Published in final edited form as:

Biol Psychiatry. 2020 February 01; 87(3): 204–214. doi:10.1016/j.biopsych.2019.09.021.

Cognition and Reward Circuits in Schizophrenia: Synergistic, not Separate

A.J. Robison, PhD¹, Katharine Thakkar, PhD^{2,3}, Vaibhav A. Diwadkar, PhD⁴

¹Dept. of Physiology, Michigan State University

²Dept. of Psychology, Michigan State University

³Division of Psychiatry and Behavioral Medicine, Michigan State University

⁴Dept. of Psychiatry & Behavioral Neurosciences, Wayne State University

Abstract

Schizophrenia has been studied from the perspective of cognitive- or reward-related impairments, yet it cannot be wholly related to one or the other process and corresponding neural circuits. We posit a comprehensive circuit-based model proposing that dysfunctional interactions *between* the brain's cognitive and reward circuits underlie schizophrenia. The model is underpinned by how the relationship between glutamatergic and dopaminergic dysfunction in schizophrenia drives interactions between cognition and reward circuits. We argue that this interaction is *synergistic*: that is, deficits of cognition and reward processing *interact*, and this interaction is a core feature of schizophrenia. In adopting this position, we undertake a focused review of animal physiology and human clinical data, and in proposing this synergistic model, we highlight dopaminergic afferents from the ventral tegmental area to nucleus accumbens (mesolimbic circuit) and frontal cortex (mesocortical circuit). We then expand on the role of glutamatergic inputs to these dopamine circuits, and dopaminergic modulation of critical excitatory pathways, with attention given to the role of glutamatergic hippocampal outputs onto nucleus accumbens. Finally, we present evidence for how in schizophrenia, dysfunction in the mesolimbic and mesocortical circuits, and their corresponding glutamatergic inputs gives rise to clinical and cognitive phenotypes, and is associated with positive and negative symptom dimensions. The synthesis attempted here provides an impetus for a conceptual shift that links cognitive and motivational aspects of schizophrenia and which can lead to treatment approaches that seek to harmonize network interactions between the brain's cognition and reward circuits with ameliorative effects in each behavioral domain.

Corresponding author A.J. Robison, PhD, Department of Physiology, Michigan State University, 567 Wilson Rd, Rm 3180, East Lansing, MI 48824, Office: 517-884-5003, robiso45@msu.edu.

Financial Disclosures

The authors report no biomedical financial interests or potential conflicts of interest.

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Keywords

Schizophrenia; circuits; reward; cognition; translation; genetics

Overview

The definitions and boundaries of what clinicians generally recognize as “schizophrenia” have evolved since its origins. In anticipating this (1), Bleuler accepted schizophrenia not as a unitary disease but an “umbrella” term representing a constellation of behavioral symptoms (2). Yet, positive (hallucinations, delusions and thought disorder), and negative symptoms (poverty of speech and thought (3, 4)) remain the most widely accepted and salient *clinical* and observational characteristics of schizophrenia. Bleuler’s work pre-dated modern neuroscience, and he remained agnostic about whether the *core* pathophysiology of schizophrenia was tractable or valuable to understand (5). He advocated for a focus on behavior over biology. However, semantic distinctions between behavior and biology have dissipated (6), and the search for biological mechanisms in terms of impaired functional brain circuits is central to understanding core characteristics of schizophrenia (7, 8).

Higher order neurocognitive domains (and corresponding brain circuits) are of traditional interest in schizophrenia; dysfunction is evident across a range of domains, with no aspect of function left intact. Studies have centered on: a) working memory, attention, and executive functioning, and their relationship to frontal-striatal circuits (9–12); and b) episodic and associative memory and learning and the relationship to frontal-hippocampal interactions, and synaptic dys-plasticity (13–19). Dys-functional dopamine (DA) and N-methyl-D-aspartate (NMDA) interactions in the prefrontal cortex, and altered glutamatergic neurotransmission in the hippocampus may underpin many of the neurocognitive deficits that characterize the illness (20), and animal models (e.g., 22q11.2 deletion, see below) show evidence of deficits in hippocampal neuronal function during memory-related processing (21). However, schizophrenia is also laced with *motivational* and *salience* deficits, assumed to stem in part from aberrant reward processing (22, 23). The relevance of reward-related deficits is most clearly shown in studies of reinforcement learning. Patients (particularly with pervasive negative symptoms), fail to represent the expected value of rewards. This failure results in impaired learning in the context of gains (but intact learning in the context of loss-avoidance) (24, 25), as patients appear *not to* make high-effort response choices in the service of maximizing reward (26). As response choice is closely associated with frontal and cingulate regions (27), impaired executive function in schizophrenia impacts reward sensitivity. A separate literature (reviewed below) links *positive symptoms* and abnormal salience with distorted representation of stimulus value, resulting in detrimental effects on cognitive integrity (28).

The corpus of empirical data is vast, but the field can benefit from an integrative framework which can distill how dys-functional interactions *between* distinct sets of sub-networks for cognition and reward interact to amplify the broad impairments, and the associated “infinite regress” of dysfunctional neuronal interactions characterizing schizophrenia (29). We argue that such amplification makes schizophrenia particularly insidious, resulting in well-known

challenges to remediation. Our translational, circuit-based framework highlights the synergistic relationship between the brain's cognitive and reward circuits, and their dopaminergic and glutamatergic innervations (30, 31). Figure 1 provides an initial *schematic* overview.

From the framework in Figure 1, we address the following: a) Is the *interaction* between cognitive deficits *and* motivational/hedonic dysfunction necessary and sufficient to explain core characteristics of schizophrenia?; b) by corollary, *how* do dys-functional interactions *between* the brain's cognitive and reward circuits amplify impairment in the illness?; c) Is the complex relationship between negative and positive symptoms (32) related to dys-functional interactions between cognition and reward, or does this framework simply account for negative syndrome schizophrenia (33)?

Negative symptoms, reward processing and cognition

Altered reward processing in schizophrenia is associated with enduring and pervasive *negative* symptoms afflicting a significant portion of patients (34), and they are associated with bleaker outcomes and greater treatment resistance (35). Aberrant reward processing is assumed to be at the core of the major negative symptoms of avolition and amotivation (36). Although hedonic responses are frequently intact (37, 38), individuals with negative symptoms show alterations in reinforcement learning (39–41), reward anticipation (39), representing values (42), exploratory behavior (43), and effort allocation (44). Negative symptoms are also associated with cognitive deficits (45–47), with both bearing on real-world functioning, onset, and illness course.

Cross-sectional correlations between negative symptoms and cognitive deficits suggest that they are the same construct, or at least share a common etiology. However, a likelier explanation given extant data and neurobiology, is that they are *independent* constructs but with *related* etiologies (48). We suggest that these related etiologies are in fact dysfunctions between cognitive and reward circuits. By implication, impaired cognition in the illness undermines reward sensitivity, because cognitive success is inherently yoked to the internal motivational drive. Concurrently, a loss of internal motivational drive undermines cognition. There is no seriality to this model (49). Rather the loss of synergy drives schizophrenia, in the way that working memory deficits impair the generation and maintenance of value representations (50–52) *and* impaired reward processing reduces effort allocation in cognitively demanding situations (53).

Positive symptoms, salience and value sensitive for reward

Understanding relationships between positive and negative symptoms in schizophrenia is a foundational challenge (54). Though frequently co-observed (55), they represent distinct dimensions in illness etiology (32), with neither particularly predictive of the emergence of the other over time (56). Although the link between impaired cognition and reward systems is more naturally associated with negative symptom dimensions, recent evidence suggests that aberrant salience is related to distorted reward attribution/processing. We outline the evidence and the logic below.

Aberrant salience in schizophrenia is hypothesized to result from dysregulated dopaminergic signaling in the mesolimbic system (57, 58). Specifically, dysregulated dopaminergic signaling increases attribution of salience to external stimuli leading to the emergence of the classic positive symptoms of delusions and hallucinations (59). Stimulus novelty drives salience because novelty is intrinsically rewarding (60), and motivational salience which is linked with the search for novelty, is an adaptive feature of the primate brain linked to basic hedonic drives (61). This inextricable link between salience and reward has been discussed in classic reviews, highlighting how dopamine neurons in the ventral striatum signal anticipatory reward (62). Furthermore, in direct support of our central thesis, mounting evidence suggests that *both* prefrontal neurons (63) *and* neurons in the dorsal NAc are modulated during working memory processing (64), evidence that units in the ventral striatum are tuned to cognitive tasks.

The primate reward system attributes value to exogenous stimuli, the consequences of overt behaviors, and/or the experience of endogenous states (65, 66). Thus, incentive-based learning is associated with accurate representation of the value associated with achieving goals intrinsic to a task. Accurate representation of value that drives successful goal-directed behavior is impaired in schizophrenia (67), particularly associated with positive symptoms in a recent study (68), which replicated findings of low value sensitivity in schizophrenia, and its association with increases in self-reported aberrant salience (69). Moreover, low value sensitivity (emerging from aberrant salience) was strongly associated with impaired cognitive performance. Finally (28), patients have increased preference for novel images, a preference both correlated with hallucination severity and which interfered with task performance. From a mechanistic perspective, aberrant salience affects the reward system by distorting value sensitivity. This distortion is associated with the genesis of positive symptoms, suggesting a compelling link between positive symptoms and dysfunctional reward sensitivity.

We next present a sampling of animal studies outlining the reward circuitry and interactions with cognitive circuits (providing a physiological basis for our framework).

Overview of Reward Circuitry

The reward circuitry is centered upon the release of dopamine (DA) from ventral tegmental area (VTA) neurons into limbic brain regions that control processing of rewarding stimuli, with additional regions/connections (70). Reward processing includes perception and prediction, and association with context and cues (71). VTA DA neurons have two major projections: the mesocortical pathway to the prefrontal cortex (PFC) and the mesolimbic pathway to the nucleus accumbens (NAc). However, they also project to the hippocampus, amygdala, and several other forebrain regions (72). VTA DA release into cortex is important for emotional responses and cognition (73), while DA release in NAc is traditionally linked to reward and motivated behaviors (74). The primary DA responsive cells of the NAc are medium spiny neurons (MSNs), and GABAergic cells that comprise two largely separate populations predominantly expressing either D1 or D2 DA receptors (DRs) (75, 76). Although these populations in the dorsal striatum are largely distinct in their projections, NAc MSN projections are more heterogeneous. The NAc MSNs expressing the D1 DR (D1

MSNs) are generally equated with the “direct” pathway, projecting to several regions critical for processing motivation including VTA, ventral pallidum (VP), and lateral hypothalamus. By comparison, the D2 MSNs are more strongly represented in the “indirect” pathway and appear to project exclusively to VP (77).

Although outputs of NAc D1 and D2 MSNs are not as categorically distinct as those of the dorsal striatum, they retain differential and largely opposing roles in reward processing. D1 neuron activation is associated with increased motivation while D2 neuron activity generally reduces motivation (78–82). Because DA signaling at D1 DRs increases the excitability of neurons but D2 DR activity decreases excitability, DA release in NAc tilts the balance toward the direct pathway, with the combined effect of *increased* motivation and reward.

Dopaminergic inputs moderate the responsiveness of NAc MSNs to multiple glutamatergic inputs that drive behavioral reinforcement. Thus, the NAc acts as a central processor for glutamatergic activity generated by multiple structures including the PFC, amygdala, hippocampus, and thalamus (83, 84). Glutamatergic inputs from ventral hippocampus (vHPC) may relay information regarding previous experiences as well as emotional states linked to context, including both aversion-based learning like context-dependent fear conditioning, and motivated behaviors like feeding and responses to drugs (85–87). PFC inputs provide executive information for planning motivated behaviors, such as seeking and acquiring food, drugs, sex, or social reward (88, 89). While the amygdala generally regulates fear-related learning and behavior, glutamatergic inputs from the amygdala onto NAc MSNs drive reward seeking and positive reinforcement (90–92).

NAc MSNs send and receive GABAergic projections to/from the VTA, and many of the regions that send glutamatergic projections to NAc also share mutual projections. Figure 2 provides a mechanistic instantiation of the general framework (Figure 1). As seen, this reward network is complex with multiple internal circuits capable of positive and negative feedback (83, 84). Dysfunction of the basal ganglia reward network is ubiquitous in neurological and psychiatric conditions (93). In schizophrenia, dysfunction of dopaminergic signaling in the striatum, glutamatergic circuits in cortex and hippocampus, and integration of the entire reward network have been implicated by human imaging studies, pharmacology, and preclinical models. Next, we review how these disparate sources paint a synergistic picture of network dysfunction in the illness.

Preclinical Studies relating to Schizophrenia Etiology

The symptoms of schizophrenia involve complex behaviors, therefore modeling the *disease* (as opposed to intermediate phenotypes) is difficult. Moreover, schizophrenia has a complex genetic basis; a simple genetic knockout or single animal model cannot encompass its symptoms. Nevertheless, the mouse model is a well-vetted compromise between sufficient complexity for behavioral analogy to schizophrenia, genetic tractability, and feasibility for high-throughput molecular studies (94, 95). Dozens of genetically altered mouse lines model one or more intermediate phenotypes (96, 97); here we restrict evidence to the most well-studied models demonstrating glutamatergic and dopaminergic synergistic molecular and behavioral phenotypes.

The most well-studied genetic mechanism of schizophrenia is DISC1. DISC1, dysfunction of which was originally linked families with high rates of schizophrenia (98), is a scaffolding protein with multiple protein-protein interaction domains allowing it to play structural and signaling roles in the nucleus, at mitochondria, and at synapses (99). DISC1 interacts with multiple proteins downstream of dopamine receptor signaling, thus controlling dopamine effects on neuronal function (100–102). Moreover, DISC1 mutant mice have increased D2 dopamine receptor expression in the striatum (103), mimicking increased D2 signaling seen in the striatum of patients. Critically, DISC1 also regulates the formation and function of glutamate synapses (104, 105). This evidence suggests that DISC1 disruption may synergistically drive dysfunction of *both* glutamate and dopamine signaling. Because mice with DISC1 mutations display deficits in pre-pulse inhibition that are reversed by antipsychotic treatment (106), uncoupled DISC1 regulation of dopamine and glutamate signaling could play a key role in schizophrenia.

Recurrent 22q 11.2 deletion is another promising neurogenic model of schizophrenia. 22q11.2 deletion syndrome (22q11DS) is caused by an autosomal dominant microdeletion within the 22nd chromosome, and ~25% of 22q11DS patients have schizophrenia (107). The deleted region contains genes including *catechol-O-methyltransferase (COMT)*, a critical enzyme for dopamine catabolism (108) and proline dehydrogenase (PRODH), which degrades the amino acid proline (109), both of which have been independently linked to schizophrenia. Proline can bi-directionally regulate glutamate transmission (110, 111), and PRODH knockout mice have decreased glutamate biosynthesis and reduced sensorimotor gating, measured by pre pulse inhibition (112). A multi-gene deletion mouse model for 22q11DS mimics many of the anatomical and behavioral abnormalities of humans with this syndrome (113), indicating the causal nature of this mutation in schizophrenia symptoms and a role for *both* dopaminergic and glutamatergic dysfunction.

Schizophrenia has been directly associated with reduced hippocampal volume and hippocampal asymmetry in patients (114). Consistent with this, many mouse models display an immature dentate gyrus (iDG), where a preponderance of neurons are arrested in a pseudo-immature state at the gene expression, morphological, and functional levels (115). Critically, many of the mutations leading to this state in mice are associated with schizophrenia in humans. Multiple mutant mice with the iDG phenotype also display behaviors associated with schizophrenia, including hyperactivity and deficits in working memory. For instance, mice with reduced expression of calcium/calmodulin-dependent protein kinase II alpha (CaMKII α) display iDG, with reduced hippocampal cell proliferation, and have multiple deficits in spatial learning, working memory, and hippocampal synaptic plasticity (116, 117). Functionally, CaMKII α is critical for glutamatergic synaptic structure and function, primarily through regulating the insertion and function of AMPA receptors (118, 119), being implicated in a variety of neuropsychiatric disorders (120). Other genes are associated with iDG, including SNAP-25, a critical mediator of glutamate and dopamine synaptic vesicle fusion that is itself linked to schizophrenia (121), and calciuneurin, a protein phosphatase important for postsynaptic signaling at both glutamate and dopamine synapses also tied to the illness (122, 123). Although studies of iDG mouse models have predominantly focused on dorsal hippocampus and attendant memory phenotypes, ventral hippocampus (vHPC) is also dysfunctional in

iDG models (115), and is likely to drive dysfunction of glutamatergic vHPC outputs to NAc (vHPC-NAc) critical for reward processing.

Dopamine, Glutamate and Schizophrenia

The dopamine and glutamate hypotheses are the leading pathophysiological accounts of schizophrenia. Both were formulated based on the psycho-mimetic effects of dopamine agonists (124) and N-methyl-D-aspartate (NMDA) receptor antagonists (125). The dopamine hypothesis garnered further clinical support because affinity for dopamine receptors was related to the effectiveness of antipsychotic drugs (126, 127), later bolstered by post-mortem studies (128, 129), human molecular imaging (reviewed in 130), and preclinical evidence (98, 131) of increased striatal D_{2/3} activation and baseline striatal dopamine. Furthermore, dopamine dysregulation is already present in the prodromal phase (reviewed in 132), meaning that it is not secondary to antipsychotic use or the psychosocial effects of illness chronicity.

The glutamate hypothesis of schizophrenia has been refined to posit a primary role of NMDA receptor hypofunction (133–135). In preclinical models, NMDAR blockade leads to a (somewhat counterintuitive) increase in glutamate release (136) and pyramidal neuron spiking (137), potentially via NMDAR hypofunction on fast-spiking gamma-aminobutyric acidergic (GABAergic) interneurons that regulate pyramidal neuron activity (138). NMDAR antagonists preferentially reduce the firing rate of these interneurons, leading to disinhibition of pyramidal neurons (139, 140). The clinical effects of NMDA receptor antagonists in healthy individuals mirror the full clinical picture of schizophrenia (including both negative and cognitive symptoms), more accurately than dopamine agonists (141). Furthermore, there is (equivocal) evidence for the clinical effectiveness of glutamatergic drugs; however, effects are modest, and it is unclear if effectiveness is directly related to a glutamatergic mechanism (reviewed in 142).

Post-mortem (143–145) and genetic studies (reviewed in 146) provide further support for the glutamate hypothesis, and proton magnetic resonance spectroscopy studies (¹H-MRS) indicate altered levels of cortical and subcortical glutamate in high-risk and patient populations across brain regions relevant to reward processing (145). The glutamate hypothesis would predict reductions in GABA concentrations, but recent meta-analyses do not provide support for a significant reduction in schizophrenia (147, 148). Methodological issues may partially explain the mixed results (149, 150). In addition, limitations to MRS are relevant: Extracellular and intracellular metabolite concentrations cannot be teased apart; nor can MRS distinguish between GABA neuron subtypes (of which only the parvalbumin basket cell class is thought to be disrupted in schizophrenia).

The dopamine and glutamate hypotheses of schizophrenia *are not* mutually exclusive. Loss of glutamatergic projections from prefrontal cortex to midbrain dopaminergic neurons due to NMDAR hypofunction will produce decreased mesocortical DA but increased mesolimbic DA release, particularly under conditions of stress (151). Furthermore, enhanced hippocampal projections onto the NAc, likely secondary to decreased functioning of GABAergic interneurons (152), lead to enhanced inhibitory signaling onto the ventral

pallidum. This in turn leads to reduced inhibition of the VTA, leading to increased dopamine release (153).

Neural circuit abnormalities underlying cognitive deficits, reward processing abnormalities and clinical symptoms

Negative symptoms, cognitive deficits, and reward processing abnormalities have traditionally been associated with impaired function of and between prefrontal areas and the basal ganglia (154). Emerging *in vivo* rsfMRI studies suggest that negative symptoms predict reduced spontaneous synchrony between the midbrain and prefrontal cortex (155), a Reward - Cognition pathway also sensitive to antipsychotic treatment (156).

Evidence from clinical and preclinical work additionally suggests that alterations in dopaminergic signaling due to vHPC abnormalities may explain both the psychotic and motivational symptoms of the illness. More specifically, abnormalities within the vHipp-NAc-VTA loop contribute to positive psychotic symptoms by leading to the abnormal generation and processing of novelty signals (157). This abnormality is central to several psychological accounts of psychotic symptoms that characterize acute stages of the illness. More specifically, psychosis may emerge due to reduced influence of statistical regularities stored in long-term memory on perception (158, 159). This results in undue salience and meaning being ascribed to irrelevant aspects of the environment (160). As noted earlier, aberrant salience subsequently engenders abnormal perceptions (hallucinations) and beliefs (delusions). Mechanistically, vHPC acts as a novelty detector, driving GABAergic neurons in the NAc that inhibit ventral pallidum, thus disinhibiting midbrain dopaminergic neurons (161, 162). In psychosis, resting vHPC activity may cause increased dopaminergic activity, resulting in inappropriate salience attributed to meaningless environmental stimuli (153).

Abnormal hippocampal afferents to the NAc also contribute to affective and motivational symptoms of schizophrenia. More specifically, acute stress leads to vHPC hyper-activity, which in turn leads to increased dopaminergic gain by way of NAc and ventral pallidum (163). Hyper-dopaminergia in response to acute stress leads to a relatively long-lasting decrease in dopaminergic gain, via increased activity of the infralimbic PFC (164, 165) homologue of the human sub-genual cingulate (166). This hypo-dopaminergic state has been associated with depressive phenotypes in rodent models. In support of this claim, glutamatergic transmission in the NAc is increased in a mouse model of chronic stress-induced depression (167–169), with a specific role for the vHPC-NAc projections in depressive behavior (170). Human neuroimaging work has revealed abnormal responses to rewarding stimuli in the NAc in clinical depression (171), and deep brain stimulation to the NAc has therapeutic effects in individuals with treatment-resistant depression (172), via inhibition of paralimbic cortical areas (173). Although negative syndrome schizophrenia and clinical depression are clinically similar with both characterized by abnormal reward processing and blunted NAc responses during reward anticipation (reviewed in 174), it unclear whether fully share pathophysiological mechanisms.

Toward a synergistic re-conception

The breath of the literature is impossible to review, but interactions between cognitive and reward pathways are unquestionably synergistic, and, as with all processing in the brain (175), contextually modulated. Schizophrenia is characterized by a loss of integrity of both cognition and reward circuits (176), resulting in a loss of a natural synergy that is necessary for healthy behavioral function. This loss, stems from both glutamatergic and dopaminergic dysregulation, fundamentally distorting behavioral processing in the illness, and resulting in global cognitive impairment (177) associated with foundational dys-connection (178) and aberrant cortical reorganization (132, 179).

Human behavioral function *can be* experimentally cleaved into cognitive *or* reward related processing. For example, human studies of reward processing typically study reward contingencies (e.g., delayed discounting) or reward choices (180). Such tasks are important probes for inducing experimentally controlled effects in the brain's reward circuits or regions. In naturalistic settings, however, the balance between reward (or hedonic drives) or salience, and cognitive/control mechanisms is bi-directional and incessantly changing (181). Thus, even in the absence of explicit reward contingencies, judgments of implicit reward relate to a balance between task difficulty and individual ability, predicting increases in functional connectivity between reward structures and cognitive networks (182). These effects are associated with *intrinsic motivational states* and traits for autonomy and competence, attributes that underpin self-determination theory (183). In principle, intrinsic motivation is itself an *inherently* rewarding process that modulates, and is itself reinforced by, cognitive activity (184). This principle provides a measure of understanding how a loss of intrinsic motivation coupled with a loss of integrity of cognitive circuits forms a *concurrent* "hit" in schizophrenia. The subsequent loss of a fundamental synergy underlying typical human behavior exerts highly negative impacts on the course of the illness. Conversely, as previously discussed, in schizophrenia abnormal salience alters value sensitivity and the perception of novelty, both of which is related to core aspects of reward processing. Abnormal salience is associated with deficits in core cognitive domains (185), as well as phenomenological alterations in self processing (186), that ultimately undermine cognition (187).

Schizophrenia is a constellation of aberrant behaviors, and modern neuroscience is built around integrative and synergistic models of normative behavior. These models address how brain circuits and regions, with relative degrees of specialization, integrate outputs in the service of complex functions (188). A complex illness like schizophrenia arises from a synergistic dysregulation of reward *and* cognition circuits, not because there is a simple causative relationship between the two, but rather because there are sustained bi-directional effects by which each sub-network class *continually* undermines the other. To re-emphasize this point, we revert to Figure 1, where rather than characterizing schizophrenia as related to deficits in cognitive or reward processing circuits (Figure 1a), we suggest it more meaningful to characterize it as an emergent property of their interaction (Figure 1b).

We imagine that this framework can redirect the search for novel molecular, cellular, and behavioral targets for therapeutic or prophylactic intervention. For example, the centrality of

cognition-reward interactions is implicit in a prominent cognitive model of negative symptoms used to guide behavioral interventions (189, 190). It is proposed that cognitive impairments result in underperformance and discouraging experiences, which in turn result in the development of defeatist beliefs (overgeneralized negative expectations about one's abilities). Defeatist beliefs lead to decreased deployment of cognitive effort in the face of potential rewards (191) and a reduction in the pursuance of goal-directed behavior, which manifests clinically as negative symptoms. Defeatist beliefs, of which interactions between cognitive and reward processes are arguably key, are promising treatment targets of psychosocial interventions aimed at reducing historically intractable negative symptoms and functional deficits (192, 193). In addition, these defeatist beliefs emerge prior to formal illness onset (194), further intimating their relevance for negative symptom development, and possible importance in prevention efforts. In this way, re-conceptualizing negative symptoms as arising from abnormal cognition-reward interactions may have real and immediate implications for treatment development.

This framework also motivates obvious shifts in mechanistic and theoretical models of schizophrenia (as we attempt to provide in Figure 2), and therefore experimental approaches toward understanding its biology. For instance, evidence that a core memory region (the hippocampus) evinces spontaneous intrinsic connectivity with regions such as the NAc and the VTA (195), implies nascent task-free connectivity between cognitive and reward systems in the human brain. It will be imperative to understand how such intrinsic connectivity is contextually modulated during tasks with explicit and/or implicit reward processing, and whether schizophrenia is characterized by dys-modulation of connectivity between reward and cognition networks.

Acknowledgements

AJR acknowledges support from the National Institutes of Mental Health (MH111604), the National Institutes of Neurological Disease and Stroke (NS085171), the National Institutes of Drug Abuse (DA040621, and DA040621-03S1) and the Avielle Foundation. KT acknowledges support from the National Institutes of Mental Health (MH112644, MH115297). VAD acknowledges support from the National Institutes of Mental Health (MH111177, MH059299), the Mark Cohen Neuroscience Endowment, the Jack Dorsey Neuroscience Endowment, the Children's Hospital of Michigan Foundation, the Prechter World Bipolar Foundation, the Ethel and James Flinn Foundation, the DMC Foundation, and the Lycaki-Young Funds from the State of Michigan.

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A Separate

B Synergistic

Figure 1: A synergistic interaction between cognition-related and reward/motivation related sub-networks underlies schizophrenia

(a) Traditional approaches focus on dysfunction within circuits sub-serving cognitive processing including working memory, learning, executive and motor function. These include regions (not restricted to) the hippocampus, basal ganglia, the dorsolateral prefrontal cortex, the thalamus and regions of the motor cortex. Dys-functional interactions between these components explain many of the cognitive deficits in schizophrenia. Complementary deficits in reward/motivation circuits are presumed to underlie aberrant salience, anhedonia, impaired reward sensitivity and amotivation. These are driven by dysfunctional interactions

between regions including the amygdala, ventral pallidum, nucleus accumbens, ventral tegmental area and the ventro-medial prefrontal cortex. (b) However, synergistic deficits between cognitive and reward/motivation circuits may be key to schizophrenia. In this view, dysfunction *between* cognitive circuits *and* reward/motivation circuits amplify deficits in cognition, which in parallel drive impaired reward/motivation. This interaction leads to the emergence of the complex phenotype that is schizophrenia (represented as the outer circle). The figure is a schematic depiction wherein the “connections” represent functional interactions between regions that may (or may not) exist in a one-to-one relationship with anatomical connections. Indeed, in presenting it in this way we acknowledge that the precise dialectic between brain structure (anatomy) and emergent function remains unresolved (171).

Figure 2: Schematic of brain reward circuitry and dysfunction in schizophrenia

Dopaminergic (green) and glutamatergic (red) inputs converge on GABAergic medium spiny neurons in the nucleus accumbens (NAc). These inputs coordinate and regulate direct and indirect outputs that differentially contribute to reward-related behaviors. In schizophrenia, DA signalling is reduced in the cortex, in part driving negative symptoms. However, DA is increased in striatum, particularly in the dorsal associative striatum, contributing to the positive symptoms of schizophrenia. BLA = basolateral amygdala; D1 = dopamine type 1 receptor; D2 = dopamine type 2 receptor; PFC = prefrontal cortex; vHPC = ventral hippocampus; VP = ventral pallidum; VTA = ventral tegmental area.