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Lancet seminar: Schizophrenia

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Abstract

Schizophrenia, characterised by psychotic symptoms and in many cases social and occupational decline, remains an aetiological and therapeutic challenge. Contrary to popular belief, it is modestly more common in men than in women. Outcome is no longer considered uniformly poor and is classifiable as good in 40% of patients. Clinically, a division of symptoms into positive, negative and disorganisation syndromes is supported by factor analysis. Catatonic symptoms are not specific to schizophrenia and 'first rank' symptoms are no longer considered diagnostically important. The clinical features of the disorder are now also recognized to include cognitive impairment. Lateral ventricular enlargement is an established structural imaging finding in the disorder and is associated with brain volume reductions of around 2%, with greater reductions in the frontal and temporal lobes. Brain functional changes are seen in different subregions of the frontal cortex and may ultimately be understandable in terms of disturbed interaction among large-scale brain networks. Neurochemical disturbance, involving increased dopamine synthesis/release and glutamatergic NMDA receptor dysfunction is supported by indirect and some direct evidence, especially in the case of dopamine. Birth cohort studies have conclusively demonstrated a role for birth and early life factors in the aetiology of schizophrenia, establishing it in some sense a lifelong, neurodevelopmental disorder. Genetically, schizophrenia is polygenic, reflecting the influence of hundreds or thousands of risk alleles exerting small effects; genetic variants with larger effects have also been identified but are rare. The mainstay of treatment remains dopamine-receptor-antagonist drugs and is unsatisfactory; one drug, clozapine, stands out as being substantially therapeutically superior to the rest. A psychological intervention, cognitive behavioural therapy (CBT), currently appears to have only small effects against its target symptoms,

delusions and hallucinations. The idea that schizophrenia is better regarded as the extreme end of a continuum of psychotic symptoms is currently influential. Other areas of active 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.

Key words: schizophrenia; clinical features; cognition; brain imaging; neurochemistry; neurodevelopment; genetics; treatment; cannabis; childhood adversity; early intervention

Introduction

Schizophrenia is regarded, with good reason, as being the most serious of all psychiatric illnesses. Many of those who develop it 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 substance use act to reduce life expectancy by 13-15 years[3]. The most reliable estimates suggest a suicide rate of around 5%[4].

Epidemiology

The most widely quoted statistics for schizophrenia are that one in a hundred people will develop it and that both sexes are affected equally. The former figure continues to be broadly supported: a systematic review[5] found a mean lifetime morbid risk of 11·9 per 1,000, with a median (which the authors considered to provide a better estimate) of 7·2 per 1,000. The view that men and women are equally susceptible has not fared so well, however: meta-analytic evidence points to a modestly higher frequency in men (male:female incidence rate ratio of 1·70 [CI 1·46 to 1·97])[6].

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

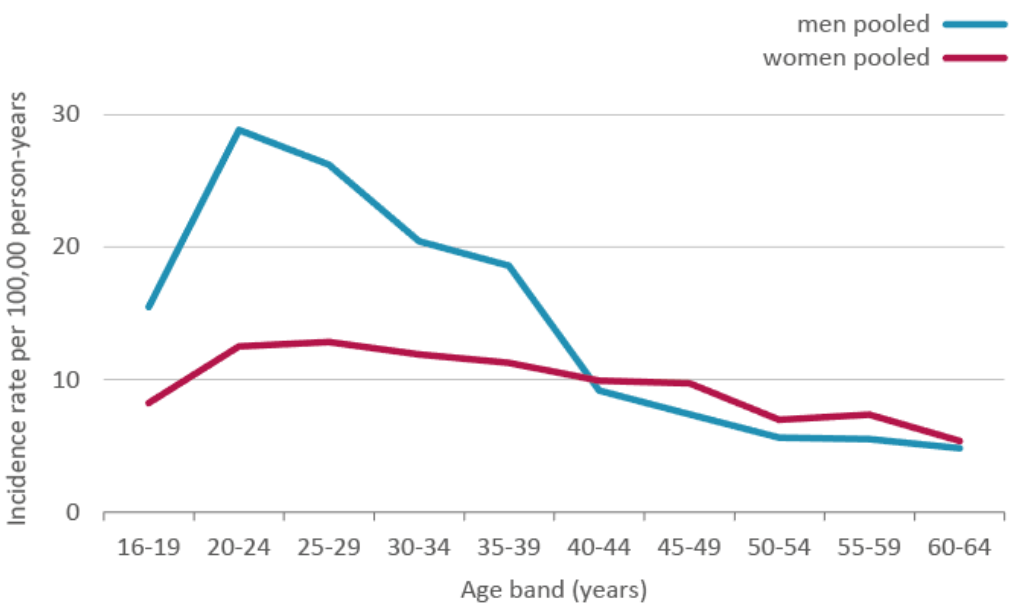


Figure 1. Pooled incidence of schizophrenia by age and gender in England, 1950-2009 (from: Kirkbride et al[7]).

As Figure 1 also makes clear, schizophrenia not-infrequently appears for the first time in adolescence. Its occurrence in childhood, ie before the age of 13 years, is also well-documented, but is rare – 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 gender differences were not conspicuous[10].

Contradicting an influential view in the 1960s and 1970s, which maintained that schizophrenia was not an illness but a socio-political construct, a large (N=811) WHO study in 1973[11] demonstrated that the disorder occurred with much the same frequency in nine countries that had very different cultures and political systems. Some relatively minor differences in frequency among countries were interpreted at the time as

reflecting differences in broadly defined forms of the disorder, with the 'core' or 'nuclear' form showing relatively little variation[12]. This conclusion is now no longer tenable: a meta-analysis of studies carried out between 1965 and 2002[5] found a five-fold variation in incidence rates. In this meta-analysis higher rates of schizophrenia were associated with migrant status and urban living. The former association has been amply supported by other studies [13]; in Britain it is particularly marked in people of Black-Caribbean and Black-African ethnicity[14]. On the other hand, the generalisability of the association with urban living has recently been questioned[15,16].

Clinical features

Leaving aside an aberration that occurred in America in the post-war period, when the concept was broadened to the point of meaninglessness, clinicians have recognised a largely similar set of clinical features as constituting schizophrenia[17]. These include on the one hand positive symptoms ('psychosis', 'the psychotic syndrome'), ie delusions, hallucinations and formal thought disorder (speech that is difficult to follow, sometimes to the point of incomprehensibility); and on the other negative symptoms, a triad of lack of volition, poverty of speech and flattening of affect (reduced emotional responsiveness). The positive:negative distinction is a slight misnomer since the symptoms of schizophrenia have been found, using factor analysis, to segregate into three groupings: reality distortion (delusions and hallucinations), disorganization (formal thought disorder, disorganized behaviour and the uncommon symptom of inappropriate affect), and negative symptoms or the 'clinical poverty' syndrome[18]. Though occasionally disputed[19], this tripartite division has been found in many studies[20] and is supported by meta-analysis[21,22].

Catatonia is another recognized 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 bizarre motor phenomena that often occur against a background of stupor or excitement. For unknown reasons, catatonic presentations of schizophrenia have become uncommon, especially in the Western world[23]; nevertheless, at just under 10% of cases, their frequency is still appreciable[24]. Once considered characteristic of schizophrenia, it is now recognized that catatonia can also be seen in patients with major affective disorder, autism and a range of neurological and medical conditions[25,26]. For this reason, 'catatonic syndrome' has been relegated to the status of a 'specifier' for several disorders in DSM-5, the latest version of the influential American diagnostic manual[23,26].

In the past, great importance was attached to the so-called first rank symptoms of schizophrenia, first described by the German psychiatrist Schneider[27] and considered by him to be pathognomonic of the disorder. Such symptoms include auditory hallucinations referring to the patient in the third person, changes in the experience 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 symptoms, and their apparent specificity to schizophrenia, has led to a long tradition of theorizing that distorted or anomalous self-experience might be the psychological core of the disorder[28].

Nevertheless, studies over the years have chipped away at the diagnostic specificity of first rank symptoms, chiefly by providing evidence that they can also be seen in

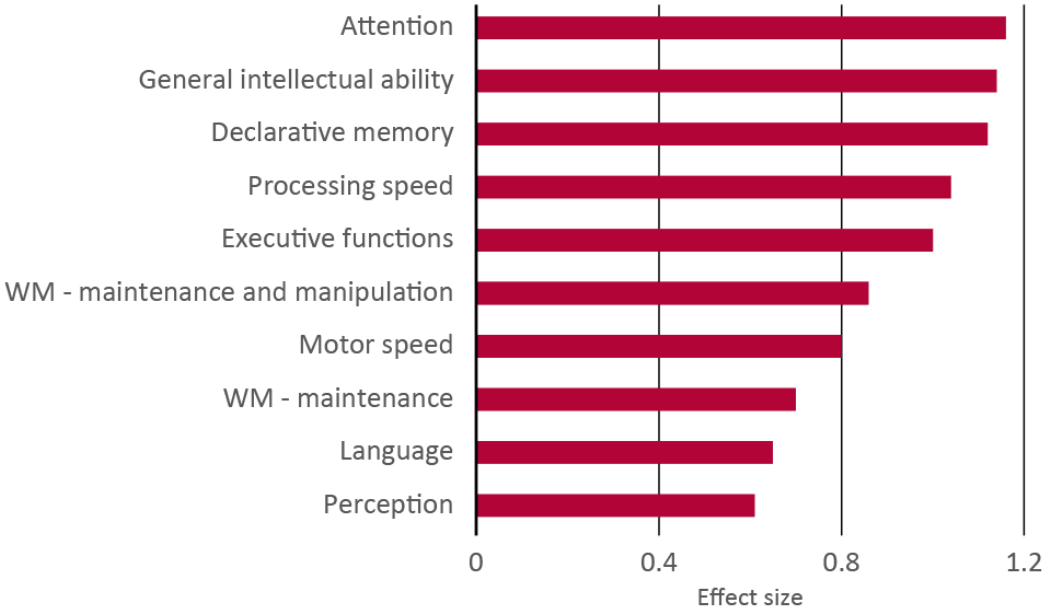
psychotic forms of major affective disorder. As a result, they no longer form part of the DSM-5 criteria for schizophrenia[29]. This rejection may be premature – a 2015 Cochrane review[30] found that first rank symptoms correctly identified people with schizophrenia 75%–95% of the time.

A final clinical feature of schizophrenia is cognitive impairment. Although minimized by Kraepelin[31], the psychiatrist who first 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 and memory and sustained attention, as well as a variable degree of general intellectual impairment (see Panel 1).

Panel 1. Cognitive impairment – part of the clinical picture of schizophrenia

At the same time that early views of schizophrenia as a disorder that did not compromise intellectual function hardened into dogma, studies from the 1930s onwards were documenting 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 its presence 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 chronically hospitalized patients fail simple 'bedside' tests of orientation, memory and general knowledge[38]. Deficits are seen in all domains of neuropsychological function, but as shown in the figure below, those 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] appears not to be a satisfactory explanation[42].



Panel 1 Figure Legend. Median effect sizes for impairments in different domains of neuropsychological function in schizophrenia, based on a range of meta-analysis (from Reichenberg et al[40]).

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 falls 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 seen in a minority of chronically hospitalized schizophrenic patients begin to increase in prevalence from the age of 65[47], a finding which is now coupled with increasing evidence for an increased rate of senile dementia in the disorder as a whole[48]. Why this occurs is unknown: post-mortem studies have revealed no excess of Alzheimer's disease or other dementing disorders in elderly patients with schizophrenia[49], although it is fair to point out that no new studies of this type have been carried out for over 20 years.

Course and outcome

Most individuals who develop schizophrenia – 73% according to one large study[50] – show prodromal symptoms. These may last from as little as a week to several years, though the median duration appears to be just under 12 months[51]. The prodromal

symptoms themselves are ill-defined and heterogeneous – they range from indefinable feelings of inner change, through new interests in philosophical and spiritual matters, anger, to irritability, anxiety, depression, 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 attenuated of psychotic symptoms and brief, self-limiting periods of psychotic symptoms lasting a few days ('BLIPS')[53,54].

When frank psychotic symptoms appear, they are often initially episodic (something that was observed even in the days before treatment). They may remain so, or alternatively become persistent, producing the picture of chronic schizophrenia. Negative symptoms also loom large in chronic schizophrenia, where they make an important contribution to the poor social and occupational functioning seen in the disorder[55].

Despite initial pessimistic views on outcome – Bleuler[32], for example, considered that full recovery never took place – improvement rates have been steadily revised upwards over the years. Two meta-analyses carried out in 1994 and 2006, which employed somewhat different inclusion criteria, both found good outcomes (defined somewhat loosely) of close to 40%[56,57]. Complete recovery, however, is less frequent: a third meta-analysis[58] found that only 13·5% (IQR 8·1% to 20·0%) of patients met strict criteria for recovery requiring the presence of at most mild symptoms and good social/occupational functioning lasting at least two years..

Aetiology

In the words of one researcher[59], '[i]t would be difficult to find many medical conditions that have been investigated with similar vigor and persistence over a century and have proved to be as intractable to understanding as schizophrenia.' Kraepelin was so convinced that the disorder was a degenerative brain disease that he established a laboratory to identify its underlying neuropathology (unsuccessfully, as it turned out, though the effort was not entirely wasted, as it was here that Alzheimer discovered his eponymous disease[60]). Bleuler[32], in contrast, was in favour of a role for both biological and psychological factors. As psychoanalysis became an increasing force in 20th century psychiatry, a model informed by psychodynamic and social thinking, became the dominant explanatory framework in America[61], and to a lesser extent all over the world.

The brain in schizophrenia

Thinking about schizophrenia was revolutionalized in the 1970s when, using one of the world's first CT scanners, Johnstone and co-workers[62] found lateral ventricular enlargement in a group of 17 chronically hospitalized patients. Forty years on, structural brain imaging in schizophrenia is a thriving industry: over 300 MRI studies have confirmed the finding of lateral ventricular enlargement, which is of the order of 25% by volume in the disorder and is accompanied by a reduction in brain volume of around 2%[63]. The latter affects grey matter more than white matter, and involves particularly the frontal lobe (ES 0.49) the temporal lobe (ES 0.43) and the hippocampus (ES 0.52); reductions are smaller in the parietal cortex (ES 0.31) and occipital cortex (ES 0.22)[63]. These findings have been substantially corroborated in studies using automated structural imaging techniques[64,65].

Evidence 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 documented at rest[66,67] and later during performance of a prototypical frontal/executive task, the Wisconsin Card Sorting Test[68]. Despite positive and negative findings in the many subsequent attempts at replication, meta-analyses eventually supported the existence of both 'resting' and 'activation' hypofrontality[69,70].

Nevertheless, it has become clear that brain functional abnormality in schizophrenia cannot be understood simply as a hypofunction. Thus, from 2000 onwards some studies also began to document evidence of increased rather than decreased frontal activation during performance of cognitive tasks[71-73] see also[70]. This 'hyperfrontality' has been found principally in parts of the medial frontal cortex, but also includes some lateral prefrontal regions[70]. Later still, another functional imaging abnormality began to be described, failure of de-activation in the medial frontal cortex during cognitive task performance[74-80]. Occasional negative findings[81,82] or reports of increased de-activation[81-84] have not prevented this finding from becoming well accepted.

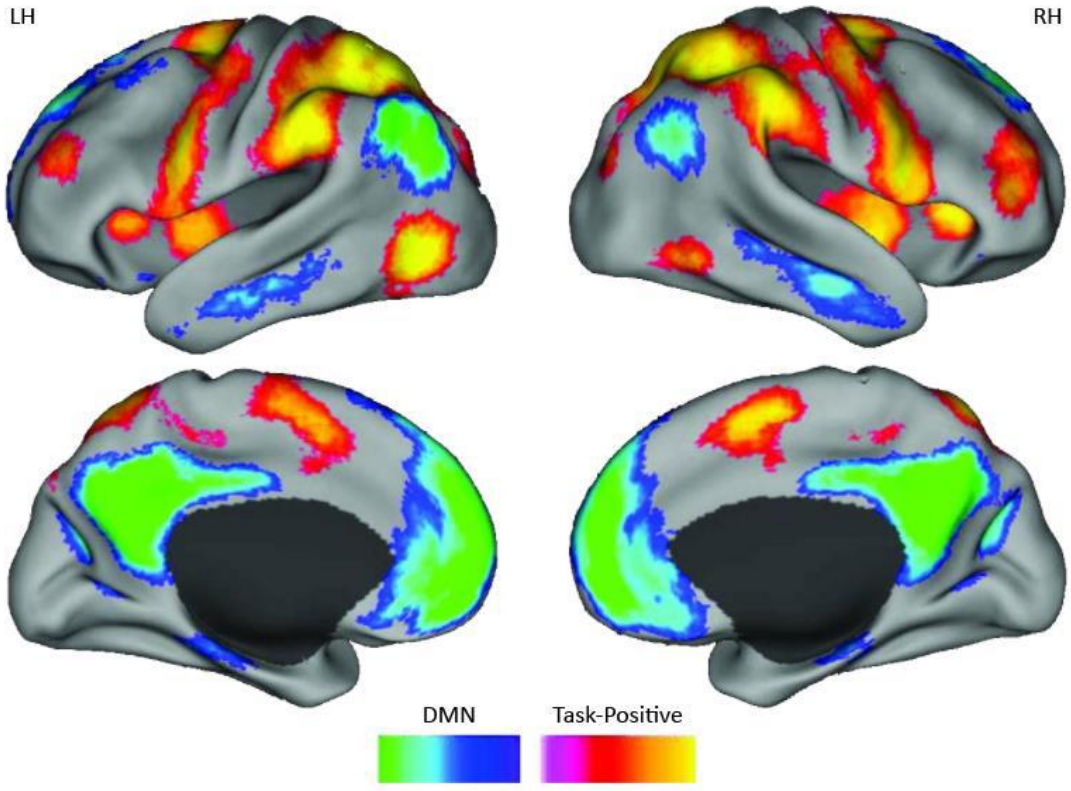
Failure of de-activation could account for the otherwise perplexing finding of simultaneous hypo- and hyperfrontality in schizophrenia (the subtractive designs typically used in fMRI studies mean that both hyperactivation and reduced de-activation will have the same appearance, see[85]). More importantly, 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. This has led to interest in the possibility 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 (see Panel 2).

Panel 2. Brain networks and schizophrenia

(Based on Blumenfeld[87], with additional text)

Since 2001 it has been recognized 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[86,88] or the task-negative network[87]. 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 – examples include recall of autobiographical memories, imagining the future and theory of mind processes[89,90]. Regions that activate during performance of attention demanding tasks are more variable, but show some general similarities and have been referred to as the task-positive network. Both the default mode and task-positive networks are also characterized by their high resting state within-network connectivity (spontaneous fluctuations in the fMRI BOLD signal) and negative correlations between the two[91,92].



Panel 2 Figure Legend. Task-positive and default-mode (task-negative) networks by

resting functional connectivity analysis (from[86,91]). The default-mode network (cool colours) includes the following cortical regions bilaterally: precuneus/posterior cingulate, posterior-inferior parietal lobule (angular gyrus), ventral-anterior medial frontal, middle temporal gyrus, and medial temporal cortex and the hippocampus. The task-positive network (warm colours) includes the anterior insula/frontal operculum, supplementary motor/dorsal medial frontal lobe, lateral premotor cortex (includes frontal eye fields), anterior middle frontal gyrus, superior parietal lobule/anterior inferior parietal lobule, lateral inferior posterior temporal gyrus (lateral area 37). Copyright (2005) National Academy of Sciences.

In 2007, based on resting-state functional connectivity analysis in healthy subjects, Seeley et al[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. They[93,94] used the term 'salience network' to describe this set of brain regions, and hypothesized that it 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 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 task-positive and task-negative (default mode) networks in schizophrenia is also of considerable interest – for example, the concept of impaired ability to switch between externally and internally directed thought ('toggling') could have potential for explaining positive symptoms, and the salience network has an obvious application to the self-referential thinking seen in the disorder. However, findings to date are contradictory, identifying increased, decreased and unaltered anticorrelations in the schizophrenia[96].

Schizophrenia - a neurochemical disorder?

The fact that schizophrenia tends to be a disorder of relapses and remissions that responds to drug treatment (see below) raises the possibility that at least some of its clinical manifestations reflect an underlying neurochemical disturbance. Over the years, two neurotransmitters have emerged as the strongest candidates for this. One is dopamine which, in addition to its well-known effects on motor function, is also involved in learning; specifically it codes a reward prediction error signal[97]. The other is glutamate, the brain's main excitatory neurotransmitter.

Dopamine: the great survivor: The origins of the dopamine hypothesis date back more than 40 years to two complementary findings: first that the therapeutic effect of antipsychotic drugs depends on their ability to reduce dopamine function by blocking post-synaptic dopamine D_2 receptors[98-101]; and secondly that abuse of amphetamine (which stimulates dopamine release among other actions) can produce a state essentially indistinguishable from schizophrenia[102]. The initial version of the theory, based on post-mortem studies, implicated increased post-synaptic dopamine D_2 receptor binding as the probable cause of the functional dopamine excess[103]. However, this theory was discredited when neurochemical imaging studies using radiolabelled dopamine ligands overwhelmingly failed to find increases in D_2 receptor numbers in living, drug-naïve 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, finding evidence for increased amphetamine-stimulate synaptic release of dopamine in antipsychotic-free (and in some cases antipsychotic naïve) patients with schizophrenia. There are currently four positive findings with this paradigm[105-108] and one negative finding[109]. In 2009, Howes and co-workers [110] also found significantly increased dopamine synthesis in individuals with prodromal symptoms of schizophrenia, an approach that avoids issues of prior drug treatment altogether. This finding has been replicated in a second cohort[111], although not in a third[112] from the same group. A 2018 meta-analysis of 14 studies[113] has also supported increased dopamine synthesis in patients with established schizophrenia, with an effect size of 0·52 (95% CI 0·21 to 0·83). Studies on the subset of studies carried out on drug free/drug naïve patients have

also been mostly positive[114-116], although two recent studies have been less clearly supportive[117,118].

Glutamate: has an angel shown the way? This neurochemical theory[119] (the heading of this section is taken from the title of a publication by the group who pioneered it[120]) grew out of the observation that individuals who took the anaesthetic drug, phencyclidine ('angel dust'), recreationally were prone to develop florid and sometimes prolonged psychotic states. Later it was shown that phencyclidine's main pharmacological action is to block N-methyl-D-aspartate receptor (NMDA) receptors, one of the two main classes of glutamatergic post-synaptic 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 may be an exception in the dorsolateral prefrontal cortex[121]. Support for the glutamate hypothesis instead comes chiefly from studies that have administered the phencyclidine-like drug, ketamine, to healthy volunteers. This reliably results in increased scoring on rating scales for both positive and negative symptoms[123], as well as a pattern of cognitive impairment that appears on current evidence to be similar to that seen in schizophrenia[124]. 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 subjects[125,126]. Auditory hallucinations, on the other hand, appear to be uncommon and minor[127].

Schizophrenia and development

One of the biggest success stories in contemporary schizophrenia research has been the confirmation of the long-held suspicion[128,129] that the roots of the disorder go back to early life, birth or even further. This has been achieved courtesy of the so-called birth cohort studies, a series of large systematic follow-ups of babies (eg all those born in a single week of one 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, 1946, British cohort are still being followed up over 50 years later). In the early 1990s several groups of investigators[131-133] realized that, by identifying the 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.

It was the birth cohort studies that established the above-mentioned presence of an IQ disadvantage in individuals destined to develop schizophrenia[43]. Minor 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 more 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 reports of psychotic-like experiences before the age of 11[137].

The genetics of schizophrenia

The observation that schizophrenia often runs in families dates back to the beginning of the 20th century, with studies of monozgotic vs dizygotic twins and of the adopted-away offspring of affected mothers ultimately putting paid to any ideas that this clustering might 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 (GWAS) 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 (the 108 identified in 2014 are only the tip of the statistical iceberg and the number has increased as further large-scale sequencing studies are 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 this study, as were genes expressed outside the CNS that have important roles in immunity, such as B-lymphocyte lineages and the complement pathway[141].

Polygenicity is not the whole story, however. In addition to common variants, a small number of rare copy number variants (CNVs)[143,144] and gene-disrupting variants, including the so-called rare-coding variants (RCVs)[145-147] and protein-truncating variants (PTVs), have been identified in schizophrenia. These have moderate to large effect sizes (odds ratios of 2-60 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 they are the strongest individual risk factors identified to date. The relative risks of common risk alleles, CNVs and RCVs /PTVs are shown in Figure 2. 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].

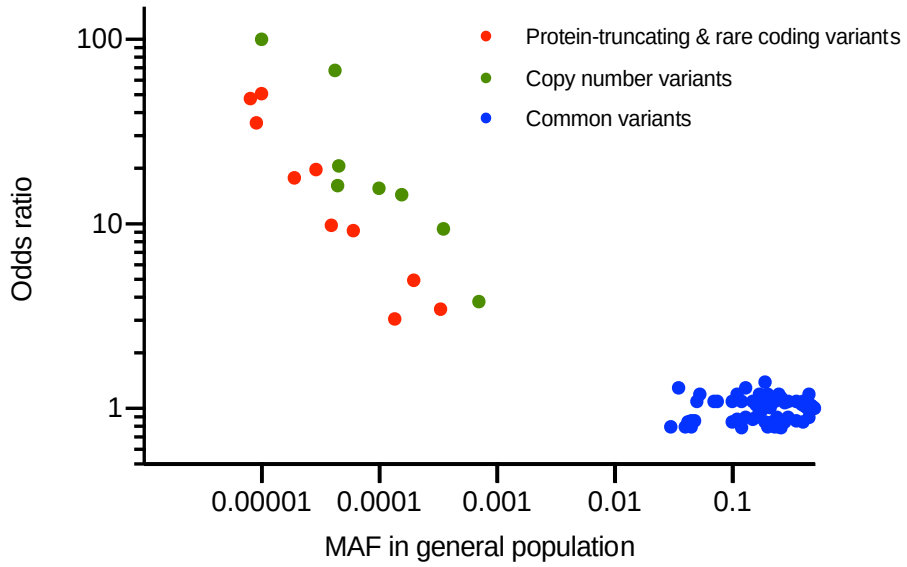


Figure 2. Genetic studies in schizophrenia. Odds ratios (y-axis, -log10) and minor allele frequency in the population (MAF, x-axis, -log10) for protein-truncating (PTVs) and rare-coding variants (RCVs), copy number variants (CNVs) and common variants (single-nucleotide polymorphisms; SNPs) derived from the respective studies (see text for references). Variants largely separate into either rare CNVs and ultra-rare protein-truncating variants or to 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 seen by the negative correlation between odds ratio and MAF.

Treatment

Antipsychotic drugs

The main, and so far the only, class of drugs of proven effectiveness in schizophrenia act by blocking postsynaptic the D_2 family of post-synaptic dopamine receptors (one potential exception, an investigational drug, SEP-363856[150], also has dopamine antagonist effects but 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]. They also have significant side-effects, including but not limited to sedation, weight gain and 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 generalized form or affects swallowing[152].

The therapeutic effect antipsychotics is often incomplete, and between 20 and 30% patients show little or no response[153]. For a long time there was little that could be offered to such patients. Then, in a landmark 1988 study one antipsychotic, clozapine, was found 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% to 43·4%). Clozapine's increased effectiveness was questioned in a 2016 meta-analysis[155] but another meta-analysis of a slightly different set of studies published in the same year then supported 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]. It is also widely considered not to cause tardive dyskinesia – a view which is not fully borne out by the evidence, which instead points to this side-effect developing with substantially lesser frequency and being usually mild[157,158]. Regular blood monitoring is necessary because of a 3·8% risk of neutropaenia/agranulocytosis (severe in 0·9%; mortality 0.01%) which mostly occurs in the first three months of treatment[159]. Rechallenge after development of neutropaenia is possible and may be more successful than previously thought[160]. Like other antipsychotics[161], clozapine is considered safe to use in pregnancy[162]. It is, however, contraindicated during breastfeeding because of the haematological risk in offspring, and also others such as seizures[162].

In the wake of clozapine several further 'atypical' or 'second generation' antipsychotics have been developed. Some, but not all of them, show a modest therapeutic advantage over conventional antipsychotics, but none rival clozapine in this respect[163] (see Figure 3). Some, though again not all, also cause little or no parkinsonism. As a class, second generation antipsychotics are also associated with a substantially lower risk of developing tardive dyskinesia, although caution is needed here since most studies to date have had follow-up periods of <2 years[158]. On the debit side, many of these drugs have their own troubling side-effects, notably weight gain and the metabolic syndrome[164].

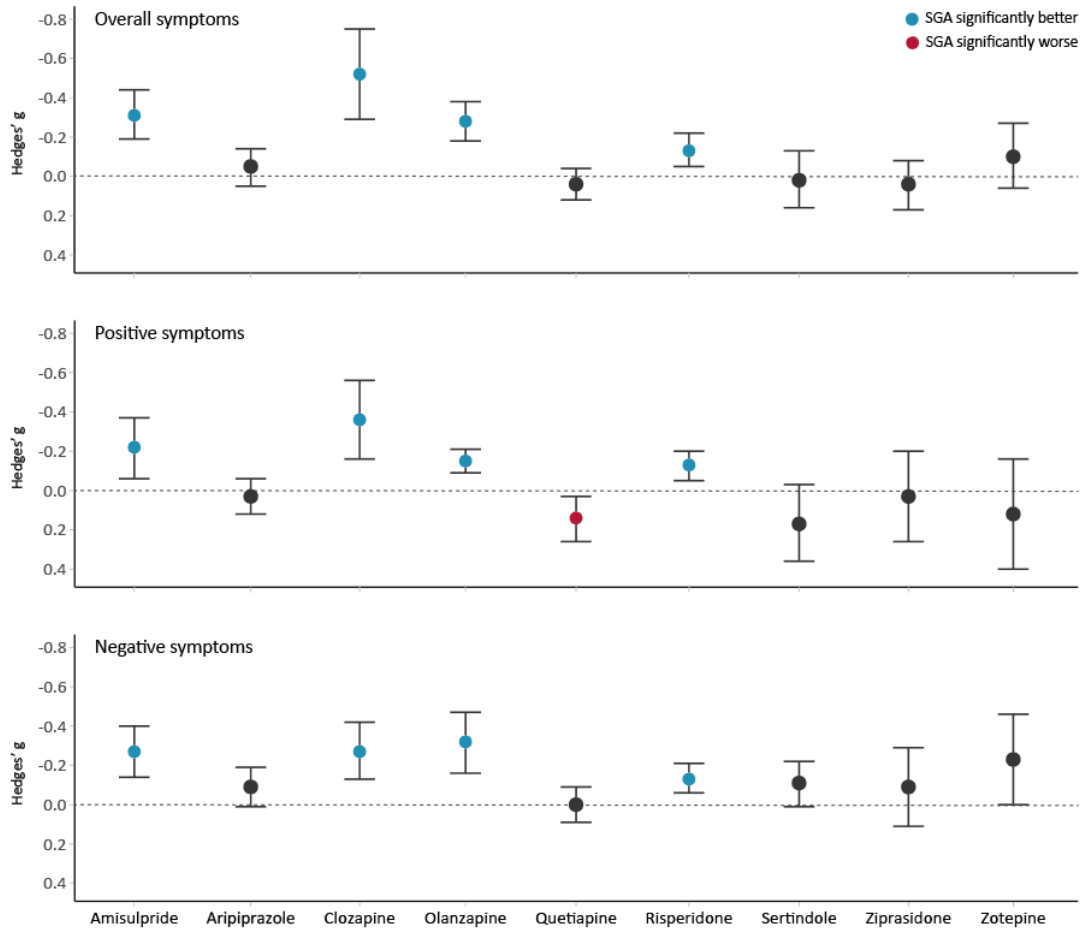


Figure 3. Therapeutic advantages of second generation antipsychotics (SGA) over conventional drugs (from Leucht et al[163]).

Psychological treatments

The biological revolution notwithstanding, interest in psychological factors in schizophrenia remains strong. One consequence of this has been the development of a new evidence-based psychotherapeutic intervention, cognitive behavioural therapy (cognitive therapy, CBT). CBT uses therapeutic techniques adapted from Beck's approach to dysfunctional cognitions in depression[165] and targets particularly delusions and hallucinations. Randomized controlled trials began to be carried out in the 1990s, and some of the approximately 50 carried out to date have been large and methodologically rigorous. On the basis of their findings the influential English

guideline development body, NICE, recommends CBT for all patients with schizophrenia[166], and several other countries have followed suit[167].

A comprehensive 2014 meta-analysis found that the effect size for CBT fell into the small range: 0·33 (95% CI 0·19 to 0·47, 34 trials) for overall symptoms and 0·25 (95% CI 0·13 to 0·37, 33 trials) for positive symptoms [168]. The effect size for positive symptoms fell further in trials that employed blinding (ES 0·08; 95% CI: –0.03 to +0·18, 20 trials). Three 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 have done little to alter the conclusion that the effect size is small.

Controversies and uncertainties

Is there a continuum of psychosis?

Psychiatric textbooks used to stress that symptoms like delusions and hallucinations are outside the realm of normal experience. This changed in 2000 when a nationwide survey by van Os and co-workers[172] found that 5·8% the non-psychiatrically ill population reported minor, sporadic or non-distressing delusions and 3·3% experienced similar 'not clinically relevant' hallucinations. The rates of such psychotic-like experiences (PLEs), 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 argue 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 (see Figure 4). This view is currently highly influential, with studies and meta-analyses now regularly investigating the 'extended phenotype' of schizophrenia.

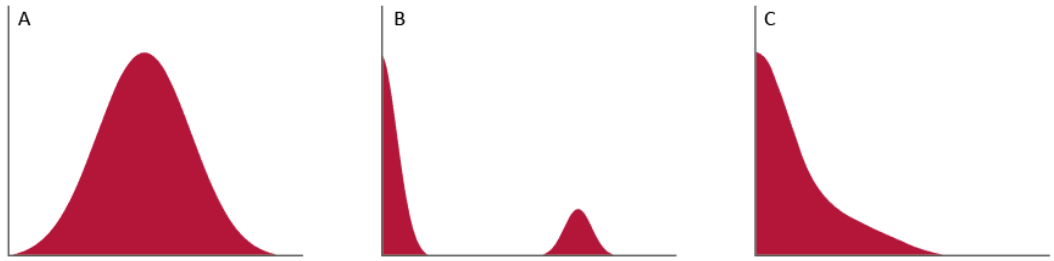


Figure 4. Models of psychosis distributions. In A, there is a continuous and normal distribution of psychotic traits in the general population, much as one would expect of, for example, weight or blood pressure. In B, there is a clear bimodal distribution, with the great majority of the population having negligible values of the psychosis trait, whereas a very small proportion has extremely high values. In C, there is a continuous but only half-normal distribution, with the majority of the population having very low values, but also a significant proportion with nonzero values (from Johns and van Os[175]).

Studies have yet to demonstrate that PLEs follow a 'half-normal' distribution in the population (van Os and co-workers' preferred model), and one group has asserted that the continuum view is 'at best premature and at worst wrong scientifically'[176]. It is also possible that the 5%-7% prevalence figure is an overestimate: the vast majority of the studies carried out to date have failed to explore the nature the experiences that their participants reported, and the few that have done so have found false positives – real persecution (eg workplace harassment), culturally accepted beliefs such as witchcraft and the 'hallucinations' of widowhood, among other things[177-179]. Nevertheless, this research initiative has succeeded in placing beyond doubt that a significant proportion of the healthy population – which includes a former director of the World Health Organization's Division of Mental Health[180] (see Figure 5) – can sometimes experience unusual and vivid psychosis-like phenomena.

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.

Figure 5. Example of a psychotic-like experience. It occurred at the age of 8 while the author was fighting with the Yugoslav partisans during the Second World War. (From Sartorius[180]).

Does cannabis cause schizophrenia?

Although only grudgingly accepted by one expert[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] found that the odds ratio for psychotic outcomes – including both clinically diagnosable psychosis and presence of psychotic symptoms – was 1·97 (CI 1·68 to 2·31). In the heaviest users this rose to 3·39 (CI 2·43 to 5·3) and 3·90 (CI 2·84 to 5·34) for psychotic symptoms and a psychotic diagnosis, respectively.

Accordingly, the real question is the public health implications of the association. Murray[184] has argued that the increasing availability of high potency forms of cannabis will translate into increasing numbers of patients presenting to psychiatric services with schizophrenia and other psychotic diagnoses. Others have pointed to the apparent absence of a rise in frequency of schizophrenia since the 1960s[182,185]. The findings from a, large multi-country study are illuminating here: Di Forti et al[186] found that having ever used cannabis was associated with a modest increase in the risk of psychotic

disorders (OR 1·3, CI 1·1 to 1·6). Daily use was associated with a higher risk (OR 3·2, CI 2·2 to 4·1), and daily use of high-potency cannabis conferred a more than four-times increase (OR 4·8, 95% CI 2·5 to 6·3).

Schizophrenia: not just a neurodevelopmental disorder?

Based on the finding that lateral ventricular enlargement is present at illness onset[187], and can also be seen in the relatives of patients with schizophrenia[188,189], for many years the orthodoxy was that brain structural changes in schizophrenia were static, part of the pattern of developmental abnormality that characterizes the disorder. This view has now been called into question, first by a meta-analysis of 27 longitudinal studies[190] and then by two large prospective studies which 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].

The same may also be true for schizophrenic cognitive impairment. Although long considered to be stable for after onset of illness until old age (see Panel 1), a recent prospective 10-year follow-up study of 65 patients from first episode found significant declines in IQ and measures of verbal knowledge and memory, although not processing speed or executive functions, 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 et al[195] meta-analyzed 36 studies carried out between 1980 and 2012 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 found (pooled odds ratio 2·78, 95% CI 2·34 to 3·31). Varese et al[195] did not separate studies diagnosing schizophrenia categorically from those examining the 'extended phenotype', but findings were similar in another meta-analysis which focused exclusively on the former[196].

This finding, however, may now need re-appraisal. The vast majority of the studies in Varese et al[195] employed 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] found only a low level of agreement (Cohen kappa of 0·19) between the two. As the authors of this meta-analysis put it: 'Prospective and retrospective measures of childhood maltreatment identify different groups of individuals.'

Can early intervention prevent poor outcome?

The last two decades have witnessed a worldwide initiative to try and mitigate the long-term consequences of schizophrenia by intervening aggressively when the illness first presents. Such programmes include occupational (vocational) support, education about medication adherence and factors that might precipitate relapse, as well as psychological therapy including but not limited to CBT. The interventions typically last one to three years.

has all the effort been justified? There seems little doubt that early intervention is successful in the short term: Correll et al[198] meta-analyzed 10 randomized trials and found benefits compared to treatment as usual on all of a range of symptomatic and other measures up to 18 months, and all but one of the measures at two years. In the longer-term, the findings are less encouraging: a systematic review of five-year outcomes[199] found little to support lower levels of positive or negative symptoms at follow-up (positive findings in 2 of 8 studies), higher rates of clinical remission (positive findings in 1 of 5 studies) and better functioning (positive findings in 3 of 7 studies).

The future

With a broad outline of structural and functional brain abnormality in schizophrenia now taking shape, the next challenge – as recognized by the American NIMH 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 found in large, well-conducted studies. On the other hand, establishing the brain functional correlates of these and other symptoms remains very much a work in progress, eg[204,205]. Neurochemistry may also have a potentially important role to play: 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 hallucinations[209].

Will it become possible to screen for schizophrenia genetically? CNVs, with their large effect size and presence in 2-3% of patients[210] are a candidate for chromosomal microarray analysis, especially where there are features such as low premorbid IQ, congenital malformations, dysmorphic features, early onset, 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, individualized predictors of genetic susceptibility to disease calculated from the weighted counts of thousands of risk variants identified from GWAS. Counselling of the highest risk individuals – who have up to a 4.6-fold higher odds ratio of schizophrenia compared to the lowest[213] – may now be a realistic possibility[214].

The need for pharmacological treatments beyond dopamine receptor blocking drugs is clearly apparent. To date, all drugs with glutamate agonist (or in one case with complex glutamatergic effects), have failed in large, well-controlled trials[215-218]. Nevertheless, some researchers continue to hopeful that sooner or later a drug of this type will prove to be effective[219,220]. After more than 30 years of trials, it does not seem likely that CBT will ever achieve much more than small effects on core schizophrenic symptoms like delusions and hallucinations. Its enduring legacy may prove to be the way in which it has stimulated efforts to develop novel, sometimes technology assisted psychological therapies, one of which, avatar therapy, currently appears promising for auditory hallucinations[221].

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Author's contributions

Peter McKenna, Sameer Jauhar and Mandy Johnstone searched the literature. Mandy Johnstone drew the original figure. Peter McKenna, Sameer Jauhar and Mandy Johnstone wrote the paper. Peter McKenna, and Sameer Jauhar reviewed and edited successive drafts of the paper. Mandy Johnstone reviewed and edited the final two drafts of the paper.

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