Review

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Neural Circuitry of Salience and Reward Processing in Psychosis

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ABSTRACT

The processing of salient and rewarding stimuli is integral to engaging our attention, stimulating anticipation for future events, and driving goal-directed behaviors. Widespread impairments in these processes are observed in psychosis, which may be associated with worse functional outcomes or mechanistically linked to the development of symptoms. Here, we summarize the current knowledge of behavioral and functional neuroimaging in salience, prediction error, and reward. Although each is a specific process, they are situated in multiple feedback and feedforward systems integral to decision making and cognition more generally. We argue that the origin of salience and reward processing dysfunctions may be centered in the subcortex during the earliest stages of psychosis, with cortical abnormalities being initially more spared but becoming more prominent in established psychotic illness/schizophrenia. The neural circuits underpinning salience and reward processing may provide targets for delaying or preventing progressive behavioral and neurobiological decline.

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Psychoses of the schizophrenia spectrum are characterized by positive symptoms, such as hallucinations and delusions, which are dominant during the psychotic stages of the disease; negative symptoms, such as lack of motivation and emotional blunting; and cognitive symptoms, such as memory dysfunctions (1). Although the underlying mechanisms leading to this complex set of symptoms are not fully understood, one of the most robust findings in psychosis and schizophrenia and even in the prodromal stages of the disease [e.g., (2)] is the elevation of striatal dopamine [e.g., (3)]. Dopamine is therefore the target of most antipsychotic pharmacological interventions (1), greatly reducing positive symptoms (4). Unfortunately, however, approximately 30% of patients with schizophrenia classify as treatment resistant to dopamine D_2 receptor antagonists and have worse long-term functional disability, with more severe positive, negative, and cognitive symptoms [e.g., (5)]. Glutamatergic systems may be more relevant than dopamine for the pathogenesis of positive psychotic symptoms in these individuals (6). Similarly, links between negative and cognitive symptoms and dysregulation of the glutamatergic system have also been observed [e.g., (7)]. However, pharmacological interventions targeting the glutamatergic system have been less successful (1). Given the strong associations between dopamine, salience/reward, and negative symptoms, this review is focused largely on subcortical dopamine systems and their associated corticostriatal networks.

In this article, we examine evidence for dysfunction of the neural circuitry subserving reward and salience processing and their links to dopaminergic dysregulation in the psychosis spectrum (Table 1). These dysfunctions are potentially highly relevant for understanding the core aspects of schizophrenia and related symptoms, including positive symptoms and negative symptoms. A brief introduction to the psychological processes included in salience, prediction error, and reward processing is provided in Figure 1. We endeavored to examine the extent to which neural dysfunctions have been linked to clinical symptoms, cognitive impairments, or functional disability because not all neural abnormalities may have deleterious consequences. Much of the work in this field is cross-sectional; however, we have endeavored to discuss jointly all stages of illness to highlight the relevant similarities and differences as much as possible.

SALIENCE PROCESSING IN PSYCHOSIS

Salience is a property that characterizes the importance of a stimulus and ultimately attracts attention to drive cognition and behavior. Salience is a multifaceted concept (8) including different dimensions, such as reward or novelty (Box 1). Abnormal salience processing following dysregulation of the dopaminergic system has been linked to the formation and maintenance of positive and negative symptoms (9–12) and is referred to as the aberrant salience hypothesis of psychosis (8,13–15). According to the aberrant salience hypothesis, elevated levels of dopamine in psychosis [e.g., (16)] create neurobiological noise, which is misinterpreted as meaningfulness and may lead to the attribution of salience to the otherwise unimportant, ordinary experiences that incidentally co-occur with this experience. The interpretation of these falsely judged–important stimuli may lead to the formation of hallucinations and delusions.

At the same time, relevant stimuli, such as a reward prediction error or an emotional stimulus, fail to be processed appropriately, leading to a blunted response, potentially

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Table 1. Psychosis Spectrum

Disease Stage	Description
At Risk	By at risk, we mainly refer to people who are at increased risk of psychotic illness due to being help-seeking patients presenting with mild (subthreshold) clinical symptoms, especially subthreshold positive psychotic symptoms, such as suspicions or hallucinations without delusional interpretations. Such individuals are sometimes termed ultra-high-risk, clinical high-risk, at-risk mental state, or prodromal psychosis, with several (slightly differing) operational criteria available to categorize people in such states (131). We note that although such groups are especially at (relatively) high risk of psychosis, they also are at risk for other adverse psychiatric outcomes (132).
Early Psychosis	By early psychosis, we refer to the early stages after the onset of established psychotic illness, such as first-episode psychosis and first-episode schizophrenia. While some studies only include patients who meet the diagnostic criteria for schizophrenia, a number of research studies include a broader mixture of patients with first-episode psychosis. These are people presenting with psychotic illness for the first time, many with nonaffective schizophrenia spectrum psychosis, and others with affective psychosis such as bipolar disorder or depressive psychosis.
Chronic Psychosis/ Schizophrenia	In general, we use the term chronic psychosis/schizophrenia for referring to patients who have been unwell beyond the early stages of illness/first 5 years of psychotic illness. Where studies have specified a minimum duration of illness, we use the term chronic schizophrenia, but we note that some studies include a mixture of patients with schizophrenia at different stages of illness.

explaining negative symptoms (12,17). The human and animal literature describes the critical role of dopamine in reward prediction error processing (18,19). Reward prediction errors are intrinsically salient (see Prediction Error Signaling in Psychosis and Reward Processing in Psychosis). The firing of dopamine neurons, however, is not exclusive to reward prediction error but has been reported in response to nonrewarding unexpected events, such as aversive or alerting (11,20), as well as novel events (21), surprising events (22), or physical change (23). Therefore, dopamine release, at least in some contexts, may reflect general salience (24).

Aberrant Salience as Altered Processing of Irrelevant Information

Several studies investigated the processing of neutral or uninformative stimuli using different methods and exploring different stages of the disease and the link to symptoms; while theoretically clear, the experimental results show inconsistencies. Roiser *et al.* (25) adapted a monetary reinforcement learning task (salience attribution task) to investigate the salience assigned to irrelevant stimuli. Their study revealed that schizophrenia patients with delusions showed higher levels of aberrant salience to irrelevant stimuli than patients without delusions (25); however, aberrant salience was correlated with negative symptoms. Applying the same task to at-risk individuals, aberrant salience attribution to irrelevant stimuli was associated with the severity of positive symptoms (26). Similarly, using novel computational approaches to investigate the differences between patients with schizophrenia and control subjects in the implicit salience task, Katthagen *et al.* (27) found that patients had a stronger bias toward irrelevant information, which was associated with stronger negative symptomatology and not with positive symptoms as conceptually expected. Partially, these inconsistencies might be explained by different

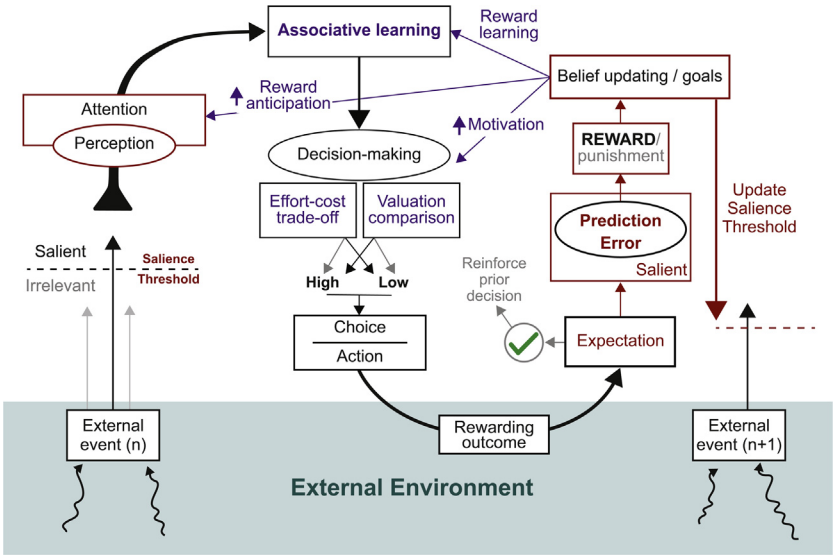

Figure 1. Conceptual interactions between external events (cyan), salience and prediction error (red), and reward processing (purple) in decision making. An external event (e.g., action outcome) will be perceived and attended to when it overcomes a certain level of salience (referred to as a salience threshold). The input is then integrated into associative learning networks to inform decision-making processes. Computation of potential rewards available (valuation) and the effort required for each (effort-cost trade-off) are then used to identify the optimal choice and whether or not it is acted upon. In this example, the outcome is rewarding (external feedback as action outcome), which is then compared with our prior expectations. Our prior expectation is associated with how accurate our valuation of the outcome is. In cases where the outcome matches the expectation (green tick), the associations are reinforced. In cases where there is a mismatch between the outcome and our expectation, a prediction error signal is generated. The prediction error is used to update our understanding of input-output relationships. Prediction error information (magnitude, precision, and so on) is then used to update our beliefs and goals associated with the initial stimuli (or action required). This updates our salience threshold so that when we encounter this same event in the future ($n + 1$), it is more likely to be considered salient. Reward processing (purple) affects multiple stages in this process to subsequently increase attention (reward anticipation), drive associative learning (reward learning), and govern our motivation to work toward a future goal. Here, we focus on a rewarding outcome; however, perceptual and attentional processes of sensory stimuli work similarly, causing belief updating and salience threshold updating via prediction errors.

Box 1. Salience

The world around us is highly complex and produces constant noisy and ambiguous sensory input to our brain. The biggest challenge for our brain is to rapidly and efficiently identify important stimuli and to process them effectively. One efficient way that the brain applies is to evaluate the saliency of incoming sensations and prioritize them accordingly considering the context. Imagine, for example, the change of the traffic lights from green to red; the change in the physical qualities of the visual input is highly informative and important to adapt our behavior and decisions. This example shows that there is a strong interaction between stimulus-driven processing and goals or belief of the individual to determine the saliency of incoming information.

We can differentiate between different forms of saliency (133), the first distinction being between incentive or motivational salience and nonmotivational salience. Incentive salience describes the desire to obtain a reward by increasing attention and motivational drive (see the sections on Prediction Error Signaling in Psychosis and Reward Processing in Psychosis for more information). Tasks used to investigate motivational salience use mainly monetary rewards. Nonmotivational salience, which is usually studied in visual/auditory oddball paradigms or when investigating the processing of irrelevant stimuli in monetary reward paradigms, can be distinguished in novelty salience and surprisal (134), which are essential drivers of intrinsic motivation (not reward related) and attention. Surprise is characterized by a change in condition through the comparison of the expected to the actually perceived (e.g., the physical change of a stimulus or emotional change) and is strongly linked to an unsigned (i.e., without valence indication, worse or better than expected) prediction error (135). For novelty, however, the concept is less concrete. Generally, novelty refers to a sensory input never encountered before (complete novelty) or not encountered for some time (short-term/long-term novelty). See Barto *et al.* (134) for details. Once some sensory input is being evaluated as salient, this is ultimately a driver for learning and behavior (136).

When experimentally investigating salience processing, two different aspects might be explored: the processing of salient, such as emotional, novel, or motivational stimuli, or the processing of irrelevant, uninformative, neutral stimuli. In schizophrenia, deficits in the first aspect conceptually relate to the development and preservation of negative symptoms (12,17); the latter suggests the overweighting of irrelevant stimuli, which is linked to the emergence of positive symptoms. The current literature provides evidence for aberrant salience processing across both aspects in early psychosis and chronic schizophrenia; however, links to symptomatology are less concise.

medication or treatment statuses. Abboud *et al.* (9), for example, showed that patients with treatment-resistant schizophrenia did not show heightened aberrant salience. This result may be explained by the nonelevated levels of dopamine synthesis capacity (28) in contrast to otherwise elevated levels in the early and chronic stages of the illness (29). A further argument explaining the inconsistencies might be the investigation of task-irrelevant information in a rewarding setting, which might not allow a clear differentiation between the underlying processes.

In a reward-independent learning setting, Ceaser and Barch (30) found that during a cognitive control task, patients with schizophrenia were more likely to inappropriately encode irrelevant distracter stimuli, showing increased prefrontal and striatal activity. In emotion recognition studies, patients with chronic schizophrenia consistently showed increased brain signaling to neutral emotional stimuli, the irrelevant stimuli in the tasks, with effects being especially strong for face stimuli (31). Similar results were also reported for emotional and neutral word processing; patients with schizophrenia and their unaffected first-degree relatives demonstrated increased attention to neutral words compared with control subjects (32). The brain regions involved varied across studies and included the amygdala, prefrontal and cingulate subregions, and hippocampus (31). Results in individuals at risk for psychosis were less consistent with regard to neutral stimuli (31). These studies provide evidence for altered processing of neutral events in subcortical regions associated with dopaminergic dysregulation. When studying the processing of neutral stimuli in a reward-independent setting, there is more consistent evidence of a link between neural dysregulation and performance and symptom strength; increased striatal activity during incorrect distracter trials correlated positively with aberrant salience symptoms (30). In a behavioral causal learning task, Morris *et al.* (33) showed that people with schizophrenia with severe positive symptoms failed to discriminate between predictive and nonpredictive cues compared with healthy adults. Furthermore, overweighting nonpredictive cues was correlated with more severe positive symptom scores in schizophrenia (33). A recent study (34) exploring neutral stimuli in a reward learning setting showed that individuals with psychotic-like experiences overattribute salience to neutral stimuli and underattribute salience to rewards, indicating that abnormal salience attribution is a trait-like feature. Together, these studies show that neutral or irrelevant stimuli are consistently overweighted in patients at different disease stages, with the exception of patients with treatment-resistant schizophrenia, showing a clear indication of aberrant salience, although associations with symptoms are inconsistent.

Aberrant Salience as Altered Processing of Relevant Information

Aberrant brain processing of informative and relevant but nonmotivational salient events in psychosis has been reported in several studies. In a recent study, Knolle *et al.* (35) used a visual, passive oddball paradigm (36) to investigate novelty, negative emotional salience, and targetness, which required a button press, in patients with antipsychotic naïve first-episode psychosis. The patients exhibited reduced substantia nigra, ventral tegmental area, and striatal and cingulate signaling to novelty; reduced substantia nigra, ventral tegmental area, amygdala, and striatal and cingulate signaling to negative emotional salience; and reduced substantia nigra, ventral tegmental area, and cingulate signaling to targetness. Modinos *et al.* (37), using the same paradigm, showed similar results for novelty processing in at-risk individuals using the same task. Similar results of altered salience processing have been reported in patients with Parkinson's disease exhibiting psychotic, mainly hallucinatory, symptoms (38), again using the same paradigm (36). Moreover, patients with schizophrenia and early psychosis show deficits when processing emotions

and intrinsic salient events, especially in the context of facial recognition (39). In a positron emission tomography (PET) study, Taylor *et al.* (40) showed impaired neuronal signaling in the ventral striatum in response to emotional salient events in people with chronic and acute psychosis. In general, experimental findings are less consistent. A study reporting overall increased arousal in patients with schizophrenia during processing of emotionally neutral and salient stimuli (41) showed that the increase resulted solely from falsely attributing salience to neutral stimuli. This view has been confirmed by a meta-analysis showing similar processing of emotionally relevant information but attribution of aberrant salience to emotionally neutral information (42).

A recent electroencephalography study (43) using a P300 auditory oddball paradigm reported that reduced P300, which reflects impaired salience processing, indicated both transition to psychosis in at-risk individuals and transition to remission from psychotic symptoms. These studies show consistent findings for altered, mainly reduced, processing of salient stimuli compared with control subjects. Bringing both accounts together, a study by Boehme *et al.* (44) investigating healthy subjects showed that individual variability in aberrant salience measures related negatively to ventral striatal and prefrontal reward prediction error signals and, in an exploratory analysis, was found to be positively associated with nucleus accumbens presynaptic dopamine levels.

Aberrant Salience and Symptomatology

The literature provides evidence for aberrant processing of nonmotivational (and motivational) salience with regard to relevant and irrelevant events. Dysregulations in salience processing are associated with a range of brain areas in early psychosis and chronic schizophrenia (Figure 2). Here, we wish to argue that aberrant salience may explain positive and negative symptoms via different, although interrelated, mechanisms. As Maia and Frank (12) discussed, the failure to distinguish between salient and nonsalient events may be reflected in the dysregulated activity of phasic firing of dopamine neurons. While increased phasic dopaminergic firing to a nonsalient event, such as a radio in the background, may lead to the attribution of attention to this otherwise irrelevant stimulus, this suddenly important information (content of the radio show) might be reinterpreted causing, e.g., delusional thinking. However, decreased dopaminergic phasic firing to a salient event, such as an unexpected positive emotional expression on a person's face, may blunt the importance of this information. The inadequate interpretation or evaluation of the situation may be linked to, e.g., anhedonia. The aberrant processing of these informative or relevant (i.e., salient) events, as seen in blunted prediction errors to rewards (see Prediction Error Signaling in Psychosis) (45,46) or decreased responses to relevant visual stimuli (38,47), seem to relate to negative symptoms, such as anhedonia or lack of motivation (47–50). In contrast, aberrant processing of irrelevant (i.e., nonsalient) events, such as neutral events in reward learning or oddball paradigms, seems to provide an explanation for positive symptoms (33,34). We do note, however, some studies with contradictory symptom associations [e.g., (25,27,51)].

PREDICTION ERROR SIGNALING IN PSYCHOSIS

Prediction error is the mismatch between expectation and outcome and is, as an intrinsically salient event, a key driver of learning (52). Several studies reported reduced midbrain, striatal, and/or cortical processing of reward prediction errors in psychosis, which may underpin aspects of the clinical manifestations of psychotic illness (45,46,50,53–55). Here, we will mainly focus on functional magnetic resonance imaging (fMRI) studies of reward prediction error; other closely related topics such as mismatch negativity, Kamin blocking, latent inhibition, and causal learning prediction error have been

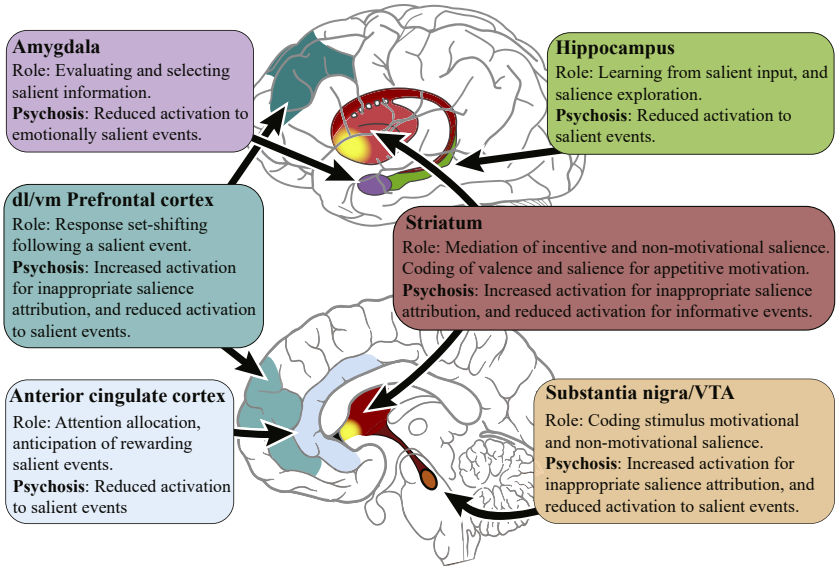

Figure 2. Salience areas and psychosis. Simplified diagram of key regions involved in salience processing and underlying problems observed in psychosis. See text for citations and details. dl, dorsolateral; vm, ventromedial; VTA, ventral tegmental area.

previously studied in schizophrenia and discussed elsewhere [e.g., (56,57)].

fMRI Studies of Reward Prediction Error in Early Psychosis and At-Risk Patients

In an early study, Murray *et al.* (45) demonstrated abnormalities in patient brain responses correlating with reward prediction error in the dopaminergic midbrain, in striatal and limbic regions, and in cortical regions such as the dorsolateral prefrontal cortex (PFC). Subsequent studies using different psychological paradigms have found similar abnormalities [e.g., (54,55)], especially in the early stages of psychosis, including in at-risk states [e.g., (58)]. Ermakova *et al.* (46) documented impaired subcortical (midbrain) reward prediction error signals in an antipsychotic-free early psychosis sample and showed that an at-risk group with mild psychotic symptoms had a degree of midbrain signaling abnormalities. Notably, there was dorsolateral PFC prediction error dysfunction in the early psychosis sample, with comparatively intact cortical function in the at-risk group with mild psychotic symptoms.

Relevant Pharmacological and Molecular Imaging Results

Although PET studies have demonstrated robustly that there is excessive dopaminergic striatal release in schizophrenia (59), neuroimaging studies have generally shown impaired striatal signaling in patients during learning, which may appear perplexing if striatal fMRI signals are considered a pure assay of dopamine release. This apparent paradox was addressed by Bernacer *et al.* (60), who showed that administration of methamphetamine (which floods the striatum with dopamine) to healthy volunteers leads to a disruption of striatal prediction error–associated activity. The degree to which methamphetamine induced mild psychotic experiences was related to the degree to which it disrupted the expected value signal in the ventromedial prefrontal and posterior cingulate cortices. The study showed that a drug that reliably increases dopamine release is not beneficial to neural or behavioral indices of learning, indicating that caution should be exercised when using fMRI signals as a clean readout of neurochemical processes. A related, nuanced finding is that antipsychotic dopamine D_2 receptor antagonist medications may enhance brain activations during reward processing in patients, in contrast to their effects in studies in healthy individuals (61).

Precision of Prediction Error

Recent interest has focused not simply on prediction error per se, but on the precision of prediction error, which theory posits should play an important role in belief updating under uncertainty. Simple models update value or beliefs in proportion to the prediction error, but it is thought that a prediction error of a given magnitude should influence belief updating depending on the degree of uncertainty with which it is estimated. Substantially updating beliefs because of an imprecisely estimated prediction error could be maladaptive (22,62), and several authors have posited that the precision of the prediction error could be a key locus of dysfunction in psychosis (27). Haarsma *et al.* (22) found behavioral and brain imaging evidence that patients with early psychosis have learning abnormalities related to the degree of precision weighting of prediction error in the superior frontal cortex. They focused on unsigned prediction error (i.e., prediction error that indicates surprise without valence evaluation, being worse or better than expected), which is often associated with cortical brain activity in human fMRI studies (63). The degree of cortical abnormality was most pronounced in early psychosis and linked to the severity of positive psychotic symptoms, with relatively less impaired cortical function in at-risk patients with fewer symptoms. This pattern fits with the relatively distinct roles of the cortical areas in modulating the level of certainty of an unsigned prediction error estimation, compared with the role of the subcortical areas in signaling signed prediction errors, and hints toward a key role for the cortical function in the progression from the at-risk state to the frank psychotic illness state (Figure 3).

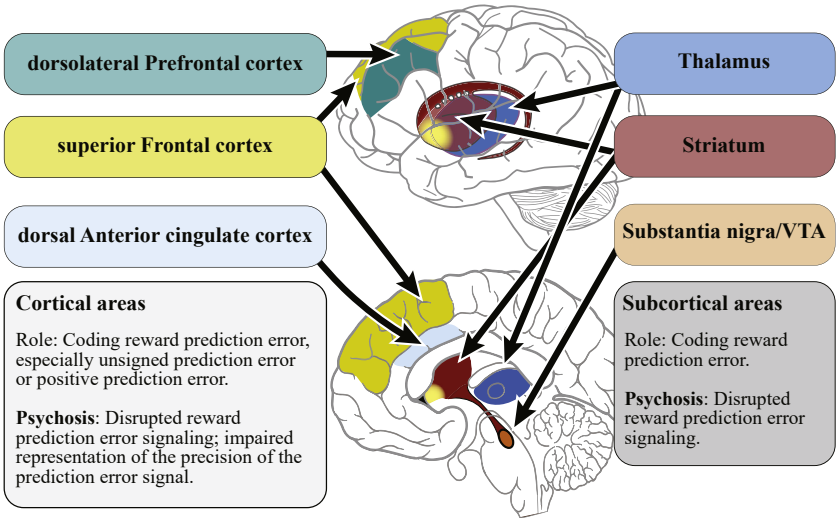

Figure 3. Prediction error areas and psychosis. Simplified diagram of key regions involved in prediction error signaling and underlying problems observed in psychosis. See text for citations and details. VTA, ventral tegmental area.

Prediction Error Signals in Psychosis May Differ Across Illness Stages

We do note that there have been inconsistencies in the literature of prediction error signaling in psychosis. This is reflected in the conflicting accounts of two meta-analyses, one of which found relatively little evidence of abnormal fMRI reward prediction error signals in patients with schizophrenia compared with control subjects, although there were differences between schizophrenia and depression (48,64). Another meta-analysis did document striatal reward prediction error abnormalities in psychosis (65). Some studies that do not show group differences in activation have shown relationships at the interindividual level between striatal activation and the severity of anhedonia (47,66). One theme that may be emerging is that predominantly medicated samples of patients with schizophrenia have relatively intact brain prediction error signals, especially in chronic illness [e.g., (67)], whereas wholly or partly unmedicated samples, especially of early psychosis or schizophrenia, often show brain reward prediction error abnormalities (35,45,50,55), as has been seen previously in the related field of latent inhibition studies in psychosis (56,68).

REWARD PROCESSING IN PSYCHOSIS

Reward describes a range of processes relating to the calculation, computation, and attainment of positive outcomes (69) (Table 2). Reward deficits feature in a variety of psychiatric disorders and are commonly associated with dopamine systems (70,71). Increased negative symptoms in people with psychosis have been associated with decreased function in the ventral striatum in particular (72), but with structural changes in the orbital frontal cortex (73,74) and increased glutamate levels in the anterior cingulate in early psychosis (75). However, a variety of brain areas are involved in reward, and understanding the discrete contributing processes is critical for an appropriate neurobiological interpretation. Growing evidence supports a specific set of problems in patients with psychosis, related primarily to motivation and reinforcement learning.

Table 2. Types of Reward Processes

Process	Role
Anticipation	Increased attention and responsiveness to upcoming rewards. In general, reward anticipation is associated with activation of the striatum, amygdala, and thalamus, and if multiple choices are available, the orbitofrontal and ventromedial prefrontal cortices can also be recruited (137). Within the striatum, the nucleus accumbens is thought to code the expected value, with the dorsal striatum (caudate) more involved in selection, action, and choice (137). Preclinical and human studies indicate that dopamine function is important in reward anticipation (82,138,139), with increasing dopamine tending to increase anticipation toward future rewards (140).
Valuation	Comparison of various reward outcomes. Reward valuation is important in multiple stages of decision-making processes. The areas involved in computing and comparing value include the orbitofrontal cortex, nucleus accumbens, amygdala, and ventromedial prefrontal cortex (119). Initially, a comparison of the various rewards that may be available is required before computing the effort-reward trade-off. Once an outcome is acquired, its value is again assessed and used to update our understanding of the relationships between actions, effort, and reward. This is critical for effective reinforcement learning and generating anticipatory or incentive motivation for future rewards.
Effort and Motivation	Calculation of the effort-reward trade-off. The dorsal striatum is potentially involved in the selection of low-effort choices (141), whereas the nucleus accumbens and anterior cingulate cortex are critical in modulating effort-cost trade-offs (142–144). In healthy people, greater endogenous striatal dopamine function or dopamine-stimulating pharmacological manipulations increase the willingness to expend effort when pursuing rewards (145,146). Preclinical studies have demonstrated that dopamine function in the nucleus accumbens is important in generating the value of work (147), although arguments that dopamine is primarily coding reward value with minimal coding for the required effort have also been put forth (148,149).
Outcome and Outcome-Specific Devaluation	Encoding the presence or absence of a reward and the actual reward value. The areas involved in monitoring and encoding reward outcomes include the nucleus accumbens, orbitofrontal cortex, ventromedial prefrontal cortex, and amygdala (137), although this depends on the specific reward learning task parameters (114). Outcome-specific devaluation is a test of goal-directed action, requiring a participant to adjust, or bias, their actions away from an outcome after it has been devalued. This requires effective reward valuation (one outcome is now less rewarding), reward comparison (between the two possible outcomes), and then using this information to guide action selection.
Learning With a Focus on Reversal Learning	Incorporating reward outcomes and experience to navigate future choices. Many approaches have been used to probe reward learning, but one of the most widely used in psychosis research is probabilistic reversal learning, which requires a participant to navigate trial-by-trial feedback to determine which of two stimuli is rewarded more often. The presence of misleading negative feedback on the better choice (often 80% reward probability), as well as positive feedback on the worse choice (often 20% reward probability), means that the participant cannot rely solely on a "follow the win" strategy. To further probe how adaptable reward learning is, after the participant has successfully demonstrated their knowledge of the correct choice (6–10 consecutive correct trials), the contingencies are reversed. The areas commonly involved in probabilistic reversal learning include the striatum, orbitofrontal cortex, and ventral prefrontal cortex (96,100). Preclinical studies have also shown that dopamine is important for probabilistic reversal learning. For example, systemic amphetamine (a dopamine stimulant) administration in rats alters punishment learning without affecting win-stay use (150). Yet, increasing phasic dopamine signaling in the nucleus accumbens during a choice can increase the tendency to win-stay, even if the choice itself was not rewarded (147). Alternatively, inactivating the nucleus accumbens (shell subregion) decreases win-stay use (151). A range of cortical areas have also been implicated in reward and punishment learning. For example, inactivating or lesioning the prelimbic, infralimbic, and orbitofrontal cortex subregions have all been shown to alter reward or punishment learning during reversal learning in rodents and marmosets (152–154). However, punishment learning may be more sensitive to cortical modulation than reward learning (152,154).

Since its original classification, schizophrenia has been associated with anhedonia (76,77), a deficit in the pleasure received from rewarding or emotional stimuli (78). Anhedonia is a core feature of major depressive disorder (79), and in schizophrenia it has been thought to contribute to broad motivational deficits. For example, if a reward is perceived to be less valuable, then the effort-reward trade-off is biased toward inaction. However, a growing amount of evidence suggests that people with schizophrenia experience the same pleasure from positive emotional and hedonic outcomes (42,80,81). Perceived levels of anhedonia may instead be impairments in other reward processes, such as the anticipatory motivation toward rewarding outcomes (80).

Reward Anticipation

Deficits in reward anticipation have consistently been observed before psychosis onset. For example, a meta-analysis (including six studies in those at risk) observed impairments in those at risk (65), and others have observed similar deficits in early psychosis (82). A combined fMRI and PET study in healthy individuals found that nucleus accumbens dopamine release during reward anticipation was associated with activation of the dorsal striatum, amygdala, hippocampus, and thalamus (83), suggesting that dopamine release in the nucleus accumbens may be causative in recruiting the necessary networks. Multiple meta-analyses have observed reduced activation of the striatum and anterior cingulate cortex in those with schizophrenia [e.g., (65,84)]. Less striatal activation was associated with greater psychotic symptoms (even after controlling for antipsychotic dosage) (84), whereas decreased activation of the nucleus accumbens in those at risk for and with chronic schizophrenia was associated with increased negative symptoms (and not with positive symptoms) (65). There is some evidence that antipsychotic treatment can improve striatal signaling during reward anticipation in people with schizophrenia but only in those who show significantly decreased positive symptoms (85) or when treated with atypical antipsychotics (86). However, the relationship between antipsychotic treatment, negative symptoms, and reward anticipation may be more complicated (87). Furthermore, impairments in reward anticipation may be an early developmental trait preceding psychosis onset. For example, Vink *et al.* (88) found that nucleus accumbens activation during reward anticipation decreased across adolescence in the children of people with schizophrenia (i.e., carrying a higher familial risk of developing psychosis) but not in the children of healthy control subjects. Conversely, it has been suggested that reduced anticipatory motivation may be a byproduct of a decreased ability to accurately maintain value representation (89) or reward learning, more generally (90).

Avolition and Effort-Reward Trade-offs

Another primary negative symptom thought to reflect reward impairments is avolition, or a lack of willingness to do tasks required for achieving a goal. Decreased motivation is evident in self-reports in those with early psychosis (91), and there is strong evidence that people with schizophrenia are less motivated and less willing to expend the same effort to attain rewards as healthy individuals (72,92). For example, people with schizophrenia reached breakpoint earlier on a progressive ratio task (93). In the progressive ratio task, the effort required to get a reward increases with each reward delivery, and the breakpoint refers to the point at which participants decide that the effort-reward trade-off is no longer worthwhile. This performance deficit was associated with greater amotivation scores and decreased ventral striatal function (93). Decreases in motivation and willingness to work toward goals may be specific to certain types of rewards and the required efforts. For example, those with early psychosis were less likely to select the high-effort, high-reward options than healthy control subjects (94). Furthermore, in a task in which increasing the effort improved the chance of receiving a high or low reward, people with schizophrenia were willing to expend the same effort regardless of reward size, whereas healthy individuals heavily biased their effort to increase the chance of higher rewards (95). This was associated with reduced functional changes in the caudate and anterior cingulate cortex during reward presentation and in the caudate during effort selection.

Goal-Directed Actions and Reward

In parallel to motivational and effort-based impairments, people with schizophrenia are less able to use reward information correctly when guiding their actions (89). A good example is the result obtained when patients with schizophrenia carry out outcome-specific devaluation tasks (96,97). Morris *et al.* (98,99) demonstrated that people with schizophrenia were able to understand that one outcome was worth less after devaluation but failed to alter their actions in response to this information. Our work suggests that this may occur in a specific subgroup of those with chronic psychosis and is less likely to be observed in early psychosis (97). These goal-directed action impairments were due to the inability to correctly relate outcomes causally to actions rather than problems in reward valuation (99). Disruptions in caudate function, but not PFC function, were associated with the deficit in responding toward the more valuable outcome (98). The observed decreases in caudate function during responses in those with schizophrenia were associated with increased negative symptom severity (including avolition) (98). Furthermore, impairments in the ability to causally relate action-outcome associations were accompanied by increased overall disability scores (100). Preclinical studies have highlighted that striatal dopamine is important in establishing causal action-outcome associations and in action selection (101,102). Whether these impairments are evident at earlier disease stages is not known, but they likely reflect impairments in reward learning rather than reward valuation.

Cognitive Control and Risk

Imaging studies focused on cognitive control have indicated that across adolescence there is a marked improvement in our ability to increase cognitive performance directed at higher reward or risk. This may contribute to impairments in effort allocation in psychosis (103). Higher stakes recruit striatal, ventrolateral PFC, thalamic, and anterior cingulate areas more so than low-stakes trials (104). Moreover, the nucleus accumbens functional coupling was greatest with the dorsal striatum in young adolescents but shifted to the ventrolateral

PFC with increased age (104). Model-based reward learning is positively associated with nucleus accumbens dopamine synthesis and activation of the nucleus accumbens and lateral PFC (105). In unmedicated patients with schizophrenia who follow similar reinforcement learning strategies as control subjects, decreased nucleus accumbens activation has been observed (55), but in those who do not follow the same strategies (i.e., poorer performers), decreased activation of both the nucleus accumbens and ventrolateral PFC has been observed (55), suggesting that model-based circuitry may be dysfunctional. In another study looking at high-reward/risk comparisons, caudate and dorsolateral prefrontal coupling increased with age (106). This may indicate that when comparing reward values in choice situations, the maturation of corticostriatal systems critical for focusing cognitive effort are impaired or delayed in people with psychosis. Evidence of functional connectivity alterations in those with early psychosis and chronic schizophrenia demonstrates progressive deviation from healthy control subjects (107), showing large alterations in functional connectivity in the thalamus, anterior cingulate cortex, and striatum (107). However, other studies have demonstrated more widespread connectivity changes in unmedicated people with early psychosis, with changes in limbic circuits still pronounced (108). Improvements in thalamocortical connectivity were associated with antipsychotic treatment, suggesting that medication status is important when interpreting changes in functional connectivity.

Reward Learning

There is ample evidence that reward learning, or reinforcement learning, is altered in psychosis. Deficits in reward learning have been associated with higher general symptoms (109) and negative symptoms (66,110). For example, people with schizophrenia tend to place more emphasis on immediate rewards, even when these choices are less advantageous over time (109). Furthermore, psychosis is associated with jumping to conclusions, whereby those with psychosis are more likely to update their beliefs using less information [e.g., (111,112)]. A study in those at risk suggested that this reasoning bias develops with the onset of psychosis and may not be evident beforehand (113). Decreased activation of the nucleus accumbens, anterior cingulate cortex, and dorsolateral PFC has been associated with impaired reward learning in those with schizophrenia (90,114). One consistently reported behavioral tendency in schizophrenia is reduced win-stay use in reversal learning tasks (50,66,97,110,115). Win-stay refers to a participant selecting the same stimulus after winning a reward on the prior trial. Poorer reversal learning performance in unmedicated people with schizophrenia has been associated with decreased activation of the ventrolateral PFC and nucleus accumbens (55). Decreased win-stay use has been observed in the Wisconsin Card Sorting Test (116), which features a greater number of stimuli and contingencies. Deficits in social reward learning (117) provide evidence of how these deficits can increase the functional burden of those with schizophrenia. Overall, it appears that people with schizophrenia are less able to use rewarding feedback to guide learning. Working memory deficits may also present as impaired reward learning processes, which has been demonstrated using task-based and computational modeling–based approaches in those with schizophrenia (118). However, other studies suggest that learning impairments in psychosis are often not explained by deficits in working memory (119–121). These conflicting studies suggest that reinforcement learning deficits may not be a universal core trait in psychosis but rather a feature in a large subgroup of those with psychosis. Deficits in reinforcement learning are observed in those at risk for psychosis (58) and with early psychosis (122,123). Those at risk for psychosis exhibited less activation of the nucleus accumbens and ventromedial PFC in reward processing (58). In contrast, reinforcement learning studies conducted in those with early psychosis suggest that deficits may include punishment learning, specifically a decreased sensitivity to punishment (97,123). However, reversal learning impairments in early psychosis are less robust than in those with persistent schizophrenia, with some studies observing relatively intact performance (118,122). Clearly more work, including longitudinal studies, is required to determine what reversal learning indices in those at risk for psychosis or with early psychosis mean for subsequent outcomes (both diagnostically and in terms of treatment efficacy).

Reward Systems in Psychosis

Overall, schizophrenia is associated with a broad group of reward deficits spread across multiple brain areas (Figure 4). These include anticipatory and effort-related motivation, reward-based decision making, and reward learning. Nevertheless, all of these processes rely heavily on corticostriatal circuitry, which corroborates well-known alterations in striatal dopamine function (65,90,100) and changes in cortical structure and function (96,107,108).

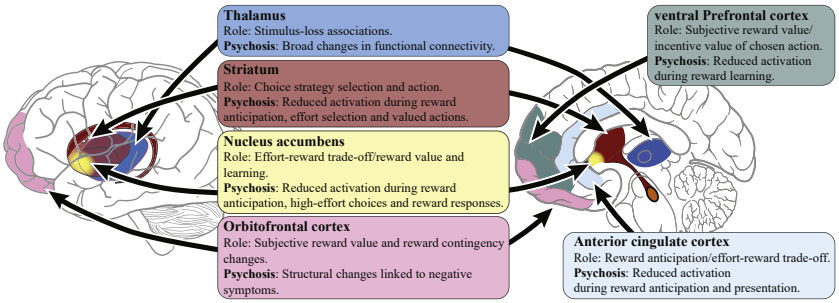

Figure 4. Reward areas and psychosis. Simplified diagram of key regions involved in reward processing and underlying problems observed in psychosis. Impairments tend to be less obvious in earlier disease stages or, in the case of reward/punishment learning, may actually be in opposition. See text for citations and details.

SALIENCE AND REWARD ACROSS THE PSYCHOSIS SPECTRUM

Our review is based heavily on cross-sectional data using different experimental paradigms. Although not surprising, this highlights the need for focused longitudinal studies to track how these processes change across illness stages. Nevertheless, a picture is emerging over several studies showing that cortical function during reward and salience processing is impaired in psychotic illness (established/chronic schizophrenia), especially in the ventral and dorsolateral PFC and the anterior cingulate cortex, but relatively spared in the earliest stages of psychosis (Figure 5). However, there is evidence of subcortical reward and salience dysfunction in at-risk patients, consistent with PET studies showing dopaminergic abnormalities, especially increased levels of striatal dopamine (59), early in the course of illness. In psychosis, antipsychotic medication may normalize some learning abnormalities and learning-related brain signals, such as prediction error signals (61), potentially explaining the alleviating effects on positive symptoms. We suggest that subcortical reward and salience dysfunction may be an early manifestation of the illness, with cortical abnormalities in these domains becoming more prominent as the illness progresses. This contrasts with the hypotheses of schizophrenia that have proposed the primary abnormalities as being cortical in origin, which proceed and/or induce subcortical dopamine dysfunction (120). However, our proposal is consistent with some animal models that show proof of principle for cortical dysfunction secondary to primary subcortical lesions (121) or developmental changes in subcortical dopamine systems (124).

Translational Potential

There are several potentially helpful new interventions at various stages of development, highly relevant for reward and salience processing domains in psychosis. For example, the behavioral intervention of cognitive remediation therapy has already been shown to be capable of modulating the aspects of reinforcement learning, such as sensitivity to rewards and punishments (125). Moreover, reward learning can be used to improve attentiveness during conversational skill learning relevant for everyday functioning, improving outcomes (126). Pharmacological interventions at numerous molecular targets are of interest in the treatment of cognitive deficits in schizophrenia, including reinforcement learning domains, and could potentially be combined with cognitive remediation interventions (127). A relevant line of inquiry in the rodent models advanced by Grace *et al.* (128) indicates that administration of prepubertal benzodiazepines mitigates the deleterious effect of perinatal or adolescent insults that otherwise lead to a hyperdopaminergic state directly relevant for salience processing. Recent advances in noninvasive brain stimulation also show potential for modulating brain circuits discussed in this article; for example, transcranial-focused ultrasound appears to be well tolerated in humans and has recently been shown to have the potential to target not only cortical but also subcortical structures and thus potentially to modulate brain activations in networks throughout the brain (129). fMRI-based techniques that draw on real-time fMRI signal decoding and neurofeedback are under investigation regarding their ability to influence various psychological states, including addressing symptom domains in schizophrenia [e.g., reduction of auditory hallucinations (130)], and merit further investigation. To fully realize the potential benefits of novel brain stimulation technology, we need to accelerate our understanding of the causal relationships between brain circuits and behavior in patients.

CONCLUSIONS

Together, salience and reward processes are integral to engaging our attention, stimulating anticipation of future

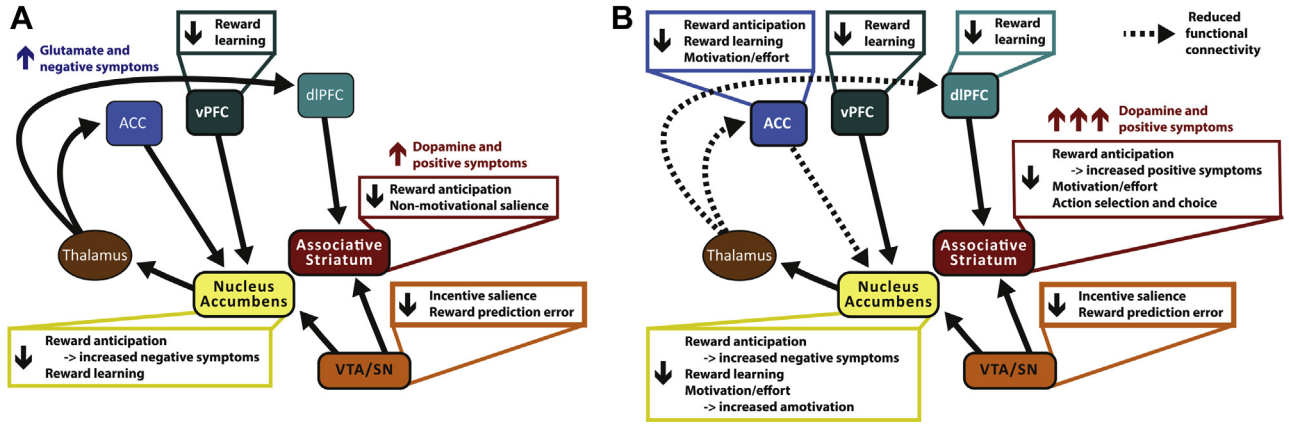

Figure 5. Neurochemical and functional imaging associations with salience and reward processing in those at risk for and in early psychosis compared with **(A)** chronic psychosis and **(B)** schizophrenia. Colored arrows reflect key neurochemical changes, and black arrows indicate functional magnetic resonance imaging changes in those with psychosis and their associated behavior. Evidence of salience and reward impairments in those at risk for and in early psychosis are commonly found in subcortical structures, such as the associative striatum, nucleus accumbens, ventral tegmental area (VTA), and substantia nigra (SN). However, evidence of cortical glutamatergic abnormalities in the anterior cingulate cortex (ACC) have been observed. In contrast, there is evidence of widespread functional impairments in those with chronic psychosis or schizophrenia. This includes reduced functional connectivity in thalamocortical and corticostriatal projections (dashed lines) and reduced functional activity during salience and reward processing in the ACC, ventral prefrontal cortex (vPFC), and dorsolateral PFC (dlPFC). Therefore, it may be that subcortical alterations precede cortical impairments in driving negative symptoms and deficits in salience and reward processing.

events, and driving goal-directed behaviors. In this review, we have summarized the current knowledge of behavioral and functional neuroimaging in salience, reward, and prediction error. Although they are specific processes, they interact in multiple feedback and feedforward systems essential for decision making and cognition more generally. Further studies focused on subcortical systems during adolescence and the transition to psychosis are warranted.

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REFERENCES

1. McCutcheon RA, Reis Marques T, Howes OD (2020): Schizophrenia-An overview. JAMA Psychiatry 77:201–210.
2. Howes OD, Egerton A, Allan V, McGuire P, Stokes P, Kapur S (2009): Mechanisms underlying psychosis and antipsychotic treatment response in schizophrenia: Insights from PET and SPECT imaging. Curr Pharm Des 15:2550–2559.
3. Howes OD, Montgomery AJ, Asselin MC, Murray RM, Valli I, Tabraham P, *et al.* (2009): Elevated striatal dopamine function linked to prodromal signs of schizophrenia. Arch Gen Psychiatry 66:13–20.
4. Kapur S, Mamo D (2003): Half a century of antipsychotics and still a central role for dopamine D2 receptors. Prog Neuropsychopharmacol Biol Psychiatry 27:1081–1090.
5. Nucifora FC Jr, Woznica E, Lee BJ, Cascella N, Sawa A (2019): Treatment resistant schizophrenia: Clinical, biological, and therapeutic perspectives. Neurobiol Dis 131:104257.
6. Demjaha A, Egerton A, Murray RM, Kapur S, Howes OD, Stone JM, McGuire PK (2014): Antipsychotic treatment resistance in schizophrenia associated with elevated glutamate levels but normal dopamine function. Biol Psychiatry 75:e11–e13.
7. Uno Y, Coyle JT (2019): Glutamate hypothesis in schizophrenia. Psychiatry Clin Neurosci 73:204–215.
8. Winton-Brown TT, Fusar-Poli P, Ungless MA, Howes OD (2014): Dopaminergic basis of salience dysregulation in psychosis. Trends Neurosci 37:85–94.
9. Abboud R, Roiser JP, Khalifeh H, Ali S, Harrison I, Killaspy HT, Joyce EM (2016): Are persistent delusions in schizophrenia associated with aberrant salience? Schizophr Res Cogn 4:32–38.
10. Murray GK, Corlett PR, Fletcher PC (2010): The neural underpinnings of associative learning in health and psychosis: How can performance be preserved when brain responses are abnormal? Schizophr Bull 36:465–471.
11. Corlett PR, Murray GK, Honey GD, Aitken MRF, Shanks DR, Robbins TW, *et al.* (2007): Disrupted prediction-error signal in psychosis: Evidence for an associative account of delusions. Brain 130:2387–2400.
12. Maia TV, Frank MJ (2017): An integrative perspective on the role of dopamine in schizophrenia. Biol Psychiatry 81:52–66.
13. Howes OD, Nour MM (2016): Dopamine and the aberrant salience hypothesis of schizophrenia. World Psychiatry 15:3–4.
14. Kapur S (2003): Psychosis as a state of aberrant salience: A framework linking biology, phenomenology, and pharmacology in schizophrenia. Am J Psychiatry 160:13–23.
15. Heinz A (2002): Dopaminergic dysfunction in alcoholism and schizophrenia—Psychopathological and behavioral correlates. Eur Psychiatry 17:9–16.
16. Fusar-Poli P, Meyer-Lindenberg A (2013): Striatal presynaptic dopamine in schizophrenia, part II: Meta-analysis of [(18)F/(11)C]-DOPA PET studies. Schizophr Bull 39:33–42.
17. Corlett PR, Honey GD, Fletcher PC (2007): From prediction error to psychosis: Ketamine as a pharmacological model of delusions. J Psychopharmacol 21:238–252.
18. Schultz W (1998): Predictive reward signal of dopamine neurons. J Neurophysiol 80:1–27.
19. Schultz W (2016): Dopamine reward prediction-error signalling: A two-component response. Nat Rev Neurosci 17:183–195.
20. Horvitz JC (2000): Mesolimbocortical and nigrostriatal dopamine responses to salient non− reward events. Neuroscience 96:651–656.
21. Bunzeck N, Doeller CF, Dolan RJ, Duzel E (2012): Contextual interaction between novelty and reward processing within the mesolimbic system. Hum Brain Mapp 33:1309–1324.
22. Haarsma J, Fletcher PC, Griffin JD, Taverne HJ, Ziauddeen H, Spencer TJ, *et al.* (2021): Precision weighting of cortical unsigned prediction error signals benefits learning, is mediated by dopamine, and is impaired in psychosis [published correction appears in Mol Psychiatry 2021; 26:5334]. Mol Psychiatry 26:5320–5333.
23. Valdés-Baizabal C, Carbajal GV, Pérez-González D, Malmierca MS (2020): Dopamine modulates subcortical responses to surprising sounds [published correction appears in PLoS Biol 2020; 18: e3000984]. PLoS Biol 18:e3000744.
24. Bromberg-Martin ES, Matsumoto M, Hikosaka O (2010): Dopamine in motivational control: Rewarding, aversive, and alerting. Neuron 68:815–834.
25. Roiser JP, Stephan KE, Den Ouden HEM, Barnes TRE, Friston KJ, Joyce EM (2009): Do patients with schizophrenia exhibit aberrant salience? Psychol Med 39:199–209.
26. Roiser JP, Howes OD, Chaddock CA, Joyce EM, McGuire P (2013): Neural and behavioral correlates of aberrant salience in individuals at risk for psychosis [published correction appears in Schizphr Bull 2016; 42:1303]. Schizophr Bull 39:1328–1336.
27. Katthagen T, Mathys C, Deserno L, Walter H, Kathmann N, Heinz A, Schlagenhauf F (2018): Modeling subjective relevance in schizophrenia and its relation to aberrant salience. PLoS Comput Biol 14: e1006319.
28. Demjaha A, Murray RM, McGuire PK, Kapur S, Howes OD (2012): Dopamine synthesis capacity in patients with treatment-resistant schizophrenia. Am J Psychiatry 169:1203–1210.
29. Howes OD, Kambeitz J, Kim E, Stahl D, Slifstein M, Abi-Dargham A, Kapur S (2012): The nature of dopamine dysfunction in schizophrenia and what this means for treatment. Arch Gen Psychiatry 69:776–786.
30. Ceaser AE, Barch DM (2016): Striatal activity is associated with deficits of cognitive control and aberrant salience for patients with schizophrenia. Front Hum Neurosci 9:687.
31. Potvin S, Tikàsz A, Mendrek A (2016): Emotionally neutral stimuli are not neutral in schizophrenia: A mini review of functional neuroimaging studies. Front Psychiatry 7:115.
32. Alfimova MV, Uvarova LG (2008): Changes in EEG spectral power on perception of neutral and emotional words in patients with schizophrenia, their relatives, and healthy subjects from the general population. Neurosci Behav Physiol 38:533–540.
33. Morris R, Griffiths O, Le Pelley ME, Weickert TW (2013): Attention to irrelevant cues is related to positive symptoms in schizophrenia. Schizophr Bull 39:575–582.

34. Li LY, Castro MK, Martin EA (2020): What you want may not be what you like: A test of the aberrant salience hypothesis in schizophrenia risk. Cogn Affect Behav Neurosci 20:873–887.
35. Knolle F, Ermakova AO, Justicia A, Fletcher PC, Bunzeck N, Düzel E, Murray GK (2018): Brain responses to different types of salience in antipsychotic naïve first episode psychosis: An fMRI study. Transl Psychiatry 8:196.
36. Bunzeck N, Düzel E (2006): Absolute coding of stimulus novelty in the human substantia nigra/VTA. Neuron 51:369–379.
37. Modinos G, Allen P, Zugman A, Dima D, Azis M, Samson C, *et al.* (2020): Neural circuitry of novelty salience processing in psychosis risk: Association with clinical outcome. Schizophr Bull 46:670–679.
38. Knolle F, Garofalo S, Viviani R, Justicia A, Ermakova AO, Blank H, *et al.* (2020): Altered subcortical emotional salience processing differentiates Parkinson's patients with and without psychotic symptoms. Neuroimage Clin 27:102277.
39. Savla GN, Vella L, Armstrong CC, Penn DL, Twamley EW (2013): Deficits in domains of social cognition in schizophrenia: A meta-analysis of the empirical evidence. Schizophr Bull 39:979–992.
40. Taylor SF, Phan KL, Britton JC, Liberzon I (2005): Neural response to emotional salience in schizophrenia. Neuropsychopharmacology 30:984–995.
41. Haralanova E, Haralanov S, Beraldi A, Möller HJ, Hennig-Fast K (2012): Subjective emotional over-arousal to neutral social scenes in paranoid schizophrenia. Eur Arch Psychiatry Clin Neurosci 262:59–68.
42. Llerena K, Strauss GP, Cohen AS (2012): Looking at the other side of the coin: A meta-analysis of self-reported emotional arousal in people with schizophrenia. Schizophr Res 142:65–70.
43. Tang Y, Wang J, Zhang T, Xu L, Qian Z, Cui H, *et al.* (2020): P300 as an index of transition to psychosis and of remission: Data from a clinical high risk for psychosis study and review of literature. Schizophr Res 226:74–83.
44. Boehme R, Deserno L, Gleich T, Katthagen T, Pankow A, Behr J, *et al.* (2015): Aberrant salience is related to reduced reinforcement learning signals and elevated dopamine synthesis capacity in healthy adults. J Neurosci 35:10103–10111.
45. Murray GK, Corlett PR, Clark L, Pessiglione M, Blackwell AD, Honey G, *et al.* (2008): Substantia nigra/ventral tegmental reward prediction error disruption in psychosis. Mol Psychiatry 13:239, 267–276.
46. Ermakova AO, Knolle F, Justicia A, Bullmore ET, Jones PB, Robbins TW, *et al.* (2018): Abnormal reward prediction-error signalling in antipsychotic naive individuals with first-episode psychosis or clinical risk for psychosis. Neuropsychopharmacology 43:1691–1699.
47. Dowd EC, Barch DM (2012): Pavlovian reward prediction and receipt in schizophrenia: Relationship to anhedonia. PLoS One 7:e35622.
48. Strauss GP, Waltz JA, Gold JM (2014): A review of reward processing and motivational impairment in schizophrenia. Schizophr Bull 40(suppl 2):S107–S116.
49. Waltz JA, Schweitzer JB, Gold JM, Kurup PK, Ross TJ, Salmeron BJ, *et al.* (2009): Patients with schizophrenia have a reduced neural response to both unpredictable and predictable primary reinforcers. Neuropsychopharmacology 34:1567–1577.
50. Katthagen T, Kaminski J, Heinz A, Buchert R, Schlagenhauf F (2020): Striatal dopamine and reward prediction error signaling in unmedicated schizophrenia patients. Schizophr Bull 46:1535–1546.
51. Smieskova R, Roiser JP, Chaddock CA, Schmidt A, Harrisberger F, Bendfeldt K, *et al.* (2015): Modulation of motivational salience processing during the early stages of psychosis. Schizophr Res 166:17–23.
52. Diederen KMJ, Fletcher PC (2021): Dopamine, prediction error and beyond. Neuroscientist 27:30–46.
53. Gradin VB, Kumar P, Waiter G, Ahearn T, Stickle C, Milders M, *et al.* (2011): Expected value and prediction error abnormalities in depression and schizophrenia. Brain 134:1751–1764.
54. Morris RW, Vercammen A, Lenroot R, Moore L, Langton JM, Short B, *et al.* (2012): Disambiguating ventral striatum fMRI-related BOLD signal during reward prediction in schizophrenia. Mol Psychiatry 17:235, 280–289.
55. Schlagenhauf F, Huys QJM, Deserno L, Rapp MA, Beck A, Heinze HJ, *et al.* (2014): Striatal dysfunction during reversal learning in unmedicated schizophrenia patients. Neuroimage 89:171–180.
56. Gray JA (1998): Integrating schizophrenia. Schizophr Bull 24:249–266.
57. Corlett PR, Honey GD, Aitken MRF, Dickinson A, Shanks DR, Absalom AR, *et al.* (2006): Frontal responses during learning predict vulnerability to the psychotogenic effects of ketamine: Linking cognition, brain activity, and psychosis. Arch Gen Psychiatry 63:611–621.
58. Millman ZB, Gallagher K, Demro C, Schiffman J, Reeves GM, Gold JM, *et al.* (2020): Evidence of reward system dysfunction in youth at clinical high-risk for psychosis from two event-related fMRI paradigms. Schizophr Res 226:111–119.
59. Howes OD, Bose SK, Turkheimer F, Valli I, Egerton A, Valmaggia LR, *et al.* (2011): Dopamine synthesis capacity before onset of psychosis: A prospective [18F]-DOPA PET imaging study. Am J Psychiatry 168:1311–1317.
60. Bernacer J, Corlett PR, Ramachandra P, McFarlane B, Turner DC, Clark L, *et al.* (2013): Methamphetamine-induced disruption of frontostriatal reward learning signals: Relation to psychotic symptoms. Am J Psychiatry 170:1326–1334.
61. Nielsen MO, Rostrup E, Wulff S, Bak N, Broberg BV, Lublin H, *et al.* (2012): Improvement of brain reward abnormalities by antipsychotic monotherapy in schizophrenia. Arch Gen Psychiatry 69:1195–1204.
62. Diederen KMJ, Spencer T, Vestergaard MD, Fletcher PC, Schultz W (2016): Adaptive prediction error coding in the human midbrain and striatum facilitates behavioral adaptation and learning efficiency. Neuron 90:1127–1138.
63. Corlett PR, Mollick JA, Kober H (2021): Substrates of human prediction error for incentives, perception, cognition, and action. PsyArXiv. https://doi.org/10.31234/osf.io/pf89k.
64. Yaple ZA, Tolomeo S, Yu R (2021): Abnormal prediction error processing in schizophrenia and depression. Hum Brain Mapp 42:3547–3560.
65. Radua J, Schmidt A, Borgwardt S, Heinz A, Schlagenhauf F, McGuire P, Fusar-Poli P (2015): Ventral striatal activation during reward processing in psychosis: A neurofunctional meta-analysis. JAMA Psychiatry 72:1243–1251.
66. Waltz JA, Kasanova Z, Ross TJ, Salmeron BJ, McMahon RP, Gold JM, Stein EA (2013): The roles of reward, default, and executive control networks in set-shifting impairments in schizophrenia. PLoS One 8:e57257.
67. Hernaus D, Xu Z, Brown EC, Ruiz R, Frank MJ, Gold JM, Waltz JA (2018): Motivational deficits in schizophrenia relate to abnormalities in cortical learning rate signals. Cogn Affect Behav Neurosci 18:1338–1351.
68. Martins Serra A, Jones SH, Toone B, Gray JA (2001): Impaired associative learning in chronic schizophrenics and their first-degree relatives: A study of latent inhibition and the Kamin blocking effect. Schizophr Res 48:273–289.
69. Der-Avakian A, Barnes SA, Markou A, Pizzagalli DA (2016): Translational assessment of reward and motivational deficits in psychiatric disorders. In: Robbins TW, Sahakian BJ, editors. Translational Neuropsychopharmacology. Cham, Germany: Springer International Publishing, 231–262.
70. Wise RA (2004): Dopamine, learning and motivation. Nat Rev Neurosci 5:483–494.
71. Kesby JP, Chang A, Markou A, Semenova S (2018): Modeling human methamphetamine use patterns in mice: Chronic and binge methamphetamine exposure, reward function and neurochemistry. Addict Biol 23:206–218.
72. Culbreth AJ, Moran EK, Kandala S, Westbrook A, Barch DM (2020): Effort, avolition and motivational experience in schizophrenia: Analysis of behavioral and neuroimaging data with relationships to daily motivational experience. Clin Psychol Sci 8:555–568.

73. Baaré WF, Hulshoff Pol HE, Hijman R, Mali WP, Viergever MA, Kahn RS (1999): Volumetric analysis of frontal lobe regions in schizophrenia: Relation to cognitive function and symptomatology. Biol Psychiatry 45:1597–1605.
74. Lacerda ALT, Hardan AY, Yorbik O, Vemulapalli M, Prasad KM, Keshavan MS (2007): Morphology of the orbitofrontal cortex in first-episode schizophrenia: Relationship with negative symptomatology. Prog Neuropsychopharmacol Biol Psychiatry 31:510–516.
75. Egerton A, Brugger S, Raffin M, Barker GJ, Lythgoe DJ, McGuire PK, Stone JM (2012): Anterior cingulate glutamate levels related to clinical status following treatment in first-episode schizophrenia. Neuropsychopharmacology 37:2515–2521.
76. Kraepelin E (1919): Dementia Praecox and Paraphrenia. Chicago: Chicago Medical Book Company.
77. Bleuler E (1950): Dementia Praecox or the Group of Schizophrenias. New York: International Universities Press.
78. Kring AM, Germans MK (2000): Anhedonia. In: Kazdin AE, editor. Encyclopedia of Psychology. New York: Oxford University Press, 174–175.
79. American Psychiatric Association (2013): Diagnostic and Statistical Manual of Mental Disorders, DSM-5. Washington, DC: American Psychiatric Publishing.
80. Gard DE, Kring AM, Gard MG, Horan WP, Green MF (2007): Anhedonia in schizophrenia: Distinctions between anticipatory and consummatory pleasure. Schizophr Res 93:253–260.
81. Vignapiano A, Mucci A, Ford J, Montefusco V, Plescia GM, Bucci P, Galderisi S (2016): Reward anticipation and trait anhedonia: An electrophysiological investigation in subjects with schizophrenia. Clin Neurophysiol 127:2149–2160.
82. Murray GK, Clark L, Corlett PR, Blackwell AD, Cools R, Jones PB, *et al.* (2008): Incentive motivation in first-episode psychosis: A behavioural study. BMC Psychiatry 8:34.
83. Schott BH, Minuzzi L, Krebs RM, Elmenhorst D, Lang M, Winz OH, *et al.* (2008): Mesolimbic functional magnetic resonance imaging activations during reward anticipation correlate with reward-related ventral striatal dopamine release. J Neurosci 28:14311–14319.
84. Leroy A, Amad A, D'Hondt F, Pins D, Jaafari N, Thomas P, Jardri R (2020): Reward anticipation in schizophrenia: A coordinate-based meta-analysis. Schizophr Res 218:2–6.
85. Wulff S, Nielsen MØ., Rostrup E, Svarer C, Jensen LT, Pinborg L, Glenthøj BY (2020): The relation between dopamine D2 receptor blockade and the brain reward system: A longitudinal study of first-episode schizophrenia patients. Psychol Med 50:220–228.
86. Juckel G, Schlagenhauf F, Koslowski M, Filonov D, Wüstenberg T, Villringer A, *et al.* (2006): Dysfunction of ventral striatal reward prediction in schizophrenic patients treated with typical, not atypical, neuroleptics. Psychopharmacol (Berl) 187:222–228.
87. Nielsen MØ., Rostrup E, Broberg BV, Wulff S, Glenthøj B (2018): Negative symptoms and reward disturbances in schizophrenia before and after antipsychotic monotherapy. Clin EEG Neurosci 49:36–45.
88. Vink M, de Leeuw M, Pouwels R, van den Munkhof HE, Kahn RS, Hillegers M (2016): Diminishing striatal activation across adolescent development during reward anticipation in offspring of schizophrenia patients. Schizophr Res 170:73–79.
89. Gold JM, Waltz JA, Prentice KJ, Morris SE, Heerey EA (2008): Reward processing in schizophrenia: A deficit in the representation of value. Schizophr Bull 34:835–847.
90. Chase HW, Loriemi P, Wensing T, Eickhoff SB, Nickl-Jockschat T (2018): Meta-analytic evidence for altered mesolimbic responses to reward in schizophrenia. Hum Brain Mapp 39:2917–2928.
91. Fervaha G, Takeuchi H, Foussias G, Hahn MK, Agid O, Remington G (2018): Achievement motivation in early schizophrenia: Relationship with symptoms, cognition and functional outcome. Early Interv Psychiatry 12:1038–1044.
92. Green MF, Horan WP, Barch DM, Gold JM (2015): Effort-based decision making: A novel approach for assessing motivation in schizophrenia. Schizophr Bull 41:1035–1044.
93. Wolf DH, Satterthwaite TD, Kantrowitz JJ, Katchmar N, Vandekar L, Elliott MA, Ruparel K (2014): Amotivation in schizophrenia: Integrated assessment with behavioral, clinical, and imaging measures. Schizophr Bull 40:1328–1337.
94. Chang WC, Chu AOK, Treadway MT, Strauss GP, Chan SKW, Lee EHM, *et al.* (2019): Effort-based decision-making impairment in patients with clinically stabilized first-episode psychosis and its relationship with amotivation and psychosocial functioning. Eur Neuropsychopharmacol 29:629–642.
95. Pretus C, Bergé D, Guell X, Pérez V, Vilarroya Ó. (2021): Brain activity and connectivity differences in reward value discrimination during effort computation in schizophrenia. Eur Arch Psychiatry Clin Neurosci 271:647–659.
96. Conn KA, Burne THJ, Kesby JP (2020): Subcortical dopamine and cognition in schizophrenia: Looking beyond psychosis in preclinical models. Front Neurosci 14:542.
97. Suetani S, Baker A, Garner K, Cosgrove P, Mackay-Sim M, Siskind D, *et al.* (2022): Impairments in goal-directed action and reversal learning in a proportion of individuals with psychosis. Cogn Affect Behav Neurosci 22:1390–1403.
98. Morris RW, Quail S, Griffiths KR, Green MJ, Balleine BW (2015): Corticostriatal control of goal-directed action is impaired in schizophrenia. Biol Psychiatry 77:187–195.
99. Morris RW, Cyrzon C, Green MJ, Le Pelley ME, Balleine BW (2018): Impairments in action–outcome learning in schizophrenia. Transl Psychiatry 8:54.
100. Kesby JP, Eyles DW, McGrath JJ, Scott JG (2018): Dopamine, psychosis and schizophrenia: The widening gap between basic and clinical neuroscience. Transl Psychiatry 8:30.
101. Lex B, Hauber W (2010): The role of dopamine in the prelimbic cortex and the dorsomedial striatum in instrumental conditioning. Cereb Cortex 20:873–883.
102. Howard CD, Li H, Geddes CE, Jin X (2017): Dynamic nigrostriatal dopamine biases action selection. Neuron 93:1436–1450.e8.
103. Culbreth AJ, Moran EK, Barch DM (2018): Effort-cost decision-making in psychosis and depression: Could a similar behavioral deficit arise from disparate psychological and neural mechanisms? Psychol Med 48:889–904.
104. Insel C, Kastman EK, Glenn CR, Somerville LH (2017): Development of corticostriatal connectivity constrains goal-directed behavior during adolescence. Nat Commun 8:1605.
105. Deserno L, Huys QJM, Boehme R, Buchert R, Heinze HJ, Grace AA, *et al.* (2015): Ventral striatal dopamine reflects behavioral and neural signatures of model-based control during sequential decision making. Proc Natl Acad Sci U S A 112:1595–1600.
106. Insel C, Charifson M, Somerville LH (2019): Neurodevelopmental shifts in learned value transfer on cognitive control during adolescence. Dev Cogn Neurosci 40:100730.
107. Li T, Wang Q, Zhang J, Rolls ET, Yang W, Palaniyappan L, *et al.* (2017): Brain-wide analysis of functional connectivity in first-episode and chronic stages of schizophrenia. Schizophr Bull 43:436–448.
108. Chopra S, Francey SM, O'Donoghue B, Sabaroedin K, Arnatkeviciute A, Cropley V, *et al.* (2021): Functional connectivity in antipsychotic-treated and antipsychotic-naive patients with first-episode psychosis and low risk of self-harm or aggression: A secondary analysis of a randomized clinical trial. JAMA Psychiatry 78:994–1004.
109. Betz LT, Brambilla P, Ilankovic A, Premkumar P, Kim MS, Raffard S, *et al.* (2019): Deciphering reward-based decision-making in schizophrenia: A meta-analysis and behavioral modeling of the Iowa Gambling Task. Schizophr Res 204:7–15.
110. Reddy LF, Waltz JA, Green MF, Wynn JK, Horan WP (2016): Probabilistic reversal learning in schizophrenia: Stability of deficits and potential causal mechanisms. Schizophr Bull 42:942–951.
111. Henquet C, van Os J, Pries LK, Rauschenberg C, Delespaul P, Kenis G, *et al.* (2022): A replication study of JTC bias, genetic liability for psychosis and delusional ideation. Psychol Med 52:1777–1783.

112. Ermakova AO, Gileadi N, Knolle F, Justicia A, Anderson R, Fletcher PC, *et al.* (2019): Cost evaluation during decision-making in patients at early stages of psychosis. Comput Psychiatr 3:18–39.
113. Catalan A, Tognin S, Kempton MJ, Stahl D, Salazar de Pablo G, Nelson B, *et al.* (2020): Relationship between jumping to conclusions and clinical outcomes in people at clinical high-risk for psychosis. Psychol Med 1–9.
114. Koch K, Schachtzabel C, Wagner G, Schikora J, Schultz C, Reichenbach JR, *et al.* (2010): Altered activation in association with reward-related trial-and-error learning in patients with schizophrenia. Neuroimage 50:223–232.
115. Deserno L, Boehme R, Mathys C, Katthagen T, Kaminski J, Stephan KE, *et al.* (2020): Volatility estimates increase choice switching and relate to prefrontal activity in schizophrenia. Biol Psychiatry Cogn Neurosci Neuroimaging 5:173–183.
116. Saperia S, Da Silva S, Siddiqui I, Agid O, Daskalakis ZJ, Ravindran A, *et al.* (2019): Reward-driven decision-making impairments in schizophrenia. Schizophr Res 206:277–283.
117. Hanssen E, van Buuren M, Van Atteveldt N, Lemmers-Jansen IL, Fett AJ (2022): Neural, behavioural and real-life correlates of social context sensitivity and social reward learning during interpersonal interactions in the schizophrenia spectrum. Aust N Z J Psychiatry 56:59–70.
118. Pantelis C, Wood SJ, Proffitt TM, Testa R, Mahony K, Brewer WJ, *et al.* (2009): Attentional set-shifting ability in first-episode and established schizophrenia: Relationship to working memory. Schizophr Res 112:104–113.
119. Griffiths KR, Morris RW, Balleine BW (2014): Translational studies of goal-directed action as a framework for classifying deficits across psychiatric disorders. Front Syst Neurosci 8:101.
120. Meyer-Lindenberg A, Miletich RS, Kohn PD, Esposito G, Carson RE, Quarantelli M, *et al.* (2002): Reduced prefrontal activity predicts exaggerated striatal dopaminergic function in schizophrenia. Nat Neurosci 5:267–271.
121. Kellendonk C, Simpson EH, Polan HJ, Malleret G, Vronskaya S, Winiger V, *et al.* (2006): Transient and selective overexpression of dopamine D2 receptors in the striatum causes persistent abnormalities in prefrontal cortex functioning. Neuron 49:603–615.
122. Murray GK, Cheng F, Clark L, Barnett JH, Blackwell AD, Fletcher PC, *et al.* (2008): Reinforcement and reversal learning in first-episode psychosis. Schizophr Bull 34:848–855.
123. Montagnese M, Knolle F, Haarsma J, Griffin JD, Richards A, Vertes PE, *et al.* (2020): Reinforcement learning as an intermediate phenotype in psychosis? Deficits sensitive to illness stage but not associated with polygenic risk of schizophrenia in the general population. Schizophr Res 222:389–396.
124. Kesby JP, Cui X, Burne THJ, Eyles DW (2013): Altered dopamine ontogeny in the developmentally vitamin D deficient rat and its relevance to schizophrenia. Front Cell Neurosci 7:111.
125. Cella M, Bishara AJ, Medin E, Swan S, Reeder C, Wykes T (2014): Identifying cognitive remediation change through computational modelling—Effects on reinforcement learning in schizophrenia. Schizophr Bull 40:1422–1432.
126. Silverstein SM, Spaulding WD, Menditto AA, Savitz A, Liberman RP, Berten S, Starobin H (2009): Attention shaping: A reward-based learning method to enhance skills training outcomes in schizophrenia. Schizophr Bull 35:222–232.
127. Acheson DT, Twamley EW, Young JW (2013): Reward learning as a potential target for pharmacological augmentation of cognitive remediation for schizophrenia: A roadmap for preclinical development. Front Neurosci 7:103.
128. Grace AA, Gomes FV (2019): The circuitry of dopamine system regulation and its disruption in schizophrenia: Insights into treatment and prevention. Schizophr Bull 45:148–157.
129. Cain JA, Visagan S, Johnson MA, Crone J, Blades R, Spivak NM, *et al.* (2021): Real time and delayed effects of subcortical low intensity focused ultrasound. Sci Rep 11:6100.
130. Humpston C, Garrison J, Orlov N, Aleman A, Jardri R, Fernyhough C, Allen P (2020): Real-time functional magnetic resonance imaging neurofeedback for the relief of distressing auditory-verbal hallucinations: Methodological and empirical advances. Schizophr Bull 46:1409–1417.
131. Thompson A, Marwaha S, Broome MR (2016): At-risk mental state for psychosis: Identification and current treatment approaches. BJPsych Advances 22:186–193.
132. McGorry PD, Hartmann JA, Spooner R, Nelson B (2018): Beyond the "at risk mental state" concept: Transitioning to transdiagnostic psychiatry. World Psychiatry 17:133–142.
133. Winton-Brown T, Schmidt A, Roiser JP, Howes OD, Egerton A, Fusar-Poli P, *et al.* (2017): Altered activation and connectivity in a hippocampal-basal ganglia-midbrain circuit during salience processing in subjects at ultra high risk for psychosis. Transl Psychiatry 7:e1245.
134. Barto A, Mirolli M, Baldassarre G (2013): Novelty or surprise? Front Psychol 4:907.
135. Fouragnan E, Retzler C, Philiastides MG (2018): Separate neural representations of prediction error valence and surprise: Evidence from an fMRI meta-analysis. Hum Brain Mapp 39:2887–2906.
136. Rumbaugh DM, King JE, Beran MJ, Washburn DA, Gould KL (2007): A salience theory of learning and behavior: With perspectives on neurobiology and cognition. Int J Primatol 28:973–996.
137. Oldham S, Murawski C, Fornito A, Youssef G, Yücel M, Lorenzetti V (2018): The anticipation and outcome phases of reward and loss processing: A neuroimaging meta-analysis of the monetary incentive delay task. Hum Brain Mapp 39:3398–3418.
138. Barbano MF, Cador M (2007): Opioids for hedonic experience and dopamine to get ready for it. Psychopharmacology (Berl) 191:497–506.
139. Juckel G, Friedel E, Koslowski M, Witthaus H, Özgürdal S, Gudlowski Y, *et al.* (2012): Ventral striatal activation during reward processing in subjects with ultra-high risk for schizophrenia. Neuropsychobiology 66:50–56.
140. Webber HE, Lopez-Gamundi P, Stamatovich SN, de Wit H, Wardle MC (2021): Using pharmacological manipulations to study the role of dopamine in human reward functioning: A review of studies in healthy adults. Neurosci Biobehav Rev 120:123–158.
141. Kurniawan IT, Seymour B, Talmi D, Yoshida W, Chater N, Dolan RJ (2010): Choosing to make an effort: The role of striatum in signaling physical effort of a chosen action. J Neurophysiol 104:313–321.
142. Croxson PL, Walton ME, O'Reilly JX, Behrens TEJ, Rushworth MFS (2009): Effort-based cost-benefit valuation and the human brain. J Neurosci 29:4531–4541.
143. Cowen SL, Davis GA, Nitz DA (2012): Anterior cingulate neurons in the rat map anticipated effort and reward to their associated action sequences. J Neurophysiol 107:2393–2407.
144. Salamone JD, Yohn SE, López-Cruz L, San Miguel N, Correa M (2016): Activational and effort-related aspects of motivation: Neural mechanisms and implications for psychopathology. Brain 139:1325–1347.
145. Michely J, Viswanathan S, Hauser TU, Delker L, Dolan RJ, Grefkes C (2020): The role of dopamine in dynamic effort-reward integration. Neuropsychopharmacology 45:1448–1453.
146. Westbrook A, van den Bosch R, Määttä JI, Hofmans L, Papadopetraki D, Cools R, Frank MJ (2020): Dopamine promotes cognitive effort by biasing the benefits versus costs of cognitive work. Science 367:1362–1366.
147. Hamid AA, Pettibone JR, Mabrouk OS, Hetrick VL, Schmidt R, Vander Weele CM, *et al.* (2016): Mesolimbic dopamine signals the value of work. Nat Neurosci 19:117–126.
148. Gan JO, Walton ME, Phillips PE (2010): Dissociable cost and benefit encoding of future rewards by mesolimbic dopamine. Nat Neurosci 13:25–27.
149. Walton ME, Bouret S (2019): What is the relationship between dopamine and effort? Trends Neurosci 42:79–91.

150. Wong SA, Thapa R, Badenhorst CA, Briggs AR, Sawada JA, Gruber AJ (2017): Opposing effects of acute and chronic d-amphetamine on decision-making in rats. Neuroscience 345:218–228.
151. Dalton GL, Phillips AG, Floresco SB (2014): Preferential involvement by nucleus accumbens shell in mediating probabilistic learning and reversal shifts. J Neurosci 34:4618–4626.
152. Clarke HF, Robbins TW, Roberts AC (2008): Lesions of the medial striatum in monkeys produce perseverative impairments during reversal learning similar to those produced by lesions of the orbitofrontal cortex. J Neurosci 28:10972–10982.
153. Dalton GL, Wang NY, Phillips AG, Floresco SB (2016): Multifaceted contributions by different regions of the orbitofrontal and medial prefrontal cortex to probabilistic reversal learning. J Neurosci 36:1996–2006.
154. Verharen JPH, den Ouden HEM, Adan RAH, Vanderschuren LJMJ (2020): Modulation of value-based decision making behavior by subregions of the rat prefrontal cortex. Psychopharmacology 237:1267–1280.