

## Neural Effects of the Social Environment

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**Epidemiological studies have suggested that the association between city upbringing and minority status with risk for schizophrenia can be explained by social mechanisms. Neuroimaging approaches hold promise for investigating this claim. Recent studies have shown that in healthy individuals, city upbringing and minority status are associated with increased activity in brain circuits involved in emotion regulation during social evaluative processing. These findings support the hypothesis that changes in the ability to regulate social stress contribute to the mechanism of risk. This is in accordance with a body of evidence demonstrating the sensitivity of the human brain to social stress, based on observational studies investigating the neurological sequelae of interpersonal trauma and experimental studies manipulating exposure to interpersonal distress. In this report, we summarize these initial findings, discuss methodological and conceptual challenges of pursuing this line of inquiry in schizophrenia, and suggest an outline for future research.**

*Key words:* neuroimaging/social risk factors/urban environment/minority status/interpersonal trauma

If city upbringing and minority status increase the risk for schizophrenia,<sup>1</sup> investigating their effect on brain structure and function should yield import clues to the pathophysiology of the disorder. However, the role of the social environment has been largely neglected in the search for the neural mechanisms underlying schizophrenia, in contrast to the wealth of studies investigating mechanisms associated with genetic risk. For one thing, the complexity of social risks may have precluded researchers from trying to pin down the neural substrate underlying their effect. In addition, social risks have traditionally been the realm of social scientists and thus an improbable target for neuroscientists. However, recent studies have shown that investigating neural mechanisms of social risk is both feasible and valuable. Here we summarize these

initial findings, discuss methodological and conceptual challenges of pursuing this line of inquiry in schizophrenia, and suggest an outline for future research.

City upbringing and minority status are complex factors that in theory may reflect a myriad of relevant variables. To understand their effect, it is useful to consider another social risk factor for mental ill-health, interpersonal trauma, which has received considerable attention from neuroscience. Both animal and human studies point to structural and functional changes in the adult brain following childhood trauma, specifically in lateral and medial prefrontal, temporal, and limbic circuits involved in emotion regulation and processing.<sup>2</sup> Persistent effects have been observed even after self-reported childhood emotional maltreatment, in the absence of physical or sexual abuse,<sup>3</sup> showing that the human brain is exceptionally sensitive to interpersonal distress. Obviously, interpersonal trauma does not lend itself to experimental manipulation, but the neural mechanisms underlying this sensitivity have been elucidated using experimental approaches. Illustrative examples are the studies on interpersonal criticism and social inequity. Experimentally presented criticism of one's behavior elicits lateral prefrontal activity to regulate the impact of that interpersonal stress<sup>4</sup> and has been shown to alter functional connectivity of brain areas involved in emotion processing and social cognition.<sup>5</sup> Possibly, differential sensitivity to interpersonal criticism in individuals at risk for psychopathology may explain the association between expressed emotion and relapse.<sup>6</sup> Viewing information relevant to social ranking is associated with increased activation of several brain regions involved in cognitive regulatory and emotion processing, including dorsolateral prefrontal cortex, anterior cingulate cortex (ACC), amygdala, and ventral striatum.<sup>7,8</sup> It has been suggested that the sensitivity to social hierarchies may be 1 explanation for the negative effects of low social-economic status on mental health and cognition.<sup>9</sup> That is, frequent reminders of social inequity may sensitize or habituate individuals

to circumstances in which social hierarchy is salient. This may repeatedly trigger specific patterns of cognition and associated brain activity that eventually become trait-like features of brain structure and function.<sup>9</sup>

Could it be that a similar mechanism underlies the risk-increasing effect of city upbringing and minority status? Epidemiological data indeed suggest that the experience of being excluded from the majority group (or social defeat) may be the common denominator of social risks associated with schizophrenia.<sup>10</sup> For example, there is evidence that certain characteristics (i.e., ethnicity, deprivation) that define individuals as being different from most other people in their local environment may increase risk of psychosis.<sup>11</sup> Two recent studies from Meyer-Lindenberg and colleagues have now provided neural evidence to support this claim. In the first study, neural response to criticism (ie, the Montreal Imaging Stress Task) was investigated in healthy individuals in relation to city living and upbringing. Current city living was associated with increased amygdala activity, whereas urban upbringing was linked to increased activity in the perigenual ACC, a key region for regulation of amygdala activity, suggesting a relationship with emotion regulation.<sup>12</sup> In the second study, subjects of German lineage were compared with ethnic minority individuals of different ethnic backgrounds on the same social stress paradigm.<sup>13</sup> Results showed diminished deactivation of perigenual ACC activation in response to criticism in the ethnic minority sample and increased functional coupling of this region to higher order dorsal ACC. Activation in perigenual ACC was correlated with perceived group discrimination, and the correlation between perceived discrimination and connectivity of perigenual and dorsal ACC was mediated by chronic stress. These studies provide preliminary neural evidence that changes in the ability to regulate social stress indeed contribute to the mechanism underlying the risk-increasing effect of urban environment and minority status. Clearly, future studies may aim to connect these findings to risk for schizophrenia, to investigate if individuals at risk for schizophrenia are more vulnerable to the behavioral and neural consequences of these social stressors. Initial neuroimaging evidence linking cortical thickness to interpersonal trauma in schizophrenia suggests that this may indeed be the case.<sup>14</sup>

### Methodological and Conceptual Challenges

Some challenges to this research program are endemic to neuroimaging in psychiatry in general but become more pronounced because of the complexity of the social risk factors. First, it is difficult to study the neural substrate of social risks in clinical populations because neuroimaging is highly sensitive to other factors associated with psychiatric disorders, such as medication. Yet, investigating the mechanisms in healthy populations may limit generalizability of the findings to disorders. Studying at-risk populations will resolve some of these confounds (ie,

medication, psychopathology), but not all (ie, risk genes). Second, because of this sensitivity to confounds, neuroimaging studies generally focus on highly selective groups, trying to exclude competing causes, such as lifestyle factors or other psychopathology. While this increases internal validity, it may further limit generalizability of the results. Similarly, functional neuroimaging studies strive to avoid systematic differences in performance or behavior between the risk and the control group because otherwise any differences in brain activation may reflect these differences rather than abnormalities in the neural system underlying the performance or behavior. Yet, experimental control of differences in performance or behavior can often only be achieved by matching the groups on a range of variables, again at the cost of external validity, and possibly even excluding the variability that we aim to explain.<sup>9</sup>

These methodological concerns reflect a key conceptual question for research on the neural mechanisms of social risk. While social defeat is a plausible common mechanism underlying social risk factors, it is unlikely to be the sole factor. For example, physical characteristics of the environment, such as the amount of green space, also impact on behavior.<sup>15,16</sup> In addition, factors that mediate the risk may be of interest in itself. For example, internalized stigma may be a mediating factor contributing to experience of social defeat.<sup>17</sup> It is therefore crucially important to distinguish *a priori* between variables that are considered confounds and variables that are theoretically relevant mediators. Isolating these mediators requires sophisticated assessment of the social and physical characteristics that define urban versus rural or minority versus majority contexts.

Clearly, neuroimaging studies establish correlations, and causality between social risk and neural alterations cannot be assumed. However, if epidemiological criteria of consistency of the association, temporal order (the exposure precedes the outcome and reverse causality is ruled out), and dose response (more exposure results in progressively greater risk) are met,<sup>1</sup> neuroimaging may add to the credibility of a causal interpretation by elucidating the underlying biological and cognitive mechanisms. In addition, experimental manipulation of the hypothesized mediators of the social risk factor does permit randomization, and converging evidence from these studies may further strengthen a causal interpretation.

Notably, research investigating neural differences between social or cultural groups should be aware of ethical risks. Even though the research actually highlights brain plasticity, the biological nature of the differences may to a lay audience suggest an interpretation in terms of essential and immutable characteristics, which could even be misused to validate undesirable societal practices.

### Future Directions

Models of normal and abnormal brain development emphasize the importance of interactions between genetic

and environmental factors, with lifetime periods of increased sensitivity to environmental adversity.<sup>18,19</sup> Now that we begin to understand the effects of social risks at the neural level, the synergistic effects of social and genetic factors on brain structure and function can be investigated. For instance, genetic research has linked specific risk genes to abnormalities in neural circuits influenced by the social environment. Examining the joint effects of genetic and social factors on these neural circuits may prove a fruitful research strategy.<sup>20</sup> Large prospective population studies that track children's development into adulthood<sup>21,22</sup> should include longitudinal measurement of brain structure and function to enable investigation of sensitive periods as well as directionality in causal effects. Further, by studying those individuals who remain healthy despite exposure to risks, we will gain insight into the factors that foster resilience.<sup>23</sup> For example, there is evidence that perceived social support moderates the link between threat-related amygdala reactivity and trait anxiety.<sup>24</sup> Finally, social science is increasingly developing methods for the dynamic assessment of behavior over time, using digital traces of mobile phones, internet use etc., that together provide comprehensive pictures of the behavior of both individuals and groups in different environments.<sup>25</sup> Neuroimaging studies of the mediators of social risks may greatly benefit from such fine-grained analysis of human social behavior.<sup>4,26</sup> Elucidating the complex interactions between genetic and environmental factors at the neural level in a developmentally sensitive approach will ultimately open up new avenues for therapy and prevention.

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