Schizophrenia Bulletin Advance Access published December 27, 2013
Schizophrenia Bulletin
doi:10.1093/schbul/sbt197

A Review of Reward Processing and Motivational Impairment in Schizophrenia

Gregory P. Strauss*[,1], James A. Waltz[2], and James M. Gold[2]

[1]Department of Psychology, State University of New York at Binghamton, Binghamton, NY; [2]Department of Psychiatry, University of Maryland School of Medicine and Maryland Psychiatric Research Center, Baltimore, MD

*To whom correspondence should be addressed; Department of Psychology, State University of New York at Binghamton, PO Box 6000, Binghamton, NY 13902; tel: 607-777-5408, fax: 607-777-4890, e-mail: gstrauss@binghamton.edu

This article reviews and synthesizes research on reward processing in schizophrenia, which has begun to provide important insights into the cognitive and neural mechanisms associated with motivational impairments. Aberrant cortical-striatal interactions may be involved with multiple reward processing abnormalities, including: (1) dopamine-mediated basal ganglia systems that support reinforcement learning and the ability to predict cues that lead to rewarding outcomes; (2) orbitofrontal cortex-driven deficits in generating, updating, and maintaining value representations; (3) aberrant effort-value computations, which may be mediated by disrupted anterior cingulate cortex and midbrain dopamine functioning; and (4) altered activation of the prefrontal cortex, which is important for generating exploratory behaviors in environments where reward outcomes are uncertain. It will be important for psychosocial interventions targeting negative symptoms to account for abnormalities in each of these reward processes, which may also have important interactions; suggestions for novel behavioral intervention strategies that make use of external cues, reinforcers, and mobile technology are discussed.

Key words: avolition/anhedonia/reward/motivation/negative symptoms/psychosis

Overview

Negative symptoms have been documented since the pre-neuroleptic era and long considered a core aspect of schizophrenia (SZ) phenomenology.[1,2] In the 1970s and 1980s Carpenter et al[3,4] confirmed that negative symptoms are indeed an aspect of psychopathology that is separable from other aspects of the illness and suggested that these symptoms can result from either primary or secondary factors that have distinct etiologies.[4] The advent of standardized clinical assessments allowed the negative symptom construct to be further refined,[5–7] with modern conceptualizations identifying 5 core components[8,9] that have been shown to separate into 2 domains: (1) a motivational dimension, consisting of avolition, anhedonia, and asociality, and (2) a diminished expressivity dimension, consisting of restricted affect and alogia.[9–11] Although investigation of both dimensions is critically important to the field because treatment approaches for these domains are largely ineffective, the motivational dimension has been theorized to be of greater importance to a number of core aspects of the illness, including functional outcome, subjective quality of life, recovery, and disease liability.[12–14]

Despite the clear importance of treating motivational abnormalities in SZ, the field has yet to achieve a comprehensive understanding of the cognitive and neurobiological processes contributing to these symptoms. Recent advances in the field of neuroscience offer a promising new means of understanding the motivational impairments in SZ at a mechanistic level.[15] The current manuscript reviews recent developments resulting from the application of cognitive and affective neuroscience frameworks to understand motivation in SZ. We focus on evidence implicating a distributed neural network that is responsible for a range of reward-related processes, including reinforcement learning, value representation, uncertainty-driven exploration, and effort-cost computation.

Intact Hedonic Response in SZ

The most straight-forward understanding of the motivational impairments in SZ is that patients fail to pursue goal-directed activities because they do not find such activities enjoyable. This notion has long been considered true, and the field has generally accepted that a significant proportion of individuals with SZ are anhedonic. However, recent empirical investigation calls these assumptions into question, suggesting that the long-held clinical understanding of anhedonia as a diminished

capacity for pleasure in SZ may be inaccurate (see Strauss and Gold[16] and Kring and Moran[17] for recent reviews). In short, studies suggest that individuals with SZ report levels of in-the-moment positive emotion[18] and subjective arousal[19] that are similar to healthy controls when exposed to pleasant stimuli in the laboratory and also similar increases in positive emotion to controls when engaged in activities during everyday life.[20,21] Patients also display comparable neural response to controls when presented with emotional stimuli and asked to report on their in-the-moment emotions.[22] Despite these apparently normal hedonic responses at the subjective and neurophysiological level, it is clear that individuals with SZ less frequently engage in motivated behaviors aimed at obtaining rewards and pleasurable outcomes.[23] Thus, an important question emerges: Why do apparently normal hedonic experiences not translate into motivated behavior in SZ?

Prediction Error Signaling, Reward Anticipation, and Reinforcement Learning

One possibility is that patients have deficits in reinforcement learning and reward anticipation that are needed for intact hedonic responses to influence decision making. A growing basic neuroscience literature has identified 2 complimentary and interactive neural systems that are involved with reinforcement learning and value representation.[24] One system, which governs rapid learning, is mediated by the prefrontal cortex (PFC), particularly the orbitofrontal cortex (OFC). This system is used to update mental representations of value for stimuli and response alternatives on a trial-by-trial basis, serving to guide decision making by allowing individuals to flexibly respond to changes in reinforcement contingency and novelty in the environment. The second system is mediated by the basal ganglia (BG) and involved with more gradual reinforcement learning. Learning achieved through this system occurs over a number of trials. Both systems make use of mismatches between expected and obtained outcomes called prediction errors (PEs). Positive PE signals are broadcast to dopamine (DA) cell target areas, which reinforce actions and representations associated with better-than-expected outcomes.[24] In contrast, transient decreases in DA cell activity signal that an action resulted in an outcome that was worse than expected and should be avoided (ie, negative PEs).[24]

Numerous behavioral and neuroimaging studies have investigated reinforcement learning in SZ, providing insight into the integrity of these 2 systems and their associations with motivational deficits. There is consistent evidence that patients are impaired at making rapid behavioral adjustments in response to feedback and that these impairments are associated with negative symptoms.[25,26] These deficits relate to the ability to use explicit representations of feedback to make trial-to-trial adjustments in responses, such as switching a response choice after experiencing negative feedback (lose-shifting), and they are associated with aberrant activation in the orbitofrontal cortex.[27,28] In contrast, many studies, using motor, serial reaction time, and cognitive skill-based learning tasks[29–31] suggest that gradual/procedural learning may be relatively intact in SZ (but see Foerde et al[32] and Kumari et al[33] for examples of evidence to the contrary). Inconsistent results among studies examining gradual learning may reflect a combination of differences in task properties and subject-related characteristics, including symptom presentation and antipsychotic medications. Antipsychotics may impact gradual learning, as chlorpromazine equivalent dosage is associated with performance on tasks reliant on procedural learning,[34] and procedural learning impairments are less severe in antipsychotic naive patients.[35] Gradual learning may therefore be impaired by very high levels of D2 blockade; however, this effect may be modest given that so many studies examining medicated patients find evidence for relatively intact gradual learning. Although behavioral studies provide compelling evidence that gradual learning is somewhat spared, neuroimaging studies suggest that normal learning may in fact be accompanied by abnormal neural activation in several brain areas, including the basal ganglia.[36,37] Patients may therefore achieve normal gradual learning through use of multiple cognitive processes and neural substrates outside of the neostriatum.

At the behavioral level, there is also consistent evidence that SZ patients with motivational impairments exhibit deficits in learning from positive outcomes (Go-learning), but intact learning from negative outcomes (NoGo-learning). This pattern of performance can be considered a perfect neurobehavioral recipe for avolition, ie, patients are capable of learning what *not to do* in order to avoid punishments, but not what *to do* in order to obtain rewards.[26,38,39] There are 2 alternative interpretations for this pattern of impaired Go- and spared NoGo-learning. First, impaired Go-learning could occur because patients fail to generate or learn from positive PEs during positive outcomes, possibly implicating aberrant DA signaling. Alternatively, patients could fail to precisely represent the value of the alternative responses during the decision process itself—a deficit driven by OFC dysfunction.

To explore these 2 alternative explanations, Gold et al[40] administered a probabilistic reinforcement-learning task that allowed for dissociation between value representation and PE abnormalities. In this experiment, participants were required to simultaneously learn 4 stimulus pairs: in 2 of the stimulus pairs, the correct choice led to a monetary reward on either 90% or 80% of trials with incorrect choices leading to a failure to make money; in the other 2 pairs, the correct choice led to the avoidance of a monetary loss on 90% or 80% of trials. Thus, in both the gain and loss avoidance pairs, selection of the correct response should be associated with the generation of a

positive PE, and both cases are known to elicit phasic DA bursts. Two critical findings were observed. First, patients with more severe avolition showed impaired acquisition of the gain pairs but spared acquisition of the loss avoidance pairs. This pattern of performance suggests that patients are able to use PEs to guide learning, at least when the positive PE is associated with successful loss avoidance (as well as intact learning from negative PEs to losses themselves). Second, in the transfer phase when stimuli learned during acquisition are presented in novel pairings, only the patients with severe avolition failed to prefer the stimuli associated with rewarding outcomes over those that had been associated with loss avoidance, which had been associated with positive PEs but have no positive expected value. In essence their choices were totally driven by the history of PEs and not by their expected value. To confirm this behavioral interpretation, a computational model was applied to estimate contributions of PE signaling in the BG (actor-critic model) and whether PEs are used to update value representations of actions in the OFC (Q-learning). The modeling results were remarkably clear: Performance of avolitional patients was well fit by a pure actor-critic model, whereas healthy controls and patients with low avolition were best fit by the model where the actor-critic model was supplemented by the contribution of Q-learning, confirming that the deficit observed in avolitional patients reflects impairments in value representation, not learning from PEs. Thus, both behavioral and modeling evidence suggest that PE signaling appears to be largely, and surprisingly, intact in patients with SZ.

The functional neuroimaging literature is not entirely consistent with the results of behavioral and computational modeling studies examining PEs. Consistent with behavioral and modeling evidence, neuroimaging data indicate intact activation in the ventral striatum in relation to negative PEs.[27,41,42] However, several neuroimaging studies indicate that positive PEs are accompanied by reduced neural response in the ventral striatum, as well as other regions such as the insula, frontal cortex, amygdala, hippocampus, putamen, and cingulate.[27,41–47] Notably, reduced striatal response has not been found in all studies (see Waltz et al[27], Dowd and Barch[48], and Simon et al[49]), and discrepancies across studies may reflect differences in characteristics of the patients that were sampled because individual differences in clinically rated negative symptoms predicted striatal response.[27,42,48,49] It is unclear how aberrant activation in areas outside of the striatum should be interpreted. Studies finding abnormal neural response outside of the striatum have primarily examined outcome-evoked responses or feedback-evoked responses, and studies reporting abnormal activation in areas outside of the striatum may not reflect reward PEs. Thus, the literature on the integrity of positive PE signaling is unclear; additional studies are needed to reconcile apparent discrepancies across levels of evidence, because there appear to be subtle, but possibly important, differences in behavioral, computational modeling, and imaging findings concerning the integrity of PE signaling.

Individuals with SZ also display impairments in reward anticipation, ie, the ability to signal reward availability when predictive cues are present. Striatal DA plays a key role in reward anticipation, allowing affective salience to become linked to predictive cues. Individuals with SZ have reduced activation in the ventral striatum in response to cues predicting upcoming rewards.[50–52] Reduced striatal response may occur in patients who are unmedicated or taking first-generation but not second-generation antipsychotics.[51,52] Blunted striatal activation during reward anticipation is also associated with greater negative symptom severity,[27,42,49] and these relationships hold true in patients taking second-generation antipsychotics.[27,49] The interpretation of results from reward anticipation studies using anticipation paradigms, such as the monetary incentive delay or other instrumental learning paradigms, is complicated by the fact that reward anticipation in these paradigms relies upon learning and several cognitive processes known to be impaired in SZ. To clarify this matter, Pavlovian conditioning paradigms have been examined, enabling an evaluation of reward anticipation and PE signaling independent of factors like action selection and response execution. Results from these studies indicate that patients with greater severity of negative symptoms display reduced activation in the ventral striatum and ventromedial PFC during reward anticipation.[42,48] Thus, impaired reward anticipation may not be an artifact of learning deficits and may play an important role in motivational impairments in SZ, impeding the initiation of goal-directed behavior.

Value Representation

Several research groups have proposed that motivational impairments in SZ may be related to deficits in generating, maintaining, and updating mental representations of value.[15,53,54] The OFC plays a critical role in value representation,[55] facilitating the calculation of an outcome's value, how much an outcome fulfills motivational needs, and the comparison of one outcome's value to alternative outcomes.[55] Thus, the OFC serves the purpose of holding information about reward value in working memory, which in turn facilitates goal-directed behavior by indicating when outcomes have changed and action plans need to be updated.

Individuals with SZ display impairments on tasks where value representations must be updated, such as probabilistic reversal learning or Intradimensional/Extradimensional set-shifting tasks[26,56–59] and the Iowa Gambling task.[60–62] Neuroimaging evidence indicates that impaired value representation on the probabilistic reversal learning task is associated with reduced deactivation of the medial PFC and that reduced deactivation predicts

elevated anhedonia and avolition.[28] One potential concern about the inferences drawn about value representation from tasks involving learning is that impairments on these tasks could result from general cognitive impairments. It seems unlikely that learning or generalized cognitive deficits fully account for value representation deficits, given data from several paradigms where subjects are simply asked to indicate preferences, where no learning or feedback processing is involved. For example, in a study of relative value judgments, which have been found to be associated with OFC function, Strauss et al[63] presented patients and controls with pairs of pleasant photographs with similar context (eg, cute puppies—border collie, poodle, etc) to examine the extent to which subjects made consistent preference choices that maintained transitivity (eg, if you prefer A to B and B to C, do you prefer A to C?).[64] Results indicated that patients were less bound by transitivity than controls as indicated by more inconsistent preference judgments and larger magnitudes of discrepant responses than controls. Furthermore, in a condition that presented a set of pleasant and unpleasant stimuli selected for gradations in valence (ie, highly positive>mildly positive>mildly negative>highly negative), controls were able to make fine-grained distinctions among the items and selected them in a normative fashion, whereas patients showed no preference for highly positive over mildly positive items or mildly negative over highly negative items (despite preferring positive to negative stimuli). Similarly, in multiple delayed discounting experiments, where participants are presented with an option for immediate or delayed rewards, there is consistent evidence that patients prefer smaller immediate rewards to larger delayed rewards.[65,66] A functional neuroimaging study of delay discounting in SZ patients and controls matched on behavioral performance indicated that patients had less activation in the inferior frontal, dorsal anterior cingulate, and posterior parietal cortices, as well as the ventral striatum.[67] These studies provide converging evidence that patients have difficulty representing the relative value of rewards and stimuli outside of the context of cognitively demanding learning paradigms. Based on the basic neuroscience literature,[68] it is likely that these decision-making deficits observed on tasks requiring value representation reflect impaired OFC function; however, neuroimaging studies are needed to directly test this interpretation.

We do not mean to imply that cognitive deficits are not involved with the accurate representation, use, and updating of value representations in SZ. Indeed, there is consistent evidence that working memory performance as measured by standardized neuropsychological tests is related to the integrity of value representations across a range of paradigms with differing levels of cognitive dem and.[36],[37,66,69–71] There is also evidence that patients have deficits in maintaining representations of value and affective experience. For example, in a psychophysiological study by Kring et al,[72] patients and controls were presented with startle probes while viewing pleasant, unpleasant, and neutral scenes as well as during the delay period when the images were removed from view. Replicating prior startle studies, SZ patients had similar modulation of the startle response when images were on-screen; however, unlike controls, who showed continued modulation of the blink response when startle probes were presented following stimulus offset, SZ patients displayed a lack of startle modulation to probes during the delay period. Similarly, an fMRI study by Ursu et al[73] found that SZ patients had comparable neural response to controls in the presence of emotional stimuli but reduced neural activation in the dorsolateral PFC and other prefrontal, limbic, and paralimbic areas during the delay period following image offset. Furthermore, delay period activity in the dorsolateral PFC was correlated with individual differences in clinically rated anhedonia on the Scale for the Assessment of Negative Symptoms (SANS). Gard et al[74] extended these findings at the behavioral level, showing that deficits in maintaining value representations over a brief delay (3 s) were predictive of impaired decision making. In a series of studies on long-term memory, Herbener and colleagues[75] have also found that while patients show normal in-the-moment responses to pleasant images or immediate rewards, they fail to retrieve those experiences after a 24-hour delay when memory consolidation should take effect. Thus, it appears that patients display deficits in generating, updating, maintaining, and retrieving mental representations of value, and these impairments are associated with motivational deficits.

Uncertainty-Driven Exploration

In everyday life, we are constantly faced with a decision-making process termed the exploration-exploitation dilemma, ie, whether to repeat actions that have resulted in positive outcomes in the past (exploit), vs trying out new actions that could yield even better results (explore). This decision-making process influences behaviors ranging from how to plan one's day to which job to apply for. How one approaches the exploration-exploitation dilemma has an important influence on the extent to which they engage in goal-directed and reward-seeking behavior.

Several neurobiological processes contribute to exploitation and exploration. In stationary environments where reward contingencies are stable, it is ideal to exploit. Exploitation is heavily influenced by DA nuclei and target areas in the BG and PFC.[76–77] In contrast, exploration may be an ideal strategy in nonstationary environments where reinforcement contingencies vary (ie, most everyday situations). Exploration involves several neural processes and can be achieved via multiple strategies. One strategy is to repeat behaviors that have best led to reward (ie, exploit), while also discovering over time whether there are better

options by occasionally choosing a different action at random.[78] Another strategy involves selecting actions based upon their level of uncertainty relative to the status quo (ie, the exploited option). Human neuroimaging evidence indicates that the rostrolateral PFC is responsible for tracking uncertainty in an ongoing manner to promote exploratory behavior.[77,79] Individual differences in uncertainty-driven exploration have also been linked to genes associated with prefrontal DA function (catechol-*O*-methyltransferase [*COMT*]), and individual differences in exploitation are associated with genes controlling striatal DA function (dopamine- and cAMP-regulated neuronal phosphoprotein [*DARPP-32*] and dopamine receptor D2 gene [DRD2]).[80] Exploration may depend on one's ability to engage more dorsal and anterior regions of the PFC that drive top-down control and limit prepotent behavioral responses in favor of selecting new actions aimed at obtaining maximal reward.[81] There is also evidence that exploration is influenced by neuromodulatory control of cortical norepinephrine, which serves to differentially promote exploration and exploitation as a function of ongoing utility estimates that are governed by frontal and medial regions of the PFC.[82,83] Thus, although there are multiple neural processes involved with exploration and exploitation, prefrontal control regions are critical for regulating the balance between decisions to explore or exploit under conditions of uncertainty.[81,83]

Given that PFC dysfunction is widely documented in SZ and linked to negative symptoms,[84] one might expect motivational deficits to be associated with abnormalities in using exploration and exploitation to guide decision making. To examine this possibility, Strauss et al[39] administered a task where participants were presented with a clock face that contained a moving "second" hand and asked to discover whether it was advantageous to respond quickly or withhold responding until the hand reached later portions of the clock face. Critically, the probability and magnitude of reward payoffs for fast and slow responding were manipulated across blocks, thereby requiring exploration to maximize rewards. Via computational modeling, trial-to-trial dynamics of reaction time adjustments were examined to estimate degree of uncertainty-driven exploration. Modeling results revealed that SZ patients were less likely to explore the different response alternatives when their values were uncertain and that this deficit was associated with anhedonia as rated by the SANS[5]—exploration was not associated with restricted affect, alogia, or avolition. The selectivity of this association with anhedonia may be informative. Anhedonia on the SANS largely reflects a behavioral component of reward seeking (eg, initiating social, sexual, and recreational activities) rather than the capacity to experience pleasure, which is often inferred from behavior. This result may therefore suggest that in environments where it is unknown whether an action could yield sufficient reward, patients may be less likely to seek out opportunities for new rewards because they do not adjust their behavior in an effort to reduce uncertainty. This may explain why many patients engage in fewer instances of pleasure-seeking behavior and persist in choices that will lead to certain rewards (eg, smoking, drinking soda-pop) even when the environment has changed and new rewards may be available. Consistent with this notion, another experiment also found that negative symptoms were related to this biased pattern of response selection, where the bias was actually adaptive in the static context imposed by task parameters.[85]

Several neural mechanisms may serve to link reduced uncertainty-driven exploration and motivational deficits in SZ. One possibility is that impaired prefrontal mechanisms reduce top-down control needed to inhibit a prepotent exploitative behavior and facilitate exploratory actions under conditions of uncertainty. This seems plausible given the link between negative symptoms and PFC function. However, several other mechanisms may also contribute to reduced exploration, such as deficits in processing expected and unexpected uncertainty and impairments in tracking long-term utility and using utility signals to promote exploration. Decisions to explore or exploit that are critically linked to ongoing utility estimates and processing uncertainty are executed by frontal structures that regulate norepinephrine release.[81,83] Thus, multiple neuromodulatory systems that have been implicated in SZ may contribute to reductions in uncertainty-driven exploration. Future studies are needed to evaluate some of alternative cognitive and neurobiological explanations proposed here.

Effort-Cost Computation

Another potential mechanism for motivational impairments in SZ is that patients have deficits in "effort-cost" computation that prevent them from making an accurate estimation of whether the benefits associated with an action outweigh the "costs" needed to obtain them (ie, physical or mental effort). Several neural mechanisms have been linked to the willingness to exert effort to receive rewards. Dopaminergic function plays an important role in effort-value computation, because studies have shown that exerting effort for high- vs low-value rewards is affected by focal DA depletion in the nucleus accumbens[86,87]and increasing DA via amphetamine administration enhances willingness to exert effortful behavior.[88] In humans, administration of d-amphetamine increases effortful behavior, and individual differences in DA release predict how willing an individual is to work for higher rewards.[88,89] Effort-value computation is also associated with anterior cingulate cortex structure and function, as indicated by animal lesion, animal positron emission tomography studies, and human neuroimaging studies.[90–94] Anterior cingulate cortex (ACC) structure and function, striatal DA release, and DA receptor availability may therefore play a critical role in whether high amounts of effort will be exerted to obtain a reward.

There are several reasons to think that effort-value computations would be impaired in SZ and potentially associated with motivational deficits. First, structural magnetic resonance imaging studies have indicated that individuals with SZ have volumetric reductions in the ACC,[95] and functional neuroimaging studies have indicated aberrant activation in the ACC during tasks requiring conflict or error monitoring (eg, Kerns et al[96]). Second, it is well documented that individuals with SZ have dopaminergic abnormalities. However, these abnormalities are not necessarily what one would expect in a disorder characterized by decreased motivation. The basic neuroscience literature on animals indicates that reduced effortful behavior is associated with *decreased* striatal DA receptor availability and release. Individuals with SZ exhibit dopaminergic abnormalities that at first glance appear inconsistent with a motivational deficit—they evidence tonic *increases* in striatal DA, as well as greater DA release in response to DA enhancing agents. It is therefore possible that another dopaminergic mechanism contributes to reduced effortful behavior in SZ. Ward et al[97] provided a compelling alternative account in a study using genetically altered developing mice, which are known to have an overexpression of postsynaptic D2 receptors, and found that these animals were less willing to work to receive rewards, despite having normal hedonic reactions (ie, the same phenomenology observed in SZ).[97] Because individuals with SZ also display an increase in D2 receptor availability,[98–99] it seems plausible that an overexpression of postsynaptic D2 receptors, rather than reduced striatal DA release, contributes to reduced effortful behavior to obtain rewards.

To date, 2 published studies have examined willingness to work for rewards in people with SZ. In the initial study, Gold et al[100] administered a task that required subjects to complete 30 trials where they had to choose between making a low physical effort option (20 button presses) to earn a low-value reward ($1) or a higher effort option to earn a higher value reward ranging from $3 to $7. The probability of reward receipt was manipulated to determine whether certain (100% probability) or uncertain (50% probability) outcomes influenced effort-based decision making. Results indicated that SZ patients were less likely than healthy controls to select the high physical effort option under the 100% probability condition when the potential reward was highest ($6 and $7). Additionally, these deficits were associated with greater severity of clinically rated negative symptoms. The second study, conducted by Fervaha et al,[101,102] administered the Effort Expenditure for Reward Task[103] and found that SZ patients were less willing to expend effort to receive high-value rewards, particularly patients with elevated symptoms of avolition. Thus, few studies to date have examined effort-value computation in SZ; however, the results of the 2 studies that have been conducted both indicate an association between negative symptoms and reductions in willingness to put forth effortful responses to obtain high-value rewards.

Several explanations for these results are possible. One possibility is that high negative symptom patients do not find high-value rewards worth the effort needed to obtain them. Alternatively, deficits in value representation may undermine the decision to engage in effortful behavior, making the cost associated with the action required to receive a reward seem prohibitively high because value is not represented precisely. Both explanations are plausible given the results of Gold et al[100] and Fervaha et al.[101] To make further progress in this area, functional neuroimaging studies are needed to clarify the neural processes leading to effort-value computation dysfunction. Based upon the neuroscience literature, one would expect abnormalities in the mesolimbic dopaminergic system and ACC, as well as the connectivity between these regions, to play a role. Furthermore, the human SZ findings are consistent with data supporting the D2 overexpression animal model, which provides evidence for intact hedonics in the context of impaired motivation. Studies examining the role of antipsychotic medications in medicated compared to medication naive patients will promote progress in this area of research, as D2 antagonists have been found to reduce the extent to which rats are willing to work for rewards.

Conclusions and Implications

The last decade has seen a number of important developments in the assessment of negative symptoms, as well as experimental studies that have served to refine our understanding of the psychological and neural mechanisms associated with impairments in motivation. There is now compelling evidence that motivational impairments do not reflect a deficit in hedonic experience, creating new interest in the possibility that impairments in different aspects of reward processing may be implicated.

The current chapter reviewed multiple aspects of reward processing that are abnormal in SZ and evaluated evidence suggesting that motivational impairments are associated with difficulty translating reward information into motivated behavior. Aberrant cortical-striatal interactions may be associated with multiple aspects of reward processing that contribute to reductions in goal-directed and pleasure-seeking behavior in SZ, including: (1) DA-mediated BG systems that support reinforcement learning and the ability to predict cues that lead to rewarding outcomes; (2) orbitofrontal cortex-driven deficits in generating, updating, and maintaining value representations; (3) aberrant effort-value computations, which may be mediated by disrupted anterior cingulate cortex and midbrain DA functioning; and (4) altered activation of the PFC, which is important for generating

exploratory behaviors in environments where reward outcomes are uncertain. New animal models of motivation in SZ, such as the D2 postsynaptic overexpression model of negative symptoms, have significant potential to clarify the role of DA in different aspects of reward processing. Translating these models directly into human studies of medicated and unmedicated patients is an important next step. However, it will also be important to examine other neurobiological processes, because it is clear that cortical-striatal interactions are only one contributing factor. Future studies should conduct whole-brain analyses to examine the contribution of areas outside of the striatum to various reward processes, as aberrant activation in regions such as the amygdala, hippocampus, and putamen has been reported in several aspects of reward processing (eg, PE signaling, reward valuation). It may also be important to examine the activation of salience and default mode networks, as it is possible that processes downstream from feedback processing may be integral to reward dysfunction.[28,104] Whether these networks play a critical role in negative symptoms is unclear; however, initial evidence suggests an association.[28] Network-level analyses may therefore provide an important new direction in understanding the architecture of negative symptoms.

Few studies have reported data on multiple aspects of reward processing in the same sample; however, it may be important to do so given that there are likely important interactions between reward processes. In particular, imprecise value representations may affect multiple aspects of reward processing, potentially reflecting a common mechanism that underlies motivational impairment in SZ. For example, aberrant value representations may contribute to deficits in computing whether an action is worth the effort needed to obtain it, making the decision to exploit actions that have lead to prior rewards or to explore new actions, and learning to make rapid trial-by-trial adjustments in response to probabilistic feedback. However, there are also likely to be other important interactions among reward processing domains. For example, SZ patients have consistently been found to have deficits in rapid learning, and these deficits may influence the flexibility with which they can update value representations and use them to exploit actions that will consistently yield reward. Effort-cost computations may also interact with other processes, such as exploration/exploitation, in tasks where there are "costs" associated with switching from one behavior to another. If patients have difficulty in judging these costs and whether the effort needed to switch to a new action is worth it, they may be less likely to try out new actions (ie, explore) and engage in goal-directed behavior.

Another important future direction is to translate the laboratory findings reviewed in this article into more effective psychosocial treatments that directly target motivational impairments. The reward processing literature lends some hints as to how novel behavioral interventions could be developed that would capitalize on the few islands of preserved reward processing that exist in SZ, while accounting for the multitude of deficits. For example, there is evidence that patients have significant impairments in rapid learning but relatively preserved gradual learning. To make use of these strengths and work around weaknesses, it may be necessary to incorporate external cues and provide frequent, repeated reinforcers to facilitate goal-directed behavior. Given the strengths in procedural learning, individuals with SZ may be able to learn new behaviors aimed at increasing goal-directed activity with consistent and regular repetition. Grant et al[105] recently developed a Cognitive Behavioral Therapy (CBT) approach for negative symptoms that incorporates some of these principles. This program has therapists adopt an engaging style (eg, direct and crisp speaking, energetic, commanding, and confident) and aims to reduce patient lapses in engagement by having them participate in activities during the therapy session (eg, playing cards, listening to music), as well as by using frequent and intense reinforcement of goal-directed behavior (eg, verbal praise, tokens, stickers). A randomized clinical trial indicated that this CBT approach significantly improved avolition more so than treatment as usual.[105] These results are promising, because few interventions have had an effect on avolition. Given that imprecise value representation may be a deficit that cuts across several aspects of reward processing, the use of external cues may be of critical importance as they would reduce the need to generate mental representations that are unlikely to have enough "pull" to facilitate the initiation of goal-directed behavior. To this end, it may be useful to take advantage of recent developments in Ecological Mometary Intervention (EMI) (ie, the use of mobile technology in the context of psychosocial treatment) to present frequent, selective cues. Apps on mobile devices may be ideal for delivering cues, reinforcers, and reminders designed to promote behavioral activation. Clinicians could use EMI to send reminders for patients to engage in specific activities and have apps deliver customized positive or negative feedback in relation to patient response. Given the relative sparing in learning from negative feedback, in the context of impairments in learning from positive feedback, the use of negative feedback may be necessary to shape behavior. Considering the increasing availability of mobile technology, as well as the development of apps specifically designed for psychosocial treatment, EMI is increasingly more viable as a treatment strategy. These methods could be useful in supplementing efficacious psychosocial treatments, such as the one developed by Grant et al.[105] Finally, measures of reward processing described in this review have potential utility as biomarkers that can be used to gauge the effectiveness of pharmacological and psychosocial treatments targeting motivational deficits in SZ.

Funding

National Institute of Mental Health (K23MH092530 to G.P.S., R01MH094460 to J.A.W., R01MH080066 to J.M.G.).

Acknowledgment

The authors have declared that there are no conflicts of interest in relation to the subject of this study.

References

1. Kraepelin E. *Dementia Praecox and Paraphrenia*. Translated by Barclay RM; edited by Robertson GM. New York: Robert E Krieger; 1919 [1971].
2. Bleuler E. Dementia Praecox or the Group of Schizophrenias. Translated by Zinkin J. New York: International Universities Press; 1950 [1911].
3. Carpenter WT, Strauss JS, Bartko JJ. Use of signs and symptoms for the identification of schizophrenic patients: A report from the International Pilot Study of Schizophrenia. *Schizophr Bull*. 1974:37–49.
4. Carpenter WT Jr, Heinrichs DW, Wagman AM. Deficit and nondeficit forms of schizophrenia: the concept. *Am J Psychiatry*. 1988;145:578–583.
5. Andreasen NC. *Scale for the Assessment of Negative Symptoms*. DesMoines: University of Iowa Press; 1983.
6. Kirkpatrick B, Buchanan RW, McKenney PD, Alphs LD, Carpenter WT Jr. The Schedule for the Deficit syndrome: an instrument for research in schizophrenia. *Psychiatry Res*. 1989;30:119–123.
7. Heinrichs DW, Hanlon TE, Carpenter WT Jr. The Quality of Life Scale: an instrument for rating the schizophrenic deficit syndrome. *Schizophr Bull*. 1984;10:388–398.
8. Kirkpatrick B, Fenton WS, Carpenter WT Jr, Marder SR. The NIMH-MATRICS consensus statement on negative symptoms. *Schizophr Bull*. 2006;32:214–219.
9. Blanchard JJ, Cohen AS. The structure of negative symptoms within schizophrenia: implications for assessment. *Schizophr Bull*. 2006;32:238–245.
10. Horan WP, Kring AM, Gur RE, Reise SP, Blanchard JJ. Development and psychometric validation of the Clinical Assessment Interview for Negative Symptoms (CAINS). *Schizophr Res*. 2011;132:140–145.
11. Strauss GP, Hong LE, Gold JM, et al. Factor structure of the Brief Negative Symptom Scale. *Schizophr Res*. 2012;142:96–98.
12. Meehl PE. Primary and secondary hypohedonia. *J Abnorm Psychol*. 2001;110:188–193.
13. Strauss GP, Harrow M, Grossman LS, Rosen C. Periods of recovery in deficit syndrome schizophrenia: a 20-year multi-follow-up longitudinal study. *Schizophr Bull*. 2010;36:788–799.
14. Strauss GP, Horan WP, Kirkpatrick B, et al. Deconstructing negative symptoms of schizophrenia: avolition-apathy and diminished expression clusters predict clinical presentation and functional outcome. *J Psychiatr Res*. 2013;47:783–790.
15. Barch DM, Dowd EC. Goal representations and motivational drive in schizophrenia: the role of prefrontal-striatal interactions. *Schizophr Bull*. 2010;36:919–934.
16. Strauss GP, Gold JM. A new perspective on anhedonia in schizophrenia. *Am J Psychiatry*. 2012;169:364–373.
17. Kring AM, Moran EK. Emotional response deficits in schizophrenia: insights from affective science. *Schizophr Bull*. 2008;34:819–834.
18. Cohen AS, Minor KS. Emotional experience in patients with schizophrenia revisited: meta-analysis of laboratory studies. *Schizophr Bull*. 2010;36:143–150.
19. Llerena K, Strauss GP, Cohen AS. Looking at the other side of the coin: a meta-analysis of self-reported emotional arousal in people with schizophrenia. *Schizophr Res*. 2012;142:65–70.
20. Gard DE, Kring AM, Gard MG, Horan WP, Green MF. Anhedonia in schizophrenia: distinctions between anticipatory and consummatory pleasure. *Schizophr Res*. 2007;93:253–260.
21. Oorschot M, Lataster T, Thewissen V, et al. Emotional experience in negative symptoms of schizophrenia–no evidence for a generalized hedonic deficit. *Schizophr Bull*. 2013;39:217–225.
22. Taylor SF, Kang J, Brege IS, Tso IF, Hosanagar A, Johnson TD. Meta-analysis of functional neuroimaging studies of emotion perception and experience in schizophrenia. *Biol Psychiatry*. 2012;71:136–145.
23. Myin-Germeys I, Delespaul PA, deVries MW. Schizophrenia patients are more emotionally active than is assumed based on their behavior. *Schizophr Bull*. 2000;26:847–854.
24. Schultz W, Dayan P, Montague PR. A neural substrate of prediction and reward. *Science*. 1997;275:1593–1599.
25. Waltz JA, Gold JM. Probabilistic reversal learning impairments in schizophrenia: further evidence of orbitofrontal dysfunction. *Schizophr Res*. 2007;93:296–303.
26. Waltz JA, Frank MJ, Wiecki TV, Gold JM. Altered probabilistic learning and response biases in schizophrenia: behavioral evidence and neurocomputational modeling. *Neuropsychology*. 2011;25:86–97.
27. Waltz JA, Schweitzer JB, Ross TJ, et al. Abnormal responses to monetary outcomes in cortex, but not in the basal ganglia, in schizophrenia. *Neuropsychopharmacology*. 2010;35:2427–2439.
28. Waltz JA, Kasanova Z, Ross TJ, et al. The roles of reward, default, and executive control networks in set-shifting impairments in schizophrenia. *PLoS ONE*. 2013;8:e57257.
29. Green MF, Kern RS, Williams O, McGurk S, Kee K. Procedural learning in schizophrenia: evidence from serial reaction time. *Cognit Neuropsychiatry*. 1997;2:123–134.
30. Goldberg TE, Saint-Cyr JA, Weinberger DR. Assessment of procedural learning and problem solving in schizophrenic patients by Tower of Hanoi type tasks. *J Neuropsychiatry Clin Neurosci*. 1990;2:165–173.
31. Gold JM, Hahn B, Strauss GP, Waltz JA. Turning it upside down: areas of preserved cognitive function in schizophrenia. *Neuropsychol Rev*. 2009;19:294–311.
32. Foerde K, Poldrack RA, Khan BJ, et al. Selective corticostriatal dysfunction in schizophrenia: examination of motor and cognitive skill learning. *Neuropsychology*. 2008;22:100–109.
33. Kumari V, Gray JA, Honey GD, et al. Procedural learning in schizophrenia: a functional magnetic resonance imaging investigation. *Schizophr Res*. 2002;57:97–107.
34. Kéri S, Nagy O, Kelemen O, Myers CE, Gluck MA. Dissociation between medial temporal lobe and basal ganglia memory systems in schizophrenia. *Schizophr Res*. 2005;77:321–328.
35. Schérer H, Stip E, Paquet F, Bédard MA. Mild procedural learning disturbances in neuroleptic-naive patients with schizophrenia. *J Neuropsychiatry Clin Neurosci*. 2003;15:58–63.

36. Reiss JP, Campbell DW, Leslie WD, et al. Deficit in schizophrenia to recruit the striatum in implicit learning: a functional magnetic resonance imaging investigation. *Schizophr Res*. 2006;87:127–137.
37. Weickert TW, Goldberg TE, Callicott JH, et al. Neural correlates of probabilistic category learning in patients with schizophrenia. *J Neurosci*. 2009;29:1244–1254.
38. Waltz JA, Frank MJ, Robinson BM, Gold JM. Selective reinforcement learning deficits in schizophrenia support predictions from computational models of striatal-cortical dysfunction. *Biol Psychiatry*. 2007;62:756–764.
39. Strauss GP, Frank MJ, Waltz JA, Kasanova Z, Herbener ES, Gold JM. Deficits in positive reinforcement learning and uncertainty-driven exploration are associated with distinct aspects of negative symptoms in schizophrenia. *Biol Psychiatry*. 2011;69:424–431.
40. Gold JM, Waltz JA, Matveeva TM, et al. Negative symptoms and the failure to represent the expected reward value of actions: behavioral and computational modeling evidence. *Arch Gen Psychiatry*. 2012;69:129–138.
41. Walter H, Kammerer H, Frasch K, Spitzer M, Abler B. Altered reward functions in patients on atypical antipsychotic medication in line with the revised dopamine hypothesis of schizophrenia. *Psychopharmacology (Berl)*. 2009;206:121–132.
42. Waltz JA, Schweitzer JB, Gold JM, et al. Patients with schizophrenia have a reduced neural response to both unpredictable and predictable primary reinforcers. *Neuropsychopharmacology*. 2009;34:1567–1577.
43. Schlagenhauf F, Sterzer P, Schmack K, et al. Reward feedback alterations in unmedicated schizophrenia patients: relevance for delusions. *Biol Psychiatry*. 2009;65:1032–1039.
44. Murray GK, Corlett PR, Clark L, et al. Substantia nigra/ventral tegmental reward prediction error disruption in psychosis. *Mol Psychiatry*. 2008;13:239, 267–276.
45. Koch K, Schachtzabel C, Wagner G, et al. Altered activation in association with reward-related trial-and-error learning in patients with schizophrenia. *Neuroimage*. 2010;50:223–232.
46. Gradin VB, Kumar P, Waiter G, et al. Expected value and prediction error abnormalities in depression and schizophrenia. *Brain*. 2011;134:1751–1764.
47. Corlett PR, Murray GK, Honey GD, et al. Disrupted prediction-error signal in psychosis: evidence for an associative account of delusions. *Brain*. 2007;130:2387–2400.
48. Dowd EC, Barch DM. Pavlovian reward prediction and receipt in schizophrenia: relationship to anhedonia. *PLoS One*. 2012;7:e35622.
49. Simon JJ, Biller A, Walther S, et al. Neural correlates of reward processing in schizophrenia–relationship to apathy and depression. *Schizophr Res*. 2010;118:154–161.
50. Juckel G, Schlagenhauf F, Koslowski M, et al. Dysfunction of ventral striatal reward prediction in schizophrenia. *Neuroimage*. 2006;29:409–416.
51. Juckel G, Schlagenhauf F, Koslowski M, et al. Dysfunction of ventral striatal reward prediction in schizophrenic patients treated with typical, not atypical, neuroleptics. *Psychopharmacology (Berl)*. 2006;187:222–228.
52. Nielsen MØ, Rostrup E, Wulff S, et al. Alterations of the brain reward system in antipsychotic naïve schizophrenia patients. *Biol Psychiatry*. 2012;71:898–905.
53. Kring AM, Elis O. Emotion deficits in people with schizophrenia. *Annu Rev Clin Psychol*. 2013;9:409–433.
54. Gold JM, Waltz JA, Prentice KJ, Morris SE, Heerey EA. Reward processing in schizophrenia: a deficit in the representation of value. *Schizophr Bull*. 2008;34:835–847.
55. Wallis JD. Orbitofrontal cortex and its contribution to decision-making. *Annu Rev Neurosci*. 2007;30:31–56.
56. Elliott R, McKenna PJ, Robbins TW, Sahakian BJ. Neuropsychological evidence for frontostriatal dysfunction in schizophrenia. *Psychol Med*. 1995;25:619–630.
57. Tyson PJ, Laws KR, Roberts KH, Mortimer AM. Stability of set-shifting and planning abilities in patients with schizophrenia. *Psychiatry Res*. 2004;129:229–239.
58. Ceaser AE, Goldberg TE, Egan MF, McMahon RP, Weinberger DR, Gold JM. Set-shifting ability and schizophrenia: a marker of clinical illness or an intermediate phenotype? *Biol Psychiatry*. 2008;64:782–788.
59. Pantelis C, Barber FZ, Barnes TR, Nelson HE, Owen AM, Robbins TW. Comparison of set-shifting ability in patients with chronic schizophrenia and frontal lobe damage. *Schizophr Res*. 1999;37:251–270.
60. Shurman B, Horan WP, Nuechterlein KH. Schizophrenia patients demonstrate a distinctive pattern of decision-making impairment on the Iowa Gambling Task. *Schizophr Res*. 2005;72:215–224.
61. Sevy S, Burdick KE, Visweswaraiah H, et al. Iowa gambling task in schizophrenia: a review and new data in patients with schizophrenia and co-occurring cannabis use disorders. *Schizophr Res*. 2007;92:74–84.
62. Lee Y, Kim YT, Seo E, et al. Dissociation of emotional decision-making from cognitive decision-making in chronic schizophrenia. *Psychiatry Res*. 2007;152:113–120.
63. Elliott R, Agnew Z, Deakin JF. Hedonic and informational functions of the human orbitofrontal cortex. *Cereb Cortex*. 2010;20:198–204.
64. Strauss GP, Robinson BM, Waltz JA, et al. Patients with schizophrenia demonstrate inconsistent preference judgments for affective and nonaffective stimuli. *Schizophr Bull*. 2011;37:1295–1304.
65. Heerey EA, Matveeva TM, Gold JM. Imagining the future: degraded representations of future rewards and events in schizophrenia. *J Abnorm Psychol*. 2011;120:483–489.
66. Heerey EA, Robinson BM, McMahon RP, Gold JM. Delay discounting in schizophrenia. *Cogn Neuropsychiatry*. 2007;12:213–221.
67. Avsar KB, Weller RE, Cox JE, Reid MA, White DM, Lahti AC. An fMRI investigation of delay discounting in patients with schizophrenia. *Brain and Behavior*. 2013;3:384–401.
68. Schoenbaum G, Roesch M. Orbitofrontal cortex, associative learning, and expectancies. *Neuron*. 2005;47:633–636.
69. Heerey EA, Bell-Warren KR, Gold JM. Decision-making impairments in the context of intact reward sensitivity in schizophrenia. *Biol Psychiatry*. 2008;64:62–69.
70. Brown JK, Waltz JA, Strauss GP, McMahon RP, Frank MJ, Gold JM. Hypothetical decision making in schizophrenia: the role of expected value computation and "irrational" biases. *Psychiatry Res*. 2013;209:142–149.
71. Strauss GP, Lee BG, Waltz JA, Robinson BM, Brown JK, Gold JM. Cognition-emotion interactions are modulated by working memory capacity in individuals with schizophrenia. *Schizophr Res*. 2012;141:257–261.
72. Kring AM, Germans Gard M, Gard DE. Emotion deficits in schizophrenia: timing matters. *J Abnorm Psychol*. 2011;120:79–87.

73. Ursu S, Kring AM, Gard MG, et al. Prefrontal cortical deficits and impaired cognition-emotion interactions in schizophrenia. *Am J Psychiatry*. 2011;168:276–285.
74. Gard DE, Cooper S, Fisher M, Genevsky A, Mikels JA, Vinogradov S. Evidence for an emotion maintenance deficit in schizophrenia. *Psychiatry Res*. 2011;187:24–29.
75. Herbener ES. Emotional memory in schizophrenia. *Schizophr Bull*. 2008;34:875–887.
76. Graybiel AM. Habits, rituals, and the evaluative brain. *Annu Rev Neurosci*. 2008;31:359–387.
77. Daw ND, O'Doherty JP, Dayan P, Seymour B, Dolan RJ. Cortical substrates for exploratory decisions in humans. *Nature*. 2006;441:876–879.
78. Sutton RS, Barto AG. *Reinforcement Learning: An Introduction*. Cambridge, MA: MIT Press; 1998.
79. Badre D, Doll BB, Long NM, Frank MJ. Rostrolateral prefrontal cortex and individual differences in uncertainty-driven exploration. *Neuron*. 2012;73:595–607.
80. Frank MJ, Doll BB, Oas-Terpstra J, Moreno F. Prefrontal and striatal dopaminergic genes predict individual differences in exploration and exploitation. *Nat Neurosci*. 2009;12:1062–1068.
81. Cohen JD, McClure SM, Yu AJ. Should I stay or should I go? How the human brain manages the trade-off between exploitation and exploration. *Philos Trans R Soc Lond B Biol Sci*. 2007;362:933–942.
82. Usher M, Cohen JD, Servan-Schreiber D, Rajkowski J, Aston-Jones G. The role of locus coeruleus in the regulation of cognitive performance. *Science*. 1999;283:549–554.
83. Aston-Jones G, Cohen JD. An integrative theory of locus coeruleus-norepinephrine function: adaptive gain and optimal performance. *Annu Rev Neurosci*. 2005;28:403–450.
84. Fischer BA, Keller WR, Arango C, et al. Cortical structural abnormalities in deficit versus nondeficit schizophrenia. *Schizophr Res*. 2012;136:51–54.
85. Kasanova Z, Waltz JA, Strauss GP, Frank MJ, Gold JM. Optimizing vs. matching: response strategy in a probabilistic learning task is associated with negative symptoms of schizophrenia. *Schizophr Res*. 2011;127:215–222.
86. HODOS W. Progressive ratio as a measure of reward strength. *Science*. 1961;134:943–944.
87. Salamone JD, Cousins MS, Bucher S. Anhedonia or anergia? Effects of haloperidol and nucleus accumbens dopamine depletion on instrumental response selection in a T-maze cost/benefit procedure. *Behav Brain Res*. 1994;65:221–229.
88. Wardle MC, Treadway MT, Mayo LM, Zald DH, de Wit H. Amping up effort: effects of d-amphetamine on human effort-based decision-making. *J Neurosci*. 2011;31:16597–16602.
89. Treadway MT, Buckholtz JW, Cowan RL, et al. Dopaminergic mechanisms of individual differences in human effort-based decision-making. *J Neurosci*. 2012;32:6170–6176.
90. Walton ME, Bannerman DM, Rushworth MF. The role of rat medial frontal cortex in effort-based decision making. *J Neurosci*. 2002;22:10996–11003.
91. Walton ME, Groves J, Jennings KA, et al. Comparing the role of the anterior cingulate cortex and 6-hydroxydopamine nucleus accumbens lesions on operant effort-based decision making. *Eur J Neurosci*. 2009;29:1678–1691.
92. Endepols H, Sommer S, Backes H, Wiedermann D, Graf R, Hauber W. Effort-based decision making in the rat: an [18F] fluorodeoxyglucose micro positron emission tomography study. *J Neurosci*. 2010;30:9708–9714.
93. Croxson PL, Walton ME, O'Reilly JX, Behrens TE, Rushworth MF. Effort-based cost-benefit valuation and the human brain. *J Neurosci*. 2009;29:4531–4541.
94. Prévost C, Pessiglione M, Météreau E, Cléry-Melin ML, Dreher JC. Separate valuation subsystems for delay and effort decision costs. *J Neurosci*. 2010;30:14080–14090.
95. Benes FM. Emerging principles of altered neural circuitry in schizophrenia. *Brain Res Brain Res Rev*. 2000;31:251–269.
96. Kerns JG, Cohen JD, MacDonald AW 3rd, et al. Decreased conflict- and error-related activity in the anterior cingulate cortex in subjects with schizophrenia. *Am J Psychiatry*. 2005;162:1833–1839.
97. Ward RD, Simpson EH, Richards VL, et al. Dissociation of hedonic reaction to reward and incentive motivation in an animal model of the negative symptoms of schizophrenia. *Neuropsychopharmacology*. 2012;37:1699–1707.
98. Fusar-Poli P, Meyer-Lindenberg A. Striatal presynaptic dopamine in schizophrenia, Part I: meta-analysis of dopamine active transporter (DAT) density. *Schizophr Bull*. 2013;39:22–32.
99. Fusar-Poli P, Meyer-Lindenberg A. Striatal presynaptic dopamine in schizophrenia, part II: meta-analysis of [(18)F/(11)C]-DOPA PET studies. *Schizophr Bull*. 2013;39:33–42.
100. Gold JM, Strauss GP, Waltz JA, Robinson BM, Brown JK, Frank MJ. Negative symptoms of schizophrenia are associated with abnormal effort-cost computations. *Biol Psychiatry*. 2013;74:130–136.
101. Fervaha G, Graff-Guerrero A, Zakzanis KK, Foussias G, Agid O, Remington G. Incentive motivation deficits in schizophrenia reflect effort computation impairments during cost-benefit decision-making. *J Psychiatr Res*. 2013;47:1590–1596.
102. Fervaha G, Foussias G, Agid O, Remington G. Neural substrates underlying effort computation in schizophrenia [published online ahead of print Sep 12, 2013]. *Neurosci Biobehav Rev*. doi:10.1016/j.neubiorev.2013.09.001
103. Treadway MT, Buckholtz JW, Schwartzman AN, Lambert WE, Zald DH. Worth the 'EEfRT'? The effort expenditure for rewards task as an objective measure of motivation and anhedonia. *PLoS One*. 2009;4:e6598.
104. Gradin VB, Waiter G, O'Connor A, et al. Salience network-midbrain dysconnectivity and blunted reward signals in schizophrenia. *Psychiatry Res*. 2013;211:104–111.
105. Grant PM, Huh GA, Perivoliotis D, Stolar NM, Beck AT. Randomized trial to evaluate the efficacy of cognitive therapy for low-functioning patients with schizophrenia. *Arch Gen Psychiatry*. 2012;69:121–127.