Hypothesis: social defeat is a risk factor for schizophrenia?

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Summary  The increased schizophrenia risks for residents of cities with high levels of competition and for members of disadvantaged groups (for example migrants from low- and middle-income countries, people with low IQ, hearing impairments or a history of abuse) suggest that social factors are important for aetiology. Dopaminergic dysfunctioning is a key mechanism in pathogenesis. This editorial is a selective literature review to delineate a mechanism whereby social factors can disturb dopamine function in the brain. Experiments with rodents have shown that social defeat leads to dopaminergic hyperactivity and to behavioural sensitisation, whereby the animal displays an enhanced behavioural and dopamine response to dopamine agonists. Neureceptor imaging studies have demonstrated the same phenomena in patients with schizophrenia who had never received antipsychotics. In humans, the chronic experience of social defeat may lead to sensitisation (and/or increased baseline activity) of the mesolimbic dopamine system and thereby increase the risk for schizophrenia.

Declaration of interest  None.

Current textbooks of psychiatry remain undecided about a causal role for psychosocial stress in the aetiology of schizophrenia. Researchers who are opposed to this possibility often point out that studies of life events occurring shortly before the first psychotic episode have yielded negative or inconclusive results. In actuality, we have no idea when a so-called schizophrenic disorder really ‘begins’. Interestingly, a study of discordant twins has shown that divergence in school performance precedes the onset of psychosis by an average of 10 years (van Oel et al, 2002). This suggests that certain causal factors may operate long before the emergence of psychotic symptoms and that the time frame of life-event studies is inadequate. The purpose of this paper is to present evidence in support of the hypothesis that a chronic and long-term experience of social defeat may lead to sensitisation of the mesolimbic dopamine system (and/or to increased baseline activity of this system) and thereby increase the risk for schizophrenia. The hypothesis is based on epidemiological findings, studies of dopamine function in humans and animal experiments.

Epidemiological findings

Some established risk factors for schizophrenia, which are not purely genetic, are the urban environment, migration, low IQ, hearing impairment and the use of illicit drugs.

Krabbendam & van Os (2005) performed a meta-analysis of studies that examined the rate of schizophrenia in urban as compared to rural areas, and obtained a mean weighted relative risk (RR) of 1.72 (95% CI 1.53–1.92). The available evidence suggests that causation (urban environment causes psychosis) is more important than selection (high-risk individuals move into urban areas) and that the effect of the environmental factors in the urban environment is conditional on genetic risk.

Considerable interest has been generated by studies of first- and second-generation migrants. A meta-analysis of incidence studies found an even greater increase in psychosis risk for the second generation (RR=4.5, 95% CI 1.5–13.1) than for the first (RR=2.7, 95% CI 2.3–3.2) (Cantor-Graae & Selten, 2005). Further subgroup comparisons showed greater effect sizes for migrants from lower and middle-income versus high income countries and a remarkably high risk for migrants from countries where the majority of the population is Black (RR=4.8, 95% CI 3.7–6.2). It is important to note, however, that very high risks have also been noted for non-Black immigrant groups. Denmark has received many immigrants from its former colony Greenland and the risk for second-generation Greenlanders, who are ethnic Inuit, is 12.4 (95% CI 4.7–33.1) times the risk for ethnic Danes (Cantor-Graae & Pedersen, 2007). In the Netherlands, the risk for second-generation Moroccan males is 6.8 times (95% CI 3.3–14.1) the risk for Dutch males (Veling et al, 2006). Selective migration of genetically vulnerable individuals has been ruled out as the sole explanation for the increased risk in migrants (Cantor-Graae & Selten, 2005).

A third risk factor for schizophrenia is low intelligence. A follow-up study of Swedish conscripts, for instance, showed that the risk for schizophrenia was strongly and linearly related to low IQ (Zammit et al, 2004). Subjects with an average IQ, for example, had a significantly greater risk of developing schizophrenia than those with an IQ of more than 126 (RR=1.3, 95% CI 1.04–1.54).

It has been estimated that the use of cannabis and other dopamine-enhancing drugs approximately doubles the risk (Arseneault et al, 2004). Hearing impairment and deafness are well-established risk factors for psychosis, but the magnitude of the relative risk for narrow schizophrenia associated with these factors is not precisely known (Thewissen et al, 2005). Finally, accumulating evidence indicates that a history of physical or sexual abuse during upbringing is a risk factor for schizophrenia, but opinions are still divided as to whether it is a causal risk factor (Read et al, 2005).

Social defeat

Previously, we have proposed that the long-term experience of social defeat, defined as a subordinate position or as outsider status, may well be the common denominator for these findings (Selten & Cantor-Graae, 2005). This interpretation is compatible with the high levels of competition in urban areas, the fewer career opportunities for people with low IQ, the social exclusion experienced by immigrants and people with
The experience of social defeat will lead to a greater need for illicit drugs and to a greater susceptibility to these substances (see below). Finally, since males may feel more pressed to achieve a social rank than females, the hypothesis may also explain the higher risk and earlier onset in males (Aleman et al., 2003), but this is uncertain.

**CONCEPTUAL ISSUES**

The experience of defeat is in the eye of the beholder. Consequently, the absence of an association between socio-economic status of the parents and risk for schizophrenia in the child does not necessarily argue against the hypothesis. Children of high socio-economic status, who may feel pressured to meet the high expectations of their parents, may feel more easily defeated than other children. Furthermore, social defeat is neither a necessary nor a sufficient condition for the development of schizophrenia, is not always followed by the development of a psychiatric disorder and is also a risk factor for depression and addiction. Other factors, including those under a strong genetic control, would determine the nature of the outcome of exposure to social defeat. The important consideration here is that the genetic vulnerability to schizophrenia may be present in 10–20% of the population. Thus, the likelihood that gene carriers may go on to develop the schizophrenia phenotype may be strongly influenced by the experience of defeat. The importance of social defeat for the development of major psychiatric disorders is not surprising, given the central role of social competition in the evolutionary process.

Finally, it is worthwhile to note that ‘social defeat’ is also a consequence of a schizophrenic disorder, even before the emergence of psychotic symptoms. One may argue that it is difficult to distinguish between the episodes of defeat that constitute causal risk factors for the disorder, and the social decline that has already been set in motion and is part-element of the schizophrenia prodrome. The fact remains, however, that defeated populations (i.e., certain immigrant groups) produce more cases than non-defeated populations. The question as to whether defeat in particular or stress in general contributes to the aetiology of schizophrenia is difficult to answer at this point in time, because stressful experiences are also, to a varying degree, humiliating. The current hypothesis remains the most viable interpretation of the available epidemiological data.

**DOPAMINE FUNCTION IN SCHIZOPHRENIA**

Evidence for the role of dopamine in the development of schizophrenia is provided by the increased occupancy of striatal D2 receptors by dopamine in patients who have not received medication, the psychotogenic effects of dopamine-enhancing drugs and the known mode of action of antipsychotic drugs, i.e. blockade of dopamine D2 receptors (reviewed by Laruelle, 2003). Furthermore, current evidence indicates that the mesolimbic dopamine system is sensitised in schizophrenia. Sensitisation is a process whereby exposure to a given stimulant results in an enhanced response at subsequent exposures, in this example excess release of dopamine or the development of psychotic symptoms. The notion that patients with schizophrenia show dopamine sensitisation is supported by neuroreceptor imaging studies which have shown that amphetamine-induced dopamine release is increased in neuroleptic-naive individuals with schizophrenia; and many patients display increased sensitivity to the psychotogenic effects of illicit drugs. This means that they develop psychotic symptoms after exposure to doses that do not induce psychosis in healthy subjects. However, dopamine only mediates psychosis. Thus, important questions remain concerning the nature of the earlier events that lead to dopaminergic dysregulation. That social defeat could well be one of these earlier events is illustrated by a series of animal experiments.

**ANIMAL STUDIES**

In non-human primates dopamine function and social dominance are related. A neuro-receptor imaging study, which examined dopamine function in individually and socially housed cynomolgus macaques, yielded intriguing findings (Morgan et al., 2002). While the monkeys did not differ during individual housing, subsequent social housing increased the amount or availability of dopamine D2 receptors in the dominant monkeys and produced no change in the subordinate monkeys. Furthermore, the defeated monkeys consumed more cocaine than the dominant ones. The results indicated that individually housed monkeys and socially subordinate hearing impairments and the humiliation of being abused.

The pattern of findings among immigrants supports this idea. A greater effect size for the second generation than for the first can be expected, because it is more humiliating to feel unwelcome in the country that you are born in than to feel unwelcome because you are born abroad. Furthermore, the immigrants with the highest risks (Moroccan males in the Netherlands, the Inuit in Denmark and African–Caribbeans in the UK) belong to the least successful and/or the most heavily discriminated groups. Moroccan males in the Netherlands are known for the highest crime and unemployment rates and have reported the highest frequency of the experience of discrimination. Remarkably, the schizophrenia risk for first- or second-generation Moroccan females is not increased (Veling et al., 2006). They have an inferior position in Moroccan society, but receive many opportunities for education and career in the Netherlands. Since migration has conferred upon them a considerable rise in social status, their low risk accords with the hypothesis. (Moroccans of either gender are exposed to the stress of acculturation and this type of stressor is therefore unlikely to explain the pattern of findings.) In Denmark, first- and second-generation Greenlanders have higher rates of schizophrenia than most other ethnic groups. It should be noted that Greenlanders and citizens from other Nordic countries are granted automatic entry into Denmark by inter-Nordic agreement, yet the rates for schizophrenia among Greenlanders are much higher than for persons from the other Nordic countries (Cantor-Graae et al., 2003). Rates of unemployment and social welfare benefits are higher among Greenlanders than among nearly all other immigrant groups, suggesting that social exclusion may play a key role in their increased risks for schizophrenia. Since the pain of social exclusion and humiliation may be mitigated by social support, the social defeat hypothesis also predicts a smaller risk increase in groups known for their strong social and family networks. Asian immigrants to the UK and Turkish immigrants to the Netherlands may serve as an example. The observation that the incidence in minority ethnic groups is smaller when they comprise a greater proportion of the local population accords with this view (Boydell et al., 2001).
animals had relatively high levels of synap-
tic dopamine (i.e. dopaminergic hyperactiv-
ity) and that the dominant animals, after
social housing, returned to a 'normal' state
of dopamine function.

An even more interesting animal model
for social defeat stress is the resident-
intruder paradigm, whereby a male rodent
(the intruder) is put into the cage of another
male (the resident). Within a minute the re-
sident attacks the intruder and prompts him
to display submissive behaviour. The ex-
periment showed that social defeat stress
leads to dopaminergic hyperactivity in the
mesocorticolimbic system, not in the
nigrostriatal system, and that the effects
depended on the housing conditions after
defeat (Tidey & Miczek, 1996). Lengthy
isolation after defeat amplified the changes
in the dopaminergic activity, whereas re-
turn to the group mitigated them (Isoivic
et al, 2001). (The reader may note a parallel
with the protective effects of social cohe-
sion and high ethnic density.) The research-
ers also found that repeated experiences of
defeat lead to a long-lasting 'behavioural
sensitisation', in which the animal displays
an enhanced behavioural and dopamine
response to dopamine agonists (e.g.
Covington & Miczek, 2001). Several
studies have confirmed this finding and
shown that the endogenous kappa opioid
system (McLaughlin et al, 2006) and the
brain-derived neurotrophic factor (BDNF)
(Berton et al, 2006) contribute to the de-
velopment of the response.

These observations lead to the import-
ant conclusion that patients with schizo-
phrenia who are antipsychotic-naive
resemble in some aspects defeated animals
and, subsequently, to the hypothesis that
the experience of social defeat is one of the
factors that can lead to behavioural
sensitisation in humans. Two other schizo-
phrenia risk factors that have been
shown to produce behavioural sensitisation
in rats are repeated exposures to dopamine-
enhancing drugs (Vanderschuren & Kalivas,
2000) and perinatal anoxia (Brake et al,
1997). Furthermore, an experimental lesion
in the ventral hippocampus, produced
during the neonatal period, leads to dopa-
mine sensitisation in the adult rat (Lipska
et al, 1993). Thus, behavioural sensitisation
seems a common pathogenetic mechanism
for several schizophrenia risk factors.

It is important to note that social defeat
is not the only social stressor that can influ-
ence dopamine function in rats. Isolation
rearing leads to elevated basal dopamine
levels and to an enhanced amphetamine-
evoked dopamine release (Hall et al., 1998).
Maternal deprivation, in contrast, leads to a diminished behavioural response to amphetamine, despite apparent increases in presynaptic dopamine function in the nu-
cleus accumbens (Hall et al., 1999).

Finally, since the gene for brain-derived
neurotrophic factor is a candidate gene for
schizophrenia, one can hypothesise that
variation in this gene contributes to varia-
tion in the genetic vulnerability for schizo-
phrenia by influencing the response to
social defeat.

TESTING THE HYPOTHESIS

Thus, a major task for research in humans
is to examine whether social defeat stress
leads to sensitisation of the mesolimbic do-
pamine system. The results may have wide
implications for our understanding of all
major psychiatric disorders. Several strat-
egies are possible; the most fruitful one
for testing the hypothesis would be a pros-
pective, longitudinal study examining
dopamine function before and after a possi-
able defeat. For example, one could com-
pare healthy young adults who leave the
same school and start competing in the
labour market and re-examine them 2 years
later. Since the experience of defeat is likely
to lead to a decrease in self-esteem, one
could conduct repeated measurements of
self-esteem. This type of research has been
facilitated by major advances in the de-
velopment of implicit association tests to
measure self-esteem (e.g., Greenwald &
Farnham, 2000; Greenwald et al., 2002).
These tests assess automatic associations of
self with positive or negative valence
(by measuring differences in reaction times)
and are less biased by the need to represent
the self in a socially acceptable manner.

A second possibility is to compare,
again, ethnic groups. It is likely that amphe-
tamine-induced dopamine release is nor-
mal only distributed and that the distribution
in defeated populations is shifted towards
the right. Consequently, one may compare
immigrants from a 'super-high' risk group
(e.g. second-generation Moroccan males in
the Netherlands) to natives (Fig. 1).

Although this type of research currently
has limited feasibility owing to the large
numbers of participants that would be
required to demonstrate a small- to
medium-size difference in amphetamine-
induced dopamine release between groups,
developments in technology may soon
make this a more realistic undertaking.

Third, since the experience of social de-
feat is not only a risk factor for schizo-
phrenia, but also for addiction and
depression, one can examine the risks for
these disorders in defeated populations. A
study conducted in the Netherlands showed
that those immigrant groups that are at an
deceased risk of schizophrenia are also at an
increased risk of drug use disorders, but not
alcohol use disorders (Selten et al., 2007).

Finally, history carries out natural experi-
ments. The social defeat hypothesis predicts
the highest risks of schizophrenia for minor-
ity ethnic groups who are lowest on the social
scale: Albanians in Greece, North-Africans in
France, African-Americans in the USA,
Ethiopian Jews in Israel. Importantly, if
these groups are successful in other host
countries, their risks should be not in-
creased. Ethnic groups characterised by
strong social and family networks (Cape
Verdians in the Netherlands, for example)
should have 'normal' risks or only mildly
increased risks.

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Incidence of schizophrenia in ethnic minorities in
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