JAMA Psychiatry | Review

Schizophrenia—An Overview

Robert A. McCutcheon, MRCPsych; Tiago Reis Marques, PhD; Oliver D. Howes, PhD

IMPORTANCE Schizophrenia is a common, severe mental illness that most clinicians will encounter regularly during their practice. This report provides an overview of the clinical characteristics, epidemiology, genetics, neuroscience, and psychopharmacology of schizophrenia to provide a basis to understand the disorder and its treatment. This educational review is integrated with a clinical case to highlight how recent research findings can inform clinical understanding.

OBSERVATIONS The first theme considered is the role of early-life environmental and genetic risk factors in altering neurodevelopmental trajectories to predispose an individual to the disorder and leading to the development of prodromal symptoms. The second theme is the role of cortical excitatory-inhibitory imbalance in the development of the cognitive and negative symptoms of the disorder. The third theme considers the role of psychosocial stressors, psychological factors, and subcortical dopamine dysfunction in the onset of the positive symptoms of the disorder. The final theme considers the mechanisms underlying treatment for schizophrenia and common adverse effects of treatment.

CONCLUSIONS AND RELEVANCE Schizophrenia has a complex presentation with a multifactorial cause. Nevertheless, advances in neuroscience have identified roles for key circuits, particularly involving frontal, temporal, and mesostriatal brain regions, in the development of positive, negative, and cognitive symptoms. Current pharmacological treatments operate using the same mechanism, blockade of dopamine D_2 receptor, which contribute to their adverse effects. However, the circuit mechanisms discussed herein identify novel potential treatment targets that may be of particular benefit in symptom domains not well served by existing medications.

JAMA Psychiatry. doi:10.1001/jamapsychiatry.2019.3360
Published online October 30, 2019.

Related article

Author Affiliations: Department of Psychosis Studies, Institute of Psychiatry, Psychology & Neuroscience, Kings College London, London, United Kingdom (McCutcheon, Reis Marques, Howes); Psychiatric Imaging Group, Medical Research Council, London Institute of Medical Sciences, Hammersmith Hospital, London, United Kingdom (McCutcheon, Reis Marques, Howes); Institute of Clinical Sciences, Faculty of Medicine, Imperial College London, London, United Kingdom (McCutcheon, Reis Marques, Howes).

Corresponding Author: Robert A. McCutcheon, MRCPsych, and Oliver D. Howes, PhD, Department of Psychosis Studies, Institute of Psychiatry, Psychology & Neuroscience, Kings College London, Box 67, De Crespigny Park, London SE5 8AF, United Kingdom (robert.mccutcheon@kcl.ac.uk and oliver.howes@kcl.ac.uk).

The Clinical Challenge[1] in this issue of *JAMA Psychiatry* describes a patient who clinicians will be familiar with: a young woman who develops auditory hallucinations, unusual beliefs, and a deterioration in cognitive abilities and social function and is diagnosed with schizophrenia in early adulthood. The diagnosis of schizophrenia is based on a clinical assessment. In response to concerns regarding diagnostic reliability, early narrative descriptions of the disorder have been replaced with codified criteria (**Box**). Positive symptoms, such as delusions and hallucinations, are often the reason the patient presents to the clinician. However, the disorder is also associated with negative symptoms, such as amotivation and social withdrawal, and cognitive symptoms, including deficits in working memory, executive function, and processing speed. While more recent descriptions emphasize positive symptoms (Box), earlier conceptualizations saw negative symptoms as core features of the disorder,[2] and negative and cognitive symptoms contribute substantially to the long-term burden associated with the disorder.[3] The disorder typically appears in early adulthood, and a prodromal period frequently precedes the first psychotic episode (**Figure 1**).

Schizophrenia has a lifetime prevalence of about 1%[4] and accounts for a huge health care burden, with annual associated costs in the United States estimated to be more than $150 billion.[5] The fact that a disorder affecting around 1% of the population is associated with such costs is attributable to the fact that typical onset is in early adulthood and the long-term impairments in social and occupational function associated with the disease (Figure 1).[6] The disorder is also associated with reduced life expectancy: someone with schizophrenia has a mean life expectancy about 15 years shorter than the general population and a 5% to 10% lifetime risk of death by suicide.[7] In this review, we discuss findings from epidemiological, genetic, neuroimaging, and preclinical research to provide an overview of schizophrenia and consider the gaps in knowledge that remain.

Theme 1: Convergence of Genetic and Early Environmental Risk Factors on Neurodevelopment

The patient in the Clinical Challenge[1] case has a history of perinatal complications. Although schizophrenia typically appears in early adulthood, multiple strands of evidence indicate that its pathogenesis begins early in neurodevelopment.[8] This evidence includes increased rates of in utero adversity, such as maternal infections and starvation during pregnancy, and obstetric complications, including preterm birth and preeclampsia.[9-11] There is also evidence consistent with disrupted early neurodevelopment, such as skin markers of altered ectodermal development and mild cognitive and motor impairments in childhood.[9,12] Such impairments may manifest as fall-

Box. *DSM-5* Criteria for Schizophrenia

Criteria A, B, and C must be fulfilled and other causes of symptoms excluded.

Two or more of the following symptoms must be present for a 1-month period or longer, and at least 1 of them must be item 1, 2, or 3:

1. Delusions
2. Hallucinations
3. Disorganized speech
4. Grossly disorganized or catatonic behavior
5. Negative symptoms, such as diminished emotional expression

Impairment in 1 of the major areas of functioning (work, interpersonal relations, or self care) for a substantial period since the onset of the disturbance.

Some signs of the disorder must last for a continuous period of at least 6 months. This 6-month period must include at least 1 month of symptoms (or less, if treated) that meet criterion A (active-phase symptoms) and may include periods of residual symptoms. During residual periods, only negative symptoms may be present.

ing behind peers in schoolwork, as is the case with the patient in the Clinical Challenge.[1]

The patient in this case also has a family history of schizophrenia. Twin and other studies have consistently shown there is a large genetic component to schizophrenia, with heritability estimated at around 80%.[13] Heritability refers to how much of the variability of the trait in the population is attributable to between-individual genetic variation and does not allow for either the estimation of risk at the individual level or the identification of any specific genetic loci associated with disorder. In recent years, technological advances and falling costs have made genome-wide association studies (GWAS) possible, allowing an unbiased, data-driven approach to identify loci associated with schizophrenia.[14] Genome-wide association studies show that multiple common variants, each of small effect, are associated with schizophrenia. After adjusting for the number of tests, more than 100 loci are significantly associated with schizophrenia.[14] Thus schizophrenia, like many other common conditions, is a polygenic disorder in most patients. The development of GWAS has also enabled the construction of polygenic risk scores, which provide a genetic risk summary of the disorder based on the number of risk alleles an individual has, weighted by the odds ratio associated with each allele. There are also some genetic variants involving the deletion or duplication of sections of DNA (copy-number variants) that are associated with a greatly increased risk of schizophrenia on their own but are only found in 2% to 3% of people with cases of schizophrenia. One of the best established is a deletion of several megabases of DNA at chromosome 22q11.2, which is associated with a 30% to 40% lifetime risk of developing schizophrenia.[15,16] It should also be recognized that, as with environmental risk factors, many of the genetic variants associated with schizophrenia may also be associated with other psychiatric disorders, suggesting overlap in risk factors and potentially mechanisms.

However, even among identical twins, pairwise concordance for schizophrenia is only around 50%.[17] This highlights the importance of environmental factors and their interactions with genetic factors to increase schizophrenia risk. For example, Ursini et al[18] recently demonstrated that the risk for schizophrenia explained by polygenic risk scores was 5 times greater in those who had experienced perinatal complications, indicating an interaction between genetic and obstetric risk factors. Furthermore, in those who did not experience any obstetric complications, the risk score did not differentiate patients and control participants. Interestingly, it was genes highly expressed in the placenta that accounted for these findings, which suggests that some schizophrenia risk variants act by increasing the outcomes (or possibly the likelihood) of environmental risks, such as obstetric complications, that may then disrupt brain development.[19]

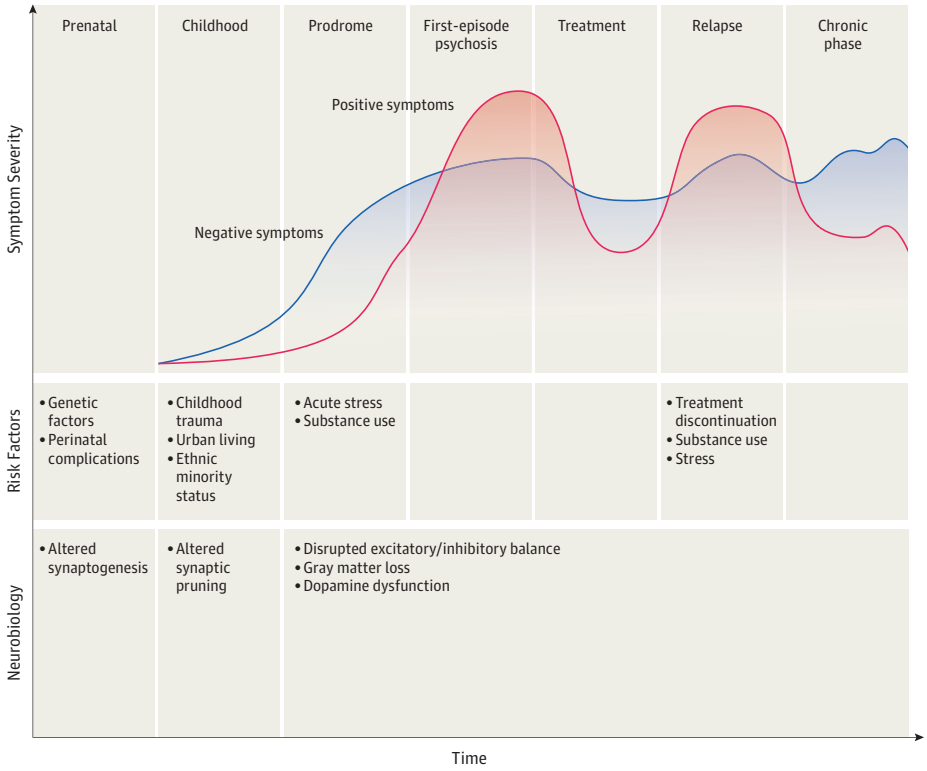
Several strategies have been used to identify molecular pathways from the GWAS findings. One approach used gene expression data from more than 500 brains to compare individuals with and without schizophrenia.[20] Relevant genes were identified by examining how gene expression data mirrored the loci implicated by GWAS, and these genes were then tested in model systems to assess functional relevance.[20] This process identified genes involved in the regulation of the postsynaptic membrane, synaptic transmission, and voltage-gated potassium channels as associated with schizophrenia. A complementary data-driven approach mapped the GWAS results onto gene expression profiles from different neuronal cell types to identify which cell types might be affected by the schizophrenia variants. These results showed that genes associated with schizophrenia risk are not expressed across all neuronal populations but instead are expressed specifically in hippocampal pyramidal cells, medium spiny neurons, and cortical interneurons.[21] A third, hypothesis-driven approach investigated the complement 4 (C4) locus within the major histocompatibility complex, one of the loci most strongly associated with schizophrenia.[22] Together with subsequent work, this indicates that disrupted complement-mediated synaptic elimination by microglia occurs in individuals with schizophrenia.[23] Several pathways identified by genetic studies have also been implicated by postmortem studies, including findings of lower levels of synaptic proteins, dendritic spines, and gamma-aminobutyric acid (GABA)–ergic and glutamatergic markers in individuals with schizophrenia relative to control participants.[24,25] Taken together, these findings suggest that aberrant functioning of complement and microglial systems in schizophrenia may lead to the loss of dendritic spines. We discuss the potential consequences of this in theme 2.

Overall, the research suggests that genetic and early environmental risk factors disrupt brain development, particularly in some neuronal subtypes and brain regions. This subsequently increases the risk of developing schizophrenia (Figure 1).

Theme 2: Cortical Excitatory-Inhibitory Imbalance and the Development of Cognitive and Negative Symptoms

Schizophrenia typically develops in early adulthood, as was seen in the Clinical Challenge[1] case; it is rare before age 16 years. This highlights that, in addition to the genetic and early developmental factors discussed above, other factors act later to lead to the disorder (Figure 1 and **Figure 2**). The patient in the Clinical Challenge[1] reported that she began to drop behind in her school work during early adolescence and noticed increasing memory difficulties in the run-up to her first psychotic episode. The cognitive deficits and negative symptoms observed in schizophrenia may attract less clinical atten-

Figure 1. The Clinical Course of Schizophrenia



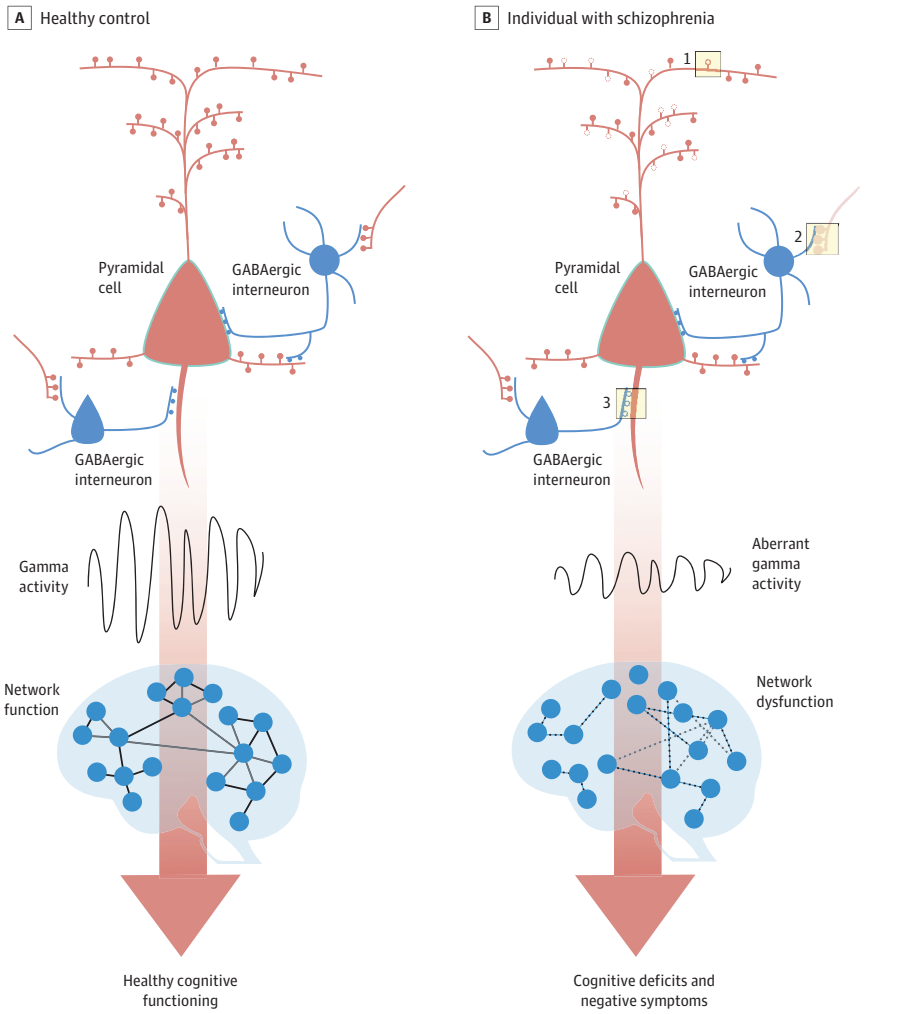
People who go on to develop schizophrenia may show subtle motor and cognitive deviation in childhood but do not show the marked developmental delays associated with autism and intellectual disabilities. During late adolescence or early adulthood, a prodromal phase characterized by attenuated psychotic, negative, and cognitive symptoms and functional impairment often precedes the first psychotic episode. The first psychotic episode occurs when symptoms meet the threshold for a clinical diagnosis, as opposed to the subthreshold symptoms seen in the prodrome (although these may still be debilitating). The first psychotic episode is frequently the first contact with services, although patients are increasingly seeking help in the prodromal period. The positive symptoms generally respond well to antipsychotic medication, but negative and cognitive symptoms show less response and may even be exacerbated by antipsychotic medication in some cases. Most patients will relapse after stopping antipsychotic treatment, and the risk of relapse is reduced by continued antipsychotic treatment even when psychotic symptoms have fully resolved. This Figure also highlights some key risk factors for the development of schizophrenia together with neurobiological changes thought to be relevant to the development of symptoms. Note that altered synaptogenesis and synaptic pruning have not been clearly demonstrated in vivo, and the precise timing regarding all the changes listed remains unclear.

tion than the positive symptoms, but they are responsible for a large proportion of the morbidity associated with the disorder.[26] They typically begin before the onset of the first psychotic episode,[27] with cognitive function considerably lower in people at risk of developing schizophrenia than matched control individuals.[28]

Early neurodevelopment is characterized by the production of synaptic connections, which continues during childhood before a switch in adolescence to synaptic pruning, such that the number of synapses in an adult is about half that of a young child.[29] The macroscale consequences of this can be observed in reductions in gray matter volume over adolescence and early adulthood and the concomitant reorganization of both structural and functional brain networks.[30] A long-standing hypothesis proposes that these processes are disrupted in schizophrenia, leading to widespread impairments in neural communication and the development of cognitive deficits in individuals with the disorder.[31] Supporting this view, imaging studies have shown that normal developmental trajectories are disrupted in schizophrenia, with increased gray matter loss and aberrant network organization apparent at illness onset, and this is associated with cognitive deficits.[32-35]

The neural circuits responsible for functional brain networks and cognition have been studied extensively. Many cognitive processes, such as working memory, are underpinned by synchronized neural oscillations,[36] particularly those occurring at approximately 40 Hertz, which are termed *gamma oscillations*. These oscillations underlie the slow fluctuations in neural activity observed using functional magnetic resonance imaging and, as such, play a major role in determining the architecture of functional brain networks.[37,38] In healthy individuals, these neural oscillations and functional networks have been linked with a wide range of cognitive abilities.[39] In schizophrenia, electrophysiological studies have consistently shown disrupted synchronization of neural oscillations in both patients with chronic schizophrenia and first-episode psychosis,[40] and these abnormalities have been associated with cognitive and negative symptoms.[40,41] These oscillations occur secondary to a finely tuned balance between groups of inhibitory and excitatory neurons (**Figure 3**). In particular, GABAergic interneurons play a central role in regulating the fast firing of pyramidal neurons required for the generation of these high-frequency rhythms.[40,42]

Figure 2. Cortical Circuits, Neural Oscillations, and Brain Networks in Schizophrenia



A, In healthy individuals, the excitatory output of cortical pyramidal cells is tempered secondary to gamma aminobutyric acid (GABA)–ergic inhibition from interneurons. The interplay between excitatory and inhibitory neurons generates gamma oscillations, which in turn are crucial to the generation of slow fluctuations in neural activity that underlie functional brain networks. B, In individuals with schizophrenia, several mechanisms appear to be altered within these cortical circuits. Loss of pyramidal cell dendritic spines leads to a net reduction in excitatory activity (1); reduced excitatory input to GABAergic interneurons leads to reduced inhibition of pyramidal cells (2); and reduced interneuron inhibition of pyramidal cells occurs (3). These alterations are proposed to lead to aberrant gamma activity and dysfunction of functional networks and thereby contribute to the cognitive and negative symptoms of the illness.

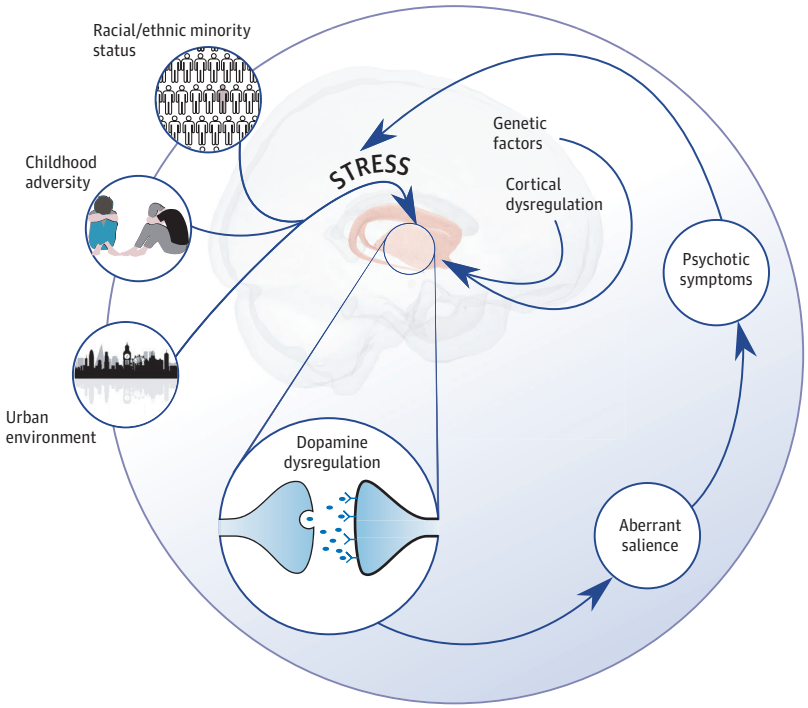
Postmortem studies provide insights into the molecular alterations that could underlie the neural oscillations and network dysfunction observed in individuals with schizophrenia (Figure 3). These studies have found a lower density of dendritic spines on pyramidal neurons,[43] lower messenger RNA levels of parvalbumin and markers of other inhibitory interneuron subtypes,[43] and lower levels of glutamate decarboxylase 67 (*GAD67*) messenger RNA and GAD67 protein, an enzyme involved in GABA synthesis, which together suggest that inhibitory mechanisms are altered.[44] As discussed in theme 1, microglia are thought to play a key role in pruning synapses,[22,23,45] and there is some in vivo evidence for altered microglial markers in individuals with schizophrenia.[45,46] This suggests that disrupted synaptic pruning could contribute to the lower dendritic spine levels in affected individuals, which would in turn affect the excitatory activity of pyramidal cells.[47] Abnormalities of *N*-methyl-D-aspartate receptor function and glutamatergic signaling may also contribute to disrupted excitatory-inhibitory balance.[48] Together, these disruptions have the potential to lead to abnormalities, such as altered gamma oscillations and disruption of coordinated brain function, leading to aberrant organization of functional brain networks. This disrupted neural function may then contribute to the development of cognitive and primary negative symptoms.[42,43]

Theme 3: Subcortical Dopamine Dysregulation and the Onset of Psychosis

The patient in the Clinical Challenge[1] is a member of a racial/ethnic minority and grew up in a densely populated city. These factors and several other later environmental risk factors are associated with an increased risk of developing schizophrenia (**Table**). Research indicates that these associations are unlikely to result from genetic differences between members of different races/ethnicities or biases among clinicians[50] and instead exert their influence via aberrant reactions within the stress-response circuitry, particularly the amygdala and frontal cortex, which are thought to lead to sensitization of the subcortical dopamine system (Figure 3).[51-56] Other stressful psychosocial factors, such as life events, also increase the risk of developing schizophrenia.[57] This is evident in the patient in the Clinical Challenge,[1] with the death of her father preceding the onset of the first episode of psychosis.

Several lines of evidence indicate that subcortical dopamine dysregulation has a role in the development of psychosis, including stud-

Figure 3. Stress, Dopamine, and Psychosis



Psychosocial stressors sensitize the subcortical dopamine system to increase the response to subsequent triggers, while cortical deficits mean that regulatory control is also impaired. Later triggers, such as stress, then lead to inappropriate striatal dopamine release. This leads to the aberrant assignment of salience to stimuli and the development of psychotic symptoms. Psychosis itself is stressful, and this in turn may provide feedback that further dysregulates the system.

Table. Association of Environmental Factors With the Risk of Schizophrenia[a]

Risk Factor	Odds Ratio (95% CI)
Obstetric complications	1.84 (1.25-2.70)
Winter birth in the northern hemisphere	1.04 (1.02-1.06)
Childhood trauma	2.87 (2.07-3.98)
Urban living	2.19 (1.55-3.09)
Migration (first generation)	2.10 (1.72-2.56)[b]
Cannabis use	5.17 (3.64-7.36)

[a] Odds ratios were taken from Radua et al.[49]

[b] An incidence rate ratio is reported, rather than an odds ratio.

ies showing that amphetamines and other drugs that release dopamine induce psychotic symptoms in healthy volunteers and worsen symptoms in patients with schizophrenia.[58,59] Molecular imaging studies have refined the understanding of the nature and anatomical location of dopamine alterations in schizophrenia. They provide in vivo evidence that striatal dopamine synthesis and release capacity is higher in patients compared with control participants and greater release of dopamine after amphetamine administration is directly associated with the worsening of psychotic symptoms in patients.[59-62] Moreover, higher striatal dopamine synthesis capacity is present in the prodromal phase,[63,64] is specific to those individuals in prodromal states who develop psychosis,[65] and worsens with psychosis onset.[66] Together with evidence that depleting striatal dopamine levels[67] or blocking dopamine receptors reduces psychotic symptoms in patients, this suggests that dopamine dysregulation is likely a final common pathway to psychosis in most patients.

Studies aimed at understanding the role of mesostriatal dopamine in normal brain function indicates how disruption of this system could potentially lead to the delusional beliefs described in the Clinical Challenge.[1] Preclinical work has demonstrated that the activity of mesostriatal dopamine neurons is associated with the discrepancy between expected and actual rewards, which is termed a *reward prediction error signal*.[68] It has subsequently been shown that in addition to signaling reward-associated information, dopamine neuron firing encodes aversive and other nonrewarding stimuli[69,70] and is specifically involved in the updating of beliefs after meaningful as opposed to merely surprising stimuli.[71] As such, dopamine neurons can be considered as signaling the salience of stimuli for learning and updating cognitive models of the world.

Evidence from many modalities suggests that schizophrenia is associated with dysregulated firing of mesostriatal dopamine neurons,[72] meaning that dopamine signaling becomes decoupled from salient stimuli. As a result, irrelevant objects may be marked as salient solely because they have been associated with aberrant dopamine signaling.[73] This provides a neuroscientific explanation for clinical phenomena frequently described by patients, such as the patient in the Clinical Challenge[1] ascribing particular relevance to her neighbor's house number for no obvious reason. Several factors may then contribute to the development and content of delusional beliefs. Early-life experiences, such as bullying or child abuse, may lead to cognitive biases, such as a tendency to view negative events as resulting from the hostile acts of others. These cognitive biases are more common in people at risk of schizophrenia.[74] This is seen in the Clinical Challenge[1] in that the patient had been bullied at school and developed a cognitive schema that people were generally threatening and not to be trusted.[75] Given these experiences and the cognitive biases that she had developed as a result, it is easy to see why she might arrive at a persecutory interpretation of her experience

and conclude that there was something highly relevant about her neighbors. It is also relevant that dopamine signaling within the dorsal striatum has been associated with threat, because this is the site of greatest dopaminergic dysregulation in schizophrenia and therefore potentially contributes to the fact that delusions are often persecutory in content.[60,69]

Theme 4: Current Treatments for Schizophrenia

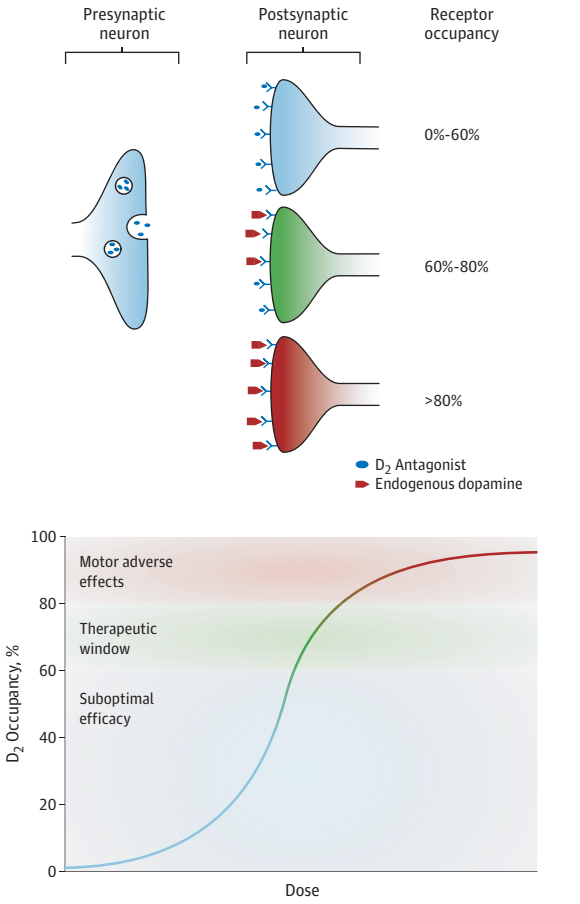
In the Clinical Challenge,[1] the patient was prescribed amisulpride and her psychotic symptoms improved, but she subsequently developed extrapyramidal adverse effects, which improved after dosage reduction. These adverse effects can be understood in terms of the neurobiology of schizophrenia and the mechanism of antipsychotic drugs. All current pharmacological treatments for schizophrenia are dopamine D_2-receptor blockers, and positron emission tomography (PET) studies in affected patients show that substantial occupancy of dopamine D_2 receptors, generally more than 60% occupancy, is required for a high likelihood of response.[76] The evidence in theme 3 provides an explanation for why this is effective, because it indicates that D_2 blockade will dampen the consequences of dysregulated striatal dopamine release. Positron emission tomography studies have shown that movement-associated adverse effects become more likely with higher D_2 occupancy, generally greater than 80%, providing an explanation for these common adverse effects and suggesting a therapeutic window for treatment (**Figure 4**).[77]

Prospective PET studies investigating receptor occupancy and clinical response have generally studied short-term responses in patients over a few weeks. Treatment of schizophrenia, however, is typically given over the long term, and, to our knowledge, it is unknown if the same level of D_2-receptor occupancy used for short-term treatment is needed over months to reduce the risk of relapse. Another potential issue is whether long-term treatment induces changes in the dopamine system. There is some (albeit limited) evidence that long-term treatment with potent D_2 blockers may be associated with upregulation of striatal D_2-receptor levels in some patients.[78] However, this was observed in patients taking relatively high doses of first-generation antipsychotic drugs rather than the second-generation antipsychotic drugs generally used at present and has yet to be shown in prospective studies.

After an initial resolution of her positive symptoms, the patient in the Clinical Challenge[1] subsequently discontinued her treatment and experienced a relapse of positive symptoms. Antipsychotic drugs appear to have little association with presynaptic dopamine function[79] and may indeed sensitize the dopamine system.[78,80] Given the lack of any permanent association with underlying dopamine dysfunction, the high rates of relapse after antipsychotic medication discontinuation are expected, and long-term maintenance treatment is recommended in clinical guidelines.[81]

Although the positive symptoms improved with treatment in the case in the Clinical Challenge,[1] negative and cognitive symptoms showed no improvement. There is little evidence that antipsychotic drugs substantially improve negative and cognitive symptoms other than in situations in which these are secondary to positive symptoms. As discussed, this is not surprising, because these symptoms most likely result from the disruption of cortical circuits rather than striatal dopamine signaling.

Figure 4. Dopamine Receptor Blockers, Treatment Response, and Adverse Effects



Positron emission tomography studies of D_2-antagonist antipsychotic drugs have shown that striatal D_2-receptor occupancy greater than 60% is generally required for a patient to have a high likelihood of improving but that occupancy levels greater than 80% are associated with a high likelihood of motor adverse effects. This suggests there is a therapeutic window of about 60% to 80% D_2-receptor occupancy by antipsychotic drugs that balances a high likelihood of improvement with a low risk of motor adverse effects. Fortunately, the licensed dosages for most recently licensed antipsychotic drugs generally correspond to this occupancy range. There are exceptions to this therapeutic window; for example, people with rapid metabolism may require higher dosages, partial agonists occupy a higher proportion of D_2 receptors, and clozapine generally leads to lower levels of D_2 occupancy. Positron emission tomography studies have also shown that high D_2 occupancy does not guarantee response, indicating that while D_2 occupancy is necessary in most patients, it is not sufficient in some patients.

Psychological treatments for psychosis have also been developed. These approaches can help individuals to address biased cognitive schema and reappraise psychotic symptoms. This has the potential to break the cycle (Figure 3) in which the stress of experiencing psychosis is itself an exacerbating and perpetuating factor. High expressed emotion, a communication style characterized by critical comments, hostility, and emotional overinvolvement towards people with schizophrenia, is associated with increased rates of relapse, and therapies to address maladaptive family communication have also been shown to be effective.[82] However, psychological treatments also appear to have minimal associations with cognitive and negative symptoms.[83]

Outstanding Questions

It should be recognized that schizophrenia has been associated with several molecular and circuit-level alterations, such as impaired mismatch negativity, altered serotonergic systems, and altered redox systems, and additional abnormalities are seen in patients with dual diagnoses.[84-87] We have not considered these here. No model accounts for all of the alterations associated with schizophrenia, and, for many of them, it remains unknown if they are causal or potentially compensatory reactions to upstream dysfunction. Studies of people at risk of schizophrenia and in the early stages of the illness, similar to ones that have been done for the dopamine system, will help clarify these issues.

While striatal hyperdopaminergia is a well-established finding in schizophrenia, the molecular mechanisms underlying this remain unclear. Likewise, the exact mechanisms leading to disrupted excitatory-inhibitory balance remain unclear; for example, it remains uncertain whether changes in GABAergic interneurons are best understood as a primary pathology or as a compensatory mechanism for dendritic spine loss. Moreover, while there is evidence that impaired cortical regulation could underlie mesostriatal dopamine dysregulation,[88,89] causality has yet to be demonstrated in vivo. Determining this could help identify new therapeutic targets for interventions.

Dopamine-receptor blockers show a benefit in terms of positive symptoms for most patients, although even in this domain, efficacy is limited for some individuals. This has been termed *treatment-resistant schizophrenia* and occurs in around one-third of individuals with chronic schizophrenia. For these individuals, clozapine appears to be of particular benefit, but the mechanism underlying this remains poorly understood. Lower striatal dopamine synthesis capacity, higher glutamate concentrations in the anterior cingulate cortex, and more pronounced gray matter changes are all associated with treatment resistance.[90] There is also some evidence that individuals with higher polygenic risk score are less likely to respond to antipsychotic treatment,[91] although this appears to depend on the population studied.[92] However, so far, neither imaging nor genetic or clinical markers[93,94] have sufficient accuracy to be suitable for prognostication at the individual patient level.[90] Greater understanding of the neurobiology of treatment resistance and other sources of heterogeneity has the potential to identify new treatment targets and potentially allow for personalized clinical treatments.

Schizophrenia is a syndrome that includes several symptom clusters and subclusters. For example, the negative symptom category includes symptoms of amotivation and anhedonia that cluster together and symptoms of affective flattening and poverty of expression that cooccur more frequently with each other than with the amotivation-anhedonic symptoms.[95] Consequently, individual patients may differ markedly in their symptom profiles, and it is thus unsurprising that there is heterogeneity in neurobiological findings and treatment response.[96] One approach proposed to address this is to focus instead on the circuits and processes underlying specific symptoms or symptom clusters (for example, the research domain criteria approach).[97]

All current licensed treatments for schizophrenia are D_2-receptor blockers. Several treatments using nondopaminergic mechanisms have been tested. There is some evidence that modulation of *N*-methyl-D-aspartate receptor function or α7 nicotinic receptor signaling could be beneficial in the treatment of negative and cognitive symptoms, but replicated evidence of efficacy remains elusive.[98] The research findings discussed suggest several novel potential treatment targets, such as microglia and the complement system (in attempts to prevent aberrant synaptic pruning) and the GABAergic system (to correct dysfunctional interneuron signaling).

Conclusions

Schizophrenia is a complex disorder with multiple symptoms clustered in 3 main domains and numerous interacting risk factors. In this review, we have described how genetic and environmental risk may converge to lead to aberrant functioning of cortical microcircuits and disinhibition of striatal dopamine signaling, which then together lead to the wide range of symptoms experienced by the case discussed in the Clinical Challenge.[1] Antipsychotic drugs are effective for positive symptoms for most patients but have little benefit for negative and cognitive symptoms, and essentially all use the same mechanism, blockade of the D_2 receptor. However, recent developments in genetics, neuroimaging, and preclinical research have identified potential upstream treatment targets to address the mechanisms underlying these symptoms as well. Integrating knowledge across these fields is vital to enable translation of these new findings into interventions of clinical benefit to individuals with schizophrenia.

ARTICLE INFORMATION

Accepted for Publication: August 6, 2019.

Published Online: October 30, 2019. doi:10.1001/jamapsychiatry.2019.3360

Author Contributions: Dr McCutcheon had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: All authors.
Acquisition, analysis, or interpretation of data: Howes.
Drafting of the manuscript: All authors.
Critical revision of the manuscript for important intellectual content: McCutcheon, Howes.
Obtained funding: McCutcheon.
Supervision: All authors.

Conflict of Interest Disclosures: Dr Reis Marques has received honoraria for speaking and chairing engagements from Lundbeck, Jansenn, and Astellas and advisory board membership with Angellini. Dr Howes has received investigator-initiated research funding from and/or participated in advisory or speaker meetings organised by Angellini, AstraZeneca, Autifony, Biogen, Bristol-Myers Squibb, Eli Lilly, Heptares, Jansenn, Lundbeck, Lyden-Delta, Otsuka, Servier, Sunovion, Rand, Recordati, and Roche. No other disclosures were reported.

Funding/Support: This work is supported by a clinical research training fellowship grant from the Wellcome trust (grants 200102/Z/15/Z [Dr McCutcheon] and 094849/Z/10/Z [Dr Howes]), the Medical Research Council (Dr Reis Marques and grant MC-A656-5QD30 [Dr Howes]), King's College London (Drs Reis Marquest and Howes), Maudsley Charity (grant 666 [Dr Howes]), Brain and Behavior Research Foundation (Dr Howes), the National Institute for Health Research Biomedical Research Centre at South London (Dr Howes), and Maudsley National Health Services Foundation Trust (Dr Howes).

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclaimer: The views expressed are those of the authors and not necessarily those of the National Health Services, the National Institute of Health

Research, or the Department of Health of the United Kingdom.

REFERENCES

1. McCutcheon RA, Marques TB, Howes OD. Treatment of first-episode schizophrenia in a young woman. *JAMA Psychiatry*. doi:10.1001/jamapsychiatry.2019.3369

2. Bleuler E. *Dementia Praecox or the Group of Schizophrenias*. New York, NY: International Universities Press; 1950.

3. Provencher HL, Mueser KT. Positive and negative symptom behaviors and caregiver burden in the relatives of persons with schizophrenia. *Schizophr Res*. 1997;26(1):71-80. doi:10.1016/S0920-9964(97)00043-1

4. Saha S, Chant D, Welham J, McGrath J. A systematic review of the prevalence of schizophrenia. *PLoS Med*. 2005;2(5):e141. doi:10.1371/journal.pmed.0020141

5. Cloutier M, Aigbogun MS, Guerin A, et al. The economic burden of schizophrenia in the United States in 2013. *J Clin Psychiatry*. 2016;77(6):764-771. doi:10.4088/JCP.15m10278

6. Andreasen NC. The lifetime trajectory of schizophrenia and the concept of neurodevelopment. *Dialogues Clin Neurosci*. 2010;12(3):409-415.

7. Hjorthøj C, Stürup AE, Mcgrath JJ, Nordentoft M. Years of potential life lost and life expectancy in schizophrenia: a systematic review and meta-analysis. *Lancet Psychiatry*. 2017;4(4):295-301. doi:10.1016/S2215-0366(17)30078-0

8. Murray RM, Lewis SW. Is schizophrenia a neurodevelopmental disorder? *BMJ (Clin Res Ed)*. 1988;296(6614):63. doi:10.1136/bmj.296.6614.63

9. Bramon E, Walshe M, McDonald C, et al. Dermatoglyphics and schizophrenia: a meta-analysis and investigation of the impact of obstetric complications upon a-b ridge count. *Schizophr Res*. 2005;75(2-3):399-404. doi:10.1016/j.schres.2004.08.022

10. Hulshoff Pol HE, Hoek HW, Susser E, et al. Prenatal exposure to famine and brain morphology in schizophrenia. *Am J Psychiatry*. 2000;157(7):1170-1172. doi:10.1176/appi.ajp.157.7.1170

11. Xu MQ, Sun WS, Liu BX, et al. Prenatal malnutrition and adult schizophrenia: further evidence from the 1959-1961 Chinese famine. *Schizophr Bull*. 2009;35(3):568-576. doi:10.1093/schbul/sbn168

12. Erlenmeyer-Kimling L, Rock D, Roberts SA, et al. Attention, memory, and motor skills as childhood predictors of schizophrenia-related psychoses: the New York High-Risk Project. *Am J Psychiatry*. 2000;157(9):1416-1422. doi:10.1176/appi.ajp.157.9.1416

13. Sullivan PF, Kendler KS, Neale MC. Schizophrenia as a complex trait: evidence from a meta-analysis of twin studies. *Arch Gen Psychiatry*. 2003;60(12):1187-1192. doi:10.1001/archpsyc.60.12.1187

14. Ripke S, Neale BM, Corvin A, et al; Schizophrenia Working Group of the Psychiatric Genomics Consortium. Biological insights from 108 schizophrenia-associated genetic loci. *Nature*. 2014;511(7510):421-427. doi:10.1038/nature13595

15. Bassett AS, Chow EWC. Schizophrenia and 22q11.2 deletion syndrome. *Curr Psychiatry Rep*. 2008;10(2):148-157. doi:10.1007/s11920-008-0026-1

16. Schneider M, Debbané M, Bassett AS, et al; International Consortium on Brain and Behavior in 22q11.2 Deletion Syndrome. Psychiatric disorders from childhood to adulthood in 22q11.2 deletion syndrome: results from the International Consortium on Brain and Behavior in 22q11.2 Deletion Syndrome. *Am J Psychiatry*. 2014;171(6):627-639. doi:10.1176/appi.ajp.2013.13070864

17. Hilker R, Helenius D, Fagerlund B, et al. Heritability of schizophrenia and schizophrenia spectrum based on the nationwide Danish Twin Register. *Biol Psychiatry*. 2018;83(6):492-498. doi:10.1016/j.biopsych.2017.08.017

18. Ursini G, Punzi G, Chen Q, et al. Convergence of placenta biology and genetic risk for schizophrenia. *Nat Med*. 2018;24(6):792-801. doi:10.1038/s41591-018-0021-y

19. Aleman A, Kahn RS, Selten J-P. Sex differences in the risk of schizophrenia: evidence from meta-analysis. *Arch Gen Psychiatry*. 2003;60(6):565-571. doi:10.1001/archpsyc.60.6.565

20. Fromer M, Roussos P, Sieberts SK, et al. Gene expression elucidates functional impact of polygenic risk for schizophrenia. *Nat Neurosci*. 2016;19(11):1442-1453. doi:10.1038/nn.4399

21. Skene NG, Bryois J, Bakken TE, et al; Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium. Genetic identification of brain cell types underlying schizophrenia. *Nat Genet*. 2018;50(6):825-833. doi:10.1038/s41588-018-0129-5

22. Sekar A, Bialas AR, de Rivera H, et al; Schizophrenia Working Group of the Psychiatric Genomics Consortium. Schizophrenia risk from complex variation of complement component 4. *Nature*. 2016;530(7589):177-183. doi:10.1038/nature16549

23. Sellgren CM, Gracias J, Watmuff B, et al. Increased synapse elimination by microglia in schizophrenia patient-derived models of synaptic pruning. *Nat Neurosci*. 2019;22(3):374-385. doi:10.1038/s41593-018-0334-7

24. Osimo EF, Beck K, Reis Marques T, Howes OD. Synaptic loss in schizophrenia: a meta-analysis and systematic review of synaptic protein and mRNA measures. *Mol Psychiatry*. 2019;24(4):549-561. doi:10.1038/s41380-018-0041-5

25. Lewis DA, Hashimoto T, Volk DW. Cortical inhibitory neurons and schizophrenia. *Nat Rev Neurosci*. 2005;6(4):312-324. doi:10.1038/nrn1648

26. Keefe RSE, Fenton WS. How should *DSM-V* criteria for schizophrenia include cognitive impairment? *Schizophr Bull*. 2007;33(4):912-920. doi:10.1093/schbul/sbm046

27. Piskulic D, Addington J, Cadenhead KS, et al. Negative symptoms in individuals at clinical high risk of psychosis. *Psychiatry Res*. 2012;196(2-3):220-224. doi:10.1016/j.psychres.2012.02.018

28. Fusar-Poli P, Deste G, Smieskova R, et al. Cognitive functioning in prodromal psychosis: a meta-analysis. *Arch Gen Psychiatry*. 2012;69(6):562-571. doi:10.1001/archgenpsychiatry.2011.1592

29. Huttenlocher PR. Synaptic density in human frontal cortex - developmental changes and effects of aging. *Brain Res*. 1979;163(2):195-205. doi:10.1016/0006-8993(79)90349-4

30. Blakemore SJ, Choudhury S. Development of the adolescent brain: implications for executive function and social cognition. *J Child Psychol Psychiatry*. 2006;47(3-4):296-312. doi:10.1111/j.1469-7610.2006.01611.x

31. Feinberg I. Schizophrenia: caused by a fault in programmed synaptic elimination during adolescence? *J Psychiatr Res*. 1982-1983;17(4):319-334. doi:10.1016/0022-3956(82)90038-3

32. Fusar-Poli P, Radua J, McGuire P, Borgwardt S. Neuroanatomical maps of psychosis onset: voxel-wise meta-analysis of antipsychotic-naive VBM studies. *Schizophr Bull*. 2012;38(6):1297-1307. doi:10.1093/schbul/sbr134

33. Kambeitz J, Kambeitz-Ilankovic L, Cabral C, et al. Aberrant functional whole-brain network architecture in patients with schizophrenia: a meta-analysis. *Schizophr Bull*. 2016;42(1)(suppl 1):S13-S21. doi:10.1093/schbul/sbv174

34. Sui J, Pearlson GD, Du Y, et al. In search of multimodal neuroimaging biomarkers of cognitive deficits in schizophrenia. *Biol Psychiatry*. 2015;78(11):794-804. doi:10.1016/j.biopsych.2015.02.017

35. Barch DM, Ceaser A. Cognition in schizophrenia: core psychological and neural mechanisms. *Trends Cogn Sci*. 2012;16(1):27-34. doi:10.1016/j.tics.2011.11.015

36. Alekseichuk I, Turi Z, Amador de Lara G, Antal A, Paulus W. Spatial working memory in humans depends on theta and high gamma synchronization in the prefrontal cortex. *Curr Biol*. 2016;26(12):1513-1521. doi:10.1016/j.cub.2016.04.035

37. Schirner M, McIntosh AR, Jirsa V, Deco G, Ritter P. Inferring multi-scale neural mechanisms with brain network modelling. *Elife*. 2018;7:1-30. doi:10.7554/eLife.28927

38. Niessing J, Ebisch B, Schmidt KE, Niessing M, Singer W, Galuske RAW. Hemodynamic signals correlate tightly with synchronized gamma oscillations. *Science*. 2005;309(5736):948-951. doi:10.1126/science.1110948

39. Van Den Heuvel MP, Pol HEH. Exploring the brain network: a review on resting-state fMRI functional connectivity. *Psiquiatr Biol*. 2011;18(1):28-41. doi:10.1016/j.psiq.2011.05.001

40. Uhlhaas PJ, Singer W. Abnormal neural oscillations and synchrony in schizophrenia. *Nat Rev Neurosci*. 2010;11(2):100-113. doi:10.1038/nrn2774

41. Sheffield JM, Barch DM. Cognition and resting-state functional connectivity in schizophrenia. *Neurosci Biobehav Rev*. 2016;61:108-120. doi:10.1016/j.neubiorev.2015.12.007

42. Cardin JA, Carlén M, Meletis K, et al. Driving fast-spiking cells induces gamma rhythm and controls sensory responses. *Nature*. 2009;459(7247):663-667. doi:10.1038/nature08002

43. Lewis DA, Curley AA, Glausier JR, Volk DW. Cortical parvalbumin interneurons and cognitive dysfunction in schizophrenia. *Trends Neurosci*. 2012;35(1):57-67. doi:10.1016/j.tins.2011.10.004

44. Marín O. Interneuron dysfunction in psychiatric disorders. *Nat Rev Neurosci*. 2012;13(2):107-120. doi:10.1038/nrn3155

45. Howes OD, McCutcheon R. Inflammation and the neural diathesis-stress hypothesis of schizophrenia: a reconceptualization. *Transl Psychiatry*. 2017;7(2):e1024. doi:10.1038/tp.2016.278

46. Marques TR, Ashok AH, Pillinger T, et al. Neuroinflammation in schizophrenia: meta-analysis of *in vivo* microglial imaging studies. *Psychol Med*. 2019;49(13):2186-2196. doi:10.1017/S0033291718003057

47. Selvaraj S, Bloomfield PS, Cao B, Veronese M, Turkheimer F, Howes OD. Brain TSPO imaging and gray matter volume in schizophrenia patients and in people at ultra high risk of psychosis: an [^{11}C]PBR28 study. *Schizophr Res*. 2018;195:206-214. doi:10.1016/j.schres.2017.08.063

48. Yang GJ, Murray JD, Wang X-J, et al. Functional hierarchy underlies preferential connectivity disturbances in schizophrenia. *Proc Natl Acad Sci U S A*. 2016;113(2):E219-E228. doi:10.1073/pnas.1508436113

49. Radua J, Ramella-Cravaro V, Ioannidis JPA, et al. What causes psychosis? an umbrella review of risk and protective factors. *World Psychiatry*. 2018;17(1):49-66. doi:10.1002/wps.20490

50. Morgan C, Charalambides M, Hutchinson G, Murray RM. Migration, ethnicity, and psychosis: toward a sociodevelopmental model. *Schizophr Bull*. 2010;36(4):655-664. doi:10.1093/schbul/sbq051

51. Egerton A, Valmaggia LR, Howes OD, et al. Adversity in childhood linked to elevated striatal dopamine function in adulthood. *Schizophr Res*. 2016;176(2-3):171-176. doi:10.1016/j.schres.2016.06.005

52. Egerton A, Howes OD, Houle S, et al. Elevated striatal dopamine function in immigrants and their children: a risk mechanism for psychosis. *Schizophr Bull*. 2017;43(2):293-301. doi:10.1093/schbul/sbw181

53. Akdeniz C, Tost H, Streit F, et al. Neuroimaging evidence for a role of neural social stress processing in ethnic minority-associated environmental risk. *JAMA Psychiatry*. 2014;71(6):672-680. doi:10.1001/jamapsychiatry.2014.35

54. McCutcheon R, Bloomfield MAP, Dahoun T, et al. Amygdala reactivity in ethnic minorities and its relationship to the social environment: an fMRI study. *Psychol Med*. 2018;48(12):1985-1992. doi:10.1017/S0033291717003506

55. Lederbogen F, Kirsch P, Haddad L, et al. City living and urban upbringing affect neural social stress processing in humans. *Nature*. 2011;474(7352):498-501. doi:10.1038/nature10190

56. McCutcheon RA, Bloomfield MAP, Dahoun T, Mehta M, Howes OD. Chronic psychosocial stressors are associated with alterations in salience processing and corticostriatal connectivity. *Schizophr Res*. 2018;pii:S0920-9964(18)30699-6. doi:10.1016/j.schres.2018.12.011

57. Beards S, Gayer-Anderson C, Borges S, Dewey ME, Fisher HL, Morgan C. Life events and psychosis: a review and meta-analysis. *Schizophr Bull*. 2013;39(4):740-747. doi:10.1093/schbul/sbt065

58. Connell P. Amphetamine psychosis. *BMJ*. 1957;5018(1):582. doi:10.1136/bmj.1.5018.582

59. Abi-Dargham A, Gil R, Krystal J, et al. Increased striatal dopamine transmission in schizophrenia: confirmation in a second cohort. *Am J Psychiatry*. 1998;155(6):761-767.

60. McCutcheon R, Beck K, Jauhar S, Howes OD. Defining the locus of dopaminergic dysfunction in schizophrenia: a meta-analysis and test of the mesolimbic hypothesis. *Schizophr Bull*. 2018;44(6):1301-1311. doi:10.1093/schbul/sbx180

61. Howes OD, Kambeitz J, Kim E, et al. The nature of dopamine dysfunction in schizophrenia and what this means for treatment. *Arch Gen Psychiatry*. 2012;69(8):776-786. doi:10.1001/archgenpsychiatry.2012.169

62. Laruelle M, Abi-Dargham A, Gil R, Kegeles L, Innis R. Increased dopamine transmission in schizophrenia: relationship to illness phases. *Biol Psychiatry*. 1999;46(1):56-72. doi:10.1016/S0006-3223(99)00067-0

63. Howes OD, Montgomery AJ, Asselin M-C, et al. Elevated striatal dopamine function linked to prodromal signs of schizophrenia. *Arch Gen Psychiatry*. 2009;66(1):13-20. doi:10.1001/archgenpsychiatry.2008.514

64. Mizrahi R, Kenk M, Suridjan I, et al. Stress-induced dopamine response in subjects at clinical high risk for schizophrenia with and without concurrent cannabis use. *Neuropsychopharmacology*. 2014;39(6):1479-1489. doi:10.1038/npp.2013.347

65. Howes OD, Bose SK, Turkheimer F, et al. Dopamine synthesis capacity before onset of psychosis: a prospective [18F]-DOPA PET imaging study. *Am J Psychiatry*. 2011;168(12):1311-1317. doi:10.1176/appi.ajp.2011.11010160

66. Howes O, Bose S, Turkheimer F, et al. Progressive increase in striatal dopamine synthesis capacity as patients develop psychosis: a PET study. *Mol Psychiatry*. 2011;16(9):885-886. doi:10.1038/mp.2011.20

67. Abi-Dargham A, van de Giessen E, Slifstein M, Kegeles LS, Laruelle M. Baseline and amphetamine-stimulated dopamine activity are related in drug-naïve schizophrenic subjects. *Biol Psychiatry*. 2009;65(12):1091-1093. doi:10.1016/j.biopsych.2008.12.007

68. Schultz W, Dayan P, Montague PR. A neural substrate of prediction and reward. *Science*. 1997;275(5306):1593-1599. doi:10.1126/science.275.5306.1593

69. Menegas W, Akiti K, Amo R, Uchida N, Watabe-Uchida M. Dopamine neurons projecting to the posterior striatum reinforce avoidance of threatening stimuli. *Nat Neurosci*. 2018;21(10):1421-1430. doi:10.1038/s41593-018-0222-1

70. Menegas W, Babayan BM, Uchida N, Watabe-Uchida M. Opposite initialization to novel cues in dopamine signaling in ventral and posterior striatum in mice. *Elife*. 2017;6:1-26. doi:10.7554/eLife.21886

71. Nour MM, Dahoun T, Schwartenbeck P, et al. Dopaminergic basis for signaling belief updates, but not surprise, and the link to paranoia. *Proc Natl Acad Sci U S A*. 2018;115(43):E10167-E10176. doi:10.1073/pnas.1809298115

72. McCutcheon RA, Abi-Dargham A, Howes OD. Schizophrenia, dopamine and the striatum: from biology to symptoms. *Trends Neurosci*. 2019;42(3):205-220. doi:10.1016/j.tins.2018.12.004

73. Kapur S. Psychosis as a state of aberrant salience: a framework linking biology, phenomenology, and pharmacology in schizophrenia. *Am J Psychiatry*. 2003;160(1):13-23. doi:10.1176/appi.ajp.160.1.13

74. Kinderman P, Bentall RP. Causal attributions in paranoia and depression: internal, personal, and situational attributions for negative events. *J Abnorm Psychol*. 1997;106(2):341-345. doi:10.1037/0021-843X.106.2.341

75. Garety PA, Bebbington P, Fowler D, Freeman D, Kuipers E. Implications for neurobiological research of cognitive models of psychosis: a theoretical paper. *Psychol Med*. 2007;37(10):1377-1391. doi:10.1017/S003329170700013X

76. Kapur S, Zipursky R, Jones C, Remington G, Houle S. Relationship between dopamine D(2) occupancy, clinical response, and side effects: a double-blind PET study of first-episode schizophrenia. *Am J Psychiatry*. 2000;157(4):514-520. doi:10.1176/appi.ajp.157.4.514

77. Kapur S, Mamo D. Half a century of antipsychotics and still a central role for dopamine D2 receptors. *Prog Neuropsychopharmacol Biol Psychiatry*. 2003;27(7):1081-1090. doi:10.1016/j.pnpbp.2003.09.004

78. Silvestri S, Seeman MV, Negrete J-C, et al. Increased dopamine D2 receptor binding after long-term treatment with antipsychotics in humans: a clinical PET study. *Psychopharmacology (Berl)*. 2000;152(2):174-180. doi:10.1007/s002130000532

79. Jauhar S, Veronese M, Nour MM, et al. The effects of antipsychotic treatment on presynaptic dopamine synthesis capacity in first-episode psychosis: a positron emission tomography study. *Biol Psychiatry*. 2019;85(1):79-87. doi:10.1016/j.biopsych.2018.07.003

80. Samaha A-N, Seeman P, Stewart J, Rajabi H, Kapur S. "Breakthrough" dopamine supersensitivity during ongoing antipsychotic treatment leads to treatment failure over time. *J Neurosci*. 2007;27(11):2979-2986. doi:10.1523/JNEUROSCI.5416-06.2007

81. National Institute For Clinical Excellence. Psychosis and schizophrenia in adults: prevention and management: clinical guideline [CG178]. https://www.nice.org.uk/guidance/cg178. Published 2014. Accessed September 23, 2019.

82. Butzlaff RL, Hooley JM. Expressed emotion and psychiatric relapse: a meta-analysis. *Arch Gen Psychiatry*. 1998;55(6):547-552. doi:10.1001/archpsyc.55.6.547

83. Jauhar S, McKenna PJ, Radua J, Fung E, Salvador R, Laws KR. Cognitive-behavioural therapy for the symptoms of schizophrenia: systematic review and meta-analysis with examination of potential bias. *Br J Psychiatry*. 2014;204(1):20-29. doi:10.1192/bjp.bp.112.116285

84. Alameda L, Fournier M, Khadimallah I, et al. Redox dysregulation as a link between childhood trauma and psychopathological and neurocognitive profile in patients with early psychosis. *Proc Natl Acad Sci U S A*. 2018;115(49):12495-12500. doi:10.1073/pnas.1812821115

85. Thompson JL, Urban N, Slifstein M, et al. Striatal dopamine release in schizophrenia comorbid with substance dependence. *Mol Psychiatry*. 2013;18(8):909-915. doi:10.1038/mp.2012.109

86. Selvaraj S, Arnone D, Cappai A, Howes O. Alterations in the serotonin system in schizophrenia: a systematic review and meta-analysis of postmortem and molecular imaging studies. *Neurosci Biobehav Rev*. 2014;45:233-245. doi:10.1016/j.neubiorev.2014.06.005

87. Erickson MA, Ruffle A, Gold JM. A meta-analysis of mismatch negativity in schizophrenia: from clinical risk to disease

specificity and progression. *Biol Psychiatry*. 2016;79(12):980-987. doi:10.1016/j.biopsych.2015.08.025

88. Kim IH, Rossi MA, Aryal DK, et al. Spine pruning drives antipsychotic-sensitive locomotion via circuit control of striatal dopamine. *Nat Neurosci*. 2015;18(6):883-891. doi:10.1038/nn.4015

89. McCutcheon R, Nour MM, Dahoun T, et al. Mesolimbic dopamine function is related to salience network connectivity: an integrative positron emission tomography and magnetic resonance study. *Biol Psychiatry*. 2019;85(5):368-378. doi:10.1016/j.biopsych.2018.09.010

90. Mouchlianitis E, McCutcheon R, Howes OD. Brain-imaging studies of treatment-resistant schizophrenia: a systematic review. *Lancet Psychiatry*. 2016;3(5):451-463. doi:10.1016/S2215-0366(15)00540-4

91. Zhang J-P, Robinson D, Yu J, et al. Schizophrenia polygenic risk score as a predictor of antipsychotic efficacy in first-episode psychosis. *Am J Psychiatry*. 2019;176(1):21-28. doi:10.1176/appi.ajp.2018.17121363

92. Wimberley T, Gasse C, Meier SM, Agerbo E, MacCabe JH, Horsdal HT. Polygenic risk score for schizophrenia and treatment-resistant schizophrenia. *Schizophr Bull*. 2017;43(5):1064-1069. doi:10.1093/schbul/sbx007

93. Wimberley T, Støvring H, Sørensen HJ, Horsdal HT, MacCabe JH, Gasse C. Predictors of treatment resistance in patients with schizophrenia: a population-based cohort study. *Lancet Psychiatry*. 2016;3(4):358-366. doi:10.1016/S2215-0366(15)00575-1

94. McCutcheon RA, Pillinger T, Mizuno Y, et al. The efficacy and heterogeneity of antipsychotic response in schizophrenia: a meta-analysis [published online August 30, 2019]. *Mol Psychiatry*. doi:10.1038/s41380-019-0502-5

95. Galderisi S, Mucci A, Buchanan RW, Arango C. Negative symptoms of schizophrenia: new developments and unanswered research questions. *Lancet Psychiatry*. 2018;5(8):664-677. doi:10.1016/S2215-0366(18)30050-6

96. Brugger SP, Howes OD. Heterogeneity and homogeneity of regional brain structure in schizophrenia: a meta-analysis. *JAMA Psychiatry*. 2017;74(11):1104-1111. doi:10.1001/jamapsychiatry.2017.2663

97. Insel T, Cuthbert B, Garvey M, et al. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. *Am J Psychiatry*. 2010;167(7):748-751. doi:10.1176/appi.ajp.2010.09091379

98. Kaar SJ, Natesan S, McCutcheon R, Howes OD. Antipsychotics: mechanisms underlying clinical response and side-effects and novel treatment approaches based on pathophysiology. *Neuropharmacology*. 2019;107704:107704. doi:10.1016/j.neuropharm.2019.107704