

## Does the Concept of “Sensitization” Provide a Plausible Mechanism for the Putative Link Between the Environment and Schizophrenia?

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**Previous evidence reviewed in *Schizophrenia Bulletin* suggests the importance of a range of different environmental factors in the development of psychotic illness. It is unlikely, however, that the diversity of environmental influences associated with schizophrenia can be linked to as many different underlying mechanisms. There is evidence that environmental exposures may induce, in interaction with (epi)genetic factors, psychological or physiological alterations that can be traced to a final common pathway of cognitive biases and/or altered dopamine neurotransmission, broadly referred to as “sensitization,” facilitating the onset and persistence of psychotic symptoms. At the population level, the behavioral phenotype for sensitization may be examined by quantifying, in populations exposed to environmental risk factors associated with stress or dopamine-agonist drugs, (1) the increased rate of persistence (indicating lasting sensitization) of normally transient developmental expressions of subclinical psychotic experiences and (2) the subsequent increased rate of transition to clinical psychotic disorder.**

*Key words:* environment/psychosis/schizophrenia/mechanisms/mediators

### Introduction

In previous issues of *Schizophrenia Bulletin*,<sup>1–9</sup> evidence has been presented suggesting that environmental risk factors (prenatal stress/malnutrition/infection/hypoxia, paternal age, developmental trauma, urbanicity, cannabis, ethnic minority group, social fragmentation) may be associated with an increased risk for schizophrenia and psychotic symptoms, resulting in widespread geo-

graphical variation in incidence and prevalence.<sup>10</sup> These studies have several themes in common that are summarized in box 1. It is clear that much remains to be clarified. For example, although the research on individual environmental risk factors is mostly consistent, effect sizes have been derived from bias and confounding-prone observational research. Also, none of the hypothesized factors are likely necessary or sufficient nor are they specific for psychosis outcomes. Finally, variables such as ethnic group, urbanicity, or prenatal maternal malnutrition merely represent proxies for one or more nongenetic factors that remain to be identified.

Given these uncertainties, relatively little attention has been paid to what arguably constitutes the most challenging issue: is there any evidence for a plausible mechanism linking exposure to the environment to psychosis outcomes? How does the environment induce change in human beings so that enduring risk states or psychopathological outcomes may result? Rutter<sup>11</sup> has argued that there are a number of ways in which the environment can impact on the individual to increase the risk for psychopathology, including effects on gene expression, effects on developmental programming of the brain, effects on neuroendocrine and neurotransmitter functioning, effects on patterns of interpersonal interactions that may shape risk for later psychopathology, and effects on affective and cognitive processing. Therefore, one way to validate the hypothesis of a link between the environment and psychosis is to examine to what degree the two may be plausibly linked to any of the above-mentioned cognitive or biological mechanisms. Given the fact that (1) it is unlikely that the extreme diversity of environmental influences associated with schizophrenia can be linked to as many different underlying mechanisms and (2) it has been suggested that environmental exposures in schizophrenia may induce psychological or physiological alterations that can be traced to a final common pathway of cognitive biases and/or altered dopamine neurotransmission,<sup>12–15</sup> this particular suggestion will be examined in more detail, subsumed under the broad header of “sensitization.”

### Sensitization

Sensitization refers to the observation that individuals who are exposed repeatedly to an environmental risk

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**Box 1.** Common Themes of Recent Reviews on the Link Between the Environment and Schizophrenia

1. Most findings are derived from observational studies that can never conclusively exclude bias and confounding.
2. It is not clear to what degree genetic liability for psychosis is the origin of the environmental influence (eg, psychosis liability contributing to later cannabis use or maternal psychosis liability giving rise to pregnancy complications).
3. For the majority of environmental risk factors, the increase in risk is associated with exposure before adulthood, suggesting an interaction with developmental processes. For example, the risk-increasing effects of urbanicity, trauma, and cannabis use are limited to exposure during childhood and adolescence, suggesting they may create enduring liabilities that, in interaction with other factors, bring about psychotic disorder in adulthood.
4. Relative risks associated with environmental exposures are modest and none are likely necessary or sufficient. Indeed, for most, interactions with genetic risk factors are hypothesized and some gene-environment interactions using direct or indirect measures of genes and environments have been reported.
5. Many, if not most, of the environmental candidate factors represent proxies for as yet unidentified non-genetic effects. For example, while ethnic group and urbanicity can be readily used as categorical variables in statistical analyses, it is not known what underlying true environmental effect they may represent.
6. The evidence for a link between the environment and psychosis is for many risk factors, at least where this has been studied, not limited to the narrow syndrome of schizophrenia, but extending to broader psychometric expressions of psychosis in the form of psychotic-like symptoms or schizotypy.
7. None of the reported risk factors can claim a specific link to psychosis—all have been associated with a range of other psychiatric and somatic disorders.

factor may develop progressively greater responses over time, finally resulting in a lasting change in response amplitude. It has been hypothesized that the process of sensitization is the substrate for the susceptibility to the psychosis-inducing effects of stress and dopamine-agonist drugs observed in patients with schizophrenia.<sup>13,16</sup> Given the fact that many environmental exposures associated with schizophrenia may be linked to stress or dopamine-agonist drugs, sensitization may represent a common mechanism linking multiple environmental influences.

*Sensitization: Cognitive and Affective Processing*

Although the precise exposure under most environmental risk factors associated with schizophrenia remains unknown, many, including trauma, ethnic minority group, urbanicity, and social fragmentation, can be plausibly traced to “social defeat”-type psychological effects<sup>17</sup> in the realm of interpersonal interactions. Such effects play a key role in recent cognitive models of psychosis.<sup>12,18–23</sup> Early exposure to environmental risk factors such as developmental trauma and discrimination may shape specific negative beliefs about the self and about others. It has been hypothesized that such negative schemas and self-beliefs may predispose individuals to employ external attributions for negative events, possibly in order to protect the self from negative self-evaluative beliefs (delusion-as-a-defense theory).<sup>18,20,24</sup> Indeed, studies have confirmed that psychotic individuals likely attribute negative events to external causes.<sup>18</sup> Accordingly, dysfunctional beliefs and schemas may moderate the psychotogenic effect of later environmental risk factors, such as adverse life events, for psychosis. It has been argued that stressful events trigger particular emotional and cognitive changes, including automatic cognitive processes and maladaptive conscious appraisals. These, in combination with cognitive biases induced by earlier exposures, may be crucial in the formation and maintenance of positive symptoms of psychosis.<sup>12,25</sup> Recent work examining these hypotheses has yielded some evidence that the path from childhood abuse or trauma to adult psychosis is mediated by disrupted self-representations and negative beliefs about others, as well as by alterations in meta-cognition that may predispose to psychosis.<sup>26–28</sup> With the advent of sophisticated virtual reality (VR) techniques, researchers now can conduct controlled experiments in order to study, eg, how paranoia may arise from cognitive biases by observing how people interact with one another and interpret interpersonal behavior in controlled social situations. Early results show that people with paranoid thinking patterns interpret social signals abnormally.<sup>29</sup> These VR experiments can be extended to test whether certain environmental exposures or, indeed, certain genotypes are associated with psychotic interpretations. If ethically acceptable, similar controlled experiments can be conducted using actual environmental exposures. For example, a recent experimental study showed that in individuals with a liability for psychosis, paranoid thoughts were exacerbated by a deprived urban environment.<sup>30</sup>

*Sensitization: Behavioral Stress Sensitivity*

It has been demonstrated that persons with a higher than average liability to psychosis are overreactive to small stressors, displaying an exaggerated affective response<sup>31</sup> and increases in the intensity of subtle psychotic

experiences associated with minor stresses in the flow of daily life.<sup>32</sup> This effect may be described as behavioral sensitization because it has been shown to result, at least in part, from a sensitization process by which previous exposures to severe stress, such as childhood trauma<sup>33</sup> or stressful life events,<sup>34</sup> increase the sensitivity to small stresses in daily life, the cumulative impact of which might lead to the development of impairment and need for care.<sup>35</sup> These findings therefore suggest that the effects of early stress may give rise to a lasting liability in the form of emotional and psychotic reactivity.

#### *Sensitization: Dopamine Neurotransmission*

Research has revealed that dopamine is released in response to stress in both animals<sup>36–38</sup> and humans,<sup>39,40</sup> although not all studies agree.<sup>41</sup> Because dopamine is often regarded as the final common pathway of the factors involved in the causation of psychosis,<sup>13,42</sup> it is attractive to speculate that dopamine plays a role in the pathway from environmental risk exposure to psychosis.

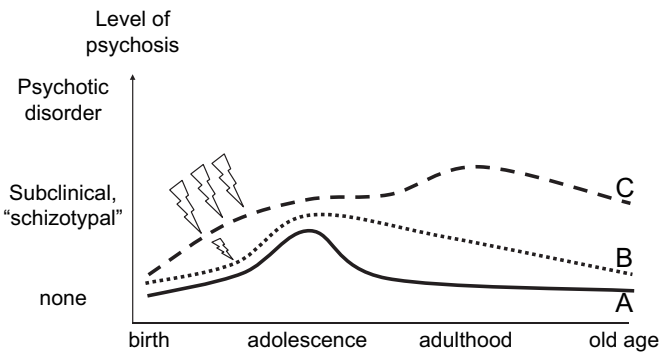
In animals, there is compelling evidence that disruptions in postnatal rearing conditions can lead to profound and lasting changes in the responsiveness of mesocorticolimbic dopamine neurons to stress and psychostimulants.<sup>43–45</sup> A similar mechanism may exist in humans as well and provide an explanation for differential dopamine reactivity in those with and without psychosis liability.<sup>32,46</sup> For example, a recent human study reported that mesolimbic dopamine release in response to psychosocial stress depended on low early life maternal care.<sup>40</sup> In rodents, there is evidence that not only early life stress but also use of agonist drugs may induce sensitization of dopamine systems.<sup>44</sup> Not only is there evidence for similar mechanisms in humans,<sup>47</sup> studies also indicate that schizophrenia is associated with increased amphetamine-induced dopamine release.<sup>48</sup>

While these findings go some way toward validating the link between environmental exposures and psychosis, the precise mechanisms and neurocircuitry underlying stress-dopamine interactions and sensitization in schizophrenia remain unknown. There is evidence that mesocortical dopaminergic innervation of the prefrontal cortex (PFC) may regulate the activity of mesolimbic subcortical DA innervations and that the impact of environmental risk factors may result in taking the PFC “off-line,” resulting in altered responsiveness of subcortical dopaminergic innervations.<sup>49</sup> Thus, when dopamine transmission is increased by exposure to stress or agonist drugs, there may be a shift in the balance of the system away from prefrontal cortical control and toward limbic predominance, facilitating the onset of psychotic symptoms.<sup>44,50</sup> Genetic variation may act synergistically with environmental risk factors in shifting the balance between mesocortical and mesolimbic dopamine neurotransmission, explaining interactions between, eg, cannabis and the catechol-O-methyltransferase<sup>val158met</sup> polymor-

phism.<sup>51,52</sup> Other models for gene-environment interactions have been proposed. For example, it has been suggested that excessive levels of catecholamine release during stress impair PFC cognitive function through intracellular signaling pathways; schizophrenia may arise in individuals with mutations in *DISC1* and *RGS4*, who may have weaker regulation of these intracellular stress pathways.<sup>53</sup> Other factors may also play a role. For example, there is animal evidence that glucocorticoids may control stress-induced sensitization by changing the sensitivity of mesencephalic dopaminergic transmission to drugs of abuse.<sup>54</sup> Similarly, prenatal stress, associated with schizophrenia,<sup>55</sup> may induce changes in dopamine sensitivity of the nucleus accumbens and in the capacity to develop amphetamine-induced sensitization in adulthood, which may be mediated by impaired control of corticosterone secretion in the prenatally stressed animal.<sup>56</sup> Finally, neurotransmitter sensitization may be associated with epigenetic mechanisms. Epigenetic factors are inherited and acquired modifications of DNA (eg, DNA methylation) and histones that occur without a change in nuclear DNA sequence but may impact on gene expression. The epigenetic state of a gene may be influenced by stress and drugs among other things and thus be considered a priori as an important factor mediating environment-schizophrenia relationships.<sup>57</sup> Many studies have identified changes in mRNA levels in key areas involved in dopaminergic neurotransmission including the ventral tegmental area and the nucleus accumbens induced by dopamine-agonist drugs (including cannabis).<sup>58–61</sup> Similarly, an epigenetic mechanism has been shown to mediate the relationship between variations in mother-infant interactions and the development of individual differences in behavioral and endocrine responses to stress in adulthood.<sup>62</sup>

#### *Sensitization: Epidemiological Predictions*

If environmental risk factors are causally associated with psychotic disorder and sensitization is the mechanism linking risk and outcome, then the challenge is to find a way to measure its behavioral phenotype and demonstrate epidemiological evidence that matches the hypothesis. Cougnard and colleagues<sup>63</sup> suggested that the behavioral phenotype for sensitization may be examined at the population level by quantifying, in populations exposed to environmental risk factors associated with stress or dopamine-agonist drugs, (1) the increased rate of persistence (indicating lasting sensitization) of normally transient<sup>64–66</sup> developmental expressions of subclinical psychotic experiences and (2) the subsequent increased rate of transition to clinical psychotic disorder (Fig. 1). In 2 large, prospective independent general population studies (Netherlands Mental Health Survey and Incidence Study [NEMESIS],  $n = 7076$ , and Early Developmental Stages of Psychopathology Study [EDSP],  $n = 3021$ ), they examined the hypothesis that relatively common,



**Fig. 1.** Sensitization Behavioral Phenotype. Person A has “normal” developmental expression of subclinical psychotic experiences that are mild and transient. Person B has similar expression but longer persistence due to additional but mild environmental exposure. Person C has prolonged persistence due to severe repeated environmental exposure and subsequent transition to clinical psychotic disorder.

subclinical developmental psychotic experiences would become abnormally persistent when synergistically combined with developmental exposures that may impact on sensitization such as cannabis, developmental trauma, and urbanicity. The authors found that the 3-year persistence rates of psychotic experiences were low at 26% in NEMESIS and 31% in EDSP. However, persistence rates were progressively higher with greater baseline number of environmental exposures in predicting follow-up psychotic experiences. The authors concluded that level of environmental risk combines synergistically with subclinical developmental expression of psychosis to cause abnormal persistence, reflecting a mechanism of sensitization.

In a subsequent study, M. Dominguez, M. Wichers, R. Lieb, H.-U. Wittchen, J. van Os (unpublished data) went 1 step further and examined the hypothesis that the probability of poor outcome (in the sense of clinical psychotic disorder) of the normally transitory developmental expression of subclinical psychosis in the general population becomes progressively greater with more tendency to persistence over time. Expression of psychosis was assessed 4 times (T0–T3) over a period of 8.4 years in a sample of 845 adolescents from the general population. Transition from subclinical psychosis at T0–T2 to clinical psychosis at T3 was examined as a function of the level of prior persistence of the subclinical phenotype over T0–T2 (subclinical psychosis present never, once, twice, or thrice at T0, T1, and T2). The authors found that the more subclinical psychosis persisted over the period T0–T2, the greater the risk of transition to clinical psychosis at T3 in a dose-response fashion.

## Conclusion

Although many questions remain, there is some evidence that environmental exposures may induce, in interaction

with (epi)genetic factors, psychological or physiological alterations that can be traced to a final common pathway of cognitive biases and/or altered dopamine neurotransmission, broadly referred to as “sensitization,” facilitating the onset and persistence of psychotic symptoms. The behavioral phenotype for sensitization may be examined at the population level by quantifying, in populations exposed to environmental risk factors associated with stress or dopamine-agonist drugs, (1) the increased rate of persistence (indicating lasting sensitization) of normally transient developmental expressions of subclinical psychotic experiences and (2) the subsequent increased rate of transition to clinical psychotic disorder.

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