Mechanisms Underlying Motivational Deficits in Psychopathology: Similarities and Differences in Depression and Schizophrenia

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Abstract Motivational and hedonic impairments are core aspects of a variety of types of psychopathology. These impairments cut across diagnostic categories and may be critical to understanding major aspects of the functional impairments accompanying psychopathology. Given the centrality of motivational and hedonic systems to psychopathology, the Research Domain Criteria (RDoC) initiative includes a "positive valence" systems domain that outlines a number of constructs that may be key to understanding the nature and mechanisms of motivational and hedonic impairments in psychopathology. These component constructs include initial responsiveness to reward, reward anticipation or expectancy, incentive or reinforcement learning, effort valuation, and action selection. Here, we review behavioral and neuroimaging studies providing evidence for impairments in these constructs in individuals with psychosis versus in individuals with depressive pathology. There are important differences in the nature of reward-related and hedonic deficits associated with psychosis versus depression that have major implications for our understanding of etiology and treatment development. In particular, the literature strongly suggests the presence of impairments in in-the-moment hedonics or "liking" in individuals with depressive pathology, particularly among those who experience anhedonia. Such deficits may propagate forward and contribute to impairments in other constructs that are dependent on hedonic responses, such as anticipation, learning, effort, and action selection. Such hedonic impairments could reflect alterations in dopamine and/or opioid signaling in the striatum related to depression or specifically to anhedonia in depressed populations. In contrast, the literature points to relatively intact in-the-moment hedonic processing in psychosis, but provides much evidence for impairments in other components involved in translating reward to action selection. Particularly, individuals

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with schizophrenia exhibit altered reward prediction and associated striatal and prefrontal activation, impaired reward learning, and impaired reward-modulated action selection.

Keywords Depression · Motivation · Prefontal cortex · Reward · Schizophrenia · Striatum

Contents

1 Introduction

Motivational and hedonic impairments are core aspects of psychopathology that cut across diagnostic categories. In particular, motivational and hedonic impairments are part of the diagnostic criteria for several disorders, like schizophrenia and depression, and deficits in these domains may be critical to understanding the functional impairments that often accompany these forms of psychopathology. The Research Domain Criteria (RDoC) initiative has recognized the importance of studying motivation and hedonic processing in psychopathology and includes a "positive valence" systems domain (Cuthbert and Insel 2010; Insel et al. 2010; Cuthbert and Kozak 2013). This domain includes numerous component constructs that may be central to understanding

the nature and mechanisms of motivational impairments in psychopathology, including initial responsiveness to reward, reward anticipation or expectancy, incentive learning, effort valuation, and action selection. One goal of the RDoC initiative is to understand whether there are core brain–behavior systems with common deficits that cut across the current diagnostic categories or whether there are truly unique or differential deficits associated with different facets of psychopathology.

An important instantiation of this goal is to understand whether there are common psychological and neurobiological mechanisms contributing to motivational and hedonic processing impairments associated with both psychosis and mood pathology or whether there are unique, differentiable mechanisms contributing to impairments in each disorder. The existing clinical literature provides support for both alternatives. On the one hand, depression and psychosis frequently co-occur and there are a number of ways in which motivational and hedonic impairments operate similarly in psychosis and mood pathology. For example, motivational/hedonic impairments can be present in individuals at risk for developing psychosis (Delawalla et al. 2006; Glatt et al. 2006; Juckel et al. 2012; Grimm et al. 2014; Schlosser et al. 2014) or at risk for developing depression (Gotlib et al. 2010; Foti et al. 2011a, b, c; McCabe et al. 2012; Kujawa et al. 2014; Macoveanu et al. 2014; Olino et al. 2014; Sharp et al. 2014). Further, there is evidence that the presence or severity of motivational/hedonic impairments is associated with the development of manifest illness for both psychosis (Chapman et al. 1994; Kwapil et al. 1997; Gooding et al. 2005; Velthorst et al. 2009) and depression (Bress et al. 2013; Morgan et al. 2013). In addition, motivation/hedonic impairments are associated with functional impairment and/or treatment non-response in psychosis (Fenton and McGlashan 1991; Herbener et al. 2005; Bowie et al. 2006; Ventura et al. 2009; Kurtz 2012) and depression (Downar et al. 2014). On the other hand, there are important *differences* in the manifestation of motivational/reward impairments across psychosis and mood pathology. Most critically, there is much more evidence of an episodic pattern of hedonic impairments associated with mood pathology than psychosis. More specifically, elevated anhedonia typically resolves along with acute depression, whereas anhedonia is much more likely to still be present among individuals with psychosis even when their acute psychotic symptoms have resolved (Blanchard et al. 2001; Herbener et al. 2005).

1.1 Translating Hedonic Experience into Motivated Behavior

These types of clinical data highlight the importance of mechanistically understanding the similarities and differences in motivational/hedonic impairments across psychopathology. In prior work primarily focused on psychosis (Barch and Dowd 2010; Kring and Barch 2014), we have used a heuristic model of the psychological processes and neural systems thought to link experienced or anticipated rewards/incentives with the action plans that need to be generated and maintained in order to obtain these rewards. As this literature is quite large, we have simplified and

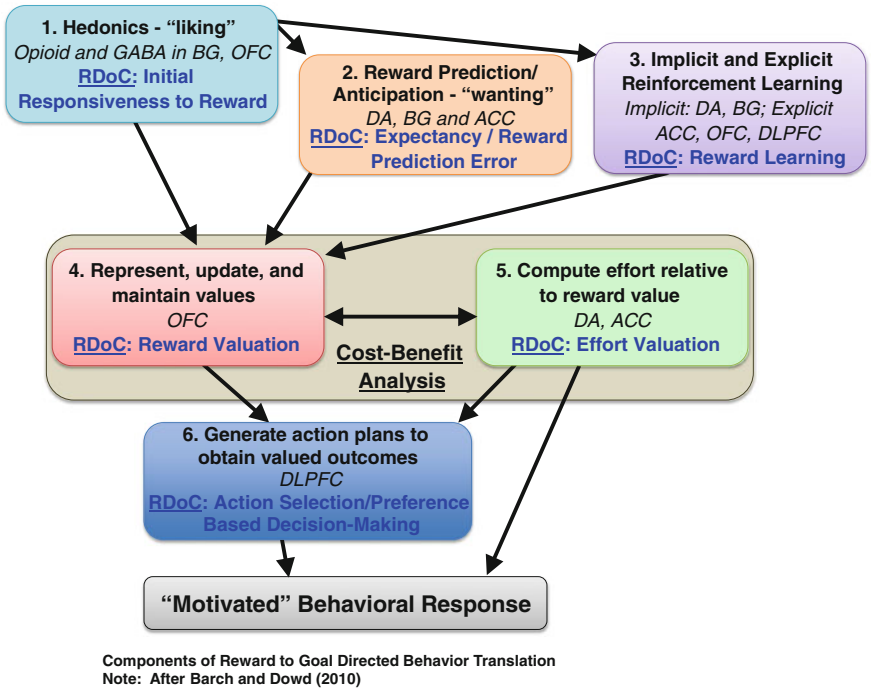

Fig. 1 Components of the translation between experience reward/pleasure and goal-directed behavior. *Notes ACC* Anterior cingulate cortex, *BG* Basal ganglia, *DA* Dopamine, *DLPFC* Dorsolateral prefrontal cortex, *OFC* Orbital frontal cortex, *RDoC* Research Domain Criteria

focused on six major components in the translation of appetitive or reward information into behavioral responses (Schultz et al. 1997; Berridge 2004; Schultz 2004, 2007; Wallis 2007) (see Fig. 1). The first component, **hedonics or liking** (component 1 in Fig. 1), reflects the ability to "enjoy" a stimulus or event that may provide pleasure or reward. In the RDoC Positive Valence system, this aligns with *initial responsiveness to reward*. Traditionally researchers have focused on the neurotransmitter dopamine (DA) as a primary substrate of liking (Berridge 2004), but more recent research instead suggests that hedonic responses (at least to primary sensory stimuli) seem to be mediated by activation of the opioid and GABA-ergic systems in the nucleus accumbens shell and its projections to the ventral pallidum, as well as in the orbital frontal cortex (OFC) (Richardson et al. 2005; Burgdorf and Panksepp 2006; Pecina et al. 2006; Smith and Berridge 2007; Berridge et al. 2009). For more information on the neurobiology of liking and the role of liking in motivated behaviors, see Robinson et al in this volume.

A second component, **reward prediction and wanting** (component 2 in Fig. 1), is mediated at least in part by the midbrain DA system, particularly projections to ventral and dorsal striatum (Berridge 2004; Schultz 2007). In the RDoC Positive Valence system, this aligns with *expectancy/reward predictor error*. Many DA

neurons in the substantia nigra and ventral tegmental area (VTA) respond to stimuli that *predict* reward, as well as to rewards themselves. Importantly, the degree of response depends on predictability—if the reward was not predicted, then the DA neurons fire strongly (positive prediction error), whereas there is a transient depression in DA neuron firing (negative prediction error) if a predicted reward does not occur (Schultz 1992, 2004, 2007; Schultz et al. 1993, 1997). Over time, DA neurons begin to fire to the predictive cues rather than to rewards themselves (Schultz 2007). Similar effects have been found in humans using functional magnetic resonance imaging (fMRI) of the ventral and dorsal striatum (Knutson et al. 2000, 2001; McClure et al. 2003; Abler et al. 2006). These types of DA/striatal responses have been captured by temporal difference models that simulate learning about stimuli that predict rewards (Montague and Sejnowski 1994; Montague et al. 1996). 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 [e.g., a "wanting" response (Berridge 2004)].

A third component is **reward or reinforcement learning** (component 3 in Fig. 1), both implicit (i.e., outside of conscious awareness) and explicit (i.e., including the use of explicit representations about potential reward associations). In the RDoC Positive Valence system, this aligns with *reward learning*. The types of DA/striatal responses described above for reward prediction are thought to underlie basic aspects of reinforcement learning that may occur without conscious awareness (Dayan and Balleine 2002; Frank et al. 2004). However, there is also evidence that the development of explicit representations that are accessible to conscious awareness can also drive reinforcement learning, albeit with a potentially different timecourse (Frank et al. 2001; Frank and O'Reilly 2006; Hazy et al. 2007; Gold et al. 2012). These more explicit forms of reinforcement learning also including neural systems involved in cognitive control and value representations, such as dorsal frontal and parietal regions and the OFC (Frank et al. 2001; Frank and O'Reilly 2006; Hazy et al. 2007; Gold et al. 2012). By cognitive control, we mean the ability to maintain goal or task representations in order to focus attentional resources on task-relevant information while filtering out task-irrelevant information (Miller and Cohen 2001; Braver 2012).

Another critical aspect of translating rewards to actions is *cost–benefit analysis*, or balancing the value of an outcome with the effort it would take to achieve that outcome. Thus, a necessary fourth component is the ability to **represent, maintain, and update value information** (component 4 in Fig. 1), which is thought to be mediated, at least in part, by OFC (Padoa-Schioppa and Cai 2011; Rudebeck and Murray 2011). In the RDoC Positive Valence system, this aligns with *reward valuation.* This construct takes into account, not only the hedonic properties of a stimulus, but also the internal state of the organism (e.g., value of juice when thirsty versus not) (Rolls et al. 1989), the delay before the reward occurs (Roesch and Olson 2005; Rudebeck et al. 2006a, b), the available reward options (e.g., juice versus wine after a hard day) (Padoa-Schioppa and Assad 2006; Padoa-Schioppa 2007), and the changing consequences associated with a stimulus (e.g., a previously

rewarded response is now punished) (Dias et al. 1996; Cools et al. 2002). Human functional neuroimaging studies also highlight activation of OFC under conditions requiring value representations (O'Doherty et al. 2003; O'Doherty 2007), particularly those in which response contingencies need to be updated, such as reversal learning (Cools et al. 2002, 2007; O'Doherty et al. 2003). In addition, humans with OFC lesions can show reversal learning impairments (Fellows and Farah 2003, 2005; Hornak et al. 2004).

A fifth component, that is also a part of *cost–benefit analysis*, is the ability to **compute effort relative to reward value** (component 5 in Fig. 1), i.e., determining the cost of engaging in actions necessary to obtain a desired outcome. In the RDoC Positive Valence system, this aligns with *effort valuation/willingness to work.* For example, you may really want to eat some chocolate candy and may perceive eating candy as rewarding, but you may not want to put forth the effort to go to the store to get the candy. Research suggests that the dorsal anterior cingulate cortex (ACC) may be important for evaluating the cognitive and physical effort associated with different action plans (Shenhav et al. 2013) with contributions of DA input from the nucleus accumbens and related forebrain circuitry (Salamone 2007; Salamone et al. 2007; Botvinick et al. 2009; Croxson et al. 2009). For example, 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 (Rudebeck et al. 2006a, b, 2007; Rushworth et al. 2007; Salamone 2007; Salamone et al. 2007; Walton et al. 2007; Hosking et al. 2014a, b, 2015).

Lastly, a sixth component is the ability to **generate and execute goal-directed action plans necessary to achieve the valued outcome** (component 6 in Fig. 1). In the RDoC Positive Valence system, this aligns with *action selection/preference-based decision making*. Many researchers have argued for the role of the lateral PFC in relation to this component in the context of reward and motivation (in particular dorsolateral PFC) (Braver and Cohen 1999; Miller and Cohen 2001; Wallis 2007). This is consistent with a number of other lines of research and theory, including the following: (1) the role of the DLPFC in top-down control of cognitive processing; (2) models suggesting that the DLPFC provides a bias signal that helps to facilitate goal-directed behavior (Miller and Cohen 2001); (3) evidence for impaired action planning following lateral prefrontal lesions (Zalla et al. 2001; Manes et al. 2002); and (4) evidence that increases in DLFPC activity mediate "motivated" cognitive control enhancements that occur with the provision of incentives in both animals (Watanabe 1996; Kobayashi et al. 2006; Krawczyk et al. 2007; Sakagami and Watanabe 2007) and humans (Tsujimoto and Sawaguchi 2005; Beck et al. 2010; Jimura et al. 2010; Savine and Braver 2010). In other words, intact DLPFC function may be necessary to translate information about value into goal representations and to maintain such information so that it can be implemented as action plans to achieve the desired outcome.

Here, we review evidence for psychosis- and depression-related impairments in these six components of mechanisms that translate hedonic experiences of rewards into goal-directed actions that then allow individuals to obtain such rewards. Further, where available, we review neuroimaging evidence as to the

neurobiological correlates of each type of impairment. As a preview, this review will suggest many impairments common across individuals with schizophrenia and depression, including consistent evidence for impairments in reward prediction and prediction errors, as well as effort allocation for incentives. However, this review will also reveal important differences that point to potentially divergent etiological pathways to impairments in motivated behavior associated with psychotic versus depressive pathology.

2 Hedonics and Liking

2.1 Schizophrenia

Numerous individual studies (e.g., Berenbaum and Oltmanns 1992; Kring et al. 1993; Dowd and Barch 2010) and several recent reviews (Kring and Moran 2008; Cohen and Minor 2010) have found that individuals with schizophrenia show relatively intact self-reported emotional responses to affect-eliciting stimuli. Further, individuals with schizophrenia show intact responses in emotion-modulated startle paradigms during the presentation of pleasant stimuli, when given sufficient time to process the stimuli (Schlenker et al. 1995; Curtis et al. 1999; Volz et al. 2003; Kring et al. 2011) and intact memory enhancement for positive stimuli (Mathews and Barch 2004; Horan et al. 2006; Hall et al. 2007) though see (Herbener et al. 2007).

2.1.1 Monetary Rewards

Neuroimaging studies examining striatal responses to the receipt of monetary rewards in schizophrenia have also shown a consistent pattern of intact responses, with robust ventral striatal responses to the receipt of money in unmedicated patients (Nielsen et al. 2012a, b) and patients treated with either typical or atypical antipsychotics (Kirsch et al. 2007; Simon et al. 2009; Walter et al. 2009; Dowd and Barch 2012; Morris et al. 2012; Gilleen et al. 2014; Wolf et al. 2014; Mucci et al. 2015). Further, studies have also shown intact feedback negativity responses, an ERP component in response to explicit feedback, to the receipts of rewards and losses in schizophrenia (Horan et al. 2011; Morris et al. 2011). However, while striatal responses to reward receipt seem to be largely intact in schizophrenia, some of these studies did report abnormal cortical responses to reward receipt. Particularly, prior work has noted reduced reward-related responses in medial PFC (Schlagenhauf et al. 2009), abnormal responses in both medial and lateral PFC (Waltz et al. 2010), and reduced salience coding in ventrolateral PFC in schizophrenia patients, which was correlated with negative symptom severity (Walter et al. 2010).

2.1.2 Primary Rewards

A more mixed picture has arisen from functional neuroimaging studies examining brain responses to other types of pleasurable or rewarding stimuli in schizophrenia (Crespo-Facorro et al. 2001; Paradiso et al. 2003). Plailly et al. (2006) found reduced activation in schizophrenia within the insula and OFC during hedonicity judgments of positive and negative odors. Schneider et al. (2007) also found reduced activation of the insula during the experience of positive olfactory stimuli in schizophrenia. Taylor et al. (2005) showed reduced phasic ventral striatal responses comparing positive versus neutral picture viewing in both medicated and unmedicated individuals with schizophrenia. In a large sample of medicated patients, we found that individuals with schizophrenia showed the same pattern of brain activation as controls 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 (Dowd and Barch 2010). However, we did find some evidence for reduced ventral and dorsal striatal responses to positive stimuli among individuals with schizophrenia, and the severity of these deficits correlated with the magnitude of self-reported anhedonia. Other research has found evidence for reduced striatal responses to the receipt of juice, with the magnitude of this reduction associated with the severity of anhedonia (Waltz et al. 2009), as well as reduced striatal responses to food cues (Grimm et al. 2012), though medications may have been a confound in both of these studies.

2.1.3 Summary of Hedonics and Liking in Schizophrenia:

In sum (see Table 1), the self-report literature in schizophrenia 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 reduced "liking" (Blanchard et al. 1994; Burbridge and Barch 2007; Herbener et al. 2007; Dowd and Barch 2010). In addition, the functional neuroimaging literature provides fairly consistent evidence for intact responses to the receipt of monetary rewards. However, the functional neuroimaging literature on responses to other types of rewarding stimuli provides a more muddled picture, with some evidence for reduced insular responses and mixed evidence for altered striatal responses. Further, studies examining individual differences in negative symptom severity do suggest an important relationship between the magnitude of striatal responses to rewarding or pleasurable stimuli and anhedonia among individuals with schizophrenia (Waltz et al. 2009; Dowd and Barch 2010).

Table 1 Summary of impairments across constructs in schizophrenia and depression

Construct	Depression	Schizophrenia	Comments
1. *Hedonic response to positive stimuli*			
Primary rewards	Mixed	Mixed	Need clearer evaluation of the potential role of smoking and medications
Secondary rewards	Impaired	Intact	–
2. *Reward anticipation/prediction*			
Reward anticipation	Impaired	Impaired	Need to determine whether these reflect impairments in DA-learning systems or problems with representation or maintenance of value representations (schizophrenia) or hedonics (depression)
Prediction errors	Impaired	Impaired	
3. Reinforcement learning			
Implicit	Impaired	Intact	Need to determine whether these reflect impairments in DA-learning systems or problems with representation or maintenance of value representations (schizophrenia) or hedonics (depression)
Explicit	Intact	Impaired	
4. *Value representation*			
	Impaired	Impaired	Not clear whether there is a distinct impairment in value representation in either schizophrenia or depression, or whether impairment is due to problems in other components of the system
5. *Effort allocation*			
Physical effort	Impaired	Impaired	–
Cognitive effort	Untested	Mixed	Additional research is needed that includes assessments of perceived cognitive effort
6. Action plans/goal-directed action			
	Unclear	Impaired	Additional research is needed on the role of goal-directed action selection in motivational impairments in depression

2.2 Depression

There is a growing and consistent literature demonstrating that adults and adolescents with or at risk for depression have impaired hedonic responses to both pleasurable stimuli (primary reward) and monetary (secondary) rewards. Such group differences have been reported using behavioral measures as well as event-related potential (ERP) and fMRI measures of brain function (Foti and Hajcak 2009; Foti et al. 2011a, b, c; Bress et al. 2012, 2013; Zhang et al. 2013) and have been related to elevated levels of anhedonia.

2.2.1 Monetary Rewards

Behaviorally, depressed individuals show reduced reward-related biases (Henriques et al. 1994; Pizzagalli et al. 2008; Pechtel et al. 2013) and reduced ability to learn from reward (Herzallah et al. 2010; Maddox et al. 2012). Reduced reward sensitivity has been specifically related to self-reported anhedonia (Pizzagalli et al. 2008; Vrieze et al. 2013) and can be predictive of treatment response (Vrieze et al. 2013). Using ERPs, a number of studies have examined feedback-related negativity (FN) in MDD. FN is an ERP component elicited by reward or loss feedback and is thought to reflect activity in the ventral striatum, caudate, and the dorsal ACC (Carlson et al. 2011; Foti et al. 2011a, b, c). Depressed adults show decreased FN to rewards (Foti et al. 2014). Increased depressive symptoms are also related to reduced FN in children (Bress et al. 2012) and prospectively predict future onset of depression in adolescents (Bress et al. 2013). In addition, a reduced FN in depressed adults is specifically related to the severity of clinically rated anhedonia (Liu et al. 2014).

fMRI studies of reward processing in adolescents and adults have also found that depression is associated with decreased activation following positive feedback (i.e., reward) in reward-related brain areas such as the caudate, the putamen, the ACC, and the insula (Knutson et al. 2008; Kumar et al. 2008; Pizzagalli et al. 2009; Remijnse et al. 2009; Smoski et al. 2009; Gradin et al. 2011; Robinson et al. 2012 Zhang et al. 2013). Such reductions have been specifically associated with anhedonia symptoms (Gradin et al. 2011; Stoy et al. 2012), have been detected in individuals at risk for depression (Gotlib et al. 2010; McCabe et al. 2012; Olino et al. 2013), and predict the development of depression in adolescents (Morgan et al. 2013). Further, research in adults has shown increased ventral striatal responses to reward following successful treatment (Stoy et al. 2012). These findings suggest that depression and risk for depression are robustly associated with reduced behavioral and neural responsivity to monetary (secondary) rewards.

2.2.2 Primary Rewards

A meta-analysis examining emotional responsivity in depression suggested that depressed patients tend to show blunted self-reported and physiological responses to positive emotional stimuli (Bylsma et al. 2008) and recent evidence suggests that this type of blunting relates specifically to elevated anhedonia, rather than depressed mood, in a non-clinical sample (Saxena et al. submitted). Further, evidence for physiological blunting (decreased attenuation of startle blink by positive stimulus viewing) in subclinical depression (e.g., individuals reporting high levels of depression on clinical scales but whom do not meet diagnostic criteria) seems to be specific to in-the-moment experience of emotional stimuli rather than anticipation (Moran et al. 2012). Further, blunted behavioral and physiological (heart rate) reactivity to amusing film clips predicts poor recovery from depression (Rottenberg et al. 2002). However, studies examining self-reported hedonic responses to tastes/

odors have been more mixed and generally do not find strong evidence for behavioral differences associated with depression. Particularly, hedonic response ratings of sucrose and odor stimuli are generally not different when comparing MDD patients and healthy controls (Berlin et al. 1998; Clepce et al. 2010; Dichter et al. 2010) and depressive symptom severity in a non-clinical sample did not correlate with pleasantness ratings of sweet, sour, salty, or bitter tastes (Scinska et al. 2004). Yet, while examining group differences has typically yielded negative results, there is some evidence that elevated levels of anhedonia negatively predict hedonic responses to sucrose across depressed, schizophrenic, and healthy individuals (Berlin et al. 1998) and that measures of anticipatory anhedonia negatively predict anticipated hedonic responses to chocolate but not actual or recalled responses (Chentsova-Dutton and Hanley 2010).

fMRI studies provide more consistent evidence for reduced reactivity to primary rewards/pleasant stimuli in MDD than the self-report studies discussed above. For example, in one study, individuals with remitted depression showed no difference in the rating of pleasant food images/tastes as compared to controls, but did show decreased ventral striatal response relative to never-depressed controls (McCabe et al. 2009). Further, adolescents/young adults at elevated risk for depression based on a parental history of MDD showed lower OFC and ACC responses to pleasant food images/tastes as compared to those with no parental history (McCabe et al. 2012). fMRI studies utilizing other types of pleasant stimuli, such as happy faces or pleasant scenes, have also found reduced striatal responses in MDD patients as compared to controls (Gotlib 2005; Smoski 2011). Importantly, reduced striatal responses to pleasant stimuli specifically related to elevated levels of anhedonia, rather than to general depressive symptom severity (Keedwell et al. 2005).

2.2.3 Summary of Hedonics and Liking in Depression:

In summary (see Table 1), across behavioral, ERP, and fMRI methodologies in-the-moment hedonic response to both primary and monetary rewards are reduced in MDD and relate to anhedonic symptoms. However, such effects are most reliably observed when using fMRI methods (versus self-report) for odor/taste stimuli and behavior (versus physiology) for positive images/film clips (Bylsma et al. 2008). This could be due to the fact that self-reports can be more influenced by expectancy effects, such that individuals realize what the "normative" response to a specific stimulus should be and report that response, rather than their actual experience. Further, while similar subcortical regions show differences between MDD and control groups in fMRI across studies examining monetary versus primary rewards (Zhang et al. 2013), there is some evidence that group differences may be larger when using primary than monetary rewards (Smoski 2011). Given that primary rewards are innately and immediately rewarding they are more closely tied to "hedonic" experience than monetary rewards, where stimulus value is abstractly linked to future reward attainment, these results offer even stronger evidence linking a core in-the-moment hedonic or "liking" deficit to anhedonia in MDD.

2.3 Hedonics in Schizophrenia versus Depression

These results in depression stand in fairly strong contrast to the data on individuals with schizophrenia, which much more consistently supports *intact* in the in-the-moment hedonic or "liking," with some exceptions, particularly in the literature on primary reward processing in psychosis. This distinction may be critical, as it suggests potentially very different fundamental pathways and mechanisms to impairments in motivation and goal-directed behavior in the context of psychosis versus depressive mood pathology. In particular, it sets the stage for the hypothesis that in depressive pathology, deficits in motivated behavior may be traced back to impairments in hedonic or liking responses to both primary and secondary rewards/positive stimuli. In contrast, the data suggest that the mechanisms giving rise to impaired motivation behavior in schizophrenia occur subsequent to immediate hedonic responses and instead may reflect alterations in the way information about hedonic experience is stored, represented, maintained, or used.

3 Reward Prediction, Anticipation, and Reinforcement Learning

3.1 Schizophrenia

3.1.1 Reward Anticipation

There is a mixed self-report literature on anticipated pleasure in schizophrenia, with some studies suggesting impairments (Gard et al. 2006, 2007; Wynn et al. 2010; Mote et al. 2014) and others not (Tremeau et al. 2010, 2014; Gard et al. 2014). However, outside of self-reports, there are relatively few behavioral studies in schizophrenia that directly measure reward anticipation/prediction, though one such study did find evidence for reduced anticipation (Heerey and Gold 2007). As such, much of the focus has been on neuroimaging studies of reward prediction ("wanting"), which have primarily examined neural responses to reward-predicting cues, sometimes following conditioning trials and sometimes through explicit instruction, such as in the monetary incentive delay (MID) task. A number of studies have reported reduced ventral striatum activity to cues predicting reward in schizophrenia. These results have been found in unmedicated individuals with schizophrenia (Juckel et al. 2006a, b; Schlagenhauf et al. 2009; Esslinger et al. 2012; Nielsen et al. 2012a, b) and medicated individuals (Juckel et al. 2006a, b; Schlagenhauf et al. 2008; Simon et al. 2009; Walter et al. 2009; Grimm et al. 2012). There is some suggestion that these deficits are not present in individuals taking atypical medication (Juckel et al. 2006a, b) nor in prodromal individuals (Juckel et al. 2012), though some of these results are in small samples and need replication. For example, (Kirsch et al. 2007) found reduced ventral striatal responses to reward

cues in individuals with schizophrenia taking typical compared to atypical antipsychotic mediation. Other work has noted reduced ventral striatal responses to anticipation cues in antipsychotic-naïve schizophrenia patients, which improved following atypical antipsychotic treatment (Nielsen et al. 2012a, b). Importantly, a number of studies also showed a relationship between negative symptom severity and deficits in anticipatory ventral striatal activity. Juckel et al. (2006a, b) showed that the severity of negative symptoms predicted the reduction in ventral striatal responses in unmedicated and typically medicated patients, Simon et al. (2009) showed that the magnitude of this response was inversely correlated with apathy ratings, and Waltz et al. (2010) showed a relationship between negative symptom severity and ventral striatal activation during anticipated gains. Reward prediction has also been studied using a Pavlovian task and found a relationship between reduced striatal response to reward-predictive cues and greater anhedonia among individuals with schizophrenia (Dowd and Barch 2012).

3.1.2 Reward Prediction Error

A number of studies have also examined the role of the striatum in reward prediction by looking at prediction error responses—an increase in striatal (potentially dopaminergic) responses to unexpected rewards and a decrease in striatal responses when predicted rewards do not occur. Several studies have now shown altered prediction error responses in schizophrenia, both in terms of reductions in responses to unpredicted rewards and larger than expected responses to predicted rewards (Murray et al. 2008; Morris et al. 2012; Schlagenhauf et al. 2014). Gradin et al. (2011) found reduced prediction error responses in the caudate, but increased activation associated with expected reward value in the ventral striatum. Waltz et al. (2009) 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. Interestingly, Waltz et al. (2009) did find that the magnitude of prediction errors in the basal ganglia among patients was negatively correlated with avolition scores, suggesting a link to clinically relevant symptoms. In other work, Walter et al. (2009) found intact prediction error responses in the striatum for both positive and negative prediction errors, though this was a population with relatively low-level negative symptom, in contrast to the high-level negative symptom population in the Waltz et al. 2009 study. There is again suggestion that medication may have an important influence; Insel and colleagues found that individuals with chronic schizophrenia taking higher doses of medication showed smaller prediction error responses (Insel et al. 2014). However, the fact that reduced prediction error responses have also been seen in unmedicated individuals (Schlagenhauf et al. 2014) argues against such abnormalities resulting only from medication effects in schizophrenia. For

further discussion on neuroimaging studies of RPE-signaling in patients with schizophrenia, see Waltz and Gold in this volume.

3.1.3 Reinforcement Learning

There are several possible mechanisms that could be contributing to altered reward prediction error and anticipation responses in psychosis. The most common interpretation is that they reflect abnormalities in the learning mechanisms supported by DA in the ventral striatum, suggesting that individuals with schizophrenia cannot appropriately learn what cues predict reward and do not update stimulus–response associations via striatal learning mechanisms. Such an interpretation would predict that individuals with schizophrenia would show deficits on reinforcement learning tasks that also tap into these mechanisms. However, the evidence suggests surprisingly intact performance on a range of tasks in which learning is either relatively easy or relatively implicit (Elliott et al. 1995; Hutton et al. 1998; Joyce et al. 2002; Turner et al. 2004; Tyson et al. 2004; Jazbec et al. 2007; Waltz and Gold 2007; Ceaser et al. 2008; Heerey et al. 2008; Weiler et al. 2009; Somlai et al. 2011), though with some exceptions (Oades 1997; Pantelis et al. 1999). Further, individuals with schizophrenia show intact learning rates on the weather prediction task, a probabilistic category-learning task frequently used to measure reinforcement learning, though with overall impaired performance (Keri et al. 2000, 2005a, b; Weickert et al. 2002, 2009; Beninger et al. 2003). 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 (Beninger et al. 2003; Keri et al. 2005a, b). Such intact reinforcement learning on more implicit tasks argues against the explanation that anticipation and prediction error deficits in schizophrenia are due solely to DA deficits in the striatum, though of course DA is involved in more than just prediction error signaling.

An alternative explanation is that such anticipatory and prediction error deficits may reflect impairments in more explicit learning and representation processes that engage cognitive control regions such as the DLPFC, the dorsal parietal cortex, and the ACC and/or the OFC. Consistent with this hypothesis, when the reinforcement learning paradigms become more difficult and require the explicit use of representations about stimulus–reward contingencies, individuals with schizophrenia show more consistent evidence of impaired reinforcement learning (Waltz et al. 2007; Morris et al. 2008; Koch et al. 2009; Gold et al. 2012; Yilmaz et al. 2012; Cicero et al. 2014). Interestingly, these impairments may be greater when individuals with schizophrenia must learn from reward versus from punishment (Waltz et al. 2007; Cheng et al. 2012; Gold et al. 2012; Reinen et al. 2014), though some studies also find impaired learning from punishment (Fervaha et al. 2013a, b; Cicero et al. 2014). Further, there is recent work suggesting that working memory impairments may make a significant contribution to reinforcement learning deficits in schizophrenia (Collins et al. 2014). Further, there is a growing literature suggesting altered activity in cortical regions involved in cognitive control during

anticipation/prediction error (Walter et al. 2009; Gilleen et al. 2014) and during reinforcement learning (Waltz et al. 2013; Culbreth et al. in submission). Such findings are consistent with the larger literature suggesting altered cognitive control function in schizophrenia and are also consistent with the growing basic science literature suggesting important interactions between what have been referred to as "model-free" learning systems (e.g., DA in the striatum) and "model-based" learning systems that engage prefrontal and parietal systems that support representations of action-–outcome models (Glascher et al. 2010; Daw et al. 2011; Doll et al. 2012; Lee et al. 2014; Otto et al. 2015). Taken together, these data and literatures point to the need to examine interactions between these systems and dopamine-mediated reinforcement learning systems.

3.2 Depression

3.2.1 Reward Anticipation

A number of studies have examined reward prediction and reward anticipation in individuals with depression. Given the literature reviewed above on the abnormalities in self-report, behavioral, and neural responses to the processing of positive stimuli and rewards, one would anticipate that individuals with depression should also show altered responses to the anticipation of prediction of reward. The literature supports this hypothesis, at least in part. For example, work by McFarland and Klein demonstrated reduced self-reports of joy in response to anticipated reward among individuals with depression (McFarland and Klein 2009). Similarly, other work supports reduced self-reports of anticipated pleasure (Sherdell et al. 2012). In addition, individuals with depression or with a family history of depression show reduced frontal EEG asymmetries during reward anticipation (Shankman et al. 2007, 2013; Nelson et al. 2013, 2014). Further, a recent meta-analysis on neural processing of rewards in depression found evidence for <reduced>? reward anticipation responses in the left caudate, along with evidence for increased activity in the right ACC (Zhang et al. 2013). Yet, there is some variability in these responses across individual imaging studies. A number of studies have found reduced activation in various regions of the striatum during reward anticipation among individuals with current depression or individuals at risk for depression (Dichter et al. 2009; Forbes et al. 2009; Pizzagalli et al. 2009; Smoski et al. 2009; Gotlib et al. 2010; Olino et al. 2011, 2014; Stoy et al. 2012; Ubl et al. 2015), as well as increased activity in the ACC (Dichter et al. 2012; Gorka et al. 2014). However, some other studies have found no differences in striatal activation during reward anticipation between healthy individuals and those with current (Knutson et al. 2008; Gorka et al. 2014) or remitted depression (Dichter et al. 2012), although in at least one case it was not clear that any participant showed activity in the striatum during reward anticipation (Chase et al. 2013). Further, at least one study found reduced ACC responses during reward anticipation (Chase et al. 2013).

3.2.2 Reward Prediction Error

There is also a small but growing literature on striatal reward prediction errors associated with depression. The majority of studies have found evidence for reduced positive prediction errors in depression in the striatum, including the caudate and the nucleus accumbens (Kumar et al. 2008; Gradin et al. 2011; Robinson et al. 2012). Further, the magnitude of these reductions was associated with the severity of anhedonia. However, two other studies did not find reduced positive prediction errors in the striatum in depression (Chase et al. 2013; Ubl et al. 2015), and one of the studies that found reduced prediction errors in the striatum also found increased prediction error responses in the VTA (Kumar et al. 2008). It is not obvious why these two studies found differing results, as they did not differ systematically form the other studies in terms of type of population, symptom severity, or medication use.

Across the reward anticipation and prediction error literatures, the findings provide support for the hypotheses that a dysfunction in striatal responses to reward, potentially reflecting altered DA function, is an important component of altered hedonic processing in depression. The evidence for altered dorsal ACC responses is also intriguing. In recent work, Shankman and others have posited the hypothesis that this increased activation may actually reflect "conflict" that individuals with depression experience when asked to anticipate processing hedonically positive stimuli that conflict with their current negative internal state (Gorka et al. 2014). If so, this would suggest that altered ACC activation is an outcome of the phenomenology of depression rather than potentially playing a causal role in anticipatory pleasure impairments. However, there is also a large literature on altered error-related negativities in depression (Olvet and Hajcak 2008; Vaidyanathan et al. 2012), thought to reflect, at least in part, altered activity in the ACC. Given these accumulated findings, more work is needed to establish what role ACC alterations may play in experienced or anticipated hedonic processing deficits associated with depressive pathology.

3.2.3 Reinforcement Learning

In contrast to the literature on reinforcement learning in schizophrenia, and consistent with an important role for striatally mediated reward processing abnormalities, there is good evidence for impairments in implicit reinforcement learning in depression. A number of studies have shown that individuals with depression show reduced biases in response to reward on a probabilistic learning task (Henriques et al. 1994; Pizzagalli et al. 2008; Vrieze et al. 2013). This is seen in remitted depression (Pechtel et al. 2013), as well as current depression, and is worse in individuals with depression who have higher anhedonia (Vrieze et al. 2013; Liverant et al. 2014). Similar impairments in depression have been found on a reinforcement learning task similar to the weather prediction task (Herzallah et al. 2010, 2013a, b), where it is typically difficult to develop explicit representations of

the reward contingencies. In contrast, the literature on explicit reinforcement learning in depression suggests surprisingly intact performance. For example, there are a number of studies showing that individuals with depression perform similarly to healthy controls on the same probabilistic selection task that shows clear impairments in schizophrenia (Chase et al. 2010; Anderson et al. 2011; Cavanagh et al. 2011; Whitmer et al. 2012). The literature on the effects of subclinical depression on reinforcement learning also provides evidence for intact learning from reward (Beevers et al. 2013) though other work observed impaired reward learning (Kunisato et al. 2012; Maddox et al. 2012). As noted above, there are at least two pathways to impaired reinforcement learning—altered striatal-mediated stimulus–response learning and the use of cognitive control processes to develop and maintain explicit representations of action–outcome contingencies that can guide behavior. One intriguing possibility is that the former is impaired in depression but that the relatively more intact function of cognitive control processes in depression (as compared to schizophrenia) may allow individuals with depression to compensate for such implicit learning impairments, but only when they can develop explicit representations to support learning.

3.3 Summary of Reward Prediction, Anticipation, and Reinforcement Learning in Schizophrenia and Depression

As with the literature on hedonics and liking, this literature provides intriguing hints about potentially different mechanisms associated with motivational impairments in psychosis and depressive pathology (see Table 1). The literature on reinforcement learning and reward prediction in schizophrenia suggests relatively intact learning on simple reinforcement learning paradigms that may be implicit in nature. On difficult tasks that may also engage explicit learning mechanisms, there is more consistent evidence for impaired performance. An open question is the degree to which these impairments reflect differences in striatally mediated implicit learning mechanisms versus more cortically mediated explicit learning 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 with mixed evidence in those taking atypical antipsychotics) 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, pointing to the importance of examining individual difference relationships among individuals with schizophrenia. Further, a number of studies have also found altered activation in frontal regions during reward prediction or reinforcement learning, suggesting a potentially important role for cortically mediated mechanisms in schizophrenia.

The literature on depression also provides evidence for impairments in both self-report and neural indicators of reward anticipation and for deficits in striatal prediction error responses. In contrast to the literature on schizophrenia, there is robust evidence for impairments in "implicit" reinforcement learning in depression on tasks that are thought to reflect slow striatally mediated reinforcement learning, consistent with the idea that impairments in hedonic responses to reward may propagate forward to impair other components of reward processing. Interestingly, there is much less evidence for impaired performance on more explicit reinforcement learning tasks in depression, raising the intriguing possibility that individuals with depression are able to recruit more intact cognitive control or other explicit learning mechanisms to compensate for impaired reward responsivity.

4 Value Computations and OFC Function

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. One prominent theory suggests that reward processing deficits in schizophrenia reflect impairments in the representation of value (Gold et al. 2008). Although many different paradigms can be interpreted in the context of value representations (Gold et al. 2012), there are two experimental paradigms in particular that have been frequently used as probes of lateral and medial OFC function: probabilistic reversal learning and the Iowa Gambling Task. Both tasks require individuals to integrate information about rewards and punishments across trials and to use such information to update value representations appropriately.

4.1 Schizophrenia

The literature on the Iowa Gambling Task in schizophrenia provides evidence for impairment (Shurman et al. 2005; Kester et al. 2006; Lee et al. 2007; Martino et al. 2007; Sevy et al. 2007; Premkumar et al. 2008; Kim et al. 2009; Yip et al. 2009), though with some exceptions (Wilder et al. 1998; Evans et al. 2005; Rodriguez-Sanchez et al. 2005; Turnbull et al. 2006). In addition, several studies suggest impaired reversal learning in schizophrenia (Elliott et al. 1995; Oades 1997; Pantelis et al. 1999; Tyson et al. 2004; Turnbull et al. 2006; Waltz and Gold 2007; Ceaser et al. 2008), though a few studies using the intra-dimensional/extra-dimensional task did not find simple reversal learning deficits in schizophrenia (Hutton et al. 1998; Joyce et al. 2002; Jazbec et al. 2007). These reversal learning impairments are present even when individuals with schizophrenia and controls are matched on initial acquisition performance (Weiler et al. 2009). However, the imaging studies on reversal learning in schizophrenia do not point to altered

activation of the OFC in relationship to these deficits, instead pointing to either alterations in striatal prediction error responses (Schlagenhauf et al. 2014), deactivation of default-mode regions (Waltz et al. 2013), or impaired activation of cognitive control networks (Culbreth et al. in submission). Thus, while there may be impairments in value computations associated with schizophrenia, there is yet little direct evidence that such impairments reflect OFC dysfunction (see Table 1).

4.2 Depression

In depression, there is also evidence for impaired performance on the Iowa Gambling Task (Must et al. 2006, 2013; Cella et al. 2010; Han et al. 2012), though with some studies not finding impairment (Westheide et al. 2007; Smoski et al. 2008). There is also evidence of impairments in reversal learning in depression (Murphy et al. 2003; Robinson et al. 2012; Hall et al. 2014). However, like the literature on schizophrenia, there is no evidence directly linking such impairments to OFC function (see Table 1), and the small imaging literature on reversal learning in depression points to altered striatal responses associated with impaired reversal learning (Robinson et al. 2012; Hall et al. 2014).

5 Effort Computations

There is a growing literature on the neurobiological mechanisms that regulate effort allocation and expenditure in both humans and animals (Salamone et al. 2007, 2009; Walton et al. 2007; McGuire and Botvinick 2010; Salamone and Correa 2012; Shenhav et al. 2013; Botvinick and Braver 2015). This literature makes distinctions between effort that needs to be allocated for cognitive demands and effort that needs to be allocated for physical demands, with evidence for both common and distinct mechanisms. In the animal literature, there is robust evidence that DA plays a key role in regulating physical effort allocation, in that blockade of DA, especially in the accumbens, reduces physical effort allocation (Salamone et al. 2009, 2012; Farrar et al. 2010; Salamone and Correa 2012), and increased D2 receptor expression in the nucleus accumbens of adult mice increases physical effort expenditure (Trifilieff et al. 2013). There is also recent evidence for important interactions between DA and adenosine (Salamone et al. 2012) in regulating effort. Consistent with this work in animals, Treadway et al. (2012a, b) found that, in humans, increased DA release in response to d-amphetamine in the left striatum and the left ventromedial PFC was associated with increased willingness to expend physical effort. However, there is recent evidence from animal work that DA antagonism may not reduce willingness to expend cognitive effort (Hosking et al. 2014a, b), though human work has shown that activity in the ventral striatum (which may reflect DA activity) predicts effort allocation for both physical and cognitive domains (Schmidt et al. 2012). It is

important to note, though, that the developmental timing of DA function may be critical for understanding the role of DA in effort allocation. Particularly, research has shown that mice with D2 receptor overexpression throughout development (developed as a murine model of the negative symptoms of schizophrenia) actually show a decrease in effort expenditure (Simpson et al. 2011; Ward et al. 2012). This overexpression across the course of development may lead to alterations in other parts of the system, such as the prefrontal cortex (Kellendonk et al. 2006; Li et al. 2011), that in turn lead to reduced effort allocation.

There is also a large literature pointing to an important role for the medial prefrontal cortex, particularly the dorsal ACC, in regulating effort allocation. Recent computational work has posited a role for dorsal ACC in computing the expected value of control (Shenhav et al. 2013), arguing that the dorsal ACC integrates information about the expected value of the outcome, the expected cognitive control needed to obtain that outcome, and the expected cost of that cognitive control, in order to make decisions about the utility of expending effort. This hypothesized function of the dorsal ACC is consistent with the rodent and primate literature showing that lesions/inactivation of the dorsal ACC reduced both physical and mental effort allocation (Walton et al. 2003; Rudebeck et al. 2006a, b; Croxson et al. 2014; Hosking et al. 2014a, b, 2015), with evidence that rodent ACC neurons encode cost–benefit computations (Hillman and Bilkey 2010, 2012), and with the human literature showing activation of the dorsal ACC during effort based decision making (Croxson et al. 2009; Prevost et al. 2010).

5.1 Schizophrenia

The vast majority of the literature on effort allocation in schizophrenia has focused on physical effort, using paradigms that either involve finger-tapping (Treadway task Treadway et al. 2009) or a balloon-popping task (Gold et al. 2013) or grip strength as metrics of physical effort allocation. The paradigms using finger taping have quite consistently found a specific pattern of reduced effort allocation on the part of individuals with schizophrenia—they do not differ from controls at low levels of reward or low levels of probability of receiving the outcome, but do not show the same increase in effort allocation as either reward or probability increase (Fervaha et al. 2013a, b; Gold et al. 2013; Barch et al. 2014; Treadway et al. 2015). Further, the majority of the studies found that the degree of reduction in effort allocation was associated with either negative symptoms (Fervaha et al. 2013a, b; Gold et al. 2013; Treadway et al. 2015) or functional status (Barch et al. 2014). The two studies using grip strength showed differing results—one found a significant reduction in effort allocation among individuals with schizophrenia rated clinically as having higher apathy (Hartmann et al. 2014), while the other study found no effects of either diagnosis or symptom severity (Docx et al. 2015). Two recent studies have also examined cognitive effort allocation. One study using a progressive ratio task found evidence for reduced effort allocation in schizophrenia,

although the design of the task was such as that cognitive effort was confounded with physical effort (Wolf et al. 2014). In contrast, Gold et al., found little evidence of reduced cognitive effort in schizophrenia across three studies, though these studies did suggest that individuals with schizophrenia had difficulty detecting variations in cognitive effect among conditions (Gold et al. 2014).

5.2 Depression

All of the studies to date on effort allocation in depression have focused on physical effort, either using the Treadway finger-tapping task, a grip strength task, or a finger-tapping task with humorous cartoons. These studies provide a relatively consistent picture. Individuals with current depression show reduced effort allocation as a function of increasing monetary incentives (Clery-Melin et al. 2011; Treadway et al. 2012a, b; Yang et al. 2014). In other words, individuals with current depression are less likely to increase their likelihood of choosing harder tasks as the reward associated with the harder task increases. Further, there is some evidence that individual differences in self-reported anticipatory and/or consumatory pleasure relate to individual differences in the severity of effort allocation impairments (Yang et al. 2014). Individuals with remitted depression do not show effects as a group, though they do still show these individual difference relationships (Yang et al. 2014). In a novel study using viewing of humor cartoons as the incentive, Sherdell et al. did not find group differences in effort allocation, though they did find that those individuals with major depression who self-reported increased anticipatory anhedonia did show reduced effort allocation (Sherdell et al. 2012).

5.3 Summary of Effort Allocation in Schizophrenia and Depression

Taken together (see Table 1), these studies point to consistent evidence of reduced physical effort allocation in both schizophrenia and depression, but do not yet suggest a clear consensus on cognitive effort allocation. As of yet, there is no neuroimaging literature examining potential neural alterations associated with these impairments. In particular, it will be important to examine whether such abnormalities in schizophrenia or depression are associated with abnormal activity in the ACC and/or the ventral striatum and to also evaluate the degree to which abnormalities in effort allocation are associated with other components of reward processing.

6 Goal-Directed Action

6.1 Schizophrenia

Numerous reviews have outlined the strong evidence for impairments in goal representation and cognitive control in schizophrenia from a variety of sources (Barch and Ceaser 2012; Lesh et al. 2013), as well as the evidence for altered activation, connectivity, and structure of brain regions, such as the DLPFC, in schizophrenia (Glahn et al. 2005, 2008; Minzenberg et al. 2009; Fornito et al. 2011). Thus, a key question is, whether some of the motivational impairments observed in schizophrenia at least in part reflect problems translating reward information into goal representations that can be used and maintained in DLPFC to guide goal-directed behavior? One means of examining this issue would be 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 (Green et al. 1992; Vollema et al. 1995; Hellman et al. 1998; Roiser et al. 2009). While there is also at least some evidence for performance improvements with reward (Kern et al. 1995; Penn and Combs 2000; Rassovsky et al. 2005), these studies have not examined executive control tasks.

There is also work on the use of token economies in schizophrenia suggesting that functioning can be improved through an explicit reward system, though 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. A recent study has examined whether or not individuals with schizophrenia could improve cognitive control on a response inhibition task. Patients were able to speed their responses when presented with specific cues about winning reward and to a certain extent could speed their responses on trials in the reward "context" even when they could not earn money, an effect thought to reflect the maintenance of reward information through proactive control mechanisms. However, the individuals with schizophrenia showed a significantly smaller incentive context effect than controls, suggesting a reduction in the use of proactive control and a greater reliance on the use of "just-in-time," reactive control strategies (Mann et al. 2013). To date, there are no published fMRI studies examining whether or not incentives modulate DLPFC activity during cognitive control or working memory tasks in schizophrenia. This is a line of work that would be critical in helping to understand the relative contributions that prefrontal cognitive control deficits versus striatal incentive processing deficits make to motivational impairments in schizophrenia (see Table 1).

6.2 Depression

There is evidence in the literature that individuals with depression may show deficits on a range of cognitive control tasks (Rock et al. 2013), though the magnitude of the deficits are typically not as large as one sees among individuals with schizophrenia. However, there is much more mixed evidence for altered activation of cognitive control regions during working memory (at least without affective challenges), cognitive control, or goal maintenance tasks in depression without psychosis, with some studies finding little or no alterations in cognitive control regions (Barch et al. 2003; Walter et al. 2007; Schoning et al. 2009) and other studies finding some evidence (Siegle et al. 2007; Halari et al. 2009). There is much more evidence for altered prefrontal activity in depression during emotion regulation paradigms, though the pattern of activation alterations varies across studies (Beauregard et al. 2006; Johnstone et al. 2007; Sheline et al. 2009; Erk et al. 2010; Kanske et al. 2012; Perlman et al. 2012). To our knowledge, there are only two studies that have looked at incentive-modulated cognitive control in depression, both of which examined adolescents. Both studies found intact effects of incentives (rewards and punishments) on reducing anti-saccade errors among depressed adolescents, but reduced effects of incentives on latencies (Jazbec et al. 2005; Hardin et al. 2007). Such reduced effects would be expected if reward were experienced as less hedonically pleasurable for depressed individuals (i.e., hedonic/"liking" deficits feeding forward to produce other deficits), but further work is needed to understand the degree to which cognitive control impairments might also contribute to altered goal-directed action in depression (see Table 1).

7 Summary of Reward and Motivational Neuroscience in Schizophrenia and Depression

Above, we reviewed evidence for impairments in six components of the mechanisms that translate hedonic experiences of rewards into goal-directed actions that allow individuals to obtain such rewards. This review provided evidence for a number of common impairments across individuals with schizophrenia and depression, including consistent evidence for impairments in both self-report and neuroimaging indicators of reward prediction and prediction errors, as well as robust evidence for impairments in effort allocation. However, this review also revealed critical differences in the nature of incentive processing impairments that point to differential etiological pathways leading to impairments in motivated behavior associated with psychotic versus depressive pathology. Specifically, individuals with schizophrenia show relatively *intact* in-the-moment hedonic experiences as well as relatively *intact* explicit reinforcement learning, where dorsal frontal and parietal cognitive control systems may contribute to deficits in reward anticipation, reversal learning, and goal maintenance/action selection. In contrast,

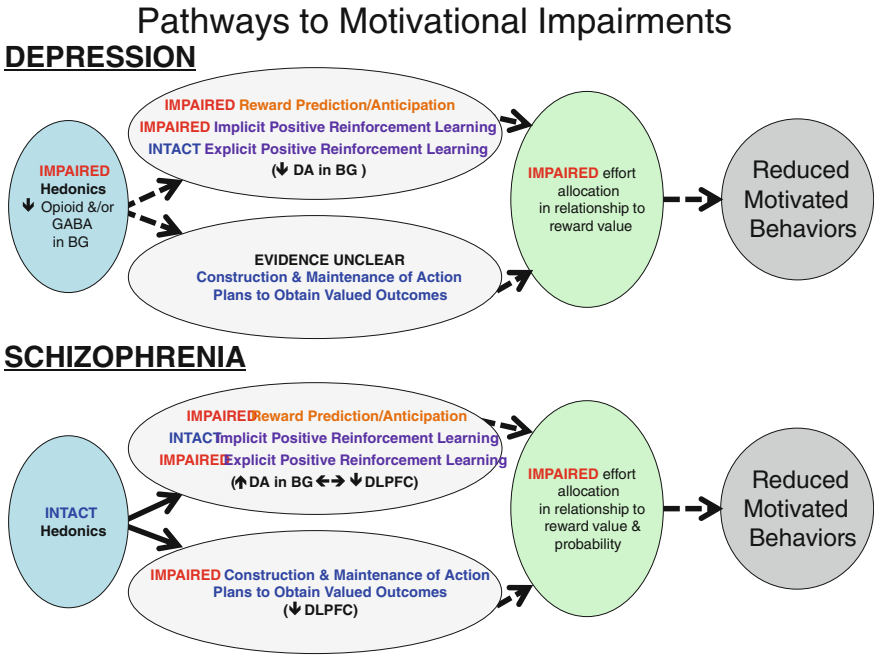

Fig. 2 Pathways to motivational impairments in schizophrenia and depressive pathology. *Dashed lines* indicated that impairment in a component may feed forward to contribute to impairments in other components. *Solid lines* indicate that input from intact components. *Down arrow* (↓) indicates evidence for reduced function of this neural mechanism. *Up arrow* (↑) indicates evidence for increased or dysregulated function of this neural mechanism. *Left arrow Right arrow* (→←) indicates interactions between neural mechanisms. *BG* Basal ganglia, *DA*, Dopamine, *DLPFC* Dorsolateral prefrontal cortex

individuals with depression show consistent evidence of *reduced* in-the-moment hedonic experience and *impaired* implicit reinforcement learning, coupled with relatively *intact* explicit reinforcement learning, and less evidence for a contribution of cognitive control systems to altered reward processing and motivated behavior.

When integrated, these patterns (see Fig. 2) suggest that impaired incentive processing in schizophrenia may be more related to impaired goal representation and utilization mechanisms rather than to fundamental deficits in hedonic experience. Such impairments may reflect both altered DA function and altered activation of dorsal frontal–parietal cognitive control systems. Specifically, recent meta-analyses point to robust evidence for increased dopamine synthesis availability and some evidence for D2 receptor overexpression (Howes et al. 2012; Fusar-Poli and Meyer-Lindenberg 2013), as well as robust evidence for altered activity of cognitive control systems (Minzenberg et al. 2009). As described above, there is intriguing evidence from a murine model of the negative symptoms of schizophrenia (Simpson et al. 2011; Ward et al. 2012) that D2 overexpression occurring throughout development contributes to altered prefrontal function and DA

sensitivity (Kellendonk et al. 2006; Li et al. 2011). Thus, even though individuals with schizophrenia can experience reward and pleasure from a variety of stimuli, they may have difficulty learning appropriate reward or salience representations (Howes and Kapur 2009) and difficulty representing and maintaining reward information over time so that information can drive further goal-directed behavior and action selection (Barch and Dowd 2010; Kring and Barch 2014).

In contrast, the data reviewed above suggest that in the context of depressive pathology (see Fig. 2), altered incentive processing may be more related to fundamental deficits in hedonic experience that propagate forward to result in impaired motivated behavior. Individuals with depression show consistent evidence for altered hedonic responses to a range of stimuli, with the severity of such deficits sometimes varying with self-reported levels of anhedonia. In turn, individuals with depression show impaired implicit reinforcement learning that is thought to be striatally mediated (and dependent on experiencing a stimulus as pleasurable) as well as impaired effort allocation for incentives. In contrast, there is less evidence that individuals with depression show impaired explicit reinforcement learning and less evidence that there are clear contributions impaired cognitive control systems to altered incentive processing and motivated behavior. As described above, the animal literature suggests that hedonic responsivity is associated with opioid and GABA-ergic function in the striatum, and this pattern is consistent with the hypothesis that altered opioid function may contribute to hedonic impairment in depression. This hypothesis is also consistent with a growing literature on opioid mechanisms in depression (Lalanne et al. 2014; Murphy 2015) and an emerging interest in modulation of the kappa opioid system as a treatment for depression (Connolly and Thase 2012), with a specific focus on anhedonia. At the same time, the results in depression could also suggest a role for altered DA function in the striatum. There is some evidence that depression may be associated with DA dysfunction, e.g., examining DA binding in the striatum (Cannon et al. 2009). However, in general, the literature on DA alterations is mixed and relatively small (Savitz and Drevets 2013; Camardese et al. 2014).

To illustrate how such differing patterns of impairments may lead to altered motivated behavior, consider the following scenarios. An individual with schizophrenia may report that they enjoy chocolate chip cookies and would find the experience of eating chocolate chip cookies quite pleasurable if you were to bring them a nice warm plateful (i.e., intact hedonics). However, they may have difficulty generating/initiating the behaviors necessary to obtain or make chocolate chip cookies on their own (Kring and Moran 2008; Barch and Dowd 2010). Planning, purchasing, preparing, or baking the cookies requires ongoing maintenance of contextual or cue information that trigger associations about the food's rewarding properties, which should drive the allocation of effort to obtain these outcomes (e.g., get dressed, leave the house, go to the store). These functions depend on the ability to associate relevant cues with rewarding outcomes, a process that is associated with striatal DA function, which is dysregulated in schizophrenia. In addition, these functions may depend on the intact ability to maintain appetitive cues or context over time—a process that may be reliant on cognitive control and working

memory mechanisms, which are compromised in schizophrenia (Barch and Dowd 2010). In contrast, an individual with depression may report that they do not enjoy chocolate chip cookies and may not find the experience of eating chocolate chip cookies enjoyable even if you bring them fresh baked ones. Such hedonic impairments might reflect altered opioid signaling in the striatum. In turn, individuals with depression (at least those with anhedonia) may fail to learn about cues associated with delicious cookies and may be unwilling/unmotivated to allocate effort to making cookies since they do not anticipate them being particularly enjoyable.

These are of course simplified examples and do not reflect the vast complexity of motivated behaviors that we need to engage in every day. Further, this example does not capture all of the interactions among these systems or the heterogeneity that exists across individuals or even within individuals across time. However, these ideas may provide a heuristic framework for future research that attempts to understand the transdiagnostic or diagnosis-specific mechanisms contributing to altered motivated behavior in psychopathology. Studies that cut across diagnostic boundaries are clearly need now to explicitly test such hypotheses about common and distinction mechanisms leading to a motivation, as a means to develop more effective and targeted interventions that will hopefully lead to enhanced quality of life, reduced public health burden, and even preventative interventions that could preclude the development of psychopathology.

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