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Review

Schizophrenia: a classic battle ground of nature versus nurture debate

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ABSTRACT

Much has been learned about the etiology and pathogenesis of schizophrenia since the term was first used by Eugene Bleuler over a century ago to describe one of the most important forms of major mental illness to affect mankind. Both nature and nurture feature prominently in our understanding of the genesis of the overall risk of developing schizophrenia. We now have a firm grasp of the broad structure of the genetic architecture and several key environmental risk factors have been identified and delineated. However, much of the heritability of schizophrenia remains unexplained and the reported environmental risk factors do not explain all the variances not attributable to genetic risk factors. The biggest problem at present is that our understanding of the causal mechanisms involved is still in its infancy. In this review, we describe the extent and limits of our knowledge of the specific genetic/constitutional and non-genetic/environmental factors that contribute to the overall risk of schizophrenia. We suggest novel methods may be required to understand the almost certainly immensely complex multi-level causal mechanisms that contribute to the generation of the schizophrenia phenotype.

1. Introduction

Although the terms were first used together in 1874 by Francis Galton to discuss human intelligence and character, the relative contributions of nature and nurture have probably been as widely discussed and disputed in the context of schizophrenia as for any other disorder that affects fundamental human attributes. Nature we tend these days to define as the biological and genetic contribution, nurture the psychological and social contribution. Non-psycho-social environmental factors occupy an ambiguous place not falling neatly into either category. Similarly, when discussing specific risk factors and the size of their contribution to nature or nurture we tend to think in terms of direct genetic and direct environmental factors as well as gene-environment interactions [1,2]. In yet others such as family history where there are genetic, cultural, and physical components, the distinctions become blurred.

The whole debate is further confounded in schizophrenia by problems of diagnosis based on face validity, phenotypic and genotypic heterogeneity, overlap with other neuropsychiatric disorders, problems associated with assortative mating, and uncertainties whether the disorder is best understood categorically or as part of a continuum. This review tries to highlight some of the research findings that have emerged and now inform the nature versus nurture debate.

Schizophrenia is a common form of severe mental illness with an estimated lifetime risk of around one percent. Indeed, there has been an ongoing debate about how schizophrenia maintains its high prevalence given that it is under negative selection due to reduced birth rates among individuals with schizophrenia. The disorder is present in both sexes and found in all populations throughout the world. It is characterized by positive symptoms such as hallucinations and delusions, negative symptoms such as poor social functioning, apathy, lack of emotion, and cognitive dysfunction with disorganized thoughts, poor concentration, and memory problems.

The diagnosis of schizophrenia is made by clinical history, symptoms, and behavior. But how good are clinical psychiatric diagnoses? The answer is complicated by the absence of a gold standard. There are no objective tests (biomarkers) for schizophrenia. Also, who makes the diagnosis? Earlier work examining Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders (DSM)-III-R Axis I (SCID-I) found inter-rater reliabilities by experienced clinicians for bipolar disorder and schizophrenia around 80% and 94%, respectively [3]. Nevertheless, the agreement between clinical diagnoses and SCID-I diagnoses was poor. Recent International Classification of Diseases (ICD)-11

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field trials have also yielded high rates of inter-rater reliability: average kappa value 0.80. However, in both DSM4 and ICD-11 field studies joint interview techniques were used. By contrast, in DSM5 field trials and studies by Chmielewski et al. [4] where patients were interviewed by clinicians on separate occasions, kappa values were much lower (0.43–0.47). Spitzer et al. [5] argued that a kappa value below 0.60 should be concerning. The operational definitions used in both ICD and DSM classification systems have been refined several times to maximize reliability but at the cost of high rates of false negatives. When first-admitted inpatients were assessed with SCID-I by trained non-clinicians, the kappa values were much more modest if compared with a consensus lifetime best diagnostic estimate (DSM-IV) by two experienced research clinicians.

There is considerable overlap of schizophrenia at both the clinical and genetic levels with bipolar affective disorders as well as neurodevelopmental disorders such as autistic spectrum disorder (ASD) [6–8]. Phenotypic and genotypic pleiotropism is the term often used to describe this phenomenon; indeed, recent work using the Danish National Registry suggests that all mental disorders are associated with an increased risk of all other mental disorders [9]. The stability of psychiatric diagnoses over time is poor. For example, one in nine patients initially diagnosed with unipolar depression converts to another psychiatric diagnosis over 15 years [10]. It is also controversial as to whether sandwiched between schizophrenia and the affective psychosis there exists a separate nosological category called schizo-affective disorder [11,12]. Thus it remains intensively arguable whether schizophrenia should be regarded as a distinct categorical disorder or part of a continuum in these circumstances[13–15].

From the point of view of clinical psychiatric practice, schizophrenia should, in our opinion, be regarded as a distinct disorder. The debate is not restricted to psychiatry. At every level from clinical, through immunology to genetics, the inflammatory bowel diseases (IBD) ulcerative colitis and Crohn's disease show some overlap, but clinically they are regarded as separate disorders and normally difficult to confuse. From a research point of view, however, the picture is different and it is probably best to keep an open mind. This is the philosophy behind the National Institute of Mental Health (NIMH) initiative in developing the Research Domain Criteria (RDoC) [16].

There is now strong evidence that schizophrenia is at least in part a neurodevelopmental disorder [17]. This means that environmental exposures and genetic perturbations that predispose to schizophrenia may predate by many years the onset of clinical presentation and indeed occur at any time from conception onwards. It is not surprising, therefore, that most attempts to find a neurodevelopmental contribution to the risk of schizophrenia have focussed on environmental exposures or genetic disturbances during the second and third trimesters of pregnancy when most early brain development occurs. There are also probable pre-conceptual influences such as parental age.

There is a limited consensus as to the pathology and pathophysiology of schizophrenia. Post mortem brains of individuals with schizophrenia have been examined for more than a century and multiple microscopic and neurochemical abnormalities have been reported [18,19]. However, post mortem studies in schizophrenia have numerous confounders and are usually underpowered due to a shortage of postmortem brain. Perhaps the most consistent findings is a dysfunction of the gamma-aminobutyric acid (GABAergic) neuronal system [20]. Similarly, structural and functional neuroimaging studies and neurophysiological studies over the last quarter century have yielded a plethora of abnormalities [21,22]. Fortunately, thanks to large international collaborative efforts through groups like Enhancing NeuroImaging Genetics through Meta-Analysis (ENIGMA) Consortium, consistent changes are now being identified. Patients with schizophrenia have patterns of brain deficits including reduced cortical thickness, subcortical gray matter volumes, and cerebral white matter integrity [23–25]. For decades the dopamine hypothesis held sway in large part because of the absence of a better hypothesis [26]. All antipsychotic drugs act to block dopamine D2 receptor and so the idea went that this neurotransmitter pathway or related pathways might in some way be abnormal in schizophrenia. At the same time, amphetamines, cocaine, and other similar drugs increase dopamine levels in the brain and can cause psychosis. However, phencyclidine and ketamine can also cause psychosis and they block glutamate (*N*-methyl-*D*-aspartate) receptors. These neurotransmitter theories of schizophrenia are consistent with the psychosis reduction effect of anti-psychotics; the other evidence is mainly circumstantial. Historically, they are important but today need to be put into a much broader and complex picture. This is in large part due to the massive increase in knowledge of the genetic architecture of schizophrenia.

2. Genetics of schizophrenia

Schizophrenia is a familial neuropsychiatric disorder, namely, there is an increased risk of schizophrenia in the relatives of probands than in the population at large. It is around 10% in first degree relatives. Twin, family, and adoption studies suggest a heritability of 70%–80%. Monozygotic (MZ) concordance is around 40%–50% [27]. However, the heritability rate probably overestimates the genetic contribution to schizophrenia. This is because concordance for MZ and dizygotic twins reflects all the contributions of both genes and shared environment to the total variance [28]. Although the evidence is not overwhelming, MZ twins discordant for schizophrenia have broadly similar rates of schizophrenia in their children [29]. Here again, while it is assumed that the genetic component is responsible for this phenomenon, transmission of a similar cultural and social environment from twin parents to offspring also should be factored in. How big is the shared environmental contribution to schizophrenia risk? It may be larger than the effect size that most classic twin studies suggest [30] and along with non-additive genetic effects and assortative mating may go some way to account for the missing heritability (discussed below) encountered in most genome-wide association studies (GWAS) of schizophrenia as well as of other major psychiatric disorders [31,32].

Assortative/non-random mating in schizophrenia is a complex phenomenon and may reflect not just personality and psychiatric problems in partners of individuals with frank schizophrenia but ancestry based assortative mating. The general conclusions at present are that assortative mating is unlikely to increase the heritability of schizophrenia and the evidence for schizophrenia genetics being influenced by ancestry-based assortative mating is speculative. For discussion see reviews by Peyrot et al. [33] and Norris et al. [34]. Similarly, most recently when Nordsletten et al. [35] evaluated the impact of non-random mating on psychiatric outcomes among the offspring of parent pairs diagnosed with schizophrenia the estimated heritability of liability for schizophrenia did not differ significantly from estimates derived from single-affected parents. However, their conclusions were based on small numbers (n = 36 pairs).

3. Mode of inheritance of schizophrenia

It was not possible from classical clinical genetic studies alone to determine the precise mode of inheritance of schizophrenia. Most models suggested that schizophrenia was likely to be genetically heterogeneous with multiple loci and alleles contributing to overall genetic risk. The number of genes involved was unknown

but prior to GWAS studies, an oligogenic model of schizophrenia was popular involving perhaps 10–20 genes [36]. A key question in the early days of gene mapping was whether schizophrenia resembled certain other common complex disorders such as Alzheimer's disease and familial breast cancer and had embedded in the familial population a subgroup of high density affected families where the inheritance pattern was Mendelian and could be mapped by linkage. In both these latter conditions, rare Mendelian subgroups proved enormously informative by allowing at an early stage the identification of key high penetrant genes involved in the molecular pathology of both disorders. The question was: could a similar subgroup in schizophrenia allow through linkage studies and positional cloning early identification of key schizophrenia related molecular pathways? The search met with very limited success. The reason appears to be that both Alzheimer's disease and familial breast cancer occur predominantly in the post-reproductive period and do not affect reproductive fitness whereas schizophrenia occurs during the peak reproductive period and affects reproductive fitness; in these circumstances, genes of major effect are usually selected against and families with recent mutations are rarely big enough to do stand on their own linkage studies.

Although they generated extensive literature, almost all the results from linkage and early individual candidate gene studies of schizophrenia have not been replicated to satisfy the stringent standards currently demanded. Two of the more interesting loci that were identified in this earlier period are *Disrupted-in-Schizophrenia 1* (*DISC1*) identified by cloning a 1:11 chromosome translocation associated with major mental illness in a large Scottish family [37,38] and chromosome 22 deletion syndrome, which is associated with schizophrenia and other neurodevelopmental disorders [39]. However, both loci are not without their problems. Only a few additional mutations outside the *DISC1* family itself have been reported to date and with 22q deletion syndrome we are still not clear, after research spanning several decades, which are the key gene/s in the deletion region causing an increased risk of schizophrenia. On the other hand, barely noticed candidate gene studies in schizophrenia have been reported continuously throughout this whole period, and from 2010 till 2017 alone, there were over 3000 studies [40]. The advent of GWAS has enormously expanded our understanding of the genetic architecture of schizophrenia. Single-nucleotide polymorphism (SNP) microarrays can interrogate hundreds of thousands of common SNP variants spanning the genome. They can detect rare high-penetrant copy number variants (CNVs) as well as common risk factors. These latter low-penetrant loci seldom have odds ratios of more than 1.2. Rare low-penetrant loci cannot be reliably detected because they require impossibly large sample sizes to reach statistical significance; the problem of sample size also applies to examining GWAS data for gene/gene interactions and epistasis [41]. By contrast, there has been much enthusiasm for looking at statistically significant common variants en masse and generating polygenic risk profiles [42].

3.1. Rare variants

There is enormous genetic heterogeneity in schizophrenia. However, only a small fraction (<5%) arises from rare high-penetrant mutations including CNVs. What's more, these latter loci show pleiotropy, and can present with intellectual impairment, ASD, attention deficit hyperactivity disorder (ADHD), and epilepsy as well as schizophrenia [43–45]. The commonest CNVs are deletions and/or duplications at 1q21.1, neurexin1 (NRXN1), 3q29, 15q11.2, 15q13.3, 16p13.11, 16p12.1, 16p11.2, and 22q11.2 plus deletions and duplications at the Angelman/Prader Willi syndrome (A/PWS) locus [46,47].

A number of other CNVs associated with intellectual impairment are also enriched in schizophrenia [48]. Many mutations, particularly in ASD but also in schizophrenia are *de novo* and are not present in parents [49,50]. This is because reduced fecundity selects against neurodevelopmental disorders. The result is that large extended pedigrees with multiple cases of schizophrenia are very rare. Indeed, Steinberg et al. [51] claimed that their identification of truncating mutations of the *RBM12* gene was the first demonstration of a mutation in a novel gene segregating with psychosis or a related phenotype in a large pedigree since the 1990 report of the segregation of t(1;11) (q43;q21) with major mental illness in a Scottish family [52]. These rare high penetrant mutations also confer increased risk of minor degrees of psychiatric or intellectual impairment in apparently unaffected carriers. There are also abnormalities on neuroimaging resembling first-episode psychosis. This was first demonstrated in the Icelandic population [53] and been subsequently in other populations including the UK biobank [54,55].

Several hundred rare non CNV associated loci are reported in schizophrenia, but in only a few cases is there good statistical evidence of genetic association [56–58]. It is not surprising therefore that most biochemical studies and modeling in animals and induced pluripotent stem cells in humans have been selected for modeling rare high penetrant loci that affect core pathways [7].

3.2. Common variants

Early modestly sized GWAS in schizophrenia identified a small number of loci that met statistical significance $P < 10^{7.5-8}$ [59]. However, over 100 loci were reported to meet genome-wide significance when total sample sizes were increased to around 130,000, and other novel loci were later found in Chinese populations [60–62]. The number of loci to date meeting the criteria for genome-wide significance in schizophrenia is probably around 200 [63]. Almost all the SNPs map outside and often quite distantly from gene-coding regions. Fine mapping of putative functional variants has proved very challenging. In these circumstances, differences in linkage disequilibrium patterns between major ethnic groups can be enormously helpful in fine-mapping [64]. However, the great majority of schizophrenia GWAS studies were performed on subjects with Caucasian or Chinese ancestry and Caucasian and East Asian genetic architectures have turned out to be unexpectedly similar [65]. Fortunately, other major ethnic groups are now being studied. These may not only help with dissecting out the functional variants at known loci but may identify hitherto unsuspected loci such as an association with disordered niacin metabolism discovered through an Indian schizophrenia GWAS [66]. It should also be pointed out that most of the GWAS data was from genotyping CHIP platforms being used over a decade ago, which explains the significantly fewer SNPs compared with the current assay and the bias is inevitable. Due to the problems of method imputation and genotyping accuracy, the GWAS hits in the X chromosome are often under-represented and ignored [67]. Developing new platforms and algorithms may offer better genome coverage especially in the X chromosome.

3.3. Transcriptome wide association studies (TWAS)

TWAS aims to overcome some of the limitations of GWAS by identifying expression quantitative trait loci (eQTLs) associated with a particular phenotype. First associations are generated between genotypes and expression patterns in reference panels such as the genotype-tissue expression (GTEx) project [62]. These panels examine expression patterns in tissues, brain regions, or single cells obtained at multiple points throughout the lifespan. It is also possible to generate a multi-omic resource and identify

SNPs significantly associated with gene expression, DNA methylation, and histone modification levels [68].

This information is then used to impute likely expression patterns associated with loci found to be significant in GWAS of the disorders under investigation. This overcomes problems associated with accessing directly RNA expression data from inaccessible tissue such as the fetal brain in disorders such as schizophrenia. The largest study to date using transcriptomics in schizophrenia by Huckins et al. [69] imputed gene expression patterns in multiple brain regions including the dorsolateral prefrontal cortex (DLPFC) to over 40,000 schizophrenia cases and 60,000 controls. They identified 413 genic associations across 13 brain regions. By stepwise conditioning, they found that 67 were not in the major histocompatibility complex region, and 14 of them had not been previously reported in GWAS. However, the power of TWAS must be seen in perspective. They only modestly improve the predictive power of GWAS on their own and interpreting the results is challenging [70]. TWAS only tests for association with genetically predicted expression, not total expression which is also influenced by environmental factors. The genetic component is also mostly derived from common cis eQTLs which Grunberg et al. [71] in a large-scale twin study found only explain around 10% of genetic variance in expression.

Polygenic risk scores (PRS) were first discussed by Purcell et al. [72] who showed that en masse thousands of common alleles of only very small effect and individually only at best modestly significant, can account for a proportion of overall genetic risk. Using much larger sample sizes PRS were estimated to account for around 18% of the variance [73–75].

Most recently, Zheutlin et al. [76] examined how PRS for schizophrenia performed in non-academic real-world settings. They found a PRS for schizophrenia was able to detect risk for diagnosis of schizophrenia and psychosis in electronic health record data on over 100,000 patients from four different health care system-based biobanks. All four were based in the USA and analysis was restricted to subjects with European-American ancestry. PRSs were robustly associated with schizophrenia. The odds ratio per standard deviation increase in PRS, however, was modest 1.55 (95% confidence interval (CI) = 1.4–1.7). PRSs were also positively associated with a number of other psychiatric conditions such as anxiety and mood disorders. These modest effects combined with a lack of specificity indicate that PRS in schizophrenia show promise but at present have limited clinical utility.

Boyle et al. [77] proposed that the genetics of complex traits needs to be rethought. They used the term "omnigenic model". Their argument went as follows. In disorders such as schizophrenia, there are myriads of associated variants. The effect sizes are tiny and the loci are widely spread across the genome with only minimal enrichment in genes and pathways thought to be core to the disease. The authors propose that cell regulatory networks are highly interconnected and any expressed genes in the same tissue may impact the function of core genes. Most heritability can therefore be explained by the effects of genes outside core pathways [77]. It is not surprising therefore that, except complement 4 [78,79] and *calcium voltage-gated channel subunit alpha1c* genes [60,80,81] few attempts have been made to model low penetrance loci for schizophrenia, either in animals or human-induced pluripotent stem cells (hiPSC). *In vivo* and *in vitro* modeling efforts have primarily focussed on rare high penetrant loci [7].

3.4. Unexplained heritability

Much of the genetic risk for schizophrenia has remained unexplained. The term missing heritability has been used to describe this phenomenon [82]. Still to be discovered are likely to be many more common and rare genetic risk factors, epistatic effects, non-additive genetic and epigenetic effects, and gene-environment interactions. As indicated above classic twin studies almost certainly underestimate the effects of shared environment, and this may well apply to schizophrenia, so that our estimates of the genetic contribution to schizophrenia are inflated. Epistasis and modeling of polygenic risk are also discussed in this context [41,72,75].

4. Environment

It is not possible to discuss in detail the evidence supporting all the putative risk and protective factors for schizophrenia. Recently, an excellent meta-analysis by Radua et al. [83] described the statistical weight of evidence for over 170 diverse putative risk and protective factors for psychosis. However, most of these data are discussed in context and follow-up studies with an independent meta-analysis still need to be warranted.

4.1. Postnatal environmental exposures

There is solid evidence for several postnatal environmental exposures that increase the risk of schizophrenia. They include urbanicity, migration, childhood trauma/adversity, and cannabis abuse.

4.1.1. Migration

There is now overwhelming evidence for elevated rates of schizophrenia immigrants affecting both first and second generations [84,85]. It is very difficult to decide what is responsible for these findings. Most of the evidence comes from the migration of people from different, often rural ethnic groups and poor backgrounds, to developed and mostly urban societies. Some of the highest rates are found in Afro-Caribbean immigrants to UK and Moroccans to the Netherlands. There is very limited literature on internal migration. A recent study from Italy showed elevated psychosis risk in native Italian migrants from Southern to Northern Italy [86]. A common predisposing factor in all these studies may be the stress of diminished social status. For reviews see Van der Ven et al. [87] and also Radua et al. [83] for additional discussion.

4.1.2. Urbanicity

Rates of schizophrenia are elevated in city dwellers. The phenomenon is found principally in high-income countries and may not generalize to middle and low-income countries [88]. The effect is restricted to individuals born and brought up in cities. The urban social environment is assumed to be responsible [89–91]. Urban living is a more demanding and stressful environment with more social fragmentation and inequalities. Exposures may cause psychosocial stress and defeat [92]. The causal mechanisms underlying these observations are assumed to be effected in part through increased amygdala activity [93] and/or increased reactivity of the hypothalamic–pituitaryadrenal (HPA) axis [94] though a recent study failed to detect associations between urbanicity and steroid hormone levels [95]. There may also be synergy between urbanicity and familial risk of psychosis [96].

The effects seem to occur during childhood with only minor predisposing influences occurring in later life [89,97]. However, it must be borne in mind that the effect sizes are still modest (odds ratios around 2) and the phenomenon may not be a permanent problem as people become accustomed to/ assimilate to urbanization. There could be cohort effects. Effects of urbanicity may be similar to the season of birth effects which appear to be diminishing in size [85,98].

4.1.3. Childhood trauma

Adverse events in childhood are the most studied postnatal stressors reported to increase the risk of schizophrenia. They include physical, sexual, or emotional abuse, and parental loss/separation [99–101]. Most of these adverse childhood events are assessed retrospectively which introduces problems of recall [102]. For discussion of other confounders see reviews by Hovdestad et al. [103] and Popovic et al. [104].

These stressors may contribute specifically to the development of schizophrenia [99,105,106] as well as increased rates of psychosis in the general population [107]. There is also some evidence of a dose–response pattern [108]. The evidence now comes not only from numerous retrospective but also from several longitudinal studies [99,109,110]. Both explore potential psychological mechanisms that may be responsible. The physical mechanisms have received less attention but it is generally assumed that many of the effects are mediated via glucocorticoids [104].

Are those with a family history of psychiatric disorders more predisposed to develop psychosis when they are exposed to major stressors in childhood? The evidence is scanty and not clear cut. Epidemiological evidence suggests that childhood adversity and a positive family history of mood or psychotic disorders do additively affect the risk of psychosis [111–113].

The complexity of integrating, analyzing, and interpreting the data on childhood adversity and risk of schizophrenia in later life is prompting researchers to use new methods such as machine learning algorithms to cope with this complexity. The approach is discussed by Popovic et al. [104] and later in this review, we discuss their use for analyzing vulnerability factors for schizophrenia in general.

4.1.4. Cannabis

Cannabis use has also been identified as a risk factor for schizophrenia especially in individuals susceptible to mental illness. Several studies have reported a dose-dependent association between cannabis use and the risk of schizophrenia, especially in young people [114–117]. Supporting a causal relationship are two Mendelian randomization studies [117,118]. The latest research by Di Forti et al. [119] suggests that daily smoking of high-potency marijuana increases fivefold the risk of developing psychosis. Whether and to what extent cannabis use on its own causes psychosis is not clear. It certainly participates in causing psychosis, and the key thing as Di Forti et al. [119] point out it is a modifiable risk factor and therefore a potential target for preventive interventions.

4.2. Prenatal environmental factors

For many reasons including the extensive time interval between conception and the development of schizophrenia, environmental influences occurring prenatally are much more difficult to study. Radua et al. [83] also demonstrate that the literature for solid and replicable evidence of prenatal exposures resulting in an increased risk of schizophrenia, is less substantial than for postnatal exposures. However, this does not mean that prenatal exposures are unimportant. They are more difficult to study and result in insufficient published data to lend themselves to meta-analysis.

Four prenatal environmental exposures have received widespread attention. They are advanced parental age at the time of conception, the season of birth, prenatal exposure to infections, and the effects of prenatal malnutrition.

4.2.1. Advanced paternal age

This is interesting since the events that determine paternal age at the time of conception are both cultural and genetic: around ten papers that have examined advanced paternal age and risk of schizophrenia have all reported positive associations [120–122].

The data on female advanced age are more difficult to interpret but recent studies suggest that advanced maternal age at first birth increases the risk of schizophrenia in offspring independent of paternal age [123]. These findings raise the plausible hypothesis that antecedents occurring at conception or preconception may predispose to increased risk of schizophrenia through potential genetic or epigenetic mechanisms (e.g., *de novo* mutation). Adverse early life events may also affect more than one generation [124,125]. This is an area that has been barely explored in schizophrenia.

4.2.2. Season of birth

There is modest good evidence of a small but consistent excess of individuals with schizophrenia born during the winter and early spring months when prenatal exposure to infective agents is assumed to be increased. Interestingly, similar positive findings are reported from both the Northern and Southern Hemispheres even though winters occur at opposite ends of the annual calendar. It is estimated that there are approximate 5%–8% more winter and spring births among patients with schizophrenia as compared with the general population [98]. The evidence of the birth seasonality in schizophrenia has mostly come from developed countries [126–128] but a recent Chinese study [129] shows similar results except the excess was in early spring and not winter. However, not all results support a link [130] and other non-infective environmental factors such as vitamin D deficiency could also be responsible, not to mention perinatal as opposed to prenatal viral exposures [131–133].

4.2.3. Prenatal exposure to infections

Influenza is one of the most studied potential prenatal infective exposures. The studies fall into two parts: ecological and longitudinal cohort studies. Ecological studies: Mednick et al. [134] reported an increased risk for schizophrenia in people exposed prenatally to the 1957 influenza epidemic. This was followed in rapid succession by studies from Scotland and Denmark essentially confirming the Mednick findings. National registry records were used and allowed examination of prenatal exposure to both the 1918–1919 and 1957 influenza epidemics. Unfortunately, since then around 20 additional ecological studies have addressed the issue, with around half supporting the hypothesis and the other half failing to confirm. However, there are confounders that make interpretation of these studies difficult. Almost all are based solely on whether an individual was *in utero* at the time of an influenza epidemic. This means that 70% of individuals who were *in utero* during the 1957 type A2 influenza epidemic would have been misclassified as having been exposed [135]. This increases the risk of false-negative (type 2 error) associations [136]. Indeed, similar problems of potential type 2 errors apply to most studies and meta-analyses of potential peri- and prenatal risk facts for schizophrenia especially if the risk for psychosis as a whole is examined and not schizophrenia alone. Most studies are also underpowered for detecting modest effect sizes of 1.5 or less. In this respect, the studies differ from prenatal exposure to famine where exposure as measured by fertility reduction and weight loss was almost universal [137–139]. Longitudinal birth cohort studies: Ideal studies have well-characterized birth cohorts in which biological specimens taken from the mother while pregnant are stored and/or clinical evidence of infection is obtained during pregnancy and evidence of schizophrenia is systematically enquired after following longitudinal assessment of offspring. The main study is derived from the prenatal determinants of schizophrenia study [140] which in turn was based on the birth cohort of the child health and development study (CHDS), a population-based cohort born from 1959 to 1967 in California,

and followed up for evidence of schizophrenia and other major psychiatric disorders in adulthood. In a nested case-control study Brown et al. [141] demonstrated a threefold elevation in risk of schizophrenia following influenza prenatal exposure during the first half of gestation. For first-trimester exposure, the risk of schizophrenia was increased sevenfold but not elevated risk following exposure during the second half of gestation. These results have been difficult to interpret especially after Selten et al. [142] pointed out that serological studies may have limited validity, because they utilize a single serum specimen. After infection, influenza antibodies can remain positive for years, so many subjects may have been infected before pregnancy. For an adequate timing of exposure one really needs a specimen taken both during the acute and a convalescent phase. In other words, serology may introduce false precision. In summary, the evidence for *in utero* exposure to influenza as a risk factor for schizophrenia is compelling but still not convincing. Our view is also supported by the recent meta-analysis by Davies et al. [143].

Herpe simplex virus type 2 (HSV-2) is a sexually transmitted virus, and maternal-offspring transmission generally occurs during passage through the birth canal. Neonatal exposure to HSV-2 is associated with congenital anomalies and neuropsychiatric disorders [141]. Three studies have examined the relationship between prenatal exposure to HSV-2 and the risk of schizophrenia in offspring. Two of these studies were derived from selected sites of the collaborative perinatal project (CPP), a multisite study of population-based birth cohorts born from 1959 to 1967. The methodology was similar to the CHDS. In the first study [144] in a Rhode Island cohort, raised maternal IgG antibody levels to HSV-2 were associated with a significantly elevated risk of schizophrenia and other psychoses in offspring with odds ratios of 3.4 to 4.4. In a much larger follow-up study [145] which included 200 case subjects with psychotic disorders from three cohorts of the CPP (Boston, Rhode Island, and Philadelphia), there was a 1.8-fold increased risk of schizophrenia psychoses were observed among offspring of mothers who were seropositive for HSV-2 but only among seropositive mothers who have regular unprotected sexual intercourse. A third study based on the CHDS cohort failed to replicate these positive associations [146]. Potential explanations for these discrepant findings are discussed by Brown et al. [147] as are limited and equivocal findings trying to implicate varicella, rabies, poliomyelitis, and other herpes viruses such as cytomegalovirus. There have been few and mostly negative subsequent studies of HSV2 and schizophrenia [148].

Toxoplasmosis is an infectious disease caused by a parasitic protozoan *Toxoplasma gondii*, which affects approximately one-third of the entire human population. *T. gondii* can be found in almost all warm-blooded animals, but cats are the only known hosts People can be infected when ingesting uncooked meat or unwashed fruit or vegetables. Toxoplasmosis can also be transmitted via the placenta and is associated with a variety of cerebral malformations, congenital brain disorders, learning difficulties, and cognitive impairments. *T. gondii* is highly neurotropic and soon after the infestation, migrates within the brain tissue to localize in astrocytes, microglia, and neurons [149]. The dormant form or bradyzoite can persist in the host brain for many years [150] without causing tangible symptoms in immune-competent individuals. Given the high level of neurotropism and the fact that *T. gondii* is endemic in almost all cultures worldwide, it has long been postulated that there may be a link with major psychiatric disorders and schizophrenia in particular [151]. Indeed, three meta-analyses of the association between *T. gondii* exposure and schizophrenia have been published [151–153]. All were conducted with necessary scientific rigor and all have demonstrated, even accounting for publication bias, an association with *T. gondii*exposure. The most recent analysis [153] also confirmed significant odds ratios (ORs) in schizophrenia (OR 1.81, $P < 0.00001$) and to a lesser extent bipolar disorder and obsessive–compulsive disorder but not major depression. Schizophrenia risk is also increased in the offspring whose mothers showed serologic signs of infection during pregnancy. Cohort studies of blood samples taken from mothers in the perinatal period also show a 2-fold increase (OR 2.61; 95% CI = 1.00–6.82) of IgG antibodies to *T. gondii* in those whose children went on to develop schizophrenia. None of the studies detected an acute infection as detected by specific IgM antibodies: this suggests the effects are due to latent infection [151,154]. Similar results have been found assaying IgG and IgM anti-*T. gondii* antibody levels in neonatal blood spots from the Danish State Serum Institute[155]. Since babies only start producing IgG antibodies around three months after birth, IgG antibodies assayed in the neonatal blood spots must be maternal in origin and suggest that earlier maternal exposure to *T. gondii* increases the risk of schizophrenia [155,156]. Three independent studies detected a significant correlation between the first psychotic episode in schizophrenia and serological markers of toxoplasmosis ($P < 0.001$), suggesting that these patients must have acquired the infection earlier [151]. The difference was less marked in patients with a long-standing disease. It was suggested that perhaps neuroleptic drugs could decrease the levels of circulating antibodies to *T. gondii* and inhibit *in vitro* growth of *T. gondii* [157]. Nevertheless, available data suggests that some neuroleptic drugs may have reduced psychosis by not only antidopaminergic action but also by inhibition of *T. gondii* [158,159]. In conclusion, the evidence for prenatal exposure to toxoplasmosis and subsequent risk of schizophrenia is compelling but not conclusive. This is reinforced by the Fusar-Poli group identifying toxoplasmosis as a strong risk factor for psychosis [83] but failing to give it more than modest support in their subsequent meta-analysis [143].

4.2.4. Prenatal exposure to famine and nutritional stress

The relationship between prenatal psychological stressors and risk of schizophrenia is long debated but remains inconsistent [160,161] which will not be discussed further. Results are also interesting but not compelling for individual prenatal nutritional stressors such as vitamin D deficiency [162]. However, there is now, in the author's view, convincing evidence for an increased risk of schizophrenia from prenatal exposure to famine (e.g., Dutch Hunger Winter famine) [137–139]. These studies where the exposure period is strictly defined in advance are much more powerful than traditional ecological studies and the story becomes very compelling when all the studies report more or less the same findings. Nevertheless, when taken together these studies make a convincing case for intrauterine exposure to famine as a general risk factor for schizophrenia, they do not point to any specific causal mechanisms.

4.3. Coronavirus disease 2019 (COVID-19)

It is not clear at present if long-term neurological or neuropsychiatric complications can occur from exposure either pre or postnatally to SARS-CoV-2. The effects could be direct from the virus itself or mediated through a hyperimmune response. Fortunately, the importance of these questions is appreciated and steps are underway to address them formally including longitudinal studies [163,164]. On the other hand, the "indirect" effects of stress-related triggers from the COVID-19 can not be fully ruled out, especially in psychiatrically vulnerable individuals [165]. Interestingly, a century ago a pandemic of a new disorder encephalitis lethargica occurred around the time of the 1918–1919 influenza pandemic and we still do not know if the two were interconnected [166].

4.4. Gut microbiota and brain endozoites

Over the last ten years, there has been an explosion of interest in microbiota-gut brain (MGB) axis signaling and its potential effect on the brain and behavior. Multiple studies report that the composition of the gut microbiota can influence brain function [167,168] partly by the release of metabolites including neurotransmitters that can enter the circulation, but also via direct neuronal communication between gut and brain (notably via the vagus nerve). For an excellent review see Sampson and Mazmanian's [168]. Animal studies also suggest that gut microbiota can reshape the concentration and dynamic turnover of monoaminergic neurotransmitters together with the expression of synaptic-plasticity related genes in the brain, thus altering brain development and behavior [169]. Apart from the canonical monoaminergic pathways, recent progress also demonstrates decreased microbiome α-diversity index and disrupted excitation-inhibition balance [170]. Given these interactions with the brain and especially the neurotransmitter effects, it is a popular idea that the gut microbiome may play a role in the development of schizophrenia. Indeed there are now some preliminary studies that suggest altered gut microbiota profiles in schizophrenia [170]. The evidence is reviewed by Kelly et al. [171] and harnessing the MGB axis has become an attractive route to develop innovative therapeutics for schizophrenia. In addition to the vertebrate gut, a diverse range of endozoites has been found in the brain itself, not only including bacteria, protozoans, archaea, and viruses, but also bacteriophages, higher eukaryotes, and plant-derived agents. What their role is in health and disease is not at present clear. A potential contribution to the genesis of schizophrenia, of other brain endozoites in addition to toxoplasmosis as described above cannot be ruled out completely.

4.5. Epigenetics

Epigenetic modification of gene expression can be influenced directly and indirectly by both genetic and environmental factors and is one of four dimensions by which information is transmitted from one generation to the next. The four main dimensions are genetic, epigenetic, behavioral, and symbolic and are elegantly described by Jablonka et al. [172] Physical transmission is often ignored but it should be remembered that the egg that produces the grandchild is present in the mother while she herself is *in utero*. Three generations can therefore be directly affected physically by a single environmental exposure. There are multiple examples of Intergenerational epigenetic transmission in *C. elegans* but few in mammals [173]. However, there is no disagreement that changes in gene expression are one of the most important mechanisms that determine our phenotype. Unfortunately, identifying specific epigenetic patterns responsible for individual psychiatric phenotypes is exceptionally difficult. While analysis of DNA sequence variation is essentially a two dimensional or bi-directional problem, epigenetics includes additional spatial and temporal dimensions. Also, epigenetics includes DNA methylation, histone changes, and RNA interference, not to mention RNA methylation and post-translational modifications. It is no surprise therefore that the epigenetics of schizophrenia is still in its infancy. Three main approaches have been pursued, twin studies [174,175] post-mortem studies [176] and whole-genome methylome scans [177–179]. Designing epigenome-wide association studies (EWAS) combined with environmental exposures are complex and because of the many potential confounders including age, sex, lifestyle, cell types, and so on, interpretation of results is often problematic [180,181]. Unfortunately, almost all these potential associations reported to date are likely, as in similar classic underpowered GWAS, to end up being false positives. Very much larger sample sizes will need to be interrogated if consistent and genuinely positive epigenetic findings are to emerge [182]. In the meantime, much is likely to be learned by the exploitation of multi-omic resources that identify SNPs significantly associated with DNA methylation and histone modification levels as well as gene expression [68,183].

5. Summary

We conclude that a modest amount has now been learned about the genetic architecture of schizophrenia. Explanations for the so-called missing heritability are mostly speculative. There are also some well recognized environmental risk factors for schizophrenia. However, little is known about the causal biochemical and molecular mechanisms involved that translate genetic and environmental risk into the schizophrenia phenotype. It is also now clear that environmental exposures that increase the risk of schizophrenia can occur at any point across the life span and probably include pre-conceptional exposures. However, obtaining good individual rather than population-based data is very difficult, especially for early exposures. Finally, we think that classical genetic and environmental risk studies cannot capture the sheer complexity of the nature and nurture interactions that contribute to the schizophrenia phenotype and suggest that now is an opportune time to consider other methods such as "omnigenic approaches" [77]. Multiple other levels of information concerning individuals and populations, as discussed above, need to be integrated if one wants to build a comprehensive model to produce the schizophrenia phenotype. Only then can we fully explore this immensely complex multi-level nature versus nurture problem and in the process throw light on causal mechanisms. In the meantime, one can only speculate as to which factor(s) pose the greatest risk and should be a key focus of current research. Perhaps too much emphasis has recently been given to the molecular genetic basis of schizophrenia and insufficient attention paid to those environmental risk factors such as nutritional status or cannabis abuse which may affect incidence rates and/or therapeutic outcomes after appropriate and timely intervention.

Conflict of interest

The authors declare that they have no conflict of interest.

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Author contributions

David St Clair and Bing Lang conceived the idea and drafted the manuscript.

Appendix A. Supplementary materials

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