

The Social Defeat Hypothesis of Schizophrenia: An Update

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According to the social defeat (SD) hypothesis, published in 2005, long-term exposure to the experience of SD may lead to sensitization of the mesolimbic dopamine (DA) system and thereby increase the risk for schizophrenia. The hypothesis posits that SD (ie, the negative experience of being excluded from the majority group) is the common denominator of 5 major schizophrenia risk factors: urban upbringing, migration, childhood trauma, low intelligence, and drug abuse. The purpose of this update of the literature since 2005 is to answer 2 questions: (1) What is the evidence that SD explains the association between schizophrenia and these risk factors? (2) What is the evidence that SD leads to sensitization of the mesolimbic DA system? The evidence for SD as the mechanism underlying the increased risk was found to be strongest for migration and childhood trauma, while the evidence for urban upbringing, low intelligence, and drug abuse is suggestive, but insufficient. Some other findings that may support the hypothesis are the association between risk for schizophrenia and African American ethnicity, unemployment, single status, hearing impairment, autism, illiteracy, short stature, Klinefelter syndrome, and, possibly, sexual minority status. While the evidence that SD in humans leads to sensitization of the mesolimbic DA system is not sufficient, due to lack of studies, the evidence for this in animals is strong. The authors argue that the SD hypothesis provides a parsimonious and plausible explanation for a number of epidemiological findings that cannot be explained solely by genetic confounding.

Key words: genetics/epidemiology/dopamine/social exclusion/migration/intelligence

Introduction

In 2005, following the principle of Occam's razor, we sought a common denominator for well-established risk

factors of schizophrenia (migration, urban upbringing, low IQ, childhood trauma, and illicit drug use) and hypothesized that long-term exposure to the experience of social defeat (SD) or social exclusion (SE) may lead to sensitization of the mesolimbic dopamine (DA) system (and/or increased baseline activity of this system) and thereby increase the risk for schizophrenia.^{1,2} Sensitization is a process whereby exposure to a given stimulus, such as a drug or a stressor, results in an enhanced response (here: DA response) to subsequent exposures. The purpose of this article is to examine the current utility of the hypothesis. We review pertinent investigations published after 2005 and discuss some findings that have not been discussed within this context before 2005. We tried to answer the following questions: (1) What is the evidence that "long-term exposure to the experience of SD or SE" explains the association between schizophrenia and the above-mentioned 5 risk factors? Are there other epidemiological findings that support or refute the SD hypothesis? (2) What is the evidence from studies in humans that SD leads to increased baseline activity and/or sensitization of the mesolimbic DA system? (3) What is the evidence from animal studies that SD leads to dopaminergic abnormalities? (4) Is SD a cause of schizophrenia?

Conceptual Issues

Although SD and SE are different terms, we aim at one type of exposure, namely the *negative experience of being excluded from the majority group*. This experience is not a specific cause of schizophrenia because many people exposed to it develop other psychiatric disorders, and it is unlikely to be a necessary or sufficient cause.

How does the SD hypothesis relate to other hypotheses in the field? Collip et al³ proposed that "environmental exposures induce psychological or physiological

alterations that can be traced to a final common pathway of cognitive biases and/or altered DA neurotransmission, broadly referred to as ‘*sensitization*’, facilitating the onset and persistence of psychotic symptoms.” Morgan et al⁴ suggested a role for cumulative social disadvantage and Hoffman⁵ formulated a social deafferentation hypothesis.

Firstly, because the sensitization hypothesis put forward by Collip et al³ does not identify specific stressors, it concerns pathogenesis rather than etiology. The SD hypothesis, in contrast, is about pathogenesis (ie, sensitization of the mesolimbic DA system) and etiology. Collip et al³ understand by sensitization also progressively greater psychological responses to the same stimulus (eg, irritation). Thus, the two hypotheses may complement each other.

Secondly, Morgan et al⁴ proposed that cumulative social disadvantage in childhood and adulthood increases risk for schizophrenia. The authors identified indicators of social disadvantage in the domains of separation from (or death of) parents, education, employment, living arrangement, housing, relationships, and social networks.⁶ Thus, the concept of social disadvantage is essentially broader than that of SD and does not specify how social disadvantage translates into increased psychosis risk. In contrast, the SD hypothesis postulates that indicators of social disadvantage may act as proxies for SD, provided that the subject interprets the situation as defeating. This is important, because no evidence exists that populations in low-income countries are at increased risk, and low socioeconomic status (SES) of the parents is generally not a risk factor for schizophrenia.⁷

Finally, Hoffman⁵ hypothesized that high levels of isolation prompt the social brain to produce spurious social meaning in the form of hallucinations and delusions representing other persons or agents. This *social deafferentation* hypothesis capitalizes on the principle that the brain, if deprived from input of information, will produce this information by itself. Thus, this hypothesis postulates that isolation is a risk factor by itself, while the SD hypothesis requires isolation to occur in a context of defeat.

Measurement

The experience of SD is difficult to measure, because humans use strategies to keep up appearances. For that reason, the SD hypothesis is mainly based on epidemiological studies that compared defeated and nondefeated groups (not individuals). Alternative measurements include firstly the use of questionnaires such as the Social Comparison Scale,⁸ the Defeat Scale,⁹ and the Brief Core Schema Scales.¹⁰ Secondly, one can use momentary assessment techniques,¹¹ or, since exclusion from the majority group will often lead to low self-esteem, tests for the measurement of implicit self-esteem.¹² Thirdly, one can simulate SE

or negative evaluation in a laboratory situation¹³ although the short duration of exposure is a drawback.

Evidence That SD Explains Association With Urban Upbringing

What is the evidence that higher levels of competition in urban areas, and correspondingly more frequent exposure to SD, explain the association between urban upbringing and risk for schizophrenia? A functional magnetic resonance imaging (fMRI) study examined the impact of urban upbringing and current city living on social evaluative stress processing in the brain.¹³ The researchers subjected psychologically healthy participants to the Montreal Imaging Stress Task (MIST), which requires individuals to solve arithmetic tasks under pressure of time and negative feedback. The results showed that current city living was associated with increased amygdala activity, whereas urban upbringing affected the perigenual anterior cingulate cortex. No urbanicity effect was seen during control experiments invoking cognitive processing without stress. Interestingly, the results may provide a neural basis for the epidemiological finding that urban upbringing, rather than current city living, is associated with increased risk for schizophrenia and provide preliminary evidence for SD as the mechanism underlying the association with urban upbringing.

Zammit et al¹⁴ examined whether individual, school, or municipality characteristics predicted the psychosis risk for Swedish adolescents. School-level variables included the *foreign-born average* (proportion of children with 1 or 2 parents born abroad), the *social fragmentation average* (the proportion of children who migrated into Sweden, moved into a different municipality between ages 8 and 16 years, or were raised in single-parent households), the *deprivation average* (proportion of children with low SES), and the *low-grade average* (proportion of children scoring low). Municipality variables included, among others, population density. Interestingly, the results showed strong evidence of interaction between certain variables at the individual level and the same variables at school level. For example, deprivation at the individual level increased psychosis risk when most children at school were not deprived. However, deprivation at the individual level protected against psychosis when the majority of most children at school were deprived. The same was true for the variables foreign birth and social fragmentation but not for low grade. The authors concluded, in line with the SD hypothesis, that any characteristic that defines a person as different from his environment may increase his psychosis risk. In conclusion, the results of the Lederbogen et al¹³ study suggest a role for SD in the etiology of schizophrenia, but do not yet, of course, establish a causal relationship. The results of the Zammit et al¹⁴ study suggest causality more strongly.

Evidence That SD Explains Association With Migration

The SD hypothesis was prompted in part by a meta-analysis of migrant studies, which showed greater effect sizes for migrants from low-income countries and for migrants with black skin color.¹⁵ Bourque et al¹⁶ found that the increased risk persists into the second generation, suggesting that rather than adverse circumstances during the migration process per se, the minority position in the host society has a more determinant role.

One of the most striking findings in this area is the crossover interaction with ethnic density. In The Hague and London, it was demonstrated that living in a neighborhood with a high proportion of residents of the own ethnic group is related to a lower risk for schizophrenia and low own-group ethnic density to a higher risk.^{17,18} Das-Munshi et al¹⁹ showed that potential markers of SD, such as discrimination, poor social support, and chronic strains, mediated the relationship between low own-group ethnic density and presence of psychotic experiences. Zammit et al¹⁴ showed that the ethnic density effect also operates at school level because it similarly applies to children with Swedish parents attending schools with a high proportion of foreign-born children.

A longitudinal study from the Netherlands demonstrated that younger age at migration predicts a higher risk for psychotic disorders among non-Western immigrants, with the most elevated risk among children who migrated between ages 0 and 4 years.²⁰ Remarkably, the risk for migrants arriving at age 20–24 or 25–29 was only modestly increased. Whether these findings support or contradict the SD hypothesis is uncertain. One could both predict a high risk for migrants who arrive in early adulthood and have to cope with difficulties at the labor market and also for migrants who are exposed to discrimination at a very young age. The results must, however, be interpreted with caution, because they could not be replicated using nationwide registry data from Denmark.²¹

Evidence That SD Explains Association With Low IQ

Low IQ is a well-established risk factor for schizophrenia and several studies attempted to identify common (poly)genetic components between the two phenotypes. Touloupoulou et al^{22,23} initially reported high (–.75) to moderate (–.38) phenotypic correlations between IQ and schizophrenia, respectively. However, the twin samples of these studies were not population based and IQ was measured after the onset of psychosis. Fowler et al²⁴ avoided these sources of bias and found a weak correlation (–.11) and a shared genetic variance of only 7%.

Goldberg et al²⁵ examined the influence of cognitive abilities and premorbid SES on the risk of hospitalization for schizophrenia. Adolescents with low cognitive ability appeared to have an increased risk for schizophrenia,

especially when they grew up in areas with a high SES. The authors argue that the increased risk may be partly conferred by the discrepancy between these high expectations and actual achievements. Nonetheless, the evidence supporting the role of SD in the association between low IQ and schizophrenia is as yet not sufficient.

Evidence That SD Explains Association With Childhood Trauma

Meta-analytic evidence demonstrates consistent patterns of increased incidence of psychotic disorder and sub-clinical psychotic symptoms in individuals who experienced several types of childhood trauma.^{26,27} Despite the association being predominantly based on results from retrospective studies susceptible to recall bias, its validity has been strengthened by comparable findings from prospective studies that did not depend on personal recollection.^{28,29}

Childhood trauma encompasses a broad range of adverse experiences. Traumas that involve an intentional harm such as sexual, physical and psychological abuse, and bullying, putatively lead to SD. In other types of childhood trauma, such as accidents or parental loss, SD might not necessarily be as directly implicated. In a longitudinal twin study, risk for psychotic symptoms at age 12 was associated with previous maltreatment by an adult (relative risk [RR] = 3.2, 95% CI = 1.9–5.2) or bullying by peers (RR = 2.5, 95% CI = 1.7–3.5), but much less so with the experience of a lifetime accident (RR = 1.47, 95% CI = 1.0–2.1).²⁸ In line with the SD hypothesis, the relationship between intentionally inflicted childhood trauma and risk of psychotic disorder stresses the putative pathogenic influence of the experience of (chronic) humiliation. Contrarily, parental separation and parental death are types of trauma associated with increased psychosis risk that do not necessarily involve an intention to harm.^{6,27} However, it is unknown whether these events are causal factors per se or whether they represent markers for family conflicts or instability.

In conclusion, consistent with the SD hypothesis, an increasing body of evidence affirms a true association between childhood trauma and psychotic disorder.

Evidence That SD Explains Association With Illicit Drugs

That people who use illicit drugs are at risk of developing schizophrenia is primarily due to a toxic effect of these substances. However, SD may contribute to the association between drug use and schizophrenia in at least two ways. Firstly, drug abuse often leads to SD. Secondly, SD may lead to drug abuse. Studies have shown a strong association between a history of childhood trauma and subsequent drug abuse³⁰ and between unemployment and drug abuse.³¹

Other Epidemiological Findings

Risk for schizophrenia is associated with single status. While there may be many reasons for being unmarried, this may act as a stressor. The same considerations apply to unemployment. There are reports of an increased risk for schizophrenia among people with a hearing impairment.³² Earlier reports of no association between autistic spectrum disorders and schizophrenia are now superseded by reports of an increased risk.³³ There is evidence that autism and schizophrenia share genes, but SD may contribute to the increased risk. Traumatic brain injury is associated with an increased risk for schizophrenia.³⁴ It would be interesting to examine whether psychosis develops especially in those patients who lose their status. Klinefelter syndrome, characterized by small genitals and infertility, is associated with an excessive risk for schizophrenia.³⁵ An investigation of the Danish psychiatric registry found no significantly increased risk for schizophrenia among people with a cleft palate, but this may have been due to insufficient power of the study.³⁶ With reference to discriminated minorities, during the period 1935–1965, there have been consistent reports of an increased risk for schizophrenia among African Americans.³⁷ More recent studies seem to confirm the earlier findings of a 2- to 3-fold elevated risk.^{38,39} One could argue that the low prevalence of schizophrenia among a religious minority in North America, the Hutterites, argues against the hypothesis, but this group is known for its social cohesion.⁴⁰ As for sexual minorities, population surveys reported an increased risk of psychotic symptoms among people with a homosexual orientation⁴¹ and there is preliminary evidence of an increased risk among people with a gender identity disorder.⁴² Other findings include the high prevalence of schizophrenia among illiterates in China, who experience discrimination,⁴³ and the negative association between tallness and risk for schizophrenia among Swedish recruits.⁴⁴

Evidence That SD in Humans Leads to Sensitization of the Mesolimbic DA System

Positron emission tomography (PET) studies have shown that nonpsychotic subjects who report a low level of maternal care in early life release more DA after exposure to the MIST.^{45,46} Another PET study using the MIST showed that neuroleptic-naive patients and clinical high-risk subjects also exhibit a sensitized dopaminergic response.⁴⁷ The negative feedback on performance, which characterizes the MIST, seems to be essential, because a mathematic stress task without negative feedback yielded negative results.⁴⁸ There have been no studies of DA function in migrants, people raised in cities, people with low IQ, or traumatized people. To summarize, the association between low-perceived maternal care and stress-related DA function and the importance of negative feedback as stressor support the SD hypothesis, but the evidence on a whole is insufficient.

Evidence From Animal Studies That SD Leads to Sensitization of Mesolimbic DA System

Several lines of experimental research have shown that the psychosocial environment, and chronic stress in particular, can mediate changes in gene expression, the hypothalamic-pituitary-adrenal (HPA) axis, mesolimbic DA neurotransmission, and behavior. Firstly, Meaney and Szyf⁴⁹ have shown that parental care during early life of rodents induces long-term behavioral and neurobiological alterations, with offspring of low-nurturing mothers showing more signs of anxiety and stronger corticosterone responses after stress exposure, while expressing lower levels of the glucocorticoid receptor in the hippocampus in adulthood. Additional experiments indicated that epigenetic mechanisms mediated these alterations, whereas further animal studies have shown intricate cross talk between the HPA axis and mesolimbic dopaminergic transmission circuitries in relation to chronic stress.^{50,51}

With respect to chronic SD stress, several animal studies using resident-intruder paradigms for modeling the effects of SD stress exposure have found strong indications that SD leads to dopaminergic hyperactivity, particularly in the mesolimbic dopaminergic neurotransmission system⁵² and to behavioral sensitization.⁵³ Interestingly, the effects of SD on the dopaminergic system seem to depend on environmental circumstances after the defeat. For example, Isovich et al⁵⁴ found that SD-induced alterations in the binding capacity of the DA transporter depended on the housing conditions after the defeat experience; ie, social isolation after the defeat amplified the alterations, whereas more social housing, ie, return to the same group as before the defeat, mitigated the changes.

It is important to note that the severe physical and social stress to experimental mice cannot directly be compared with the SD experience as occurring in everyday life of humans. Nevertheless, experimental SD exposure in rodents has been shown to induce striking alterations in anxiety-like behavior, prolonged elevations in corticosterone levels, and a range of other molecular, cellular, and behavioral changes⁵⁵ such as alterations in neurogenesis,⁵⁶ besides the above-mentioned effects on dopaminergic transmission and behavioral sensitization.

Accumulating evidence indicates that chronic SD paradigms elicit a striking differential susceptibility in social behavior as well as in distinct neurobiological phenotypes of SD-exposed mice.⁵⁵ At the behavioral level, one group of mice displays social avoidance after the SD experience (these mice are called “susceptible”) and signs of anhedonia, while a second group of mice still shows social interaction rates that are comparable with the control group (and is therefore called “unsusceptible” or “resilient”). At the neurobiological level, the susceptible mice display increased firing rates of dopaminergic ventral tegmental area (VTA) neurons (ie, the mesolimbic system,

particularly those projecting to the nucleus accumbens),⁵⁷ connected to upregulated voltage-gated K⁺ channels and epigenetic aberrations of the brain-derived neurotrophic factor gene, while unsusceptible mice displayed normal firing rate of dopaminergic VTA neurons.⁵⁵

Thus, findings from animal studies are providing strong and replicated evidence that SD increases baseline activity of the mesolimbic dopaminergic system and induces sensitization of DA-related behavioral, electrophysiological, and neurochemical features, while the more recent studies also illustrate that animals may strongly differ in DA-related effects of SD exposure, that chronic stress-induced alterations of the HPA axis are connected to dopaminergic alteration, and that the differential susceptibility to SD may be (at least in part) of epigenetic origin.

Is SD a Cause of Schizophrenia?

Before addressing this question, we will respond to the following criticisms: (1) the association between SD and schizophrenia is due to genetic confounding and (2) SD is not a specific risk factor for schizophrenia.

An explanation in terms of genetic confounding assumes that people who are genetically predisposed to schizophrenia move to urban areas because they prefer to live in anonymity, emigrate because they fail to integrate in their home country, are victimized during childhood because of their poor social skills, and use illicit drugs because they are unhappy. In other words, SD is the consequence, not the cause. This explanation meets with at

least four challenges. Firstly, there is little supportive evidence.^{15,27} Secondly, the explanations do not allow for the possibility that causality operates in both directions. Individuals genetically predisposed to schizophrenia, eg, may be more likely to use illicit drugs, but this does not preclude a toxic effect of these drugs. Thirdly, some assumptions are contradictory: children who carry genes for schizophrenia are presumed to be socially vulnerable, but migrants are enterprising and constitute a positive selection in terms of physical health.⁵⁸ Finally, the genetic confounding hypothesis rests on too many unproven assumptions: certain genes cause schizophrenia and the same genes also cause their carriers to move to cities, to emigrate, to use drugs, to be bullied, and to be victimized.

As for the issue of specificity, risk factors are rarely specific for a particular psychiatric disorder.⁵⁹

We conclude that the SD hypothesis provides a more parsimonious and therefore more plausible explanation for the schizophrenia risk pattern than an explanation solely in terms of genetic confounding. Moreover, it may explain why a large part of the genome is involved in etiology, because any change in a gene that renders the carrier more prone to SD will influence his risk. Another corollary of the SD hypothesis is that the presence of any mental disorder will increase the patient's risk for schizophrenia, because having a mental disorder is usually associated with a degree of SE. The literature provides support for this idea: mood, anxiety, and substance use disorders are common precursors for schizophrenia.^{60,61} See figure 1 for a schematic illustration.

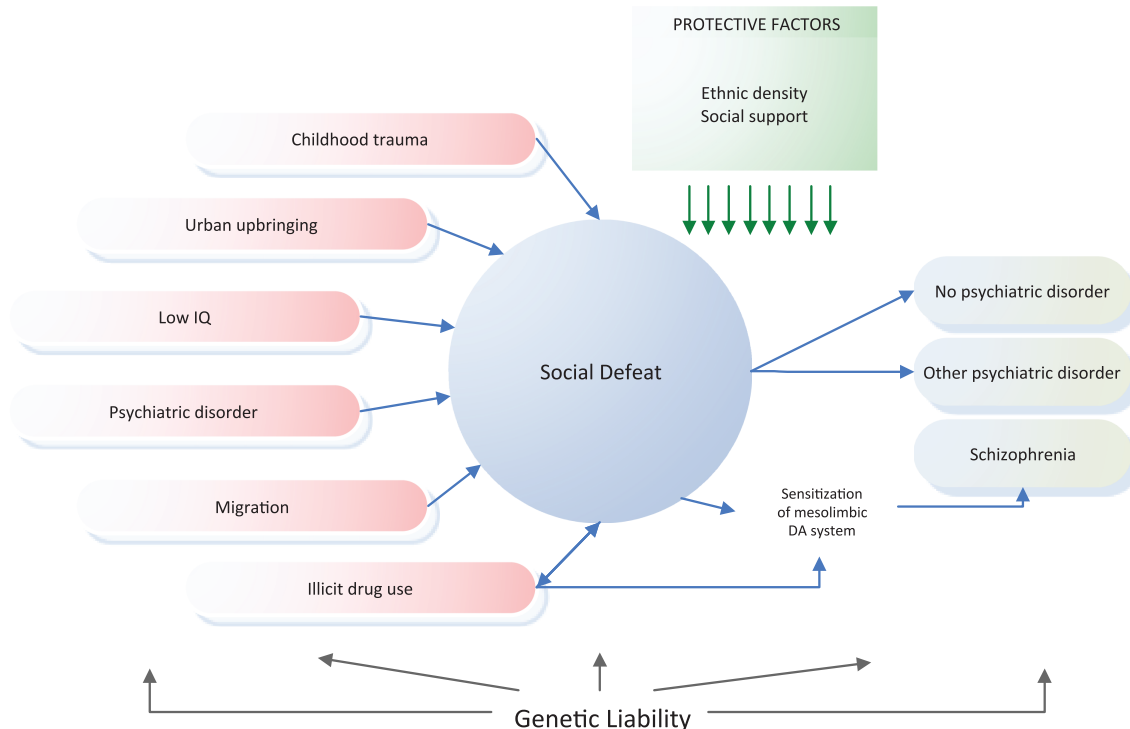


Fig. 1. Schematic illustration of the experience of social defeat as the common mechanism underlying 6 major schizophrenia risk factors.

In sum, the evidence for the first part of the SD hypothesis (SD is the common denominator for the 5 major risk factors) is fairly strong and we contend that long-term exposure to SD is a cause of schizophrenia indeed. The evidence for the second part of the hypothesis (SD leads to DA dysregulation), however, is insufficient.

Future Studies

Hypotheses should be evaluated by subjecting them to crucial tests. There are many possibilities. For example, our prediction that a study of ethnic subgroups within the Israeli population would find the highest risk for Ethiopian Jews was confirmed.^{1,62} Future studies could examine whether people with a genetic risk for schizophrenia react differently to simulated SE using fMRI and investigate which (epi)genetic profiles are associated with susceptibility to SD. Neuroreceptor imaging studies can examine DA response during stressful circumstances and DA function in high-risk groups. Thus, the SD hypothesis seems to provide many promising avenues for investigating epidemiological patterns that are still lacking a satisfactory explanation.

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