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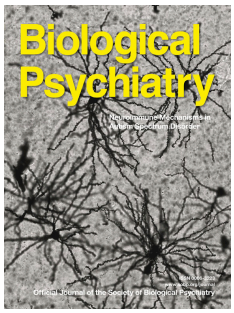

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Integrative brain network and salience models of psychopathology and cognitive dysfunction in schizophrenia

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Abstract

Brain network models of cognitive control are central to advancing our understanding of psychopathology and cognitive dysfunction in schizophrenia. This review examines the role of large-scale brain organization in schizophrenia, with a particular focus on a 'triple network model' of cognitive control and its role in aberrant salience processing. We first provide an overview of the triple network involving the salience, frontoparietal and default mode networks and highlight the central role of the insula-anchored salience network in the aberrant mapping of salient external and internal events in schizophrenia. We summarize the extensive evidence that has emerged from structural, neurochemical, and functional brain imaging studies for aberrancies in these networks and their dynamic temporal interactions in schizophrenia. We then consider the hypothesis that atypical striatal dopamine release results in misattribution of salience to irrelevant external stimuli and self-referential mental events. We propose an integrated triple-network salience-based model incorporating striatal dysfunction and sensitivity to perceptual and cognitive prediction errors in the insula node of the salience network, and postulate that dysregulated dopamine modulation of salience network-centered processes contributes to the core clinical phenotype of schizophrenia. A powerful paradigm to characterize the neurobiology of schizophrenia thus emerges when we combine conceptual models of salience with large-scale cognitive control networks in a unified manner. We conclude by discussing potential therapeutic leads on restoring brain network dysfunction in schizophrenia.

1. Introduction

Schizophrenia is a severe and disabling psychiatric disorder that affects an estimated 51 million individuals world-wide (1, 2). Prominent clinical phenotypic features include positive symptoms of delusions and hallucinations (3, 4), negative symptoms of blunted affect, anhedonia, poverty of speech, lack of motivation, and poor sociability, as well as disorganized speech, which together add to the chronic burden of this illness (5). Drawing on two decades of research, here we synthesize theoretically motivated systems neuroscience frameworks for investigating brain dysfunction in schizophrenia and their relation to the positive and negative symptoms of the disorder. Central to this endeavor are brain network and salience models of psychopathology and cognitive dysfunction in schizophrenia.

Misattribution of salience, characterized by contextually inappropriate assignment of significance to seemingly irrelevant events (6-9), has been proposed to underlie the positive symptoms of schizophrenia. Misattribution of salience often persists despite treatment, making it a particularly pernicious feature of schizophrenia (10). In the intervening two decades since Kapur's focused synthesis of Miller and Spitzer's hypotheses (8), considerable evidence has emerged in support of the misattribution of salience as a key driver of the onset and severity of psychotic symptoms (11). In addition to providing a theoretical framework for understanding the onset, progression, and presentation of positive symptoms, aberrant salience may also explain several negative symptoms of schizophrenia (12, 13).

In parallel, network models based on large-scale functional brain organization (14) are advancing systems neuroscience approaches to investigations of cognitive dysfunction and the clinical phenotype of schizophrenia. A common underlying aberration is the inability to

adaptively regulate or control behavior in relation to changing goals and salience of external stimuli and self-referential mental events. Dysregulation of the brain's cognitive control system is thus posited to lie at the crux of both cognitive and clinical impairments in schizophrenia. Large-scale functional networks are a collection of interconnected brain areas, or nodes, that are linked together to perform circumscribed functions (14). An extensive body of research using multiple methodologies has established that the human brain is intrinsically organized into networks, each consisting of a distinct set of cortical and subcortical areas linked by temporally synchronous neural activity. The intrinsic connectivity of brain networks displays a close correspondence with task-related co-activation of brain regions, and this correspondence has allowed intrinsic and task-related connectivity to be demarcated and studied under a common systems neuroscience framework (15).

Research related to salience and network models of psychopathology in schizophrenia has largely proceeded in parallel, but these are tightly linked at the neural level through a hierarchical cortical-subcortical information processing architecture; a deeper synthesis of these two models is therefore essential to further our understanding of the full spectrum of symptoms of schizophrenia. This review examines the role of large-scale brain organization in schizophrenia with a particular focus on a 'triple network model' (TPN) of cognitive control in aberrant salience processing (**Figure 1**). The TPN model posits a central role for the salience network (SN) in the aberrant mapping of salient external stimuli and self-referential mental events leading to altered dynamic temporal interactions with the frontoparietal network (FPN), and the default mode network (DMN). We examine the close unifying links between brain systems involved in salience detection and their influence on control systems underlying cognitive and affective dysfunction in schizophrenia. A central thesis and novel perspective of this review is that this seemingly disparate profile of

symptoms can be traced to the assignment of markedly deviant importance to external and internal stimuli, which impacts brain systems involved in cognitive control and self-relevant information processing which are clinically manifested as positive and negative symptoms.

We begin with an overview of the TPN model of cognitive control dysfunction in schizophrenia and describe the extensive evidence that has emerged in recent years from structural, functional, and neurochemical studies for aberrancies in each of these three networks in schizophrenia. We then consider models of aberrant salience and their relation to reward prediction errors, and aberrant dopaminergic signaling and reinforcement learning in schizophrenia. We develop an integrative framework and a mechanistic model incorporating multiple lines of experimental evidence and theoretical perspectives on aberrant salience processing and dysfunction of cognitive control networks. Our integrative model offers a powerful paradigm for characterizing the neurobiology of schizophrenia in a more coherent and unified manner than previously possible (16, 17). We conclude by describing the clinical implications of our integrated model and by highlighting avenues for future work.

2. Overview of a triple network model of cognitive dysfunction in schizophrenia

Cognitive impairments are a prominent feature of schizophrenia (18), and the course of cognitive decline often begins long before the onset of clinical symptoms (19). Cognitive control processes are implemented by distinct large-scale brain networks, each with unique spatial and temporal properties. Three brain networks have received considerable attention in the context of impaired cognitive control in schizophrenia: SN, anchored in the anterior insula and dorsal anterior cingulate cortex, with prominent subcortical nodes in the affect and reward processing regions; FPN, anchored in the dorsolateral prefrontal cortex and posterior

parietal cortex; and the DMN, anchored in the medial posterior cingulate cortex, ventromedial prefrontal cortex, medial temporal lobe, and angular gyrus (20, 21) (**Figure 1**).

In the most general framing of the TPN model of cognitive function, the SN is hypothesized to play a prominent role in network switching between context-dependent engagement and disengagement of the FPN and DMN (22). In particular, the anterior insula node of the SN is proposed to play a key role in identifying relevant stimuli from the vast and continuous stream of sensory stimuli that impact the senses. Crucially, switching between the DMN and FPN facilitates disengaging from self-referential mental processes to respond to current task goals. Evidence for a causal role for the SN has emerged in multiple studies involving a wide range of cognitive control tasks (23).

In the context of schizophrenia, the model posits that misattribution of salience, characterized by circumstantially inappropriate assignment of significance to events can trigger a cascade of aberrant switching processes and cognitive control circuit dynamics (17, 24) (**Figure 1**). Moreover, aberrant self-referential mental events such as auditory hallucinations arising from the sensory cortex may also trigger aberrant switching processes. The question of dysfunctional cognitive control mechanisms arising from the misattribution of salience is discussed in subsequent sections. Here we note that once such a misattribution of either external stimuli or internally generated spontaneous neural events has occurred, and is detected by the anterior insula, what ensues are large-scale changes in brain network dynamics and the emergence of aberrant brain states, as elaborated below.

3. SN, FPN, and DMN dysfunction in schizophrenia

Neuroimaging studies over the past two decades have identified functional abnormalities in multiple brain regions in schizophrenia (25-28). Mapping the complex behavioral and cognitive deficits in schizophrenia to individual brain areas, however, is now widely regarded as being inadequate, and there is a growing consensus that these deficits are caused by aberrant functional connectivity and interregional communication between brain regions (17, 29, 30). Models of functional dysconnectivity arising from synaptic dysfunction and excitatory/inhibitory imbalance, have been a central theme of schizophrenia research (31). Early investigations of functional connectivity in schizophrenia emphasized dysconnectivity between lateral temporal-prefrontal regions implicated in auditory hallucinations (32), and frontoparietal regions implicated in working memory deficits (33).

These early findings paved the way for increasingly sophisticated investigations of functional large-scale brain networks associated with cognitive control in schizophrenia. Notably, strong evidence has emerged that the SN, FPN, and DMN are among the most consistently implicated dysfunctional brain networks in schizophrenia. Meta-analyses of structural brain imaging studies point to SN nodes as key loci of gray matter abnormalities and its insula and anterior cingulate cortex nodes display the most consistent structural deficits in chronic as well as recently diagnosed schizophrenia patients (34, 35) (**Figure 2**; see **Supplementary Materials** for details).

Abnormalities in intrinsic functional connectivity within and between SN, FPN, and DMN are also a prominent feature of schizophrenia (16, 36-53) (**Figure 3, Figure S1**; see **Supplementary Materials** for details). A recent meta-analysis of 56 rsfMRI datasets from 52 articles (2115 patients with schizophrenia and 2297 healthy controls) found a consistent pattern of hypo-connectivity within the DMN, FPN, and SN, as well as between the DMN

and SN, FPN and SN (54). Moreover, aberrant intrinsic connectivity centered on the SN is associated with the severity of positive, disorganized, and cognitive deficits in schizophrenia (51, 55-57). Analysis of time-varying dynamic functional interactions between the SN, FPN, and DMN has provided strong and replicable evidence that dysregulated dynamic cross-network interactions among them contribute to positive symptoms in patients with schizophrenia (44, 58). Notably, dynamic SN-centered cross-network interactions are significantly reduced, less persistent, and more variable in patients with schizophrenia compared with control subjects (**Figure 4**). Crucially, this finding was replicated in two independent cohorts and in both cohorts, patients with the least persistent and most volatile time-varying SN-centered cross-network interactions exhibited the most severe positive symptoms, including conceptual disorganization (**Figure 4**). Task-based functional brain imaging studies have consistently shown aberrant activity and connectivity within and between SN, FPN, and DMN in patients with schizophrenia across a wide range of tasks including working memory and reward processing (see **Supplementary Materials** for details) (37, 59-68).

In sum, these studies suggest that aberrancies in SN, FPN, and DMN and their interactions are prominent in schizophrenia both intrinsically and during a wide range of cognitive tasks. Crucially, the extant findings are consistent with the triple-network model which posits that deficits in access, engagement, and disengagement of the SN, FPN, and DMN may underlie maladaptive behaviors and cognitive deficits in schizophrenia (17, 69-72).

4. Aberrant salience, prediction error, and dopamine

Schizophrenia is sometimes referred to as a salience dysregulation disorder (73). Salience dysregulation in patients with schizophrenia involves multiple components (74), including deficits in reward prediction and anticipation (75), reward-based reinforcement learning (76), and belief updating (77-79). In addition, aberrant salience processing also involves deficits in the detection of unexpected events, including those that are novel but not explicitly rewarding (80), and personally salient environmental stimuli with either positive or negative valence. Early articulations of the aberrant salience hypothesis of schizophrenia proposed that atypical mesostriatal dopamine release results in an over-attribution of meaning, value and incentive salience to irrelevant environmental stimuli and self-referential mental events (6). Kapur further suggested that delusions are a cognitive effort by the patient to make sense of these aberrantly salient experiences, whereas hallucinations reflect a direct experience of the aberrant salience of internal representations (6). Aberrations in salience have also been linked to motivational deficits and negative symptoms of schizophrenia including avolition and anhedonia (13, 81, 82).

Centered on midbrain dopaminergic dysfunction, Kapur's aberrant salience argues that 'meaningfulness' is ascribed aberrantly to innocuous stimuli due to periodic dopamine surges during the incipient stage of psychosis. Across-species, midbrain dopamine signaling is considered a correlate of the mismatch between expectation and experience, i.e., prediction errors (83-85). Computational work on prediction errors has been most extensively carried out in the context of reward processing (86), from both model-based and model-free reinforcement learning perspectives (76, 87-90). Reward prediction error signals generated by striatal neurons are a key neural signal that facilitates optimal choice behavior and allows learning from past experiences (85, 91). Prediction errors are an important learning cue and

play a direct role in forming and strengthening associations, which in turn enhances memory for attended events (83-85).

Behavioral studies have highlighted aberrant reinforcement learning in schizophrenia during probabilistic selection tasks which assess a participant's ability to learn from feedback (87-90); these deficits have been linked to both the positive and negative symptoms of schizophrenia (13, 74, 78, 90, 92-94). Disrupted processing of salient and rewarding stimuli in schizophrenia are closely linked to dysregulated striatal dopamine signaling (95-99). This striatal dopaminergic dysregulation has been linked to aberrant reward prediction errors that are prominent in schizophrenia (100).

Computational modeling of dopaminergic striatal circuits suggests that increased spontaneous dopamine release can result in a decreased response to reward cues and paradoxically enhance the response to neutral cues, two key features that contribute to aberrant reward prediction errors in schizophrenia (101). This is consistent with the observed reduction in the activation of the ventral striatum, midbrain, and other limbic regions to reward cues and outcomes in schizophrenia on the one hand (101-104) and the increased activation of the same regions to neutral cues, neutral outcomes, and neutral prediction errors on the other (90, 101).

These aberrations likely arise from elevated baseline levels of striatal dopamine observed in patients with schizophrenia. PET imaging studies in schizophrenia have reported increased presynaptic dopamine synthesis and availability in the dorsal striatum (105, 106) [but see (107)]. Tonically elevated dopamine levels in the striatum in patients with schizophrenia may

reduce the capacity to modulate responses to relevant events while increasing responses to neutral, irrelevant stimuli (90, 106).

In sum, impaired prediction errors arising from aberrancies in dopamine tone are key mechanisms underlying assigning appropriate salience to relevant stimuli, difficulties in learning from rewarding cues, and erroneously forming associations about irrelevant or neutral information in schizophrenia.

5. Integrated model of triple network dynamics and aberrant salience

While striatal dopaminergic dysfunction has been proposed as a final common pathway leading to psychosis in schizophrenia (108), how this neurochemical abnormality is related to psychopathology, and cognitive dysfunction more broadly, is less clear. Impaired prediction errors arising from dopamine signaling in the ventral striatum are not sufficient to explain how cognitive control functions are impaired by aberrant salience and how aberrant salience is detected, attended to, and acted upon in the first place. A general idea here is that disruptions in prediction error firing from lower-level systems in the information processing hierarchy may impair or alter the function of higher-level cognitive systems (109). Crucially, the striatum is not the only locus of reward prediction errors and dopaminergic signaling, and a recent meta-analysis of over 250 studies suggests that prediction errors are prominent in the SN, FPN and DMN, and most notably in the anterior insula node of the SN across the perceptual and cognitive domains, regardless of reward contingencies (110, 111) (**Figure S3**). Furthermore, dopaminergic signaling is associated not just with prediction errors but also perceived salience independent of rewards (112). Here we consider an integrated model

of aberrant salience and dopaminergic signaling in schizophrenia from a systems neuroscience and dynamic circuits perspective (**Figure 5**).

Salience, as defined here, is a feature assigned by an individual to a stimulus, rather than being an inherent property of a stimulus per se (69). In this regard, what is salient may differ based on expectancy (surprisal salience), prior encounters (novelty salience), learned values, and outcomes (motivational salience). Importantly, one's present state is a critical determinant of the afforded salience (food is salient when we are hungry, not otherwise). In other words, a stimulus that needs to be processed further to reduce a state of uncertainty or homeostatic imbalance in the agent is deemed salient (113). This downstream processing demands a change in one's ongoing physiological state, e.g., holding stimuli (attention), manipulating the environment (action), or epistemic update of one's model of the world (learning). These downstream processes aim to reduce an uncertain state (or imprecise prediction) in the future.

To capture the physiological cascade that follows both nonincentive and incentive-based significance afforded to stimuli, the term 'proximal salience' was employed in an earlier work (24), on the basis of the functional description of the SN (69). Proximal salience refers to a momentary state of evaluation of external or internal stimuli in the context of interoceptive awareness. This state precedes the subsequent choice of action and/or a representational change to optimize the future predictions of the stimulus. As this appraisal guides the nearest (next) action or representation, rather than a distant motivational representation or goal, the term 'proximal' appears more relevant. This concept has its roots in the systems-level description of the insula (and SN) function in selecting and acting on homeostatically relevant stimuli (21). The boundaries of the present context and the future

are demarcated by changes in interoceptive signals that arrive at the anterior insula (114), while the engagement of brain systems required to bring about state changes is enacted via the multimodal responses generated by the dorsal anterior cingulate cortex, and the extensive connectivity of SN with emotion processing regions of the brain (115).

In the TPN model, external stimuli or self-referential events become salient when they generate transient neural activity within the SN that is large enough to trigger the physiological switching function of the SN (69). In particular, the switching mechanisms between FPN and DMN mediated by the SN (22) are crucial for the appropriate allocation of attentional and working memory resources (69, 116). This switching marks the further downstream processes evoked by a salience-mapped stimulus that leads to resolving current uncertainty and optimizing predictions for the future. The SN centered cortical salience mapping incorporates nonincentive and active inference aspects of prediction, and consistent with emerging evidence of both a core ventral striatal and insular substrate for domain general prediction errors (110) leading to the initiation of downstream processes (action policy or model updates) evoked by a stimulus that is afforded salience.

A growing body of work has now emerged pointing to the modulatory influence of striatal dopamine on large-scale brain networks, specifically the SN. Specifically, dopamine synthesis and release capacity in the ventral and dorsal striatum, but not the sensorimotor striatum, predicts connectivity within the SN (117) [also see(118)] (**Figure 6**). Extensive review of neurotransmitter influences on large-scale networks further reinforces the specificity of the dopaminergic basis of mesolimbic-SN connectivity (119) (**Figure 6**).

The role of dopamine on SN function is not limited to the striatal-SN pathways alone. Reducing dopamine availability by depleting its precursors leads to a prominent reduction in the connectivity of SN with other large-scale brain networks (120). More specific D2 antagonism reduces the connectivity between subcortical-cortical nodes of SN (121), besides diminishing reward-related activation of both components of the SN (122). Interestingly, dopamine agonism may also reduce SN centered cortico-cortical connectivity, reducing its sensory inputs (123) while restoring the disrupted segregation within the TPN in certain disease states (124). In sum, dopaminergic pathways play a key role in the cortico-subcortical connectivity within the SN and its extrinsic connectivity.

Observational studies have reported an association between striatal D2 blocking drugs and normalized activity of SN nodes (125) and cortico-subcortical connectivity within the SN (126); and a dynamic SN-centered interaction within the TPN (127) [but see (128, 129)]. Randomized, controlled human pharmaco-fMRI experiments have repeatedly demonstrated that striatal-SN connectivity can be enhanced by dopaminergic agonism in healthy volunteers (121, 130). More recent evidence supports a role for dopamine in enhancing (precision-weighting) cortical prediction errors in the dorsal anterior cingulate cortex and reduced tracking uncertainty in the SN (131).

Synthesizing these observations, we propose that the striatal assignment of salience based on phasic dopamine release is a physiological continuum with the downstream cortical salience processing cascade implemented by the switching function of the SN. In schizophrenia, dopamine-mediated misattribution of salience to external stimuli and self-referential events thus places competing demands on the SN and its inter-network interactions.

From the point of view of internal brain states, elevated striatal dopamine signaling characterized by noisy dopamine transients may result in more frequent modulation of the SN, resulting in less persistent brain states. This process may also underlie the attentional capture of irrelevant sensory events which then take on inappropriate proximal salience and awareness (132, 133). Consistent with this view, it was found that patients with the least persistent and most volatile time-varying SN-centered cross-network interactions exhibited the most severe positive symptoms (58). In conjunction with these aberrancies in network dynamics, higher levels of presynaptic dopamine in the striatum are also correlated with positive symptoms (102).

This cortical processing aspect of dysregulated dopamine signaling has two distinct consequences. First, reduced phasic responses to task and goal-relevant stimuli would result in an inability of large-scale brain networks to switch adaptively in a context-sensitive manner. The resulting lack of engagement of the FPN likely contributes to the attentional and working memory deficits observed in patients (61, 134, 135). In turn, weaker feedback from the FPN working memory system alters reward prediction errors and impairs learning (136, 137). Thus, while striatal prediction error signals are a major component of learning, FPN-mediated working memory signals may play a crucial interactive role resulting in a cascade of working memory and learning deficits.

Second, the lack of task-relevant downregulation of the DMN would result in continued engagement with ongoing internal mental processes when it is maladaptive to do so. The upshot is a mismatch between what needs to be attended to and what needs to be ignored in the ongoing flux of sensory stimuli (133). Both of these aberrations may disrupt control signals to language networks and the DMN, resulting in features of disorganized speech (see

(138) for a review). The incessant SN volatility induced by recurrent dopamine-mediated cascading of prediction error results in higher uncertainty about the environment and our operations upon it. This may manifest as tamed expectations of value from a changing environment, even in the presence of rewarding cues (anhedonia), and reduced operations upon the environment to bring about desired changes (withdrawal).

In summary, our integrated model of aberrant salience posits that dysregulated dopamine modulation of TPN dynamics may contribute to both clinical and cognitive features of schizophrenia. Aberrant engagement of attentional switching systems by behaviorally irrelevant events and enhanced associations with irrelevant information arising from dysregulated striatal dopamine signaling is a key mechanism underlying the emergence of positive symptoms of schizophrenia. In contrast, a decrease in processing salient and reward-related cues and orienting attention to them, may underlie negative symptoms and the inability to disengage from task-irrelevant mental processes. Both contribute to the cognitive and behavioral problems observed in the daily lives of individuals with schizophrenia.

6. Clinical implications and future directions

An important strength of our integrative TPN model is its ability to relate to the major symptoms that occur together in schizophrenia. In addition to the conventional positive and negative symptoms, cognitive deficits, thought disorder, language, and anomalies in the sense of self also occur in this illness; these are not explicable by a striatal focussed aberrant salience account without extending it to the TPN dysfunction. While the positive symptoms of reality distortion and negative symptoms have been previously well linked to TPN dysfunction (51, 56), emerging observations provide a strong link to disorganization (138) as

well. More broadly, anomalies in the sense of self and social cognition have been linked to the SN, DMN, and their interactions (139), arising from the right insula role in interoception and awareness (114) and the DMN role in establishing shared meaning and narratives about the self in the world (140). Furthermore, within the context of the TPN saliency model, aberrations in salience arising from stimuli that violate world model predictions are likely to further impact the integration of external and internal information, affecting the ability to establish shared meanings and social communication (141). Thus, TPN dysfunction as a model of schizophrenia provides a platform to study how disparate features of this illness come to co-occur in individuals diagnosed with it.

Translating from illness models to therapeutics in schizophrenia has been a daunting task (142). To date, almost all circuit-level models for this illness were derived from animal models or postmortem tissue examinations; TPN dysfunction is an outlier that emerged mostly, if not wholly, from human in vivo studies. This could potentially serve as a bridge for the next decade of therapeutic advancement in schizophrenia. Here, it is noteworthy that clinically relevant cognitive subtypes of schizophrenia may be associated with distinct differences in connectivity in the TPN (55). In particular, the SN-centered hypoconnectivity subgroup had more persistent negative symptoms at 6-week follow-up than the hyper-connectivity subgroup. Identification of such network connectivity-based features may guide therapeutic choices for achieving personalized treatment goals.

To this end, employing markers of network integrity may aid as a form of broad-filter in vivo screening assay of target engagement of potential therapeutic agents. The spatial profile of TPN has been recently recovered in mice (143) and rodents (144), making relevant animal assays feasible. Preclinical indices of network interaction akin to those obtained from human

imaging studies are required. Furthermore, multiple cortical nodes of the TPN might be amenable to direct noninvasive electrical and magnetic modulation (145, 146). Studies have already demonstrated that targeted neuromodulation of deeper SN structures is feasible via a connectivity-guided approach that utilizes spatial inferences from the TPN model (147, 148). Larger scale randomized trials, especially targeting cognitive impairment and treatment-resistant symptoms are urgently needed in this regard. The TPN model will also be particularly relevant to developments in closed-loop neuromodulation in the future, wherein the delivery of therapeutic stimulation can be triggered by and tuned to normalize the network-level connectivity-based biomarker (149).

The focus on cortical networks that are inherently plastic in their interactions has important implications for non-pharmacological interventions. Cognitive remediation has been a moderately successful endeavour in schizophrenia; this approach is either centred around 'lesion' based neuropsychological models or on domain-specific approaches (auditory/visual perception) that are expected to generalise or transfer (150). Based on our framework that puts the SN-centred TPN system as a critical target, selecting tasks with more direct engagement of the SN may have the greatest potential for cognitive remediation. Furthermore, combining such targeted approaches with focal noninvasive neuromodulation may provide higher therapeutic yield (151).

We lack experimental data for the presumed defects in momentary switching among cognitive subsystems when encountering input data (proximal salience). Integrative studies with PET, MRS, fMRI, and EEG/MEG in combination with models from computational psychiatry and brain circuit analysis hold promise in the future. Network analysis using EEG/MEG data are needed to better characterize temporal abnormalities, their hierarchy, and

frequency specificity in relation to cortical and subcortical areas associated with the TPN model. Specifically, analysis of temporal irregularities has the potential to complement findings from fMRI studies and may provide additional insights into the varied phenomenology of schizophrenia (152).

Finally, given their rich cortical and subcortical connectivity, the operations of large-scale networks such as the SN are unlikely to be modulated by a single neurotransmitter system. Our focus here has been on dopamine, but other neurotransmitters, notably GABA and glutamate, are also relevant for understanding the neurochemical basis of cognitive control network dysfunction and psychopathology in schizophrenia and for informing treatment (see Supplementary Materials).

7. Conclusion

Impairments in cognitive control networks that regulate the ability to adaptively engage with and respond to changing goals and contexts have emerged as a hallmark of schizophrenia psychopathology. We have described an integrative network model (**Figure 5**) involving the salience, frontoparietal and default mode networks, the salience misattribution model, and the findings of aberrant striatal dopamine and (glutamatergic) function to advance knowledge of how aberrancies in cognitive control networks contribute to both psychopathology and cognitive dysfunction in schizophrenia.

Figure Captions

Figure 1. Overview of triple network model and aberrant salience processing in schizophrenia. (**A**) Brain maps of the salience network (SN), frontoparietal network (FPN), and default mode network (DMN). (**B**) The triple network model posits a central role for the SN in the aberrant mapping of salient external and internal events leading to altered dynamic temporal interactions with the FPN and the DMN. Misattribution of salience, characterized by contextually inappropriate assignment of significance to seemingly irrelevant events and stressors, together with disruptions in dopaminergic and glutaminergic signaling associated with the striatal and cortical systems contribute to both positive and negative symptoms associated with schizophrenia.

Figure 2. **Gray matter loss in the anterior insula and dorsal anterior cingulate cortex nodes of the salience network is prominent in patients with schizophrenia and psychosis.** (**A**) Metanalysis of structural brain imaging studies reveals convergent gray matter reduction in patients with chronic schizophrenia compared to healthy controls across 113 voxel-based morphometry studies (FWE-corrected at .05 with cluster-forming value at $p < .001$). N (SZ) = 5,263. N (HC) = 6,007. Adapted from (34). (**B**) Functional network decomposition of the clusters of gray matter reduction in clinical high-risk subjects (c-HR), recently diagnosed (RDSZ) and chronic SZ patients (ChSZ) groups reveals replicable aberrations in the SN. (i, ii) Graphical representation of the number of altered volumes (mm^3) falling within a functional network. (iii) Graphical representation of the altered volumes falling within a functional network (percentage). AuN: auditory network; DMN: default mode network; preMN: premotor network; R-VAN: right ventral attention network; DAN: dorsal attention network; SMN: sensorimotor network; MN: motor network; L-VAN: left

ventral attention network; Th-BN-N: thalamus-basal nuclei subcortical network; OFC-N: orbito-frontal cortex network; SN: salience network. (**C**) Transdiagnostic evidence for gray matter loss in patients with psychosis across diagnostic categories. *z*-scores show activation likelihood estimates for gray matter loss. N (SZ) = 7381. N (HC) = 8511. Adapted from (35).

Figure 3. Meta-analysis of abnormal intrinsic functional connectivity in schizophrenia. (**A**-**B**) Meta-analysis of intrinsic functional connectivity studies in patients with schizophrenia points to consistent patterns of hypo-connectivity between the salience network (SN) and posterior parietal cortex (PPC), precuneus (PCS) and inferior parietal lobule (IPL) within the default mode network (DMN); hypo-connectivity between the SN seeds and caudate nucleus within the frontoparietal network (FPN); hypo-connectivity between the SN seeds and the thalamus network (TN), and hypo-connectivity within the SN between the SN seeds and the regions of the putamen and ACC. Schizophrenia was associated with hypo-connectivity between the FPN seeds and the TN and the insula node of the SN. Patients with schizophrenia exhibited hypo-connectivity within the DMN, between DMN and the medial prefrontal cortex (MPFC) and anterior cingulate cortex (ACC); hypo-connectivity between the DMN and the insula and ACC nodes of the SN; hypo-connectivity was also observed between the DMN and dorsolateral prefrontal cortex (DLPFC), a key hub of the FPN. All results are significant at $P < .05$, corrected for family-wise error rate. N (SZ) = 2,115. N (HC) = 2,297. Adapted from (54).

Figure 4. Dysregulated brain dynamics in a triple network salience model of schizophrenia and its relation to psychosis. (**A**) Triple-network salience model of psychosis in schizophrenia investigated from the viewpoint of aberrant functional circuit

dynamics associated with the salience network (SN), frontoparietal network (FPN) and default mode network (DMN). Specifically, the dynamical circuit model posits a key role for the SN in the aberrant mapping of external and internal salient events, leading to altered dynamic temporal interactions with the FPN and DMN. (**B**) Dynamic time-varying cross-network interactions among the SN, FPN, and DMN in the schizophrenia and control groups. (**C-E**) The schizophrenia group showed seven states (S1 to S7), significantly higher than the two states in the control group. Color codes show distinct states of each participant. Mean lifetimes of dynamic brain states were shorter in the schizophrenia group compared with the control group. The network interaction index (NII) of dynamic brain states shows intermittently reduced and more variable salience network–centered cross-network interaction in the schizophrenia group compared with the control group. (**F**) The temporal mean and variability of dynamic NIIs were strongly correlated with positive symptoms of schizophrenia, as revealed by canonical correlation analysis. N-primary cohort (SZ) = 35. N-primary cohort (HC) = 35. N-replication cohort (SZ) = 30. N-replication cohort (HC) = 30. Adapted from (58).

Figure 5. Integrated model of cognitive control networks and aberrant saliency in schizophrenia. Our integrated salience-based cognitive control systems model posits that aberrant dopamine release results in the assignment of markedly deviant importance to external and internal stimuli, which impacts triple network brain systems involved in cognitive control and self-relevant information processing. Striatal dysfunction and sensitivity to perceptual and cognitive prediction errors in the insula node of the salience network are key drivers of aberrant circuit dynamics**.** The ensuing disruption of cognitive control circuit dynamics underlies both positive and negative symptoms as well as cognitive

dysfunction in schizophrenia. ACC: anterior cingulate cortex; AI: anterior insula; DA: dopamine; DMN: default mode network; FPN: fronto-parietal network; Hyp: hypothalamus; PE: prediction error; PI: posterior insula; NAc: nucleus accumbens; SN: salience network; TPN: triple network; VTA: ventral tegmental area.

Figure 6. Mesolimbic dopamine influences salience network (SN) connectivity.

(A) Dopamine synthesis capacity is correlated with SN strength and is positively correlated with the difference between SN and default mode network (DMN) strengths. Dopamine release capacity negatively correlated with SN strength ($r_p = -.42$, $p = .049$). Adapted from Adapted from (117). **(B)** Network-based statistics (NBS) identifies subnetworks significantly associated with dopamine synthesis and/or release capacity across a range of thresholds. Characterization of dopamine-associated subnetworks. Adapted from Adapted from (117). **(C)** SN hubs and dopamine-associated subnetworks: red nodes represent network combination hubs and green nodes and edges represent the dopamine-associated network, in which edge strength correlates with limbic dopamine synthesis capacity. Graph displaying whether the overlap between dopamine-associated nodes and combination hubs is significant. Adapted from (117). **(D)** Dopamine signaling is associated with an increase in functional connectivity and activity in the SN, and a decrease in functional connectivity and activity in DMN. N = 21. Adapted from (119). DA: dopamine; fALFF: fractional amplitude of low-frequency fluctuations; FC: functional connectivity; SD: standard deviation/neuronal variability; SMN: sensorimotor network..

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