Schizophrenia

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Abstract | Schizophrenia is a chronic psychiatric disorder with a heterogeneous genetic and neurobiological background that influences early brain development, and is expressed as a combination of psychotic symptoms — such as hallucinations, delusions and disorganization — and motivational and cognitive dysfunctions. The mean lifetime prevalence of the disorder is just below 1%, but large regional differences in prevalence rates are evident owing to disparities in urbanicity and patterns of immigration. Although gross brain pathology is not a characteristic of schizophrenia, the disorder involves subtle pathological changes in specific neural cell populations and in cell–cell communication. Schizophrenia, as a cognitive and behavioural disorder, is ultimately about how the brain processes information. Indeed, neuroimaging studies have shown that information processing is functionally abnormal in patients with first-episode and chronic schizophrenia. Although pharmacological treatments for schizophrenia can relieve psychotic symptoms, such drugs generally do not lead to substantial improvements in social, cognitive and occupational functioning. Psychosocial interventions such as cognitive–behavioural therapy, cognitive remediation and supported education and employment have added treatment value, but are inconsistently applied. Given that schizophrenia starts many years before a diagnosis is typically made, the identification of individuals at risk and those in the early phases of the disorder, and the exploration of preventive approaches are crucial.

Schizophrenia is a complex syndrome with a heterogeneous combination of symptoms. Characteristic, but by no means exclusive, symptoms of schizophrenia can be divided into 'positive', 'negative' and 'cognitive' categories. Positive symptoms are behaviours and thoughts that are not normally present, such as recurrent psychosis, which is the 'loss of contact with reality' consisting of delusions, hallucinations and disorganized speech and behaviour. The amotivational syndrome is characterized by negative symptoms, which include social withdrawal, affective flattening, anhedonia (the inability to feel pleasure) and diminished initiative and energy. Finally, cognitive symptoms are expressed as a broad set of cognitive dysfunctions.

The onset of the illness, although often not recognized as such, is referred to as the prodromal phase (that is, before the manifestation of the first psychotic episode) and consists of a decline in cognitive and social functioning, which generally begins in the early adolescent years and precedes the onset of psychotic symptoms by >10 years[1]. However, patients are typically not referred for consultation until psychosis presents in late adolescence or early adulthood. The outcome of schizophrenia can range from complete recovery to chronic need of care, and, on average, the life expectancy of those with the disorder is reduced by 20 years compared with the general population[2]. Patients with schizophrenia generally experience serious impairments in multiple domains of everyday life, including the ability to maintain social relationships, sustain employment and live independently[3]. These deficits typically persist after patients achieve remission from psychotic symptoms. The ability for patients with schizophrenia to live independently can be achieved for the vast majority of patients using a combination of antipsychotic medication and psychosocial interventions, which increase quality of life (QOL), but have little effect on social and professional functioning. Instead, functional outcomes largely depend on the presence and severity of cognitive and negative symptoms at disease onset[4]. Thus, several research projects currently focus on psychological, social or pharmacological interventions to reduce cognitive impairments in schizophrenia[5].

The past decade has witnessed an increase in research studies in the field of schizophrenia. First, it has become clear that schizophrenia is much more than a psychotic disorder, and that a renewed focus on cognition is warranted[1]. Second, with the realization that schizophrenia debuts in early adolescences[1], and not in early adulthood as initially thought, the early identification of individuals at increased risk is now viewed as both clinically and scientifically imperative. Last, progress is rapidly being

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made using genetic studies of schizophrenia, in which large collaborative efforts are leading to a rapid increase in the number of included patients. These efforts, in combination with advances from structural and functional neuroimaging and post-mortem studies, might help to identify some of the biological mechanisms — and the various environmental factors influencing them — of this disorder that has been the focus of study for over a century. However, the increasingly productive effort to elucidate the pathogenesis of schizophrenia should not overshadow the present need of implementing the considerable fundamental and practical knowledge that we have gathered so far. In this Primer, we provide an overview on the current state of knowledge of schizophrenia, including epidemiology, aetiology, pathogenesis, diagnosis, course of illness, treatment and prevention.

Epidemiology

Morbidity and mortality

The average lifetime prevalence of narrowly defined schizophrenia, for instance, according to the diagnostic criteria from the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV), is just under 1%. The most detailed study on schizophrenia prevalence was conducted in Finland and found a rate of 0.87%[6]. However, prevalence rates vary geographically by up to fivefold[7].

People with schizophrenia have, on average, a shorter life than the rest of the population. A systematic review of mortality studies reported that the standardized mortality ratio was 2.6, with suicide being the main contributor early in the course of the illness and cardiovascular disease the main contributor in later years[7]. The persistently high rate of cigarette smoking among people with schizophrenia, the increased likelihood they will have an unhealthy lifestyle and the obesity-promoting effects of antipsychotic drugs contribute to metabolic syndrome, diabetes and excess cardiovascular and respiratory deaths among these patients[8]. Disappointingly, the disparity in life expectancy between people with schizophrenia and the general population has been worsening (FIG. 1).

Risk factors

Certain groups are at particular risk of the disorder, with various modifiable and non-modifiable risk factors influencing the development of schizophrenia.

Prenatal and perinatal events. Individuals who experience an excess of complications in fetal life and at birth have an increased risk of developing schizophrenia. For instance, one meta-analysis demonstrated associations between complications of pregnancy, abnormal fetal growth and complications of delivery with schizophrenia[9]. In addition, people who were born in late winter and spring are slightly over-represented among patients with schizophrenia (signifying an increase of 7–10%). This excess could be due to a greater likelihood of the fetal brain being exposed to maternal respiratory infections or to maternal malnutrition, including folic acid or vitamin D deficiency, during the winter months. However, none of the explanations for this phenomenon have been firmly established. Presumably, these early-life risk factors have an effect on the neural connectivity of the developing brain.

Paternal age. Men who are older when fathering a child have a greater chance of having a child who develops schizophrenia than younger men[10]; however, whether this risk is due to psychological or biological factors is unclear. For example, men with a schizotypal personality might be more likely to marry later, or, alternatively, older men might harbour more risk-increasing mutations as a result of repeated mitosis in progenitors of sperm cells. The evidence currently favours the idea that the association between late fatherhood and schizotypal personality is the predominant driver of this effect[11].

Sex. Schizophrenia is generally reported to be slightly more frequent in men than in women, with a risk ratio of 1.4/1. The disorder is also more severe in men[12]. In addition, men tend to develop severe schizophrenia earlier than women; the peak age of onset of frank psychotic symptoms is 20–24 years in men, but 5 or more years later in women[13–15].

Urban environment. Schizophrenia is most common in disadvantaged areas of inner cities, a finding first noted in Chicago in 1939 (REF. 16). This association was recently replicated in an epidemiological study in England, the Aetiology and Ethnicity in Schizophrenia and Other Psychoses (AESOP) study, which reported that the incidence of schizophrenia in the smaller cities of Nottingham and Bristol was less than half of that in London. The highest rates of people with schizophrenia in London were in areas with the lowest social cohesion[17,18], a finding that was also reported in the original Chicago study. Scandinavian studies have shown increased incidence of schizophrenia in people born or raised in urban areas compared with those born or raised in rural areas. For example, a Danish study showed that the risk of developing schizophrenia was greater in those not only born but also raised exclusively in large cities[19] compared with individuals who had experienced less urbanized environments.

Migration status. An increased incidence of schizophrenia has been demonstrated among many migrant groups compared with those comprising individuals who do not have a personal or family history of migration[20]. However, recent literature has focused on black migrants to European countries who show much higher rates of schizophrenia than white or Asian migrants to Europe, or indeed migrants to other continents[20]. For example, the AESOP study showed that in the population of black migrants and their children there was at least a sixfold greater incidence of schizophrenia than in the white British population[14]. In support of this conclusion, in this study diagnosis was made blind to ethnicity to exclude the contribution of possible racial or cultural bias by clinicians. Interestingly, studies of the relatives of African-Caribbean patients with schizophrenia who live in England have shown that the risk of developing the disorder is much lower in those siblings living in the Caribbean than in those who reside in England[21]. Such findings suggest the influence of an environmental factor in the European host country but not in the country of origin. Ethnic density also seems to be important; as the relative proportion of non-white minorities in a neighbourhood increases, the risk of schizophrenia in the minority population decreases. Thus, lack of social support or increased exposure to discrimination might operate to increase the risk of developing the disorder, especially in areas with only a small minority population[22].

Drug abuse. Persistent abuse of amphetamine, methamphetamine and cocaine, as well as cathinone-derived 'legal highs' can produce a state that is almost identical to that of paranoid schizophrenia[23]. Moreover, experimental administration of cannabis or its active ingredient tetrahydrocannabinol can precipitate transient psychotic symptoms[24] and smoking cannabis is known to exacerbate existing psychotic illness[25]. In addition, a series of prospective studies have shown that young people who heavily use cannabis have an increased risk of subsequent schizophrenia and that this relationship is dose-dependent[10]. The risk is greater in those who start cannabis use in early adolescence than in those who start use later in life and in those using high-potency varieties of cannabis[26]. In recent years, even more potent synthetic cannabinoids (spice) have become widely available over the Internet and have been linked to acute psychotic reactions[23].

Social adversity. A range of childhood adversities including physical abuse, sexual abuse, maltreatment and bullying are associated with increased risk of later schizophrenia[16]. People with psychosis also report an increased rate of particularly intrusive life events, such as assault, before the onset of illness[27]. Whether these environmental factors are independent risk factors is debated. Evidence supporting their independence comes from PET studies showing that most factors have an effect on striatal dopamine synthesis[28]. However, it is possible that people who are genetically predisposed to schizophrenia might be more likely to be exposed to social risk factors, such as being bullied. Resolution of this question should be achievable by examining the polygenic risk score, which is produced by summing the risk values of the various genetic loci that have been associated with schizophrenia among people experiencing these adversities.

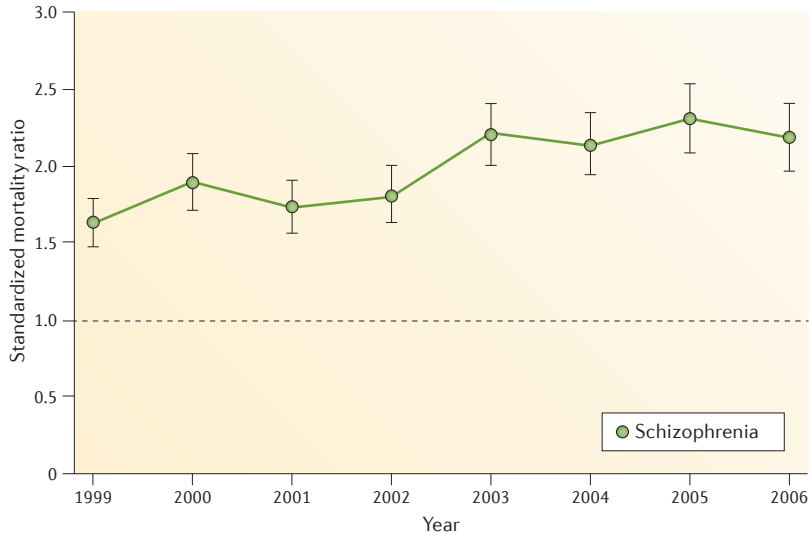

Figure 1 | **Historical mortality rates for people with schizophrenia compared with the general population.** The disparity in mortality rates between people with schizophrenia and the general population in England increased between 1999 and 2006. Figure from REF. 8. Reproduced from Mortality after hospital discharge for people with schizophrenia or bipolar disorder: retrospective study of linked English hospital episode statistics, 1999–2006, Hoang, U., Stewart, R. & Goldacre, M. J., **343**, d5422, © 2011 with permission from BMJ Publishing Group Ltd.

Mechanisms/pathophysiology

Schizophrenia is hypothesized to be the result of a complex interplay between genetic and environmental risk factors that influence early brain development and the trajectory of biological adaptation to life experiences[28,29]. Archival post-mortem studies of patients who had been diagnosed with schizophrenia suggest that the brains of these individuals have gross cellular abnormalities, but these findings have not been confirmed by rigorous controlled investigations over the past two decades, indicating that gross brain pathology is not a characteristic of schizophrenia[30]. Recent studies have focused instead on the molecular signatures of a more-subtle pathology that primarily involves the functional state of specific cell populations and the architecture of cell–cell communication. Although some replicated findings that are suggestive of a molecular neuropathology of schizophrenia have been reported, this work is fundamentally hindered by the limitations of determining causality in this context, thus making it difficult to disambiguate what is related to the state of illness and the epiphenomena of illness — such as the effects of treatment, disease chronicity and co-morbidity — from basic mechanisms that lead to illness. Pharmacological studies of psychotogenic and antipsychotic drugs have fuelled hypotheses focused on neurotransmitter mechanisms, but these also have been difficult to translate into explanations of the complex clinical syndrome. The discovery of genetic risk factors has transformed research about mechanisms, as

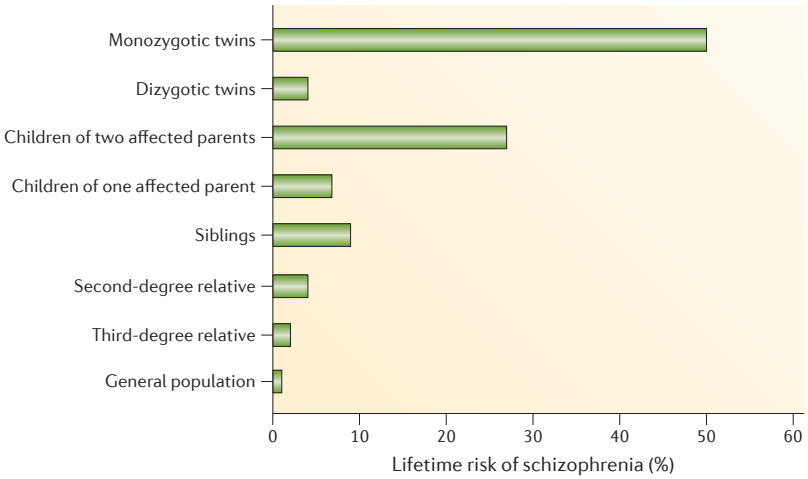

Figure 2 | **Lifetime risk of schizophrenia in relatives of people with schizophrenia.** General population estimates and those for siblings, second-degree (as the average of multiple classes of relative) and third-degree relatives are from data collated and presented in REF. 242. Risks for children of affected parents are from REF. 243. Risks in monozygotic and dizygotic twins, defined as proband-wise concordance, are taken from REF. 47; unlike the older studies presented in REF. 242, all studies summarized in REF. 47 use explicit operational diagnostic criteria for schizophrenia (*Diagnostic and Statistical Manual of Mental Disorders*, Revised Third Edition). Risk of illness increases with the degree of genetic relatedness, maximizing for identical (monozygotic) twins of affected individuals. Risk in dizygotic twins is much lower than in the book by Gottesman[242] of about 17%; this may reflect the use in the more recent studies of stricter diagnostic criteria and sampling variance due to sample size.

risk-associated genes at least in part contribute to the mechanisms underlying the condition. Although genetic associations and molecular alterations in tissue offer insights about basic brain mechanisms, schizophrenia reflects abnormal brain information processing. As such, studies of brain function in living individuals have been crucial in providing links between genetic risk, brain biology and clinical state, and have re-established schizophrenia in the mainstream of neuroscience.

Post-mortem brain studies

Before the recent surge in discovery of genetic associations with schizophrenia, a large body of circumstantial evidence implicated the neurotransmitters dopamine, glutamate and γ-aminobutyric acid (GABA) as pathogenetic factors[31]. Post-mortem studies of patients with schizophrenia have produced evidence in support of each of these neurotransmitter systems as being altered in schizophrenia, but whether these alterations reflect primary pathogenetic mechanisms is controversial.

Studies of molecular markers of dopaminergic function in post-mortem brains of patients who had schizophrenia, while inconclusive, have generated spirited discussions[32,33]. Dopamimetic drugs induce paranoid states and bizarre behaviour, whereas dopaminolytic drugs are the only currently available antipsychotic agents. These effects are mirrored to some degree by studies of dopamine synaptic markers in the striatum, such as dopamine receptors. Although inconsistent, there have been reports of increased expression of dopamine receptors in this region of the brain in individuals with schizophrenia[34].

N-methyl-D-aspartate (NMDA) receptors are a subtype of glutamate receptor that are important for learning and memory. NMDA antagonists such as ketamine and phencyclidine induce psychosis-like dissociative states, cognitive deficits and bizarre behaviour similar, in some respects, to patients with schizophrenia. Despite several reports of glutamatergic abnormalities in the post-mortem brains of patients with schizophrenia, including reductions in glutamatergic neuronal number, dendritic arborization and dendritic spine density, the findings have tended to be inconsistent and variable across studies[35]. Likewise, alterations of glutamate receptor subunits — including those comprising the heterotetrameric NMDA receptor (GluN1, GluN2A, GluN2C and GluN3A, which are encoded by *GRIN1*, *GRIN2A*, *GRIN2C* and *GRIN3A*, respectively), the heterotetromeric AMPA receptor (GluA1, GluA2 and GluA4, which are encoded by *GRIA1*, *GRIA2* and *GRIA4*, respectively) and various kainate subunits (GluKs) of the homotetrameric or heterotetrameric kainate receptor — have been reported in some studies but not in others[35]. Differences in other post-mortem markers of glutamatergic synapses between individuals with or without schizophrenia are similarly inconsistently reported. The interpretation of these inconsistencies is not straightforward, as methodological limitations of the individual assays and tissue processing issues are potentially important confounders in both positive and negative studies.

In contrast to the variable post-mortem findings of possible dopamine or glutamate dysfunction in patients with schizophrenia, post-mortem evidence of abnormal GABAergic function has been a consistent observation[36–39]. Whereas GABAergic neurons are not diminished in number, the expression of glutamate decarboxylase 1 (*GAD1*) — the gene encoding the biosynthetic enzyme for GABA synthesis — is altered, and related molecular markers associated with reduced GABA neuronal activity are found at the tissue and cellular level in the brains of those with schizophrenia[39,40]. This set of findings involves multiple GABA cell types and multiple brain regions, although emphasis has been placed on hypofunction of prefrontal GABAergic neurons that express parvalbumin, as these cells are crucial for establishing cortical activity profiles, such as gamma frequency oscillations, that are considered abnormal in schizophrenia[41] and might underlie some of the abnormalities in brain connectivity discussed below. Interesting recent work has suggested that the downregulation of *GAD1* expression is directly related to an epigenetic shift towards repressive chromatin structure that regulates this gene[42,43]. Although evidence for alterations in GABA molecular markers in schizophrenic brain tissue is strong, the implications for pathogenesis are uncertain. It is unclear, for example, whether these findings reflect secondary adaptations to reduced synaptic activity or perhaps to diminished excitatory drive through altered glutamate neuronal function in these cells[41]. Similar GABA abnormalities have also been implicated in many other neuropsychiatric disorders, including depression, anxiety and autism[37]. Intriguingly, GABA agonists can occasionally induce psychosis, and GABA antagonists are not antipsychotic.

Given that dopamine modulates the excitability of both glutamatergic and GABAergic neurons in the cortex, which are also reciprocally connected in networks that tune cortical physiology, the findings in the brain concerning these neurotransmitters might reflect complex interactions within neuronal networks. Nevertheless, drugs that affect these systems have differential behavioural effects, suggesting both convergent and divergent effects on brain function. Post-mortem research about schizophrenia has also highlighted several other potential factors that might contribute to brain dysfunction in this illness, including abnormal oligodendrocyte biology[44], inflammatory response[45] and expression of genes associated with general synaptic function[30,46]. Recent clinical work has suggested a role for the serotonin 5-hydroxytryptamine 2 (5-HT_2) receptors and the muscarinic acetylcholine M1 receptor in antipsychotic treatment. These are preliminary areas of work in need of critical exploration.

Genetic clues to molecular mechanisms

Schizophrenia is highly heritable as demonstrated, for instance, by twin studies[47] (FIG. 2). To the extent that genetic discoveries identify molecular mechanisms of risk, contemporary genetic studies have provided evidence for many of the foregoing factors involved in the risk architecture of schizophrenia across diverse populations (FIG. 3). Included among the loci containing common variants that have achieved genome-wide significance are those containing *DRD2* (encoding the dopamine D2 receptor), glutamate receptor components (*GRM3*, *GRIN2A* and *GRIA1*, encoding metabotropic glutamate receptor 3 (mGluR3), GluN2A and GluA1, respectively), *SRR* (encoding serine racemase, an enzyme for biosynthesis of an NMDA receptor allosteric site ligand) and a large region of chromosome 6, including the major histocompatibility complex region. Each of these loci by themselves account for a very small increment in individual risk[48], and the differences in risk-associated allele frequency between cases and controls is typically <2%. Moreover, it is unclear how the genetic signals translate into molecular mechanisms; so far, the associations do not explain the post-mortem findings or how, or even whether, the signals reflect a change in the biology of the implicated gene rather than another gene at the associated locus. Nevertheless, the genetic associations are clues to the underlying molecular mechanisms that are being actively explored with various biological and bioinformatic strategies. For example, multidimensional *in silico* analyses of gene sets and gene pathways linked to both common and rare variants suggest that schizophrenia risk loci converge on aspects of neuronal biology, synaptic function, glutamate and calcium signalling, developmental pathways and genes implicated in the immune response[48–51].

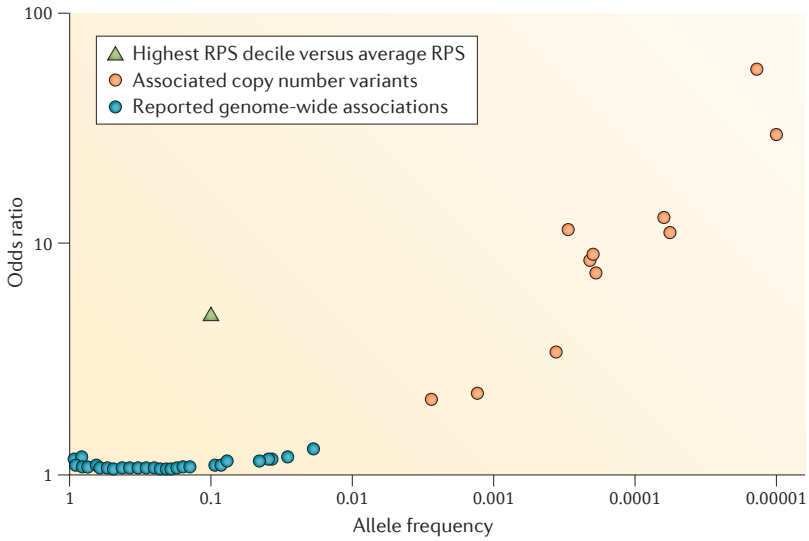

Figure 3 | **Effect size and frequency of schizophrenia-associated alleles.** Plot of effect size as allelic odds ratios by population risk allele frequency. Both axes are transformed to a logarithmic scale. Blue data points represent associations reported in the largest published schizophrenia genome-wide association study[48]. Orange data points represent copy number variants that are considered to be robustly associated with schizophrenia in the largest evaluation of such data to date[144]. For comparison of individual allelic effects with polygenic risk profile scoring (RPS), we depict (green triangle) an estimate of the odds ratio that is expected for the highest RPS decile compared with the average RPS score, as estimated from REF. 48.

Neurodevelopmental factors

Interestingly, many of the genes that have been associated with schizophrenia show preferential expression during fetal development[52–54], suggesting that the genetics of schizophrenia is at least in part the genetics of brain development. This observation supports the prevailing general hypothesis that schizophrenia has its origins in early life[28,29]. This hypothesis is also consistent with a large body of epidemiological data revealing a link between obstetric complications and increased risk of developing the disorder[9], with evidence that individuals who manifest schizophrenia as adults have compromised early neurodevelopmental milestones[55–57], that neurodegeneration is not found in individuals with schizophrenia[30] and that cognitive development is compromised in patients long before they manifest the condition in early adult life[1]. It is unclear why such early development antecedents would manifest as cognitive and social difficulties for the first two decades of life and then emerge as a profound psychotic illness in early adulthood, but the changing landscape of cortical biology in early adult life, including dramatic alterations in cortical synaptic organization[37,58], might be an important factor that interacts with the earlier developmental disposition. It is conceivable that schizophrenia is not a disease per se but a state of brain maturation with a particular pattern of emergent responses to experience, which, for various diverse and complex genetic and environmental reasons, 1% of the world population manifests[59].

Neuroimaging and systems neuroscience

The molecular and cellular alterations in schizophrenia are far removed from the behavioural symptoms and course of the disorder. To bridge this gap, neuroimaging, and systems neuroscience more generally, has proven to be helpful.

Structural neuroimaging. Brain volumes, as measured on MRI scans, are abnormal in patients with both first-episode and chronic schizophrenia compared with unaffected individuals[60]. Reductions are found in total grey and white matter as well as whole-brain volume compared with healthy controls. Ventricular volume is correspondingly increased. These reductions in brain volume are more pronounced in patients with a poor outcome[61]. Furthermore, changes in cortical thickness (mostly decreases), gyrification and subcortical shapes have been reported in these patients (FIGS 4,5). There is evidence of progression: initially, volume decreases are localized to the bilateral insula and the anterior cingulate cortex, as well as the hippocampus, thalamus and left uncus and/or amygdala[62]. As the disorder progresses, cortical volume reductions become widespread[63,64] and are associated with worsening cognitive function[65]. Volume increases at the beginning of the disease are restricted to the putamen, but later spread to the entire dorsal striatum[63,64], although this is probably at least in part a consequence of antipsychotic treatment[66]. One recent technique to identify regions both structurally and functionally abnormal in schizophrenia, and hence with a high degree of evidence for localized pathology, has identified the perigenual cingulate cortex and bilateral anterior insula[67]. In interpreting these data, it should be stressed that there are multiple potential confounders — including the effects of drugs[68] and co-morbidities — that can complicate the interpretation of MRI findings as volume changes, especially in longitudinal studies[69]. However, some of these changes might be of a genetic origin, suggesting that at least some of the progressive loss of brain tissue in patients with schizophrenia cannot be attributed to the effects of illness or to illness-related confounding factors, such as medication[70].

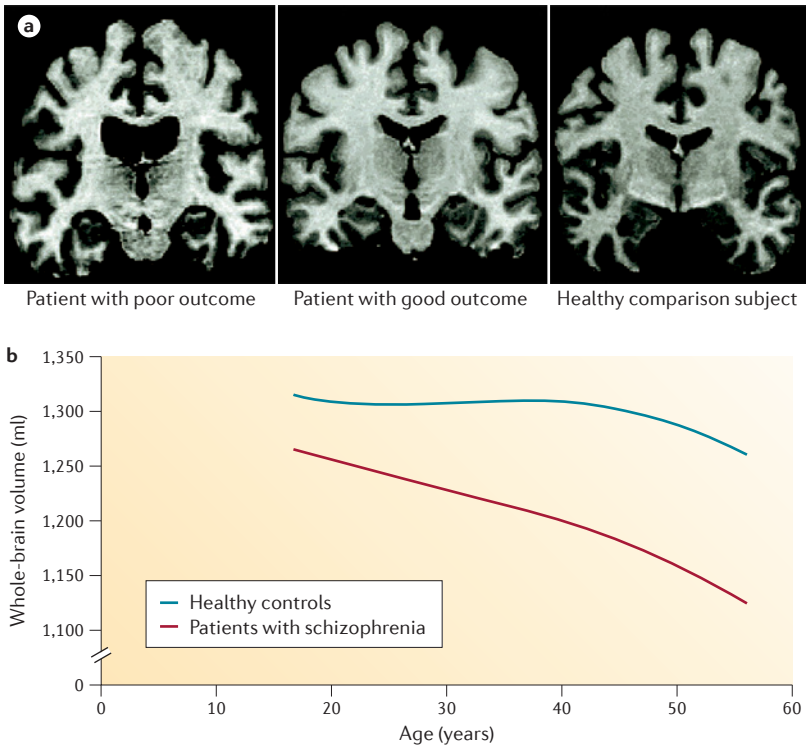

Figure 4 | **Changes in brain volume in schizophrenia. a** | Coronal sections of the brains of a patient with schizophrenia with poor outcome, a patient with good outcome and a healthy comparison subject, as denoted in the original image published in the respective article in *The Journal of American Psychiatry*. **b** | Annual whole-brain volume changes from a longitudinal study[64] were modelled as time derivatives of the brain volume–age function by applying a locally weighted running line smoother (degrees of freedom = 3)[245]; the integral of this fit yielded brain volume as a function of age for healthy control individuals and patients with schizophrenia. Part **a** reproduced with permission from REF. 244.

Functional neuroimaging of regional activation. Abnormal information processing has been linked to positive, negative and cognitive symptoms of schizophrenia. Related to that, neuroimaging has shown altered activation in cortical and subcortical structures in patients with schizophrenia. Positive symptoms are characterized by abnormal salience processing and the emergence of hallucinations. Salience processing depends on signals from midbrain dopaminergic neurons that project to the ventral striatum and dorsolateral prefrontal cortex. Molecular neuroimaging studies of dopamine uptake using the PET tracer 18-fluorine dihydroxyphenylalanine have consistently revealed increased striatal uptake in individuals with schizophrenia with both psychosis and in those in the so-called prodromal state[31,71], and have linked striatal uptake to prefrontal activity[72]. In perceptual salience, increases in midbrain activation have been found both in patients with schizophrenia[73] and in individuals at risk of schizophrenia. Outside the salience system, contributions to delusions might come from the tendency of patients to 'hypermentalize', that is, to show activation for stimuli without clear social or intentional content[74]. For hallucinations, which are another key positive symptom, activation of auditory and speech processing cortices has been linked to 'hearing voices' (REF. 75). Connectivity of these regions also seems to be altered and correlates with abnormal activation[76].

Abnormalities linked to negative symptoms have been found with regard to reward processing and social cognition, including emotional regulation. Ventral striatal responses to reward are consistently reduced in schizophrenia[76]. In emotional regulation, activation of the amygdala to emotional pictures seems to be consistently reduced in patients with the disorder[77]. In addition, interactions between the medial prefrontal cortex and amygdala are reduced in patients with schizophrenia but not in their unaffected relatives[78]. Key regions of the 'social brain' — notably the medial prefrontal cortex, temporoparietal junction and amygdala — have been shown to be abnormal in those with schizophrenia and might be linked to prominent deficits in social cognition that occur in the illness[79].

Finally, schizophrenia is associated with broad impairment in cognitive function, and this is reflected in systems-level alterations. For example, one process that has been extensively studied is executive processing, which refers to the ability to regulate and control cognitive processes. Neural substrates of executive dysfunction include working memory, in which patients show

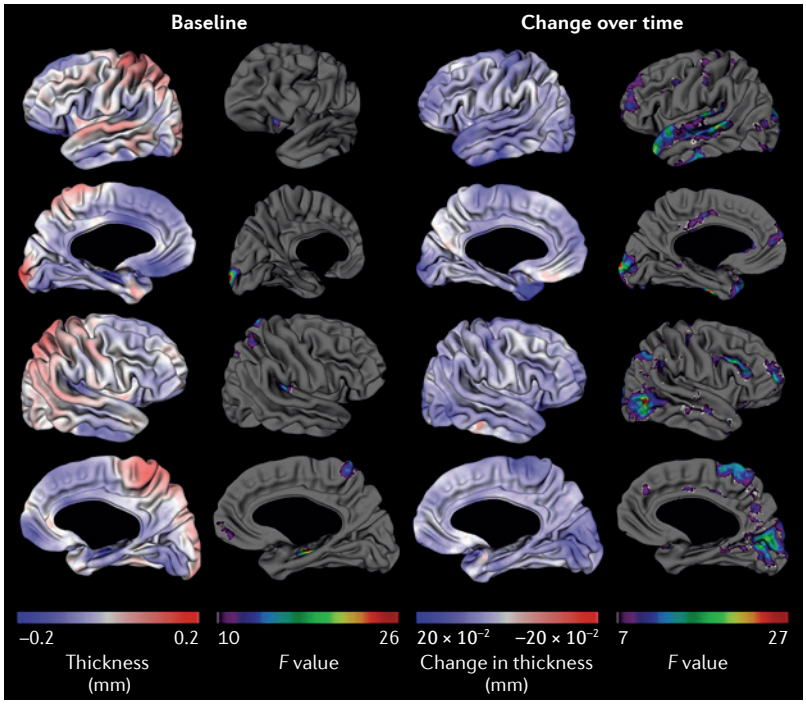

Figure 5 | **Schizophrenia involves changes in cortical thickness.** Maps of change in cortical thickness (mm) and *F* values, comparing patients with schizophrenia and healthy control individuals. Patients with schizophrenia show cortical thinning or excessive thinning (blue), or thickening or excessive thickening (red) compared with healthy controls. Maps with *F* values show where patients ($n = 154$) have significantly thinner or thicker cortex relative to controls ($n = 156$) at baseline or where change in cortical thickness during the 5-year interval is significantly more pronounced in patients with schizophrenia ($n = 96$) relative to controls ($n = 113$). Figure reproduced from REF. 64, Copyright © (2011) American Medical Association. All rights reserved.

quantitative abnormalities in the dorsolateral prefrontal cortex, rostral anterior cingulate cortex and inferior parietal lobule. These dysfunctions might precede manifest illness and index a state of vulnerability because they are also evident in individuals at high risk of developing schizophrenia[80]. Other executive functions impaired in those with schizophrenia include task switching, flexibility and planning. An additional process that has been widely studied in relation to the disorder is episodic memory. In this context, patients with schizophrenia show reduced dorsolateral prefrontal cortex activation[81] and, in many but not all studies[80,81], decreased activation of the hippocampal formation. Recent interest in cognitive impairment in patients with schizophrenia has been directed at deficits in meta-cognitive function, or 'thinking about thinking', in which those with the disorder show deficits, such as a tendency to jump to conclusions, possibly through a mechanism linked to striatal perceptual salience activation[82]. The relationship between cognition and brain function is not straightforward; accordingly, neuroimaging findings using cognitive activation paradigms must be approached cautiously. For instance, the Consortium on the Genetics of Schizophrenia (COGS) study has suggested that, although both cognitive and neurophysiological measures have evidence for heritability, they might have different genetic bases[83].

Functional neuroimaging of connectivity. Recent neuroimaging results suggest that the regional alterations discussed in the previous section are best understood as abnormalities in circuits, that is, functional interactions in schizophrenia that are altered beyond regional functional and structural abnormality. For example, dorsolateral prefrontal cortex connectivity is altered in patients with schizophrenia and in those at risk of the disorder[84,85]. During working memory, interhemispheric, prefrontal connectivity is reduced and connectivity with the hippocampal formation is increased in those experiencing first-episode and chronic psychosis[86] and in individuals at risk of schizophrenia[62]. In addition, increases in connectivity might be found within the extended limbic system during rest in those with schizophrenia and in individuals at risk of the disorder[87]. Recently, methods from topology have shown that so-called small-world properties might be altered in those with schizophrenia[82,88,89] and might predict impaired cognitive performance[64]. In particular, prefrontal cortical 'hubs' are implicated in schizophrenia[90,91]. Of emphasis are interactions between the amygdala and perigenual cingulate cortex, which were originally identified as disrupted in those harbouring variants of serotonergic candidate genes, such as the serotonin transporter-linked polymorphic region of solute carrier family 6 member 4 (*SLC6A4*; encoding the serotonin receptor) and variable numbers of tandem repeats in the X-linked monoamine oxidase A (*MAOA*).

Approaches to imaging genetics. Neuroimaging can also be helpful for understanding how genetic risk variants for schizophrenia affect brain function to bring about manifest illness. There is evidence that several abnormalities described above are related to genetic risk. This evidence relates to prefrontal activation during working memory[92], prefrontal–hippocampal connectivity[93], hippocampal activation during episodic memory[94] and striatal activation during reward[93]. The imaging genetics strategy, which uses imaging to evaluate genetic variation through detecting neuroimaging phenotypic differences, has been successfully used to interrogate genetic risk variants for schizophrenia, and has been applied to candidate genes — such as catechol-*O*-methyltransferase (*COMT*)[94], neuregulin 1 (*NRG1*)[95] and disrupted in schizophrenia 1 (*DISC1*)[96] — and, more recently, to common[97] and rare[98] variants identified as significantly associated with the illness through genome-wide association studies.

Neuroimaging of environmental risk mechanisms. Neuroimaging can also be used to define mechanisms by which the environment acts to increase schizophrenia risk. Two strongly validated risk factors — city birth and upbringing[99], and migration[100] — were both found to alter activation and connectivity in a perigenual cingulate–amygdala circuit during social stress. This circuit is also modulated in the same way (that is, the same regions, with connectivity between them changed in the same directionality) by serotonergic candidate genes that show gene–environment interactions[101,102] and genome-wide significant variants for schizophrenia, such as in

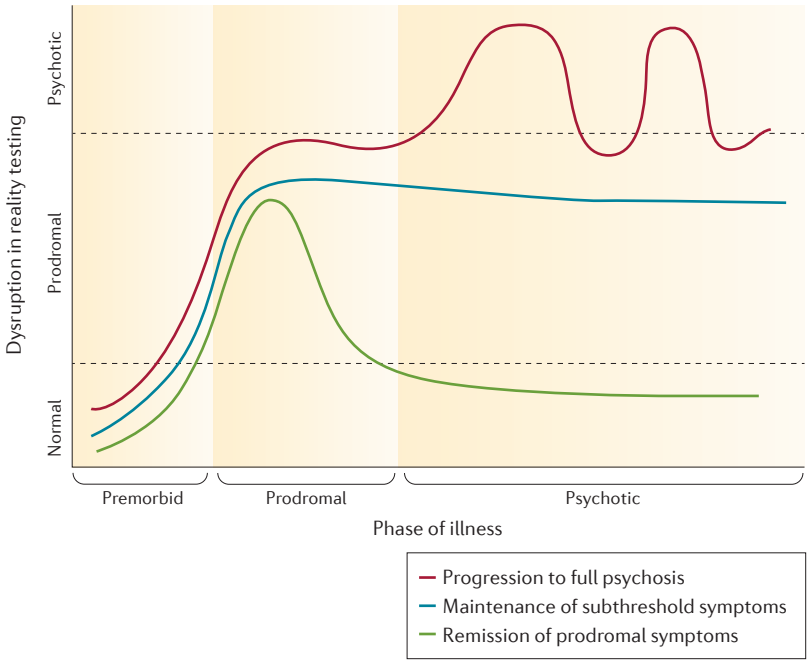

Figure 6 | **Descriptive model of the onset and course of psychotic symptoms among individuals who develop a prodromal risk syndrome.** Approximately one-third of prodromal patients progress to full psychosis (red line), one-third maintain stable levels of subthreshold symptoms (blue line) and one-third remit the prodromal symptoms (green line).

calcium channel voltage-dependent L type-α1C subunit (*CACNA1C*). As such, it has been proposed that this circuit might be a pathway for risk for mental disorders where social and environmental risk factors converge[80].

Diagnosis, screening and prevention

Prediction and prevention of psychosis

Given that currently available pharmacological treatments for schizophrenia are limited and sometimes poorly tolerated[103], with most patients continuing to show substantial deficits in social, cognitive and occupational functioning throughout their lifetime, there is considerable interest in exploring preventive approaches to the disorder[104]. The primary challenges for realizing such a prevention strategy are: developing reliable and efficient means to predict psychosis so that we can identify populations at the greatest risk; elucidating changes at the neural and molecular levels that participate mechanistically in functional decline and the onset of symptoms; and developing and testing interventions that target the molecular signalling pathways that contribute to schizophrenia. Progress on these fronts could yield novel or 'repurposed' compounds with more than palliative efficacy — that is, drugs that are capable of preventing or mitigating the changes in brain structure and function that underlie functional decline and the onset of full symptoms in patients with schizophrenia[105]. Such compounds, combined with psychosocial interventions, could also help to redirect a young person who is otherwise predisposed to schizophrenia towards a trajectory of social engagement, educational completion and independent living.

Risk syndrome ascertainment. The onset of psychotic symptoms is often preceded by the emergence of subtle changes in belief, thought and perception that seem to represent attenuated forms of delusions, formal thought disorder and hallucinations, respectively[106] (FIG. 6). Approximately 80–90% of patients with schizophrenia have such a prodrome, which has a median duration of about 52 weeks; psychotic symptoms emerge without an appreciable prodrome in the remaining 10–20% of patients[107]. Operational criteria have been developed that can be used to ascertain a set of prodromal or clinically high-risk (CHR) syndromes. These criteria are based on the emergence of attenuated or subthreshold psychotic symptoms, or the presence of a family history of schizophrenia in the context of a recent and substantial decline in functioning[108,109]. It is important to note that CHR patients are generally distressed and seeking help — typically for mood or anxiety issues and/or school failure — and often keep their changing thoughts and perceptions to themselves until specifically asked about these experiences during screening. Given the distributions of age of onset for psychosis, assessing for a prodromal risk syndrome is recommended for such presentations among individuals 12–35 years of age.

Outcomes of CHR cases. The CHR construct is a potent predictor of psychosis. According to a meta-analysis that incorporated data from 27 studies comprising a total of 2,502 patients, 22% of patients transitioned to a psychotic form of illness by 1 year and 36% by 3 years from initial ascertainment of being in an at-risk mental state[110]. As most studies use follow-up periods of ≤3 years, the rate of conversion after this point remains unclear. Nevertheless, most of the conversions occur during the first year following ascertainment, and the conversion rate significantly declines thereafter, suggesting that the CHR criteria are sensitive to an imminent risk for the onset of full psychosis[111]. Among those who convert, about 80% of the diagnostic outcomes are in the schizophrenia spectrum and the remaining 20% are to mood-related and atypical forms of psychosis. Importantly, among approximately 64% of patients who do not convert, roughly half remit the symptoms that indexed their initial risk status and improve functionally, whereas the remainder show continuing levels of attenuated psychotic-like symptoms and functional impairment[112,113] (FIG. 6). It remains unclear whether some of those who remit subsequently revert to a CHR state and, if so, whether such reversions are preceded by particular risk factors such as major life stressors.

Multivariate prediction. Numerous studies have examined whether combinations of clinical and demographic variables at baseline can predict psychosis beyond the approximate 36% risk that is associated with a CHR syndromal status[71]. In general, multivariate algorithms that require particular combinations of symptoms and demographic factors achieve high positive predictive power and specificity, in the 70–80% range, but low sensitivity in the 10–30% range[111]. There is consistency among studies in showing, intuitively, that higher levels of the

prodromal symptoms at baseline are the best predictors of conversion. Nevertheless, the most predictive multivariate profiles vary widely across studies[71]. Although it should be noted that few studies have attempted direct replication of each other's risk algorithms, this pattern hints at the strong likelihood of substantial heterogeneity among profiles of clinical and demographic risk indicators among those who convert. Whether such heterogeneity also exists at the level of biological pathways underlying conversion remains unclear.

Biological assays in CHR patients are less confounded with exposure to antipsychotic treatments and other secondary factors than in patients with established schizophrenia. Some promising leads on the use of biological assays to improve prediction among those deemed CHR have emerged that use empirically based discovery approaches, including machine-learning algorithms for grey matter variations in structural brain images[114,115] and so-called greedy regression algorithms for proteomic and metabolic plasma parameters[116]. The ultimate value of such algorithms awaits validation tests in independent data sets.

The value of using these behavioural and biological measures as predictors of psychosis is currently limited to individuals with a prodromal risk syndrome; these measures are not expected to perform as well (or at all) as predictors in the general population.

Given that some of the contributing causal factors to schizophrenia are likely to change dynamically in the transition to psychosis, the CHR paradigm is also valuable for tracking potential progressive biological processes that are predictive of conversion. One of the most promising initial findings supporting this is a steeper rate of reduction in cortical grey matter — most prominent in the prefrontal and parahippocampal regions — that in turn correlates with higher levels of pro-inflammatory cytokines at baseline among CHR patients who convert to psychosis than among those who do not[117]. Whether immune activation during this phase is a primary or secondary phenomenon is unclear, but evidence of pro-inflammatory signalling is at least circumstantially consistent with altered genetic regulation of immune pathways, such as those involving major histocompatibility complex and microglial activation. Preliminary evidence produced using PET imaging also supports a progressive increase in dopamine availability among those who convert to full psychosis[118–120].

Prevention studies. A small number of controlled prevention trials in CHR patients have been conducted. Collectively, the results support the view that any targeted intervention, whether biological or psychological in approach, is associated with better outcomes than less-targeted control conditions[121]. Results of two small trials with antipsychotic drugs do not support a prophylactic effect on conversion risk beyond the period of active treatment[122,123]. In general, the use of such medicines in individuals who are below the threshold of full psychosis is not recommended. Intriguing results have been obtained in an initial trial of omega-3 fatty acid supplementation[124], but this finding awaits confirmation in independent studies. Psychosocial interventions such as cognitive–behavioural therapy and family-focused psychoeducation might be beneficial in deflecting the course of illness severity and chronicity[125,126]; however, it remains unclear whether such approaches can prevent the onset of the illness.

In summary, the CHR paradigm seems to be useful for elucidating predictors and mechanisms of onset of psychosis and for the development and testing of preventive interventions. Challenges to be addressed in the next phase of research using this paradigm include the need for larger sample sizes, probably necessitating multisite collaborations, that can help to expose the heterogeneity of risk profiles and outcomes, and greater cooperation across research groups to permit direct replication tests of principal findings across independent studies.

Diagnosis and screening

Diagnosis of schizophrenia is made on the basis of operational criteria, such as those documented in DSM or *International Statistical Classification of Diseases and Related Health Problems* (ICD). These criteria take into account characteristic positive, negative and cognitive symptoms of schizophrenia along with symptom duration, their effect on social and occupational functioning and the potential contribution of other psychiatric conditions, mood disorders and substance abuse issues (BOX 1). The high heritability of schizophrenia[47] suggests that, in principle, genetic data might inform risk prediction, diagnostics and possibly stratification approaches to treatment selection. However, given that heritability is not 100%, for the general population of patients, genetics is unlikely to provide definitive risk prediction or diagnostic discrimination.

Approximately 120 chromosomal loci containing schizophrenia susceptibility alleles have been identified, most of which ($n = 108$) were found by genome-wide association studies. These loci contain risk alleles with frequencies of ≥1%, and each individual allele confers only a small amount of risk (FIG. 3), with allelic odds ratios of approximately ≤1.1 (REF. 127). Despite the number of implicated loci, cumulatively, they only explain about

Box 1 | **Criteria for schizophrenia**

The criteria for schizophrenia from the *Diagnostic and Statistical Manual of Mental Disorders*, Fifth Edition[240]:

- A criterion: two or more of the following symptoms for >1 month unless treated successfully include delusions; hallucinations; disorganized speech; disorganized or catatonic behaviour; and negative symptoms, such as affective flattening or loss of initiative
- B criterion: level of functioning is significantly decreased in work, personal relationships and/or personal care
- C criterion: symptoms of the disorder last ≥6 months
- D criterion: exclusion of schizo-affective disorder, unipolar and bipolar affective disorder
- E criterion: symptoms cannot be attributed to the use of drugs or medication, or to a somatic disorder
- F criterion: in the case of a pre-existing autism spectrum disorder, at least 1 month with prominent hallucinations or delusions

3.5% of the variance in liability to schizophrenia[127]. One way of capturing more of the variance is through polygenic risk profile scoring (RPS)[127,128]. In RPS, alleles that meet some *P*-value threshold for an association are classified as risk alleles. Risk profile scores are then assigned to individuals based on the number of risk alleles carried that have been weighted by their estimated effect size. RPS currently captures about 7% of the liability for schizophrenia in populations of European ancestry, a level that is far short of a clinically useful test[127]. Moreover, the predictive power in non-European ancestry populations, particularly of African origin, is even lower[127,129,130]. In principle, 25–33% of liability[131,132] might ultimately be indexed by RPS, but modelling suggests that, as sample sizes increase, accessing this variance will become progressively incremental[133,134]. Fuller coverage of common variation on genome arrays might boost the information captured by RPS by perhaps another 5 percentage points. Other possible gains might come from allowing for interactive effects. These effects clearly exist at the molecular level, but whether this has the potential to significantly enhance the measured variance in liability has been disputed for decades[135]. For now, we can only note that there is no strong evidence for non-additive effects in genome-wide analyses of psychosis[136] or between pairs of genome-wide significant schizophrenia loci[127], although the analyses so far certainly do not preclude these or higher-order interactions.

RPS and other analogous approaches have revealed a substantial overlap between schizophrenia and both major depressive disorder and bipolar disorder[48,128,137] and, to a lesser extent, with attention-deficit/hyperactivity disorder (ADHD)[138]. Findings such as these, as well as non-specificity with respect to other indices or risks, have led to calls for novel ways of classifying psychiatric disorders on the basis of, for example, symptom profiles, cognitive measures or brain imaging variables[139–141]. The hope is that these might index pathogenetic brain changes that map better onto genetic risk and, as a result, perform better in predicting treatment and prognosis than current approaches. However, thus far, this approach has not delivered strong findings upon which to revise diagnostic practices. Unless genetically valid subtypes are defined, shared liability adds a constraint on the future use of RPS to discriminate between psychiatric diagnoses as opposed to the less challenging, or less useful, distinction between those who do and do not have a major psychiatric syndrome.

The remaining known schizophrenia risk loci are copy number variant (CNV) deletions or duplications of DNA segments from a thousand to a few million bases[142]. CNVs have relatively large effects on risk (FIG. 3) with odds ratios of between 2 and 60 (REFS 143,144), although, because they are rare, individual CNVs do not contribute substantially to the overall population risk of schizophrenia. Even for individual carriers, the diagnostic value of these CNVs with respect to schizophrenia is limited, with 2–20% of carriers — depending on the CNV — developing the disorder[51,145]. However, all known schizophrenia-associated CNVs are pleiotropic and contribute to a range of other disorders, including intellectual disability, autism spectrum disorder, ADHD, epilepsy and congenital malformations[51,143]. The proportion of carriers who develop one or more of the above conditions is very high (approximately 50%) and for some loci is even higher[51].

For those already affected with schizophrenia, knowledge of CNV carrier status might be relevant mainly for its explanatory power — as people have a strong desire for an explanation of their condition — but also because several CNVs are associated with high risks of co-morbid medical phenotypes that might be overlooked in people with psychosis who often do not gain access to general health care[144,146]. Owing to the high risk of developmental disorder for the offspring of these carriers, there is a case for making pathogenetic CNV testing available for patients with schizophrenia, of whom 2.5–8% are estimated to be carriers[144,146].

Other classes of rare mutation play a part in schizophrenia[51,146,147], but early indications suggest that their overall contribution might be much lower than for common variation[147], which limits their role in general prediction and diagnostics. However, evidence supports the notion that deleterious point mutations in a subset of genes act analogously to CNVs in terms of effect size and pleiotropic effects[51], suggesting that when relevant mutations are identified, similar arguments for the screening of affected individuals might be applicable.

At present, with the exception of the small number of known pathogenetic CNVs that we consider to be of possible clinical use, genetic findings might be useful in a research setting but do not provide the high precision that is required for diagnosis or accurate risk prediction. Indeed, it is unlikely that genetics alone will ever achieve this goal. However, as more of the genetic variance that underlies schizophrenia is captured, risk profile scores derived from common, and possibly rare, genetic variation could plausibly contribute to risk algorithms. Undoubtedly, those algorithms will need to incorporate additional indicators of risk, such as family history, environmental variables (for example, drug use and severe childhood adversity) and developmental markers that either index risk or are themselves early markers of the disorder (for example, developmental delay, neurological soft signs — minor abnormalities in sensory and motor performance identified by clinical examination — and educational failure). Developing these algorithms will require much better research that is aimed at determining whether these indicators add to genetic risk, are non-independent manifestations of genetic risk (for example, family history) or are even perhaps mediators of that risk (for instance, drug use)[143,148]. Moreover, even if prediction becomes possible, the benefits of implementation and the required degree of specificity and sensitivity are crucially linked to the availability of interventions that can prevent or ameliorate the course of the disorder.

Management

Approximately 60 years have passed since the discovery of chlorpromazine, but antipsychotics still remain the cornerstone of treatment for schizophrenia[148]. Although all antipsychotics act to block receptors of the dopamine

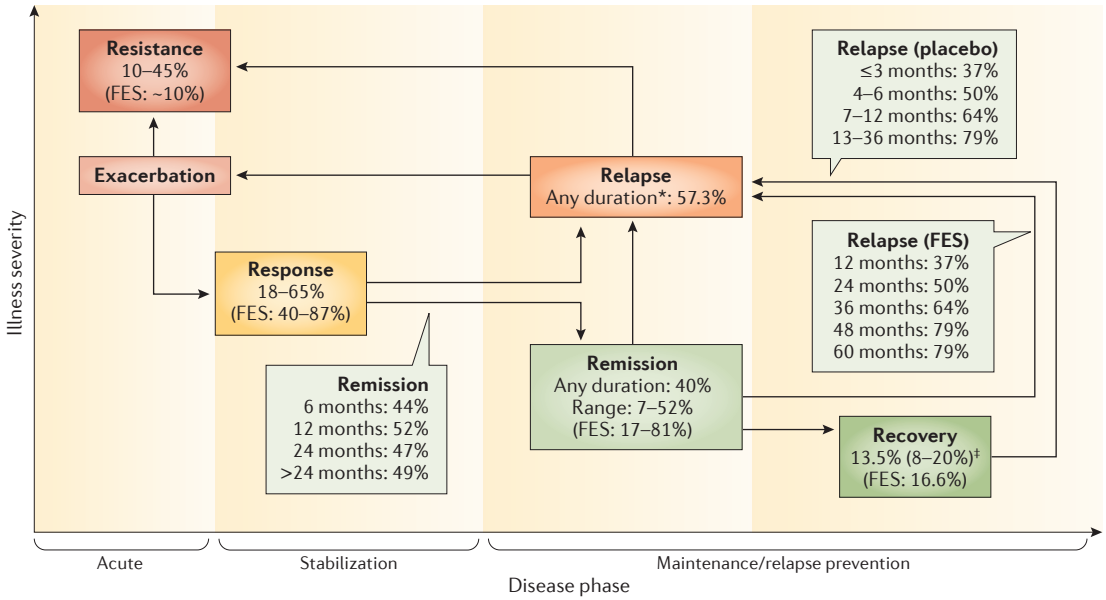

Figure 7 | **Treatment phases and outcomes in schizophrenia.** Percentages denote the proportion of patients with schizophrenia at that particular stage of the disease. FES, first-episode psychosis. *In antipsychotic discontinuation studies. ‡Median (interquartile range). Figure from REF. 173. Figure modified from *Dialogues in Clinical Neuroscience* with the permission of the publisher (AICH-Servier Research Group, Suresnes, France). Carbon, M. & Correll, C. U. Clinical predictors of therapeutic response to antipsychotics in schizophrenia. *Dialogues Clin. Neursci.* **16**, 505–524 (2014) © AICH-Servier Research Group.

pathway, different antipsychotics have been developed that have been classified into 'typical' or first-generation antipsychotics (FGAs), and 'atypical' or second-generation antipsychotics (SGAs, for which clozapine is the prototype drug)[149]. However, the classification of antipsychotics into FGAs and SGAs has been challenged[150], as all antipsychotics are believed to act via reducing dopaminergic tone and because both classes are heterogeneous in molecular structure, extra-dopaminergic targets and adverse effects[151]. Extrapyramidal adverse effects, such as Parkinsonism, had been believed to be the unavoidable result of antipsychotic efficacy conferred by dopamine D2 receptor blockade. Indeed, antidopaminergic-related adverse effects of these drugs include hyperprolactinaemia, dystonia, Parkinsonism, akathisia and tardive dyskinesia. Subsequently developed SGAs block serotonin receptors at lower concentrations than they block dopamine receptors and/or might block subcortical dopamine D2 receptors more than striatal dopamine D2 receptors. These drugs are associated with less Parkinsonism, akathisia and tardive dyskinesia than FGAs at therapeutic doses. However, no SGA is entirely free of associated Parkinsonism, and all currently available antipsychotics are believed to work predominantly via dopamine D2 receptor blockade[152]. Moreover, most SGAs are associated with other adverse effects, such as weight gain, diabetes and — consequently — increased risk of cardiovascular complications.

Although preclinical data strongly indicate the involvement of the glutamatergic and cholinergic systems, especially regarding negative and cognitive symptoms of schizophrenia, so far treatments targeting these systems have not gone beyond either successful or suggestive Phase II studies[153]. Hence, the successful development of new antipsychotic agents has largely followed the principle of maintaining antidopaminergic efficacy while attempting to improve tolerability. However, the focus has shifted from reducing the risk of predominantly antidopaminergic-related adverse effects to developing antipsychotics with little effect on cardiac conduction and, especially, a low propensity for cardiometabolic adverse effects, including weight gain, dyslipidaemia, glucose abnormalities and metabolic syndrome. There has been debate about the magnitude of the effect of atypical antipsychotics on cognition, but most studies have shown only minimal improvement. Even this small degree of improvement could also be attributed to a large degree to practice effects. The most recent meta-analysis on the cognitive effects of antipsychotics indicated that atypical antipsychotics yield only minimal and isolated improvements in some specific neurocognitive domains[154], despite the varied putative neuropharmacological effects of these drugs[152,155].

Treatment phases and goals

Treatment of schizophrenia targets various domains, including positive symptoms, agitation and aggression, negative symptoms, cognitive dysfunction, mood symptoms, suicidality, QOL, and social, academic and vocational functioning. Accordingly, management goals include reduction of acute symptoms, 'response', which is defined as the reduction of total symptoms compared with baseline by at least 20% (that is, at least minimally improved) to 40–50% (that is, at least much improved), and remission, which is defined as only mild positive and negative symptoms sustained for at least

Box 2 | **Management of individuals who do not respond to antipsychotics**

Management should be approached in a stepwise manner for patients with schizophrenia who do not respond to treatment with antipsychotics[241]:

1. Reassess diagnosis and rule out medical or substance-related conditions
2. Identify co-morbidities and optimize their management
3. Review the nature and effectiveness of current and past treatments
4. Assess for adverse effects that could potentially contribute to refractoriness to antipsychotics
5. Rule out potentially interfering drug–drug interactions
6. Check and address reasons for non-adherence
7. Optimize non-pharmacological treatments
8. Continue treatment and wait for a potentially delayed response*
9. Increase dose to a level that achieves symptom response or therapeutic level*
10. Reduce antipsychotic dose to minimize adverse effects
11. Switch to an agent of the same pharmacological class‡
12. Switch to an agent of a different pharmacological class§
13. Augment with an agent of the same pharmacological class‖
14. Augment with an agent of a different pharmacological class‖

*Very limited data to support this approach. ‡Good data for clozapine. §No data to support this approach. ‖Limited data to support this approach.

6 months[156]. In addition, management strategies aim to achieve recovery — defined as concurrent symptom remission plus adequate self-care, and social and vocational functioning sustained for at least 2 years[157] — as well as maintenance treatment or relapse prevention. FIGURE 7 shows the success rates achieved with currently available antipsychotics for each of the different treatment phases or goals. Unfortunately, probably owing to the mainly antidopaminergic mechanism of these treatments, current management goals are largely restricted to improving positive psychotic symptoms and related agitation and aggression[148,149]. Furthermore, suicidality is decreased with clozapine use[158,159] and mortality is decreased with antipsychotic treatment compared with no antipsychotic treatment[160,161]. However, negative symptoms[162] and cognitive dysfunction[155] are largely unimproved with these strategies. Similarly, both remission[163] and, in particular, recovery[164] are only achieved in a minority of patients with schizophrenia who use available treatments. At the same time, however, problems with medication adherence[165] and inadequate access to psychosocial treatments and supported employment and education[149] might contribute substantially to high rates of relapse and low rates of recovery.

Response predictors

There are only a few features that can predict patient responses to pharmacological treatments, and most are of an epidemiological or clinical nature[166]. Biological markers of poor treatment response or refractoriness to antipsychotics in patients with schizophrenia include variation in *DRD2* (REF. 167), a lack of abnormally upregulated striatal dopamine synthesis[168], increased levels of glutamate in the context of normal dopamine functioning upon PET imaging[169], cortical thinning and less cortical lateralization[170], individual differences in intrinsic striatal connectivity[171], a lack of improvement in P50 gating[172] and increased levels of plasma homovanillic acid[169]. However, it should be noted that most of these findings are based on individual — hence unreplicated — studies in small samples of patients. By contrast, more-consistent evidence has been produced with clinical predictors of poor antipsychotic response, such as male sex, younger age at disease onset, longer duration of untreated illness, poor premorbid adjustment, severe baseline psychopathology, non-adherence to antipsychotics, co-morbidities (especially substance use disorders), a lack of early minimal antipsychotic response and longer illness duration or non-first-episode illness[173]. Moreover, emerging evidence suggests that, after each relapse, a certain percentage of patients do not respond as well to the same or different antipsychotics as they did originally[174,175]. Conversely, a lack of improvement with non-clozapine antipsychotics predicts clozapine response[173]. Furthermore, although therapeutic blood monitoring of antipsychotic concentrations has been proposed in the past, current established thresholds only exist for clozapine, for which a minimum level of 350–450 ng per dl is thought to be needed for robust clozapine response[176].

Efficacy in first-episode schizophrenia

In first-episode schizophrenia, response rates are generally higher than in patients who have experienced multiple episodes of psychosis. In addition, lower doses of antipsychotics are effective in patients with first-episode schizophrenia who generally require approximately 50% of the dose necessary or used in patients who have had multiple episodes of the illness. There is no significant difference in the efficacy of different antipsychotics in reducing total psychopathology, including between FGAs and SGAs (with all but one study using haloperidol as the FGA, precluding generalization to all FGAs)[177]. However, on a pooled level, SGAs seem to have small effect size advantages over FGAs regarding improvement of negative and cognitive symptoms as well as in promoting relapse prevention. SGAs also have moderate effect size advantages compared with FGAs in terms of all-cause and specific-cause discontinuation owing to inefficacy and, especially, intolerability[177].

Efficacy in multi-episode schizophrenia

Acute antipsychotic efficacy in patients who have experienced multiple episodes of schizophrenia has been compared in several meta-analyses in recent years. In head-to-head meta-analyses, all studied antipsychotics were superior regarding total psychopathology compared with placebo[178]. In addition, some SGAs were more effective than pooled FGAs (mostly consisting of haloperidol)[179] as well as other SGAs[180], but overall effect size differences between antipsychotics were generally small. Conversely, no relevant differences between antipsychotics emerged in relation to negative symptom improvement[180]. A more recent network meta-analysis that includes estimates from indirect comparisons found that all marketed antipsychotics were superior to placebo regarding total psychopathology, with effect sizes ranging from 0.33 for iloperidone and lurasidone to 0.56–0.66 for risperidone, olanzapine and amisulpride and 0.88 for clozapine[150].

In patients with multi-episode schizophrenia, oral antipsychotics reduce the risk of relapse and re-hospitalization compared with placebo by 60–65%[181], with favourable numbers needed to treat (3–5 patients). Similar effect sizes compared with placebo have also been shown for long-acting injectable antipsychotics (LAIs)[182]. Comparison of oral SGAs with oral FGAs for relapse prevention demonstrated that SGAs showed some advantage only at a pooled class level, with a 20% risk reduction and a number needed to treat of 17 patients[183]. Although a recent meta-analysis of randomized controlled trials did not show conclusive advantages for LAIs compared with oral antipsychotics for all-cause discontinuation and relapse[184], results were probably confounded by greater adherence in those patients participating in such trials[184]. By contrast, mirror image studies, which compare outcomes before the initiation of an LAI (that is, on oral antipsychotics) with outcomes after a switch to an LAI in the same patients, showed consistent advantages of LAIs over oral formulations regarding hospitalization risk and numbers of hospitalizations[185]. In addition, studies using population-wide registers, such as those available in Finland, show that patients on LAIs are less often re-hospitalized than those treated with the equivalent oral antipsychotic drugs[160].

Efficacy in treatment-resistant schizophrenia

BOX 2 summarizes the recommended steps to evaluate and treat patients with treatment-resistant schizophrenia. In such patients, the best evidence supports a switch to clozapine[186,187]; however, meta-analyses of randomized trials that compared clozapine to other SGAs produced mixed results[150,180]. A secondary analysis suggested that clozapine might be more effective than SGAs when used at doses above 400 mg per day[180].

Antipsychotic safety and tolerability

Tolerability differences among antipsychotics are generally larger and more predictable than differences in efficacy, as the well-known antipsychotic pharmacodynamic profiles are more closely related to adverse-effect type and frequency[188]. TABLE 1 summarizes the propensity of specific antipsychotics for different adverse effects, and BOX 3 outlines the mechanisms that underlie these effects. These associations are certainly generalizations, as different individuals with schizophrenia might respond differently to the same treatment. Although clozapine is associated with a particularly broad and difficult adverse-effect profile, management strategies exist that can enable patients to initiate and stay on clozapine[189].

Table 1 | **Adverse effect profiles of selected antipsychotics**

Adverse effect	Second-generation antipsychotics												First-generation antipsychotics		
	AMI	*ARI*	*ASE*	*CLO*	*ILO*	*LUR*	*OLA*	*PALI*	*QUE*	*RIS*	*SER*	*ZIP*	*CPZ*	*HAL*	*PER*
Anticholinergic	0	0	0	+++	0	0	++	0	+/++	0	0	0	++	0	0/+
Acute Parkinsonism	+	+	++	0	0/+	+/++	0/+	++	0	++	0/+	+	+	+++	++
Akathisia	+	++	++	+	0/+	+/++	+	+	+	+	+	+/++	+	+++	++
Cerebrovascular events*	+?	+	+?	+?	+?	+?	+	+?	+	+	+?	+?	+?	+?	+?
Diabetes	0/+	0/+	0/+	+++	+	0/+	+++	+	++	+	+	0/+	+++	0/+	+
Blood lipids	+	0/+	0/+	+++	+	0/+	+++	+	++	+	+	0/+	+++	0/+	+
Hypersalivation due to an overproduction of saliva	0	0	0	++	0	0	0	0	0	0	0	0	0	0	0
Neutropenia	0/+	0/+	0/+	++	0/+	0/+	0/+	0/+	0/+	0/+	0/+	0/+	0/+	0/+	0/+
Orthostasis	0/+	0/+	+	+++	+++	0/+	++	+	++‡	+	+	0	++	0	+
Prolactin and sexual dysfunction	+++	0	+	0	0/+	+	+	+++	0	+++	+	+	+	++/+++	++
Prolactin	0	+	0	0	0	0	0	0	0	0	0	0	0	0	0
QTc interval (prolonged cardiac conduction repolarization)	++	0/+	+	+	++	0/+	0/+	+	+	+	++/+++	++	0/+	0+	+
Sedation	0/+	0/+	+	+++	0/+	+/++	+/++	0/+	++‡	+	0/+	+	++	+	+
Seizures	0/+	0/+	0/+	++	0/+	0/+	0/+	0/+	0/+	0/+	0/+	0/+	0/+	0/+	0/+
Tardive dyskinesia	0/+	0/+	0/+	0	0/+	0/+	0/+	0/+	0/+	0/+	0/+	0/+	++	++	++
Withdrawal, dyskinesia	+	+/++	+	0	+	+	0/+	+	0/+	+	0/+	+	0/+	++	+/++
Weight gain§	0/+	0/+	+	+++	+/++	0/+	+++	++	++	++	++	0/+	+++	+	++

Effect: 0, absent; +, mild; ++, moderate; +++, marked; ?, questionable. AMI, amisulpride; ARI, aripiprazole; ASE, asenapine; CLO, clozapine; CPZ, chlorpromazine; HAL, haloperidol; ILO, iloperidone; LUR, lurasidone; OLA, olanzapine; PALI, paliperidone; PER, perphenazine; QUE, quetiapine; RIS, risperidone; SER, sertindole; ZIP, ziprasidone. *Evidence derived only from studies in elderly patients with dementia; data were available only for OLA, QUE, RIS and ARI, but all medications have received a class label by the US FDA. ‡Risk from extended-release QUE might be lower than that of immediate-release QUE. §Extent or risk depends on the degree of prior weight gain while on psychotropic medications, weight gain potential of specific medication and patient susceptibility. Table modified and extended from REF. 246, and incorporated additional data from REF. 150.

Box 3 | **Mechanisms underlying adverse effects of antipsychotics**

The adverse effects associated with antipsychotic use and their corresponding mechanisms of action include:

- Anticholinergic effects: muscarinic acetylcholine M1–M4 receptor blockade
- Acute Parkinsonism: dopamine D2 receptor blockade
- Akathisia: dopamine D2 receptor blockade (?) and α-adrenergic receptor and/or serotonin receptor interaction with transmission (?)
- Cerebrovascular events: dopamine D2 receptor-mediated hypercoagulability (?)
- Diabetes: weight gain and direct effects (?)
- Increased concentration of blood lipids: weight gain and direct effects (?)
- Hypersalivation due to an overproduction of saliva: muscarinic acetylcholine M4 receptor agonism
- Neutropenia: unknown
- Orthostasis: α1-adrenergic receptor blockade
- Increased prolactin and sexual dysfunction: dopamine D2 receptor blockade
- Decreased prolactin: dopamine D2 receptor agonism
- QTc interval (prolonged cardiac conduction repolarization): cardiac ion channel effects
- Sedation: histamine H1 receptor blockade
- Seizures: dopamine D2 receptor blockade (?)
- Tardive dyskinesia: unknown
- Withdrawal, dyskinesia: dopamine D2 receptor blockade rebound
- Weight gain: histamine H1 receptor blockade (?), dopamine D2 receptor blockade and serotonin 5-hydroxytrypamine 2C (5-HT_{2C}) receptor blockade (?)

Potential and limitations of available antipsychotics

Antipsychotics have therapeutic effects for positive symptoms, agitation, aggression and, to some extent, suicidality — acutely and as relapse prevention treatment. The amelioration of negative and cognitive symptom domains remain a largely unmet medical need. Owing to strong associations between negative and cognitive symptoms and poor functional outcomes, effective interventions for these domains are urgently needed. Owing to the heterogeneity of schizophrenia, treatment approaches that take advantage of clinical and biological markers that can help to identify homogeneous subgroups of patients for whom specific treatments might have a particular efficacy are needed. Pathophysiological insights leading to more-personalized, mechanism-based interventions have the greatest chance of generating better treatments with efficacy in various illness domains. Such progress would lead to major advances in improving overall outcomes for patients with schizophrenia.

Efficacy of non-drug biological interventions

Electroconvulsive therapy. Electroconvulsive therapy (ECT) involves the induction of seizures through the use of electric currents while patients are under general anaesthetic. Randomized controlled trials of ECT in the treatment of schizophrenia are scarce. A meta-analysis found that ECT was superior to no ECT in patients with schizophrenia in 10 trials, but inferior to antipsychotic medication in three trials[190]. By contrast, one published trial has shown superior efficacy of ECT when added to clozapine than treatment using only clozapine in patients with insufficient response to clozapine alone[191].

Repetitive transcranial magnetic stimulations. Transcranial magnetic stimulation therapy uses electromagnetic induction to stimulate particular brain regions. Whereas early meta-analyses of small and short-term trials found repetitive transcranial magnetic stimulation to be significantly more effective than sham treatment for auditory verbal hallucinations with moderate effect sizes[192,193], results for the treatment of negative schizophrenia symptoms have been mixed[192,194]. Adverse outcomes of repetitive transcranial magnetic stimulation include stimulation site pain, muscle twitching during treatment sessions, post-treatment headache and toothache and, rarely, seizures — which is why seizure disorder is a contraindication.

Efficacy of augmentation strategies

Augmentation strategies involve the addition of other agents to antipsychotics and should be reserved for when clozapine is not effective, not tolerated or refused despite multiple attempts at discussing the evidence favouring clozapine with the patient, their family and other relevant individuals. Evidence for all augmentation strategies is limited and none have sufficient data for regulatory approval. However, in patients experiencing severe symptoms and marked impairment despite several attempts at treatment with antipsychotics that were used at adequate dose (at least medium range of the approved doses), for sufficient duration (≥6 weeks) and with good adherence (such as >80% confirmed by blood drug concentration, supervised intake or LAI use), clinicians might choose to try certain combined treatments. Even if the clinical trial evidence is inconclusive, the mean results in heterogeneous study populations might not apply to individuals. Augmentation strategies make the most sense in clozapine-refractory schizophrenia[195], as there is generally no other recommended option. TABLE 2 summarizes agents with some evidence for efficacy in improving total positive, negative and cognitive symptoms of schizophrenia[196,197].

Efficacy of non-pharmacological interventions

Several psychosocial interventions have shown efficacy when used in conjunction with antipsychotic treatment. These include social skills training[198], cognitive–behavioural therapy[199], assertive community treatment[200], crisis intervention[201] and supported employment[202]. Furthermore, exercise might improve mental state and negative symptoms in addition to physical health[203]. Finally, family interventions might help to reduce relapse rates[204,205].

Cognitive remediation and training has gained substantial recognition as an efficacious strategy for improving cognitive functioning, including social cognition[206]. Cognitive remediation therapy has been shown to improve cognition with medium effect sizes, and further improved efficacy when applied to patients who were clinically stable and when combined with adjunctive psychiatric rehabilitation[206,207]. These conclusions have held up even when the data were scrutinized methodologically, which suggests that cognitive remediation that is combined with psychiatric

Table 2 | **Efficacy of pharmacological augmentation strategies for specific symptom domains**

Symptom domain	Medications	Results
Positive symptoms or total psychopathology	None	Efficacious
	Aspirin	Suggestive efficacy
	Antipsychotic co-treatment	Mixed results
	Topiramate	
	Lamotrigine	
	Omega-3 fatty acids	
	Valproate	Suggestive inefficacy
	Lithium	
	NMDA agonists	
	Carbamazepine	Lack of efficacy
	Benzodiazepines	
	Beta blockers	
	COX-2 inhibitors	
	N-acetyl cysteine	
	Modafinil	
Negative symptoms	None	Efficacious
	Antidepressants: SSRIs and α2-adrenergic antagonists	Suggestive efficacy
	NMDA agonists: glycine, cycloserine, D-serine and D-cycloserine	Mixed results
	N-acetyl cysteine	
	Male sex steroids	
	Female sex steroids	
	MAOB inhibitors, such as selegiline	
	Serotonin 5-HT_{2A} receptor blockers	Suggestive inefficacy
	Dopamine D2 receptor agonists: stimulants, modafinil and armodafinil	
	Antipsychotic co-treatment	Lack of efficacy
	Lithium	
	Valproate	
	Topiramate	
	Carbamazepine	
	Benzodiazepines	
	Beta blockers	
Cognitive symptoms	None	Efficacious
	None	Suggestive efficacy
	Nicotine receptor agonists	Mixed results
	Ampakines	
	Modafinil	
	Dopamine D2 receptor agonists (stimulants)	Suggestive inefficacy
	NMDA agonists: glycine, cycloserine, D-serine and D-cycloserine	
	Antipsychotic co-treatment	Lack of efficacy
	Lithium	
	Valproate	
	Topiramate	
	Carbamazepine	
	Benzodiazepines	
	Beta blockers	

MAOB, monoamine oxidase B; NMDA, *N*-methyl-D-aspartate; SSRI, selective serotonin reuptake inhibitor. Data based on REFS 97,196.

Table 3 | **Drugs in Phase II and Phase III development for schizophrenia**

Compound	Receptor or mechanism of action	Stage of development	Company
ABT-126	Nicotinic acetylcholine receptor subunit-α7 agonist Neuronal nicotinic agonist	Phase II	AbbVie
ADX71149 (JNJ-40411813)	Glutamate receptor 2 positive allosteric modulator	Phase II	Addex and Janssen Pharmaceuticals
ALKS-3831 (fixed-dose combination of olanzapine plus ALKS 33 (also known as samidorphan))	μ-opioid antagonist plus olanzapine	Phase II	Alkermes
AQW051	Nicotinic acetylcholine receptor subunit-α7 agonist	Phase II	Novartis
Aripiprazole lauroxil (ALKS 9070), a long-acting injectable formulation	Dopamine D2 receptor agonist Serotonin 5-HT_{1A} receptor agonist Serotonin 5-HT_{2A} receptor antagonist	Phase III	Alkermes
AVN-211	Serotonin 5-HT_6 receptor antagonist	Phase II	AVINEURO
Bitopertin (RG-1678; RO-4917838)	Sodium-dependent and chloride-dependent glycine transporter 1 inhibitor	Phase III	Chugai (Roche)
Blonanserin (transdermal patch) DSP-5423P	Dopamine D2 receptor antagonist Serotonin 5-HT_2 receptor antagonist	Phase II	Sumitomo Dainippon Pharma
Brexpiprazole (OPC-34712)	Dopamine D2 receptor (partial) agonist Dopamine D3 receptor (partial) agonist Serotonin 5-HT_{1A} receptor agonist Serotonin 5-HT_{2A} receptor antagonist	Phase III	Otsuka
Cariprazine (RGH-188)	Dopamine D2 receptor (partial) agonist Dopamine D3 receptor (partial) agonist	Pre-registration	Gedeon Richter
Eltoprazine (PGI-256)	Serotonin 5-HT_{1A} receptor (partial) agonist Serotonin 5-HT_{1B} receptor (partial) agonist	Phase II	PsychoGenics
Encenicline hydrochloride (EVP-6124)	Nicotinic acetylcholine receptor subunit-α7 agonist	Phase III	FORUM
GWP-42003	Cannabinoid receptor agonist	Phase II	GW Pharmaceuticals
ITI-007	Serotonin 5-HT_{2A} receptor antagonist Serotonin 5-HT receptor reuptake inhibitor Dopamine D2 receptor (partial) agonist (presynaptic) Dopamine D2 receptor antagonist (postsynaptic)	Phase II	Intra-Cellular Therapies
MT-210 (CYR-101)	Serotonin 5-HT_{2A} receptor antagonist Sigma-2 receptor antagonist	Phase II	Mitsubishi Tanable Pharma
Neboglamine (XY-2401; nebostinel)	Glycine NMDA-associated agonist Adrenergic transmitter uptake inhibitor	Phase II	Rottapharm Madaus
OMS-824	PDE10 inhibitor	Phase II	Omeros
PF-2545920 (MP-10) is the lead in a series of PDE10 (PDE XA) inhibitors	PDE10 inhibitor	Phase II	Pfizer
Pimavanserin tartrate (ACP-103)	Serotonin 5-HT_{2A} receptor (inverse) agonist	Phase II	ACADIA
PNB-02 (fixed-dose combination: pipamperone plus risperidone)	Serotonin 5-HT_{2A} receptor antagonist Dopamine D2 receptor antagonist Dopamine D4 receptor antagonist α-adrenergic antagonist	Phase II	PharmaNeuroBoost
Risperidone RBP-7000 (sustained-release formulation)	Serotonin 5-HT_{2A} receptor antagonist Dopamine D2 receptor antagonist	Phase III	Reckitt Benckiser
Risperidone-ISM (using *in situ* microparticle)	Serotonin 5-HT_{2A} receptor antagonist Dopamine D2 receptor antagonist	Phase II	Rovi Pharmaceuticals

Table 3 (Cont.) | **Drugs in Phase II and Phase III development for schizophrenia**

Compound	Receptor or mechanism of action	Stage of development	Company
RP-5063 (RP-5000)	Dopamine D2 receptor (partial) agonist Dopamine D3 receptor (partial) agonist Dopamine D4 receptor (partial) agonist Serotonin 5-HT_{1A} receptor (partial) agonist Serotonin 5-HT_{2A} receptor (partial) agonist Serotonin 5 -HT_{6} receptor antagonist Serotonin 5-HT_{7} receptor antagonist	Phase II	Reviva Pharmaceuticals
SAM-101 (combination of minocycline and antipsychotic drugs)	Protein 30S ribosomal subunit inhibitor	Phase II	XTL Biopharmaceuticals
Zicronapine (LU-31-130)	Serotonin 5-HT_{2A} receptor antagonist Serotonin 5-HT_{2c} receptor antagonist Dopamine D1 receptor antagonist Dopamine D2 receptor antagonist	Phase III	Lundbeck

5-HT, 5-hydroxytryptamine; NMDA, *N*-methyl-D-aspartate; PDE, phosphodiesterase. Adapted with permission from REF. 153, Taylor and Francis.

rehabilitation improves functioning relative to psychiatric rehabilitation alone[206]. Similarly, social cognitive training has been shown to improve social behaviour and functioning with medium effect sizes[208].

Pharmacological treatments in development

TABLE 3 summarizes current medications that are in Phase II and Phase III development for the treatment of different illness domains in schizophrenia. In addition to the development of new antidopaminergic agents, other mechanisms of action continue to be explored, including the serotonergic, glutamatergic, cholinergic, phosphodiesterase, cannabinoidergic and opioidergic systems[153].

Quality of life

As mentioned earlier, the course of schizophrenia is characterized by widespread variation[209]. In follow-up studies of patients with first-episode psychosis, in which outcome categories were described as 'good' or 'poor', good outcomes were reported in 42% and poor outcomes in 27% of cases[210], and the remainder of cases fell into the 'intermediate' category. Although 'well-being' and 'QOL' are measured in many different ways across different studies[211,212], some patterns in how to evaluate these have emerged (TABLE 4). QOL of patients with a diagnosis of schizophrenia is negatively affected by negative stereotyping, resulting in public and internalized stigma[213], poor physical health and adverse effects of medication[214], a predominant 'acute care' model of treatment that does little to manage patients unless they are acutely ill[215], unmet needs for care[215], persistent low mood[211,212,216] and treatment resistance[217].

Stigmatization refers to a set of negative attitudes that has its basis in stereotypes in the form of incorrect beliefs and fears about the diagnosis of schizophrenia. Exposure to stigma might result in internalized stigma, in which the patient internalizes social myths and negative expectations. There is some evidence that interventions targeting public stigma can reduce prejudice[218,219]. Internet-based programmes might be as effective in reducing public stigma as face-to-face delivery methods. However, there is no evidence that such interventions are effective in reducing internalized stigma[218,219].

Although more research is required, resource-oriented or strength-oriented models of care, with a focus on positive qualities or assets rather than deficits, and using social relationships to induce therapeutic change[220] might offer advantages in terms of QOL[221–224], as could care models with a focus on employment[225]. Resource-oriented or strength-oriented models of care recognize the need for the integration of social recovery and personal recovery goals with the traditional focus on symptomatic recovery of deficit-based care models. Personal recovery — in the sense of living a satisfying, hopeful and contributing life — beyond the psychiatric diagnosis, even with continuing limitations caused by the illness, has been widely accepted as the guiding principle of 'recovery-oriented' mental health services. However, in practice, this might be difficult to implement[215].

People with schizophrenia have a life expectancy of approximately 20 years below that of the general population[2]. The contribution to the reduction of life expectancy by medical conditions, particularly diabetes, cardiovascular disease, chronic obstructive pulmonary disease and cancer, is much greater than the contribution by accidents, suicide and homicide. Assessment and treatment of common physical and dental health problems in people with schizophrenia fall well below acceptable standards, and this negatively affects QOL[216,226,227]. Although there is much pressure on services to provide general physical health advice to people with schizophrenia, research on the effects of this intervention remains inconclusive[228]. However, there is evidence that interventions aimed at reducing medication-related weight gain can be successful in improving QOL[229].

Outlook

Predicting the future is a fool's errand, especially in a scientific area that is moving so quickly, as demonstrated in the previous sections of this Primer. Nevertheless, we can identify some current trends that might serve as a foundation for progress and suggest some likely outcomes.

We begin by recalling that, when the term schizophrenia was first introduced in 1911, Bleuler wrote of the "group of schizophrenias" (REF. 230). He used the term to cover a range of disorders rather than a single form of pathology. Although this insight was largely forgotten over the past century, recent research suggests that there might indeed be many forms of schizophrenia that all share a few common features but result from different genetic or neurobiological mechanisms[231]. Diagnosis based on presenting symptoms alone will not identify these subtypes; biological measures will be essential to define the taxonomy of the schizophrenias. Precision medicine, a diagnostic approach that includes the '-omics', is transforming diagnosis in oncology by dividing cancers into separate diseases requiring different treatments. For schizophrenia, precision medicine will probably depend on data from cognitive science and social science, as well as genomics, transcriptomics and connectomics[232].

In this era of precision medicine, it has become popular to claim that better diagnostics are the pathway to better therapeutics and better outcomes. For schizophrenia that might depend not only on the incorporation of biomarkers and cognitive assessments but also on the conceptual shift to view the schizophrenias as neurodevelopmental disorders with trajectories that can be divided into four stages[233] (TABLE 5). Each of these has been described above, but going forward we can begin to define them as discrete stages that require different interventions. Although most of our research and practice has heretofore focused on stage 4 (the residual phase of the disorder), there is increasing interest in stage 3 (the progressive phase), which is marked by the onset of psychosis. Results from several recent projects support the suggestion that comprehensive interventions delivered with a patient-centred focus might improve outcomes if delivered early after the onset of the first episode of psychosis, potentially pre-empting stage 4 (REFS 1–3,234–236).

Even more transformative is the idea of pre-empting the psychosis stage by detecting and intervening during stage 2 (the prodromal or CHR state). Studies in Australia, Europe, Canada and the United States have identified factors that greatly improve the prediction of developing psychosis in patients who are prodromal and at high risk for schizophrenia. As noted above, combinations of symptoms and demographic factors achieve high positive predictive power and specificity, such as in the 70–80% range, but low sensitivity in the 10–30% range[111]. Multivariate approaches that combine physiology and symptoms show high predictive value, which is in the range of prediction of dementia or myocardial infarction[4,237].

Can we pre-empt psychosis in those at high risk? Not yet[126]. However, clearly, this will be one of the promising opportunities for progress in the next few years. Progress might not require an innovative drug; targeting cognitive

Table 4 | **Factors that affect quality of life**

Type of effect	Factors and approaches	Description
Negative effect on quality of life	Public stigma	The great majority of patients struggle with the consequences of negative stereotyping and the resulting factors of exclusion from work, study, housing and relationships[213,215]
	Internalized stigma	The tendency to internalize negative stereotypes is embedded in language, as schizophrenia translates as a 'devastating brain disorder' (REF. 97) that is 'totally disabling' (REF. 247)
	Poor physical and dental health and adverse effects associated with medication	Schizophrenia often co-occurs with advanced dental disease and chronic medical illnesses, especially cardiovascular disease and diabetes. Adverse effects of antipsychotic medications contribute to these co-morbidities. Co-morbidities are associated with a more-severe course of mental illness, reduced quality of life and premature mortality[214,216,227]
	Sick care model of treatment	Models of care in most countries are deficit based rather than resource based. Deficit-based models are characterized by a persistent focus on symptom stabilization using medication, resulting in unmet needs for care in the areas of social and personal recovery
	Depression and treatment resistance	Depressive symptoms co-vary with and impact on quality-of-life measures, more than other symptom dimensions[212]; general treatment resistance is associated with 20% lower quality of life[217]
Positive effect on quality of life	Resource-oriented model of treatment	These are therapeutic models that emphasize working with the personal and social resources and strengths of the patient rather than a monistic focus on symptom reduction and remediation of hypothesized deficits. These models can include interventions such as open dialogue, positive psychotherapy, therapeutic communities, peer support workers, solution-focused therapy, self-help groups and systemic family therapy. The models share a focus on social relationships as a key resource, comprising the broad array of relationships with peers, friends, professionals and family
	Reduction of stigma and discrimination	Research indicates that the work of reducing stigma and discrimination can include various modules, such as media campaigns, education, having contact with people with mental illness, training, or various combinations of these strategies. There is a need for scientific evaluation of the effectiveness of such programmes and the underlying mechanisms to improve impact. Much less is known about stigma resilience and the reduction of internalized stigma
	Integration of symptomatic recovery with social and personal recovery care approaches	The traditional focus on symptomatic recovery is limited as quality of life is contingent on recovery in terms of studies, daytime activities, housing and relationships (social recovery), and particularly in the perspective of having a meaningful and fulfilling life, in the face of continuing vulnerability and impairments, beyond the psychiatric diagnosis (personal recovery)

Table 5 | **Stages of schizophrenia and associated features**

Stage	Description	Features	Diagnostic needs	Requirements for improved outcomes
1	Risk	• Genetic and environmental risk • Asymptomatic	Genomic risk score	Public health measures
2	Prodrome	• Cognitive and social deficits • Help seeking	Predictive biomarkers	Safe and effective pre-emption
3	Acute psychosis	• Relapse and remitting • Suicide risk	Deconstruction of psychosis into multiple syndromes	Toolkit of medical and psychosocial interventions
4	Chronic psychosis	• Medical complications • Disability	Rehabilitation and treatment of co-morbidities	Detection of co-morbid conditions

skills through cognitive remediation or altering the trajectory of brain development associated with the onset of psychosis through emerging neurotechnologies, such as brain circuit stimulation techniques, might prove effective. Indeed, early results with cognitive interventions are promising[126]. Even if these interventions do not prevent stage 3, if they could forestall psychosis by a few years — permitting young adults to finish their education and acquire life skills — the public health impact would be considerable. It is important to realize that many adolescents who appear to be at high risk of schizophrenia and who do not develop psychosis have less than optimal outcomes[238]. As such, improving the outlook for this high-risk group will ultimately have to do more than prevent psychosis.

What is the outlook for pre-empting stage 2? Before developing the prodrome, in which symptoms are already at a level to prompt needing treatment, stage 1 is the period of asymptomatic risk. Genomics could presumably define some fraction of children who are at risk based on common or rare variants identified by sequencing. Although the polygenic risk score, as we know it today, can identify as much as a 20-fold increase in risk between those with the highest and lowest scores (corresponding to a 4–5-fold increase over the population mean), we do not have a genomic or environmental predictive biomarker that can be used clinically to identify individual risk within the general population[48]. The effect of labelling a healthy child as being 'high risk' needs careful consideration, especially in the absence of interventions that will reduce risk.

There can be little doubt that scientific progress in genomics and neuroscience will provide new insights into the fundamental biology of the schizophrenias. As we define the molecular, cellular and systems levels of pathology in schizophrenia, there will be many surprises and, no doubt, many of our current theories will prove overly simplistic or wrong. How much any of these discoveries will change the outlook for people with schizophrenia remains to be seen. What is paradoxically most distressing and most helpful in forecasting the future is the realization that outcomes could be much better today if we simply apply what we know already in clinical settings.

Over the past three decades, a generation of research has shown the powerful effects of psychosocial interventions for facilitating recovery in people with schizophrenia. Supported employment or supported education, family psycho-education, cognitive remediation and assertive community treatment have all been shown to improve outcomes, yet they are in short supply in both the developing and the developed world[239]. Although antipsychotic medication is useful and might be essential for reducing delusions and hallucinations, these symptoms are only a part of the disorder and might not be as disabling as the cognitive and motivational aspects of the disorder — aspects that are not targeted by current antipsychotic medications. A holistic approach to this complex syndrome that combines medication and evidence-based psychosocial treatments can improve outcomes, especially if the treatment plan engages the patient as a collaborator. Thus, although predicting the future for schizophrenia research is not straightforward, there can be little doubt that we could make progress in the immediate future if we close the unconscionable gap between what we know from research and what we deliver in practice. If we are to improve outcomes going forward, closing this gap must be among our highest priorities.

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Introduction (R.S.K. and I.E.S.); Epidemiology (R.M.M.); Mechanisms/pathophysiology (A.M.-L. and D.R.W.); Diagnosis, screening and prevention (M.O.D. and T.D.C.); Management (C.U.C. and J.M.K.); Quality of life (J.v.O.); Outlook (T.R.I.); Overview of Primer (R.S.K.).

Competing interests
J.M.K. has received honoraria for lectures and/or consulting from Alkermes, Bristol-Myers Squibb, Eli Lilly, Forest Laboratories, FORUM Pharmaceuticals, Genentech, Intra-Cellular Therapies, Janssen, Johnson and Johnson, Lundbeck, Merck, Novartis, Otsuka, Pfizer, Reviva Pharmaceuticals, Roche and Sunovion Pharmaceuticals. He has received grant support from Genentech, Johnson and Johnson and Otsuka. He is a shareholder of MedAvante and the Vanguard Research Group. T.D.C. is a consultant to the Los Angeles County Department of Mental Health and Boehringer Ingelheim and is a co-inventor on a pending patent for a blood-based predictive biomarker for psychosis. C.U.C. has been a consultant and/or adviser to, or has received honoraria from AbbVie, Actavis, Alkermes, Bristol-Myers Squibb, Eli Lilly, Genentech, the Gerson Lehrman Group, Intra-Cellular Therapies, Janssen Pharmaceuticals, Johnson and Johnson, Lundbeck, MedAvante, Medscape, Otsuka, Pfizer, ProPhase, Reviva Pharmaceuticals, Roche, Sunovion Pharmaceuticals, Supernus Pharmaceuticals and Takeda. He has received grant support from Bristol-Myers Squibb, Otsuka and Takeda. A.M.-L. is a consultant for AstraZeneca, Elsevier, F. Hoffmann-La Roche, the Gerson Lehrman Group, Lundbeck, Outcome Europe Sàrl, Outcome Sciences, Roche Pharma, Servier International and Thieme Verlag. He has held lectures that included the receipt of travel fees for Abbott, AstraZeneca, Aula Médica Congresos, BASF, Groupo Ferrer International, Janssen-Cilag, Lilly Deutschland, LVR Klinikum Düsseldorf, Servier Deutschland and Otsuka. He holds grants from Hans-Jörg Weitbrecht Award, European College of Neuropsychopharmacology (ECNP) Neuropsychopharmacology Award and Prix ROGER DE SPOELBERCH. R.S.K. has served as a member of the Data Safety Monitoring Board (DSMB) for Janssen-Cilag, Otsuka and Sunovion Pharmaceuticals, been consultant to Forrest, Gedeon Richter, FORUM Pharamaceuticals and Roche, and has received speaking fees from AstraZeneca, Eli Lilly and Lundbeck. M.O.D. has received a consultancy fee from Roche. R.M.M. has received honoraria for lectures from Janssen, Lundbeck, Otsuka and Roche. I.E.S., T.R.I., D.R.W. and J.v.O. declare no competing interests.