Biological Psychiatry

Review

Aberrant Salience, Information Processing, and Dopaminergic Signaling in People at Clinical High Risk for Psychosis

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ABSTRACT

The aberrant salience hypothesis proposes that striatal dopamine dysregulation causes misattribution of salience to irrelevant stimuli leading to psychosis. Recently, new lines of preclinical evidence on information coding by subcortical dopamine coupled with computational models of the brain's ability to predict and make inferences about the world (predictive processing) provide a new perspective on this hypothesis. We review these and summarize the evidence for dopamine dysfunction, reward processing, and salience abnormalities in people at clinical high risk of psychosis (CHR) relative to findings in patients with psychosis. This review identifies consistent evidence for dysregulated subcortical dopamine function in people at CHR, but also indicates a number of areas where neurobiological processes are different in CHR subjects relative to patients with psychosis, particularly in reward processing. We then consider how predictive processing models may explain psychotic symptoms in terms of alterations in prediction error and precision signaling using Bayesian approaches. We also review the potential role of environmental risk factors, particularly early adverse life experiences, in influencing the prior expectations that individuals have about their world in terms of computational models of the progression from being at CHR to frank psychosis. We identify a number of key outstanding questions, including the relative roles of prediction error or precision signaling in the development of symptoms and the mechanism underlying dopamine dysfunction. Finally, we discuss how the integration of computational psychiatry with biological investigation may inform the treatment for people at CHR of psychosis.

Keywords: Computational psychiatry, Imaging, Prodrome, Psychosis, Risk, Schizophrenia

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ROLE OF SUBCORTICAL DOPAMINE IN INFORMATION PROCESSING

The main origins of dopaminergic projections in the midbrain are the ventral tegmental area and substantia nigra, which project to the ventral striatum (VS), dorsal striatum, and frontal cortex, among other areas (1). Early animal cell recordings showed that midbrain dopamine neurons respond to unexpected reward (2). When a cue is repeatedly presented before reward, these neurons activate to the cue instead of the reward. If the reward is unexpectedly omitted at this stage, the same neurons decrease their activity (Figure 1A) (2). This phasic signal represents the difference between the predicted and the observed outcome, which is used to update the model such that future predictions are more accurate (3). This quantity is operationalized within computational models of learning as prediction error (PE) (see Box S1) (2,4–6) and is dependent on dopamine in humans (7). Subsequent animal cell recordings have shown that other dopamine neurons are excited by outcomes other than rewards and by the cues predicting these outcomes (5,8–13). Thus, evidence suggests that dopamine neurons also encode PEs (or some attribute of PEs) about outcomes other than just reward (Figure 1B) (6,10). However, it should be recognized that this is still debated (14). Recent work in humans indicates that dopamine neurons projecting to the striatum do not respond to information that is purely surprising with no implications for internal models. Rather, these neurons signal information that indicates that a belief update is required (Figure 1C) (15). This suggests that the dopamine PE is a teaching signal that highlights meaningful new information to update internal models of the world.

To optimally update a model of the environment, it is important to resolve mismatches between expectations and observations according to their relative certainty (16). Other theoretical accounts have proposed that neuromodulators (including dopamine) could encode the precision (inverse variance) of predictions or PEs, as they can adjust the gain or responsiveness of neurons to their synaptic inputs (17,18). There is evidence that dopamine alters the precision of sensory input (19); some dopamine neurons signal the uncertainty of perceptual judgments (20,21) and of rewards (22), although this is far from conclusively established (23–25). Indeed, some dopamine neurons may signal not just PE or precision, but a combined precision-weighted PE (26): research using functional magnetic

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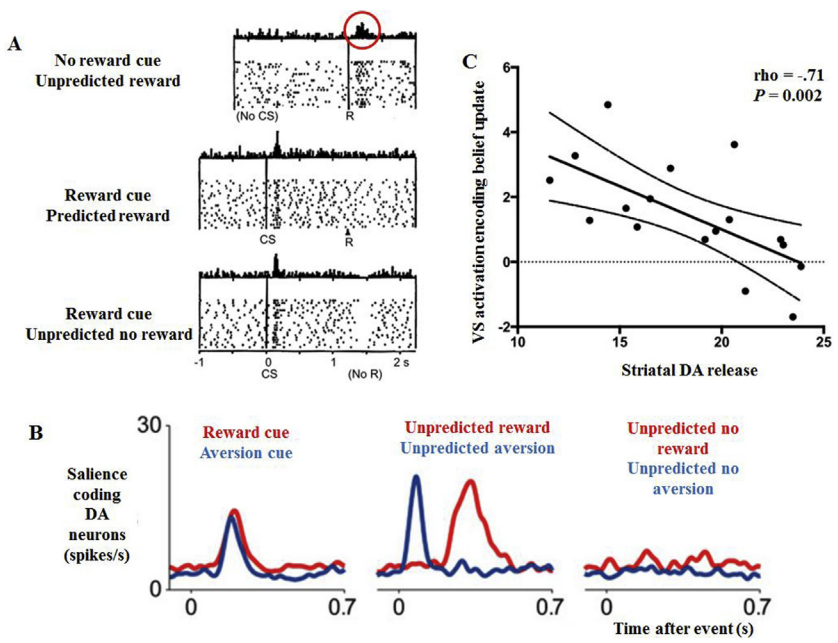

Figure 1. Dopamine (DA) signals salient outcomes. **(A)** Monkey midbrain DA neurons activate to unpredicted reward (R), as depicted by the red circle (upper panel); after conditioning to a conditioned stimulus (CS) that predicts the reward, these neurons activate to the CS and no longer activate to the reward (middle panel); after conditioning, if the CS is presented but the predicted reward is not delivered, DA neurons decrease their activity at the point the reward is expected. As well as a phasic response to reward seen here, research shows a tonic ramping of DA signaling over time (145). **(B)** DA neurons signaling salience activate to cues predicting reward (red) and aversion (blue) (left panel); DA neurons activate to delivery of both salient rewarding (red) and aversive (blue) outcomes (middle panel); salience-signaling DA neurons do not differentiate the unpredicted absence of reward and aversion (right panel). **(C)** There is a negative relationship between ventral striatal (VS) activation encoding belief updates and DA release across the whole striatum in humans ($\rho = -.71$ with 95% confidence intervals). Note that DA release was measured on a different occasion to the functional magnetic resonance imaging response during belief updating. Greater DA release is interpreted as indicating greater spontaneous DA neuron firing and consequently a lower signal-to-noise ratio of stimulus-locked DA firing and hence reduced activation (145). [Panel **(A)** adapted with permission from Schultz *et al.* (2). Panel **(B)** adapted with permission from Bromberg-Martin *et al.* (11).]

resonance imaging has shown that PE signals in the midbrain and striatum in humans are modulated by the variance of the distribution generating the PE (27). It should also be acknowledged that the relationship between dopamine, uncertainty, and PE signaling is not yet fully understood, and other neurotransmitter systems, such as the glutamatergic, acetylcholine, and serotonin systems, may also be involved (28). Notwithstanding these limitations, overall the evidence points to a role for dopamine signaling in updating internal models of the world.

DOPAMINE SIGNALING IN PSYCHOSIS

A large number of functional magnetic resonance imaging studies indicate that midbrain and striatal responses to rewarding and to neutral outcomes are altered in patients with psychosis (29–42) and that these alterations are associated with positive and negative symptoms. However, functional magnetic resonance imaging is not a direct measure of dopamine activity (43). The functioning of dopamine neurons can be more directly quantified in vivo using molecular neuroimaging, such as positron emission tomography or single photon emission computed tomography (44). These techniques indicate that striatal dopamine synthesis, storage, and release are elevated in patients with psychosis compared with healthy control (HC) subjects (45–48) with large effect sizes (49). Synaptic dopamine is also increased in psychosis (50,51). In contrast, the levels of postsynaptic D_2/D_3 receptors are largely unaltered (44). Finally, individuals who have psychotic symptoms associated with bipolar disorder, temporal lobe epilepsy, or schizotypal personality disorder also have increased striatal dopamine synthesis capacity (52–54). Taken together, these studies indicate a robust association between dysregulated striatal presynaptic dopamine function and psychotic symptoms.

The striatum can be divided into limbic, associative, and sensorimotor functional subregions (1), which receive different dopamine projections from the midbrain (55). Psychosis was initially thought to reflect dysfunction of the mesolimbic midbrain dopamine pathway, which projects to the limbic (ventral) striatum (49). However, recent positron emission tomography studies with higher spatial resolution permit study of the subdivisions. Meta-analysis indicates that the main changes in dopamine function occur in the associative and sensorimotor dorsal striatum (49). This suggests that aberrant dopamine functioning in psychosis occurs more within nigrostriatal than mesolimbic pathways (56).

DOPAMINE SIGNALING IN INDIVIDUALS AT CLINICAL HIGH RISK OF PSYCHOSIS

The findings in patients with psychosis raised the question of whether dopamine function differed before the onset of frank illness. To address this, dopamine function was investigated in people at clinical high risk of psychosis (CHR) using molecular imaging (Table 1) (45,46,57–60). Neither dopamine D_2/D_3 receptor availability nor synaptic dopamine levels differ in CHR subjects relative to HC subjects (61). In contrast, CHR subjects show increased dopamine synthesis capacity relative to HC subjects with effect sizes of about 0.8 in the striatum (57–59) and its associative (57–59,62) and sensorimotor (58,59), but not limbic, subdivisions. Dopamine synthesis capacity is greater in individuals who later transition to psychosis than individuals who do not transition (63) and is positively correlated with the severity of psychosis symptoms in some (57), but not all (59), studies. Moreover, in HC subjects, schizotypal traits are associated with dopamine release in parts of the striatum (64), including the associative striatum (65). Furthermore, CHR subjects show increased dopamine release to stress in the associative and sensorimotor striatum compared with HC subjects (46,66).

Table 1. Studies Examining Dopamine Activation in CHR Subjects

Reference	Sample Size	Radiotracer	Study Type	Regions Reported	Significant Results	Effect Size
Howes *et al.* (57)[a]	24 CHR, 12 HC	[^{18}F]-DOPA	Dopamine synthesis capacity	Striatum	CHR ↑	0.75
				AS	CHR ↑	0.83
Howes *et al.* (58)	9 CHR-T, 29 HC	[^{18}F]-DOPA	Dopamine synthesis capacity	Striatum	CHR ↑	1.18
				LS	↔	
				SMS	↔	
				AS	CHR ↑	1.24
Egerton *et al.* (59)	26 CHR, 20 HC	[^{18}F]-DOPA	Dopamine synthesis capacity	Striatum	CHR ↑	0.81
				LS	↔	
				SMS	↔	
				AS	CHR ↑	0.73
Mizrahi *et al.* (46)[b]	12 CHR, 12 HC	[^{11}C]-1-PHNO	Stress-induced dopamine release	Striatum	CHR ↑	–
				LS	↔	–
				SMS	CHR ↑	–
				AS	CHR ↑	–
Bloemen *et al.* (60)	14 CHR, 15 HC	[^{123}I]IBZM	Synaptic dopamine concentration	Striatum	↔	–
Tseng *et al.* (45)[c]	24 CHR, 25 HC	[^{11}C]-1-PHNO	Stress-induced dopamine release	Striatum	↔	–

AS, associative striatum; CHR, clinical high risk of psychosis; CHR-T, clinical high risk individuals who developed psychosis subsequent to scanning; HC, healthy control; LS, limbic striatum; SMS, sensorimotor striatum; ↓, less than; ↑, more than; ↔, no difference; –, effect size not reported.

[a]The data from this study were used as a subsample in 2 later studies, which showed increased dopamine synthesis capacity in the associative striatum in CHR compared with HC subjects (62,131).

[b]The data from this study were used in a later study that examined dopamine responses on the sensorimotor control component of the cognitive task and showed no differences in the regions of interest, namely, the caudate, putamen, ventral striatum, thalamus, globus pallidus, and substantia nigra pars compacta, between HC and CHR subjects (61).

[c]Twelve of 24 of the CHR subjects and 12 of 25 of the HC subjects were taken from a previous cohort (46).

Overall, these molecular imaging studies indicate an increase in presynaptic dopamine synthesis and release capacity in CHR subjects, but no alteration in postsynaptic D_2/D_3 receptors. This is broadly consistent with patients with psychosis (44,49). When compared using equivalent scanners, patients with psychosis have higher striatal dopamine synthesis capacity than CHR subjects (67). Thus, dopamine dysregulation in CHR subjects may not be as marked as in psychosis and may become more dysregulated as the individual transitions to frank psychosis (59). This is consistent with a model of psychosis where emerging symptoms feed back on the dopamine system to further dysregulate it (68).

In CHR subjects in general as well as in the subgroup that later become psychotic, the greatest alterations in dopamine synthesis and release capacity have been found in the associative striatum (57–59,62), paralleling findings in patients with psychosis (50,69). One challenge to integrating these dopamine metrics with theoretical models of psychotic symptoms is that positive and negative symptoms may have different striatal and cognitive loci. Reconciling these relationships between brain structure, neurotransmission, cognition, and psychopathology will be a key target for future work (70).

SALIENCE ABNORMALITIES IN INDIVIDUALS AT CHR

In its original formulation (71,72), the aberrant salience theory was partly based on the role of dopamine in signaling the incentive salience of reward (73) and evidence that this is altered in patients with psychosis (74). Subsequent studies have used a variety of tasks to measure reward and salience processing in people at CHR for psychosis (Table 2) (75–83). CHR subjects show increased activity during reward anticipation in the pallidum and midbrain (77) and the cingulate cortex and frontal gyrus (76), although these findings were not replicated in a subsequent study (75). CHR subjects also show increased reward-related modulation of functional connectivity in the VS, pallidum, and midbrain as shown on a modified monetary incentive delay task (77). Finally, VS activation during reward anticipation correlates with symptom severity in psychosis and in schizotypal personality disorder (84), and with polygenic risk score for psychosis in HC subjects (85). These results suggest that CHR subjects as well as individuals in the early stages of psychosis show increased VS activation to reward anticipation.

The salience attribution task tests whether subjects respond to cues that predict reward (indicating adaptive salience) or to irrelevant cues that do not predict reward (indicating aberrant salience) (82). It combines explicit salience measures, such as asking subjects to indicate how salient a stimulus was for an outcome, with implicit measures, such as reaction times during a choice. CHR subjects rate irrelevant cues as more relevant than HC subjects do (80,82), and VS activation to adaptive salience is decreased in CHR subjects compared with HC subjects (80). Moreover, VS activation during aberrant salience processing correlates with delusion-like symptoms (82), and at follow-up increased VS activation during adaptive salience correlates with a reduction of abnormal beliefs (80). Another study showed decreased blood oxygen level–dependent activity during adaptive salience in CHR subjects compared with both HC subjects and patients with a first episode of psychosis

Table 2. Studies Examining Reward or Salience Processing in CHR Subjects

Reference	Sample Size	Task	Measure	Significant Results
Juckel *et al.* (75)	13 CHR, 13 HC	MID	Behavioral	↔
			fMRI	↔
Wotruba *et al.* (76)	21 CHR, 24 HC	MID	Behavioral	↔
			fMRI	CHR ↑ (posterior cingulate cortex and R/L medial and superior frontal gyrus)
Winton-Brown *et al.* (77)	29 CHR, 32 HC	SIT	Behavioral	CHR ↓
			fMRI	CHR ↑ reward anticipation (L ventral pallidum and L midbrain)
			DCM	CHR ↑ reward-induced modulation of connectivity (VS and pallidum-midbrain)
Millman *et al.* (78)	22 CHR, 19 HC	MID	Behavioral	↔
			fMRI	↔
		RL	Behavioral	CHR ↓ RL
			fMRI	CHR ↓ (VS and vPFC)
Ermakova *et al.* (79)	30 CHR, 39 HC, 14 FEP	RL	Behavioral	↔
			fMRI	CHR ↓ (vs. HC) (midbrain)
				CHR ↑ (vs. FEP) (midbrain)
Schmidt *et al.* (80)	23 CHR, 13 HC	SAT	Behavioral	CHR ↑ implicit aberrant salience
				CHR ↓ implicit adaptive salience
				CHR ↓ explicit adaptive salience
			fMRI	CHR ↓ adaptive salience (R/L VS, R/L calcarine sulcus and midbrain, L cuneus, middle temporal gyrus)
Smieskova *et al.* (81)	34 CHR, 19 HC, 29 FEP (17 unmedicated and 12 medicated)	SAT	Behavioral	↔
			fMRI	CHR ↓ (vs. HC) adaptive salience (R inferior parietal lobule)
				CHR ↓ (vs. unmedicated FEP) adaptive salience (L dorsal cingulate gyrus)
				CHR ↑ (vs. medicated FEP) adaptive salience (anterior cingulate gyrus)
Roiser *et al.* (82)	18 CHR, 18 HC	SAT	Behavioral	CHR ↑ explicit aberrant salience
			fMRI	↔
			PET	↔

CHR, clinical high risk of psychosis; DCM, dynamic causal modeling; FEP, first-episode psychosis; fMRI, functional magnetic resonance imaging; HC, healthy control; L, left; MID, monetary incentive delay; PET, positron emission tomography; R, right; RL, reinforcement learning; SAT, salience attribution task; SIT, salience integration task; vPFC, ventral prefrontal cortex; VS, ventral striatum; ↓, less than; ↑, more than; ↔, no difference.

(81). Overall, the tendency is for CHR subjects to show increased explicit (but not implicit, such as that measured with reaction time) aberrant salience compared with HC subjects (80,82).

Evidence for aberrant decision making in CHR subjects is provided by altered performance on a reinforcement learning task. CHR subjects show PE-associated signal in the midbrain that is intermediate between that in HC subjects and patients with psychosis (79), who show a decreased reward PE signal in the midbrain and striatum compared with HC subjects (36). Further, CHR subjects exhibit impaired reinforcement learning and associated blunting in VS PE signaling (78). Indeed, this decreased reward PE signal may be related to the alterations in reward anticipation seen in the VS in patients with psychosis and in CHR subjects (75–77).

Taken together, this evidence indicates altered salience processing (80–83), reward anticipation (75–77), and PE signaling (78,79) in CHR subjects relative to HC subjects. However, the large variety of tasks, the heterogeneity of the population, and the variability in results means that more research is needed to confirm findings. One key avenue is to follow subjects longitudinally to identify whether these alterations increase in severity when CHR subjects transition to psychosis.

COMPUTATIONAL ACCOUNTS OF PSYCHOSIS

Salience was not operationalized in the initial accounts of psychosis, and its nonspecific nature is reflected in the heterogeneity of studies in the area (Table 2). Computational modeling forces such concepts to be formalized mathematically, and likewise rival models can be formally compared. The predictive processing framework is one framework that explains symptoms of psychosis as an alteration in specific elements of information processing (86–91). Predictive processing treats the brain as a Bayesian agent, which makes inferences about the causes of its noisy and dynamic sensory inputs using an internal model of the world. Incoming sensory data are compared against prior predictions, generating PEs, which are used to refine these predictions to produce posterior beliefs, which can then be modified based on further evidence

in an iterative process termed hierarchical predictive processing (92).

The influence of prior predictions or of PEs during inference is weighted by their respective precision. An uncertain, imprecise prior prediction would have less impact on inference than a precise prediction. Similarly, a noisy sensory channel would generate PEs of low precision, which would have little influence on inference, whereas a very precise PE would have more impact (93). An alteration in prior prediction and PE weighting could theoretically cause hallucinations through altered perceptual inference and could cause delusions through altered learning about the structure of the world. The computational machinery of predictive processing (PE, predictions, and precision) can be related to the neurophysiological circuits discussed above. This framework explains psychosis and associated alterations in salience processing as a result of aberrant encoding of precision in different regions or circuits (Figure 2) (28,94). This is unlikely to be attributable to dopamine alone: there is likely to be a widespread loss of signal-to-noise ratio in cortical neurotransmission, likely owing to glutamatergic receptor abnormalities and interneuron dysfunction (86). The resulting cortical disinhibition may result in a failure to suppress this noisy sensory information and a loss of influence of prior beliefs in multiple domains (28). Increased dopaminergic signaling may be secondary to this more fundamental pathology and may even be the brain's attempt to bolster the precision of prior predictions. This is a key empirical question.

This account of psychosis as a disorganization of precision weighting is particularly relevant because the incentive salience account, which emphasizes the role of dopamine release in the ventral striatum (71,73), has been challenged by recent studies indicating that aberrant dopamine functioning in psychosis occurs more within nigrostriatal than mesolimbic pathways (56). But how might the concept of salience translate into this framework? The encoding of precision is one answer, but another relates to the modeling of attention and the salience of objects. Here, salience refers to the expected information gain (or Bayesian surprise, i.e., how much an individual's beliefs change on acquiring some information) from sampling a stimulus (95). For example, faces are salient because they give us information about that person's mental state. This kind of salience is also likely perturbed in schizophrenia, given that people with psychosis attend to less informative areas of images (96). Interestingly, midbrain dopamine signaling also seems to relate to Bayesian surprise (15). Moreover, dopamine also appears to be involved in encoding the precision of perceptual predictions (19,20,97). For example, in a task in which subjects had to reproduce the duration of a target tone, their responses were more affected by preceding tones (i.e., empirical, or learned, prior beliefs) if they had higher striatal dopamine release capacity (97).

Studies have explored the application of predictive processing to clinical outcome. Excess weighting of prior predictions (or underweighted PE) might mean that perception is strongly influenced by prior predictions about the world rather than sensory input, which could generate hallucinations. Indeed, dopamine release in the associative striatum, a key area of disruption in psychosis (49), is associated with increased weighting of prior predictions (97). Auditory hallucinations are a common psychotic symptom, and computational modeling indicates that patients with hallucinations have more heavily weighted prior predictions than patients who do not experience hallucinations (97,98) and that this is associated with striatal dopamine function (97). PE signaling in the auditory cortex and bottom-up connectivity from Wernicke's areas to Broca's areas are decreased in patients with hallucinations (99,100), which suggests a reduction in PE signaling.

It should also be recognized that overly precise PE signals (or underweighted prior predictions) could explain some phenomena in psychosis (101). For example, passivity delusions may be due to overly precise PEs generated by the mismatch between the sensations associated with an action and the individual's predictions about those sensations, leading to the action being perceived as unpredicted and thus externally driven (86). A critique of computational accounts is that it is not clear if excess weighting of prior predictions/underweighting of PE or underweighting of prior predictions/excess weighting of PE underlies psychotic symptoms. These are key areas for future research.

If aberrant precision leads to psychosis, then we predict this to be present in CHR subjects at an intermediate level, in line with their subclinical symptoms (Figure 2B, C). Aberrant precision of either prior predictions or PE could theoretically exist in different circuits in the same brain, which could help to explain why delusions and hallucinations co-occur in so many individuals. Although reward PE signaling in CHR subjects has been shown to be altered in one recent study using computational methods (79), this is yet to be validated further, and alterations in precision of prior predictions or PE have not yet been examined in CHR subjects. However, increased dopamine availability is associated with a tendency toward unfounded beliefs and a greater reliance on prior expectations in HC subjects (102), which suggests a relationship between dopamine function, prior predictions, and psychosis-associated traits even in healthy subjects. Moreover, HC subjects show aberrant precision weighting as well as aberrant frontostriatal PE signaling associated with psychotic-like experiences (98,103).

FROM ENVIRONMENT TO BIOLOGY AND SYMPTOMS

The content of prior predictions within which aberrant precision weighting is interpreted will vary based on an individual's experience, particularly the predictability of an individual's experience and of their environment. Volatile and unpredictable environments are fertile breeding grounds for psychosis (104). This could account for the cultural and personal variation in the nature and severity of hallucinations and delusions (71,105,106). For example, an individual who experiences punitive life events might develop prior predictions with a paranoid content. When combined with dopamine dysfunction, this could lead to paranoid psychotic symptoms (71,105,107). Stressful and adverse experiences are associated with an increased risk of developing a psychotic disorder (108), although this relationship may be partially mediated by familial risk factors (109). Being an immigrant or the child of an immigrant substantially increases the risk of psychosis (110), as does growing up in an urban environment (111) and

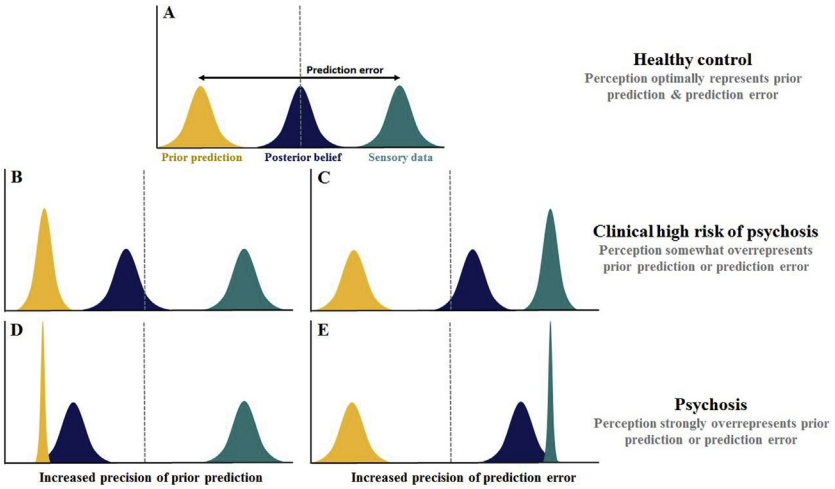

Figure 2. Aberrant precision of prior predictions or sensory data in the progression from clinical high risk of psychosis to psychosis. **(A)** In healthy control subjects, accurate representation of the precision (in this illustrative example, the precisions are equal) of prior predictions and sensory data (likelihood) generates a posterior belief midway between the two (dashed line). In individuals with clinical high risk of psychosis, an overly precise prior prediction **(B)** or an overly precise likelihood **(C)** biases the posterior belief toward the more precise distribution. In schizophrenia, an even more precise prior prediction **(D)** or prediction error **(E)** biases inference still further.

experiencing physical or sexual abuse (112). In HC subjects and patients, the intensity of psychotic-like experiences correlates with stress sensitivity, aberrant salience, and threat anticipation (113,114). Stress-induced cortisol release is altered in CHR subjects compared with HC subjects (115–117) and correlates with striatal dopamine release in HC subjects (118). Social stressors increase dopamine responses (118,119) and are thought to be etiological factors for psychotic disorders (120). Increased dopamine release to an experimental social stressor has been described in CHR and psychotic subjects compared with HC subjects (46). Furthermore, both striatal stress-induced dopamine release and dopamine synthesis capacity are increased in immigrants (independent of their clinical status) relative to nonimmigrants, indicating that the increased risk of psychosis in this population might be mediated by altered dopamine function (121). Similarly, physical or sexual abuse and unstable family arrangements in childhood have been related to increased striatal dopamine function in early adulthood, suggesting a link between childhood adversity and altered dopamine activity (122). However, to date, surprisingly few studies have investigated the biological mechanisms underlying the influence of psychosocial adversity on psychosis risk, and these initial findings need to be replicated.

Adverse experiences may increase the likelihood of developing psychosis in two ways. First, early adversity could increase the persecutory content of predictions (68,105). Second, adversity is often stressful, and as reported above, there is evidence that stress sensitizes the dopamine system (118). This could result in higher presynaptic dopamine synthesis and release capacity (123). Stress-induced aberrant PE signals could be interpreted as threatening, based on the tendency toward persecutory prior predictions, which could generate paranoid delusions. In turn, this would elicit further stress and generate a cycle of further dopamine dysregulation, greater aberrant precision, error signaling, and more stress. The dopamine system has the capacity to become sensitized over time (124). Thus, changes in the dopamine system might underlie the gradual development of psychosis from the premorbid phase, to the CHR state, to frank psychosis. Delusions and hallucinations may represent attempts to explain dopamine-dependent aberrant PEs using prior predictions, but if they are maladaptive to the environmental contingencies, these immutable prior predictions themselves could engender further PE and dopamine release. This is consistent with a model of psychosis that proposes that emerging symptoms feed back on the dopamine system to further dysregulate it (68).

ROLE OF OTHER BRAIN REGIONS

While we have largely focused on subcortical dopamine in this review, it is important to recognize that this is only one component of the circuits involved in information processing and that other brain regions are involved (56). Indeed, midbrain dopamine neurons are directly innervated by projections from the frontal cortex, as well as sending projections to the frontal cortex (1), and also receive indirect inputs from the hippocampus and frontal cortex (125). The frontal cortex differentiates salient outcomes (126), and task-related frontal and striatal activation and frontostriatal connectivity have been repeatedly shown to be altered across the psychosis continuum, suggesting that high-level prior predictions have greater influence on perception in psychosis (33,34,36–38,82,127–130). Moreover, the relationship between striatal dopamine and frontal activity is altered in patients with psychosis and CHR subjects compared with HC subjects (62,131), indicating that the function of these circuits is disrupted. There is also evidence that dopamine release is decreased in the frontal cortex in patients with psychosis (132,133). This could be due to dysfunction in midbrain dopamine neurons projecting to cortical regions or a primary disruption in the function of neurons in the cortex (134). However, decreased prefrontal dopamine release has not been observed in CHR subjects, although the study examining this may have been underpowered to detect effects (135). Another key brain area implicated in psychosis is the hippocampus, in which aberrant activity is thought to cause hyperactivity of dopamine neurons in the midbrain and striatum (136). In line with this, connectivity from the hippocampus to the striatum and

from the midbrain to the hippocampus is modulated by novelty more in CHR subjects than in HC subjects (83).

OUTSTANDING QUESTIONS AND FUTURE DIRECTIONS

One important question in computational psychiatry is whether disruption in PE, precision, or a combination of both underlies the development of psychosis (see Box S2). Moreover, as discussed above, either overweighting or underweighting of prior predictions relative to PEs could theoretically lead to distinct symptoms. It would be useful to formally compare different computational accounts to resolve these issues. It should also be recognized that there are several outstanding questions regarding the role of dopamine in predictive processing. Whether and how dopamine neurons encode precision and the relationship between dopamine signaling and perceptual prior predictions remain to be fully understood. Clarifying these areas in translational preclinical studies and in human studies is an important future direction to inform computational models of psychosis.

As discussed above, the most marked dopamine dysfunction is in the associative striatum (50,69,137,138), while PE signaling typically involves the ventral striatum (15). A further discrepancy is that while there is hypoactivation in patients with established psychosis, our review identifies that the picture is less clear cut in CHR subjects, and greater ventral striatal activation has been linked to subclinical symptoms (76,77). Longitudinal studies in CHR subjects who develop psychosis will clarify whether the ventral striatal function changes during the development of psychosis.

A key outstanding question is what mechanism underlies abnormal dopaminergic signaling. It has been suggested that subcortical dopamine dysfunction is the downstream consequence of dysregulation in glutamatergic function in frontal cortical regions linked to altered synaptic pruning and/or hippocampal regulation of midbrain dopamine neurons (134,136,139). Studies have begun to investigate links between frontal cortical and hippocampal alterations and striatal dopamine function in people with psychosis (140), but studies are needed to test the links between these systems in individuals at CHR. It is also not clear to what degree dysfunction in cortical regions might contribute to disrupted PE in CHR subjects or patients with psychosis, and this would be another useful area for further investigation.

There is a need for interventions in CHR, as there are currently no licensed interventions to reduce symptoms or prevent transition to psychosis (141,142), although there is some evidence that interventions may decrease the risk of transitioning to psychosis (143). Novel cognitive therapeutic approaches could draw on computational models by aiming to change an individual's prior predictions. Moreover, understanding the interaction between subconscious, experiential hierarchical processing and conscious beliefs could help patients understand their psychotic experiences. However, aberrant precision or PE signaling may not be within the conscious control of the individual, and pharmacological interventions may be useful to address this. The evidence of presynaptic dopamine dysfunction in people at CHR suggests that novel approaches to target the regulation of dopamine neurons may be effective (144).

CONCLUSIONS

Presynaptic striatal dopamine function and salience processing are altered in subjects at CHR, although effects are not as marked as in patients with psychosis and differ in some respects. Informed by this and by preclinical evidence on the function of subcortical dopamine neuron signaling, computational models provide a framework to understand the development of psychosis in terms of PE signaling and precision weighting. This framework provides a heuristic to link biological and cognitive dysfunction to clinical symptoms, which could facilitate the stratification of individuals at CHR and inform the development of novel clinical interventions. However, further work is required to evaluate this model in individuals at CHR, particularly to determine if it explains the transition to psychosis.

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ARTICLE INFORMATION

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