Circuit-Based Approaches to Understanding Corticostriatothalamic Dysfunction Across the Psychosis Continuum

Kristina Sabaroedin, Jeggan Tiego, and Alex Fornito

ABSTRACT

Dopamine is known to play a role in the pathogenesis of psychotic symptoms, but the mechanisms driving dopaminergic dysfunction in psychosis remain unclear. Considerable attention has focused on the role of corticostriatothalamic (CST) circuits, given that they regulate and are modulated by the activity of dopaminergic cells in the midbrain. Preclinical studies have proposed multiple models of CST dysfunction in psychosis, each prioritizing different brain regions and pathophysiological mechanisms. A particular challenge is that CST circuits have undergone considerable evolutionary modification across mammals, complicating comparisons across species. Here, we consider preclinical models of CST dysfunction in psychosis and evaluate the degree to which they are supported by evidence from human resting-state functional magnetic resonance imaging studies conducted across the psychosis continuum, ranging from subclinical schizotypy to established schizophrenia. In partial support of some preclinical models, human studies indicate that dorsal CST and hippocampal-striatal functional dysconnectivity are apparent across the psychosis spectrum and may represent a vulnerability marker for psychosis. In contrast, midbrain dysfunction may emerge when symptoms warrant clinical assistance and may thus be a trigger for illness onset. The major difference between clinical and preclinical findings is the strong involvement of the dorsal CST in the former, consistent with an increasing prominence of this circuitry in the primate brain. We close by underscoring the need for high-resolution characterization of phenotypic heterogeneity in psychosis to develop a refined understanding of how the dysfunction of specific circuit elements gives rise to distinct symptom profiles.

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The symptoms of psychosis are proposed to lie on a continuum of severity (1), with the subclinical expression of schizotypal traits and transient psychosis-like experiences at one end and clinically diagnosed psychotic disorders such as schizophrenia at the other (2–5). Interposed between these extremes lie various levels of symptom expression that include prodromal state or at-risk mental state (ARMS) (6–8) and first-episode psychosis (FEP), which is commonly operationalized as the period of first treatment contact following symptom onset (9). Each incremental level of severity across the continuum is associated with an increased risk of developing a more severe form of illness (10–12).

Since the seminal discovery more than half a century ago that dopamine (DA) antagonists are effective in treating psychotic symptoms (13,14), extensive evidence has supported a central role for DA, and the corticostriatothalamic (CST) systems that regulate its release, in the pathogenesis of psychosis (15–19). Different models of CST and DA dysregulation in psychosis have been proposed. Many of these models are based on preclinical studies and vary in the degree to which different circuit elements are emphasized as primary sites of dysfunction. In parallel, advances in circuit mapping techniques with noninvasive neuroimaging have progressed our understanding of CST disruptions in patients at different stages of the illness. Here, we review this work in relation to existing preclinical models of CST dysfunction, with the aim of identifying continuities and discontinuities between these models and the human literature. We focus principally on classical models of the dorsal and ventral CST circuits (15,18,20–23) because of their central role in DA regulation and extensive characterizations of these circuits in past work, which have been central to pathophysiological models of psychosis. Other systems also likely play an important role in symptom expression [e.g., (24–26)], but they have not been subjected to the same degree of translational investigation. We also focus on findings from human resting-state functional magnetic resonance imaging (fMRI), which has become the most popular method for studying CST dysconnectivity in psychosis. We examine findings across different stages of the psychosis continuum to understand how CST dysfunction evolves with illness progression. We close by emphasizing the need for high-resolution phenotyping of the psychosis spectrum to better understand the individual clinical and neurobiological heterogeneity that characterizes symptom expression along the continuum. We begin with a brief description of CST circuit anatomy and function.
CST CIRCUITRY AND DA FUNCTION

CST circuitry is classically divided into 5 parallel, integrated circuits that topographically link the striatum with the prefrontal cortex (PFC) along a rostroventral to dorsocaudal gradient, with each circuit subserving a specific set of functions (27–31). These prefrontal systems are accompanied by additional CST circuits connecting to early and associative sensory cortices and the cerebellum (32–34).

Two CST circuits that are frequently implicated in psychosis are the ventral limbic and dorsal associative circuits. The ventral circuit links the ventral region of the striatum, including the nucleus accumbens, with PFC regions subserving emotion function and regulation, such as the ventromedial PFC and orbitofrontal cortex (27,29,31). The ventral striatum also has extensive connections to the hippocampus and amygdala (17,18,35–38). The dorsal circuit links the dorsolateral PFC (DLPFC) with the dorsal caudate and putamen and plays a role in information integration and associative learning (27,31,39,40). Interposed between the dorsal and ventral systems is the anterior cingulate cortex circuit, which links reward and affective valuation with executive cognition, and projections from this cortical area terminate at the intersection of the ventral and dorsal striatum (29,41–43). Each striatal subregion then projects back to the cortex via the pallidum and thalamus, forming a series of closed corticostriatal feedback loops (44,45).

DA neurons in the midbrain project diffusely throughout the striatum and cortex via the mesolimbic, nigrostriatal, and mesocortical pathways, respectively (46–48). At baseline, or during normal contexts, DA neurons exhibit tonic, spontaneous firing driven by membrane currents of DA neurons that are regulated by inhibitory projections from the striatum (49,50). Classical views of DA function posit that, in salient contexts such as the presentation of an unexpected reward, DA neurons switch to phasic activity, characterized by transient, high-amplitude burst firing, which is integral to reinforcement learning (51,52). In addition to this form of prediction error signaling, DA neurons also play essential roles in the maintenance of internal states, value computation, action selection, and motivation, with each behavior associated with the firing of specific, spatially clustered neurons within the midbrain and striatum (53–55). Only tonically active neurons can switch to phasic firing; as such, cortical and medial temporal areas can govern the responsivity of the DA system through the striatum (52) and through direct projections to the midbrain. The latter projections control midbrain activity via 2 opposing mechanisms: one that increases the likelihood of DA release through direct glutamatergic input to dopaminergic neurons (56) and another that inhibits dopaminergic cells via glutamatergic synapses onto GABA (gamma-aminobutyric acid) cells in the midbrain (15). These 2 mechanisms, respectively, act like an accelerator and brake on DA neurons, ensuring the appropriate regulation of DA release (15,57).

The striatum is positioned between the cortex and the midbrain and is therefore regulated by glutamatergic cortical and thalamic projections in addition to dopaminergic afferents from the midbrain (58,59). The ventral striatum also receives inputs from the hippocampus and amygdala, and these regions, in turn, regulate pallidal inhibition of midbrain neurons (60,61). Midbrain dopaminergic afferents control information flow from the striatum to the thalamus by modulating the activity of striatal GABAergic medium spiny neurons, which constitute approximately 95% of neurons in the striatum (15,58,62). These ascending striatothalamic pathways are classified into the D1 receptor–mediated direct pathway and D2 receptor–mediated indirect pathway; the former relays signals from the striatum to the internal segment of the pallidum before terminating in the thalamus, while striatal outputs of the latter inhibit the internal pallidum indirectly via the external segment of the pallidum and subthalamic nucleus, suppressing information transmission to the thalamus (63,64). The balance of activity in direct and indirect pathways is modulated by DA and is thought to subserve learning, action selection, and value computation (22,53). An overview of key aspects of dorsal and ventral CST connectivity is presented in Figure 1.

PRECLINICAL MODELS OF CST DYSFUNCTION

CST circuitry influences, and is influenced by, DA release. DA dysregulation is therefore intimately linked to CST dysfunction in psychosis (15,65,66). Leading preclinical models of psychosis, based on a detailed delineation of the circuit mechanisms regulating DA release and their impact on psychosis-like behaviors in animals, have highlighted a role for deficient cortical-subcortical control, either from the cortex or medial temporal areas, particularly the hippocampus, over midbrain dopaminergic cells (23,60). In fact, these proposed mechanisms are not mutually exclusive but are likely to interact as part of an extended network. For instance, PFC dysfunction is thought to be central to the pathophysiology of psychosis because this area reaches full maturity during the period of peak risk of psychosis onset (20). PFC dysfunction is prominent in patients with psychosis (67), and lesions of the DLPFC impair working memory performance in adolescent monkeys compared with younger groups (68). Medial prefrontal lesions in rats lead to diminished PFC DA, increased DA concentration and uptake in the nucleus accumbens and striatum, upregulation of postsynaptic DA receptors in the ventral tegmental area (VTA), and hyperactivity, suggesting disinhibition of DA release in the striatum (20,69,70). This abnormally elevated dopaminergic activity in the striatum is thought to imbue innocuous stimuli with inappropriate salience, triggering psychosis onset (26,71,72). Notably, neonatal excitotoxic lesions of the ventral hippocampus in rats also elicit PFC-related working memory deficits and compromise the integrity of PFC neurons in adolescence (73,74).

Together, these findings suggest that an early medial temporal lesion may disrupt subsequent maturation of the PFC, which in turn dysregulates subcortical DA transmission (20,75). However, other factors can trigger PFC dysfunction. Psychosocial stress and early-life adversity, known risk factors for psychosis (76,77), can compromise PFC function, increase DA release, and increase DA metabolite levels in genetically high-risk individuals (78–80). Convergent evidence from preclinical models and human postmortem findings indicates that hypofunction of NMDA receptors on cortical GABA neurons, which is thought to disinhibit cortical pyramidal cells, augments the activity of glutamatergic projections to the midbrain and ultimately disinhibits DA activity (81,82). Pharmacological studies in...
rodents demonstrate that administration of either ketamine or phencyclidine, both of which act on NMDA receptors, produces schizophrenia-like behaviors in rodents such as sensorimotor gating disruptions, cognitive deficits, and social impairments (83–86). Acute administration of phencyclidine can trigger DA release in the nucleus accumbens and medial PFC in rats (87,88), whereas chronic administration in monkeys induces poor response inhibition and reduced DA signaling in the DLPFC (89).

Medial temporal and subcortical structures can also directly trigger the dysregulation of midbrain neurons. The hippocampus and amygdala exert opposing effects on the VTA; specifically, the VTA is inhibited by the amygdala and disinhibited by the ventral hippocampus (90). Hyperactivity of the hippocampus leads to augmented dopaminergic cell activity in the midbrain (81,91), and ventral hippocampal lesions sustained after birth (92) lead to behavior consistent with schizophrenia symptoms in adolescence, including impaired social interaction (93) and spatial learning (94), along with symptoms of DA hyperactivity such as impaired sensorimotor gating (95) and enhanced sensitivity to DA agonism (96,97). One prominent developmental model in which pregnant rats are treated with the neurotoxin methylazoxymethanol leads to hyperactivity of the ventral subiculum in the hippocampus of offspring during adolescence, which releases inhibitory control of the striatum over the midbrain and elicits psychosis-like behaviors such as augmented amphetamine-induced locomotion (60,61). Hippocampal hyperactivity in this model is proposed to arise from the loss of parvalbumin-containing GABAergic interneurons in the

![Figure 1](https://example.com/fi.png)

**Figure 1.** An overview of the dorsal and ventral corticostriatal-thalamic connections identified by tract-tracing and neuroimaging studies. The blue to pink coloring represents a gradient of function that spans cognitive (blue) and emotional (pink) function. Circles at the ends of a line represent bidirectional connectivity. A single circle represents a directed connection. Note that this anatomical model is largely derived from tract-tracing studies in rodents and primates and the underlying circuit in humans may vary somewhat. ACC, anterior cingulate cortex; Amyg, amygdala; Ant, anterior thalamus; Bas, basal amygdala; Aux Bas, auxiliary basal; CA1/CA2/CA3/CA4, cornu ammonis hippocampal subfields; Cd, caudate; CeN, central amygdala; CoN, cortical nuclei; DG, dentate gyrus; DLPFC, dorsolateral prefrontal cortex; Dors, dorsal; excit, excitatory; GPi, globus pallidus external; GPe, globus pallidus internal; Hipp, hippocampus; inhib, inhibitory; Lat, lateral amygdala; LD, lateral dorsal nucleus; LG, lateral geniculate body; LP, lateral posterior nucleus; MD, mediodorsal nucleus; MG, medial geniculate body; MPFC, medial PFC; NAcc, nucleus accumbens; OFC, orbitofrontal cortex; Pall, pallidum; Pu, putamen; Pulv, pulvinar; SN, substantia nigra; STN, subthalamic nucleus; Stri, striatum; Sub, subiculum; Thal, thalamus; VA, ventral anterior nucleus; Vent, ventral; VL, ventral lateral nucleus; VP, ventral posterior nucleus; VTA, ventral tegmental area.

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the hippocampus as well alterations in glutamate metabolism (18,98–100). Hyperactivity of the hippocampus also interferes with the segregated activity of discrete hippocampal subfields, which is thought to give rise to positive and disorganized dimensions of psychosis symptomatology (101). Activity of midline thalamic neurons can also trigger firing of dopaminergic cells in the VTA indirectly through their effect on the ventral subiculum of the hippocampus (102). Dysregulation of DA can affect striothalamic signaling along both direct and indirect pathways. An imbalance of these striatothalamic pathways is thought to compromise striatal indirect pathways. An imbalance of these striatothalamic pathways is thought to compromise striatal function (103).

Together, preclinical models suggest that DA dysregulation can arise from deficient cortical or medial temporal regulation of midbrain neuronal activity, but whether cortical or hippocampal deficits are primary remains unclear. It is well known that early hippocampal lesions can lead to prefrontal deficits that only emerge in adolescence (97,104). Administration of phencyclidine of the PFC has not produced similar effects (105), suggesting that the effects of dopaminergic dysregulation may be more pronounced in the dorsal CST circuit and hippocampal hippocampal circuitry appear unique to humans. For instance, caudate regions receiving afferents from lateral PFC subserve higher-order functions that are unique to human behavior, such as language and complex social cognition; and humans also show more extensive connectivity of the limbic CST with frontal and temporal cortices (109,115).

In line with more prominent dopaminergic innervation of the dorsal striatum in humans, positron emission tomography (PET) studies have consistently found evidence of DA dysfunction in the dorsal striatum of both clinically high-risk and antipsychotic-naïve patients with schizophrenia, measured through either DA depletion or stress-induced DA release paradigms (116,117). Such findings challenge the mesolimbic, ventral CST focus of preclinical models and suggest that the dorsal CST may play a more prominent role in disease pathophysiology. Of particular note, PET studies using the tracer 18F-DOPA have consistently reported increased DA synthesis capacity in the dorsal striatum of ARMS and other high-risk individuals, particularly those who later transition to psychosis (116,118–121). Increased 18F-DOPA in the ventral striatum has been reported (122), but the findings have not been consistent (123).

These PET findings align with fMRI studies, particularly those examining patterns of coupled spontaneous fluctuations of the blood oxygenation–level dependent signal—so-called resting-state functional connectivity (FC) (124–126). A summary of FC findings reported in the literature at different stages of the psychosis continuum is provided in Figure 2 (see also Tables S1–S4). Although direct comparison across these various studies and illness stages is complicated by numerous factors (see the Supplement), Figure 2 offers a heuristic summary of general trends reported in the literature. We discuss 4 particularly noteworthy trends in the following.

One robust trend in the fMRI literature is that reduced FC of the dorsal CST circuit is found across the psychosis continuum (Figure 3), consistent with preclinical models supporting a primary role of PFC dysregulation of subcortical areas (127–130). Multiple studies have reported reduced FC between the dorsal striatum and anterior cingulate cortex and the DLPCF in nonclinical individuals with psychosis-like experiences, as well as ARMS individuals, healthy first-degree relatives of patients with schizophrenia, affective and nonaffective FEP cohorts, and patients with chronic schizophrenia (127–129,131–139). Reduced FC between the thalamus (mapped through seeding either the whole thalamus or dorsomedial, ventral, or anterior regions) and various striatal and prefrontal regions has also been consistently found in clinically significant stages of illness, from the ARMS to established schizophrenia (129,136,140–145).

A second trend presented in Figure 2 is that lower FC between the hippocampus, when either seeding the whole structure or just the anterior hippocampus, and striatum has also been reported across all stages, with the ventral striatum being involved consistently when symptom severity triggers help-seeking behavior (i.e., from ARMS individuals to chronic patients) (132,146–151). A third trend in Figure 2 is that dysconnectivity of the midbrain has been reported only in at-risk and clinical cohorts, with little involvement in subclinical psychosis (140,147,150–155). This trend suggests that midbrain dysfunction may be a trait marker of genetic risk and/or clinically significant symptoms. Accordingly, PET studies have not
Figure 2. A summary of dorsal and ventral corticostriatothalamic (CST) dysconnectivity across the psychosis continuum. Affected connections were identified in studies investigating resting-state functional connectivity (FC) of corticostriatal circuits, which were found using a PubMed search using keywords that included "psychosis," "schizophrenia," "schizotypy," "psychosis-like experiences," or "functional connectivity," and one of each of the listed brain regions within the dorsal and ventral CST systems, yielding a total of 74 studies (see the Supplement for further details on the studies and selection process). The top row depicts FC differences identified in nonclinical samples with subthreshold, schizotypal traits and/or psychosis-like experiences, and at-risk groups that include at-risk mental state individuals and first-degree relatives of patients. The bottom row maps connections identified as different in the first-episode psychosis and established schizophrenia cohort. Blue lines depict connections within the dorsal circuit, whereas pink lines are connections within the ventral circuit. Dotted lines depict reduced FC, whereas solid lines depict increased FC. We draw an edge if at least one study has found a difference in FC between the corresponding pair of regions; as such, the figure does not encode quantitative information about the robustness of a given result across the literature (see the Supplement for a more detailed discussion on this issue). The polarity of the FC difference (i.e., increased or decreased in patients) in this figure is determined by the effect reported in the majority of studies finding a difference at that particular connection. Note that the anatomical precision of functional magnetic resonance imaging studies is often lower than that used to describe CST anatomy (e.g., Figure 1) owing to resolution limits of the technique (~2–3 mm³) and preprocessing strategies used (e.g., spatial smoothing). ACC, anterior cingulate cortex; Amyg, amygdala; Cð, caudate; DLPFC, dorsolateral prefrontal cortex; Dors, dorsal; Hipp, hippocampus; MPFC, medial PFC; NAcc, nucleus accumbens; OFC, orbitofrontal cortex; Pu, putamen; SN, substantia nigra; Stri, striatum; Thal, thalamus; Vent, ventral; VLPFC, ventrolateral PFC; VTA, ventral tegmental area.
found evidence of elevated striatal 18F-DOPA in healthy people with subthreshold psychosis symptoms or in ARMS individuals who do not transition to psychosis (120,156,157). Thus, the fMRI and PET findings converge to indicate that dysregulation of midbrain dopaminergic afferents to the striatum is closely linked to the emergence of clinically significant symptoms. However, elevated DA in the dorsal striatum has not been identified in patients who do not respond to antipsychotic treatment, suggesting that treatment-resistant patients may represent a pathophysiologically distinct subtype of psychotic illness (158,159).

Taken together, these findings indicate that lower dorsal CST and hippocampal-striatal FC may represent a trait-like vulnerability marker for psychosis. In line with this view, delusional ideation is thought to arise from aberrant DA signaling in the dorsal striatum, which influences striatothalamic gating mechanisms (22,103) and the prefrontal and striatal functions that subserve associative and executive functions (160,161). Indeed, the dorsal striatum plays a critical role in action valuation and habit formation, offering a plausible mechanism through which certain trains of thought may be consolidated into rigid and persistent beliefs (113,160,162,163). Reduced coupling between the hippocampus and striatum may reflect diminished regulation of the former region over the latter, as predicted by preclinical models (60,61), and may sensitize striatal neurons to dopaminergic transmission. Symptoms may only reach clinical severity once there is a dysregulation of dopaminergic transmission from the midbrain to striatum, which can be detected with fMRI as altered FC between these regions.

A fourth trend evident in Figure 2 is that reduced FC in CST circuitry is a common finding across all illness stages, with the reductions being particularly widespread in schizophrenia (135,141,144,164). There is some evidence for increased FC within the ventral circuitry across clinically significant stages of illness (i.e., at-risk, first-episode, and established schizophrenia). While the specific circuit elements affected vary across stages, the amygdala is consistently involved in these increases (165–168). This evidence of selective FC increases, coupled with widespread FC reductions, aligns with prior reports that consistent FC increases within specific neural systems, such as between sensorimotor corticostriatal circuits (141,145,169), may occur against a backdrop of globally reduced FC in patients (170). Clinical differences of the patient cohorts studied in different investigations are also likely to play a role. For instance, the dominant trend for widespread reductions of FC in patients with established illness may either reflect the natural progression of the illness or the effects of prolonged exposure to medication, which can be difficult to disentangle (171–173).

Preclinical work indicates that persistent elevations of midbrain activity, arising from chronic stress or drug administration, are dampened by regulatory feedback from the amygdala (38,174). One might therefore expect that amygdala dysconnectivity should emerge later in the illness, as a response to ongoing DA dysfunction. Patients with established schizophrenia do show widespread amygdala dysconnectivity (154,168), while amygdala-related FC changes in FEP appear to be more circumscribed (Figure 2). Cortico-amygdala dysconnectivity has been implicated in both schizotypy and at-risk individuals, with the latter also showing prominent dysconnectivity between the amygdala and subcortical areas, including the midbrain (Figure 2A, B). The amygdala is involved in fear, paranoia, and emotion regulation (161) and shows aberrant reactivity to threat and adverse environments in cohorts that are at an increased risk of psychosis (175), suggesting that this region may influence psychosis liability through its effects on stress reactivity.

A particular limitation of FC studies is that they cannot identify primary sites of pathology or disentangle the relative influence of cortical-subcortical versus subcortical-cortical signals. This is because FC is often quantified as a correlation between fMRI signals recorded in two or more regions; therefore, it cannot resolve the directionality of influences between areas and is susceptible to differences in regional to signal-to-noise ratio (176). Thus, while the consistent identification of disrupted dorsal CST and hippocampal-striatal FC across the psychosis continuum aligns with preclinical models emphasizing cortical and hippocampal control over DA signaling (23,60,61,68–70,97,104), the fMRI findings do not allow us to determine whether cortical or hippocampal abnormalities are primary. Indeed, it is possible that hippocampal dysregulation is linked to a diminished influence from the cortex, given that reduced FC between the medial PFC and hippocampus has been reported in people with clinically diagnosable illness (i.e., patients with FEP, patients with schizophrenia); in this sense, disrupted cortico-hippocampal communication may be a trigger for clinically significant symptom expression by altering hippocampal regulation over DA transmission (137,177–180). It is also important to note that, because of the small size of the midbrain, whole-brain
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fMRI studies have limited sensitivity for mapping effects in this region unless they specifically try to investigate the area. The extant literature may therefore underestimate the involvement of this region.

Dynamic causal modeling (DCM) has emerged as a popular approach for quantifying causal interactions—known as effective connectivity—between neuronal populations with fMRI (176,181). One recent DCM study of dorsal and ventral CST circuitry compared effective connectivity in antipsychotic-naive FEP and schizophrenia patients with matched control subjects (182). Both patient groups showed a relative disinhibition of the midbrain. Aberrant influences from the midbrain to the ventral striatum and hippocampus were also identified in FEP patients with schizophrenia, whereas bidirectional effective connectivity between the midbrain and dorsal striatum was disrupted in patients with established schizophrenia. Both FEP and schizophrenia patients showed a stronger inhibitory influence of the thalamus on the ventral striatum. Positive symptom severity was also prominently associated with midbrain connectivity in both FEP and schizophrenia patients. These findings suggest a prominent role for midbrain dysfunction in clinically significant illness and do not provide strong evidence of early disruptions of cortical-subcortical control over midbrain activity, as suggested by preclinical models. However, these effects may be state dependent—DCM studies of task-evoked activity in ARMS individuals have identified an increased influence of the ventral striatum on the midbrain during rewarding stimuli (183) and an increased influence of the hippocampus on the striatum during novel stimuli (184). Together, these DCM findings suggest that spontaneous activity in psychosis is characterized by aberrant tonic firing of dopaminergic neurons, perhaps resulting from an intrinsic dysfunction of the midbrain. This dysfunction interacts with altered cortical-subcortical regulation of medial temporal structures to result in dysregulated phasic, stimulus-evoked DA release.

CONCLUSIONS AND FUTURE DIRECTIONS

In summary, preclinical models have emphasized a primary role for aberrant cortical or medial temporal regulation over midbrain DA neuron activity, leading to elevated DA release and disrupted striatothalamic signaling, particularly within the ventral CST (20,23,60,61,68,90). Human neuroimaging studies are partially consistent with these models, suggesting that disrupted corticostralial and hippocampal-striatal FC are apparent across the psychosis spectrum and may thus represent a vulnerability marker of psychosis. Midbrain dysfunction may emerge when symptoms require some level of clinical attention. However, dysconnectivity of both ventral and dorsal CSTs is found across the continuum, with elevated markers of DA function being more robustly identified in the latter system (116,118–121), consistent with the increasing prominence of dorsal circuitry in the primate brain (109,112,113). These findings therefore suggest that dysfunction of distinct elements of the ventral and dorsal systems may emerge contemporaneously and may influence different aspects of psychosis, with the ventral system driving aberrant salience signaling and the dorsal system contributing to the development of persistent thought patterns (16,22,160–162,185). Preliminary work modeling effective connectivity also suggests that spontaneous neural dynamics may be driven by intrinsic midbrain deficits apparent from the outset of illness (186), whereas stimulus-evoked dynamics may be more robustly associated with diminished cortical control over the midbrain (183,184), highlighting the importance of understanding both tonic and phasic DA release in models of psychosis (22).

One critical consideration is that the precise relationship between DA levels and interregional functional or effective connectivity is unclear. While several studies have examined how pharmacological manipulation of DA levels influences regional activity and FC (187,188), links with psychosis are complicated because the manipulations themselves may not accurately mimic the underlying DA disruption in psychosis. The link between DA and fMRI signals is complex, and the influence of DA on brain function may not be sufficiently captured by FC analyses (187,188). Thus, while mapping CST dysconnectivity across different stages of psychosis can help identify candidate causes or consequences of DA dysregulation, the precise relationship between DA function and FC is yet to be established.

Another consideration is that comparisons of findings across different studies, cohorts, and illness stages should not be overinterpreted. Differences between studies may be driven by variations in statistical power, the clinical characteristics and medication exposure of patients, data processing strategies, analytic methods, and publication bias. Such influences underscore the need for the recruitment of large, longitudinally followed samples. We propose that future research should focus on high-resolution characterization of the psychosis phenotype, across all levels of the continuum. Within clinical groups, there is evidence to suggest that positive, negative, and disorganized symptoms can be further differentiated into multiple subdimensions (161,189). These distinctions are rarely addressed in fMRI research, which mostly focuses on associations with symptom scales that aggregate across diverse domains, such as total symptom scores. Differentiating between the various subdomains of these symptom dimensions may reveal distinct neurobiological correlates, and detailed work is now beginning to characterize the putative computational processes and neural circuitry involved in specific symptom domains such as delusions (161), hallucinations (71), and particular negative symptoms (22,190).

The same approach could be extended to subclinical aspects of the psychosis continuum, given that they are phenotypically continuous with clinical psychosis (191,192). Indeed, evidence for genetic and environmental etiological continuity between subclinical and clinical psychosis suggests that a unified model of subclinical and clinical symptom expression may prove useful (4). Our review above offers some insight into neurobiological continuities across several levels of the psychosis spectrum with respect to CST and DA dysfunction, but a more systematic investigation may provide further clues regarding the risk mechanisms of psychotic illness. Such an approach will benefit strongly from a psychometrically rigorous investigation of the latent architecture of psychosis to develop a hierarchical model that specifies how specific symptoms covary with each other, and which specific
hierarchical levels correlate most strongly with biological measures. Recent work has shown that such an approach can substantially improve associations between schizotypy-related constructs and polygenic risk for schizophrenia (193). We anticipate that such high-resolution phenotyping will also yield more detailed insights into the neurobiological correlates of psychosis risk and help delineate the transdiagnostic influence of CST function, given its involvement in other psychiatric disorders (194). Other circuits, such as those involving auditory and cerebellar networks, are also likely to contribute to symptom onset (24–26) but are beyond the scope of this review.

It is probable that there is no single pattern of dysfunction that inevitably leads to psychotic illness; instead, genetic, environmental, and neurodevelopmental factors are likely to conspire to distinctly alter the function of CST circuit elements in any individual patient. Thus, much like plucking different strings of a guitar gives rise to a specific melody, it is probable that dysfunction at different points within the ventral and dorsal CST circuit, in combination with alterations to other neural systems, ultimately determines the unique constellation of symptoms expressed by any individual patient.

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ARTICLE INFORMATION

From the Departments of Radiology and Paediatrics (KS), Hotchkiss Brain Institute and Alberta Children’s Hospital Research Institute, University of Calgary, Calgary, Alberta, Canada; and Turner Institute for Brain and Mental Health (JT, AF), School of Psychological Sciences and Monash Biomedical Imaging, Monash University, Clayton, Victoria, Australia.

Address correspondence to Kristina Sabaroein, Ph.D., at kristina.sabaroein@ucalgary.ca.

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