites, in contrast, show increased gray matter density in right TPJ, left middle temporal gyrus, and right entorhinal cortex [109]. Together, these

structures form a human neural circuitry in which critical subcomponents of social perception are processed such as the recognition of the intentions of others and memory for faces and names [109–111]. While cross-sectional studies do not support any inferences on causality the data are in line with the idea that stable differences in the composition of social networks influence the organization of brain networks crucial to social-emotional information processing.

Urbanicity

While overall, health seems to be better in large cities compared to rural areas [112], meta-analyses show that individuals born and raised in urban environments have an strongly increased risk for schizophrenia [71, 113–115]. The urban landscape is complex and harbors a multitude of adverse environmental factors that may relate to this observation (e.g., environmental pollution, exposure to toxins and infectious agents, drug abuse). However, prior analyses suggest that the increase in schizophrenia incidence persists when many of these variables are accounted for, arguing that they are unlikely central to this association. Also, other pieces of information show that the association of urban upbringing and schizophrenia is not merely explained by social drift, i.e., the hypothesis that individuals with pre-existing mental disorders tend to cluster in urban areas as a consequence of a disorder-related decline in socioeconomic status [114, 116]. First, there is a dose–response relationship between time of urban exposure and schizophrenia risk and a linear association between city size and schizophrenia incidence [71]. Second, it has been shown that schizophrenia incidence is attenuated in individuals at high psychosis risk that relocate to rural areas [71], a reversibility in risk that argues for the presence of causative agents in the urban landscape itself.

Since city life also harbors a multitude of social stressors (e.g., increase in population density, competition, social fragmentation), many researchers currently favor the hypothesis that that increased exposure to social stress may be at the core of the association of urbanicity and schizophrenia risk. In a recent work we have combined fMRI techniques and methods from laboratory stress experiments to identify the brain mechanisms that translate the effects of urbanicity on social stress processing in humans [117]. It was shown that healthy individuals that currently reside in larger cities show increased activation of the amygdala during the induction of social stress, a finding that supports the idea that on a short-term scale, the social stress associated with urban life may challenge the neural alarm system that mediates the processing of imminent threats (see Fig. 2). Moreover, exposure to an urban environment during the first 15 years of life was associated with an increased activation of pACC during social stress processing, a region that a meta-analysis has highlighted as structurally and functionally abnormal in schizophrenia [118]. The observed alterations in pACC followed a dose–response relationship and were specific to pACC and neural stress processing, making it plausible that altered social stress processing may be a mediator for increased psychosis risk for individuals that are born and raised in urban environments.

Minority status and migration

Migration is one of the best-established environmental risk factors for schizophrenia [14, 119] with meta-analyses showing that relative risk is about doubled in immigrant populations across many countries [5, 119–121]. Since this increase in risk persists into the second generation of migrants who have never experienced pre-migratory and migratory events [119, 120, 122], and since alternative accounts such as cultural diagnostic bias and selective migration have not received convincing empirical support [14, 119], current pathophysiological models emphasize the possibility of adverse causal contributors in the post-migratory social environment [14, 119, 120]. Interestingly, psychosis risk in migrants is influenced by socially relevant aspects such as skin color and the relative density of ethnic minorities in the neighborhood [14, 123, 124]. Here, individuals that stand out from their immediate social environment (e.g., through darker skin color or the fact that few other migrants live in the same neighborhood) seem to be at greater risk for psychosis compared to those that tend to "blend in" to the surrounding social environment. These data suggest that it is not migration itself, but ethnic minority status in a society that explains the association to psychosis risk [14, 55, 119, 123, 125]. Again, social stress may play a crucial role here since social marginalization and discrimination in the majority society are commonly reported as adverse social experiences in minorities [126, 127]. Negative appraisal of perceived social threat, rejection and/or discrimination, in turn, may plausibly result in conditions of chronic social stress, and consequently disordered stress responses and disturbed psychological and somatic well-being [34, 55]. Consistent with this, researchers have proposed a causal role of social stress in migrants, including experiences of social threat and chronic social defeat. While neuroimaging studies on this topic are currently under way [128], this hypothesis is awaiting neurobiological validation.

Conclusions

While the study of risk-associated genetic and environmental factors per se has a long tradition in psychiatry

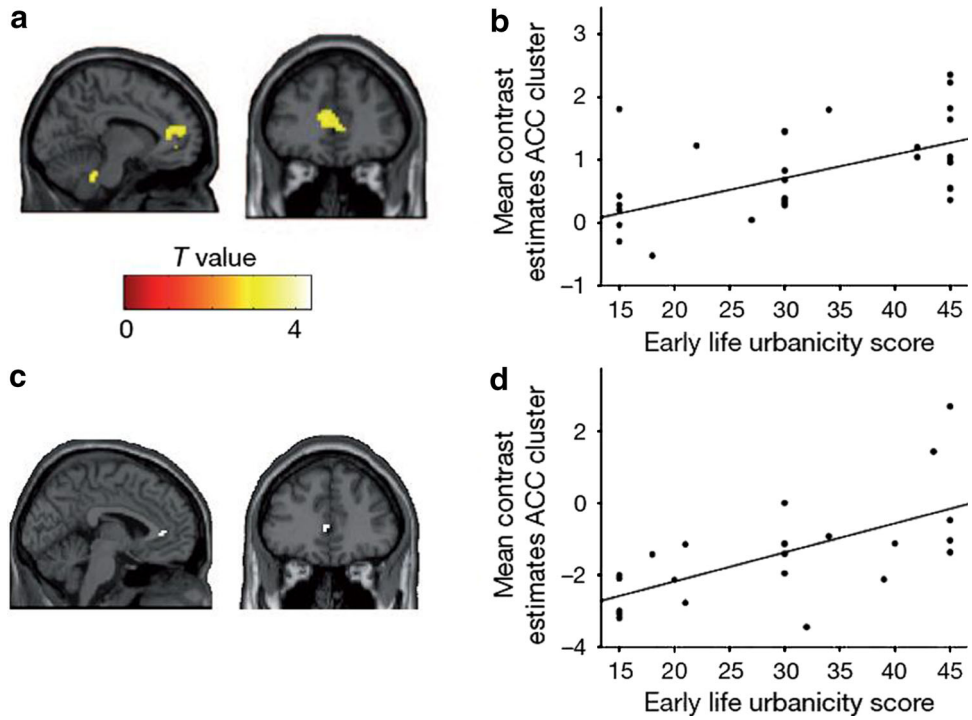

Fig. 2 Relationship between urban upbringing and anterior cingulate function. Significant association of urbanicity and social stress-related brain activation in the perigenual anterior cingulate cortex (pACC) in healthy individuals [117]: In two independent samples (a, b and c, d), authors observed a positive correlation of the individual degree of urban upbringing, an established environmental risk factor for schizophrenia, and pACC function, an important higher order regulatory area of the network processing stress and negative emotion in humans. Figure is reprinted from Lederbogen and colleagues [117]

research, the appreciation of the effects of the social milieu and its influence on structural and functional organization of the brain has just gained impetus. The studies and concepts that we have discussed in this review provide only a limited selection of the current work in the field, yet they echo the first milestones of an evolving integrative research discipline, the neuroimaging investigation of the biological mechanisms that translate social risk and resilience factors into variant outcomes for mental health [2, 13, 23]. Current evidence suggests that many of these factors may impact on individual levels of perceived social stress and engage neural stress regulatory circuits in the brain whose functional and structural architecture undergoes detrimental, but also beneficial reorganizations in response to a prolonged exposure to these influences.

The research we summarized above converges on the social stress regulatory mechanisms where ACC seems to be a key neural node. To date, accumulating evidence suggests that the effects of several genetic [28, 129–134] and environmental risk factors [20, 28, 78, 100, 117, 135] for mental health converge on ACC and conjointly impact the structural and functional organization of this network during brain development. Gene–environment interactions on the epigenetic level likely play a crucial role here, for example, hypermethylation of the promoter region of the glucocorticoid receptor gene (*NR3C1*) in the context of early social adversity which is known for promoting increased sensitivity to stress and HPA dysregulation in adulthood [136]. While the precise neural system level effects await clarification, this suggests that genetic, epigenetic, and environmental risk factors interact to affect this neural circuitry in vulnerable periods of development and that the resulting neurobiological alterations promote a decompensation of the system and psychopathology when the individual is exposed to acute stress later in life (see Fig. 1).

The organization of the individual risk and resilience matrix is likely complex and involves multiple levels on both the biological (e.g., genetics, epigenetics, cellular, and system level) and social environmental end (e.g., individual preferences, family, neighborhood, social network, regional, and global societal characteristics). Therefore, in humans, existing social, cognitive, and behavioral models of psychiatric disease should be modified and combined with neuroscience methods to investigate social environmental risk comprehensively. This also requires the thorough modeling of exiting genetic vulnerability as well as gene–environment interactions. Here, researchers will face the challenge to start disentangling the complex genetic–genetic, genetic–environmental, environmental–environmental interactions that shape, and at times reverse the sign of, the overall neural risk matrix of an individual. A good example for this complexity is the observation that ethnic minority groups bear a decreased risk for psychosis in urban areas [123, 127]. From a social psychology standpoint this interaction makes sense since urban areas often bear a high density of ethnic minorities in the immediate social environment that may carry, for a fellow minority individual, a less alienating and instead supportive, and ultimately also stress-buffering, and health protective

social surrounding [13, 69, 97]. While we expect that many of these complex risk and resilience factors will converge on neural stress regulation and involve (dys)balancing effects in downstream dopaminergic systems [55, 62, 97], researchers need to invest more time in planning comprehensive studies in future. For this purpose, multidisciplinary approaches involving researchers from sociology, psychology, cognitive sciences, and medicine should be followed. This approach will likely be better to grasp complex structure of social environmental risks. Studying not only healthy or patient populations, but also at risk populations, as well as including genetic and family history of participants would give the opportunity to observe possible gene–environment interactions. Moreover, multisite research combined with a longitudinal design which can capture early developmental factors is certainly necessary to comprehensively address this immense challenge. In terms of the investigation of neural underpinnings, use of standardized paradigms and innovative tools (such as in vivo experience sampling techniques) for the measurement of environmental, social, and neurobiological components are vital.

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Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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