

## Goal Representations and Motivational Drive in Schizophrenia: The Role of Prefrontal–Striatal Interactions

Deanna M. Barch<sup>\*,1–3</sup> and Erin C. Dowd<sup>4</sup>

<sup>1</sup>Department of Psychology, Washington University, Box 1125, One Brookings Drive, St. Louis, MO; <sup>2</sup>Department of Psychiatry, Washington University, Box 1125, One Brookings Drive, St. Louis, MO; <sup>3</sup>Department of Radiology, Washington University, Box 1125, One Brookings Drive, St. Louis, MO; <sup>4</sup>Neuroscience Program, Washington University, St. Louis, MO

\*To whom correspondence should be addressed; tel: 314-935-8729, fax: 314-935-8790, e-mail: dbarch@artsci.wustl.edu.

The past several years have seen a resurgence of interest in understanding the psychological and neural bases of what are often referred to as “negative symptoms” in schizophrenia. These aspects of schizophrenia include constructs such as asociality, avolition (a reduction in the motivation to initiate or persist in goal-directed behavior), and anhedonia (a reduction in the ability to experience pleasure). We believe that these dimensions of impairment in individuals with schizophrenia reflect difficulties using internal representations of emotional experiences, previous rewards, and motivational goals to drive current and future behavior in a way that would allow them to obtain desired outcomes, a deficit that has major clinical significance in terms of functional capacity. In this article, we review the major components of the systems that link experienced and anticipated rewards with motivated behavior that could potentially be impaired in schizophrenia. We conclude that the existing evidence suggests relatively intact hedonics in schizophrenia, but impairments in some aspects of reinforcement learning, reward prediction, and prediction error processing, consistent with an impairment in “wanting.” As of yet, there is only indirect evidence of impairment in anterior cingulate and orbital frontal function that may support value and effort computations. However, there are intriguing hints that individuals with schizophrenia may not be able to use reward information to modulate cognitive control and dorsolateral prefrontal cortex function, suggesting a potentially important role for cortical–striatal interactions in mediating impairment in motivated and goal-directed behavior in schizophrenia.

*Key words:* reward/cognitive control/anhedonia

### Introduction

The past several years have seen a resurgence of interest in understanding the psychological and neural bases of what

are often referred to as “negative symptoms” in schizophrenia. These aspects of schizophrenia include constructs such as asociality, avolition (a reduction in the motivation to initiate or persist in goal-directed behavior), and anhedonia (a reduction in the ability to experience pleasure) as well as flat affect or the diminished expression of emotion. This resurgence of interest in negative symptoms in schizophrenia has been driven by at least 2 factors. The first factor is the realization that addressing the pervasive cognitive impairment present in schizophrenia may not be enough to fully understand and remediate the functional impairments that can make life so difficult for individuals with this disorder.<sup>1</sup> This is not to say that cognitive impairment is not a critical constraint on functional capacity in schizophrenia. Rather, the point is that we may also need to understand how cognitive impairments interact with reward and emotional processing systems in a way that leads to abnormalities in motivated behavior in this disorder. A second factor is that major advances have occurred in the field of affective neuroscience that provide a theoretical and empirical foundation upon which to draw in order to identify candidate psychological and neural mechanisms that drive interactions between cognitive function, reward, and motivation.<sup>2,3</sup>

In the current discussion, we will focus on the constructs of anhedonia, avolition, asociality, and amotivation (collectively referred to as anhedonia/avolition for ease of discussion) as distinct and separable from the construct of flat affect or diminished expression of emotion. This distinction is supported by a range of exploratory and confirmatory analyses of symptom assessment scales that have consistently provided evidence for separate negative symptom factors for flat affect and anhedonia/avolition. As nicely articulated by Malaspina and colleagues,<sup>4</sup> separable factors for flat affect and anhedonia/avolition have been identified in: (1) mixed groups of patients with a range of psychotic disorders<sup>5–7</sup>, (2) schizophrenia spectrum patients<sup>8–12</sup>, (3) deficit syndrome

patients<sup>4,13</sup>, (4) patients on medications<sup>4,9</sup>, (5) patients off medications<sup>12</sup>, (6) first-episode patients<sup>8</sup>, (7) chronic patients<sup>11</sup>, and (8) patients across many different cultures.<sup>5,6,8,10,13</sup>

The constructs of anhedonia/avolition play a major role in many theories of schizophrenia, including those that focus on liability to the disorder.<sup>14–17</sup> However, as reviewed below, studies suggest that when provided with potentially enjoyable stimuli, events or experiences, individuals with schizophrenia seem to enjoy such experiences as much as controls.<sup>18–23</sup> Nonetheless, one of the fundamental challenges in the development of therapeutic interventions is that individuals with schizophrenia seem less motivated to engage in goal-directed behavior that would bring them into contact with potentially enjoyable experiences, despite an apparently intact ability to enjoy those experiences once achieved.<sup>22</sup> This dissociation has been referred to as a distinction between “wanting” vs “liking” or between anticipatory and consummatory pleasure.<sup>24–26</sup> These problems are a major public health concern, as a failure to engage in motivated goal-directed behavior can manifest as reduced educational, occupational, and social achievement. If anhedonia/avolition does not reflect a deficit in the “enjoyment” of positive experiences in schizophrenia, then we need to understand the mechanisms that may lead to deficits in the ability to translate information about potentially rewarding events into action plans that will allow an individual to obtain such positive outcomes. The goal of this review is to outline and describe the key processes that link experienced and anticipated rewards to action plans, to review the existing literature on the integrity of these systems in schizophrenia, and to provide a summary and suggestions for future research aimed at understanding the psychological and neural bases of motivational impairments in schizophrenia.

### Components of the Systems Linking Experienced or Anticipated Rewards to Action Plans

Our hypothesis is that individuals with schizophrenia seem to have difficulties using internal representations of emotional experiences, previous rewards, and motivational goals to drive current and future behavior that should allow them to obtain desired outcomes, a deficit that has major clinical significance in terms of functional capacity. However, there are many processes that contribute to linking internal representations to behavior, and it is important to understand which of these are impaired in schizophrenia so as to design appropriate intervention strategies. Fortunately, a burgeoning affective neuroscience literature in humans and animals has begun to outline the core neural systems that serve to process and integrate reward and penalty signals and then translate these signals into value and/or utility estimates that can be used to drive action selection and goal planning.

Although an oversimplification, it helps to organize this large literature by thinking of 4 major components to the translation of appetitive or reward information into behavioral responses<sup>3,24,27–29</sup> (see figure 1). The first component, referred to as “hedonics or liking,” reflects the ability of the organism to “enjoy” the stimulus or event that may provide pleasure or reward. For many years, it was suggested that the neurotransmitter dopamine (DA) was the primary substrate of liking.<sup>24</sup> However, more recent research has shown that experimental depletion of DA does not reduce liking when it can be measured by facial expression and/or subjective reports.<sup>24</sup> Instead, hedonic responses (at least to primary sensory stimuli) seem to be mediated by activation of the opioid and gamma amino butyric acidergic systems in the nucleus accumbens shell and its projections to the ventral pallidum as well as in the orbital frontal cortex (OFC).<sup>30–33</sup>

A second component, called “reward prediction and wanting,” is thought to be mediated by the midbrain DA system, particularly the projections to ventral and dorsal striatal regions of the basal ganglia.<sup>24,29</sup> Many DA neurons in the substantia nigra and ventral tegmental area respond to stimuli that predict reward as well as to food and liquid rewards themselves. The degree to which these DA neurons respond to rewards seems to depend on reward predictability. If the reward was not predicted, then the DA neurons fire strongly (positive prediction error); if a predicted reward does not occur, then there is a transient depression in DA neuron firing (negative prediction error).<sup>27–29,34–35</sup> Furthermore, over time, DA neurons learn to fire to cues that predict reward rather than to rewards themselves. Similar effects have been found in humans in the ventral/dorsal striatum, with evidence from functional magnetic resonance imaging (fMRI) for activation of ventral and dorsal striatum to cues that predict reward<sup>36,37</sup> as well as both positive and negative prediction error responses.<sup>38,39</sup> These types of DA/striatal responses have been captured by temporal difference models that learn about stimuli in the environment that predict rewards.<sup>40,41</sup> These mechanisms are also thought to underlie basic aspects of reinforcement learning that may occur without conscious awareness.<sup>42,43</sup> A prominent, though slightly different theory, emphasizes the role of the DA-learning process in transferring incentive salience from the reward itself to reward-predicting cues, thus imbuing these cues with motivational properties themselves (eg, a wanting response<sup>24</sup>).

A third component is “cost-benefit analysis” or the ability to integrate information from different sources to derive and update the value of potentially rewarding outcomes (figure 1). One aspect, thought to be mediated at least in part by OFC, is the ability to “represent value information,” ie, to take into account not only the hedonic properties of a stimulus but also the internal or motivational state of the organism (eg, value of juice when

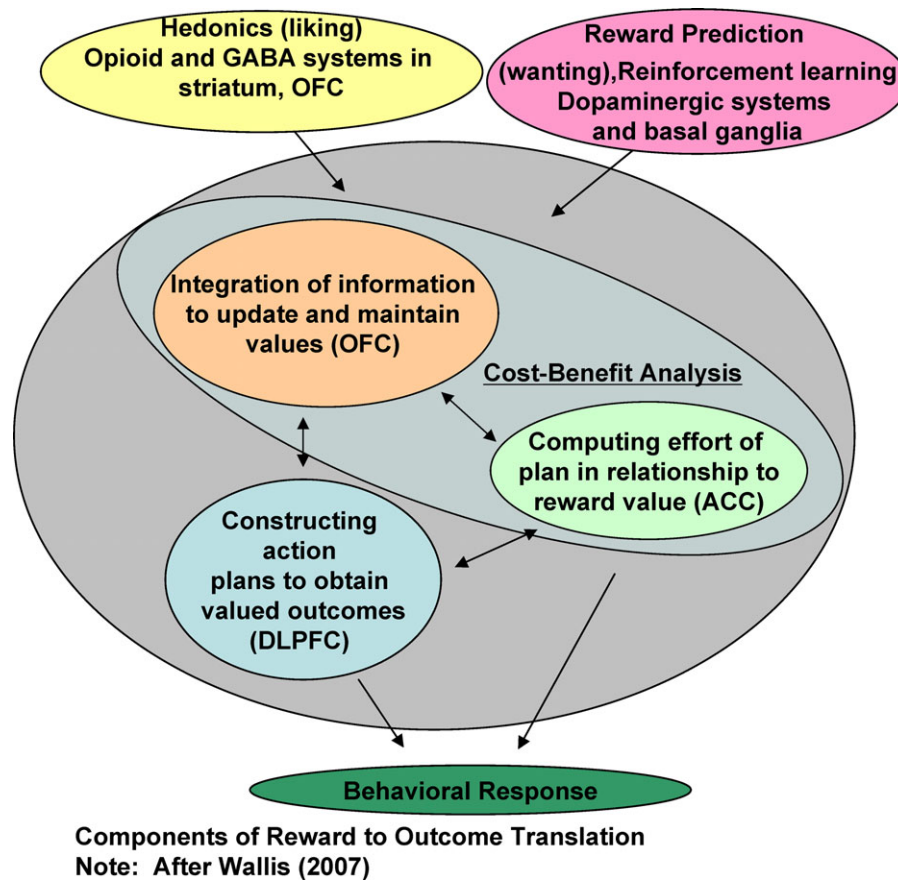


Fig. 1. Components of Reward to Outcome Translation.

thirsty vs not),<sup>44</sup> the delay before the reward occurs,<sup>45,46</sup> the different reward options available (eg, juice vs wine after a hard day),<sup>47,48</sup> and the changing contingencies associated with a stimulus (a previously rewarded response is now punished).<sup>49</sup> Some researchers have described the OFC as being involved in “working memory for value” or the ability to maintain, update, and integrate different sources of information about value over a short period of time.<sup>3,50</sup> Human functional neuroimaging studies also highlight activation of OFC under conditions requiring value representations,<sup>51,52</sup> including those in which response contingencies need to be updated, such as reversal learning.<sup>51,53,54</sup> In addition, humans with OFC lesions can show reversal learning impairments.<sup>55–57</sup>

Another aspect of representing value information is “effort computation,” ie, determining the cost of engaging in whatever actions it will take to obtain that outcome. For example, one may really want to obtain chocolate cookies and may perceive eating these cookies as rewarding, but the effort associated with having to go to the store may prevent the person from pursuing actions to obtain the cookies. A growing body of research suggests that the dorsal anterior cingulate cortex (ACC) may be important for evaluating the effort associated with different action plans, in concert with DA input

from nucleus accumbens and related forebrain circuitry.<sup>58–61</sup> For example, research has shown that ACC lesions as well as depletions of accumbens DA lead animals to choose low effort but low reward options over higher reward but higher effort options.<sup>46,58,59,62–65</sup> The potential role of ACC in computing effort may fit nicely with its suggested role in responding to conflict and error-related signals,<sup>66–68</sup> as feedback about conflict and errors may be an important source of information about the amount of effort a particular course of action is likely to require. Indeed, some work in healthy populations has suggested that error/conflict effects in ACC are modulated by motivational/affective and reward variables.<sup>69,70</sup> However, it is not yet clear whether the same regions of ACC that respond to conflict/error are those involved in effort computations or whether these represent different functional subdivisions of ACC, though both types of studies have shown activation of similar regions of dorsal anterior cingulate.<sup>60,61,66,71</sup> Nonetheless, even if it should turn out that this reflects a common mechanism, it helps to outline the role that ACC may play in a range of decision-making domains.

A fourth component is the ability to “generate and execute goal-directed action plans necessary to achieve the valued outcome.” Wallis and others have suggested that

this function is carried out by the lateral prefrontal cortex (PFC) (in particular, dorsolateral PFC [DLPFC]).<sup>3,72,73</sup> Such a role for the DLPFC in motivated behavior would be consistent with its role in top-down control of cognitive processing, planning, and response execution is consistent with models suggesting that the DLPFC provides a bias signal that helps to facilitate goal-directed behavior<sup>72</sup> and is consistent with evidence for impaired action planning following lateral prefrontal lesions.<sup>74,75</sup> In other words, intact DLPFC function may be necessary to translate information about value into goal representations that can be implemented as action plans to achieve the desired outcome. Furthermore, some theories of goal maintenance in DLPFC emphasize the importance of phasic DA input as a gating signal that serves to update the contents of DLPFC and protect against interference.<sup>76–78</sup> There is also growing evidence from the human and nonhuman primate literature that the potential for reward can enhance firing in DLPFC neurons and increase fMRI responses in DLPFC during cognitive control tasks<sup>79–82</sup> and that such changes may mediate improved performance as a function of reward.<sup>83,84</sup>

### Hedonics and Liking in Schizophrenia

Numerous studies<sup>18,19,21,23,85–105</sup> and a recent review by Ann Kring<sup>106</sup> have demonstrated that individuals with schizophrenia and controls show similar patterns of valence and arousal (eg, liking) in their self-reported emotional responses to affect eliciting stimuli. Almost all studies show that individuals with schizophrenia discriminate between positive and negative stimuli, though some studies have found differences between individuals with schizophrenia and controls in terms of “absolute levels” of emotional experience.<sup>91–93,95,96,105,107</sup> Findings of apparently intact hedonic responses have held true for patients with and without blunted affect<sup>90,108</sup> and for samples of individuals with schizophrenia who have clinical ratings of overall increased anhedonia.<sup>90</sup> Evidence for intact affective responses has also been found in emotion-modulated startle, such that individuals with schizophrenia show similar reductions of startle responses when presented with pleasant stimuli and given sufficient time to process the stimuli.<sup>92,97,109</sup> Furthermore, several studies have shown intact memory enhancement for positive stimuli in schizophrenia,<sup>21,110,111</sup> again suggesting intact “in-the-moment” response to affect eliciting stimuli (though see Herbener<sup>99</sup>). Experience sampling studies in schizophrenia find that patients report less intense and less variable positive emotions.<sup>108</sup> It may be the case that individuals with schizophrenia encounter fewer pleasurable events in their everyday lives and that their reduced reports of pleasure are an accurate reflection of their life experiences. However, recent work suggests that such reductions may be more apparent for goal-directed (eg, work and school) than nongoal-directed activities (eg, eat-

ing and watching TV) and that individuals with schizophrenia report less anticipatory pleasure than do controls even for those goal-directed events that they do experience.<sup>26</sup>

Despite the robust evidence for relatively intact self-reports of experienced pleasure or valence in group analyses of studies with individuals with schizophrenia, it is also increasingly clear that there are important individual differences in the level of anhedonia/avolition that may influence these experiences. For example, we and others have found that patients who self-report greater levels of social and physical anhedonia report experiencing less-positive responses to putatively positive stimuli such as pictures, faces, and words.<sup>100,105</sup> Interestingly, however, these relationships are not unique to positive stimuli. Individuals with schizophrenia (and controls) with higher self-reports of anhedonia also rate their experiences of negative stimuli as less negative. Such findings have 2 important implications. The first is that group comparisons of individuals with schizophrenia and controls may not be sufficiently informative and that it is critical to examine the level of clinically rated or self-reported anhedonia/avolition in relation to the processes of interest. The second is that these individual differences in anhedonia/avolition have relevance for understanding the experience of negative emotions and experiences as well as positive emotions and experiences.

Studies that have used functional imaging to examine brain responses to pleasurable or rewarding stimuli have provided a more mixed picture.<sup>91,112</sup> A number of brain regions have been implicated in the processing of positive emotional or rewarding stimuli, including the dorsal and ventral striatum, midbrain, orbitofrontal cortex, medial PFC, amygdala, and insula, and the literature is mixed as to whether recruitment of these regions is intact in schizophrenia. For example, Plailly<sup>107</sup> found reduced activation in schizophrenia in insula and OFC during hedonicity judgments of positive and negative odors but intact activation of the amygdala. Schneider also found reduced activation of the insula during the experience of positive olfactory stimuli in schizophrenia but found reduced amygdala activation.<sup>102</sup> Taylor reported that both medicated and unmedicated individuals with schizophrenia showed reduced phasic ventral striatal responses in the comparison of positive vs neutral pictures. In our own work, we have found that individuals with schizophrenia show the same pattern of brain activation in response to both negative and positive stimuli in a range of brain regions associated with the perception and experience of emotion, including medial frontal cortex, insula, OFC, and the amygdala.<sup>105</sup> However, we did find some evidence for reduced ventral and dorsal striatal responses to positive stimuli among individuals with schizophrenia, with the severity of these deficits correlated with the magnitude of self-reported anhedonia.

In terms of studies using explicit rewards, robust ventral striatal responses to the receipt of money have been observed in patients treated with either typical or atypical antipsychotics.<sup>113–115</sup> Interestingly, Simon found that the magnitude of the reward receipt response in the ventral striatum was inversely associated with severity of depression but not with anhedonia.<sup>114</sup> Schlagenhauf did not find group differences in the response to rewards in the ventral striatum, though they did not clearly see intact responses in patients, and there were reduced striatal responses to loss avoidance among the individuals with schizophrenia.<sup>116</sup> Furthermore, they did see reduced reward-related responses in medial PFC.<sup>116</sup> At least one study did find some evidence for reduced striatal responses to the receipt of juice (though medication and smoking confounds were possible), with the magnitude of this reduction associated with the severity of anhedonia scores.<sup>117</sup>

### *Hedonics and Liking Summary*

In sum, the self-report literature provides relatively consistent evidence for intact self-reports of liking in schizophrenia, though there is evidence that greater self-reports of anhedonia or negative symptom ratings are associated with less liking.<sup>23,100,105,118</sup> The relatively small functional imaging literature provides a somewhat confusing picture, with some evidence for reduced insular responses, and mixed evidence for altered striatal responses. However, these studies have not always clearly established effects specific to positive stimuli (leaving open the possibility that some alterations reflect general task deficits) and relatively few have addressed clinical heterogeneity in regards to negative symptoms levels. In other words, it is increasingly clear that there are important individual differences in the level of anhedonia/avolition that may influence the magnitude of responses in regions such as the striatum. Specifically, those studies that have examined individual differences in negative symptoms do suggest an important relationship between the magnitude of striatal responses to rewarding or pleasurable stimuli and anhedonia among individuals with schizophrenia.<sup>105,117</sup>

### **Reward Prediction and Wanting in Schizophrenia**

There is a clear sense in the literature that the basal ganglia play an important role in cognitive/affective impairments in schizophrenia. However, the precise nature of this impairment remains elusive.<sup>119–124</sup> In both animal and human studies, the DA–basal ganglia neural circuit has been shown to be critically involved in reward prediction as well as reinforcement learning processes that are interdependent with reward prediction. Yet surprisingly, a large number of studies have suggested intact reinforcement learning in schizophrenia using a range of tasks in

which learning is relatively easy,<sup>125–134</sup> though with a few exceptions.<sup>135,136</sup>

In contrast, when the paradigms become more difficult and include varying levels of probability and discrimination, individuals with schizophrenia show more evidence of impaired reinforcement learning.<sup>137,138</sup> For example, Gold and colleagues<sup>139</sup> found evidence for impaired learning in schizophrenia on the Frank Probabilistic Discrimination Task. A novel feature of this task is that it enables examination of reward value learning through transfer effects. In the transfer phase, individuals with schizophrenia showed less of a tendency to choose the stimulus previously associated with higher reward value. Although this pattern could reflect impaired basal ganglia-mediated reinforcement learning mechanisms, it may also reflect impaired rapid online learning mechanisms that may be mediated in part by OFC and/or DLPFC, as hypothesized by Gold and colleagues<sup>140</sup> and discussed in more detail below.

Another task frequently used to measure reinforcement learning is a probabilistic classification task called the Weather Prediction Task. In this task, participants are presented with 4 multidimensional stimuli (tarot cards) and asked to predict whether the cards indicate that it will rain or not rain. The stimuli are complex enough to make explicit learning difficult. Whether or not one considers individuals with schizophrenia to show intact or impaired performance on this task depends on whether one focuses on asymptotic performance level or learning rate. Numerous studies have shown what appears to be a relatively intact learning rate in schizophrenia, coupled with overall impaired performance.<sup>141–146</sup> In other words, individuals with schizophrenia start out the task more impaired, learn at relatively the same rate as controls (but see these for evidence of an exception<sup>147,148</sup>), yet never reach the same asymptotic level of performance. There is some evidence that reinforcement learning may be more intact for patients on atypical than typical antipsychotics, though it has been found in those on typicals as well.<sup>141,143</sup> One of the difficult aspects of interpreting performance on the Weather Prediction Task is that it can also be influenced by both implicit learning mechanisms thought to be mediated by the striatum, and explicit learning mechanisms that may be supported by OFC and DLPFC regions.<sup>149</sup> Thus, one interpretation of the Weather Prediction Task results is that the normal learning curve reflects relatively intact striatal learning mechanisms, while the impaired overall performance reflects relatively impaired cortically supported explicit learning mechanisms that may be particularly important during specific phases of learning.<sup>78,140</sup>

Studies of reward prediction/wanting in the neuroimaging literature have tended to focus on paradigms that directly examine neural responses to reward-predicting cues following conditioning trials. Some

paradigms involve passive (ie, Pavlovian) conditioning, whereas others, such as the Knutson paradigm,<sup>37</sup> require speeded responses to obtain rewards. Several studies have reported reduced ventral striatum activity in schizophrenia using the Knutson paradigm. Juckel and Schlagenhauf found such effects in unmedicated individuals with schizophrenia<sup>116,150</sup> as well as in individuals taking typical antipsychotics but not in individuals treated with atypicals.<sup>151,152</sup> However, in the Schlagenhauf study, the apparent improvement in reward cue responses among the individuals switched to olanzapine (eg, lack of group difference) was strongly influenced by reduced reward cue responses in controls at follow-up. Juckel also found that the severity of negative symptoms predicted the reduction in ventral striatal responses in unmedicated and typically medicated patients, suggesting important variability in schizophrenia. Kirsch reported a reduction in ventral striatal responses to reward cues in individuals with schizophrenia taking typicals compared with atypicals, though the groups were matched on behavioral performance and did not differ in ventral striatal responses to reward receipt.<sup>113</sup> In contrast, in more recent work, both Simon<sup>114</sup> and Walter<sup>115</sup> found intact striatal responses to reward anticipation in medicated patients with schizophrenia, though Simon did find that the magnitude of this response was inversely correlated with apathy ratings, and Walter et al studied a relatively low negative symptom level group of individuals with schizophrenia. Together, these findings suggest that anticipatory activation in the striatum reflecting reward prediction/wanting may be reduced in individuals with schizophrenia but that this reduction is likely influenced by individual differences in anhedonia/avolition and by dopaminergic medications.

An alternative way to examine the role of the striatum in reward prediction is to look at what is referred to as prediction error responses—an increase in striatal (presumably dopaminergic) responses to unexpected rewards and a decrease in striatal responses to a failure to receive predicted rewards. Murray et al<sup>153</sup> found evidence for reduced prediction error responses to rewards among schizophrenia spectrum patients in bilateral midbrain and right ventral striatum, coupled with enhanced prediction error responses to neutral stimuli. Waltz and colleagues<sup>117</sup> examined positive and negative prediction error responses in a passive paradigm that required participants to learn about the timing of a potential reward. These researchers found evidence for reduced positive prediction error responses in a range of regions that included the striatum (dorsal and ventral) as well as insula but relatively intact negative prediction errors in these same regions. The reduced positive prediction error is consistent with the hypothesis that individuals with schizophrenia may not learn to predict (or “want”) the upcoming rewards, though one might expect that such deficits should also lead to reduced negative prediction

errors, which in theory should also depend on a representation of expected reward. As noted above, this study did not control for the effects of smoking on taste processing in schizophrenia (which could alter responses to juice), representing a confound for assessing positive prediction errors (responses to unexpected juice rewards). Interestingly, however, Waltz et al did find that the magnitude of prediction errors in basal ganglia among patients was negatively correlated with avolition scores, suggesting a link to clinically relevant symptoms. In more recent work, Walter et al found intact prediction error responses in the striatum for both positive and negative prediction errors, though again this was a relatively low negative symptom sample.

There has also been one imaging study looking at the Weather Prediction Task. Weickert et al<sup>146</sup> found that controls showed greater activation than individuals with schizophrenia in both DLPFC and caudate. This was true even when analyses were restricted to a subset of controls and patients considered to be good learners. However, these differences were apparent throughout the course of the task and did not vary as a function of learning rate or time on task, raising questions as to the specific processes that they reflected.<sup>146</sup> In a related study, Koch et al<sup>138</sup> found reduced activation among individuals with schizophrenia in DLPFC and ACC in a probabilistic learning paradigm when the predictability of reward outcomes was low. Furthermore, these researchers also found reduced positive prediction error responses in frontal cortex, cingulate, and putamen.

#### *Reward Prediction and Wanting Summary*

In sum, the literature on reinforcement learning and reward prediction in schizophrenia suggests relatively intact learning on simple reinforcement learning paradigms, though this absence of impairment could reflect a lack of discriminating power of such easy tasks. In contrast, on more difficult tasks that can include multiple probabilistic learning levels, we find more consistent evidence for impaired performance, though more in terms of absolute levels of performance than in learning rates. The open question in regards to this literature is the degree to which these impairments reflect differences in striatum-influenced learning mechanisms that may be more implicit vs explicit learning mechanisms that may be more cortically mediated. Consistent with the hypothesis that some of these reinforcement learning impairments may reflect striatal mechanisms, a growing number of studies in the imaging literature suggest reduced ventral striatal reward prediction/wanting responses in unmedicated and typically medicated individuals with schizophrenia (though not in those taking atypicals) and evidence for reduced positive prediction errors. However, not all studies have found impaired striatal responses to reward prediction cues or to prediction error, and there is also evidence that the magnitude of these striatal impairments may be

related to the severity of negative symptoms, again pointing to the importance of examining individual difference relationships among individuals with schizophrenia. Furthermore, at least 2 studies have also found altered activation in frontal regions during probabilistic reinforcement learning, suggesting a potentially important role for cortically mediated mechanisms.

### Value Computations and OFC Function in Schizophrenia

As described above, one hypothesis is that the OFC supports the computation of value or the integration of the reinforcing properties of the stimulus with the internal state of the organism, which includes updating changes in the reinforcing properties of the stimulus. There are 2 experimental paradigms that have been frequently used as probes of lateral and medial OFC function: probabilistic reversal learning and the Iowa Gambling Task. Both require individuals to integrate information about rewards and punishments across trials and to use such information to update value representations appropriately. A number of studies suggest impaired reversal learning in schizophrenia,<sup>125,130,131,133,135,136,154</sup> though a few studies using the Intra-Dimensional-Extra-Dimensional task did not find simple reversal learning deficits in schizophrenia.<sup>127–129</sup> These reversal learning impairments are present even when individuals with schizophrenia and controls are matched on initial acquisition performance.<sup>126</sup> The literature on the Iowa Gambling Task in schizophrenia also provides evidence for impairment,<sup>155–162</sup> again with some exceptions.<sup>154,163–165</sup> There is also evidence for structural and functional changes in OFC in schizophrenia,<sup>107,166–169</sup> though such changes have not been directly related to reversal learning or Iowa Gambling Task performance. There is some evidence for an association between reduced OFC volume and negative symptoms.<sup>166,167</sup> There is also reasonable evidence for olfactory functioning deficits in schizophrenia, which could be related to OFC function (given that olfactory cortex is located in OFC).<sup>170</sup> However, it is not clear whether olfactory functions rely on the same OFC regions that support value computations. In sum, there is good evidence from the behavioral literature for deficits in tasks thought to reflect OFC function in schizophrenia, and at least some data suggesting that OFC changes may be related to negative symptoms. However, as of yet, there is no direct evidence of impaired OFC function in relationship to deficits in value computation, as one might find in imaging studies of probabilistic reversal learning.<sup>53</sup> Furthermore, it will be important to make a stronger link between laboratory paradigms assessing value representations and how such representations may play a role in everyday life function. It is relatively straightforward to understand how value is represented and updated for primary rewards such as juice or food in relationship to hunger and thirst levels, but more work is needed on making

the translation to more abstract representations that are likely to govern daily life function.

### Effort Computations and ACC Function in Schizophrenia

To our knowledge, there is no work directly addressing effort computations in schizophrenia. However, research has examined ACC function in schizophrenia using a variety of conflict and error processing paradigms. As noted above, it is not clear whether conflict monitoring and/or error processing share similar cognitive mechanisms with effort computation or rely on the same ACC regions, though there is growing evidence that both are associated with activation of the dorsal ACC.<sup>60,61,66,71</sup> Nevertheless, this literature does provide hints as to the functional integrity of ACC in schizophrenia. Several studies suggest that individuals with schizophrenia show reduced error-related ACC responses<sup>137,171–177</sup> as well as reduced post-error slowing<sup>171,172</sup> on the Stroop task as well as other tasks. However, there is also evidence that patients with schizophrenia can show normal error correction performance even in the context of reduced ACC responses to errors<sup>173,178</sup> and that the relationship between the magnitude of the error related negativity and error-related behaviors is intact in schizophrenia.<sup>175</sup> Individuals with schizophrenia also show reduced conflict-related ACC activation on the Stroop task<sup>172,173</sup> as well as reductions in conflict adaptation effects.<sup>172</sup> There is also evidence for ACC abnormalities in schizophrenia from structural and postmortem studies, eg.<sup>179,180</sup> Thus, there is some reason to believe that conflict monitoring, error processing, and ACC function may be altered in individuals with schizophrenia, but direct work on effort computations and ACC function in schizophrenia is needed, along with an assessment of these functions in relationship to other components of the system.

### Goal-Directed Action and DLPFC Function in Schizophrenia

There is a very large body of evidence for impairments in cognitive functions thought to be mediated by DLPFC in schizophrenia,<sup>181–183</sup> including those involving goal maintenance and planning.<sup>181,184,185</sup> Furthermore, there is robust evidence for altered DLPFC function in schizophrenia during cognitive control tasks,<sup>186–188</sup> though the direction (hypoactivity vs hyperactivity) varies as a function of factors such as load and performance.<sup>189</sup> In addition, structural studies have found alterations in gray matter volume in DLPFC,<sup>190–193</sup> in some cases specifically associated with altered executive function.<sup>194</sup> Studies have also found a variety of cellular and molecular abnormalities in DLPFC.<sup>191,192,195–198</sup> In addition, magnetic resonance spectroscopy studies have found reductions in N-acetylaspartate (NAA) concentrations (a measure of the metabolic integrity of neurons) in PFC

in schizophrenia.<sup>199–204</sup> However, there have been a few nonreplications,<sup>205,206</sup> and some suggestions that reduced NAA may result from antipsychotic treatment.<sup>207</sup> An important question is whether the cognitive control impairments observed in schizophrenia that have been associated with altered DLPFC function reflect problems in translating reward information into goal representations. One means to examine this issue is to determine how motivational incentives impact cognitive performance, potentially via modulation of DLPFC activity. Several studies suggest that individuals with schizophrenia are not able to improve their performance on cognitive tasks when offered monetary incentives,<sup>208–211</sup> but an equal number suggest at least some evidence for improvement with reward.<sup>212–214</sup> There is also work on the use of token economies in schizophrenia that suggests functioning can be improved through an explicit reward system. However, token economies provide a number of “external” supports for maintaining reward-related information that could compensate for deficits in the ability to translate reward information into action plans. Thus, the schizophrenia literature provides very consistent evidence for impaired cognitive control, action planning, and DLPFC function but relatively few direct tests of the ability to use internal representations of reward information to modulate behavior and brain function.

### Summary, Suggestions for Future Research, and Significance

The review of impairments in schizophrenia related to reward processing provided above suggests a number of key points. First, there is a good deal of variability across studies, and few studies have examined more than one mechanism in the same individuals. This is unfortunate, as it is difficult to determine whether variability across studies reflects sample differences (with the level of negative symptoms being key) or true differences across tasks or neural systems. Second, there is clearly heterogeneity among individuals with schizophrenia, with deficits potentially varying as a function of negative symptom severity (anhedonia/avolition in particular). These factors make it difficult to know whether variability across studies or mechanisms reflect differential impairment, different clinical profiles, differing medication states, or some combination of all. Thus, it is critical in future studies to examine the relationships between impairments at both the behavioral and neural level and the level of impairment in symptoms such as anhedonia and avolition. The importance of examining this question suggests that researchers will need to alter the design of their studies in the future, either by explicitly ascertaining a large enough sample to examine individual difference relationships with sufficient power or by including samples of individuals with schizophrenia specifically selected for varying levels of negative symptom impairment. Which-

ever approach one chooses to use, the large body of literature demonstrating an important effect of negative symptom severity indicates that small sample studies of unselected patients are no longer useful or informative for moving the work in this area forward. Of course, arguing that one should examine individual differences in anhedonia and avolition in schizophrenia in both behavioral and imaging studies begs the question of whether our existing measures are adequate for these purposes.<sup>215</sup> Recent consensus-building work has argued that the existing measures are in fact not adequate<sup>1</sup> and the development of new measures is underway, with a focus on incorporating constructs and findings from the basic science literature. Importantly, such measures may allow us to more validly map the phenomenology of schizophrenia to the types of deficits in specific functions described in this review rather than focusing only on global measures of severity that may conflate a number of different processes or mechanisms.

As a general summary, the current literature is consistent with the hypothesis that hedonics are relatively intact in schizophrenia, with the majority of self-report and imaging data suggesting relatively intact self-report and neural responses to pleasurable and rewarding stimuli. However, at the same time, the literature suggests that there may be a deficit in one or more of the neural mechanisms that help to translate reward information into goal-directed actions. As reviewed above, a growing body of work suggests evidence for reinforcement learning impairments on difficult tasks with varying probabilities of reinforcement and relatively consistent evidence for impaired striatal responses to cues that predict reward and to positive prediction errors. Although not all studies show these results, and the magnitude of impairment is influenced by the level of negative symptom severity, such findings suggest that impairment in striatal reward prediction mechanisms may influence wanting in schizophrenia in a way that reduces the ability of individuals with schizophrenia to use anticipated rewards to drive motivated behavior.

As of yet, there is less direct evidence for or against impairments in value or effort computation, mechanisms putatively mediated by OFC and ACC, respectively. As described above, there is certainly ample indirect evidence for impairments on OFC and ACC function, but none of these studies have directly linked OFC or ACC functions to processing involved in linking experienced or anticipated rewards with goal representations, action plans, or motivated behavior. Similarly, there is ample evidence for impaired DLPFC function and action planning in schizophrenia but relatively little work directly examining the influence of rewards on the ability to modulate these mechanisms in schizophrenia. Our prior work suggests that individuals with schizophrenia are impaired in representing goal information that enables action plans to obtain desired outcomes and that such impairments are due to altered DLPFC function.<sup>216–219</sup> However, our work



has not directly tied such deficits to impairments in reward processing. Moreover, it is also difficult to disentangle DLPFC-dependent mechanisms related to reward processing from other similar processes, such as cue-based reward prediction and/or value-effort computations. Nonetheless, there are intriguing hints that individuals with schizophrenia may not be able to use reward information to modulate cognitive control and DLPFC function, suggesting a potentially important role for cortical–striatal interactions in mediating impairment in motivated and goal-directed behavior in schizophrenia. Thus, in future studies, it will be critical to examine the interaction of these mechanisms in the same individuals, taking into account clinical heterogeneity.

The above discussion reviews the potential mechanisms of impairment in schizophrenia as potentially dissociable psychological and neural systems that may make independent contributions to impairments in goal-directed behavior in schizophrenia. However, it is also possible that there are impairments in several of these functions and systems that reflect a common mechanism. One potential common denominator that could lead to impairments in each of the functions (outside of hedonics) is altered DA function in both subcortical and cortical regions.<sup>220,221</sup> Almost all the functions described above are heavily influenced by DA function, which has widespread influences on both cognitive and motivational systems. Thus, should future research indicate that many or all the processes involved in translating reward into goal-directed action are impaired in schizophrenia, it may suggest a role for a core deficit in DA function that modulates multiple components of the system as a parsimonious explanation. However, it is also possible that ongoing research will provide evidence for more selective impairments in some components of the system, providing important clues as to pathways for intervention.

Given the widespread effects of DA on this system, antipsychotic medications that block DA receptors have the potential to impact cognitive and motivational systems at several stages and addressing potential medication confounds will therefore be critical to future work in this field. While practical constraints make rigorous examination of medication effects difficult, there are several strategies that, when combined, may yield a fuller picture of how reward-related functions are affected by medications in this population. The reward prediction literature has begun to tackle these questions by examining unmedicated patients and comparing results between different medication types. Other approaches could include: examining genetically related, medication-naïve populations such as first-degree relatives and schizotypal personality disorder patients; delaying a dose of medication in order to perform within-subjects comparisons at high and low D2R blockade and/or performing positron emission tomography studies in the same sample to gain information about individual levels of DA receptor availability.

We believe that studying the neural mechanisms of reward processing in schizophrenia is critically important for understanding the poor functional outcomes that are prominent in this population. Research has identified the persistence of cognitive deficits even with treatment as one of the key mechanisms constraining functional ability in schizophrenia.<sup>222,223</sup> However, symptoms such as anhedonia and avolition also represent significant constraints on functional outcome in this illness. The presence of anhedonia is associated with poor community and social function<sup>99,224–228</sup> and predicts poor long-term outcomes.<sup>99,229–231</sup> It may turn out that some of the same mechanisms leading to cognitive deficits in schizophrenia also contribute to anhedonia and avolition, such as DLPFC-mediated disturbances in goal maintenance.<sup>232,233</sup> If so, then treatments aimed at improving cognitive function in schizophrenia may also improve anhedonia and avolition, though there is not yet clear evidence for this.<sup>234</sup> However, if the mechanisms leading to anhedonia and avolition are different, then we need to understand the source of these impairments so as to develop more effective interventions that can enhance functional outcome and quality of life in this debilitating illness. For example, if research continues to indicate that individuals with schizophrenia show deficits in the ability to use cues to predict future rewarding outcomes, it might suggest that rehabilitation approaches should utilize environmental supports that could in a sense compensate for such deficits in the internal evaluation and/or maintenance of such cues. As another example, if research suggests that individuals with schizophrenia are impaired in the ability to use potential reinforcement to enhance goal-directed action (eg, action steps necessary for social engagement, job completion, etc.), rehabilitation approaches may again need to use environmental supports that make such outcomes more salient (eg, frequent external reminders of the payoffs associated with engagement in work, social, or occupationally related goal-directed behaviors; enhancing the immediacy or salience of small payoffs that may serve as scaffolds or bridges to more long-term positive outcomes). This suggestion is consistent with the work of Medalia and others, who have argued for a contextualized approach to rehabilitation that maximizes internal motivation.<sup>235,236</sup> Lastly, if the literature continues to support the crucial importance of individual differences in the degree to which schizophrenia have deficits in these different processes, this may suggest a basis for more individually tailored treatment approaches.

## Funding

National Institute of Mental Health (R01 MH066031, P50 MH62130).

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