



# Schizophrenia

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Schizophrenia is a complex, heterogeneous behavioural and cognitive syndrome that seems to originate from disruption of brain development caused by genetic or environmental factors, or both. Dysfunction of dopaminergic neurotransmission contributes to the genesis of psychotic symptoms, but evidence also points to a widespread and variable involvement of other brain areas and circuits. Disturbances of synaptic function might underlie abnormalities of neuronal connectivity that possibly involves interneurons, but the precise nature, location, and timing of these events are uncertain. At present, treatment mainly consists of antipsychotic drugs combined with psychological therapies, social support, and rehabilitation, but a pressing need for more effective treatments and delivery of services exists. Advances in genomics, epidemiology, and neuroscience have led to great progress in understanding the disorder, and the opportunities for further scientific breakthrough are numerous—but so are the challenges.

## Introduction

Schizophrenia is a severe psychiatric disorder that has a profound effect on both the individuals affected and society. Although outcomes might not be as uniformly negative as is commonly believed, more than 50% of individuals who receive a diagnosis have intermittent but long-term psychiatric problems, and around 20% have chronic symptoms and disability.<sup>1</sup> Unemployment is staggeringly high at 80–90%,<sup>2,3</sup> and life expectancy is reduced by 10–20 years.<sup>4</sup> In England, schizophrenia costs £11·8 billion per year, with around a third of this figure accounted for by direct expenditure on health and social care, provided both in hospitals and in the community.<sup>5</sup> Two of the most formidable challenges are to understand the causes and pathogenesis of the disorder, and to develop new, effective, and acceptable treatments. However, the past decade has seen substantial advances in the application of genomics, epidemiology, and neuroscience to schizophrenia research, and the opportunities for progress have never been greater.

## Clinical presentation, signs, and symptoms

Schizophrenia is characterised by diverse psychopathology (table); the core features are positive symptoms (delusions and hallucinations; so-called psychotic symptoms in which contact with reality is lost), negative symptoms (particularly impaired motivation, reduction in spontaneous speech, and social withdrawal), and cognitive impairment (patients had poorer performance than controls over a wide range of cognitive functions, although much individual variability was reported).<sup>6</sup> The positive symptoms tend to relapse and remit, although some patients have residual long-term psychotic symptoms.

### Search strategy and selection criteria

We searched publications in PubMed using the search term “schizophrenia” for reviews and meta-analyses published in English between March 1, 2010, and March 1, 2015. The manuscripts were assessed for relevance to the topics selected. Further focused searches on PubMed were then done on the selected topics.

The negative and cognitive symptoms tend to be chronic and are associated with long-term effects on social function. The first episode of psychosis usually occurs in late adolescence or early adulthood, but it is frequently preceded by a prodromal phase or a so-called at-risk mental state.<sup>7,8</sup> In some instances, premorbid impairments in cognition or social functioning, or both, can manifest many years before the first psychotic episode.<sup>9</sup> However, in other instances, onset is sudden in previously well functioning individuals.

## Diagnosis and differential diagnosis

Diagnosis is made clinically on the basis of history and by examination of the mental state; no diagnostic tests or biomarkers are available. Schizophrenia usually presents with psychosis; according to the fifth edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-5),<sup>10</sup> the main differential diagnoses are affective psychoses (bipolar disorder with psychotic features and major depressive disorder with psychotic features), other closely related non-affective psychoses (schizoaffective disorder, schizophreniform disorder, delusional disorder, brief psychotic disorder, and psychotic disorder not otherwise specified), psychotic disorders induced by alcohol or other substances, and psychotic disorders caused by a general medical illness. Differential diagnosis takes into account the duration of illness, the nature and pattern of associated substance abuse, the co-occurrence of depression or mania, and the presence of somatic illness.

Schizophrenia, like most psychiatric diagnoses, remains a syndromic concept. The use of operational criteria, such as those embodied in DSM-5<sup>10</sup> or the WHO International Classification of Diseases (ICD),<sup>11</sup> has provided a reliable approach to psychiatric diagnoses in the clinic. However, the assumption that the clinical syndromes defined in this way represent valid disease entities with distinct underlying causes and pathogenesis is increasingly being seen as having impeded research.<sup>12–14</sup> Indeed, psychiatric diagnoses have the unusual feature of being simultaneously too broad and too narrow.<sup>14</sup> On the one hand, individuals with a diagnosis of schizophrenia vary greatly in predominant symptoms, response to treatment, course, and outcome. However, attempts to

	Schizophrenia	Bipolar disorder	Schizoaffective disorder	Autism	ADHD
Core features	Delusions, hallucinations, impaired motivation, reduction in spontaneous speech, and social withdrawal	Episodes of elated mood and episodes of depressive mood	Delusions, hallucinations, and mood episodes (depressive, manic, or mixed)	Social and communication difficulties, and restricted repetitive behaviours	Inattention, hyperactivity, and impulsivity
Additional features	Cognitive impairment, episodes of elated mood, and episodes of depressive mood	Delusions and hallucinations	Cognitive impairment	Cognitive impairment, delusions, and hallucinations	Cognitive impairment
Heritability estimate	Roughly 80%	Roughly 85%	Roughly 85%	Roughly 58%	Roughly 75%
Average age of onset	16–30 years	18–40 years	25–35 years	<3 years	7–12 years
Drug treatment	Antipsychotics	Antidepressants and mood stabilisers	Antipsychotics, antidepressants, and mood stabilisers	No recommended drug treatment; treatment for comorbidities if present	Stimulants

ADHD=attention deficit hyperactivity disorder.

**Table: Clinical features of schizophrenia, bipolar disorder, schizoaffective disorder, autism, and ADHD**

resolve this heterogeneity into valid subtypes have repeatedly failed. On the other hand, many psychiatric diagnoses have symptoms in common (table), and the boundaries between schizophrenia and other disorders are indistinct, as are the boundaries between disorder and wellness. An increasing realisation is that psychotic symptoms, such as auditory hallucinations and paranoid thinking, occur in attenuated form in 5–8% of the healthy population,<sup>15</sup> leading to suggestions that dimensional approaches to diagnosis and classification might replace or enhance existing categorical methods.<sup>14,16,17</sup>

## Genetics

Many genetic epidemiological studies have shown, for more than 50 years, that genetic factors contribute substantially, but not exclusively, to the underlying cause of schizophrenia.<sup>18,19</sup> What has changed in the past 8 years is that, with large-scale genomic studies, the contribution of specific DNA variants and different types of risk alleles to the disorder has begun to emerge. Three lessons of general importance can be drawn from these findings.

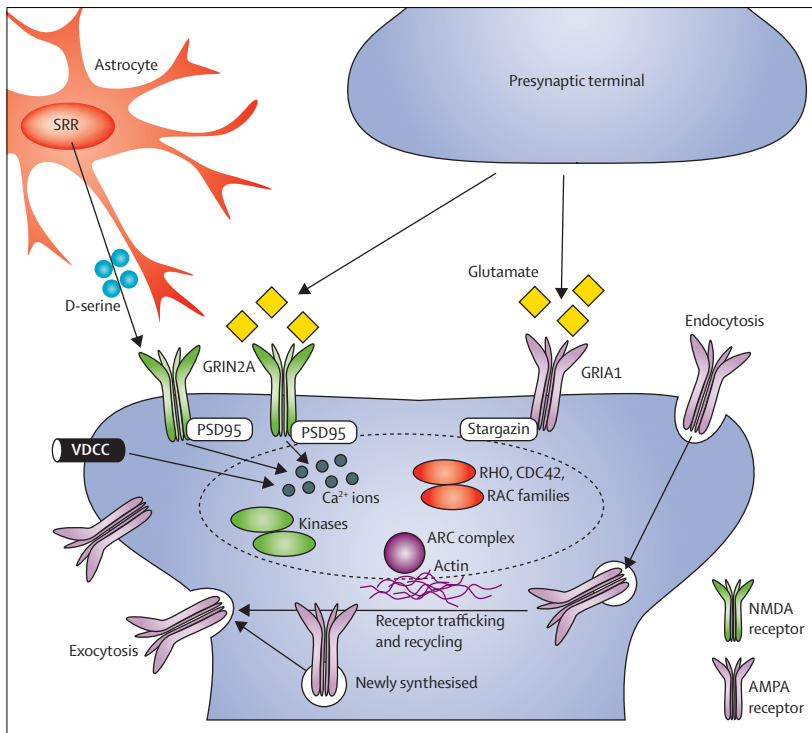
First, schizophrenia is highly polygenic, as predicted in the 1960s on the basis of genetic epidemiological findings.<sup>20</sup> Genome-wide association studies have identified more than 100 distinct genetic loci containing fairly common alleles of small effect and the en-masse effects of many hundreds of such loci,<sup>21,22</sup> suggesting that single-nucleotide polymorphisms (SNPs) with a range of population frequencies contribute to risk (appendix). Genomic studies have also identified 11 rare, but recurrent, copy number variants (CNVs; large regions of the genome that have been deleted or duplicated) that individually confer a relatively high risk of schizophrenia (appendix),<sup>23,24</sup> and also a role for newly occurring (ie, de-novo) CNVs in the disorder.<sup>23,25,26</sup> Whole-exome sequencing studies have implicated rare, inherited, and de-novo SNPs, and insertion and deletion variants (indels) in schizophrenia,<sup>27,28</sup> although the net contribution of mutations of this type is unknown, and much larger sequencing studies, with tens of thousands of cases and controls, are pending. In view of the fact that

schizophrenia is associated with reduced fecundity,<sup>29</sup> the emerging picture is that alleles conferring high individual risk are rare in the population because of the effects of natural selection,<sup>30</sup> whereas those with small effects on individual risk can become common as a result of genetic drift or balancing selection (appendix).

Second, genetic risk seems to be highly pleiotropic (ie, one gene or allele can affect multiple seemingly unrelated phenotypic traits) and does not map onto existing definitions of disease. Pleiotropy has been reported for common variants at the level of individual risk alleles and en-masse effects. A study showed significant sharing of common risk variants between schizophrenia and bipolar disorder, between bipolar disorder and major depressive disorder, between schizophrenia and major depressive disorder, between attention deficit hyperactivity disorder (ADHD) and major depressive disorder, and, to a lesser extent, between schizophrenia and autism spectrum disorder.<sup>31</sup> An overlap in risk variants between schizophrenia and ADHD has also been reported.<sup>32</sup> Pleiotropy is also seen in rare variants: CNVs that confer risk to schizophrenia also affect generalised epilepsy and a range of childhood neurodevelopmental disorders, such as autism spectrum disorder, intellectual disability, and ADHD.<sup>23,33,34</sup> Additionally, some rare SNPs and indels are associated with a similar range of outcomes.<sup>27</sup> Risk alleles that are relatively non-specific to the diagnostic group will be easier to detect than those that confer risk to particular diagnoses or subgroups; indeed, alleles with fairly specific risk profiles are beginning to be identified.<sup>12,35,36</sup> However, the pleiotropic effects reported so far, along with the absence of clear boundaries between disorders in clinical studies, suggest that overlapping mechanisms are likely to be at work and that existing diagnostic categories might not be best for stratification of cases for research into disease cause and pathogenesis.

Third, despite the fact that much of the genetic risk for schizophrenia remains unaccounted for at the DNA level and the complexity of the picture that has already emerged, there are encouraging signs of convergence

See Online for appendix



**Figure 1: A representative molecular pathway for schizophrenia—fine-tuning of the glutamate synapse**

Advances in human genetics, from both genome-wide association studies and large-scale sequencing, have lent further support to the importance of fine-tuning of glutamatergic neurotransmission in the pathology of schizophrenia. The genes implicated in these studies include *GRIN2A* (which encodes a subunit of the NMDA receptor), *GRIA1* (which encodes a subunit of the AMPA receptor), *SRR*, *CACNA1C*, genes encoding the ARC complex, and several genes encoding proteins located in, or associated with, the post-synaptic density of glutamatergic synapses. The NMDA-type glutamate receptors are fine-tuned by the co-agonist D-serine, which is synthesised by SRR. VDCCs (eg, the protein encoded by *CACNA1C*) are also likely to be involved in tuning neural excitability and synaptic transmission via intracellular calcium signalling. In response to activation of glutamate receptors, proteins associated with the post-synaptic scaffold—eg, PSD95, stargazin (also known as *CACNG2*), several kinases, the RHO, CDC42, and RAC family of small G proteins, and the ARC complex—convey intracellular signalling that underlies cytoskeletal regulation and receptor trafficking, which are crucial for synaptic plasticity. The dashed oval represents converged intracellular protein networks that underlie synaptic plasticity. AMPA=α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid. NMDA=N-methyl-D-aspartate. PSD=post-synaptic density protein. SRR=serine racemase. VDCC=voltage-dependent calcium channel.

onto a set of plausible biological processes. Rare mutations, CNVs, SNPs, and indels have been reported in genes encoding a range of synaptic proteins, including components of the post-synaptic density (PSD) protein and members of the voltage-dependent calcium channel family of proteins (figure 1).<sup>37</sup> A large-scale genome-wide association study<sup>22</sup> has also implicated common variation at genes encoding glutamate receptors, the voltage-dependent calcium channel family of proteins, and dopamine receptor D2 (*DRD2*), which is the principal target of antipsychotic drugs. The relation between glutamatergic dysfunction and abnormalities of dopamine signalling might provide a clue as to how psychosis and cognitive deficits arise in schizophrenia and related disorders. These are very unlikely to be the only mechanisms involved, and more possible processes are expected to emerge as we move into the next phase of genomic studies. Of note, the most significant association from genome-wide association studies of schizophrenia

is with multiple highly correlated variants in major histocompatibility complex (MHC). This locus contains many genes that are not involved in immune function, but preliminary data suggest that variants associated with schizophrenia are also enriched in genomic regions outside MHC that are potentially involved in acquired immunity.<sup>22</sup> These findings are in accord with epidemiological and clinical studies implicating immune and inflammatory processes occurring at various developmental stages in psychiatric disorders.<sup>38,39</sup>

Most genetic discoveries in schizophrenia do not yet have direct clinical application. CNV testing with chromosomal microarray analysis is now a routine first-line diagnostic test for autism and intellectual disability, disorders in which 10–20% of affected cases have a clinically relevant deletion or duplication. Since the prevalence of clinically relevant CNVs in schizophrenia is around 5%, the use of chromosomal microarray analysis has been suggested as a diagnostic test.<sup>40</sup> A positive test would have implications for genetic counselling and medical management because many CNVs are associated with specific patterns of physical morbidities. A genetic diagnosis might also have psychological benefits for patients and their families by reducing internalised stigma and self-blame.<sup>40</sup>

### Epidemiology and environmental risk factors

Schizophrenia occurs worldwide, and for decades it was generally thought to have a uniform lifetime morbid risk of 1% across time, geography, and sex. The implication is either that environmental factors are not important in conferring risk or that the relevant exposures are ubiquitous across all populations studied. This view of uniform risk was efficiently dismantled only in 2008 in a series of meta-analyses by McGrath and colleagues.<sup>41</sup> They provided central estimates of an incidence per 100 000 population per year of roughly 15 in men and 10 in women, a point prevalence of 4·6 per 1000, and a lifetime morbid risk of around 0·7%. These estimates were based on fairly conservative diagnostic criteria; when broad criteria—including other psychotic disorders such as delusional disorder, brief psychotic disorder, and psychosis not otherwise specified—were applied, the rates were higher by 2–3 times.<sup>42</sup> However, more importantly, McGrath and colleagues documented a large variation (more than five times) across studies that could not be ascribed to diagnostic or other methodological differences, but that pointed to real differences in occurrence and exposure to risk factors. These findings have revitalised the epidemiology of schizophrenia, and the resulting new wave of studies, together with advances in genetics, have begun to cast light on how the disorder might arise.

For more than three decades, the dominant paradigm for understanding the environmental contributions to schizophrenia has been the neurodevelopmental hypothesis.<sup>43</sup> This hypothesis has directed attention

towards established risk factors for schizophrenia that affect early neurodevelopment during pregnancy, including maternal stress,<sup>44</sup> maternal infections,<sup>45,46</sup> nutritional deficiencies,<sup>45,47</sup> intrauterine growth retardation, and pregnancy and birth complications.<sup>48,49</sup> However, socioeconomic factors,<sup>50–52</sup> childhood adversity,<sup>53</sup> and immigration (both first and second generation)<sup>54,55</sup> have also been associated with schizophrenia. Additionally, high rates of schizophrenia have been consistently reported in individuals born in late winter or early spring,<sup>56</sup> in individuals born or raised in cities,<sup>57</sup> and in individuals with relatively old fathers (aged 40 years or older) or young parents (below age 20 years).<sup>58,59</sup> The association with advanced paternal age has been ascribed to the increased rate of de-novo mutations in their offspring,<sup>60,61</sup> but alternative or complementary explanations have been proposed—eg, higher paternal age suggests selection of individuals with reduced fertility, including being less likely to find a partner.<sup>62</sup> Accumulating evidence has implicated cannabis use in adolescence, particularly misuse of compounds with high tetrahydrocannabinol content.<sup>63,64</sup> Moreover, factors such as head injury,<sup>65</sup> epilepsy,<sup>66</sup> autoimmune diseases,<sup>67,68</sup> and severe infections<sup>69–71</sup> have been associated with an increased risk.

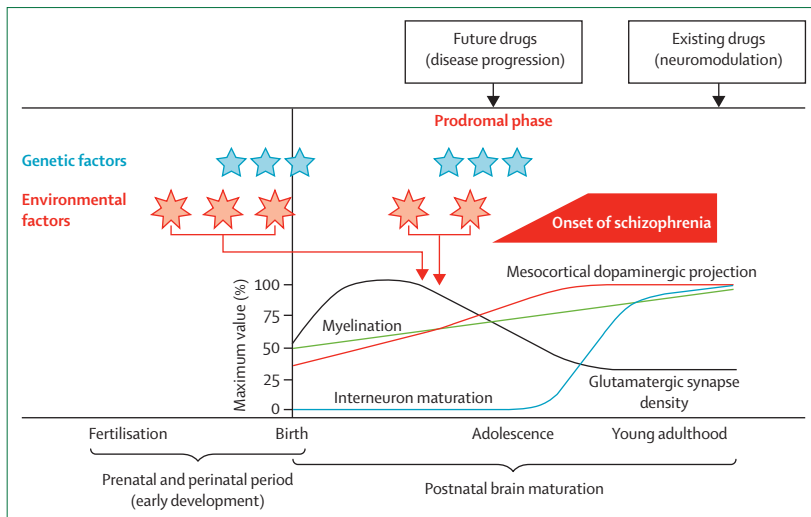
Several environmental exposures associated with schizophrenia, especially those directly affecting early brain development, are also associated with a range of other neurodevelopmental outcomes, such as intellectual disability, autism, ADHD, and epilepsy.<sup>34,72</sup> This finding is similar to the range of outcomes associated with large, rare CNVs<sup>23,33,34</sup> and suggests that schizophrenia might be best conceived as one of a spectrum of clinical outcomes that result from disruption to the developing brain induced by genetic or environmental factors, or both. Therefore, future epidemiological studies need to look carefully at the range of outcomes associated with particular exposures and should not be constrained by existing diagnostic approaches.

Many of the associations with environmental risk factors seem to be robust, and the odds ratios typically range from 1.5 to 3.0. However, observational epidemiology is unable to distinguish true causation from association because of confounding, pleiotropy, or reverse causation. Thus, at present, caution is required when interpreting these associations, and more work is needed before preventive intervention is justified. Animal models can be used to obtain evidence to support a causative role for environmental risk factors, and a rapidly growing literature of such studies is now corroborating epidemiological findings. These include studies of infections, prenatal maternal inflammation, stressors from postnatal stages onwards, and the effect of these stressors on behavioural and neurobiological variables that model aspects of schizophrenia.<sup>73,74</sup> In some of these studies, prenatal factors and prepubertal stressors have been found to interact,<sup>75</sup> which suggests that the effect of

environmental exposures is modified by earlier events and that longitudinal epidemiological studies will need to integrate prenatal and postnatal factors.

Another limitation of observational epidemiological studies is the inability to control efficiently for confounding as a result of differences in genetic liability—ie, are differences associated with, say, infections, because of a high rate of infections among those who are genetically predisposed to schizophrenia? Until now, epidemiology has, at best, been able to control for this only by taking psychiatric family history into account; since only a minority of patients have family members with the disease, this measure of liability is highly imprecise. This situation is now changing with advances in the identification of common genetic variants associated with schizophrenia risk. Although of no use as an individual predictor of disease risk, a polygenic risk score summarising associations with around 20 000 variants has been shown to reliably predict risk differences of 5–10 times.<sup>22</sup> This method is expected to develop and improve rapidly in the next few years, providing researchers with an efficient approach to separate nature from nurture and to study how genetic and environmental factors interact.<sup>76</sup> Such interactions are plausibly of substantial importance in schizophrenia, as in other complex disorders. The concept of gene–environment interactions, in its broadest sense, means that the effect of an environmental factor depends on one or more genetic variants, and vice versa. Although such interactions are conceptually simple, their study presents several challenges, and different approaches have been used.<sup>76,77</sup> Some studies have focused on one candidate gene interacting with a specific environmental exposure. Since these studies have a specific prior hypothesis, they can be done with a fairly modest sample size. However, because the choice of candidate genes has to be based on the understanding of the genetic architecture of schizophrenia and the probable mechanisms involved in the interactions between these genes and the environment, this approach, albeit relevant in its own right, cannot discover the majority of relevant gene–environment interactions. However, the search for interactions across the genome in a hypothesis-free manner requires unrealistically large sample sizes. Therefore, several new techniques have been developed for so-called gene–environment wide interaction studies, and these methods have begun to be applied in schizophrenia research.<sup>78,79</sup>

Another application of genetic data to enhance the causal interpretation of environmental factors is the mendelian randomisation design, in which genes associated with the level of exposure are used as instrumental variables,<sup>80</sup> and this method can be used to assess the extent to which risk factors are mediated through measures of genetic liability.<sup>81</sup> For example, Agerbo and colleagues<sup>82</sup> showed that a large proportion of the association between a family history of psychosis



**Figure 2: Interaction of genetic and environmental risk factors in the developmental pathology of schizophrenia** Several genetic and environmental risk factors might affect long-term neurodevelopmental processes and lead to schizophrenia. The disorder typically presents when the first episode of psychosis occurs in late adolescence or early adulthood, but it is frequently preceded by a prodromal phase; in some instances, premorbid impairments in cognition or social functioning, or both, are seen many years before the first episode of psychosis. Disturbances caused by susceptibility genes and environmental insults during early development and adolescence were proposed to disturb postnatal brain maturation. These factors are likely to impair some of the crucial processes in early development, including progenitor cell proliferation, neuronal migration, and dendritic arborisation and outgrowth. Independent of such initial risks and insults, intrinsic disease-associated factors might also directly affect postnatal brain maturation. Accumulation of such deleterious insults results in overall disturbance of proper postnatal brain maturation, including maturation of interneurons and dopaminergic projections, pruning of glutamate synapses, and myelination. Interneuron maturation is plotted as an increase in interneuron response to dopamine D2 agonists in the prefrontal cortex, whereas mesocortical dopaminergic projection is based on levels of tyrosine hydroxylase. The relative levels of glutamatergic synapse density and myelination are depicted. Adapted from Jaaro-Peled and colleagues.<sup>83</sup>

and schizophrenia risk was mediated through a polygenic risk score, whereas this was not the case for socioeconomic risk factors.

In summary, a large body of published work suggests that several risk factors, particularly those affecting early neurodevelopment, contribute to schizophrenia. Environmental factors, both biological and psychosocial, might have an effect at later timepoints (figure 2). The effects on the developing brain of early environmental exposures and genetic factors might also increase susceptibility to these risk factors. However, caution is needed before inferring causality, and future studies need to combine both prenatal and postnatal factors with measures of genetic liability. The integration of genomics with large-scale epidemiological approaches offers new and exciting ways to understand the causal role of the environment, hopefully leading to primary prevention.

### Pathophysiology

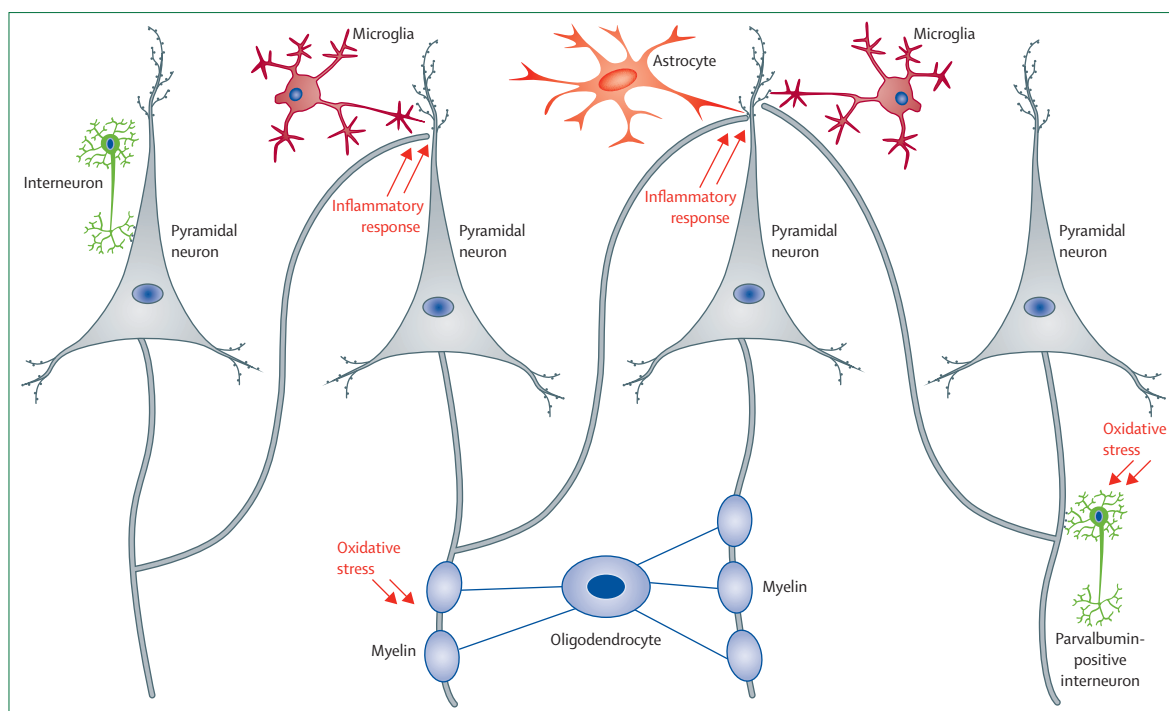
Many brain imaging and neuropathological studies have attempted to relate the manifestations of schizophrenia to altered structure or function of particular brain regions and circuits.<sup>84,85</sup> Some aspects of the disorder have been associated with specific underlying neurobiology, and several lines of evidence implicate the involvement of the prefrontal cortex in specific cognitive deficits (eg, working

memory and executive control).<sup>86–88</sup> However, subtle reductions in grey matter and abnormalities of white matter have been reported in many brain regions and circuits of patients.<sup>89</sup> The reduction of grey matter, especially in the temporal lobe, progresses with the duration of illness<sup>90</sup> and seems to be associated with antipsychotic treatment.<sup>91</sup> However, even patients who did not receive any antipsychotics show volume reductions (albeit not as pronounced as treated patients), especially in the caudate nucleus and thalamus.<sup>89</sup> Moreover, despite many hundreds of studies, no circumscribed anatomical or functional abnormalities that are specific to the disorder have been identified,<sup>85</sup> probably because of the complexity and heterogeneity of the psychopathology and associated cognitive impairments, and the absence of clear boundaries separating schizophrenia from other disorders or wellness.

A coherent body of evidence from pharmacological and brain-imaging studies implicates dysfunction of dopaminergic neurotransmission in the genesis of psychotic symptoms such as delusions and hallucinations.<sup>92</sup> However, although these symptoms are reported in almost all cases of schizophrenia, they are also present in many other psychiatric disorders.<sup>92</sup> Moreover, pharmacological and other studies show that dopaminergic dysfunction is unlikely to explain the full range of clinical features of the disorder. Evidence from clinical pharmacology, brain imaging, and clinical physiology suggests that disturbed glutamatergic function might contribute to the biological processes underlying some clinical features, particularly cognitive dysfunction, in schizophrenia.<sup>86,93,94</sup> One theory is that glutamatergic dysfunction in schizophrenia is related to dysfunction of parvalbumin-positive interneurons in the cerebral cortex and hippocampus, which are sensitive to alterations in N-methyl-D-aspartate (NMDA)-type glutamate receptors.<sup>87</sup> These fast-spiking neurons synchronise the firing of pyramidal neurons and underlie the generation of gamma oscillations, which is critical to proper cognitive function.<sup>95</sup> As a result, dysfunction of this population of neurons might lead to the cognitive deficits in schizophrenia (figure 3).<sup>95</sup>

Advances in human genetics, from both genome-wide association studies and large-scale sequencing, have further lent support to the importance of fine-tuning of synaptic transmission, particularly at glutamatergic and dopaminergic synapses, in schizophrenia.<sup>22,27,28</sup> Nonetheless, a gap exists between genetic and other molecular knowledge and its application in translational research. Although psychiatric genetics now convincingly implicates specific sets of genes involved in synaptic function (eg, genes encoding glutamate and dopamine receptors and signalling proteins),<sup>22,27,28,37,96</sup> it does not provide information about the developmental stages, brain regions, and circuitries in which the molecules have roles in pathogenesis. Therefore, further studies of brain imaging, post-mortem brains, clinical physiology, and animal models will need to build on genetic findings.





**Figure 3: Neuron-glia interactions in the cerebral cortex—key neural substrates for the pathology of schizophrenia**

In the cerebral cortex, interneurons (inhibitory neurons) regulate the output of pyramidal neurons (excitatory neurons). Many studies have reported abnormalities of interneurons (particularly parvalbumin-positive interneurons) and deficits of dendritic spines in the pyramidal neurons in schizophrenia. Imbalance of excitatory and inhibitory neurons might be a key feature that underlies disease pathology. Parvalbumin-positive interneurons are particularly vulnerable to oxidative stress, reflecting an imbalance between the production of reactive oxygen species and the availability of antioxidants, which leads to cellular damage. Astrocytes and microglia have key roles in the maintenance and pruning of dendritic spines, which involves immune inflammatory mechanisms. Oligodendrocytes create the myelin sheath, which is crucial for signal transmission inside the axon. Abnormalities of these glial cells have also been reported in schizophrenia.

At least two types of mechanisms might be involved in schizophrenia. First, the development and maintenance of normal synaptic function depends on a large number of molecular pathways (figure 1), which will be affected by several environmental factors as the brain develops. Second, stress-associated signalling cascades, particularly those involving inflammatory processes and oxidative stress, are well known to modulate the development and maintenance of synaptic connectivity (figure 3). For example, microglia (the glial cells that mediate brain inflammation) are involved in synaptic maintenance and deterioration, particularly synaptic pruning in adolescence,<sup>97–99</sup> and the MHC class I and complement system has been implicated in synaptic plasticity.<sup>99–105</sup> Furthermore, the fast-spiking parvalbumin-positive interneurons are particularly vulnerable to oxidative stress.<sup>106,107</sup> In addition, oxidative stress also causes deficits in myelination.<sup>108,109</sup> Both of these mechanisms have been shown in recent studies of preclinical models of schizophrenia.<sup>106–109</sup>

In summary, the neurobiology of schizophrenia remains poorly understood. Strong evidence implicates dysfunction of dopaminergic neurotransmission in the genesis of psychotic symptoms, and abnormalities of glutamate signalling might account for the negative and cognitive symptoms. Some brain areas have been linked

to specific cognitive dysfunctions (eg, the prefrontal cortex in working memory impairment), but a widespread and variable involvement of other brain areas and circuits is also likely. Disturbances of synaptic function might underlie abnormalities of neuronal connectivity, possibly through effects on interneurons, but the nature, location, and timing of these events remain unclear. Progression towards schizophrenia can be triggered by postnatal environmental exposures—which might be modulated by genetic factors and environmental factors in early development—and, in some cases, also by oxidative and inflammatory mechanisms (figure 3).

### Management and outcome

Since the serendipitous discovery of chlorpromazine more than 50 years ago, almost all antipsychotic drugs available in the clinical setting for schizophrenia work via DRD2 blockade.<sup>110,111</sup> A group of antipsychotics, of which clozapine is the most potent, binds and affects not only DRD2 but also other neurotransmitter receptors, such as serotonin receptors 2 (5HT-2R).<sup>112</sup> In the UK, clozapine is only licensed for use in those who did not respond to other antipsychotics because of the risk of agranulocytosis and neutropenia (1–3%), and therefore a need for continuous blood monitoring. Antipsychotic drugs are relatively effective, compared with placebo, in

reducing positive symptoms, such as auditory hallucinations and delusions, and remain the mainstay of both acute and long-term pharmacological treatment. However, they are not effective for other important clinical features of schizophrenia, such as negative symptoms and cognitive dysfunction, which are more strongly associated with functional impairment than are positive symptoms. Evidence shows that long-term maintenance treatment with antipsychotic drugs is effective in preventing relapse of psychotic symptoms, but troublesome side-effects such as weight gain, movement disorders, and sedation are common and contribute to poor adherence.<sup>113</sup> Moreover, a substantial number of patients show no, or at best partial, response in positive symptoms with existing antipsychotic drugs.<sup>114–116</sup> Individual response is often idiosyncratic and difficult to predict. New, so-called second-generation, antipsychotic drugs can be effective in treatment of psychotic symptoms, with fewer movement disorders, but they carry a higher risk of cardiometabolic side-effects than do first-generation drugs. Choice of the optimum drug is therefore usually pragmatic and balances individual benefits with costs and risks. Clozapine is effective in around 60% of patients who are previously treatment refractory,<sup>116</sup> but evidence shows that it is underprescribed.<sup>5</sup>

Although antipsychotic drugs remain the main treatment approach, effective management requires pharmacotherapy to be embedded within a framework of strong psychological and social support—eg, approaches aimed at improving adherence, vocational and educational support, and rehabilitation. Therefore, a multidisciplinary approach, involving a range of health-care professionals and agencies, delivered in a community-care setting is necessary. Specialist early intervention services, which focus on those who are experiencing their first psychotic episode and the following 3 years, are available in many developed countries, and are popular with service users and carers.<sup>5</sup> These services have beneficial effects on outcome in the first few years, but their long-term effect remains uncertain.<sup>117</sup> Psychological treatments have been mandated by the UK National Institute for Health and Care Excellence (NICE) guidelines, which recommend that all patients with schizophrenia should be offered cognitive behavioural therapy (CBT) and family intervention in addition to antipsychotic drugs. A role for CBT is justified by evidence that various potentially mutable psychological mechanisms increase the risk of specific symptoms.<sup>118</sup> However, the treatment and cost effectiveness of CBT in schizophrenia is controversial,<sup>119</sup> and little evidence shows that CBT can target the underlying psychological mechanisms. One possibility is that the effectiveness of CBT depends on non-specific factors, such as the quality of the relationship between the therapist and the patient (ie, therapeutic alliance), and evidence supports this in regard to schizophrenia.<sup>120</sup> Medical management also focuses on physical

health—particularly preventive measures such as dietary advice, exercise, smoking cessation, and prevention of drug abuse; and monitoring of cardiovascular and metabolic risk factors. In many countries, care is provided by a multidisciplinary team of mental health professionals in primary, secondary, and community settings and focuses on both health and social care.<sup>42</sup>

In the past 10 years, the perception that outcome is necessarily poor has been challenged by results of prospective studies, which show great heterogeneity with fairly good outcome in 20–50% of cases.<sup>42</sup> However, although most patients with schizophrenia live independently outside hospitals, many need continuing support either from services or from their relatives. Moreover, all-cause mortality is substantially increased.<sup>121,122</sup> The relative risk for suicide is increased by 12 times, with a lifetime risk of roughly 6·5%,<sup>123</sup> but mortality from most natural causes, especially cardiovascular disorders, is the strongest contributor to the 10–20 year reduction in life expectancy. The causes of this increase in mortality are thought to include smoking and other lifestyle factors, suboptimal treatment of physical disorders,<sup>121,124</sup> and side-effects of pharmacological treatment (especially cardiometabolic outcomes). Several trials to reduce the excess mortality are being done.

### Unresolved research questions and opportunities for progress

Although progress has been great in the past 5–10 years, much is still to be learnt about what causes schizophrenia and how to treat it effectively. Genomic studies have begun to reveal the complex genetic architecture of the disorder and to converge on some tractable areas of biology. The focus for the next few years will be to identify more rare and common risk alleles, and rare variants conferring high individual risk will be of particular importance for the design of cellular and animal models. Somatic de-novo mutations have been shown to contribute to some neurodevelopmental disorders,<sup>125</sup> and another important focus is to determine the extent to which these mutations contribute to schizophrenia; to do so, deep sequencing of brain tissue will be necessary. Extensive pleiotropy shown in genetic studies has challenged existing categorical notions of classification, but the large samples needed for robust studies have come at the expense of detailed phenotypic data. Therefore, to deepen our insights into the relations between genetic risk and phenotypic outcome, a major goal will be to include more detailed clinical and endophenotypic data in large-scale genetic studies. These data will be necessary to understand how genetic risk affects brain mechanisms that lead to particular clinical outcomes and to develop new approaches to diagnosis and classification with improved representation of the underlying disturbances in brain function.

As genetic studies continue to drive mechanistic studies in patients and model systems, and bioinformatic

analyses become increasingly informative with large study sizes, a key challenge is to determine how, where, and when genetic risk affects brain development and function. Genetically engineered cells obtained directly from patients, such as induced pluripotent stem cells and induced neuronal cells, provide an opportunity to investigate neuronal mechanisms *in vitro*.<sup>126</sup> New genome engineering approaches, such as the clustered regularly interspaced short palindromic repeat (CRISPR) system, can be used to introduce risk alleles, and combinations thereof, into human stem cell lines. Many types of CNS cells, including different subtypes of neurons (eg, glutamatergic and dopaminergic neurons) and glial cells, can be differentiated from induced pluripotent stem cells or progenitors derived from such cells *in vitro* to partially recapitulate neurodevelopmental processes.<sup>127</sup> However, whether these differentiated cells can capture features of mature neural networks *in vivo* is still unclear. Nonetheless, such patient-derived neuronal cells will be useful to address cell-autonomous intrinsic susceptibility to the disease. Moreover, if such cellular susceptibility provides valid drug targets, human cell culture could be used for compound screening.<sup>128</sup>

The study of animal models (particularly rodents), in combination with human brain imaging, will be needed to address mechanisms at the level of neural circuits. The validity of many animal models can be questioned, but advances in genetics allow models of human risk mutations to be developed. The polygenic basis of psychiatric disorders restricts the usefulness of genetic rodent models, which often include one specific mutation; at present, rare high-penetrance alleles offer the best approach to generating models with high construct validity. However, the CRISPR system is a useful way to introduce genetic variations at multiple sites.<sup>129</sup> Additionally, neural circuits in genetic animal models will need to be examined with respect to behavioural changes, with a particular attention to the pathological trajectory from early development to full onset of disease in adulthood. Such studies will benefit from new approaches, such as optogenetics, to intervene with specific neural cells and circuits.<sup>130</sup> Since environmental stressors have key roles in schizophrenia,<sup>17</sup> the study of gene–environment interactions in cell and animal models will become increasingly important to answer key questions such as which biological contexts, cells, and mechanisms are the key sites of convergence of genetic and environmental stressors.

Besides the impressive advances in genetics, epidemiological studies have also been highly productive in pinpointing several biological and psychosocial risk factors. However, observational epidemiology has little explanatory power. To understand the relevance of environmental risk exposures to disease causation, the integration of genomics with epidemiological studies will be helpful. Longitudinal epidemiological research will need to address how environmental exposures at

different timepoints interact with each other and with genetic risk to produce clinically relevant outcomes. These studies are likely to benefit from access to routinely obtained electronic clinical data, although ethical and other challenges remain. Such data should also allow the identification of protective factors and guide the implementation of public health measures.

A clear need is to develop antipsychotic compounds with reduced side-effects, particularly those affecting metabolic processes that result in adverse cardiovascular outcomes.<sup>131</sup> Efforts are being made to develop compounds that are effective not only for positive symptoms but also for negative and cognitive symptoms—eg, by modulation of glutamate and acetylcholine neurotransmission through interfering with glycine transporter 1 and  $\alpha 7$  nicotinic acetylcholine receptor.<sup>132–134</sup> Interest in the use of pharmacogenetics is increasing—eg, to identify patients at particular risk of specific side-effects,<sup>135,136</sup> and, in combination with other biomarkers, to identify patients who might respond differently to drugs with different modes of action;<sup>137</sup> this follows the general trend to investigate the potential of stratified medicine, in which drugs are targeted efficiently to specific subgroups of patients. The road from advances in genetics and biology to the discovery of new treatments is likely to be a long one, and progress will depend on insights from cellular and animal modelling and from clinical trials.<sup>138</sup> To achieve this goal, the key issues of cell type and circuit specificity, and also of the timing of crucial events, will need to be addressed, and improvements in high-throughput methods and *in-vitro* modelling of cell circuits will be necessary.<sup>138</sup>

A burgeoning interest lies in the possibility of treating individuals at high risk to prevent the development of full-blown psychosis and to reduce functional impairment. Meta-analyses of randomised controlled trials suggest a positive, if modest, outcome of such treatment, despite the wide range of interventions used (psychological, pharmacological, and nutritional);<sup>139,140</sup> however, further well controlled trials will be necessary.<sup>141–143</sup> Stress-associated signalling cascades are likely to affect synaptic pruning and the maturation of neural networks in adolescence, and compounds that can regulate inflammation and oxidative stress are being developed. For example, omega-3 fatty acids had beneficial effects in a clinical trial.<sup>144</sup> Preclinical studies have shown that application of antioxidants, including N-acetyl cysteine, ameliorate physiological and behavioural deficits associated with schizophrenia.<sup>108</sup> Encouraged by such preclinical studies, increasing numbers of investigator-initiated clinical trials with antioxidants are being done. High research priorities include applications of genetic and other biomarkers, together with early neuropsychological, developmental, and behavioural risk markers, to identify high-risk groups as relevant recipients of preventive interventions, and controlled studies of the interventions in high-risk children.



Arguably, the greatest challenge facing future research into disease cause, pathogenesis, and treatment is the failure of existing syndromic definitions to delineate a valid disease entity. New approaches to patient stratification will need to recognise the varying degree of overlap between syndromes and use measures that plausibly index the pathophysiology underlying the various clinical features and impairments. This will require a closer dialogue between basic neuroscientists and clinical researchers.<sup>14</sup> In view of the complex and variable clinical features and cognitive impairments associated with the disorder, multiple brain systems are likely to be affected to varying extents in different individuals, and dysfunction of one brain region or circuit is unlikely to account for the full range of features of schizophrenia and distinguish it from other disorders. Rather, different features probably result from disturbances of different brain functions, crossing existing diagnostic boundaries. These considerations also imply that new treatments should target particular symptoms, or groups of symptoms, that share common underlying mechanisms, making them applicable across diagnostic groups.

### Controversies and uncertainties

Schizophrenia has long divided opinion: do its origins lie in nature or nurture? Does it have a psychosocial or biological origin? Is it a myth, an illness, or a sane response to an insane society? That controversies are not as polarised at present is perhaps a sign of increased knowledge. However, as should be clear from this Seminar, many debates and uncertainties do remain—eg, how should we diagnose schizophrenia? Should we use categories or dimensions? What clinical features, or combination of features, will map best onto underlying neurobiological disturbances? Which environmental risk factors are truly casual, and which are secondary to illness or genetic confounding? Is it better viewed as a disorder of circumscribed brain regions and circuits, or a disorder of the whole brain? Is a progressive, neurodegenerative component present in addition to a neurodevelopmental one? Is it one disorder, several disorders, or part of a continuous landscape of psychopathology, analogous to, say, metabolic syndrome? What is the relation between schizophrenia and disorders such as autism and ADHD, with which it shares several clinical features and risk factors?

One area that we have not discussed, which is perhaps of greatest immediate concern, is the poor quality of care for schizophrenia even in developed countries. The Schizophrenia Commission reviewed this issue in 2012 and described services in the UK as “broken and demoralized”.<sup>5</sup> Not only did the Commission document, in uncompromising terms, the shortcomings of present approaches to clinical management, but it also made many recommendations to improve policy and practice.<sup>5</sup> Undoubtedly, the implementation of these changes would greatly improve the lives of those with schizophrenia.

In view of the need for an overhaul in the ways in which care is provided, to point out the inadequate investment in research in mental disorders relative to burden is perhaps inappropriate.<sup>145</sup> Some have argued that the low research investment is a result rather than a cause of insufficient progress and capacity in this area. However, a counterview is that this is yet another example of the way in which mental disorders fail to achieve parity of esteem with physical illnesses. Whatever the explanation, we hope that the advances and unprecedented opportunities documented in this Seminar will help to redress this imbalance.

### Contributors

All authors developed the structure of the Seminar, did literature searches, wrote the manuscript, constructed the figures, and approved the final manuscript.

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