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COMMENTARY

Understanding the Causal Pathway of Social Determinants of Psychosis: The Role of Social Functioning, Relevance of Animal Models, and Implications for Treatment

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There is mounting evidence that the social determinants of psychosis operate via a long and circuitous route. Here, we comment on the striking findings from a recent study by Ku et al., that area-level social environmental factors yield social disability and increased risk for schizophrenia through intervening variables and over a long time course. We discuss the relevance of animal models of social isolation to understand how environmental factors interrelate with individual-level mechanisms. We also discuss treatment implications, including the search for novel psychopharmacological treatments for reduced social motivation, and the need for a comprehensive prediction and prevention model.

Social contextual factors have a large influence on risk for developing psychosis. However, the influence is not necessarily direct or concurrent. Poor social functioning is a hallmark of schizophrenia, which is often characterized by a reduction in contact with friends and family, engagement in fewer group or structured activities, and decreased motivation to engage in these behaviors. These reduced social tendencies seem to be determined by factors that predate the onset of the illness.

One of those factors, examined in Ku et al. (this issue[1]) is social fragmentation. The Ku et al. paper is a compelling extension of prior research on the social determinants of psychosis, and in particular, the mounting evidence that environmental characteristics during childhood play a causal role in schizophrenia and other psychotic disorders. Within this literature, it is notable that some of the factors that lead to higher social fragmentation (eg, neighborhood turnover, high percentage of renters) are relatively common and do not seem obviously noxious. Yet, childhood exposure to these area-level characteristics apparently confers risk to psychosis, though not immediately and not directly. Indeed, Ku et al. found that the level of social fragmentation at the area level (defined, in this case, by Census data at the county level) during childhood impacts school adaptation in childhood which in turn affects later, but not concurrent, social functioning. Importantly, this effect is greater in those who are at clinical high risk for schizophrenia compared to those who are not.

Disrupted social functioning is thus part of the explanation for why social fragmentation is causally associated with the onset of schizophrenia. Youth already at clinical high risk may find it particularly difficult to engage and connect with others in a community or neighborhood that is socially fragmented. This could, in turn, delay or exacerbate delays in the development of social skills. Based on the findings of Ku et al., poor adjustment in elementary school, where social connections often begin, may be an early warning of a longer-term disrupted social process. Social network disruption acts as a stressor, particularly in children at high risk, during this sensitive early period. Such early stressors could initiate a cycle of social withdrawal, poor social skill development, and marginalization that becomes magnified into adolescence, closer to the time of onset of psychosis. The overall implication is that social neighborhood factors work, albeit through intervening variables and over a long time course, to yield social disability and increased risk for the disorder.

One curious aspect to the paper, and a potential limitation, is that social fragmentation was determined at the county level, even though it was described as an area or community-level analysis. That decision raises some questions regarding the interpretation of the findings. The use of a single metric for an entire county homogenizes the presumably large amount of variability in social fragmentation within a county. In addition, the performance sites for this project are located in large to medium size cities. Since each site recruited participants locally, it is likely that most of the participants at a given site came from the county in which the site was located. Conversely, it is unlikely that the participants at a given site came from a

county where another site is located. Hence, site and social fragmentation appear to be confounded. Perhaps not, but it would help to know if this possibility was formally evaluated. If site and social fragmentation are indeed confounded, then the effects currently attributed to social fragmentation could equally be attributed to site, especially regarding any differences in how and from where sites recruited their participants. The authors suggest that future studies should examine social fragmentation at the level of census tracts (closer to the neighborhood level). We fully agree because it would ensure variability within site, and we wonder if that approach could have been used for the current study.

Despite this limitation, the striking results from this paper highlight the daunting complexity of schizophrenia etiology. Given the multiple paths that contribute risk to onset of illness, understanding the social determinants of psychosis and how they interrelate with individual-level risk factors presents a substantial scientific challenge. That is why it is fortunate that some of these questions lend themselves to rigorous experimental examination that can provide insights about the mechanisms of social disability in schizophrenia. Two recent papers in this journal provide clear examples of animal models of social isolation, and novel psychopharmacological treatments for reduced social motivation.

A recent review by Powell and Swerdlow[2] described innovative work in rodents on the mechanisms through which social isolation leads to impaired social functioning. Direct manipulation of the degree of social interactions in a rat pup during critical developmental periods has profound effects on the neural circuitry involved in social information processing and observable social behavior. For example, social isolation rearing (SIR) of rats results in dopamine hyperreactivity and neuronal abnormalities in prefrontal cortex and other limbic-forebrain regions. The early social isolation also triggers stress-mediated inflammatory responses that may exacerbate these negative impacts on neural circuitry. Furthermore, SIR rats show aberrant locomotor response to novelty (perhaps analogous to disorganized behavior in schizophrenia) increased aggression, impulsivity, and anxiety-like behaviors, learning and memory deficits, and abnormal patterns of social interactions with unfamiliar rats later in life.

Of course, manipulation of a pup's social environment through experimenter-induced social isolation is not entirely equivalent to social fragmentation as defined here. Importantly, in a socially fragmented neighborhood, a buffering factor (ie, stable and enduring social connection or support) has been removed that may have otherwise protected individuals from developing psychosis. In contrast, for those animals that were exposed to social isolation rearing, a risk factor for psychosis was imposed. The animal models elucidate effects of social deprivation early in development. The more precise human analog may be naturalistic studies of early environmental deprivation (eg, Romanian orphanage studies[3,4]). In the case of social fragmentation, the quality of emotional support within the home is not known or included in the analyses. Still, both Powell and Swerdlow and Ku et al. implicate the importance of social factors and, although they have different real-world contexts, the results have similar implications for etiology of psychosis.

Given the circuitous route from environmental social determinants to social deficits and to risk for schizophrenia, where does that lead us in terms of intervention? Social functioning deficits are an elusive target for psychopharmacological intervention. The burgeoning field of social psychopharmacology has identified pharmacological agents that improve social processing abilities and increase motivation to engage in social behavior. Such agents could prove beneficial to individuals with psychiatric conditions with social impairment, including schizophrenia.

As reviewed by Bershad and De Wit[5] two of the more promising social psychopharmacological compounds are oxytocin and MDMA. Intranasal administration of oxytocin in healthy adults has been shown to increase the salience of social stimuli. In individuals with schizophrenia, findings are promising but mixed. Some studies have shown positive effects of acute oxytocin administration (eg, enhancing eye gaze, increasing subjective valuation of social reward) while others have not. So far, the effects of multiple administrations of oxytocin in the context of clinical trials for social functioning deficits is also mixed, although this important work continues to show potential as methods improve and specific treatment targets become clearer.

In healthy adults, MDMA has been shown to increase sociability, enhance response to social stimuli, and increase subjective feelings of empathy. MDMA-assisted therapy is currently being tested in the treatment of PTSD, with encouraging results thus far. Although we do not know the mechanism by which MDMA administered concurrently with psychotherapy ameliorates PTSD symptoms, it is suggested that the powerful interpersonal and prosocial effects of the drug enhance engagement and efficacy of the therapeutic process. As Bershad and De Wit point out, it would be well worth investigating MDMA effects similarly in schizophrenia, either as a standalone treatment or as a way to potentially augment psychosocial treatments of negative symptoms and poor social functioning in the disorder. Overall, while both MDMA and oxytocin show promise for addressing social functioning deficits in schizophrenia, there has been very limited research on the mechanisms of the effects, and whether the mechanisms would fit with what we know to be aberrant in schizophrenia. Thus, better understanding of the mechanisms of the drug effects in terms of social processing will facilitate future research in this area.

While the field of social psychopharmacology is moving intervention science for social deficits in schizophrenia in exciting directions, a focus on the individual level has limitations. The work by Ku et al. as well as others, eg,[6,7] highlight that beyond the individual level, which starts post-diagnosis and in adulthood, we should be thinking about the early impact of neighborhood factors and ways to intervene more globally, toward a prediction and prevention model.[8] In particular, at the neighborhood level, policy change is needed to address inequitable social conditions such as food insecurity and housing instability[9] and introduce social cohesion to socially fragmented communities.[10]

Clearly, there is exciting work going on in the rather disparate fields of research into social determinants of psychosis, development of neural circuits of relevance to psychosis, and the promise of social psychopharmacology to address social deficits of psychosis. The theoretical approach and associated methodologies of each are distinct, yet they clearly touch and inform one another. A unifying interdisciplinary conceptualization of these various avenues of psychosis research is needed but remains out of reach. Large gaps remain and bridges are needed to connect them. Still, the three papers highlighted here are good examples of just how interconnected research into social deficits of psychosis are at the neural, interpersonal, and societal levels.

Disclosures

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References

1. Ku BS, Addington J, Bearden CE, *et al*. Associations between childhood area-level social fragmentation, maladaptation to school, and social functioning among healthy youth and those at clinical high risk for psychosis. *Schizophr Bull* n.d. doi:10.1093/schbul/sbad093.
2. Powell SB, Swerdlow NR. The relevance of animal models of social isolation and social motivation for understanding schizophrenia: review and future directions. *Schizophr Bull* 2023:sbad098. doi:10.1093/schbul/sbad098.
3. Chisholm K, Carter MC, Ames EW, Morison SJ. Attachment security and indiscriminately friendly behavior in children adopted from Romanian orphanages. *Dev Psychopathol* 1995;7:283–294. doi:10.1017/S0954579400006507.
4. Kaler SR, Freeman BJ. Analysis of environmental deprivation: cognitive and social development in Romanian orphans. *J Child Psychol Psychiatry* 1994;35:769–781. doi:10.1111/j.1469-7610.1994.tb01220.x.
5. Bershad AK, de Wit H. Social psychopharmacology: novel approaches to treat deficits in social motivation in schizophrenia. *Schizophr Bull* 2023:sbad094. doi:10.1093/schbul/sbad094.
6. Morgan C, Hutchinson G. The social determinants of psychosis in migrant and ethnic minority populations: a public health tragedy. *Psychol Med* 2010;40:705–709. doi:10.1017/S0033291709005546.
7. Shah J, Mizrahi R, McKenzie K. The four dimensions: a model for the social aetiology of psychosis. *Br J Psychiatry* 2011;199(1):11–14. doi:10.1192/bjp.bp.110.090449.
8. Anglin DM. Racism and social determinants of psychosis. *Annu Rev Clin Psychol* 2023;19:277–302. doi:10.1146/annurev-clinpsy-080921-074730.
9. Alegría M, Alvarez K, Cheng M, Falgas-Bague I. Recent advances on social determinants of mental health: looking fast forward. *Am J Psychiatry* 2023;180:473–482. doi:10.1176/appi.ajp.20230371.
10. Anglin DM, Espinosa A, Addington J, *et al*. Association of childhood area-level ethnic density and psychosis risk among ethnoracial minoritized individuals in the US. *JAMA Psychiatry* 2023:1–9. doi:10.1001/jamapsychiatry.2023.2841.