Aberrant salience, information processing and dopaminergic signalling 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. Here we review these and summarise the evidence for dopamine dysfunction, reward processing and salience abnormalities in people at clinical risk of psychosis (CHR) relative to findings in patients with psychosis. This identifies consistent evidence for dysregulated subcortical dopamine function in 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 signalling 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 signalling 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.
The role of subcortical dopamine in information processing

The main origins of dopaminergic projections in the midbrain are the ventral tegmental area (VTA) and substantia nigra, which project to the ventral (VS), dorsal striatum (DS) 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(2) (Figure 1A). 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 operationalised within computational models of learning as ‘prediction error’ (PE) (see Supplemental Information box 1) (2, 4–6) and is dopamine-dependent in humans (7). Subsequent animal cell recordings have shown that other dopamine neurons are excited by outcomes other than rewards, and to 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 (6, 10) (Figure 1B). However, it should be recognised 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 a belief update is required (15) (Figure 1C). 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 judgements (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 resonance imaging (fMRI) 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 signalling 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 signalling in updating internal models of the world.

**Dopamine signalling in psychosis**

A large number of fMRI 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, fMRI 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 (PET) or Single Photon Emission Computed Tomography (SPECT)(44). These techniques indicate that striatal dopamine synthesis, storage and release are elevated in patients with psychosis compared to healthy controls (HC) (45–48) with large effect sizes (49). Synaptic dopamine is also increased in psychosis(50, 51). In contrast, the levels of post-synaptic D2/D3 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 PET studies with higher spatial resolution permit study of the sub-divisions. 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 signalling in clinical high-risk individuals**

The findings in patients with psychosis raised the question of whether dopamine function differed prior to 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 D2/D3 receptor availability, or synaptic dopamine levels differ in CHR relative to HC (61).

In contrast, CHR subjects show increased dopamine synthesis capacity relative to HC 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 sub-divisions. Dopamine synthesis capacity is greater in individuals who later transition to psychosis than those 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, 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 to HC (46, 66).

Overall, these molecular imaging studies indicate an increase in presynaptic dopamine synthesis and release capacity in CHR subjects but no alteration in postsynaptic D2/3 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 subject 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 psychotic patients(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 CHR**

In its original formulation (71, 72), the aberrant salience theory was partly based on dopamine’s role in signalling 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 (see 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 MID 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(85). These results suggest that CHR subjects, and those in the early stages of psychosis, show increased VS activation to reward anticipation.

The salience attribution task (SAT) tests whether subjects respond to cues which predict reward (indicating adaptive salience) or to irrelevant cues which 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 do (80, 82), and VS activation to adaptive salience is decreased in CHR compared to HC (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 BOLD activity during adaptive salience in CHR subjects compared to both HC and first-episode psychosis patients (FEP) (81). Overall, the tendency is for CHR to show increased explicit
(but not implicit, such as that measured with reaction time) aberrant salience compared to controls (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 and patients with psychosis (79), who show a decreased reward PE signal in the midbrain and striatum compared to HC (36). Further, CHR subjects exhibit impaired reinforcement learning and associated blunting in their VS PE signalling (78). Indeed, this decreased reward PE signal may be related to the alterations in reward anticipation seen in the VS in psychosis and in CHR subjects (75–77).

Taken together, this evidence indicates altered salience processing (80–83), reward anticipation (75–77) and PE-signalling (78, 79) in CHR relative to HC. 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 operationalised in the initial accounts of psychosis, and its non-specific nature is reflected in the heterogeneity of studies into the area (table 2). Computational modelling forces such concepts to be formalised mathematically, and likewise rival models can be formally compared. The predictive processing framework is one framework which 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 and so on, in a 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 (28, 94) (figure 2). This is unlikely to be attributable to dopamine alone: there is likely to be a widespread loss of signal-to-noise in cortical neurotransmission, likely due 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 signalling 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 disorganisation of precision-weighting is particularly relevant because the incentive salience account, which emphasises 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 modelling 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 people with psychosis attend to less informative areas of images(96). Interestingly, midbrain dopamine signalling 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 modelling indicates that patients with hallucinations have more heavily weighted priors than non-hallucinators (97, 98), and that this is associated with striatal dopamine function (97). PE signalling in the auditory cortex and bottom-up connectivity from Wernicke’s to Broca’s areas are decreased in patients with hallucinations (99, 100), which suggests a reduction in PE signalling.

It should also be recognised 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 priors/ underweighting of PE or under weighting of priors/ 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 sub-clinical symptoms (figure 2B & C). Aberrant precision of either priors or PE could theoretically exist in 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 signalling 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 priors or PE have not yet been examined in CHR subjects. However, increased dopamine availability is associated with a tendency towards unfounded beliefs and a greater reliance on prior expectations in HC (102), which suggests a relationship between dopamine function, priors and psychosis associated traits even in healthy subjects. Moreover, HC show aberrant precision-weighting, as well as aberrant frontostriatal PE signalling 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 priors with a paranoid content. When combined with dopamine dysfunction, that 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 experiencing physical or sexual abuse (112). In HC 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 to HC(115–117) and correlates with striatal dopamine release in HC (118). Social stressors increase dopamine responses (118, 119) and are thought to be aetiological factors for psychotic disorders (120). Increased dopamine release to an experimental social stressor has been described in CHR and psychotic subjects compared to HC (46). Furthermore, both striatal stress-induced dopamine release and dopamine synthesis capacity are increased in immigrants (independent of their clinical status) relative to non-immigrants, 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 sensitises 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 towards 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 signalling, and more stress. The dopamine system has the capacity to become sensitised 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 DA-dependent aberrant PEs using prior predictions, but, if they are maladaptive to the environmental contingencies, these immutable priors 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) (see figures 3 & 4).

The role of other brain regions

Whilst we have largely focused on subcortical dopamine in this review, it is important to recognise that this is only one component of the circuits involved in information processing and that other brain regions are involved (56). Indeed, midbrain DA 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 fronto-striatal connectivity have been repeatedly shown to be altered across the psychosis continuum, suggesting that high-level priors 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 to HC(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 under-powered 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(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 Supplemental Information box 2). Moreover, as discussed above, either over-weighting or under-weighting of priors 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 recognised that there are several outstanding questions around the role of dopamine in predictive processing. Whether and how dopamine neurons encode precision, and the relationship between dopamine signalling and perceptual priors, remain to be fully understood. Clarifying these areas in translational preclinical 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), whilst PE gbthe ventral striatum (15). A further discrepancy is that, whilst 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 sub-clinical
symptoms (76, 77). Longitudinal studies in CHR subjects who develop psychosis will clarify whether
the ventral striatal function alters during the development of psychosis.

A key outstanding question is what mechanism underlies abnormal dopaminergic signalling. 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 CHR
subjects. 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 (141, 142), albeit some evidence 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 priors. Moreover, understanding the
interaction between sub-conscious, experiential hierarchical processing and conscious beliefs could
help patients understand their psychotic experiences. However, aberrant precision or PE signalling
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 risk of
psychosis 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 CHR subjects, 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 signalling, computational models provide a framework to understand the development of psychosis in terms of PE signalling 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 CHR individuals, particularly to determine if it explains the transition to psychosis.
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Footnotes

1 The data from this study were used as a sub-sample in two later studies, which showed increased DA synthesis capacity in the associative striatum in CHR compared to HC (131, 145).

2 The data from this study were used in a later study which examined DA responses on the sensory motor control component of the cognitive task, and showed no differences in the ROIs of interest, namely the caudate, putamen, VS, thalamus, GP and SNC, between HC and CHR (61).

3 12/24 of the CHR and 12/25 of the HC subjects were taken from a previous cohort (46).
Table legends

Table 1: Columns represent authors, sample size, radiotracer, study type, regions reported, significant effects and effect size. CHR, clinical high risk of psychosis; HC, healthy control; CHR-T, clinical high risk individuals who developed psychosis subsequent to scanning; [18F]-DOPA, 6-[18F]fluoro-L-dihydroxyphenylalanine; [11C]-1-PHNO, [11C]-(1)-4-propyl-9-hydroxynaphthoxazine; [123I]IBZM, [123I](S)-(-)-3-iodo-2-hydroxy-6-methoxy-N-[1-ethyl-2-pyrrolidinyl)methyl]benzamide; LS, limbic striatum; SMS, sensorimotor striatum; AS, associative striatum; †, less than; ‡, more than; ↔, no difference; -, effect size not reported

Table 2: Columns represent authors, population, task, measure, significant results and effect size. CHR, clinical high risk; HC, healthy control; FEP, first episode psychosis; MID, monetary incentive delay task; SIT, salience integration task; RL, reinforcement learning; SAT, salience attribution task; fMRI, functional magnetic resonance imaging; DCM, dynamic causal modelling; PET, positron emission tomography; R, right; L, left; †, less than; ‡, more than; ↔, no difference, -, no effect size reported
Figure legends

Figure 1: dopamine signals salient outcomes. (A) Monkey midbrain dopamine 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, dopamine neurons decrease their activity at the point the reward is expected. Adapted with permission from Schultz et al. (1997). As well as a phasic response to reward seen here, research shows a tonic ramping of dopamine signalling over time (146) (B) dopamine neurons signalling salience activate to cues predicting reward (red) and aversion (blue) (left panel); dopamine neurons activate to delivery of both salient rewarding (red) and aversive (blue) outcomes (middle panel); salience-signalling dopamine neurons do not differentiate the unpredicted absence of reward and aversion (right panel). Adapted with permission from Bromberg-Martin et al. (2010). (C) There is a negative relationship between ventral striatal activation encoding belief updates and dopamine release across the whole striatum in humans (rho=-0.71 with 95% confidence intervals). Note that the dopamine release was measured on a different occasion to the fMRI response during belief updating. Greater dopamine release is interpreted as indicating greater spontaneous dopamine neuron firing and, consequently, a lower signal-to-noise ratio of stimulus-locked dopamine firing, and hence reduced activation (146).

Figure 2: aberrant precision of prior predictions or sensory data in the progression from CHR to psychosis. (A) In healthy controls, accurate representation of the precision (in this illustrative example, the precisions are equal) of prior predictions and sensory data (likelihood) generate a posterior belief midway between the two (dashed line). In clinical high-risk individuals, an overly precise prior (B) or an overly precise likelihood (C) biases the posterior towards the more precise
distribution. In schizophrenia, an even more precise predictive prior (D) or PE (E) bias inference still further.

### Tables

**Table 1: studies examining dopamine activation in CHR subjects**

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<td>CHR↑</td>
<td>0.73</td>
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<tr>
<td>Mizrahi et al.</td>
<td>12 CHR</td>
<td>[11C]-1-PHNO</td>
<td>Stress-induced dopamine release</td>
<td>Striatum</td>
<td>CHR↑</td>
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<tr>
<td>(46)</td>
<td>12 HC</td>
<td></td>
<td>Stress-induced dopamine release</td>
<td>LS</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>AS</td>
<td>CHR↑</td>
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<tr>
<td>Bloemen et al.</td>
<td>14 CHR</td>
<td>[123I]IBZM</td>
<td>Synaptic dopamine concentration</td>
<td>Striatum</td>
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<td>-</td>
</tr>
<tr>
<td>(60)</td>
<td>15 HC</td>
<td></td>
<td>Synaptic dopamine concentration</td>
<td></td>
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<tr>
<td>Tseng et al</td>
<td>24 CHR</td>
<td>[11C]-1-PHNO</td>
<td>Stress-induced</td>
<td>Striatum</td>
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</tbody>
</table>

1. Howes et al. (57)
2. Mizrahi et al. (46)
3. Bloemen et al. (60)
Table 2: studies examining reward or salience processing in CHR subjects.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Population</th>
<th>Task</th>
<th>Measure</th>
<th>Significant results</th>
<th>Effect size</th>
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<tbody>
<tr>
<td>Juckel et al.</td>
<td>13 CHR</td>
<td>MID</td>
<td>Behavioural fMRI</td>
<td></td>
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<tr>
<td>(75)</td>
<td>13 HC</td>
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<td>Wotruba et al.</td>
<td>21 CHR</td>
<td>MID</td>
<td>Behavioural fMRI</td>
<td>CHR↑ (posterior cingulate cortex &amp; R/L medial &amp; superior frontal gyrus)</td>
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<tr>
<td>(76)</td>
<td>24 HC</td>
<td></td>
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<tr>
<td>Winton-Brown et al.</td>
<td>29 CHR</td>
<td>SIT</td>
<td>Behavioural fMRI</td>
<td>CHR↓ reward anticipation (L ventral pallidum &amp; L midbrain)</td>
<td>-</td>
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<tr>
<td>(77)</td>
<td>32 HC</td>
<td></td>
<td></td>
<td>DCM</td>
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<td></td>
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<td></td>
<td>CHR↑ reward-induced modulation of connectivity (VS &amp; pallidum-midbrain)</td>
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<tr>
<td>Millman et al.</td>
<td>19 HC</td>
<td>MID</td>
<td>Behavioural fMRI</td>
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<td>(78)</td>
<td>22 CHR</td>
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<td></td>
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<td></td>
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<td>Behavioural fMRI</td>
<td>CHR↓ RL</td>
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<tr>
<td>Ermakova et al.</td>
<td>30 CHR</td>
<td>RL</td>
<td>Behavioural fMRI</td>
<td>CHR↓ (vs. HC) (midbrain)</td>
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<tr>
<td>(79)</td>
<td>39 HC</td>
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<tr>
<td>Schmidt et al.</td>
<td>23 CHR</td>
<td>SAT</td>
<td>Behavioural fMRI</td>
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<td>(80)</td>
<td>13 HC</td>
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<tr>
<td>Study</td>
<td>Participants</td>
<td>Task</td>
<td>fMRI Study</td>
<td>PET Study</td>
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<tr>
<td>Smieskova et al. (81)</td>
<td>34 CHR, 19 HC, 29 FEP (19 unmedicated &amp; 12 medicated)</td>
<td>SAT Behavioural fMRI</td>
<td>CHR explicit adaptive salience</td>
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<td></td>
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<td>CHR ↓ adaptive salience (R/L VS, R/L calcarine sulcus &amp; midbrain, L cuneus, middle temporal gyrus)</td>
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<tr>
<td>Roiser et al. (82)</td>
<td>18 CHR, 18 HC</td>
<td>SAT Behavioural fMRI</td>
<td>CHR↑ explicit aberrant salience</td>
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<td>CHR↑ (vs. HC) adaptive salience (R inferior parietal lobule)</td>
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<td>CHR↓ (vs. unmedicated FEP) adaptive salience (L dorsal cingulate gyrus)</td>
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<td></td>
<td>CHR↑ (vs. medicated FEP) adaptive salience (anterior cingulate gyrus)</td>
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</tr>
</tbody>
</table>
Prior prediction | Posterior belief | Sensory data
--- | --- | ---

**Healthy control**
Perception optimally represents prior prediction & prediction error

**Clinical high risk**
Perception somewhat overrepresents prior prediction or prediction error

**Psychosis**
Perception strongly overrepresents prior prediction or prediction error

Increased precision of prior prediction | Increased precision of prediction error