SPECIAL ARTICLE

Urbanicity, social adversity and psychosis

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In recent years, there has been increasing interest in research on geographical variation in the incidence of schizophrenia and other psychoses. In this paper, we review the evidence on variation in incidence of schizophrenia and other psychoses in terms of place, as well as the individual- and area-level factors that account for this variation. We further review findings on potential mechanisms that link adverse urban environment and psychosis. There is evidence from earlier and more recent studies that urbanicity is associated with an increased incidence of schizophrenia and non-affective psychosis. In addition, considerable variation in incidence across neighbourhoods has been observed for these disorders. Findings suggest it is unlikely that social drift alone can fully account for geographical variation in incidence. Evidence further suggests that the impact of adverse social contexts – indexed by area-level exposures such as population density, social fragmentation and deprivation – on risk of psychosis is explained (confounding) or modified (interaction) by environmental exposures at the individual level (i.e., cannabis use, social adversity, exclusion and discrimination). On a neurobiological level, several studies suggest a close link between social adversity, isolation and stress on the one hand, and monoamine dysfunction on the other, which resembles findings in schizophrenia patients. However, studies directly assessing correlations between urban stress or discrimination and neurobiological alterations in schizophrenia are lacking to date.

Key words: Urbanicity, social adversity, psychosis, schizophrenia, social fragmentation, isolation, discrimination, stress

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In recent years, interest has been increasing in the role of the social environment in the origins of schizophrenia and other psychotic disorders (1). One area of research that has received particular attention is the association between social risk factors – such as urbanicity, social adversity and exclusion – and psychosis (2-4). Understanding geographical variation in the incidence of psychosis and identifying social factors that account for this variation may provide valuable insights into the etiology of, and treatment for, psychosis (1,5).

In this paper, we review the evidence on: a) variation in the incidence of schizophrenia and other psychoses in terms of place; b) individual- and area-level factors that explain this variation, including social stress and exclusion; and c) potential mechanisms that link adverse urban environment and psychosis.

GEOGRAPHICAL VARIATION IN INCIDENCE

The first studies on geographical variation in the incidence of schizophrenia and other psychoses were conducted in Chicago (6-9) and Bristol (10) since the 1920s.

Faris and Dunham (9), in their pioneering study in Chicago, were the first to report that first admission rates of schizophrenia were highest in the city centre. While rates of schizophrenia decreased as the distance from the centre increased, rates of affective psychosis (i.e., psychotic depression, bipolar disorder with psychotic features) were more evenly distributed across central and peripheral areas (9). Building on this work, other early studies reported a similar pattern in nine other American cities (11).

In the first study outside of the USA, Hare (12) found higher rates of schizophrenia in inner-urban areas of Bristol. In this study, rates also varied within inner-urban areas across neighbourhoods (12). Consistent with Faris and Dunham (9), variation in incidence of affective psychosis and, in addition, depression was limited (12).

Subsequent studies carried out in Nottingham (13,14) and Mannheim (15,16) also reported that rates of schizophrenia, but not affective psychosis, were elevated in inner-urban areas. However, in contrast to Hare (12), they found only limited variation within these areas across neighbourhoods. Notably, there was also evidence of higher rates of depression in inner-urban areas (13-16).

Elevated rates in inner-urban areas

Later studies produced similar findings in a number of countries (i.e., the UK, Denmark, Finland, Germany, Ireland, Scotland, Sweden, and the United States) (17-39). Mortensen et al (28), in a study of Danish registry data, found that urbanicity was associated with a more than 2-fold increased risk of schizophrenia. Similarly, urbanicity has been shown to be associated with a 2- to 3-fold increase in the incidence of non-affective psychosis (22,25). This broadly concurs with findings from most other studies, reporting that degree of urbanicity (indexed by population density) is associated with an approximately 1.5- to 4-fold increase in rates of schizophrenia and other non-affective psychoses (40-43). Consistently, Vassos et al (31) estimated in a recent meta-analysis a pooled effect of 2.37 (95% CI 2.01–2.81) for exposure to urban environment on the incidence of schizophrenia. A similar effect was observed when estimates were extended to all non-affective psychoses (OR 2.38, 95% CI 1.6-3.5).

As in earlier studies, evidence on geographical variation in the incidence of affective psychosis was less consistent.

While Marcelis et al (26) reported significantly higher rates of affective psychosis in those exposed to urban areas, most studies investigating this issue found no evidence to support geographical variation in incidence (21,25,30,36,44). Concerning depression, rates in inner-urban areas have been found to be elevated, though to a lesser degree than for non-affective psychosis (37,45,46).

Variation across neighbourhoods

In line with the earlier study by Hare (10) in Bristol, and in contrast to what was found in Nottingham (13,14) and Mannheim (15,16), later studies investigating the incidence of psychosis at the neighbourhood level reported at least some variation across neighbourhoods within cities (39,47-60). Standardized incidence ratios of schizophrenia (57,59,60), non-affective psychosis (56) and all psychotic disorders (47) have been shown to vary considerably across neighbourhoods. Further, statistically significant random effects of neighbourhoods, indicating geographical variation in the incidence of schizophrenia (57,60) and non-affective psychosis (57), have been found.

However, to date, only three studies have reported on the magnitude of this variation (39,56,59). In these studies, estimates of the proportion of variation in incidence attributable to the neighbourhood level ranged from 4% (39,57) to 12% (4) for schizophrenia and from 2% (39) to 11% (5,56) for non-affective psychosis. These estimates are broadly in line with what has been reported for neighbourhood-level variation in depression (61-66). As in the earlier studies (9,10), later studies did not find evidence in support of variation in the incidence of affective psychosis across neighbourhoods (56).

Several studies in migrant and minority ethnic groups suggest that the risk of schizophrenia and other psychoses is substantially increased in first as well as second generation migrants (43,67,68), and that this risk is especially high in some groups that are potentially exposed to high levels of social exclusion and racist discrimination, e.g., individuals from the Black African and Black Caribbean group (69-73).

While a multitude of individual- as well as area-level factors – including poverty, access to health care, social support, rates of drug use and their respective neurobiological correlates – may contribute to the higher rates of psychosis, cannabis use appears not to explain the higher rates in Black Caribbean migrants (1), and access to health care may be less relevant than institutional exclusion prior to first presentation to mental health services (41,74-76). The finding that lack of social cohesion and support is associated with the higher rates emphasizes the relevance of social exclusion as a stress factor, which in animal experiments has been shown to interact with brain networks implied in the development of psychotic disorders (4,77-81).

Drift or causation?

An important question from the above findings is whether the elevated rates of schizophrenia in urban areas are a cause or a consequence of the disorder or its prodrome. While for a long time the most commonly accepted explanation was that it is selection into urban areas following onset of disorder or its prodrome (drift), rather than exposure to urban environment (causation), that increases risk, early studies were limited in addressing this question (24,41).

A number of studies have since investigated temporality and dose-response gradient, predominantly focusing on the association of urbanicity with schizophrenia. There is good evidence from studies investigating temporality of this association to suggest that the risk of schizophrenia and other non-affective psychosis increases as degree of urbanization at birth increases (17,21,22,28). In contrast, evidence on a dose-response relationship of urban birth with affective psychosis and depression remains limited (21,26,46).

In an attempt to discriminate exposure to urbanicity at birth and time of illness onset, Marcelis et al (27) used Dutch national psychiatric case register data to demonstrate an approximately 2-fold increased incidence of schizophrenia in individuals born in urban areas. However, no increase in incidence was observed in those not exposed at birth but living in an urban environment at the time of illness onset (27). Lewis et al (24) further reported an increased risk of schizophrenia in those brought up in an urban environment. In the only study to date that sought to disentangle the effects of urban birth and upbringing, Pedersen and Mortensen (18) found that it is exposure to urban environment during upbringing rather than urbanicity at birth that increases the risk of schizophrenia later in life. What is more, there was strong evidence of a dose-response relationship between cumulative exposure to urbanicity during upbringing and risk of schizophrenia (18). A dose-response gradient for urbanicity has also been reported for other non-affective psychosis (21,37) and depression without psychotic features (37), though not for affective psychosis (21). These findings, taken together, suggest that it is unlikely that social drift alone can fully account for geographical variation in incidence (41). This raises the question of what it is in the urban environment that places more individuals at risk of non-affective psychotic disorders.

INDIVIDUAL- AND AREA-LEVEL RISK FACTORS

Various environmental factors have been proposed to account for geographical variation in the incidence of schizophrenia and other non-affective psychoses ever since the first evidence has been reported. These can be broadly grouped into environmental exposures of individuals living in inner-urban areas (i.e., individual-level exposures) and

exposure to characteristics of these areas (i.e., area-level exposures) (see Table 1).

Individual-level factors

Based on evidence of an association between exposure to early neurodevelopmental insults and risk of schizophrenia (91), and assuming these insults may be more common in inner-urban areas, their impact on early brain development has been posited to contribute to the higher rates of psychosis in these areas.

For example, building on evidence suggesting that the risk of schizophrenia is increased in offspring exposed to obstetric complications, Harrison et al (22) examined the impact of such complications on the association of urbanicity with schizophrenia and other non-affective psychoses. While these authors did find that obstetric complications were more common in inner-urban areas (22), consistent with Eaton et al (21), no attenuation in the strength of association was observed after adjustment for obstetric complications (22).

Evidence on season of birth, as a proxy for seasonal differences in exposure to infections that may explain the observed increases in incidence in inner-urban areas, remains equivocal. Takei et al (92) reported a significant interaction of urbanicity and season of birth on the multiplicative scale. In this study, the association between urban birth and risk of schizophrenia was stronger in individuals born in winter (92). A similar finding has been reported by Harrison et al (22) for other non-affective psychoses. However, in line with others (17,18,28), these authors found no evidence that season of birth modifies the association between urbanicity and risk of schizophrenia (22,28). Coupled with evidence that, as Pedersen and Mortensen (18) reported, it is urban upbringing rather than birth that increases risk of schizophrenia, these latter findings tentatively suggest that pre- and perinatal exposure to neurodevelopmental insults is likely to be less relevant to the elevated rates of schizophrenia in inner-urban areas.

Another potential explanation of the elevated rates is cannabis use (83). Findings suggest that cannabis use in adolescence is associated with an increased risk of adult psychotic disorder (93,94), and cannabis use has been found to be more common in urban areas (24). Zammit et al (82) reported an attenuation of the association between cannabis use and risk of schizophrenia after adjustment for urban birth (82). In a prospective cohort study, Kuepper et al (83) found evidence of additive interaction between cannabis use and urbanicity in increasing the risk of developing psychotic symptoms: individuals reporting cannabis use and exposed to urban environment were at greater risk than those with either factor alone (83).

Some authors have proposed the physical environment of inner-urban areas as a potential explanatory factor. In a small study by Pedersen et al (84), there was evidence that traffic density is associated with risk of schizophrenia (84). Probing these findings further, Pedersen and Mortensen (35) found no evidence that the association between urbanicity and risk of schizophrenia is modified or confounded by distance from nearest major road. However, this variable was only a very crude proxy for traffic-related exposures such as noise and air pollution. Better measures of exposures in the physical environment are required to elucidate whether these may account for the elevated rates of psychosis in inner-urban areas and to rule out that traffic noise is just a proxy for social adversity and poverty.

Indeed, a number of individual-level markers of social adversity have been suggested to account for the increased incidence of psychosis in urban areas. These include markers of social disadvantage in childhood, such as parental unemployment, poor parental education, growing up in a single-parent household, parent receiving welfare benefits, low parental income, poor housing, and low parental socio-economic status (22,24,39,85). Markers of social disadvantage in adulthood that have been proposed as potential explanatory factors include single or divorced marital status (59), poor education (37,86) and low socio-economic status (87).

While some (limited) attenuation has been reported after adjustment for these factors (37,39,86), in most studies investigating this issue to date, the strength of the association between urbanicity and psychosis remained largely unchanged (22,24,59,87) and statistically significant (22,24,37,39,59,87). In other words, individual-level markers of social adversity in these studies explained only to a limited extent the association between urbanicity and psychosis. However, as for genetic liability (33,95) and cannabis use (83), there is only a limited number of studies investigating whether markers of social adversity interact with urbanicity to increase the risk of psychosis.

One potential research area where urbanicity and social adversity can overlap and interact is the presence of social minorities and migrants in inner cities. Due to relatively low housing prices in certain inner city areas, there is a relatively high proportion of migrants and social minorities living in European and American inner cities, which are often exposed to social exclusion and discrimination, health care services that are unprepared to cater to their needs, and interactions with professionals that fail to take different explanatory models of health and disease into account (96-99). Moreover, minorities and migrants often earn less money than other citizens, suffer from social exclusion at the work place and can be reluctant to report problems with illegal drugs of abuse due to the threat of being deported (100). Unfortunately, studies directly addressing the interaction between social exclusion and discrimination on the one hand and the risk to develop schizophrenia on the other are still lacking to date.

Table 1 Individual- and area-level explanatory factors for geographical variation in incidence of psychosis

Social risk factor	Outcome	Principal finding	Reference
Individual-level factors			
Neurodevelopmental insults			
Obstetric complications	Schizophrenia, non-affective psychosis, affective psychosis	N	Eaton et al (21)
	Schizophrenia, non-affective psychosis	N	Harrison et al (22)
Season of birth	Schizophrenia	I_U	Takei et al (38)
	Schizophrenia	N	Mortensen et al (28)
	Schizophrenia	N	Pedersen et al (17)
	Schizophrenia	N	Pedersen et al (18)
	Schizophrenia	N	Harrison et al (22)
	Non-affective psychosis	I_U	Harrison et al (22)
Cannabis use	Schizophrenia	C	Lewis et al (24)
	Schizophrenia	C	Zammit et al (82)
	Psychotic symptoms	I_U	Kuepper et al (83)
Physical environment			
Traffic density	Schizophrenia	C	Pedersen et al (84)
	Schizophrenia	N	Pedersen and Mortensen (35)
Air pollution	Schizophrenia	C	Pedersen et al (84)
Markers of social disadvantage			
Childhood	Schizophrenia	C	Lewis et al (24)
	Schizophrenia, non-affective psychosis	N	Harrison et al (22)
	Schizophrenia, other psychoses	N	Wicks et al (85)
	Schizophrenia, non-affective psychosis, affective psychosis	C	Zammit et al (39)
Adulthood	Schizophrenia	N	van Os et al (59)
	Psychotic symptoms	N	van Os et al (86)
	Psychotic symptoms	N	Spauwen et al (87)
	Any psychosis	C	Sundquist et al (37)
	Schizophrenia, non-affective psychosis, affective psychosis	C	Zammit et al (39)
Area-level factors			
Social deprivation	Non-affective psychosis	A	Croudace et al (52)
	Schizophrenia	N	Boydell et al (60)
	Schizophrenia	N	Silver et al (88)
	Schizophrenia	A	Allardyce et al (50)
	Schizophrenia	N	Drukker et al (54)
	Schizophrenia, non-affective psychosis	N	Kirkbride et al (56)
	Non-affective psychosis	N	Zammit et al (39)
	Non-affective psychosis	A	Kirkbride et al (67)
Social capital			
Social mobility	Schizophrenia	A	Silver et al (88)
Informal social control	Schizophrenia	N	Drukker et al (54)
Social cohesion/trust	Schizophrenia	N	Drukker et al (54)
	Schizophrenia	A	Kirkbride et al (49)
Social disorganization	Schizophrenia	N	Kirkbride et al (49)

Table 1 Individual- and area-level explanatory factors for geographical variation in incidence of psychosis *(continued)*

Social risk factor	Outcome	Principal finding	Reference
Voter turnout	Schizophrenia, non-affective psychosis	A	Kirkbride et al (56)
	Schizophrenia	A	Lofors and Sundquist (48)
	Non-affective psychosis	N	Kirkbride et al (67)
Social fragmentation	Schizophrenia	A	Allardyce et al (50)
	Non-affective psychosis	A	Zammit et al (39)
	Non-affective psychosis	N	Kirkbride et al (67)
Individual- and area-level factors			
Individual-level ethnicity x area-level ethnic density	Schizophrenia	I_C	Boydell et al (60)
	Schizophrenia	I_C	Kirkbride et al (57)
	Any psychosis	I_C	Veling et al (47)
	Any psychosis	I_C	Schofield et al (89)
	Psychotic experiences	I_C	Das-Munshi et al (90)
Individual- x area-level social fragmentation	Any psychosis	I_C	Zammit et al (39)
Individual- x area-level social deprivation	Any psychosis	I_C	Zammit et al (39)
Individual- x area-level ethnic fragmentation	Any psychosis	I_C	Zammit et al (39)

A – evidence of association (with psychosis); C – evidence of confounding (the association between urbanicity and psychosis); I_U – evidence of interaction (individual-/area-level factor interacts with urbanicity to increase risk of psychosis); I_C – evidence of interaction (individual- and area-level factor interact to increase risk of psychosis); N – no evidence of interaction, confounding, or association

Area-level factors

Already in the early studies carried out in Chicago (9,10), Nottingham (13,14) and Mannheim (15,16), geographical variation in incidence was sought to be explained by adverse social characteristics of areas for which higher rates of disorder had been reported. For example, Faris and Dunham (9) explained their finding of higher rates of schizophrenia in the inner city of Chicago by decreasing levels of social disorganization as the distance from the centre increased. This explanation was not only supported by their own data but also by later investigations in Chicago (6-8) and Mannheim (15,16). Similarly, Giggs (13) reported social and material resources to account for geographical variation in incidence in Nottingham.

However, these earlier studies failed to examine the effects of area-level factors simultaneously with, but independent from, individual-level factors (39), taking into account clustering of individuals within geographic units (i.e., inner-urban areas, neighbourhoods). It is only more recently that appropriate statistical methods such as multilevel modelling have been used to disentangle effects of individual- and area-level factors. Several studies have investigated the role of social deprivation at the area level and found a significant association with the incidence of schizophrenia (50,54,57,60,88) and non-affective psychosis (39,52,57). However, there is consistent evidence from these studies that, after adjustment for potential confounders at both the individual and area level, this association is attenuated (50) and ceases to be statistically significant (39,50,54,57,60). By contrast, in a recent analysis by Kirkbride et al (42), the association between area-level deprivation and non-affective psychosis remained, even after adjustment for other individual- and area-level factors.

The concept of "social capital" remains a frequently proposed explanation of variation in incidence across neighborhoods. Silver et al (88) reported that social mobility (operationalized as the proportion not living at the same address five years earlier and the proportion with rented accommodation) is associated with risk of schizophrenia after adjustment for a number of individual-level factors. Drukker et al (54) distinguished two components of "social capital", informal social control as well as social cohesion and trust, and investigated residential instability as a separate area-level characteristic. While these authors found significant associations of residential instability and social cohesion and trust with risk of schizophrenia, none of these associations held in adjusted analyses. In contrast, Kirkbride et al (49) reported a non-linear association between social cohesion and trust and the incidence of schizophrenia, such that adjusted rates were increased in neighbourhoods with low and high compared with medium levels of social cohesion and trust. However, social disorganization, identified as another component of social capital in this study, was not associated with the incidence of schizophrenia (49). Finally, Lofors and Sundquist (48) used voter turnout as a proxy of "social capital" and, consistent with Kirkbride et al (56), found that lower turnout was associated with an increased incidence of non-affective psychosis.

A related, and potentially overlapping, concept posited to account for geographical variation in incidence across

neighbourhoods is social fragmentation. Allardyce et al (50) reported a dose-response relationship between area-level social fragmentation (operationalized as mobility in the previous year and number of rented households, single-person households, and unmarried persons) and first-admission rates of schizophrenia. Similarly, there is evidence from a Danish register study (39) that the incidence of non-affective psychotic disorders is increased in areas with higher levels of social fragmentation (operationalized as 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), even after adjusting for potential confounding by a number of individual- and area-level factors. However, no evidence of association between area-level social fragmentation and non-affective psychosis was found by Kirkbride et al (42).

While these findings, taken together, suggest that area-level exposures are likely to be relevant in explaining geographical variation in incidence, they also point to considerable conceptual, operational, and empirical overlap of the environmental exposures investigated to date (101,102). Empirical investigations, informed by social theory (41), are now required to identify underlying categorical or continuous variables of social exclusion and deprivation, social capital, and social fragmentation, using, for example, multilevel latent variable modelling to validate existing operationalizations of these constructs.

Interaction of individual- and area-level factors

More recent studies using multilevel modelling have further investigated how individual- and area-level factors interact with each other to increase risk of psychosis (39). The most prominent and, overall, best replicated finding from these studies is that individuals from migrant and minority ethnic groups are at an increased risk of psychosis in areas with low ethnic density (i.e., areas in which these groups constitute a small proportion of the local population) (47,57,60,89,90). This interaction between individual-level ethnicity and area-level ethnic density has been reported for schizophrenia (60), non-affective psychosis (57), all psychotic disorders (47,89), and psychotic experiences (90). This is particularly interesting as urban areas in which low numbers of migrants live tend to be characterized by rather high levels of average income and general health care.

Becares et al (103) suggested that experiences of discrimination may be buffered by neighbourhood-level ethnic group density. Therefore, it does not seem to be general poverty in an area per se, but rather social support or exclusion that contributes to higher rates of psychosis in migrants living in such (relatively well-off) areas. These considerations are supported by a recent study by Zammit et al (39), reporting an interaction of individual- and area-level social fragmentation, "ethnic" fragmentation, and social deprivation. In accordance with the hypothesis that it is social exclusion in an area that contributes to high psychosis rates, the authors found evidence that risk of any psychosis increases as individual-level deprivation, social and "ethnic" fragmentation increase, and area-level deprivation, social and "ethnic" fragmentation decrease (39). This suggests that risk of psychosis differs in individuals exposed to social adversity depending on the context where they were raised or currently live in.

POTENTIAL MECHANISMS

The above findings, taken together, suggest that there is considerable geographical variation in the incidence of schizophrenia and other non-affective psychoses both across urban-rural areas and across neighbourhoods within inner-urban areas. Since there is evidence on temporality (i.e., urban upbringing rather than current city living) and dose-response gradient (i.e., risk increases in a linear fashion as cumulative exposure to urban environment during upbringing increases), it is unlikely that social drift alone can fully account for this variation.

Current findings further suggest that the impact of adverse social contexts – indexed by area-level exposures such as population density, social fragmentation and deprivation – on risk of psychosis is: a) explained (confounding) or b) modified (interaction) by environmental exposures at the individual level (i.e., cannabis use, ethnic minority group position, social adversity, exclusion and discrimination). This raises the question of which biological and psychological mechanisms may link these (individual- and area-level) environmental exposures and psychosis.

Genetic factors can play a role in individuals exposed to urban environment (4). Since a large proportion of the general population is exposed to urbanicity, development of psychosis in only a few individuals may depend on the degree of familial liability (104). In line with this, two studies have reported a positive interaction on an additive scale between urbanicity and family history of psychosis, suggesting that individuals exposed to urban environment and with familial liability are at significantly greater risk of psychosis than those with either factor alone (33,95). Along similar lines, Weiser et al (105) reported evidence of additive interaction between cognitive and social functioning, as a marker of genetic liability, and population density on risk of schizophrenia. While these findings tentatively suggest that the impact of environmental exposures may depend on genetic risk, to date, there is no evidence of gene x urban environment interaction from studies using direct measure of genes. Moreover, the substantially higher rates of psychosis in migrants from the Caribbean and Africa in London (particularly in areas with low ethnic density), compared with psychosis rates and outcomes in, for instance, the Caribbean, West Africa and India, suggest that there are specific factors related to

migration and associated exposure to social exclusion stress (106-109).

On a neurobiological level, it has been suggested that the risk of developing schizophrenia is associated with a tendency for imprecise information processing potentially based on disturbed cortico-cortical plasticity (110,111), which may also be present in the relatives of schizophrenia patients (112). Therefore, "dysconnectivity" may be a potential biological characteristic of individuals with schizophrenia (113) and with increased genetic risk or an at risk mental state (114,115). It was demonstrated that the dorsolateral prefrontal cortex exerts reduced control over activity in the parietal cortex during working memory (113) and this mechanism may contribute to impairments in habitual recognitions and automatic responding to environmental cues and contexts (116).

In acute psychosis, elevated subcortical dopamine turnover and release (117-119) may then be a secondary phenomenon, which increases the signal-to-noise ratio at the expense of salience attribution to otherwise irrelevant stimuli; these cues may be misinterpreted as indicators of persecution or social threat and thus contribute to delusional mood and delusion formation (67,77,120).

Several authors have proposed social stress as a potential mechanism through which exposure to urban environment may impact on individuals and particularly on dopaminergic neurotransmission to increase risk of psychosis (3,57,77,121). Indeed, animal experiments showed that subcortical dopamine release, particularly in the striatum, is directly affected by social stress factors as well as the intake of drugs of abuse (122,123). The concept of "sensitization" – which denotes an increased sensitivity or "response" of dopamine release and has been used to explain increased dopaminergic neurotransmission following social defeat and other forms of social adversity – was originally developed in the context of drug addiction, where repeated exposure to drugs of abuse can sensitize striatal dopamine release and the associated behavioral responses (2,77,124). Social exclusion stress as well as the consumption of drugs of abuse may thus both sensitize subcortical dopamine release, and stress-associated dopamine dysfunction may further be increased following developmentally early impairment of mesolimbic-prefrontal networks, e.g., following obstetric complications or intra-uterine infections (91).

Animal experiments confirmed that developmentally early temporolimbic dysfunction can impair prefrontal regulation of subcortical dopaminergic neurotransmission, resulting in increased striatal dopamine release following prefrontal catecholamine application to mimic stress exposure (2,125,126). While elevated presynaptic dopamine synthesis is a well-replicated finding in schizophrenia patients (117,127), a recent human positron emission tomography (PET) imaging study in mono- and dizygotic twins demonstrated that non-shared individual-specific environmental factors account for more than 50% of variance in striatal dopamine synthesis and that this effect is even more pronounced in the ventral-limbic striatum (128).

These observations suggest that biological as well as social factors and drug consumption can interact and affect striatal dopamine release as a "final common pathway" in the development of frank psychosis. However, to date studies are missing that directly assess the interaction between social stress factors, individual vulnerability and the risk of developing psychosis in humans.

With respect to urban stress exposure, Lederbogen et al (129) recently investigated whether urban living and upbringing modify neural processing of social evaluative stress. While controlled exposure to social evaluative stress was associated with increased activity in the perigenual anterior cingulate cortex in individuals brought up in an urban environment, amygdala activity was increased in those currently living in urban areas (129). This observation is in line with a potential bias towards threat anticipation (130,131) as a possibly important mechanism in the development of psychotic disorders. However, increased amygdala activation and impaired connectivity between the amygdala and the prefrontal cortex has been reported in non-psychotic affective disorders rather than psychosis per se, and appears to be modulated by serotonin rather than dopamine-related genetic variation (132).

The serotonergic system has indeed been shown to be strongly affected by social isolation stress, and the observed alterations in serotonin turnover and transporter availability were associated with anxiety, aggressiveness and increased drug intake (133,134). The sensitivity to social isolation stress appears to be modified by serotonin transporter genotype, which was also implicated in amygdala activation by aversive stimuli and amygdala-prefrontal coupling (135,136). However, most studies to date reported a predominantly decreased response of the amygdala to affective stimuli in schizophrenia (137-139), so the relevance of the observation of Lederbogen et al (129) in healthy controls for urban psychosis risk remains to be further elucidated.

Interestingly, one recent study in patients suffering from schizophrenia separately assessed the responses of the amygdala to affectively positive and negative stimuli (rather than averaging all responses independent of the valence of the emotional probe) and observed increased responses to affectively negative and decreased activation in response to affectively positive stimuli (140). Together with the observation that dopamine turnover is increased in unmedicated schizophrenia patients (118), and that such an increase in dopamine turnover positively enhances amygdala responses to aversive stimuli in healthy controls (141), these findings may suggest that increases in dopamine production and turnover in acute psychosis can interact with urban upbringing and other chronic stress-associated factors to increase limbic processing of aversive stimuli.

Indeed, studies from our own group and others found that genetic variation in genes regulating the metabolism

and reuptake of monoamines such as dopamine, noradrenaline and serotonin additively affect amygdala responses in healthy controls (142,143). Therefore, further studies are required that simultaneously assess genetic variance as well as social stress factors and their respective interactions in striatal, limbic and prefrontal processing of rewarding and affective stimuli and their potential impairment in psychosis. However, due to the complex nature of these interactions, such studies need to be controlled for overfitting of genetic and potentially also environmental data (144), and independently replicated in separate samples.

CONCLUSIONS

Taken together, the findings reviewed in this paper suggest that urbanicity is associated with an increased risk of schizophrenia and other non-affective psychosis, and that the impact of adverse social contexts – indexed by area-level exposures such as population density, social fragmentation and deprivation – on risk of psychosis is explained (confounding) or modified (interaction) by environmental exposures at the individual level (i.e., cannabis use, social adversity, exclusion and discrimination).

While animal experiments and human studies suggest plausible mechanisms linking social stress and biological alterations found in schizophrenia, specific studies directly testing such mechanisms are lacking to date.

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