

The environment and schizophrenia

Jim van Os^{1,2}, Gunter Kenis¹ & Bart P. F. Rutten¹

Psychotic syndromes can be understood as disorders of adaptation to social context. Although heritability is often emphasized, onset is associated with environmental factors such as early life adversity, growing up in an urban environment, minority group position and cannabis use, suggesting that exposure may have an impact on the developing 'social' brain during sensitive periods. Therefore heritability, as an index of genetic influence, may be of limited explanatory power unless viewed in the context of interaction with social effects. Longitudinal research is needed to uncover gene–environment interplay that determines how expression of vulnerability in the general population may give rise to more severe psychopathology.

The disorder schizophrenia, diagnosed in around 0.5–1.0% of the population during their lifetimes¹, may be considered the poor outcome fraction of a truly 'complex', multidimensional psychotic syndrome (lifetime prevalence 2–3%, ref. 2), that in turn can be traced to measurable, age-dependent (young > old) expression of liability in a substantial proportion—around 10–20%, ref. 3—of the non-ill general population⁴. The correlated symptom dimensions of the psychotic syndrome are: psychosis (hallucinations and delusions), motivational impairment (avolition or amotivation), affective dysregulation (depression, mania) and alterations in information processing (cognitive impairment).

High heritability estimates indicate a strong genetic influence. Although the well known 'stress-vulnerability' model of aetiological influence in psychiatry assumes that genetic factors operate by making individuals selectively vulnerable for environmental risks (gene-environment interaction, or GxE), it has proven very difficult to provide data substantiating this supposition. However, recent evidence of substantial variation in the incidence across places and minority groups, associated with high attributable fractions^{1,5–8}, suggests that environmental factors do have an important role. Here, we will review the evidence linking environmental risks to psychotic syndrome, and examine to what degree such associations may be methodologically valid and indicative of causal influence; which aspects of the environment actually explain, or mediate (as factor between the environmental exposure and the outcome that actually occasions the effect), for example, variation in incidence across places; and which biological and cognitive mechanisms may underlie such effects. Finally, is there evidence that genetic influence for psychotic syndrome may operate in part by creating subgroups that are more vulnerable to environmental risks and, if so, how should the issue of genetically influenced sensitivity to the environment be developed further in clinical and translational research?

Phenotype, environment and heritability

Whereas classical twin studies (the study of twins without inclusion of twins' relatives) indicate that shared environmental effects are small, quantitative biometric analyses show that this type of twin methodology represents a singularly poor method to characterize the effects of the environment in any way—including the argument that shared environmental effects are small⁹. Furthermore, there is evidence that the level of familial clustering of psychotic disorder is greater if it is measured in risk environments, for example urban environment or



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minority group^{10,11}, suggesting that heritability estimates from classical twin studies not only reflect genetic influence, but also underlying gene–environment interactions^{12,13}. Thus, the heritability estimates for the behavioural expressions of liability for psychotic disorder in the non-patient general population, indexed by subtle manifestation of psychotic experiences¹⁴, affective dysregulation¹⁵, motivational impairments¹⁶ and cognitive alterations¹⁷, are in the order of 40–70%. Interaction between the genes influencing these liability traits and environmental risk factors may give rise to more 'co-morbid'¹⁸ disease phenotypes with higher heritability estimates (as they now also include GxE effects), and greater probability of passing the 'filters' on the pathway to mental health services^{19,20} (Fig. 1).

Cities, minorities, trauma and drug use

Increasingly sophisticated studies, summarized in a growing body of meta-analytical work, suggest that psychotic outcomes are associated with growing up in an urbanized area, minority group position, cannabis use and developmental trauma. Relative risks are mostly in the order of 2, although as high as 5 in certain subgroups. However, definitive conclusions about association between environment and psychotic syndrome critically depend on a number of qualitative and quantitative issues described in Box 1.

The evidence for developmental trauma

Although systematic reviews on the association between developmental trauma and psychosis are not consistent^{21–23}, an explosion of new studies have since consistently demonstrated dose–response associations across a range of designs, natural experiments and endpoints, including a number of strong prospective studies establishing temporal order and ruling out reverse causality^{24–26}. Reports of developmental trauma in patients may be different compared to controls due to the presence of psychotic symptoms or because of patients searching for reasons for their predicament; studies have therefore introduced (semi-) prospective designs^{24,26}, assessment of trauma through independent sources^{25,26} and validation procedures for reporting of trauma by patients²⁷. Studies have addressed genetic confounding by controlling, directly or indirectly, for genetic risk^{24,25,28}. The association with developmental trauma may be mediated by a combination of both neglect and abuse^{21–23}; however, more work is needed to examine the important issue of what mediates the effect.

The evidence for minority group position

Meta-analytical work shows consistency for the association between psychotic syndrome and minority group position across a wide range

¹European Graduate School for Neuroscience, SEARCH, Maastricht University Medical Centre, 6200 MD Maastricht, The Netherlands. ²King's College London, King's Health Partners, Department of Psychosis Studies, Institute of Psychiatry, London SE5 8AF, UK.

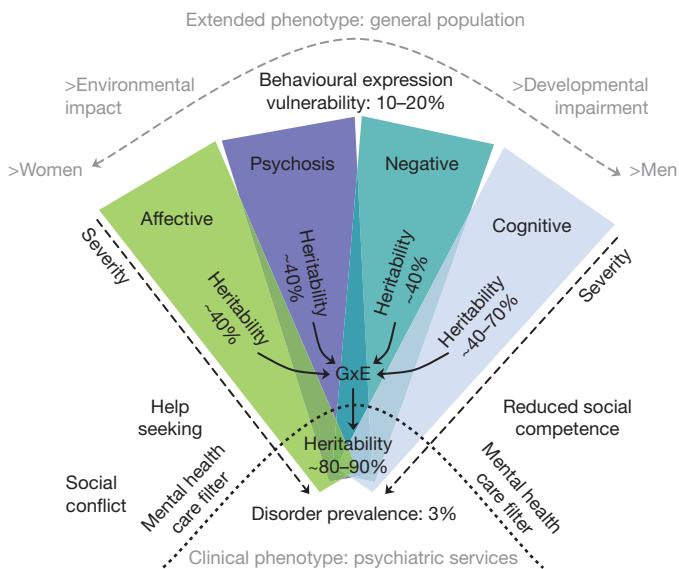


Figure 1 | Complexity of the psychotic disorder phenotype in aetiological research. Four main dimensions of affective dysregulation (depression, mania, anxiety), psychosis (delusions, hallucinations), negative symptoms (motivational impairment) and cognitive alterations characterize the general psychotic syndrome. In the general population, low levels of these dimensional phenotypes represent the behavioural expression of vulnerability (extended phenotype in figure, prevalence 10–20%), which display moderately high heritability levels, and display low levels of correlation (as indicated by less overlap of the four dimensions at the level of behavioural expression of vulnerability). Gene–environment interactions give rise to more severe levels of phenotypic expression, which in turn contribute to likelihood of clinical detection by psychiatric services by passing the filters on the pathway to mental health care (mental health care filter in figure) in a dimension-specific fashion. For example, higher levels of affective dysregulation are likely to lead to active help-seeking, whereas psychosis may lead to clinical detection through social conflict and cognitive symptoms through reduced social competence. As dimensions contribute independently to clinical detection by psychiatric services, symptom dimensions are subject to co-morbidity bias (that is, are much more correlated and ‘co-morbid’ at the level of psychiatric services), giving rise to clinical diagnostic descriptions such as schizophrenia that have a relatively low prevalence. These diagnostic descriptions have higher heritability as they include the effect of gene–environment interactions underlying severity of dimensional expression. Evidence suggests that environmental influences associated with psychotic disorder may have greater impact on affective and psychotic dimensions, which are more common in women, whereas negative and cognitive dimensions may be more strongly associated with developmental impairment and male sex. GxE, gene–environment interaction.

of approaches, endpoints, settings and cultural group definitions^{5,29}, and after adjustment for a range of confounders. The possibility of cultural bias in diagnosis and selective migration has been examined but not found to have a major impact on the association. The association with minority group position is observed in both first and second generation migrants^{5,29}, as well as in minority groups without recent migration³⁰, indicating that pre-migration factors or migration itself are unlikely to mediate effects. Studies in four different countries have shown that the effect of minority ethnic group on psychotic syndrome depends on the ethnic density of the area the person is living in: the greater the proportion of the own ethnic group in the area, the lower the risk for psychotic disorder^{31,32}. These findings suggest that it is not ethnic group per se that increases risk, but rather the degree to which one occupies a minority position, or stands out in relation to the wider social environment. Additional research suggests that effects associated with minority group position may be mediated by chronic social adversity and discrimination³³, resulting in social marginalization or a state of social ‘defeat’ (chronic experience of an inferior position or social exclusion³⁴).

BOX 1

Weighing the epidemiological evidence for environmental association and causality

- Methodological explanations, such as bias or (genetic) confounding, must be ruled out.

Bias may arise, for example, when cases or controls are selected, followed over time, or interviewed in such a way that they are more or less likely to report environmental exposure in the case-control comparison (for example, a case-control study of psychotic syndrome and cannabis use recruiting controls from a selected community with very strict lifestyle rules).

Confounding occurs when, for example, an apparent difference in exposure rate between cases and controls is due to a third factor associated with both exposure and, independent of that, with the illness (for example, cases are much younger than controls therefore report more cannabis use resulting in a spurious association between cannabis and disease).

Genetic confounding refers to the fact that, for example, genetic liability for schizophrenia may predispose to cannabis use, so that the association between cannabis use and schizophrenia in fact represents a genetic epiphenomenon. Similarly, genes predisposing for psychotic syndrome may cause selective migration to another country, resulting in minority group position, or an urban environment. Genetic confounding may be unlikely *a priori*, as the genetic effect on cannabis use would need to be very substantial. However, a degree of genetic confounding is difficult to exclude.

- It is critical that observational research provides consistent evidence for an association between illness and environmental risk across a mix of different strategies, natural experiments, designs, endpoints and levels of genetic sensitivity. If this is the case, validity is more likely.
- Exposures such as urban environment and minority position really represent proxies for as yet unidentified environmental factors, which represent the mediators of the effect, that require identification.

In humans, experimental support for causality, in the sense of randomized allocation to exposure, is only possible for acute outcomes such as induction of transient delusions or hallucinations or cognitive impairment following experimental cannabis use, experimental stress or other experimental situations. Causality from observational studies may be inferred using criteria of consistency of the association, temporal order (that is, the exposure precedes the outcome and reverse causality is ruled out, for example early psychotic symptoms causing cannabis use rather than the other way round), evidence for dose–response (more exposure results in progressively greater risk) and a plausible link to underlying biological and cognitive mechanisms.

The evidence for growing up in an urban environment

Meta-analytical work shows consistency in a dose–response association with the urban environment across a wide range of settings, endpoints, data collection approaches and definitions of ‘urbanicity’^{1,6–8}. Confounding can occur as, for example, high rates of schizophrenia in cities could be secondary to higher rates of drug use or ethnic minority groups living in urban environments; however, studies have controlled for a wide range of possible confounders^{6–8}, including variables indexing genetic risk in order to exclude genetic confounding^{6–8,35}. Longitudinal studies of natural experiments show that changing the environmental exposure, for example moving from an urban to a rural environment in childhood, brings about a corresponding decrease in risk for psychotic outcome³⁶, which argues against urbanicity representing a non-causal genetic epiphenomenon.

Similar to the effect of minority group position, contextual effects involving the wider social environment may point to what mediates the effect of urban environments. Thus, there is evidence that risk for psychotic syndrome associated with indicators of social maladjustment, for example single parent family, single marital status and residential instability, similarly varies with the degree to which this represents the exception in relation to the wider social environment^{37,38}. This type of interaction between individual-level and area-level social 'fragmentation' may mediate the effect of the urban environment³⁸.

The evidence for cannabis use

Randomized experimental studies show that delta-9-tetrahydrocannabinol, the main psychotropic component of cannabis, causes transitory psychotic symptoms and impaired cognition in healthy volunteers³⁹, and that individuals at genetic risk for psychotic syndrome display an exaggerated psychotic response⁴⁰. Meta-analytical work shows that the association between psychotic syndrome and cannabis is consistent, also after adjustment for a range of confounding factors⁴¹. Cannabis use may reflect self-medication for early expression of psychotic vulnerability or symptoms, and there is evidence that both self-medication (psychosis proneness may induce cannabis use) and causation (cannabis induces psychosis proneness) apply⁴², although other work has failed to produce evidence for self-medication (ref. 43 and R. Kuepper, J. van Os, R. Lieb, H. U. Wittchen and C. Henquet, results not shown). Studies addressing genetic confounding by examining if indices of genetic risk predict exposure⁴⁴, and by controlling for genetic risk^{45,46}, do not suggest that genetic confounding can explain much of the observed association between cannabis and psychotic syndrome.

The association between cannabis use and psychotic outcomes has been demonstrated at the level of (1) cognition outcomes, cerebral neuroimaging phenotypes, and at the clinical level of psychotic syndrome as well as at the subclinical level of behavioural expression of vulnerability in the form of subtle psychotic experiences in non-patients; (2) in case-control, case-sibling, longitudinal (birth) cohort and cross-sectional studies; (3) in experimental studies as well as observational studies; (4) across individuals at average (healthy controls), higher than average (for example, siblings of patients) and high genetic risk (for example, patients) for psychotic syndrome and across natural variation in potency⁴⁷.

Prenatal environmental influences

A very wide variety of specific prenatal environmental exposures (for example, prenatal maternal stress, prenatal maternal nutritional deficiency, maternal serum lead and homocysteine levels, rhesus incompatibility, low and high neonatal vitamin D, prenatal toxoplasmosis, specific viral and bacterial infections, miscellaneous pregnancy and birth complications (PBC)) has been reported in relation to adult psychotic outcomes. There are, however, few true (that is, corresponding in trimester timing, exposure definition, subgroup-only effects, specific exposures within the miscellaneous group of PBC that are thought to signal hypoxia-related events during pregnancy⁴⁸) replications, such that no definitive conclusions about association can be drawn at this stage.

Is there evidence for vulnerable subgroups?

Exposure to urban environment, cannabis use, developmental trauma and minority group position represents, in combination, a common occurrence, whereas the rate of psychotic syndrome is low. This suggests that beneath the relatively small marginal risks linking the environment to psychotic syndrome at the population level, vulnerable subgroups exist that are more sensitive to a particular environmental risk factor at a much larger effect size. Thus, the validity of observed associations with urban environment, developmental trauma, cannabis use and minority group position hinges on evidence of vulnerable subgroups. Genetically sensitive studies indicate that differential sensitivity to the psychosis-inducing effects of environmental factors may be mediated by genetic factors¹². For example, in siblings of patients with a psychotic

disorder, who are at increased genetic risk to develop psychotic disorder, the psychotomimetic effect of cannabis is much greater than in controls⁴⁵, as is the risk to develop psychotic disorder when growing up in an urban environment^{11,49} (Fig. 2).

Cognitive mechanisms of environmental impact

A large body of literature indicates that early social, cognitive and emotional development is important to later health and material outcomes. However, the cognitive alterations in schizophrenia and related psychotic disorders not only include the neuropsychological domains of attention, memory, processing speed and reasoning, but also the correlated, although not entirely overlapping, higher order domain of social cognition. Social cognition revolves around concepts such as attribution, intention, agency and emotion, that underlie the mental operations guiding social behaviour (for example, the correct interpretation of another person's intentions or emotions, referred to as mentalizing ability or 'theory of mind'⁵⁰) and self-representation (the differentiation between the 'self' and 'other' that prevents misattribution of agency—failure to recognize oneself as the source of one's actions, thoughts or feelings, due to malfunction in the normal capacity to ignore self-generated sensations because they are predictable). In other words, social cognition is an important mediator in shaping a representation of one-self in relation to the social environment; impaired social cognition may result in aberrant representations and psychotic symptoms.

A direct link between mentalizing ability and symptoms is suggested by the fact that delusions observed in psychotic disorder frequently present as alterations in social inference; for example, paranoid delusions involve erroneous attribution of harmful intentions to behaviour observed in others. Mentalizing ability is also associated with reasoning biases observed in psychotic disorder, particularly a data gathering bias, referred to as 'jumping to conclusions', underlying severity of delusional

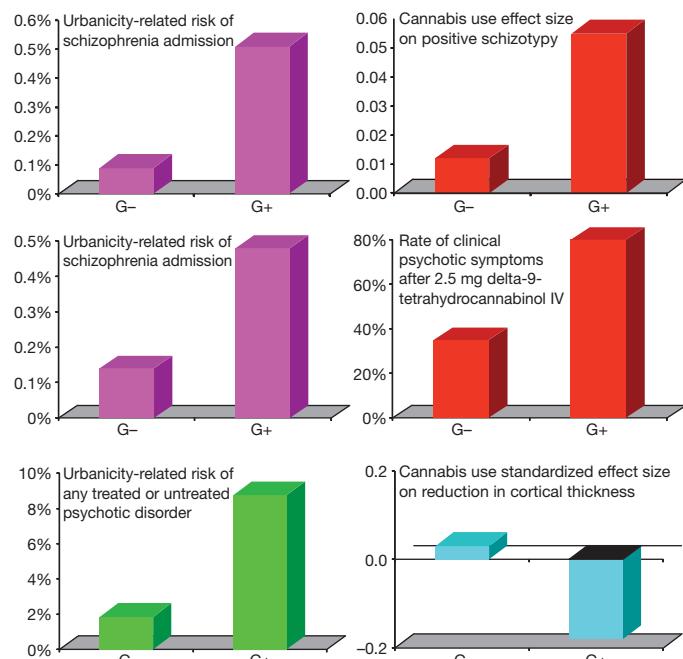


Figure 2 | Evidence for vulnerable subgroups and gene-environment interaction using proxy measures of genetic risk. Selected studies demonstrating differential sensitivity for urbanicity (left side, from top to bottom: refs 89, 49 and 11) and cannabis use (right side, from top to bottom: refs 45, 40 and 90) are shown. Colours correspond to type of psychotic outcome assessed. G+ and G- refer to, respectively, groups with and without genetic risk for psychotic disorder as defined by combination of premorbid cognition and social functioning⁸⁹, family history of psychotic disorder in first-degree relative^{11,49}, being a sibling of a patient with psychotic disorder⁴⁵ and being a patient with psychotic disorder^{40,90}.

ideation. Similarly, psychotic symptoms such as 'made' feelings or movements (passivity phenomena), thought insertion, or auditory hallucinations can be understood as impaired sense of agency, secondary to sensory prediction deficits⁵¹, resulting in attribution of one's own actions, feelings, thoughts and inner speech to external sources. Latent vulnerability in this domain can become expressed following environmental exposure. For example, exposure to environmental variation in the form of short-term sensory deprivation or random noise has been shown to result in hallucinatory experiences in susceptible individuals^{52,53}.

Mentalizing ability normally emerges during preschool years and is environment-driven in that it is highly dependent on day-to-day social interactions. Selective deprivation of access to early social interactions and actively seeking out social information by, for example, hearing impairment or exposure to adversity/deprivation during critical developmental phases, may interfere with the acquisition of mentalizing ability and increase risk of later psychotic symptoms. Evidence to support this notion comes from studies showing significant delays in the mastery of mentalizing ability in hard-of-hearing⁵⁴ and maltreated⁵⁵ children on the one hand, and, on the other, an association between hearing impairment^{56,57} and developmental trauma²¹ and later psychotic symptoms or psychotic disorder in young people. There is evidence that other exposures that may increase risk for schizophrenia, such as head injury⁵⁸ and methamphetamine use⁵⁹, also interfere with the development of mentalizing ability^{60,61}, suggesting a more general link between the environment, social cognition and psychotic disorder.

The clinical relevance of social cognition is apparent in its association with course and outcome of schizophrenia and related psychotic disorders, particularly as regards social competence and community functioning. A recent study presenting 48 independent meta-analyses on associations between 12 a priori identified neuropsychological and social cognitive domains and 4 domains of functional outcome showed

that social cognition was more strongly associated with community functioning than neuropsychological domains of cognition. This finding was mostly due to stronger associations with theory of mind⁶², suggesting that environment-cognition-symptoms-outcome relationships in psychotic disorder may be mediated to a degree by the ability to correctly infer the mental states of others in the social environment.

Biological mechanisms of environmental impact

Exposures to environmental variation during developmentally sensitive periods are essential for the normal development of neuronal connectivity underlying functional abilities of the human brain. Early neglect and life course environmental insults that disinhibit stress signalling pathways can lead to impaired neuronal responsiveness and symptoms of profound prefrontal cortical dysfunction, providing a direct link between the environment and the cognitive impairments observed in psychotic syndrome⁶³.

Whereas genetic factors moderate the sensitivity of specific types of neural cells or circuits as well as the timing of environmental sensitivity during development⁶⁴, other mechanisms have been described that mediate imprinting of environment and experience, acting in parallel at different biological levels (Fig. 3b). The timing of environmental exposures associated with psychotic disorder, viewed in relation to the developmental biology of normal experience-dependent brain development (Fig. 4), is compatible with extensive developmental alterations having an impact in the areas of cognition and emotion, as observed in psychotic disorder.

Age-dependent, developmental expression of subclinical psychotic experiences in adolescence are mostly transient; however, repeated exposure to environmental risk factors may cause subclinical psychotic experiences to persist and become more severe, resulting in onset of psychotic illness in a minority of individuals²⁰. These data are suggestive of a mechanism of sensitization. There is evidence that exposure to

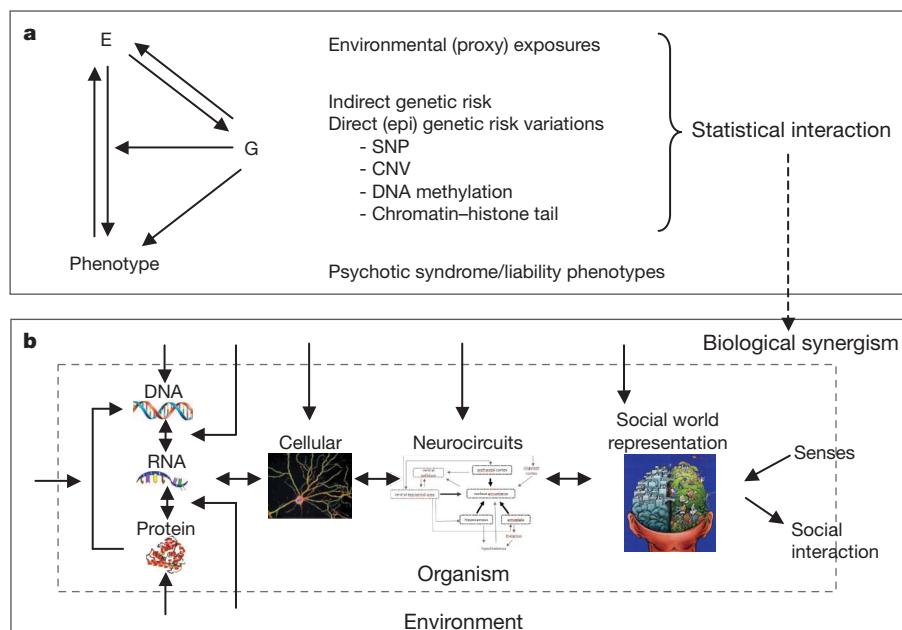


Figure 3 | Schematic illustration of gene-environment interplay at the levels of epidemiology and biology. The left part of a represents relationships between environmental exposures (E), genetic liability (G) and the phenotype, that is, psychotic syndrome and related liability phenotypes. Genes may control environmental exposure (arrow from G to E), genes may control environmental sensitivity (arrow from G to arrow E to phenotype), the phenotype may induce reverse causality (arrow from phenotype to E) and the environment may occasion (epigenetic) mutations (arrow from E to G). Measurement of environmental exposures often represent proxies of unknown mediating factors, and measures of genetic risk may be epidemiological (indirect) or molecular (direct). Current genetic and epigenetic variations comprise single nucleotide polymorphisms (SNP), copy number variations

(CNV), DNA methylation, chromatin structure and histone tail alterations. Epidemiological studies may focus on the identification of statistically significant marginal effects of individual factors or the statistical interaction between (proxy) environmental exposures and genetic variant(s); evidence for statistical interaction may be pursued to identify biological synergism, or the co-action of genes and environment at the biological level. Panel b illustrates the interrelations between the various levels of biology mediating mental representation of the social world, and the numerous ways that environmental factors may impact on or interact with these. These interactions may be studied in different organisms and model systems using observational and experimental study designs.

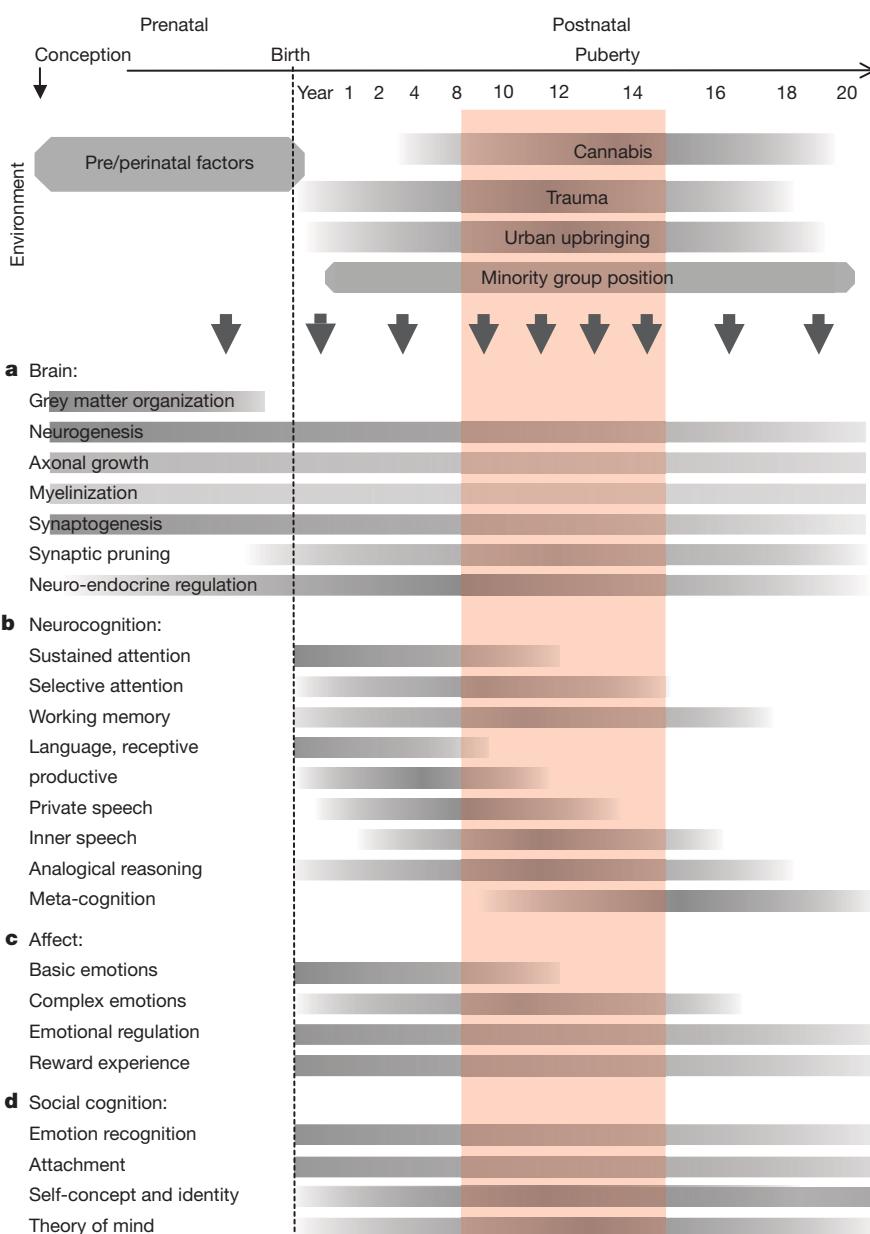


Figure 4 | Schematic illustration of the approximate timing of the development of the human brain, functional abilities, and impact of environmental exposures. Arrows reflect impact of environmental factors associated with psychotic syndrome. Grey bars indicate the approximate developmental periods during which the processes depicted in the column are active (in a, around environmental exposures) or are being established/develop

(in b, c and d). The grey colour intensities of the bars in a–d, and around the environmental exposures, indicate the approximate magnitude of the process or the approximate strength of development or maximum exposure over time. The developmental windows for the functional abilities in neurocognition, affect and social cognition (in b, c and d) are only given for the postnatal period. The red box indicates the window of maximum additive environmental impact.

adversity early in life renders individuals more sensitive to the effects of stress in adulthood and more prone to experience anomalous perceptions (such as flashbacks)—referred to as behavioural sensitization^{65,66}. It has been proposed that early/repeated exposure to environmental risks results in increased mesolimbic dopamine reactivity⁶⁷—known as endogenous sensitization. Exposure to many relevant environmental risk factors in animals, for example prenatal infection, prenatal stress, prenatal malnutrition, early life adversity, adolescent cannabis use, repeated psychostimulant exposure and social defeat stress, have all been shown to induce altered dopamine neurotransmission and sensitization of mesolimbic dopamine neurons in early adulthood, resulting in augmented expression of psychosis-related phenotypes. In humans, a sensitized state of the striatal dopamine system may be brought about by administration of a few doses of the psychostimulant amphetamine, another exposure associated with psychotic illness⁵⁹. Evidence from

studies in a variety of mammalian species has shown that repeated exposure has sustained impact on regulation of mesolimbic dopaminergic neurotransmission at different biological levels: (1) molecular biological alterations including induction of transcription factors and altered chromatin plasticity; (2) chemical alterations including abnormal dopaminergic drive associated with alterations in phasic and tonic dopaminergic firing; (3) induction of several signal transduction pathways; (4) altered ratio of dopamine D2 and D1 receptor levels; (5) electrophysiological alterations; (6) structural alterations of dendritic spines; and (7) increased levels of dopamine receptors in the high-affinity state. Animal research shows that many environmental exposures (for example prenatal stress⁶⁸) also disrupt prefrontal cortex function and corticolimbic interactions, which may be linked to observations of impaired social cognition following childhood trauma in humans. Although it may be attractive to propose that perturbation of corticolimbic circuits precedes and/or

mediates mesolimbic sensitization, research regarding this issue remains inconclusive.

Most of the work on the neurobiology of psychotic syndrome to date has focused on alterations in neurotransmitter systems. The dopamine hypothesis has survived several decades, its current version⁶⁹ postulating that multiple environmental and genetic risks during development interact to funnel through a single final common pathway of presynaptic striatal hyperdopaminergia causing delusions and hallucinations. Given that dopaminergic function is intertwined with, and regulated by, GABAergic, glutamatergic and endocannabinoid signalling, current views about environmental impact not only incorporate neurodevelopmental aberrations in these systems, but also attempt to take into account possible alterations in myelination, synapse formation, the immune system and mitochondrial energy metabolism. Figure 5 illustrates neural circuits thought to be relevant in mesolimbic neurotransmission and psychotic disorder, the impact of environmental exposures on these regions and circuits as shown in human studies, and the effect of repeated environmental exposures on top-down cognitive control over bottom-up sensory input in the nucleus accumbens, giving rise to aberrant development of mentalizing ability and self-representation. Whether or not psychotic disorder results from a single pathway of functional interaction between prefrontal network dysregulation and altered mesolimbic dopamine signalling remains to be established.

The challenge of translational approaches

Novel translational approaches using both observational and experimental human and animal studies will be essential to decipher further

the consequences of exposures during environmentally sensitive periods on different biological levels during brain development as well as on psychological and behavioural phenotypes. Extension of multidisciplinary translational studies modelling environmental impacts, genetic moderation thereof, and their impact on behaviours associated with human mental illness liability phenotypes, for example social cognition, is therefore necessary. Table 1 summarizes potentially fruitful strategies, and challenges, of animal studies in this area. These strategies will be particularly fruitful when they entail the integration of (1) biological underpinning of social phenotypes, (2) biological read-outs at various cellular and molecular levels, (3) biological read-outs from various brain regions and cell types, (4) experimental designs of (repeated) environmental exposures during developmentally sensitive time windows, and (5) dynamic genetic manipulations during development, followed by multidomain behavioural phenotyping.

Mechanisms of gene–environment interplay

Given evidence that genes may have an impact on risk for psychotic syndrome by altering environmental sensitivity, gene–environment interaction research is a logical next step but in practice remains very rare, because to date there has been little collaboration between ‘environmental’ and ‘genetic’ groups in this area. Gene–environment interaction studies are extremely cost-effective, as both genetic and environmental information is collected in a single effort under the same phenotypic assessment, replacing the current duplicated and unrelated efforts to collect genetic information in one sample and environmental information in another.

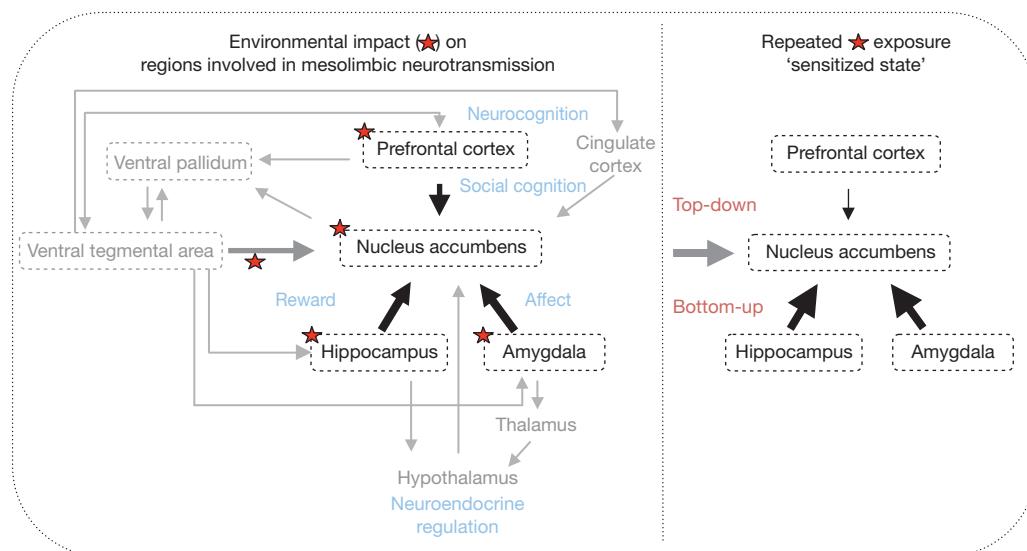


Figure 5 | Schematic overview of neural circuits thought to be relevant in mesocorticolimbic neurotransmission and psychotic disorder, illustration of reported environmental impact on these regions and circuits in human studies, and the effect of repeated environmental exposures on the regulation of bottom-up sensory input and top-down cognitive control by the nucleus accumbens. The left panel schematically summarizes the main brain regions and their interconnections involved in the pathophysiology of schizophrenia. Evidence suggests a close connection between positive symptoms in psychotic disorder, altered mesolimbic dopaminergic neurotransmission in the brain, and environmental exposures. Mesolimbic neurotransmission encompasses the nucleus accumbens as the site of integration of bottom-up sensory experiences with top-down cognitive control of dopamine neurotransmission, thus regulating dopamine firing in the ventral tegmental area via GABAergic feedback through the ventral pallidum. The activity of the mesocorticolimbic circuit is thus subserved by reciprocal connections with limbic and frontal cortical areas; it mediates various functions among which to maintain an updated representation of the social world. The integration is co-determined by the magnitude of the dopaminergic input from

the ventral tegmental area, increased dopamine levels enhancing limbic signalling and attenuating cortical control⁹¹. A mesolimbic hyperdopaminergic state may thus diminish the impact of regulatory cognitive processes and contribute to aberrant representations of salient stimuli and altered reward-related learning, two features of impaired information processing in patients with psychotic syndrome. Red star symbols indicate reported associations between exposure to childhood trauma^{90,92–95} and cannabis use^{96–99} on the one hand, and functional or structural alterations from human studies on the other; findings of environmental impact only refer to brain regions enclosed by dashed lines. The right panel illustrates how repeated exposure to environmental factors may result in a ‘sensitized state’, representing a dysregulated balance between, on the one hand, activation of the nucleus accumbens by hippocampal and amygdalar projections and, on the other, inhibitory control of the nucleus accumbens by glutamatergic projections from the prefrontal cortex⁹¹. The resulting enhancement of bottom-up sensory experiences without appropriate top-down cognitive control is proposed to underlie aberrant representations of the social world. Note: for reasons of clarity, this schematic overview does not depict all anatomical brain regions and their interconnections.

Table 1 | Future perspectives and challenges for animal studies of psychotic disorder phenotypes

Research domain	Strategy	Challenges
Development	Identification of environmentally sensitive periods during development of higher cerebral functional abilities, and key regulatory signalling pathways.	Valid measurement of relevant functional abilities across species. Differential developmental timing between species.
Timing, severity, duration and frequency of environmental exposures in effect on adult phenotypes	Well-controlled experimental administration and manipulation of environmental exposures. Deciphering pre- and postnatal effects using cross-fostering experiments. Investigation of multiple offspring generations after environmental exposure of first generation. Combined exposure to different environmental factors.	Exact factors underlying 'proxy' risk factors currently unknown. Transferability of (experience of) social stress between humans and other animal species unclear. Temporal sequence of exposures in psychotic disorder not clear.
Genetic control of environmentally sensitive developmental windows	Dynamic manipulation of gene expression during development, for example, using Cre-lox technology and/or tetracycline-activated systems, small interference RNAs, or optogenetic manipulation of neuronal activity.	Translating neurodevelopmental periods across species. Differentiating the effects of the homologous endogenous gene that is expressed in conjunction with the corresponding human transgene. Extrapolation of rodent genetic manipulation to human genetic risk variants, including copy number variations. Deciphering putative differences in genetic drive of phenotypes in various animal species.
Multidomain phenotyping	Combined assessment of various behavioural domains: neurocognition, motivation, stress reactivity, social cognition, socially transferable learning. Combined assessment of experience-dependent adaptation at different biological levels: molecular (gene expression, epigenetics), cellular (dendritic spines), and functional (electrophysiology) levels.	Enhancing uniformity in behavioural testing across laboratories. Assessing subjective experience of psychiatric phenotypes in species other than humans.
Temporal sequence of biological alterations underlying the path from environmental exposure to psychosis domains	Studying environmental impact on salience attribution using behavioural measures of reward representation and associative learning. Linking sensitization of mesolimbic to other neurotransmitter systems, neuronal circuits, including their myelinated connections, and neuroendocrine regulation. Explore other possible mechanisms not yet clearly linked to environment and need to conduct experimental studies of environmental impact on these.	Detection of 'real' hallucinatory experiences and delusions in animals. Differentiation of mediating and moderating role of biological processes that are changed after environmental exposure.
Comparative ethology	Explore various animal species and strains for naturally occurring differences in psychosis-related phenotypes, such as social cognitive abilities, and underlying neurobiology.	Experimental manipulation of social environmental factors in different social contexts, including the natural habitat.

To date, the vast majority of gene–environment interaction studies of the psychosis syndrome have used indirect measures of genetic risk, such as genetic risk for psychotic syndrome that is shared with an ill first-degree relative, or expressed as psychotic syndrome-related cognitive impairments^{12,13}. Studies modelling genetic risk as a single variable reflecting the hypothesized net genetic effect will continue to be of importance; the next wave of studies may benefit from enhanced integration of the timing, severity and experience of environmental exposures, richer genetic contrasts (for example, by including first-, second- and third-degree relatives or using extended twin-family designs), (semi-)experimental designs and more extended characterization of the relevant liability phenotypes within the same study design.

A considerable novel challenge will be to examine differential sensitivity for the environment using molecular genetic measures of risk (Fig. 3). Several approaches can be envisaged. First, interactions between molecular genetic variation (common and rare single nucleotide polymorphisms, copy number variants, epigenetic modifications) and environmental measures can be modelled using statistical approaches (Fig. 3a). Although this requires new approaches, the field is developing very rapidly, providing a range of possible solutions⁷⁰. Even though statistical models do not provide direct information on the parameter of interest—how genes and environment jointly have an impact on biology (biological synergism)—methods exist that allow for an estimation of the relevance of the statistical interaction in relation to underlying biological synergism⁷¹. Statistical interaction can be examined using a hypothesis-based approach, based on insights into the biological mechanisms associated with environmental risks and molecular genetic effects, allowing for the formulation of functionally plausible hypotheses^{72,73}, a discovery approach using mass marker information⁷⁰, or a combination of the two⁴⁶. Second, synergism between genes and environment can be examined dynamically, in animals or humans, at the level of an experimental biological, cerebral or psychometric phenotype (Fig. 3b). Experimental studies thus represent an important source of follow-up validation of findings from initial studies focusing on statistical interaction.

As individual genes interact in complex manners with other genes and with non-coding sequences, it may be furthermore productive to (1) combine pathway analyses in genome-wide-association studies with environmental-wide assessments and explore gene–environment-wide interactions (GEWIS)⁷⁰, (2) study the effect of complete patient genomes in interaction with specific environmental exposures by sampling accessible tissue sources and expose cultured cells to specific environmental factors to observe subsequent biological alterations, (3) study prospectively sampled biological tissues in order to investigate longitudinal changes in (regulation of) gene expression as a result of environmental exposures⁷⁴ during the follow-up period, and correlate these to longitudinal alterations in liability phenotypes. Finally, (4) recent work suggests that rare structural DNA variants, or copy number variants, contribute broadly to neurodevelopmental phenotypes including both schizophrenia and autism⁴, and similar evidence of non-specific contribution to both schizophrenia and autism has been reported for minority group position^{75,76} and advanced parental, particularly paternal, age^{76,77}. These findings may point to specific forms of gene–environment interplay having an impact on neurodevelopmental alterations. For example, advanced paternal age may reflect a mechanism of cumulative environmental exposure affecting the male germline through epigenetic mechanisms, causing developmental perturbations that increase risk across a spectrum of neurodevelopmental disorders.

Beyond GxE: environmental sensitivity outcomes

Aetiological research in psychiatry overwhelmingly focuses on proposed disorder-specific causes. However, a diagnosis of schizophrenia is highly predictive of virtually all other Axis I and Axis II psychiatric disorders in the same person⁷⁸. In addition, research has shown that the cognitive alterations, psychosis (hallucinations and delusions) and affective dysregulation observed in psychotic disorders (schizophrenia, bipolar disorder) are also prevalent in common mental disorders (anxiety disorders, depression), and that differences between the two groups are quantitative rather than qualitative^{79,80}. The relative non-specificity of

symptoms in psychiatric disorders extends to the level of familial aggregation. For example, the non-affected siblings of patients with psychotic disorder display cognitive alterations compared to well controls, one of the reasons why cognitive alterations are considered a 'core' marker of genetic risk for schizophrenia. However, siblings of patients with common mental disorders also display cognitive alterations, albeit to a lesser degree⁸¹. Similarly, although a family history of schizophrenia is associated with the strongest relative risk, almost any psychiatric disorder in first-degree relatives is associated with an increased risk for schizophrenia. Indeed, in terms of attributable risk, nearly 30% of schizophrenia in the population can be attributed to psychiatric family history in general, compared to 6% that is attributable to a family history of schizophrenia specifically³⁵. These data suggest that, in addition to possible specific factors impacting on liability to specific psychiatric disorders, shared genetic and environmental factors occasion neurodevelopmental alterations resulting in liability to broad dimensions of mental ill-health⁸², expressed in the form of variable combinations of affective dysregulation, psychosis, motivational impairment and cognitive alterations.

For example, one of the factors that may broadly increase risk for both psychotic⁸³ and common mental disorders⁸⁴ is the personality trait of negative affectivity, or the stable tendency to develop negative emotions in the face of small daily life stressors. Environmental negative reactivity is difficult to capture in cross-sectional questionnaires, but can be assessed in the flow of daily life using context-sensitive momentary assessment technology, the mental health equivalent of ambulatory, 'real life' measurement of physiological parameters such as blood pressure, heart rate, brain waves and muscle tone. By sampling affective and environmental experience at random moments in the flow of daily life over protracted periods of time (typically a week or more), in combination with simultaneous, non-invasive sampling of a range of biological parameters, individual differences in affective and associated biological responses to small variations in environmental stress can be analysed directly, allowing for a comparison of different psychiatric disorders and determination of the genetic and environmental factors that contribute to individual differences in the 'film' rather than the 'snapshot' of environmental reactivity⁸⁵. Momentary assessment research suggests that altered negative affective reactivity to stress (stress-sensitivity) is associated with, for example, psychotic disorder, depression and borderline personality disorder, and is also present in the first-degree relatives of patients⁸⁵. In addition, research indicates that the familial liability to psychotic disorder is manifested as the momentary subtle expression of 'aberrant salience' in response to stress (psychotic reactivity, for example, subtle perceptual anomalies or paranoid ideas) in the flow of daily life⁸⁶. Furthermore, there is evidence that motivational states, conceptualized as the momentary positive affective responses to daily life positive events, are sensitive to specific molecular genetic variation⁸⁷ that predicts similar effects in experimental neuroimaging designs of motivational states⁸⁸.

These data indicate that the behavioural expression of liability to psychiatric disorders can be conceptualized as alterations in context-sensitivity expressed as environmental reactivity. Subsequent work has suggested that the origins of environmental reactivity phenotypes, such as stress sensitivity, can be traced to gene-environment interactions occurring over the life course⁶⁶. The implication for aetiological research is that the causes of psychiatric disorders such as psychotic syndrome may be productively studied by focusing on liability phenotypes, such as relatively non-specific alterations in environmental reactivity, rather than on hypothesized specific, confound-free and static disease entities.

Conclusions

The human brain has evolved as a highly context-sensitive system, enabling behavioural flexibility in the face of constantly changing environmental challenges. There is evidence that genetic liability for psychotic syndrome is mediated in part by differential sensitivity to environments of victimization, experience of social exclusion and substances affecting brain functioning, having an impact during development. Given the complexity of the phenotype and evidence of dynamic

developmental trajectories, with environmentally sensitive periods, longitudinal research on gene-environment interplay driving variation in behavioural expression of liability, that subsequently may give rise to more severe and more 'co-morbid' expressions of psychopathology and need for care, is required to identify the causes and trajectories of the psychotic syndrome. Examination of differential sensitivity to the environment requires technology to assess directly situated phenotypes indexing dynamic, within-person environmental reactivity as substrate for molecular genetic studies; parallel multidisciplinary translational research, using novel paradigms, may help identify underlying mechanisms and point the way to possible interventions.

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