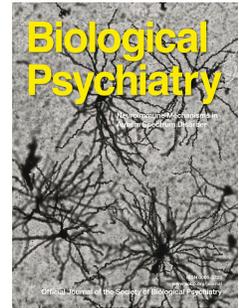# Journal Pre-proof

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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

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(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).

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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

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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

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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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References

1. Haber SN, Fudge JL, McFarland NR (2000): Striatonigrostriatal pathways in primates form an ascending spiral from the shell to the dorsolateral striatum. *J Neurosci*. 20: 2369–82.

2. Schultz W, Dayan P, Montague PR (1997): A Neural Substrate of Prediction and Reward. *Adv Sci*. 275: 1593–1599.

3. Seymour B, O'Doherty JP, Dayan P, Koltzenburg M, Jones AK, Dolan RJ, *et al.* (2004): Temporal difference models describe higher-order learning in humans. *Nature*. 429: 664–667.

4. Mirenowicz J, Schultz W (1994): Importance of unpredictability for reward responses in primate dopamine neurons. *J Neurophysiol*. 72: 1024–1027.

5. Ljungberg T, Apicella P, Schultz W (1992): Responses of monkey dopamine neurons during learning of behavioral reactions. *J Neurophysiol*. 67: 145–163.

6. Guarraci FA, Kapp BS (1999): An electrophysiological characterization of ventral tegmental area dopaminergic neurons during differential pavlovian fear conditioning in the awake rabbit. *Behav Brain Res*. 99: 169–179.

7. Pessiglione M, Seymour B, Flandin G, Dolan RJ, Frith CD (2006): Dopamine-dependent prediction errors underpin reward-seeking behaviour in humans. *Nature*. 442: 1042–1045.

8. Joshua M, Adler A, Mitelman R, Vaadia E, Bergman H (2008): Midbrain Dopaminergic Neurons and Striatal Cholinergic Interneurons Encode the Difference between Reward and Aversive Events at Different Epochs of Probabilistic Classical Conditioning Trials. *J Neurosci*. 28: 11673–11684.

9. Anstrom KK, Woodward DJ (2005): Restraint increases dopaminergic burst firing in awake rats.

Neuropsychopharmacology. 30: 1832–1840.

10. Brischoux F, Chakraborty S, Brierley DI, Ungless MA (2009): Phasic excitation of dopamine neurons in ventral VTA by noxious stimuli. *PNAS*. 106: 4894–4899.

11. Bromberg-Martin ES, Matsumoto M, Hikosaka O (2010): Dopamine in Motivational Control: Rewarding, Aversive, and Alerting. *Neuron*. 68: 815–834.

12. Rebec G V. (1998): Real-Time Assessments of Dopamine Function during Behavior: Single-Unit Recording, Iontophoresis, and Fast-Scan Cyclic Voltammetry in Awake, Unrestrained Rats. *Alcohol Clin Exp Res*. 22: 32.

13. Horvitz JC (2000): Mesocortical and mesostriatal dopamine responses to salient non-rewards events. *Neuroscience*. 96: 651–656.

14. Schultz W (2016): Dopamine reward prediction-error signalling: A two-component response. *Nat Rev Neurosci*. 17: 183–195.

15. Nour MM, Dahoun T, Schwartenbeck P, Adams RA, FitzGerald THB, Coello C, *et al.* (2018): Dopaminergic basis for signaling belief updates, but not surprise, and the link to paranoia. *Proc Natl Acad Sci*. 115: E10167–E10176.

16. Bach DR, Dolan RJ (2012): Knowing how much you don't know: A neural organization of uncertainty estimates. *Nat Rev Neurosci*. 13: 572–586.

17. Fitzgerald THB, Dolan RJ, Friston K (2015): Dopamine, reward learning, and active inference. *Front Comput Neurosci*. 9: 1–16.

18. Friston K, Schwartenbeck P, FitzGerald T, Moutoussis M, Behrens T, Dolan RJ (2014): The anatomy of choice: Dopamine and decision-making. *Philos Trans R Soc B Biol Sci*. 369. doi: 10.1098/rstb.2013.0481.

19. Vilares I, Kording KP (2017): Dopaminergic medication increases reliance on current information in Parkinson's disease. *Nat Hum Behav*. 1: 1–18.

20. de Lafuente V, Romo R (2011): Dopamine neurons code subjective sensory experience and uncertainty of perceptual decisions. *Proc Natl Acad Sci*. 108: 19767–19771.

21. Lak A, Nomoto K, Keramati M, Sakagami M, Kepecs A (2017): Midbrain Dopamine Neurons Signal Belief in Choice Accuracy during a Perceptual Decision. *Curr Biol*. 27: 821–832.

22. Schultz W, Preuschoff K, Camerer C, Hsu M, Fiorillo CD, Tobler PN, Bossaerts P (2008): Review. Explicit neural signals reflecting reward uncertainty. *Philos Trans R Soc B Biol Sci*. 363: 3801–3811.

23. Lloyd K, Dayan P (2015): Tamping Ramping: Algorithmic, Implementational, and Computational Explanations of Phasic Dopamine Signals in the Accumbens. *PLoS Comput Biol*. 11: 1–34.

24. Mikhael JG, Kim HR, Uchida N, Gershman SJ (2019): Ramping and State Uncertainty in the Dopamine Signal. .

25. Song MR, Lee SW (2019): Ramping and phasic dopamine activity accounts for efficient cognitive resource allocation during reinforcement learning. *bioRxiv*. 381103.

26. Gershman SJ (2017): Dopamine, Inference, and Uncertainty. *Neural Comput*. 29: 3311–3326.

27. Diederen KMMJ, Spencer T, Vestergaard MDD, Fletcher PCC, Schultz W (2016): Adaptive Prediction Error Coding in the Human Midbrain and Striatum Facilitates Behavioral Adaptation and Learning Efficiency. *Neuron*. 90: 1127–1138.

28. Adams RA, Stephan KE, Brown HR, Frith CD, Friston KJ (2013): The Computational Anatomy of Psychosis. *Front Psychiatry*. 4: 1–26.

29. 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.

30. Jensen J, Willeit M, Zipursky RB, Savina I, Smith AJ, Menon M, *et al.* (2008): The formation of abnormal associations in schizophrenia: Neural and behavioral evidence.

Neuropsychopharmacology. 33: 473–479.

31. Romaniuk L, Honey GD, King JRL, Whalley HC, McIntosh AM, Levita L, *et al.* (2010): Midbrain Activation During Pavlovian Conditioning and Delusional Symptoms in Schizophrenia. *Arch Gen Psychiatry*. 67: 1246.

32. Juckel G, Schlagenhauf F, Koslowski M, Wüstenberg T, Villringer A, Knutson B, *et al.* (2006): Dysfunction of ventral striatal reward prediction in schizophrenia. *Neuroimage*. 29: 409–416.

33. Schlagenhauf F, Sterzer P, Schmack K, Ballmaier M, Rapp M, Wrase J, *et al.* (2009): Reward Feedback Alterations in Unmedicated Schizophrenia Patients: Relevance for Delusions. *Biol Psychiatry*. 65: 1032–1039.

34. Waltz JA, Schweitzer JB, Gold JM, Kurup PK, Ross TJ, Jo Salmeron B, *et al.* (2009): Patients with schizophrenia have a reduced neural response to both unpredictable and predictable primary reinforcers. *Neuropsychopharmacology*. 34: 1567–1577.

35. Gradin VB, Waiter G, O'Connor A, Romaniuk L, Stickle C, Matthews K, *et al.* (2013): Salience network-midbrain dysconnectivity and blunted reward signals in schizophrenia. *Psychiatry Res - Neuroimaging*. 211: 104–111.

36. 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: 267–276.

37. Waltz JA, Schweitzer JB, Ross TJ, Kurup PK, Salmeron BJ, Rose EJ, *et al.* (2010): Abnormal responses to monetary outcomes in cortex, but not in the basal ganglia, in schizophrenia. *Neuropsychopharmacology*. 35: 2427–2439.

38. Diaconescu AO, Jensen J, Wang H, Willeit M, Menon M, Kapur S, McIntosh AR (2011): Aberrant Effective Connectivity in Schizophrenia Patients during Appetitive Conditioning. *Front Hum Neurosci*. 4: 1–14.

39. 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: 1–23.

40. 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: 280–289.

41. Nielsen MØ, Rostrup E, Wulff S, Bak N, Lublin H, Kapur S, Glenthøj B (2012): Alterations of the brain reward system in antipsychotic nave schizophrenia patients. *Biol Psychiatry*. 71: 898–905.

42. 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. *Psychopharmacology (Berl)*. 187: 222–228.

43. Düzel E, Bunzeck N, Guitart-Masip M, Wittmann B, Schott BH, Tobler PN (2009): Functional imaging of the human dopaminergic midbrain. *Trends Neurosci*. 32: 321–328.

44. 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.

45. Tseng H-H, Watts JJ, Kiang M, Suridjan I, Wilson AA, Houle S, *et al.* (2018): Nigral Stress-Induced Dopamine Release in Clinical High Risk and Antipsychotic-Naïve Schizophrenia. *Schizophr Bull*. 44: 542–551.

46. Mizrahi R, Addington J, Rusjan PM, Suridjan I, Ng A, Boileau I, *et al.* (2012): Increased stress-induced dopamine release in psychosis. *Biol Psychiatry*. 71: 561–567.

47. Abi-Dargham A, van de Giessen E, Slifstein M, Kegeles LS, Laruelle M (2009): Baseline and Amphetamine-Stimulated Dopamine Activity Are Related in Drug-Naïve Schizophrenic Subjects. *Biol Psychiatry*. 65: 1091–1093.

48. Howes OD, Williams M, Ibrahim K, Leung G, Egerton A, McGuire PK, Turkheimer F (2013): Midbrain dopamine function in schizophrenia and depression: A post-mortem and positron

emission tomographic imaging study. *Brain*. 136: 3242–3251.

49. McCutcheon R, Beck K, Jauhar S, Howes OD (2018): Defining the Locus of Dopaminergic Dysfunction in Schizophrenia: A Meta-analysis and Test of the Mesolimbic Hypothesis. *Schizophr Bull*. 44: 1301–1311.

50. Kegeles LS, Abi-Dargham A, Frankle WG, Gil R, Cooper TB, Slifstein M, *et al.* (2010): Increased Synaptic Dopamine Function in Associative Regions of the Striatum in Schizophrenia. *Arch Gen Psychiatry*. 67: 231.

51. Abi-Dargham A, Rodenhiser J, Printz D, Zea-Ponce Y, Gil R, Kegeles LS, *et al.* (2000): Increased baseline occupancy of D2 receptors by dopamine in schizophrenia. *Proc Natl Acad Sci U S A*. 97: 8104–9.

52. Abi-Dargham A, Kegeles LS, Zea-Ponce Y, Mawlawi O, Martinez D, Mitropoulou V, *et al.* (2004): Striatal amphetamine-induced dopamine release in patients with schizotypal personality disorder studied with single photon emission computed tomography and [123I]iodobenzamide. *Biol Psychiatry*. 55: 1001–1006.

53. Reith J, Benkelfat C, Sherwin A, Yasuhara Y, Kuwabara H, Andermann F, *et al.* (1994): Elevated dopa decarboxylase activity in living brain of patients with psychosis. *Proc Natl Acad Sci*. 91: 11651–11654.

54. Jauhar S, Nour MM, Veronese M, Rogdaki M, Bonoldi I, Azis M, *et al.* (2017): A Test of the Transdiagnostic Dopamine Hypothesis of Psychosis Using Positron Emission Tomographic Imaging in Bipolar Affective Disorder and Schizophrenia. *JAMA psychiatry*. 74: 1206–1213.

55. Björklund A, Dunnett SB (2007): Dopamine neuron systems in the brain: an update. *Trends Neurosci*. 30: 194–202.

56. McCutcheon RA, Abi-Dargham A, Howes OD (2019): Schizophrenia, Dopamine and the Striatum: From Biology to Symptoms. *Trends Neurosci*. xx: 1–16.

57. Howes OD, Montgomery AJ, Asselin M-C, 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.

58. Howes O, Bose S, Turkheimer F, Valli I, Egerton A, Stahl D, *et al.* (2011): Progressive increase in striatal dopamine synthesis capacity as patients develop psychosis : a PET study. 16: 885–886.

59. Egerton A, Chaddock C, Winton-Brown TT, Bloomfield MAP, Bhattacharyya S, Allen P, *et al.* (2013): Presynaptic Striatal Dopamine Dysfunction in People at Ultra-high Risk for Psychosis: Findings in a Second Cohort. *Biol Psychiatry*. 74: 106–112.

60. Bloemen OJN, Koning MB de, Gleich T, Meijer J, Haan L de, Linszen DH, *et al.* (2012): Striatal dopamine D2/3 receptor binding following dopamine depletion in subjects at Ultra High Risk for psychosis. *Eur Neuropsychopharmacol*. 23: 126–132.

61. Suridjan I, Rusjan P, Addington J, Wilson AA, Houle S, Mizrahi R (2013): Dopamine D2 and D3 binding in people at clinical high risk for schizophrenia, antipsychotic-naive patients and healthy controls while performing a cognitive tasks. *J Psychiatry Neurosci*. 38: 98–106.

62. Fusar-Poli P, Howes OD, Allen P, Broome M, Valli I, Asselin MC, *et al.* (2010): Abnormal frontostriatal interactions in people with prodromal signs of psychosis: A multimodal imaging study. *Arch Gen Psychiatry*. 67: 683–691.

63. 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.

64. Chen KC, Lee IH, Yeh TL, Chiu NT, Chen PS, Yang YK, *et al.* (2012): Schizotypy trait and striatal dopamine receptors in healthy volunteers. *Psychiatry Res - Neuroimaging*. 201: 218–221.

65. Woodward ND, Cowan RL, Park S, Ansari MS, Baldwin RM, Li R, *et al.* (2011): Correlation of individual differences in schizotypal personality traits with amphetamine-induced dopamine release in striatal and extrastriatal brain regions. *Am J Psychiatry*. 168: 418–426.

66. Mizrahi R, Kenk M, Suridjan I, Boileau I, George TP, McKenzie K, *et al.* (2014): Stress-Induced

Dopamine Response in Subjects at Clinical High Risk for Schizophrenia with and without Concurrent Cannabis Use. *Neuropsychopharmacology*. 39: 1479–1489.

67. Jauhar S, Veronese M, Nour MM, Rogdaki M, Hathway P, Turkheimer FE, *et al.* (2018): Determinants of treatment response in first-episode psychosis: an 18 F-DOPA PET study. *Mol Psychiatry*. 1–11.

68. Howes OD, Murray RM (2014): Schizophrenia: an integrated sociodevelopmental-cognitive model. *Lancet*. 383: 1677–1687.

69. Maia T V., Frank MJ (2016): An Integrative Perspective on the Role of Dopamine in Schizophrenia. *Biol Psychiatry*. 81: 52–66.

70. Corlett PR, Honey GD, Fletcher PC (2016): Prediction error, ketamine and psychosis: An updated model. *J Psychopharmacol*. 30: 1145–1155.

71. 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.

72. Heinz A (2002): Dopaminergic dysfunction in alcoholism and schizophrenia - Psychopathological and behavioral correlates. *Eur Psychiatry*. 17: 9–16.

73. Berridge KC, Robinson TE (1998): What is the role of dopamine in reward: Hedonic impact, reward learning, or incentive salience? *Brain Res Rev*. 28: 309–369.

74. 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.

75. 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.

76. Wotruba D, Heekeren K, Michels L, Buechle R, Simon JJ, Theodoridou A, *et al.* (2014):

Symptom dimensions are associated with reward processing in unmedicated persons at risk for psychosis. *Front Behav Neurosci*. 8: 1–9.

77. 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: 1–8.

78. Millman ZB, Gallagher K, Demro C, Schiffman J, Reeves GM, Gold JM, *et al.* (2019): Evidence of reward system dysfunction in youth at clinical high-risk for psychosis from two event-related fMRI paradigms. *Schizophr Res*. . doi: 10.1016/j.schres.2019.03.017.

79. 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.

80. Schmidt A, Antoniades M, Allen P, Egerton A, Chaddock CA, Borgwardt S, *et al.* (2017): Longitudinal alterations in motivational salience processing in ultra-high-risk subjects for psychosis. *Psychol Med*. 47: 243–254.

81. Smieskova R a, 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.

82. Roiser JP, Howes OD, Chaddock CA, Joyce EM, McGuire P (2013): Neural and Behavioral Correlates of Aberrant Salience in Individuals at Risk for Psychosis. *Schizophr Bull*. 39: 1328–1336.

83. Modinos G, Allen P, Zugman A, Dima D, Azis M, Samson C, *et al.* (2019): Neural Circuitry of Novelty Salience Processing in Psychosis Risk: Association with Clinical Outcome. 1–10.

84. Kirschner M, Hager OM, Muff L, Bischof M, Hartmann-Riemer MN, Kluge A, *et al.* (2018): Ventral Striatal Dysfunction and Symptom Expression in Individuals with Schizotypal Personality Traits and Early Psychosis. *Schizophr Bull*. 44: 147–157.

85. Lancaster TM, Linden DE, Tansey KE, Banaschewski T, Bokde ALW, Bromberg U, *et al.* (2016): Polygenic risk of psychosis and ventral striatal activation during reward processing in healthy adolescents. *JAMA Psychiatry*. 73: 852–861.

86. Sterzer P, Adams RA, Fletcher P, Frith C, Lawrie SM, Muckli L, *et al.* (2018): The Predictive Coding Account of Psychosis. *Biol Psychiatry*. 1–10.

87. Friston K (2009): The free-energy principle: a rough guide to the brain? *Trends Cogn Sci*. 13: 293–301.

88. Corlett PR, Frith CD, Fletcher PC (2009): From drugs to deprivation: A Bayesian framework for understanding models of psychosis. *Psychopharmacology (Berl)*. 206: 515–530.

89. Friston KJ, Stephan KE, Montague R, Dolan RJ (2014): Computational psychiatry: The brain as a phantastic organ. *The Lancet Psychiatry*. 1: 148–158.

90. Sterzer P, Mishara AL, Voss M, Heinz A (2016): Thought Insertion as a Self-Disturbance: An Integration of Predictive Coding and Phenomenological Approaches. *Front Hum Neurosci*. 10: 1–12.

91. Mishara AL, Sterzer P (2015): Phenomenology is Bayesian in its application to delusions. *World Psychiatry*. 14: 184–185.

92. Sterzer P, Voss M, Schlagenhauf F, Heinz A (2019): Decision-making in schizophrenia: A predictive-coding perspective. *Neuroimage*. 190: 133–143.

93. Feldman H, Friston KJ (2010): Attention, uncertainty, and free-energy. *Front Hum Neurosci*. 4. doi: 10.3389/fnhum.2010.00215.

94. Corlett PR, Horga G, Fletcher PC, Alderson-Day B, Schmack K, Powers AR (2019): Hallucinations and Strong Priors. *Trends Cogn Sci*. 23: 114–127.

95. Mirza MB, Adams RA, Friston K, Parr T (2019): Introducing a Bayesian model of selective attention based on active inference. *Sci Rep*. 9: 1–22.

96. Beedie SA, St.Clair DM, Benson PJ (2011): Atypical scanpaths in schizophrenia: Evidence of a trait- or state-dependent phenomenon? *J Psychiatry Neurosci*. 36: 150–164.

97. Cassidy CM, Balsam PD, Weinstein JJ, Rosengard RJ, Slifstein M, Daw ND, *et al.* (2018): A Perceptual Inference Mechanism for Hallucinations Linked to Striatal Dopamine. *Curr Biol*. 28: 503–514.

98. Powers AR, Mathys C, Corlett PR (2017): Pavlovian conditioning–induced hallucinations result from overweighting of perceptual priors. *Science (80-)*. 357: 596–600.

99. Ćurčić-Blake B, Liemburg E, Vercammen A, Swart M, Knegtering H, Bruggeman R, Aleman A (2013): When Broca goes uninformed: Reduced information flow to Broca's area in schizophrenia patients with auditory hallucinations. *Schizophr Bull*. 39: 1087–1095.

100. Horga G, Schatz KC, Abi-Dargham A, Peterson BS (2014): Deficits in Predictive Coding Underlie Hallucinations in Schizophrenia. *J Neurosci*. 34: 8072–8082.

101. Heinz A, Schlagenhauf F (2010): Dopaminergic dysfunction in schizophrenia: Salience attribution revisited. *Schizophr Bull*. 36: 472–485.

102. Schmack K, Rössler H, Sekutowicz M, Brandl EJ, Müller DJ, Petrovic P, Sterzer P (2015): Linking unfounded beliefs to genetic dopamine availability. *Front Hum Neurosci*. 9: 1–10.

103. Corlett PR, Fletcher PC (2012): The neurobiology of schizotypy: Fronto-striatal prediction error signal correlates with delusion-like beliefs in healthy people. *Neuropsychologia*. 50: 3612–3620.

104. Selten JP, Van Der Ven E, Rutten BPF, Cantor-Graae E (2013): The social defeat hypothesis of schizophrenia: An update. *Schizophr Bull*. 39: 1180–1186.

105. Howes OD, Kapur S (2009): The dopamine hypothesis of schizophrenia: Version III - The final common pathway. *Schizophr Bull*. 35: 549–562.

106. Kim KI, Hwu H, Zhang LD, Lu MK, Park KK, Hwang TJ, *et al.* (2001): Schizophrenic delusions in Seoul, Shanghai and Taipei : A transcultural study. *J Korean Med Sci*. 16.

107. Howes OD, McCutcheon R, Owen MJ, Murray RM (2017): The Role of Genes, Stress, and Dopamine in the Development of Schizophrenia. *Biol Psychiatry*. 81: 9–20.

108. Lataster J, Myin-Germeys I, Lieb R, Wittchen H-U, van Os J (2012): Adversity and psychosis: a 10-year prospective study investigating synergism between early and recent adversity in psychosis. *Acta Psychiatr Scand*. 125: 388–399.

109. Sariaslan A, Larsson H, D'Onofrio B, Långström N, Fazel S, Lichtenstein P (2015): Does Population Density and Neighborhood Deprivation Predict Schizophrenia? A Nationwide Swedish Family-Based Study of 2.4 Million Individuals. *Schizophr Bull*. 41: 494–502.

110. Cantor-graae E, Selten J (2005): Schizophrenia and Migration : A Meta-Analysis and Review. *Am J Psychiatry*. 162: 12–24.

111. Krabbendam L, Van Os J (2005): Schizophrenia and urbanicity: A major environmental influence - Conditional on genetic risk. *Schizophr Bull*. 31: 795–799.

112. Varese F, Smeets F, Drukker M, Lieverse R, Lataster T, Viechtbauer W, *et al.* (2012): Childhood adversities increase the risk of psychosis: A meta-analysis of patient-control, prospective-and cross-sectional cohort studies. *Schizophr Bull*. 38: 661–671.

113. Howes OD, Kapur S (2014): A neurobiological hypothesis for the classification of schizophrenia: Type a (hyperdopaminergic) and type b (normodopaminergic). *Br J Psychiatry*. 205: 1–3.

114. Reininghaus U, Kempton MJ, Valmaggia L, Craig TKJ, Garety P, Onyejiaka A, *et al.* (2016): Stress Sensitivity, Aberrant Salience, and Threat Anticipation in Early Psychosis: An Experience Sampling Study. *Schizophr Bull*. 42: 712–722.

115. Day FL, Valmaggia LR, Mondelli V, Papadopoulos A, Papadopoulos I, Pariante CM, McGuire P (2014): Blunted Cortisol Awakening Response in People at Ultra High Risk of Developing Psychosis. *Schizophr Res*. 158: 25–31.

116. Cullen AE, Zunszain PA, Dickson H, Roberts RE, Fisher HL, Pariante CM, Laurens KR (2014):

Cortisol awakening response and diurnal cortisol among children at elevated risk for schizophrenia: Relationship to psychosocial stress and cognition. *Psychoneuroendocrinology*. 46: 1–13.

117. Walker EF, Trotman HD, Pearce BD, Addington J, Cadenhead KS, Cornblatt BA, *et al.* (2013): Cortisol levels and risk for psychosis: Initial findings from the North American Prodrome Longitudinal Study. *Biol Psychiatry*. 74: 410–417.

118. Wand GS, Oswald LM, McCaul ME, Wong DF, Johnson E, Zhou Y, *et al.* (2007): Association of Amphetamine-Induced Striatal Dopamine Release and Cortisol Responses to Psychological Stress. *Neuropsychopharmacology*. 32: 2310–2320.

119. Brunelin J, d'Amato T, van Os J, Cochet A, Suaud-Chagny M-F, Saoud M (2008): Effects of acute metabolic stress on the dopaminergic and pituitary–adrenal axis activity in patients with schizophrenia, their unaffected siblings and controls. *Schizophr Res*. 100: 206–211.

120. Corcoran C, Walker E, Huot R, Mittal V, Tessner K, Kestler L, Aalaspina D (2003): The Stress Cascade and Schizophrenia: Etiology and Onset. *Schizophr Bull*. 29: 671–692.

121. Egerton A, Howes OD, Houle S, McKenzie K, Valmaggia LR, Bagby MR, *et al.* (2017): Elevated Striatal Dopamine Function in Immigrants and Their Children: A Risk Mechanism for Psychosis. *Schizophr Bull*. 43: 293–301.

122. Egerton A, Valmaggia LR, Howes OD, Day F, Chaddock CA, Allen P, *et al.* (2016): Adversity in childhood linked to elevated striatal dopamine function in adulthood. *Schizophr Res*. 176: 171–176.

123. Abercrombie ED, Keefe KA, DiFrischia DS, Zigmond MJ (1989): Differential Effect of Stress on In Vivo Dopamine Release in Striatum, Nucleus Accumbens, and Medial Frontal Cortex. *J Neurochem*. 52: 1655–1658.

124. Boileau I, Dagher A, Leyton M, Gunn RN, Baker GB, Diksic M, Benkelfat C (2006): Modeling Sensitization to Stimulants in Humans: An [11C]Raclopride/Positron Emission Tomography

Study in Healthy Men. *Arch Gen Psychiatry*. 63. doi: 10.1001/archpsyc.63.12.1386.

125. Nestler EJ, Human SE, Malenka RC (2014): *Molecular Neuropharmacology: A Foundation for Clinical Neuroscience*, Third. (A. Sydor & R. Y. Brown, editors). McGraw-Hill Companies.

126. Zenon A, Filali N, Duhamel J-R, Olivier E (2010): Salience Representation in the Parietal and Frontal Cortex. *J Cogn Neurosci*. 22: 918–930.

127. Corlett PR, Honey GD, Fletcher PC (2007): From prediction error to psychosis: Ketamine as a pharmacological model of delusions. *J Psychopharmacol*. 21: 238–252.

128. 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.

129. Schmack K, Gomez-Carrillo de Castro A, Rothkirch M, Sekutowicz M, Rossler H, Haynes J-D, *et al.* (2013): Delusions and the Role of Beliefs in Perceptual Inference. *J Neurosci*. 33: 13701–13712.

130. Schmack K, Rothkirch M, Priller J, Sterzer P (2017): Enhanced predictive signalling in schizophrenia. *Hum Brain Mapp*. 38: 1767–1779.

131. Fusar-Poli P, Howes O, Allen P, Broome M, Valli I, Asselin M-C, *et al.* (2011): Abnormal prefrontal activation directly related to pre-synaptic striatal dopamine dysfunction in people at clinical high risk for psychosis. *Mol Psychiatry*. 16: 67–75.

132. Slifstein M, Giessen E van de, Snellenberg J Van, Thompson JL, Narendran R, Gil R, *et al.* (2015): Deficits in Prefrontal Cortical and Extrastriatal Dopamine Release in Schizophrenia. *JAMA Psychiatry*. 72: 316.

133. Rao N, Northoff G, Tagore A, Rusjan P, Kenk M, Wilson A, *et al.* (2018): Impaired Prefrontal Cortical Dopamine Release in Schizophrenia During a Cognitive Task: A [11C]FLB 457 Positron Emission Tomography Study. *Schizophr Bull*. 45: 670–679.

134. Mccutcheon RA, Marques TR, Howes OD (2019): Schizophrenia—An Overview. 1–10.

135. Tagore A, Schifani C, Rao N, Tseng H-H, Zakzanis KK, Rusjan PM, *et al.* (2019): Prefrontal cortical dopamine release in clinical high risk for psychosis during a cognitive task: a [11C]FLB457 positron emission tomography study. *Eur Neuropsychopharmacol*. 29: 1023–1032.

136. Lodge DJ, Grace AA (2011): Developmental pathology, dopamine, stress and schizophrenia. *Int J Dev Neurosci*. 29: 207–213.

137. Dang LC, O'Neil JP, Jagust WJ (2012): Dopamine Supports Coupling of Attention-Related Networks. *J Neurosci*. 32: 9582–9587.

138. Moran L V., Tagamets MA, Sampath H, O'Donnell A, Stein EA, Kochunov P, Hong LE (2013): Disruption of anterior insula modulation of large-scale brain networks in schizophrenia. *Biol Psychiatry*. 74: 467–474.

139. Howes OD, McCutcheon R (2017): Inflammation and the neural diathesis-stress hypothesis of schizophrenia: A reconceptualization. *Transl Psychiatry*. 7: e1024-11.

140. Jauhar S, McCutcheon R, Borgan F, Veronese M, Nour M, Pepper F, *et al.* (2018): The relationship between cortical glutamate and striatal dopamine in first-episode psychosis: a cross-sectional multimodal PET and magnetic resonance spectroscopy imaging study. *The Lancet Psychiatry*. 5: 816–823.

141. Davies C, Radua J, Cipriani A, Stahl D, Provenzani U, McGuire P, Fusar-Poli P (2018): Efficacy and acceptability of interventions for attenuated positive psychotic symptoms in individuals at clinical high risk of psychosis: A network meta-analysis. *Front Psychiatry*. 9. doi: 10.3389/fpsyt.2018.00187.

142. Cathy D, Cipriani A, Ioannidis JPA, Radua J, Stahl D, Provenzani U, *et al.* (2018): Lack of evidence to favor specific preventive interventions in psychosis: a network meta-analysis. *World Psychiatry*. 17: 196–209.

143. Van Der Gaag M, Smit F, Bechdolf A, French P, Linszen DH, Yung AR, *et al.* (2013): Preventing a first episode of psychosis: Meta-analysis of randomized controlled prevention trials of 12month and longer-term follow-ups. *Schizophr Res*. 149: 56–62.

144. Kaar SJ, Natesan S, McCutcheon R, Howes OD (2019): Antipsychotics: Mechanisms underlying clinical response and side-effects and novel treatment approaches based on pathophysiology. *Neuropharmacology*. 107704.

145. Fusar-poli P, Howes OD, Allen P, Broome M, Valli I, Asselin M (2010): Abnormal Frontostriatal Interactions in People With Prodromal Signs of Psychosis. *Arch Gen Psychiatry*. 67: 683–691.

146. Fiorillo, C. D., Tobler, P. N., Schultz W (2003): Discrete coding of reward probability and uncertainty by dopamine neurons. *Science (80-)*. 299: 1898–1902.

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; [^{11}C]-1-PHNO, [11C]-(1)-4-propyl-9-hydroxynaphthoxazine;
[^{123}I]IBZM, [^{123}I](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

Authors	Sample size	Radiotracer	Study type	Regions reported	Significant results	Effect size
Howes et al. (57)[1]	24 CHR 12 HC	[^{18}F]-DOPA	dopamine synthesis capacity	Striatum AS	CHR ↑ CHR ↑	0.75 0.83
Howes et al. (58)	9 CHR-T 29 HC	[^{18}F]-DOPA	dopamine synthesis capacity	Striatum LS SMS AS	CHR ↑ ↔ ↔ CHR ↑	1.18 1.24
Egerton et al. (59)	26 CHR 20 HC	[^{18}F]-DOPA	dopamine synthesis capacity	Striatum LS SMS AS	CHR ↑ ↔ ↔ CHR ↑	0.81 0.73
Mizrahi et al. (46)[2]	12 CHR 12 HC	[^{11}C]-1-PHNO	Stress-induced dopamine release	Striatum LS SMS AS	CHR ↑ ↔ CHR ↑ CHR ↑	- - - -
Bloemen et al. (60)	14 CHR 15 HC	[^{123}I]IBZM	Synaptic dopamine concentration	Striatum	↔	-
Tseng et al	24 CHR	[^{11}C]-1-PHNO	Stress-induced	Striatum	↔	-

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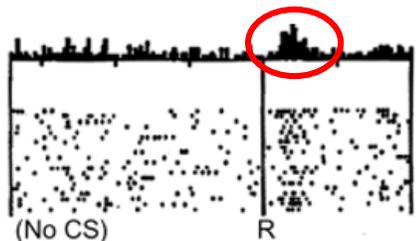| (45)[3]	25 HC		dopamine release			

Table 2: studies examining reward or salience processing in CHR subjects.

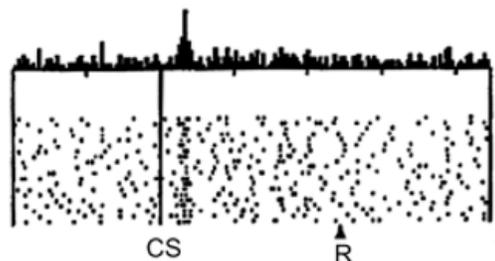| Authors	Population	Task	Measure	Significant results		Effect size
Juckel et al. (75)	13 CHR 13 HC	MID	Behavioural fMRI	↔ ↔		
Wotruba et al. (76)	21 CHR 24 HC	MID	Behavioural fMRI	↔ CHR↑ (posterior cingulate cortex & R/L medial & superior frontal gyrus)		-
Winton-Brown et al. (77)	29 CHR 32 HC	SIT	Behavioural fMRI DCM	CHR↓ CHR↑ reward anticipation (L ventral pallidum & L midbrain) CHR↑ reward-induced modulation of connectivity (VS & pallidum-midbrain)		- - -
Millman et al. (78)	19 HC 22 CHR	MID RL	Behavioural fMRI Behavioural fMRI	↔ ↔ CHR↓ RL CHR↓ (VS & vPFC)		-
Ermakova et al. (79)	30 CHR 39 HC 14 FEP	RL	Behavioural fMRI	↔ CHR↓ (vs. HC) (midbrain) CHR↑ (vs. FEP) (midbrain)		- -
Schmidt et al. (80)	23 CHR 13 HC	SAT	Behavioural	CHR↑ implicit aberrant salience CHR↓ implicit adaptive salience		- -

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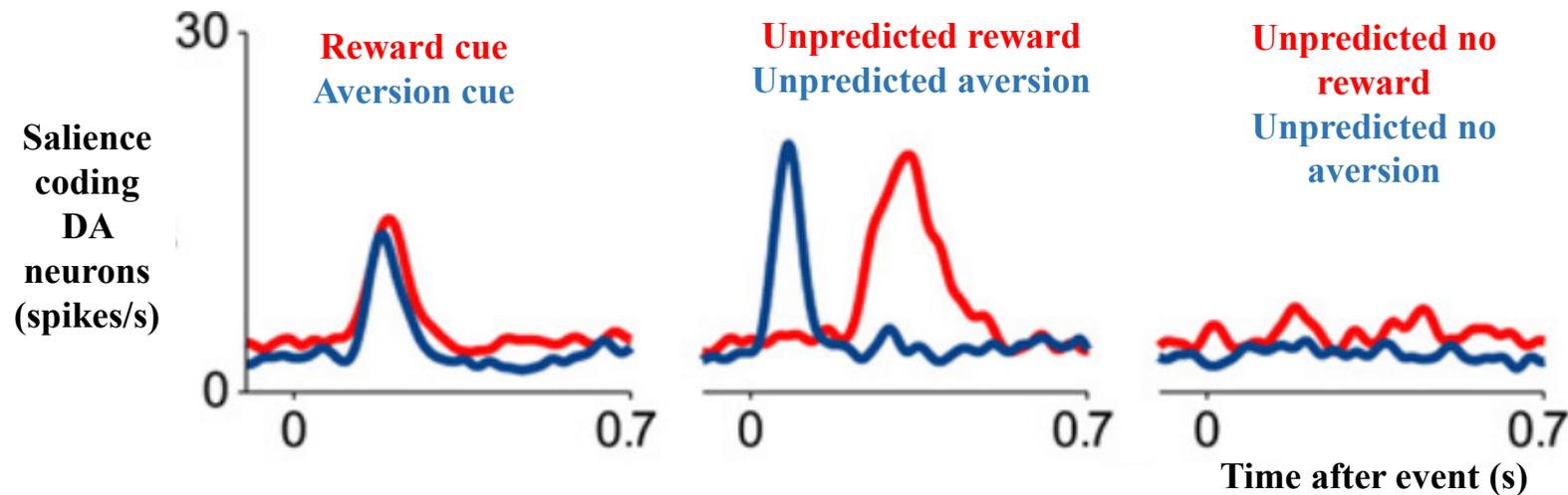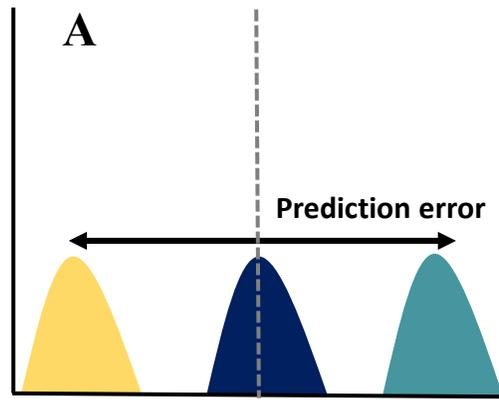|				CHR explicit adaptive salience	-
			fMRI	CHR ↓ adaptive salience (R/L VS, R/L calcarine sulcus & midbrain, L cuneus, middle temporal gyrus)	-
Smieskova et al. (81)	34 CHR 19 HC 29 FEP (19 unmedicated & 12 medicated)	SAT	Behavioural	↔	
			fMRI	CHR ↓ (vs. HC) adaptive salience (R inferior parietal 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	Behavioural	CHR ↑ explicit aberrant salience	-
			fMRI	↔	
			PET	↔	

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A

No reward cue
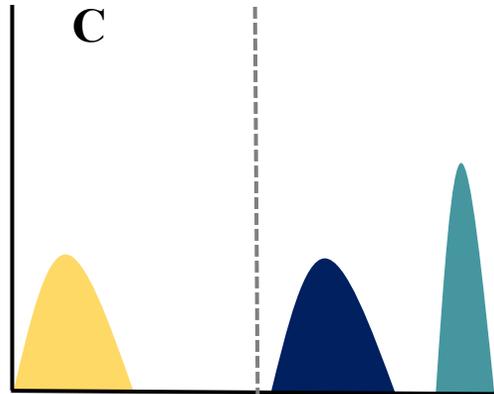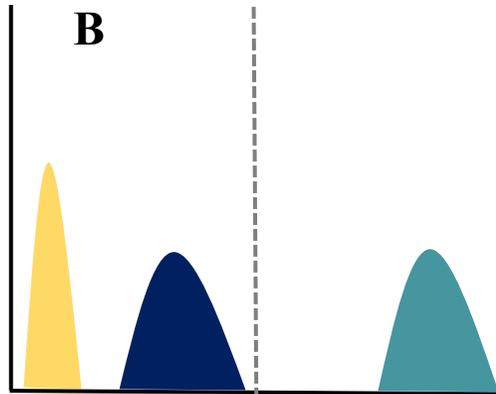Unpredicted reward

(No CS)   R

Reward cue
Predicted reward

CS   R

Reward cue
Unpredicted no reward

-1   0   1   2 s
      CS   (No R)

C

rho = -.71
P = 0.002

VS activation encoding belief update

Striatal DA release

B

Salience
coding
DA
neurons
(spikes/s)

Reward cue
Aversion cue

Unpredicted reward
Unpredicted aversion

Unpredicted no
reward
Unpredicted no
aversion

0   0.7   0   0.7   0   0.7
Time after event (s)

A Prediction error

Prior prediction Posterior belief Sensory data

B

C

D

E

Increased precision of prior prediction

Increased precision of prediction error
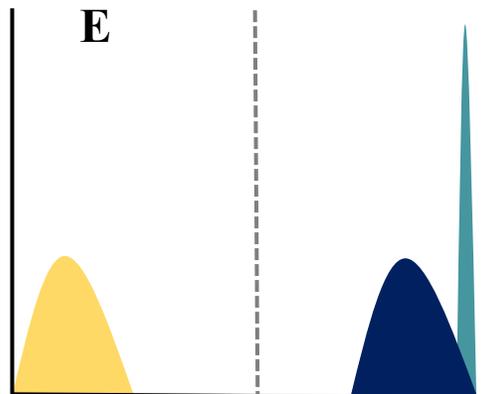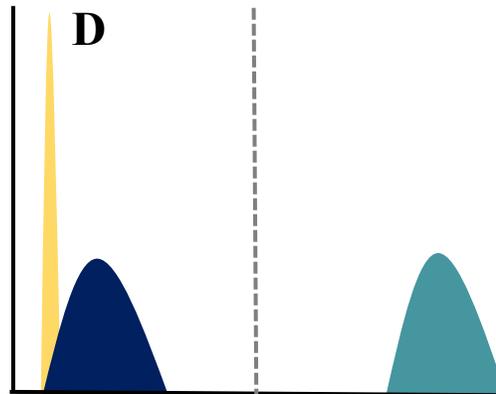
Healthy control
Perception optimally represents prior prediction & prediction error

Clinical high risk
Perception somewhat overrepresents prior prediction or prediction error

Psychosis
Perception strongly overrepresents prior prediction or prediction error