Review

Biological Psychiatry

The Mechanisms of Persisting Disability in Schizophrenia: Imprecise Predictive Coding via Corticostriatothalamic-Cortical Loop Dysfunction

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ABSTRACT

Persisting symptoms and disability remain a problem for an appreciable proportion of people with schizophrenia despite treatment with antipsychotic medication. Improving outcomes requires an understanding of the nature and mechanisms of the pathological processes underlying persistence. Classical features of schizophrenia, which include disorganization and impoverishment of mental activity, are well-recognized early clinical features that predict poor long-term outcome. Substantial evidence indicates that these features reflect imprecise predictive coding. Predictive coding provides an overarching framework for understanding efficient functioning of the nervous system. Imprecise predictive coding also has the potential to precipitate acute psychosis characterized by reality distortion (delusions and hallucinations) at times of stress. On the other hand, substantial evidence indicates that persistent reality distortion itself gives rise to poor occupational and social function in the long term. Furthermore, abuse of psychotomimetic drugs, which exacerbate reality distortion, contributes to poor long-term outcome in schizophrenia. Neural circuits involved in modulating volitional acts are well understood to be implicated in addiction. Plastic changes in these circuits may account for the association between psychotomimetic drug abuse and poor outcomes in schizophrenia. We propose a mechanistic model according to which unbalanced inputs to the corpus striatum disturb the precision of subcortical modulation of cortical activity supporting volitional action. This model accounts for the evidence that early classical symptoms predict poor outcome, while in some circumstances, persistent reality distortion also predicts poor outcome. This model has implications for the development of novel treatments that address the risk of persisting symptoms and disabilities in schizophrenia.

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The classical descriptions of schizophrenia by Kraepelin (1) and Bleuler (2) emphasized disorganized and impoverished mental activity. Kraepelin (1) emphasized disjointed and weakened volition; Bleuler (2) regarded loose associations and blunted affect as fundamental symptoms. However, in the quest for increased diagnostic reliability in the second half of the 20th century (3), focus shifted to delusions and hallucinations. These symptoms are prominent in contemporary diagnostic criteria, i.e., DSM-5 (4) and ICD-11 (5).

DSM-5 and ICD-11 place schizophrenia at the severe end of a continuum of psychotic disorders. Some authors argue that the term schizophrenia should be dropped on account of potentially harmful expectations of poor outcome (6). Nonetheless, an appreciable proportion of individuals with schizophrenia do experience persisting symptoms or disability despite current treatments (7). If we are to improve outcome, we need to understand the pathological processes leading to persistence.

Diverse symptoms occur in schizophrenia. Factor analysis of scores based on the Signs and Symptoms of Psychotic Illness scale reveals 5 distinguishable clusters of symptoms (Table 1) (8).

The Signs and Symptoms of Psychotic Illness scale was designed to cover the major symptoms of psychotic illness in a jointly exhaustive, yet mutually exclusive manner. Meta-analysis of factor structure of the widely used Positive and Negative Syndrome Scale reveals 5 similar clusters of symptoms (9). The grouping of symptoms identified by factor analysis depends on choice of symptom scale, sample selection, and analysis procedure. Nonetheless, clusters of symptoms reflecting impoverished and disorganized mental activity emerge in many analyses (10–13).

Our aim in this review is to delineate the clinical features associated with persistent symptoms and disability and to propose underlying mechanisms. We focus on 2 disparate descriptions of the illness:

1. A classical description based on the accounts by Kraepelin (1) and Bleuler (2) in which disorganization and impoverishment of mental activity reflect a core process predisposing to cognitive impairment and impaired role function (14). This description is consistent with the evidence that a developmental process associated with impaired social and

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Table 1. Symptom Dimensions in Psychotic Illness Derived From Signs and Symptoms of Psychotic Illness Scale Scores

Symptom Cluster	Symptoms
Reality Distortion	Delusions
	Hallucinations
Disorganization	Positive formal disorder
	Impaired attention
	Inappropriate affect
Psychomotor Poverty	Poverty of speech
	Flat affect
	Anhedonia
	Motor underactivity
Psychomotor Excitation	Pressure of speech
	Elevated mood
	Motor overactivity
	Insomnia
Depression/Anxiety	Depressed mood
	Anxiety

occupation function before onset of psychosis predicts poor outcome (15).

2. A description in which delusions and hallucinations are the core process with the potential to exert toxic effects leading to cognitive impairment, negative symptoms, and poor outcome. This latter description is consistent with evidence that duration of untreated psychosis (DUP) is associated with poor outcome (16).

After presenting these disparate descriptions, we produce a synthesis uniting the proposed underlying mechanisms.

CLASSICAL SCHIZOPHRENIA

The availability of dopamine-blocking antipsychotic medication has led to only a modest improvement in long-term outcome of schizophrenia (17,18). While DUP predicts outcome in the short and medium term (16), it has weaker long-term predictive power. A meta-analysis of studies with a mean follow-up duration of 8.1 years found that DUP exhibited a correlation with poor social outcome of 0.18 and no significant correlation with employment or hospitalization (19).

In a longitudinal study of 3021 young people, Dominguez *et al.* (20) found that premorbid signs of disorganized mental activity and negative symptoms predicted subsequent onset of psychosis and further predicted poor long-term outcome.

Hafner *et al.* (21) found that prodromal symptoms preceded onset of psychosis by a mean period of 5 years. These prodromal symptoms included negative symptoms such as social withdrawal and features of disorganized mental activity such as difficulties in thinking and concentration. In young people exhibiting features indicative of high risk of psychosis, Ziermans *et al.* (22) found that disorganized mental activity was the strongest predictor of poor long-term outcome. In the PRONIA (Personalised Prognostic Tools for Early Psychosis Management) study, a large multicenter, longitudinal study of individuals at high risk of psychosis, the prodromal symptom scores at baseline that most strongly predicted poor role function at follow-up were poor occupational function, lack of ideational richness, and disorganized communication (23).

Analysis of the speech of young people at high risk of psychotic disorder reveals that subtle abnormalities of the form of thought and communication predict subsequent onset of overt psychosis and/or poor role function. For example, Bearden *et al.* (24) found that formal thought disorder and illogical thinking predicted conversion to overt psychosis, while poverty of content of speech and lack of referential cohesion predicted poor social and role functioning, respectively. Using automated natural language processing, Bedi *et al.* (25) demonstrated that semantic coherence (meaningful relationships between words) and speech complexity predicted subsequent overt psychosis. Mota *et al.* (26) demonstrated that disorganization of speech quantified using graph theory in individuals at high risk for psychosis predicted onset of overt psychosis and severity of negative symptoms within the following 6 months.

In summary, substantial evidence indicates that prodromal features of classical schizophrenia, including disorganization and impoverishment of mental activity, predict the onset of overt psychosis and the risk of long-term functional deficits. Longitudinal studies of cases with established illness reveal that cognitive impairment at baseline also predicts poor functional outcome (27). In the stable phase of illness, psychomotor poverty and disorganization are associated with poor occupational and social function (28,29). Furthermore, the evidence that disorganization is the feature of schizophrenia with the highest heritability and that polygenic score for schizophrenia predicts disorganization and, to a lesser extent, negative symptoms and cognitive impairment (30,31) is consistent with the proposal that classical symptoms are primary features.

Liddle (14) proposed the term classical schizophrenia to describe the condition in which disorganization and impoverishment of mental activity, as described by Kraepelin (1) and Bleuler (2), reflect a core process predisposing to persisting cognitive impairment and impaired role function and to overt psychosis at times of stress.

However, contrary to the progressive decline implied by Kraepelin's term dementia praecox, classical schizophrenia tends to resolve in the long term in many cases. Ciompi (32) identified 8 distinguishable trajectories of illness in 1642 cases followed for an average of 37 years. Overall course of illness was favorable in more than half of the cases. Similar findings were reported by Huber *et al.* (33) and Bleuler (34). Harding *et al.* (35) followed 118 patients satisfying DSM-III criteria for schizophrenia and representative of the most impaired third of the Vermont State Hospital inpatient population before active rehabilitation in the mid-1950s. Three decades after resettling in the community, 68% of individuals had recovered or had improved substantially. Nonetheless, in contrast, a recent longitudinal study of illness time course over 25 years from first admission reported that patients with schizophrenia exhibited stable remission and recovery rates of 0% and 0.6%, respectively (36).

MECHANISM OF CLASSICAL SCHIZOPHRENIA

Classical schizophrenia is related to diverse abnormalities of brain function. Rathnaiah *et al.* (37) demonstrated that a latent variable representing shared variance between the classical

features is correlated with reduction in post-movement beta rebound (PMBR). PMBR is an increase of power of brain electrical oscillations in the beta frequency band (13–30 Hz) for several seconds after movement. Hunt *et al.* (38) demonstrated that disorganization and negative schizotypal features are associated with diminished PMBR in a nonclinical sample. Gascoyne *et al.* (39) confirmed that disorganized mental activity is associated with reduced PMBR in chronic schizophrenia. It is noteworthy that PMBR is also diminished in several neurodevelopmental conditions, including attention-deficit/hyperactivity disorder (40) and autism (41).

Beta oscillations play an important modulatory role in the motor system. Jenkinson and Brown (42) concluded that beta oscillations reflect the likelihood of the need to prepare a new voluntary movement. They noted that dopamine levels in the basal ganglia, modulated by salient internal and external cues, determine the magnitude of beta oscillations. They proposed that resulting beta activity is predictive, facilitating the allocation of neural resources for subsequent action.

In studies in healthy participants in which the consequences of movements were covertly manipulated by the experimenter to influence the participant's confidence in the outcome of the motor act, Tan *et al.* (43) demonstrated that high-amplitude PMBR reflects confidence in the current motor plan, whereas low-amplitude PMBR might indicate the need for adaptive changes driven by the sensory feedback. Palmer *et al.* (44) demonstrated that beta power preceding and following movement during sensorimotor adaptation was inversely correlated with the uncertainty assigned to sensory prediction errors.

Employing concurrent electroencephalography and functional magnetic resonance imaging, Briley *et al.* (45) confirmed the association between reduced PMBR and the clinical features of classical schizophrenia. Furthermore, the patients exhibited fewer bursts of beta oscillations relative to healthy control participants throughout a working memory task. The relationship between beta bursts and blood oxygen level–dependent signal supported the hypothesis that beta bursts reactivate the neural representation of sensorimotor information maintained in a latent state during the working memory task. The patients exhibited increased magnitude and spatial extent of the blood oxygen level–dependent signal associated with beta bursts, possibly indicating inefficiency of cortical synchrony mediated by beta bursts. This suggests that latent neural representation of the content of working memory is less precisely specified in schizophrenia, potentially generating the loose associations characteristic of disorganized mental activity.

More generally, beta bursts appear to play a role in wide-ranging functional connectivity (46). Substantial evidence indicates that the features of classical schizophrenia are associated with widespread disturbance of functional and effective connectivity between brain regions. Palaniyappan *et al.* (47) found that a composite measure of clinical features characteristic of classical schizophrenia was associated with impaired effective connectivity in a neural pathway extending from occipital cortex to insula and then to dorsolateral prefrontal cortex (DLPFC).

On the basis of the evidence regarding abnormal beta oscillations during working memory performance and various other abnormalities indicating imprecise neural representation of perceptions and plans for action, Liddle and Liddle (48) proposed that the disorganization and impoverishment of mental activity characteristic of classical schizophrenia arise from imprecise predictive coding. Predictive coding provides an overarching framework for understanding efficient function of the nervous system. It accounts for efficient generation of coherent perceptions from sensory input and for the guidance of action by internally generated plans. Furthermore, other electrophysiological abnormalities including reduced mismatch negativity, reduced P300, and reduced 40-Hz oscillatory responses are also consistent with the proposal that imprecise predictive coding is associated with classical clinical features and persistent disability (48).

Reviews of brain regions engaged in predictive coding reveal that extensive frontal and temporal cortical regions and related subcortical nodes are involved (49,50). The insula is involved in both encoding predictions and detection of prediction errors (49). The insula is a key node of the salience network, which includes a regulatory corticostriatothalamic-cortical (CSTC) circuit that is modulated by dopamine. The salience network plays a cardinal role in diverse mental disorders (51), including schizophrenia (52). Meta-analysis and mega-analysis of gray matter density in schizophrenia indicate widespread abnormalities, though the most significant deficits are in the insula (53,54).

Imprecise predictive coding provides a mechanism by which prior disorganization and/or impoverishment of mental activity may lead to reality distortion at times of stress. Ongoing imprecise neural representation of plans for action and/or perceptions would be expected to lead to frequent prediction errors and increased net dopamine levels (55,56). Haarsma *et al.* (57) examined the effects of dopaminergic agents on learning from information varying in precision. They concluded that the weighting of precision is modulated by dopamine, and this weighting is perturbed in psychosis.

The proposal that imprecise predictive coding is the core feature of classical schizophrenia is consistent with the proposal by Adams *et al.* (58) that trait abnormalities of schizophrenia, including disorganized or impoverished mental activity, arise from lack of precision of internally generated predictions (or allocation of excessive weight to sensory evidence). Adams *et al.* (58) proposed that the trait features might arise from abnormal glutamatergic or GABAergic (gamma-aminobutyric acidergic) transmission. Furthermore, they proposed that a compensatory increase in dopaminergic transmission might result in increased precision of internally generated predictions leading to acute psychotic symptoms.

While Adams *et al.* (58) focused on the way in which a trait reflecting imprecise predictions might lead to a compensatory increase in precision of prediction and consequent acute psychosis, we propose not only that imprecise predictive coding associated with prodromal disorganized and/or impoverished mental activity might lead to subsequent overt psychosis, but also that over time a persisting tendency to prediction errors might impair decision making and memory formation, leading to impaired cognition and persisting disability characteristic of classical schizophrenia.

TOXIC EFFECTS OF REALITY DISTORTION

Delusions and hallucinations (reality distortion) are characteristic features of a spectrum of psychotic disorders that differ in

their tendency toward persisting symptoms and disability. This spectrum extends from schizophrenia to schizoaffective disorder, schizophreniform disorder, and brief psychotic disorder. Whereas the DSM-5 criteria for schizophrenia specify continuous mental disturbance for at least 6 months, brief psychotic disorder entails the occurrence of psychotic symptoms with sudden onset and full remission within 1 month (4). Thus, reality distortion can be part of a transient disorder, but in other circumstances, it reflects a more persistent disorder.

Effective treatment of realty distortion is associated with favorable long-term outcome. Wyatt (59) reanalyzed data from 19 studies of early-phase cases of schizophrenia and found that early intervention with antipsychotic medication improved the long-term course of illness. He proposed that psychosis itself might have a toxic effect on the brain.

The observation that in schizophrenia, early deterioration in function stabilizes within 2 to 5 years of onset, together with evidence that DUP predicts poor outcome, led McGorry *et al.* (60) to propose that recognition and management of early psychosis might prevent deterioration. As noted in Classical Schizophrenia, a recent meta-analysis confirms that long DUP predicts poor outcome, at least in the short term (16), though meta-analysis of studies with long duration of follow-up found only a weak association between long DUP and poor outcome (19).

Complex methodological issues arise in identifying mechanisms by which DUP might lead to poor long-term function. For example, in cases with insidious onset, it might be that some cases of extended DUP are cases with an extended classical prodromal state with subclinical psychotic features. It may be the classical features rather than reality distortion that drive the later loss of function. Furthermore, it is difficult to exclude the possibility that any neural abnormality associated with proposed toxic effects of untreated psychosis might have arisen before the onset of the psychotic symptoms. It is nonetheless noteworthy that Crespo-Facorro *et al.* (61) found that length of delay in receiving antipsychotic treatment in first-episode schizophrenia was associated with reduced volume of the caudate nucleus, a site rich in dopaminergic nerve terminals.

Another source of evidence suggesting that reality distortion might be toxic is the observation that drugs that induce reality distortion can worsen prognosis in schizophrenia (62). A meta-analysis including more than 40,000 participants showed that likelihood of transition from substance-induced disorder to schizophrenia appeared to mirror psychotomimetic potency (i.e., ability to induce reality distortion) with high rates (36%–22%) for cannabis, hallucinogens, and amphetamines and comparatively low rates (<12%) for opioids, alcohol, and sedatives (63). Meta-analysis reveals that psychotomimetic substance use predicts earlier onset of illness (64). Continued use predicts relapse and hospitalization (65). Psychotomimetic substance use is associated with worse long-term function and higher disability (62). Large prospective cohort studies have examined the effect of substance misuse on outcomes of psychosis by comparing dual diagnosis and psychosis-only groups (summarized in Table S1).

In the CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) study, the largest publicly funded randomized clinical trial in schizophrenia to date (N = 1423), post hoc analysis at 18 month follow-up found significantly worse symptom scores and quality of life for moderate to severe substance abuse compared with mild substance use or no use (66). In the OPUS (Implementation of Early Intervention Services) trial, a randomized clinical trial assessing early intervention services, 5-year follow-up (N = 314) showed that continuous cannabis use was associated with persisting psychosis, only partly accounted for by insufficient antipsychotic medication (67). Overall, there is replicated evidence showing the following: 1) substance users, including cannabis users, with psychosis have worse long-term outcome than individuals without substance use; 2) this remains after adjusting for confounding associations; 3) poorer symptoms in this group are not limited to reality distortion or positive symptoms and include poorer function and disability; and 4) decreasing substance use within 1 to 2 years modifies both short- and long-term outcome. Nonetheless, it should also be noted that in the presence of adequate blockade of dopamine receptors, therapeutic use of stimulants can reduce the risk of hospital admission for psychosis (68).

The effects of cannabis use in psychotic disorders illustrate the trajectory of damage. Initially there is neurocognitive sparing illustrated by fewer neurological soft signs and less neurodevelopmental burden compared with non-users (62). However, function deteriorates over time. In the UK National EDEN (Evaluating the Development and Impact of Early Intervention Services) study, more than a year of continued use of cannabis was associated with higher Positive and Negative Syndrome Scale total scores, Positive and Negative Syndrome Scale negative symptoms scores, and Calgary Depression Scale for Schizophrenia scores and worse global functioning (69). A 10-year follow-up of cases of first-episode psychosis found higher symptom scores and poorer function in cannabis users compared with non-users (70).

The review by Sami and Bhattacharyya (62) showed that patients using cannabis also exhibit greater deterioration in neurobiological markers than non-users after the first 5 years of a psychotic disorder. These include increased ventricular size; cortical thinning; reduced gray matter; and shape changes in hippocampus, striatum, globus pallidus, and thalamus. The evidence regarding clinical features and neurobiological markers indicates that substance users have less neural impairment initially but develop increasing functional impairment such that after several years they resemble cases of classical schizophrenia.

MECHANISM OF TOXIC EFFECTS OF REALITY DISTORTION

The role of dopamine in schizophrenia has been a focus of research since Seeman and Lee (71) demonstrated that the efficacy of antipsychotics was strongly correlated with affinity for the dopamine D_2 receptor. After reviewing research up to 2009, Howes and Kapur (72) concluded that “multiple environmental and genetic risk factors interact to funnel through one final common pathway of presynaptic striatal hyperdopaminergia.” Howes and Kapur proposed that dopamine-blocking medication acts downstream of the critical neurotransmitter abnormality.

Subsequent studies have supported the conclusions drawn by Howes and Kapur (72). For example, using positron emission tomography with ^{18}F-fluorodopa to assess presynaptic dopamine synthesis in the striatum, Jauhar *et al.* (73) confirmed that presynaptic dopamine synthesis is elevated in both schizophrenia and bipolar affective disorder. Relevant to the question of persisting symptoms and disability, 2 positron emission tomography studies using ^{18}F-fluorodopa found that patients who responded to antipsychotic medication had evidence of greater presynaptic dopamine synthesis in the striatum than patients who did not respond to treatment, while patients with nonresponsive symptoms exhibited no elevation of ^{18}F-fluorodopa uptake relative to healthy control participants (74,75). This suggests that some process other than elevation of presynaptic dopamine in the striatum contributes to treatment-resistant symptoms.

Abnormal glutamatergic neurotransmission might contribute. Glutamate concentration in anterior cingulate cortex is inversely related to striatal dopamine synthesis capacity in patients with psychosis (76). There is evidence for a similar relationship between striatal dopamine and hippocampal glutamate for individuals at risk for psychosis (77). Some studies have indicated that perturbed glutamatergic indices are a marker of treatment resistance (78–80).

Nonetheless, studies of psychotomimetic drugs indicate that dopamine overactivity plays a role in persistent symptoms. In a review, Wearne and Cornish (81) demonstrated that chronic psychosis associated with repeated use of methamphetamine, a stimulant that enhances dopamine release from presynaptic terminals, exhibits diverse clinical features similar to schizophrenia including cognitive impairments.

The mechanism of subcortical and cortical neuroplastic changes occurring during addiction are potentially relevant to the mechanism of the toxic effects of reality distortion. These changes were described in detail by Everitt and Robbins (82) and by Koob and Volkow (83). An essential feature is that dopamine overactivity in the striatum is associated with plastic changes that disrupt the balance of inputs from prefrontal cortex, amygdala, and hippocampus to the striatum. These striatal inputs shape the regulatory role of subcortical nuclei on the cortical activity supporting volitional behavior. Disruption of the balance between the influence of amygdala and hippocampus would be expected to disrupt the balance between influence of immediate sensory information transmitted via the amygdala and contextual information mediated by the hippocampus on the regulation of voluntary behavior. This might lead to the secondary features associated with addiction such as decreased volition, apathy, and impaired role function.

In light of the evidence that repeated use of psychotomimetics that enhance dopamine release in the striatum can lead to a psychotic disorder resembling chronic schizophrenia (81), that psychotomimetics can worsen prognosis in schizophrenia (62), and that dopamine overactivity is associated with reality distortion (72), we propose that plastic changes in CSTC loops induced by persistent reality distortion can lead to persisting symptoms and disability in schizophrenia. In light of the evidence that patients whose symptoms do not respond to dopamine-blocking antipsychotic medication do not exhibit evidence of elevated presynaptic dopamine synthesis (74,75), some other pathological process must be involved. Such processes might involve other neurotransmitters involved in the CSTC circuits, i.e., glutamate, GABA, or acetylcholine.

When Alexander *et al.* (84) first delineated the role of multiple CSTC loops in regulating cortical activity in primates, they identified 5 distinguishable loops involving different areas of cortex and corresponding regions of striatum and thalamus. Subsequent studies have shown a similar but more complex pattern of CSTC loops in humans. Resting-state functional magnetic resonance imaging studies reveal the salience loop involving bilateral insula, anterior cingulate cortex, parts of the striatum, and dorsomedial thalamus (85), mentioned earlier in Mechanism of Classical Schizophrenia. This loop is involved in the identification of behaviorally salient stimuli and in recruitment of relevant brain circuits (86). Substantial evidence indicates that abnormality of the salience loop is involved in diverse symptoms of schizophrenia, including reality distortion, disorganization, and psychomotor poverty (52).

There is also substantial evidence for involvement of DLPFC in schizophrenia, especially in the cognitive impairments such as impaired executive function (87). We therefore propose that a CSTC loop involving DLPFC, striatum, and dorsomedial thalamus also plays a role in persisting symptoms and

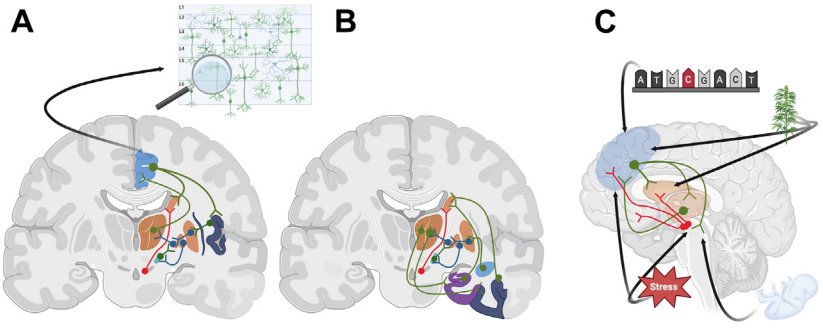

Figure 1. The corticostriatothalamic-cortical circuits that play a central role in reality distortion and classical schizophrenia. These corticostriatothalamic-cortical circuits interact with extensive cortical networks contributing to wide-ranging dysfunction in schizophrenia. **(A)** Coronal section illustrating the salience circuit, with inset illustrating interactions between interneurons and pyramidal cells that might modify synaptic gain of pyramidal neurons. Brain regions: light blue, anterior cingulate cortex; dark blue, insula cortex and claustrum; orange, thalamus and basal ganglia. **(B)** Schematic illustration of the contribution of medial temporal lobe structures to regulation of the corticostriatothalamic-cortical circuits. Brain regions: dark blue, parahippocampal gyrus and fusiform gyrus; purple, hippocampal formation; light blue, amygdala; orange, thalamus and basal ganglia. **(C)** Sagittal view illustrating some likely sites of action of predisposing and exacerbating factors, including genetic load (represented by a DNA strand with nucleotides adenine [A], thymine [T], guanine [G], and cytosine [C]), cannabis, neurodevelopmental injury, and stress. Brain regions: light blue, frontal cortex; orange, thalamus and basal ganglia. Anatomical locations are approximate for purpose of demonstration. Projections: green, glutamatergic; blue, GABAergic; red, dopaminergic projections from midbrain. (Created with BioRender.com.)

disability in schizophrenia. Dopaminergic abnormalities in schizophrenia are especially pronounced in associative regions that are involved in both the DLPFC and the salience CSTC loops (88). There is interaction between the loops, and it is likely that other loops also undergo plastic change.

SYNTHESIS

Our proposed mechanisms of classical schizophrenia and of the toxic effects of reality distortion are complementary. Both mechanisms entail plastic changes in CSTC circuits, especially the DLPFC and salience loops (Figure 1). The mechanisms differ in the nature of the postulated primary problem.

In classical schizophrenia, we propose that the primary abnormality is disorganization and impoverishment of mental activity reflecting relatively widespread cortical and subcortical abnormality. We propose that the associated imprecision of predictive coding leads to excessive dopamine release in the striatum predisposing to reality distortion, especially at times of stress.

Conversely, in the case of primary reality distortion arising from causes such as repeated use of psychotomimetic drugs, we propose that sustained reality distortion leads to plastic changes in the CSTC loops that result in impaired regulation of cortical regions supporting voluntary activity. This sustained aberrant regulation might lead to the loss of synaptic gain in pyramidal cells, which Adams *et al.* (89) demonstrated accounts for electrophysiological abnormalities associated with trait features of schizophrenia. These plastic changes result in disorganized and impoverished mental activity and sustained impairment of cognition and role function.

IMPLICATIONS FOR RESEARCH AND PRACTICE

Our proposal opens paths to further investigation of the mechanisms of persisting symptoms and disability in schizophrenia. Mathematical predictive coding models provide a promising approach to delineating neural mechanisms underlying classical clinical features. We propose modeling interactions between cortical regions and subcortical nuclei, including the modeling of plastic change over time (90,91), with the goal of comparing modeled predictions with observed longitudinal changes in brain function. We also propose modeling the generation of transient beta oscillations (92) to clarify the role of imprecise predictive coding in abnormal sensorimotor beta oscillations in classical schizophrenia. A major classical feature is abnormal speech and language (14,93). During speech processing, beta oscillations in the left hemisphere are diminished and delayed in schizophrenia (94), possibly reflecting abnormal modulation of prediction error precision (95). Computational predictive coding models offer a promising approach to investigating relevant speech abnormalities (95). Our proposals also have implications for the development of novel therapies, such as neuromodulation techniques targeting CSTC circuits (51), as outlined in the Supplement.

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ARTICLE INFORMATION

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