Schizophrenia

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Schizophrenia, characterised by psychotic symptoms and in many cases social and occupational decline, remains an aetiological and therapeutic challenge. Contrary to popular belief, the disorder is modestly more common in men than in women. Nor is the outcome uniformly poor. A division of symptoms into positive, negative, and disorganisation syndromes is supported by factor analysis. Catatonic symptoms are not specific to schizophrenia and so-called first rank symptoms are no longer considered diagnostically important. Cognitive impairment is now recognised as a further clinical feature of the disorder. Lateral ventricular enlargement and brain volume reductions of around 2% are established findings. Brain functional changes occur in different subregions of the frontal cortex and might ultimately be understandable in terms of disturbed interaction among large-scale brain networks. Neurochemical disturbance, involving dopamine function and glutamatergic N-methyl-D-aspartate receptor function, is supported by indirect and direct evidence. The genetic contribution to schizophrenia is now recognised to be largely polygenic. Birth and early life factors also have an important aetiological role. The mainstay of treatment remains dopamine receptor-blocking drugs; a psychological intervention, cognitive behavioural therapy, has relatively small effects on symptoms. The idea that schizophrenia is better regarded as the extreme end of a continuum of psychotic symptoms is currently influential. Other areas of debate include cannabis and childhood adversity as causative factors, whether there is progressive brain change after onset, and the long-term success of early intervention initiatives.

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Introduction

Schizophrenia is regarded, with good reason, as being one of the most serious of all psychiatric illnesses. Many people who develop the disorder do not make a full recovery, and even among those who have good outcomes, the diagnosis has life-changing consequences, including but not limited to social isolation, stigma, and reduced prospects of finding a partner. Unemployment rates run at between 70% and 90% in Europe[1] and are similar, though with more variability, in the USA.[2] Poor dietary habits, weight gain, smoking, and comorbid substance use all act to reduce life expectancy by 13–15 years.[3] The most reliable estimates suggest a suicide rate of around 5%.[4]

Epidemiology

The traditionally quoted statistics for schizophrenia are that one in a hundred people will develop it in their lifetime and that both sexes are affected equally. The idea that the disorder affects one in a hundred people continues to be broadly supported: a systematic review[5] reported a mean lifetime morbid risk of 11·9 per 1000, with a median (which the authors considered to provide a better estimate) of 7·2 per 1000. However, the view that men and women are equally susceptible is no longer supported: evidence from a meta-analysis suggests a modestly higher frequency in men (male-to-female incidence rate ratio of 1·70 [95% CI 1·46–1·97]).[6]

Schizophrenia typically develops in early adult life. Pooled evidence from 15 English studies[7] indicates that incidence peaks in the early twenties in men and declines steadily thereafter (figure 1). In women, the peak is less sharp and the decline less steep, and from the mid-forties to late forties onwards new cases in women outnumber those in men. Figure 1 provides only limited support for the widely held view that there is a second peak of onset in women in later life.[8]

Schizophrenia can appear for the first time in adolescence (figure 1). Occurrence of the disorder in childhood—ie, before the age of 13 years—is also well documented but is unusual: evidence from the world's largest series of childhood-onset cases suggests an approximate population frequency of 1 in 40 000.[9] The mean age of onset in this series was 10 years, ranging down to 4 years, and sex differences were not conspicuous.[10]

Contradicting a leading view in the 1960s and 1970s, which maintained that schizophrenia was not an illness but a sociopolitical construct, a large WHO study in 1973 involving 811 participants[11] showed that the disorder occurred in all of nine countries with varying cultures and political systems. Some relatively minor differences in rates across countries were interpreted at the time as reflecting differences in broadly defined forms of the disorder, with the so-called nuclear form showing relatively little variation.[12] This conclusion now appears untenable: a meta-analysis of studies conducted between 1965 and 2002[5] found a five-fold variation in

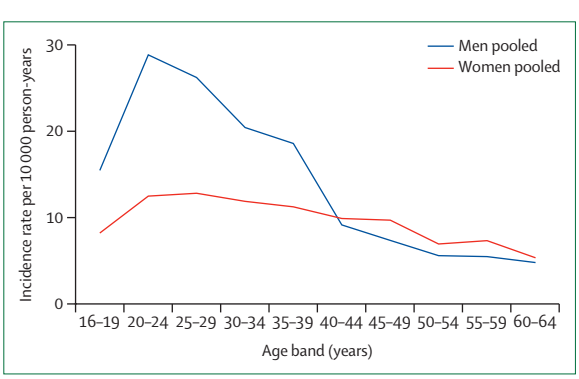

Figure 1: **Pooled incidence of schizophrenia by age and sex in England, 1950–2009**
Adapted from Kirkbride and colleagues.[7]

incidence rates, with higher rates of schizophrenia associated with migrant status and urban living. The association of increased schizophrenia incidence with migrant status has been amply supported by other studies;[13] in England, it is particularly marked in people of Black-Caribbean and Black-African ethnicity.[14] However, the generalisability of the association with urban living has been questioned.[15,16]

Clinical features

Leaving aside a period in the USA after World War 2, when the concept of schizophrenia was broadened to the point of near meaninglessness, clinicians have always recognised a largely similar set of clinical features as constituting the disorder.[17] These include positive symptoms, also known as psychosis or the psychotic syndrome (ie, delusions, hallucinations, and formal thought disorder [speech that is difficult to follow, sometimes to the point of incomprehensibility]), and negative symptoms, which consist of lack of volition, reduced speech output, and flattening of affect (ie, decreased expression of emotions). The positive–negative distinction is a slight misnomer given that the symptoms of schizophrenia have been found, using factor analysis, to segregate into three groupings: reality distortion (delusions and hallucinations), disorganisation (formal thought disorder, disorganised behaviour, and the uncommon symptom of inappropriate affect), and negative symptoms or the so-called clinical poverty syndrome.[18] Though occasionally disputed,[19] this tripartite division has been reported in many studies[20] and is supported by meta-analysis.[21,22]

Catatonia is another recognised feature of schizophrenia. The catatonic syndrome includes stereotypies (repetitive non-goal-directed movements and gestures) and mannerisms (goal-directed movements that are executed in an idiosyncratic way, often affecting gait), as well as a host of other abnormal motor behaviours that often occur against a background of stupor or excitement. For unknown reasons, catatonic presentations of schizophrenia have become uncommon, especially in high-income countries;[23] nevertheless, being seen in just under 10% of cases, their frequency is still appreciable.[24] Originally considered characteristic of schizophrenia, catatonia is now also recognised in patients with major affective disorder, in autistic people, and in patients with a range of neurological and medical conditions.[25,26] For this reason, catatonia has been relegated to the status of a so-called specifier for several disorders in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), the latest edition of the diagnostic manual published by the American Psychiatric Association.[23,26]

In the past, great importance was attached to the so-called first rank symptoms of schizophrenia, first described by the German psychiatrist Kurt Schneider,[27] and argued by him to be pathognomonic of the disorder. Among other things, first rank symptoms include auditory hallucinations referring to the patient in the third person, subjective changes in the ownership of thinking (thought insertion, thought withdrawal, and thought broadcasting), and passivity—the experience that one's actions, bodily sensations, or emotions are controlled by outside forces. The nature of these apparently unique symptoms of schizophrenia has given rise to much theorising that distorted or anomalous self-experience might be the psychological core of the disorder.[28] Whether this view is correct or not, studies over the years have moved to diminish the diagnostic specificity of first rank symptoms, chiefly by providing evidence that they can also be observed in psychotic forms of major affective disorder. As a result, first rank symptoms no longer form part of the DSM-5 criteria for schizophrenia.[29] This rejection might be premature—a 2015 Cochrane review[30] reported that first rank symptoms correctly identified people with schizophrenia 75–95% of the time.

A recent addition to the set of clinical features of schizophrenia is cognitive impairment. Although minimised by Kraepelin,[31] the psychiatrist who described the disorder, and denied vigorously by Bleuler,[32] who gave it its name, it is now universally accepted that patients commonly show poor performance on tests of executive (frontal) function, long-term memory, and sustained attention, as well as a variable degree of general intellectual impairment (panel 1, figure 2).

Course and outcome

Most individuals who develop schizophrenia—73% according to one large study[50]—show prodromal symptoms. These symptoms might last from as little as a week to several years, though the median duration appears to be slightly under 12 months.[51] The prodromal symptoms themselves are ill-defined and heterogeneous, ranging from indefinable feelings of inner change, through to the development of new interests (eg, in philosophical and spiritual matters), to anger, irritability, anxiety, and depression, and to social withdrawal and deterioration in role functioning.[51,52] Recent initiatives aimed at identifying (and treating) individuals who are at high risk of developing schizophrenia have also highlighted the occurrence of brief, limited intermittent psychotic symptoms (also known as BLIPS) lasting a few days.[53,54]

When frank psychotic symptoms appear, they are often initially episodic (something that was observed even in the days before treatment). Symptoms might remain episodic, or alternatively might become persistent, forming the presentation of chronic schizophrenia. Negative symptoms also tend to be substantial in chronic schizophrenia, and they make an important contribution to the poor social and occupational functioning observed in the disorder.[55]

Despite initial pessimistic views—Bleuler,[32] for example, considered that full recovery never took place—many patients with schizophrenia now have a favourable

outcome. Two meta-analyses conducted in 1994[56] and 2006,[57] which used different inclusion criteria, both reported "improved" or "good" outcomes in 40% and 42% of patients, respectively. However, complete recovery appears to be less frequent: a third meta-analysis[58] reported that only 13·5% (IQR 8·1–20·0) of patients met strict criteria for recovery, requiring the presence of at most mild symptoms and good social functioning, with at least one of these lasting at least 2 years.

Causes

Biology versus psychology

In the words of one researcher, "[i]t would be difficult to find many medical conditions that have been investigated with similar vigour and persistence over a century and have proved to be as intractable to understanding as schizophrenia."[59] Kraepelin was convinced that the disorder was a brain disease and established a laboratory to identify its underlying neuropathology (unsuccessfully, though the effort was not entirely wasted, as Alzheimer discovered his eponymous disease while working there[60]). By contrast, Bleuler was in favour of a role for both biological and psychological factors.[32] As psychoanalysis became an increasing force in 20th century psychiatry, the dominant explanatory framework became one emphasising individual and family psychodynamic factors, particularly in the USA[61] and, to a lesser extent, all over the world.

The brain in schizophrenia

Thinking about schizophrenia was revolutionised in 1976 when, using one of the world's first CT scanners, Johnstone and co-workers[62] found lateral ventricular enlargement in a group of 17 patients who were hospitalised for the long term. 45 years on, structural brain imaging in schizophrenia is a thriving industry: over 300 MRI studies have confirmed the finding of lateral ventricular enlargement; this enlargement is of the order of 25% by volume and is accompanied by a reduction in brain volume of around 2%.[63] Brain volume reduction affects grey matter more than white matter, and particularly involves the frontal lobe (mean weighted effect size Cohen's d –0·49 [95% CI –0·64 to –0·34]), the temporal lobe (–0·43 [–0·60 to –0·26]), and the hippocampus (–0·52 [–0·60 to –0·44]); reductions are smaller in the parietal cortex (–0·31 [–0·54 to –0·08]) and occipital cortex (–0·22 [–0·37 to –0·07]).[63] These findings have been substantially corroborated in studies using automated structural imaging techniques, such as cortical thickness analysis.[64,65]

Presence of brain functional abnormality in schizophrenia is also established beyond reasonable doubt. The original functional imaging finding was hypofrontality (reduced activity in the prefrontal cortex), especially its dorsolateral prefrontal division, which was initially reported at rest[66,67] and later during performance of a prototypical executive task, the Wisconsin Card Sorting Test.[68] Despite subsequent studies having conflicting findings, meta-analyses have provided clear support for both resting and activation hypofrontality.[69,70]

Panel 1: Cognitive impairment—part of the clinical picture of schizophrenia

Even as early views of schizophrenia as a disorder that did not compromise intellectual function developed into dogma, studies from the 1930s and onwards were finding that patients performed more poorly than healthy individuals on a wide range of tests of cognitive function. By the end of the 1970s, this evidence had become impossible to ignore,[33] and an influential 1998 meta-analysis later established the presence of cognitive impairment in the disorder beyond all doubt.[34]

Schizophrenic cognitive impairment varies greatly in degree. There is no doubt that some patients remain neurocognitively normal or near-normal,[35,36] and it is perfectly possible to have schizophrenia in the context of superior intellectual ability.[37] At the other end of the spectrum, some severely ill patients with schizophrenia who are hospitalised for the long term perform poorly on simple bedside tests of orientation, memory, and general knowledge.[38] Deficits are observed in all domains of neuropsychological function, but as shown in figure 2, deficits in executive function, memory, and sustained attention appear to be particularly marked.[39,40] A proposal that all neuropsychological deficits in schizophrenia can be attributed to a primary slowing of processing speed[41] now appears to be unlikely.[42]

Cognitive impairment in schizophrenia follows a different trajectory from the other features of the disorder. As a group, individuals who are destined to develop schizophrenia show a lifelong IQ disadvantage of around 7–8 points (ie, half a standard deviation).[43] There is no compelling support for the view that IQ decreases progressively in the years leading up to illness onset,[44,45] but evidence for a more abrupt cognitive decline in the months before psychotic symptoms appear has been found.[46] Thereafter, cognitive function remains stable, at least until late life.[39]

States of severe cognitive impairment observed in a minority of long-term hospitalised patients with schizophrenia begin to increase in prevalence from the age of 65 years,[47] a finding which is now coupled with increasing evidence for an increased rate of senile dementia in the disorder as a whole.[48] The reason for this occurrence is unknown: post-mortem studies have revealed no excess of Alzheimer's disease or other dementing disorders in older patients with schizophrenia,[49] although no new studies of this type have been carried out for over 20 years.

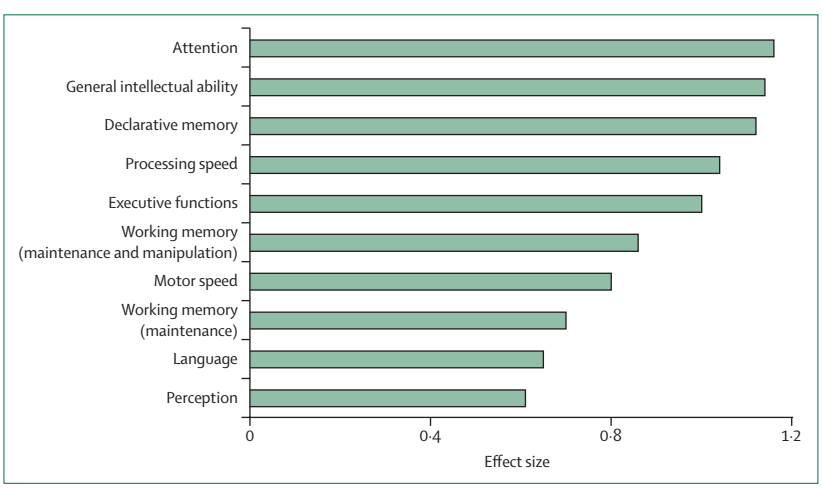

Figure 2: **Median effect sizes for impairments in different domains of neuropsychological function in schizophrenia, based on a range of meta-analyses**
Adapted from reference 40, by permission of Reichenberg and colleagues.

Panel 2: Brain networks and schizophrenia*

Since 2001, it has been recognised that a series of brain regions tend to de-activate rather than activate during performance of a wide range of attention-demanding tasks. These brain regions are collectively termed the default mode network,[86,87] or the task-negative network.[88] This network also activates in response to a small number of tasks, whose common feature appears to be the involvement of internally oriented, non-stimulus-directed thought (eg, recall of autobiographical memories, imagining the future, and theory of mind processes).[89,90] Regions that activate during performance of conventional attention-demanding tasks are more variable, but show some general similarities and have been referred to as the task-positive network (figure 3). Both the default mode and task-positive networks are also characterised by their high resting state within-network connectivity (spontaneous fluctuations in the functional MRI blood oxygenation level-dependent signal) and negative correlations between the two.[91,92]

In 2007, based on resting-state functional connectivity analysis in healthy people, Seeley and colleagues[93] argued for the existence of a third network (or perhaps a subdivision within the task positive network) comprising the anterior insula, the dorsal anterior cingulate cortex, and the amygdala, substantia nigra, ventral tegmental area, and thalamus. The authors[93,94] used the term salience network to describe this set of brain regions, and hypothesised that the network functions to identify the most relevant among competing internal and external stimuli for goal-directed behaviour.

Functional connectivity is currently a highly researched topic in schizophrenia, with studies finding evidence for both reduced and increased connectivity in the default mode network and in the task-positive network.[95] The possibility that there is a disturbed interaction between the two networks is also of considerable interest; for example, the concept of impaired ability to switch between externally and internally directed thought (also known as toggling) could have potential for explaining positive symptoms, and the salience network has an obvious application to the self-referential thinking observed in schizophrenia. However, findings to date are contradictory, identifying increased, decreased, and unaltered anticorrelations in the disorder.[96]

*Based on Blumenfeld, with additional text.[88]

Brain functional abnormality in schizophrenia does not take the form solely of hypofunction. From 2000 onwards, some studies also began to document evidence of increased, rather than decreased, frontal activation during performance of cognitive tasks.[70–73] This "hyperfrontality" has been reported principally in parts of the medial frontal cortex, but also includes some lateral prefrontal regions.[70] A more recent wave of studies has also documented a third functional imaging abnormality—failure of deactivation in the medial frontal cortex during cognitive task performance.[74–80] Occasional negative findings[81,82] or reports of increased deactivation[81–84] have not prevented failure of medial frontal cortex deactivation from becoming well accepted.

Failure of deactivation could account for the otherwise perplexing finding of simultaneous hypofrontality and hyperfrontality in schizophrenia (the subtractive designs typically used in functional MRI studies mean that both hyperactivation and reduced deactivation will have the same appearance[85]). More importantly, the medial frontal cortex is a key region of the so-called default mode network,[85,86] a set of brain regions that are active at rest but de-activate during performance of a wide range of attention-demanding tasks. Accordingly, the possibility now exists that schizophrenia ultimately reflects a disturbance of the interaction between task-positive networks (one of which, the executive or cognitive control network, includes the lateral prefrontal cortex) and the task-negative or default mode network (panel 2, figure 3).

Schizophrenia—a neurochemical disorder?

Given that schizophrenia tends to be a disorder of relapses and remissions that responds to drug treatment, it has long been considered that at least some of its clinical manifestations might reflect an underlying neurochemical disturbance. Two neurotransmitters have emerged as the leading contenders for such a pathology. One is dopamine, which, in addition to its well known effects on motor function, is also involved in learning; specifically, this neurotransmitter codes a reward prediction error signal.[97] The other candidate is glutamate, the brain's main excitatory neurotransmitter.

Dopamine

The origins of the dopamine hypothesis date back more than 50 years to two complementary findings: first, that the therapeutic effect of antipsychotic drugs depends on their ability to reduce dopamine function by blocking the dopamine D_2 family of postsynaptic receptors;[98–101] and second, that abuse of amphetamine (which stimulates dopamine release among other actions) can produce a state indistinguishable from schizophrenia.[102] The initial version of the theory implicated increased postsynaptic dopamine D_2 receptor binding as the probable cause of the functional dopamine excess, based on post-mortem findings.[103] However, this theory was discredited when neurochemical imaging studies using radiolabelled dopamine receptor ligands overwhelmingly showed no evidence of increases in D_2 receptor numbers in living, drug-naive patients.[104] Drug naivety is important because antipsychotic drug treatment itself is known to induce increases in post-synaptic D_2 receptor numbers.

Subsequent versions of the dopamine hypothesis have had more success. One finding has been increased amphetamine-stimulated synaptic release of dopamine

in antipsychotic-free (and in some cases antipsychotic-naive) patients with schizophrenia. Currently four studies are in support of this proposal[105–108] and there is one study with negative findings.[109] In 2009, Howes and colleagues[110] reported increased dopamine synthesis capacity in individuals with prodromal symptoms of schizophrenia; investigating individuals with prodromal symptoms of schizophrenia avoids issues associated with previous drug treatment. The finding of increased dopamine synthesis capacity in prodromal schizophrenia has been replicated in a second cohort,[111] although a third study did not support the finding.[112] A 2018 meta-analysis of 14 studies[113] has also supported increased dopamine synthesis capacity in patients with established schizophrenia, with an effect size of 0·52 (95% CI 0·21–0·83). Studies on drug-free or drug-naive patients with established schizophrenia have also found evidence of increased dopamine synthesis capacity,[114–116] although two recent studies are not fully supportive.[117,118]

Glutamate

The glutamate hypothesis of schizophrenia[119,120] emerged largely as a result of the observation that individuals who took the anaesthetic drug phencyclidine recreationally were prone to develop florid and sometimes prolonged psychotic states. Later, it was shown that phencyclidine's main pharmacological action is to block the N-methyl-D-aspartate (NMDA) receptor, one of the two main classes of glutamatergic postsynaptic receptor, leading to the concept of altered glutamate function in schizophrenia, this time a deficiency rather an excess.

Post-mortem studies have not provided clear evidence for alterations in NMDA receptor numbers in schizophrenia,[121,122] although there might be an exception in the dorsolateral prefrontal cortex.[121] Support for the glutamate hypothesis instead comes mainly from studies that have administered the phencyclidine-like drug, ketamine, to healthy volunteers. Giving this drug reliably results in increased scoring on rating scales for positive and negative symptoms,[123] as well as a pattern of cognitive impairment that appears on rather limited evidence to be similar to that observed in schizophrenia.[124] Notably, the ketamine experience does not closely mimic schizophrenia—its main effects are heightened, dulled, and distorted perception in different sensory modalities[125]—but psychosis-like referential ideas occur in approximately half of individuals.[125,126] On the other hand, auditory hallucinations appear to be uncommon and minor.[127]

Schizophrenia and development

One of the biggest success stories in contemporary schizophrenia research has been confirmation of the long-held suspicion[128,129] that the causes of the disorder involve events in early life, at birth, or even in utero. This "neurodevelopmental" theory is strongly supported by

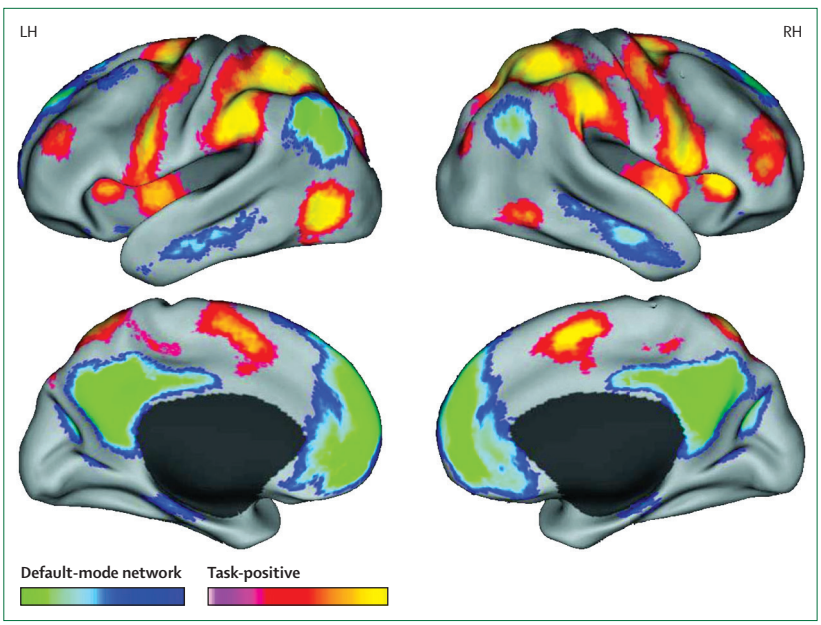

Figure 3: **Task-positive and default-mode (task-negative) networks by resting functional connectivity analysis**
Adapted from Fox and colleagues.[91] The default-mode network (cool colours) includes the following cortical regions bilaterally: precuneus and posterior cingulate gyrus, posterior inferior parietal lobule (angular gyrus), ventral anterior medial frontal cortex, middle temporal gyrus, and medial temporal cortex and the hippocampus. The task-positive network (warm colours) includes the anterior insula and frontal operculum, supplementary motor and dorsal medial frontal cortex, lateral premotor cortex (includes frontal eye fields), anterior middle frontal gyrus, superior parietal lobule and anterior inferior parietal lobule, and the lateral inferior posterior temporal gyrus (lateral area 37). Copyright (2005) National Academy of Sciences. LH=left hemisphere. RH=right hemisphere.

birth cohort studies, a series of large systematic follow-ups of babies (eg, all those born in a single week of 1 year) that began to be undertaken from the 1940s onwards.[130] The children in such studies are typically assessed on a wide range of physical and psychological measures at regular intervals, with assessments then often continuing into adult life (members of the first British cohort from 1946 are still being followed up 75 years later). In the early 1990s, several groups of investigators[131–133] realised that, by identifying the approximate 1% of these cohort members who went on to develop schizophrenia and comparing them with the 99% who did not, early life variables potentially relevant to the disorder could be examined in a robust way that was free of bias (eg, from parental recall).

The birth cohort studies have established the presence of a minor IQ disadvantage in individuals who go on to develop schizophrenia (panel 1).[43] Mild delays in achieving early developmental milestones, speech and language problems, and childhood behavioural deviance are other reliable findings.[43] Whether individuals who develop schizophrenia have experienced a greater number of birth complications than those who do not is more open to debate, but support for an increased frequency of hypoxia-inducing events is strong.[134,135] Other intriguing findings include an increased rate of tremors, tics, spasms and athetoid movements in childhood,[136] and subjective reports of psychotic-like experiences before the age of 11 years.[137]

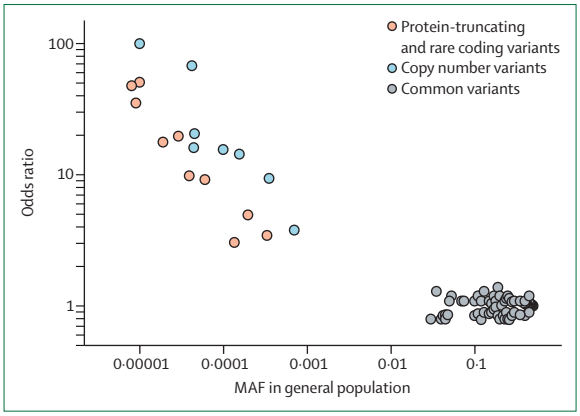

Figure 4: **Genetic studies in schizophrenia**
Odds ratios (y-axis, –log10) and minor allele frequency in the population (MAF, x-axis, –log10) for protein-truncating and rare coding variants,[149] copy number variants,[148] and common variants (single-nucleotide polymorphism)[142] derived from the respective studies. Variants largely separate into either rare copy number variants and ultra-rare protein-truncating variants or into common variants, which have typically been identified in genome-wide association studies. High-risk alleles appear to be removed from the population by selection, as shown by the negative correlation between odds ratio and MAF. MAF= minor allele frequency.

The genetics of schizophrenia

The observation that schizophrenia tends to run in families dates back to the beginning of the 20th century, with studies of monozgotic versus dizygotic twins and the adopted-away offspring of affected mothers, ultimately making it improbable that this clustering could be due to a toxic family environment.[138] Current heritability figures range from 64% in pedigree studies,[139] to 81% in twin studies.[140]

In 2014, the then largest genome-wide association study identified, at a stringent statistical threshold, 108 genetic loci that were associated with schizophrenia.[141] This finding finally established that schizophrenia is a polygenic disorder, representing the cumulative effects of hundreds or possibly thousands of genes (since the identification of these 108 genetic loci in 2014, the number has increased as further large-scale sequencing studies have been reported[142]), each with small effect sizes and dispersed widely across the genome. Genes expressed in the brain, including the dopamine receptor D_2 (*DRD2*) gene and several genes involved in voltage-gated calcium channels and glutamatergic neurotransmission were highlighted in the 2014 study, as were genes expressed outside the CNS that have important roles in immunity, such as B-lymphocyte lineages and the complement pathway.[141]

In addition to common variants, a small number of rare copy number variants[143,144] and gene-disrupting variants, including the so-called rare-coding variants[145–147] and protein-truncating variants, have been identified in schizophrenia. These variants have moderate to large effect sizes (odds ratios [OR] of 2–60-fold and 3–50-fold, respectively).[148,149] Because these variants are so rare and often occur de novo, they do not explain much of the genetic heritability of schizophrenia, although these variants are the strongest individual risk factors identified to date. The relative risks of common risk alleles, copy number variants, as well as rare-coding variants and protein-truncating variants are shown in figure 4. The evidence also suggests that common and rare genetic risk factors at least partially converge on the same underlying neuronal genes important to synaptic organisation, differentiation, and transmission relevant to schizophrenia pathogenesis.[142,149]

Treatment

Antipsychotic drugs

The main, and so far the only, class of drugs of proven effectiveness in schizophrenia work by blocking the D_2 family of postsynaptic dopamine receptors (one potential exception, an investigational drug, SEP-363856,[150] also has dopamine antagonist effects but acts via a different mechanism). A large body of trial evidence supports the conclusion that these drugs reduce symptoms, particularly positive symptoms but also to some extent negative symptoms, and improve social functioning.[151] However, the drugs also have major side-effects, including sedation, weight gain, and particularly the extrapyramidal symptoms of parkinsonism, acute dystonic reactions, akathisia (subjective restlessness), and tardive dyskinesia.[152] Tardive dyskinesia, which takes the form of involuntary movements that develop after months or years of treatment, is of particular concern as it is usually irreversible and can occasionally be life-threatening; for example, when it takes a generalised form or affects swallowing.[152]

The response to antipsychotics is commonly incomplete, and between 20% and 30% of patients are resistant to treatment.[153] For a long time there was little that could be offered to such patients. Then, in a landmark 1988 study, one antipsychotic drug, clozapine, was shown to bring about improvement in approximately 30% of patients who met strict criteria for treatment resistance.[154] Current evidence puts the response rate slightly higher, at 40·1% (95% CI 36·8–43·4). Clozapine's increased effectiveness was questioned in a 2016 meta-analysis,[155] but another meta-analysis published the same year, which pooled data from a slightly different set of studies, continued to support its superiority.[156]

Clozapine is also unusual among antipsychotics in that it does not produce parkinsonism or acute dystonic reactions, even in high doses.[152] Clozapine is also widely considered not to cause tardive dyskinesia—a view which is not fully borne out by the evidence, which instead points to the side-effect occurring with substantially lesser frequency than with other antipsychotics and usually taking a mild form.[157,158] Regular blood monitoring is necessary because of a 3·8% risk of neutropaenia and agranulocytosis (severe in 0·9% of cases; fatal in 0·01% of cases); this type of complication or side-effect mostly occurs in the first 3 months of treatment.[159] Rechallenge

after development of neutropaenia is possible and might be more successful than previously thought.[160]

Like other antipsychotics,[161] clozapine is considered safe to use in pregnancy.[162] However, clozapine is contraindicated during breastfeeding because of the haematological risk in offspring and other side-effects, such as seizures.[162]

In the wake of clozapine several further atypical or second-generation antipsychotics have been developed. Some but not all of these drugs show a modest therapeutic advantage over conventional antipsychotics, but none rival clozapine (figure 5).[163] Some, though again not all, also cause little or no parkinsonism. As a class, second-generation antipsychotics are associated with a substantially lower risk of developing tardive dyskinesia, although caution over this conclusion is needed because most studies to date have had follow-up periods of less than 2 years.[158] However, many of these drugs have their own troubling side-effects, notably weight gain and the metabolic syndrome.[164]

Psychological treatments

The biological revolution notwithstanding, interest in the role of psychological factors in schizophrenia remains strong. One consequence of this interest has been the development of an evidence-based psychotherapeutic intervention, cognitive behavioural therapy (CBT). CBT uses therapeutic techniques adapted from Beck's approach to dysfunctional cognitions in depression[165] and especially targets delusions and hallucinations. Randomised controlled trials began in the 1990s, and some of the approximately 50 trials to date have been large and methodologically rigorous. On the basis of their findings, the influential English guideline development body, the National Institute for Health and Care Excellence, recommends CBT for all patients with schizophrenia,[166] and several other countries have produced their own similar recommendations.[167]

A comprehensive 2014 meta-analysis reported that the effect size for CBT was in the small range: 0·33 (95% CI 0·19–0·47) for overall symptoms in 34 trials and 0·25 (0·13–0·37) for positive symptoms in 33 trials.[168] The effect size for positive symptoms decreased further in trials that used blinding (effect size 0·08, 95% CI –0·03 to 0·18; 20 trials). More recent meta-analyses[169–171] have disputed the finding of a lower effect size for positive symptoms in studies at low risk of bias, but collectively these meta-analyses have done little to alter the conclusion that the effect size for this class of symptoms lies in the small range.

Controversies and uncertainties

Is there a continuum of psychosis?

Psychiatric textbooks have traditionally stressed that symptoms like delusions and hallucinations are outside of the realm of normal experience. Perceptions changed in 2000 after a Dutch national survey by van Os and colleagues[172] reported that 5·8% of the population without psychiatric illness reported minor, sporadic, or non-distressing delusions and 3·3% experienced hallucinations that were likewise deemed not clinically relevant. The rates of such psychotic-like experiences, as they have become known, is currently estimated to lie between 5·2%[173] and 7·2%.[174] This and other findings led Johns and van Os[175] to propose that psychosis should no longer be regarded as an all-or-none entity but rather as a quantitative trait that is distributed across the population (figure 6). This view is currently highly influential, with studies and meta-analyses now regularly investigating the so-called extended phenotype of schizophrenia.

Studies have yet to show that psychotic-like experiences follow a half-normal distribution in the population (van Os and colleagues' preferred model), and according to some the continuum view is "at best premature and at worst wrong scientifically".[176] The 5–7% prevalence figure might also be an overestimate: most studies to date have not explored the nature of the experiences their participants reported, and the few that have done so have reported a substantial rate of false positives—real persecution (eg, workplace harassment), culturally accepted beliefs (eg, in witchcraft), and the so-called hallucinations of widowhood, among other things.[177–179] However, if nothing else this research

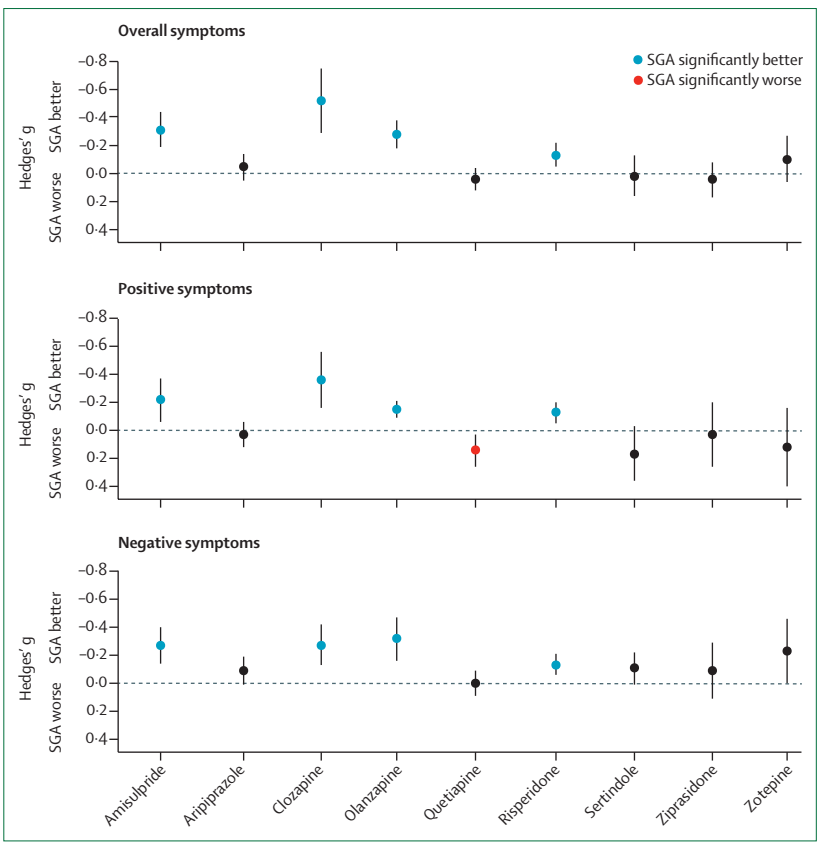

Figure 5: **Therapeutic advantages of SGAs over conventional drugs**
Adapted from Leucht and colleagues,[163] by permission of Elsevier. Data are Hedges' g (95% CI). SGA=second-generation antipsychotic.

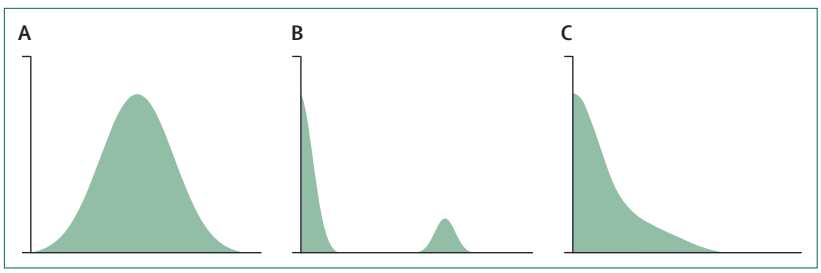

Figure 6: **Models of psychosis distributions**
Reproduced from Johns and van Os,[175] by permission of Elsevier. (A) A continuous and normal distribution of psychotic traits in the general population, much as one would expect of, for example, weight or blood pressure. (B) A clear bimodal distribution, with most of the population having negligible values of the psychosis trait, whereas a very small proportion has extremely high values. (C) A continuous but only half-normal distribution, with the majority of the population having very low values, but also a non-trivial proportion having non-zero values.

Panel 3: **Example of a psychotic-like experience**

The experience of Professor Norman Sartorius, former director of WHO's Division of Mental Health, occurring at the age of 8 years while he was fighting with the Yugoslav Partisans during World War 2.

"We had completed many hours of enforced march and had come to a road that we had had to cross: it was well guarded and it was necessary to wait for a period between the enemy patrols to get to the other side. Everyone had to remain absolutely quiet. We held that position for hours waiting for the signal to proceed. It was there that I saw a cortege, a carriage with six white horses, with attendants dressed in eighteenth century costumes and finery pass by on the protected road. It was quite beautiful and I remember how extremely clear it seemed to me. I heard the sound of the hoofs and muted voices of the attendants. The carriage was moving slowly and once it passed another came along. This hallucination lasted for what seemed a long time. When I pointed to the sight and described it to others they looked at me puzzled and ordered me to stop talking about it."[180]

initiative has placed beyond doubt the fact that otherwise healthy individuals can sometimes have quite arresting unusual beliefs and experiences, with one example being a former director of WHO's Division of Mental Health (panel 3).[180]

Does cannabis cause schizophrenia?

Although only grudgingly accepted by one expert in the field[181] and categorically denied by another,[182] the evidence linking cannabis use to schizophrenia actually lies somewhere between strong and overwhelming. Thus, a 2016 meta-analysis of 10 studies[183] reported that the OR for psychotic outcomes, including both clinically diagnosable psychosis and presence of psychotic symptoms, was 1·97 (95% CI 1·68–2·31). In the heaviest users of cannabis, the OR increased to 3·39 (95% CI 2·43–5·3) for psychotic symptoms and to 3·90 (2·84–5·34) for a psychotic diagnosis.

Accordingly, the real concern is the public health implications of the association. Meacher and colleagues[184] have argued that the increasing availability of high-potency forms of cannabis (also known as skunk in the UK) will inevitably translate into increasing numbers of patients presenting with schizophrenia and other psychotic diagnoses. Others have highlighted the apparent absence of an increase in schizophrenia prevalence since the 1960s.[182,185] The findings from a large multi-country study provide more evidence on the association of cannabis and schizophrenia: Di Forti and colleagues[186] reported that having ever used cannabis was associated with a modest increased risk of psychotic disorders (OR 1·3, 95% CI 1·1–1·6). Daily use of cannabis was associated with a higher risk (OR 3·2, 95% CI 2·2–4·1). Daily use of high-potency cannabis conferred a risk of more than four times that of having ever used cannabis (OR 4·8, 95% CI 2·5–6·3).

Schizophrenia: not just a neurodevelopmental disorder?

Based on the finding that lateral ventricular enlargement is present at illness onset,[187] and that the same finding can also be observed in the relatives of patients with schizophrenia,[188,189] for many years the orthodoxy was that brain structural changes were static and part of the pattern of neurodevelopmental abnormality that characterises the disorder. This view has now been called into question, first by a meta-analysis of 27 longitudinal studies,[190] and subsequently by two large prospective studies that documented progressive loss of brain volume over periods of 5–15 years.[191,192] On current evidence, the rate of progression is relatively small (approximately twice that seen in healthy controls),[192] is most marked in the frontal lobes,[192] and does not appear to be attributable, or at least wholly attributable, to antipsychotic drug treatment.[193]

Something similar might also be true for schizophrenic cognitive impairment. Although long considered to be stable after onset of illness, at least until old age (panel 1), a 2019 prospective 10-year follow-up study of 65 patients from their first episode reported significant declines in IQ and measures of verbal knowledge and memory, although not in processing speed or executive function, compared to 103 healthy controls.[194]

Childhood adversity: a risk factor for schizophrenia?

Another example of the enduring allure of the psychological approach to schizophrenia has been the claim that there is a link between traumatic events in childhood and later development of the disorder. Varese and colleagues performed a meta-analysis of 36 studies carried out between 1980 and 2012[195] that examined the association between sexual, physical, and emotional abuse, as well as neglect, bullying, and death of a parent, and later development of schizophrenia. A significant effect was reported (pooled OR 2·78, 95% CI 2·34–3·31). Varese and colleagues[195] did not separate studies

diagnosing schizophrenia categorically from those examining the extended phenotype, but findings were similar in a meta-analysis that focused exclusively on patients with a diagnosis of schizophrenia.[196]

This finding of a link between childhood trauma and later schizophrenia might now need reappraisal. Most of the studies in Varese and colleagues' meta-analysis[195] used retrospective designs—ie, information about childhood abuse was based on self-reports and interviews carried out in adult life. However, this methodology is flawed: a 2019 meta-analysis that compared retrospective measures of childhood maltreatment with prospective ones (eg, official records, contemporaneous interviews with parents, teachers, and the children themselves)[197] reported only a low level of agreement (Cohen kappa of 0·19) between the two. As the authors of this meta-analysis stated: "prospective and retrospective measures of childhood maltreatment identify largely different groups of individuals".[197]

Can early intervention prevent poor outcome?

The past two decades have witnessed a worldwide effort to try and mitigate the long-term consequences of schizophrenia by intervening aggressively when the illness first appears. Such programmes include occupational (vocational) support, education about medication adherence and factors that might precipitate relapse, as well as psychological therapy, including CBT. The interventions typically last 1–3 years.

There is little doubt that early intervention is successful in the short term. A meta-analysis of ten randomised trials by Correll and colleagues[198] reported benefits of early intervention compared with treatment as usual on all of a range of symptomatic and other measures at up to 18 months, and on all but one of the measures at 2 years. In the longer term, the findings are less encouraging: a systematic review of 5-year outcomes[199] reported little to support lower severity of symptoms at follow-up—beneficial effects on positive, negative, or disorganisation symptoms were only shown in three of eight studies. Higher rates of clinical remission were found in one of five studies, and better functioning was reported in three of seven studies.

The future

With a broad outline of structural and functional brain abnormality in schizophrenia now taking shape, the next challenge—as recognised by the US National Institute of Mental Health in a major shift of its research strategy[200]—is to understand how these changes might translate into the symptoms of the disorder. Associations between negative symptoms and reduced orbitofrontal cortex thickness,[201] between positive symptoms and reduced superior temporal gyrus thickness,[202] and between hallucinations and altered paracingulate morphology,[203] have been reported in well conducted studies. However, establishing the brain functional correlates of these and other symptoms remains a work in progress.[204,205] Neurochemistry might also have an important role in explaining the symptoms of the disorder: for example, it is now clear that increased and aberrant reward prediction error, as signalled by dopamine,[97] can provide a credible explanation of delusions,[206–208] and possibly also of hallucinations.[209]

The future seems optimistic for the possibility of genetically screening for schizophrenia. Copy number variants, with their large effect size and presence in 2–3% of patients,[210] are a candidate for chromosomal microarray analysis, especially if there are features such as low premorbid IQ, congenital malformations, dysmorphic features, early onset, or cognitive impairment,[211] or alternatively a strong family history of schizophrenia or other developmental disorders.[212] The much larger polygenic contribution can be studied using so-called polygenic risk scores, individualised predictors of genetic susceptibility to disease calculated from the weighted counts of thousands of risk variants identified from genome-wide association studies. Counselling of individuals at the highest risk (who have up to a 4·6-fold higher OR of schizophrenia compared with those with the lowest risk[213]) might now be a realistic possibility.[214]

The need for pharmacological treatments beyond drugs that block dopamine receptors is apparent. To date, no drugs with glutamate agonist actions (or in one case with complex glutamatergic effects) have shown benefit in large, well controlled trials.[215–218] Nevertheless, some researchers continue to be hopeful that a glutamatergic drug of some type will prove to be effective.[219,220] After more than 30 years of trials, it does not seem likely that CBT will ever have much more than small effects on core schizophrenic symptoms like delusions and hallucinations. The enduring legacy of CBT might instead prove to be the way in which it has stimulated efforts to develop novel, sometimes technology-assisted, psychological therapies, one of which, so-called avatar therapy, currently appears promising for auditory hallucinations.[221]

Contributors

PJM, SJ, and MJ searched the literature. MJ contributed to figure 4. PJM, SJ, and MJ wrote the paper. PJM and SJ reviewed and edited successive drafts of the paper. MJ reviewed and edited the final two drafts of the paper.

Declaration of interests

SJ has received honoraria from Sunovian for educational talks, and his institution has received honoraria for talks he has given for Lundbeck. MJ and PJM declare no competing interests.

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