Review

Dopaminergic basis of salience dysregulation in psychosis

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Disrupted salience processing is proposed as central in linking dysregulated dopamine function with psychotic symptoms. Several strands of evidence are now converging in support of this model. Animal studies show that midbrain dopamine neurons are activated by unexpected salient events. In psychotic patients, neurochemical studies have confirmed subcortical striatal dysregulation of dopaminergic neurotransmission, whereas functional magnetic resonance imaging (fMRI) studies of salience tasks have located alterations in prefrontal and striatal dopaminergic projection fields. At the clinical level, this may account for the altered sense of meaning and significance that predates the onset of psychosis. This review draws these different strands of evidence together in support of an emerging understanding of how dopamine dysregulation may lead to aberrant salience and psychotic symptoms.

Dopamine and schizophrenia

Dopaminergic systems have been implicated in the pathophysiology of schizophrenia and psychosis for more than 40 years, following seminal early work showing that reserpine depleted dopamine stores [1] and that neuroleptics are dopamine receptor antagonists [2]. Box 1 summarises the early lines of evidence linking dopaminergic alterations to schizophrenia. Subsequent studies (reviewed below) have refined this understanding, and led to the hypothesis that the dopamine system is altered in schizophrenia, leading to a dysregulated firing of dopamine neurons and heightened levels of dopamine release. But why does a biochemical disturbance in brain dopamine systems lead to delusional ideas, perceptual abnormalities, and the phenomenon of psychosis? There remains an explanatory gap between what we understand about the neurobiology of psychosis and what we understand about its subjective psychopathological experience.

In recent years, there have been attempts to bridge this gap. We will critically review here the evidence for the recent interpretation of dopaminergic dysfunction in psychosis, according to which delusions emerge as an individual's own explanation of the experience of aberrant salience. We start by examining normal aspects of salience and salience processing and how these relate to dopamine function in the human brain. We then describe the experience of aberrant salience in those experiencing early symptoms of psychosis, before examining experimental evidence of aberrant salience from animal studies and from neuroimaging studies in humans. We conclude by considering the specificity of salience dysregulation to psychosis in different contexts and the effects of treatment.

What is salience? Vision, attention, and goal-directed behaviour

The broad challenge for any organism negotiating a sensorially complex world is how to efficiently and effectively choose and respond to relevant stimuli, whether predator, prey, or potential mate. The human world is particularly complex and the demands of seemingly limitless and changing perceptual inputs compete for limited cognitive and, particularly, limited motor resources. This allocation involves the processes of attention [3], filtering, sensory and behavioural orientation, motivation, action selection, and execution [4]. Stimuli are prioritised according to their 'saliency': their features are compared to their context. For vision, certain features tend to be more salient [5]; brightness, movement, colour, contrast, and orientation sum together in a topographic map of features within a scene that draw attention [6,7]. Maps that add higher semantic features are being developed for robotics [8].

There are analogous features for other senses and highly salient stimuli, such as a loud bang or a flash of light, are considered largely independent of the organism's state. Mostly, however, stimulus-driven processing interacts with internal factors of the organism, such as goals, beliefs, history, and so on, to determine the most salient stimulus at a given point in time and place for a given organism, pulling attention and cognition, and driving behaviour. Such stimuli are necessarily multifaceted (Figure 1). For example, a hungry field mouse will mostly ignore everything that is not the smell, sight, or sound of food until an unexpected novel and potentially dangerous event, such as

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Box 1. Early evidence for the involvement of dopamine in the pathophysiology of schizophrenia

- Drugs that increase synaptic dopamine levels (e.g., amphetamine, levodopa) can induce psychotic symptoms in people and worsen psychotic symptoms in patients with schizophrenia
- Drugs that deplete dopamine levels (e.g., reserpine) reduce psychotic symptoms in patients with schizophrenia
- All currently licensed antipsychotic drugs block dopamine receptors
- There is a close indirect relationship between the dose of different antipsychotic drugs used to treat patients and their affinity for dopamine receptors
- Dopamine levels are elevated post-mortem in the brains of patients with schizophrenia, but prior antipsychotic treatment is a confound
- In some studies, dopamine metabolite levels are elevated in plasma and cerebrospinal fluid in antipsychotic-free patients with schizophrenia

the shadow of a bird of prey overhead, rightly overrides the search.

This has been characterised as a 'selection problem', instantiated in the functional loops of the basal ganglia [9]. It extends to internal stimuli also: emotions, thoughts, memories, action plans, and movements are represented across the functional loops of the basal ganglia [10], and are prioritised and selected on the basis of a 'common currency' – their salience [4]. Prioritisation here presumably requires selecting the most salient competitors and suppressing their rivals, and probably involves the actions of dopamine.

What does dopamine do? Reward prediction, prediction error, and learning

A key influence on goal-directed behaviour is the pursuit of reward and the avoidance of punishment. Reward here refers to the positive value given to an object, a behavioural act, or an internal state [10] (Table 1). The role of dopamine has received particular attention in this context: many drugs of addiction work by increasing or prolonging the action of dopamine in its main projection targets [11], and animals with electrodes implanted in dopamine-related areas will repeatedly choose to stimulate these over food and sex, sometimes until death [12]. It is well established that dopamine neurons are involved in reward processing [13,14] and it has been suggested that they encode a reward prediction error rule [15], which drives learning, that is, they are selectively excited by unexpected rewards or unexpected reward-predicting stimuli and inhibited when expected rewards fail to appear. Along these lines, optogenetic activation of dopamine cells paired with reward delivery has recently been used to demonstrate overcoming of associative blocking and prevent extinction learning of reward cues [16]. In these models, large prediction errors, represented by large phasic dopamine signals, are highly salient, leading the organism to switch behaviour and cognition at ascending scales [17].

This switching is affected by changes in dopamine levels, and it was recognised early on that mild to moderate increases in dopamine neurotransmission facilitates behavioural switching [18], that is, makes it easier for competing inputs to interrupt current selections. This may have relevance for the effect of altered dopamine levels in psychosis, which is characterised by a number of domain-specific intrusions, which are discussed below.

More recently, focus has shifted to dopamine's importance in the incentive properties of a stimulus, rather than the prediction error, reward, or hedonic properties [19,20]. How restricted such responses are to reward has also become the subject of considerable debate [21].

Non-reward aspects of dopamine and salience: novelty, aversion, and emotion

It has been suggested that dopamine-driven prediction error signalling may not be selective for rewards, but instead may reflect general salience [21–23]. In support of this suggestion, animal studies demonstrate that novel

Figure 1. Salience is multifaceted and signalled (in part) by dopamine.

Table 1. Assessing salience in subjects with psychosis

Salience dimension	Task examples	Main contrast
Reward prediction	Classical conditioning task, cues predict reward/loss (e.g., money, +/− dependent on performance)	Main contrast at cue onset of reward or loss predicting cue – neutral cue +/− scaled according to amount of gain/loss
Threat prediction	Classical conditioning type task, cues predict aversive stimulus – (e.g., loud noise/footshock/airpuff, +/− dependent on performance)	Main contrast at cue onset of threat predicting cue – neutral cue
Prediction error	Classical conditioning type task, dynamic cue contingencies create quantifiable outcome expectations	Main contrast models extent of 'prediction error' at outcome, sometimes quantified trial to trial by temporal difference or Q-learning models
Emotional salience	Emotional and neutral scenes/faces/words	Main contrast model difference between emotional and neutral stimuli
Novelty salience	Novel and familiar scenes	Main contrast model difference between novel vs. prefamiliarised pictures
Explicit salience attribution	Reward learning task	Main contrast quantifies attributions to outcome relevant vs. outcome irrelevant stimulus dimensions

lights and tones (which do not appear to be overtly rewarding) often excite dopamine neurons [24,25] and faster (50–100 ms) than would allow accurate reward prediction calculations [22]. Like reward, novel stimuli have a high propensity for behavioural interrupt and also reinforcement. In humans, there is considerable evidence for the role of novelty in salience – novelty may be itself intrinsically rewarding, or provide a 'bonus' in the search for reinforcers [26]. Novel stimuli are associated with fMRI activations in the dopaminergic midbrain [27] and enhance memory formation [28,29], possibly via recurrent hippocampal–ventral tegmental area (VTA) loops [30].

It has also long been established in animal studies that aversive events, such as footshocks, pinches, or airpuffs (which are clearly not rewarding), and prolonged anxiogenic events (e.g., restraint) increase dopamine release in projection target regions and increase firing in some putative dopamine neurons [31–35]. In human fMRI studies, dopaminergic regions activate in response to aversive stimuli and their anticipation [36].

Similarly, the experience and recognition of emotion is highly salient, although not as easily modelled in animals [37]. In humans, emotion captures attention and behaviour, enhances memory, and interacts with the processing of reward in dopaminergic areas [38]. Presynaptic dopaminergic function both in the amygdala [39] and in the midbrain [40] modulates the processing of emotional stimuli.

Although attempts have been made to fit these observations within a reward framework (e.g., [21] and more recently [41]), recent animal studies point towards an alternative resolution – that there are functionally distinct subgroups of dopamine neurons [42–44]. Much progress has come through the use of single-cell labelling combined with electrophysiological recording, fast neurochemical sampling of dopamine, and through reinvestigation of the issue using standard electrophysiology and behavioural approaches. For example, although it appears that some putative dopamine neurons in the rodent VTA that are excited by aversive stimuli are in fact not dopaminergic [45], it has also been confirmed that distinct subgroups of neurochemically-identified VTA dopamine neurons (using single-cell labelling) can be either excited or inhibited by aversive events [42] and by stimuli predicting aversive events [46]. Similarly, in monkeys at least two distinct groups of putative dopamine neurons have been proposed that code for either reward prediction errors or salience prediction errors (Figure 2A) [43,47]. It has been recently argued that these activations may be more closely related to physical salience, or stimulus intensity, rather than aversiveness [41,48].

In both the VTA [42,49] and substantia nigra pars compacta (SNc) [43] these functionally-distinct dopamine groups appear to be somewhat anatomically segregated, which suggests that they may innervate different target regions. It may be that different parts of the striatum (or different target regions including the prefrontal cortex and amygdala) receive either a reward prediction error signal or a salience prediction error signal depending on the source of their dopaminergic innervation. Consistent with this, unexpected aversive stimuli evoke fast, phasic dopamine release (as measured using fast-scan cyclic voltammetry) in the dorsal striatum and core of the nucleus accumbens, but not the shell of the nucleus accumbens (where rewards do increase dopamine) [50,51]. In addition, even reward-predicting stimuli do not appear to evoke dopamine release in all regions of the striatum [52] (Figure 2B). Moreover, optogenetic activation of dopamine neurons projecting to the nucleus accumbens can induce conditioned place preference, whereas activation of those projecting to the prefrontal cortex induces conditioned place aversion [53].

Taken together, these findings suggest that dopamine neurons may be functionally heterogeneous, and that distinct subgroups may code for either salience or reward prediction errors [41]. If this is the case, then presumably target regions, or particular microcircuits within those regions, will receive input from only one subgroup. Indeed, it is well established that there is mediolateral topography within this system, such that, for example, more medial dopamine neurons innervate more medial target regions [54,55]. With respect to the salience dysfunction hypothesis of schizophrenia, these findings are consistent with the original suggestion that dopamine function relates to the multifaceted nature of salience, and that dopamine dysfunction can lead to aberrant salience attribution. Which aspects are most crucially disturbed remains to be established (Box 2). Although

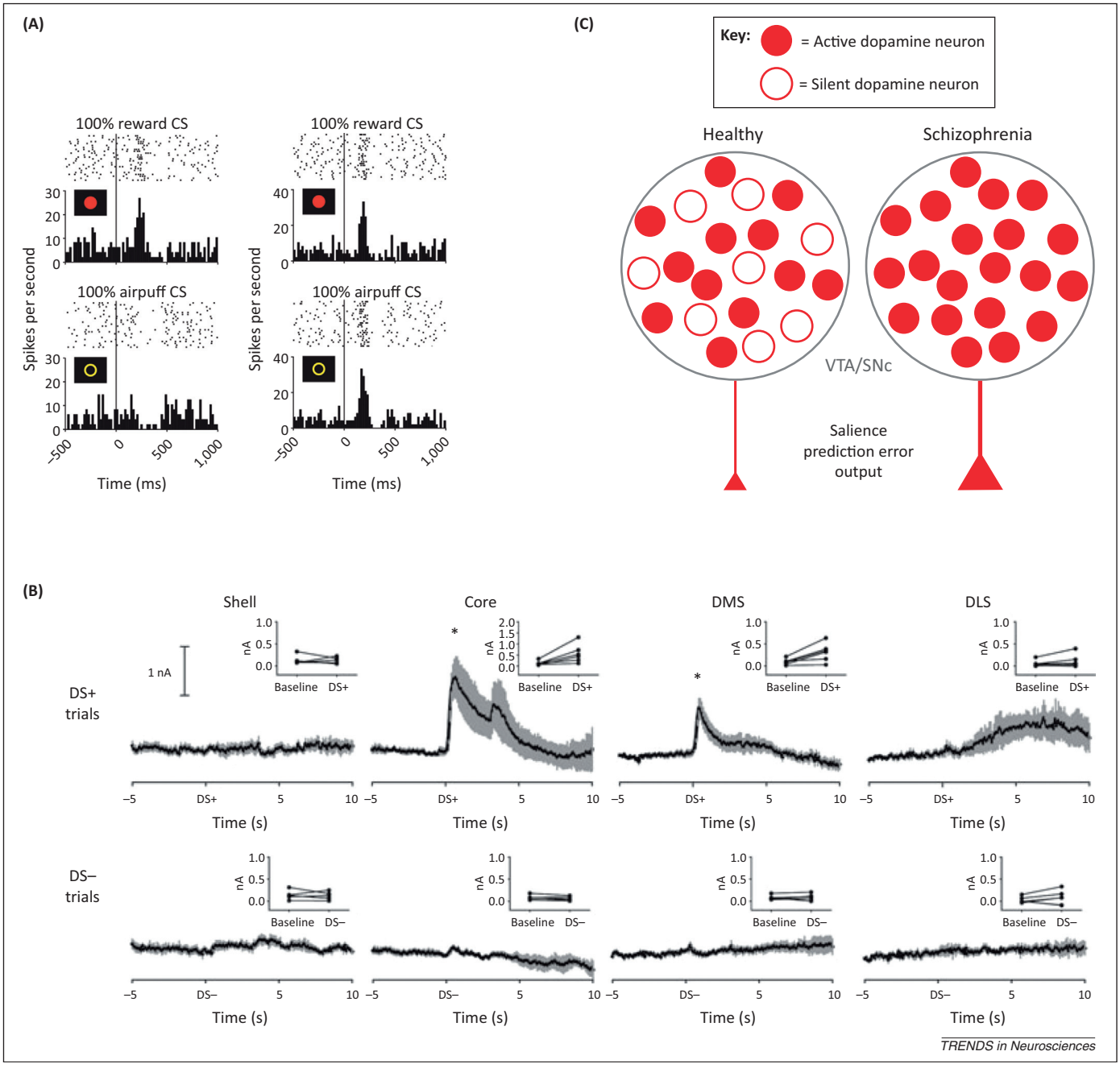

Figure 2. Animal studies of salience in psychosis. **(A)** Two examples (raster plots and histograms) of substantia nigra dopamine neuron activity in response to conditioned stimuli (CS) that predict either reward or an aversive airpuff. Left: shows a putative dopamine neuron that is selectively excited by the stimulus that predicts reward. Right: shows a putative dopamine neuron excited by both stimuli (i.e., coding for salience prediction error [40]). **(B)** Fast-scan cyclic voltammetry measurements of dopamine release reveal region-specific differences. A stimulus predicting reward (DS+) evokes release in the nucleus accumbens core, but not shell, and in the dorsomedial (DMS), but not dorsolateral (DLS), striatum [45]. No responses are seen to the control stimulus that was not paired with reward (DS–). **(C)** Schematic illustrating the hypothesis that in schizophrenia the number of spontaneously active ventral tegmental area/substantia nigra pars compacta (VTA/SNc) dopamine neurons is increased, leading to enhanced salience prediction error output (based on [53]).

reward and reward prediction error processing typically involve ventromedial striatal systems that are activated by amphetamine, preclinical schizophrenia models implicate more dorsolateral striatum [56], corresponding to the region where elevations in the prodrome to psychosis and in schizophrenia patients appear most robust [57,58]. This region is functionally linked to associative cortical regions such as the dorsolateral prefrontal cortex and is thought to be involved in the attentional salience of stimuli [10], suggesting that this may be important in the development of psychosis.

The experience of aberrant salience in early psychosis

Clinicians have long noted that, prior to the onset of frank psychosis, there is typically a prodromal period, often lasting months or longer, during which the patient often has the sense that something odd but important or threatening is going on around them that they cannot quite explain. This has been referred to as 'delusional mood', which was well known to early phenomenologists of psychosis. Conrad termed this period 'trema' (stage fright) [59], whereas Jaspers described that a 'general delusional atmosphere with all its vagueness of content' is emotionally 'unbearable' and

Box 2. Outstanding questions

- Although preclinical evidence suggests that an altered balance between phasic and tonic dopamine neurotransmission (leading to disordered phasic responses) is central to salience dysregulation and psychosis, the time scale and other limitations of fMRI and PET imaging mean this remains an open question in human subjects.
- A key aspect of the model is that salience dysregulation predates the onset of psychosis – this remains to be determined.
- Investigations in psychosis have largely focussed on reward, but it seems likely that the non-rewarding aspects of salience regulation, such as novelty and emotion, may be more critical.
- The inputs that dysregulate dopamine dysfunction and lead to salience dysregulation need to be determined in patients with psychosis, particularly as this could provide novel treatment targets.

'patients obviously suffer terribly under it' (p. 68 in [60]). Binswanger described the delusions as taking place on this delusional 'theater stage (Wahnbühne)', where the inner contents of the patient's minds are played out in front of them [61]. More recently this has also been described as the 'Truman Sign' because patients describe this experience as akin to that experienced by the eponymous hero in the film *The Truman Show* [62]. In this film, the hero unknowingly lives on a film set where all the people in his life are actors, and his life is being filmed for the entertainment of others. It is the hero's slow realisation that what he took to be reality is in fact a fabrication that many of our patients liken to their experience of the prodrome of psychosis. They describe an emotional and sensory overload, with a growing sense that things and events around them have a hidden important meaning, although, at this stage, they are unsure what this is, and often describe a sense that the world has changed in some way they cannot pin down. These experiences may create a new world ('everything gets a new meaning'), thus represent clinical features of an impending onset of psychosis [61].

From the preceding sections, it is conceivable how dysregulated salience processing could underlie this experience. Increases in dopamine neurotransmission in animals increase the propensity for competing internal and external stimuli to interrupt current selections, and reduce the threshold for behavioural switching [18]. In humans this may be experienced as aberrations in salience processing where attention and action selection are redirected to irrelevant stimuli, internal or external, or directed diffusely, leading to sensory overload.

The delusions that characterise psychosis emerge out of this context when, usually over many months, the patient becomes convinced of an explanation for this preoccupying and distressing experience. The individual's interpretation of the experience will likely reflect their own prior beliefs and experience [63,64]. It is not surprising then that delusional beliefs are often personal and rooted in long-held beliefs, and that the content of delusions varies according to culture, influenced by sociocultural factors [65].

Animal models of schizophrenia and the link to salience dysregulation

Electrophysiological studies in animal models of schizophrenia suggest that dopamine neuron activity may be altered in a way that is likely to strongly affect the salience prediction error signal and may therefore contribute to salience dysregulation. For example, in a rat developmental model of schizophrenia, administration of the mitotoxin methylazoxymethanol acetate (MAM) to pregnant rats, leads to increased numbers of spontaneously active dopamine neurons in their offspring [49]. It is estimated that, in wild type animals, up to 50% of dopamine neurons may be silent *in vivo*, presumably because of strong inhibitory inputs from regions such as the ventral pallidum. It has been suggested that this inhibition from the ventral pallidum is reduced in schizophrenia, leading to an increase in the number of spontaneously active dopamine neurons [66]. Consequently, it may be that the number of dopamine neurons participating in providing prediction error signals is upregulated in schizophrenia, which in turn could contribute to salience dysregulation (Figure 2C) [66]. Increased dopaminergic tonic transmission is likely to mainly affect high affinity D2/3 receptors, which are the target of antipsychotics, whereas increased phasic transmission may be more likely to affect low affinity D1 receptors. In addition, it has long been established that although acute antipsychotics increase dopamine neuron activity, chronic antipsychotic treatment decreases the number of spontaneously firing dopamine neurons in control animals [67,68]. Interestingly, the MAM-induced increased dopamine neuron population activity appears to be greatest in lateral dopamine neurons, whereas effects of amphetamine are mostly medial [56]. Moreover, it can be rapidly reversed with antipsychotic treatment, suggesting that regulation of population activity, and thereby the magnitude of the dopamine signal, may be a therapeutic mechanism [69].

Neurochemical imaging studies of dopaminergic neurotransmission in psychosis

Molecular imaging with positron emission tomography (PET) or single-photon computed tomography has enabled dopaminergic neurotransmission to be studied *in vivo* in humans. There have now been over fifty studies using these techniques to probe presynaptic and postsynaptic aspects of striatal dopamine neurotransmission in patients with psychotic disorders [57]. The first step in neurotransmission is the synthesis of dopamine ready for release from nerve terminals. Dopamine synthesis capacity can be measured using radiolabelled 3,4-*l*-dihydroxyphenylalanine (L-DOPA). Studies using this technique have found elevated dopamine synthesis capacity in schizophrenia [58,70–74] and recent meta-analyses indicate that the effect size is large [75,76].

The next step in neurotransmission is the release of dopamine into the synapse. This can be indexed by measuring the change in radiotracer binding following a challenge known to alter dopamine neurotransmission [77,78]. Studies have applied amphetamine challenges to probe dopamine release capacity in schizophrenia compared to controls. In these studies, radiotracer displacement following amphetamine has consistently been found to be much greater than that in controls, and to be directly correlated with the transient worsening of psychotic symptoms induced by amphetamine [79–81]. This is not specific to

amphetamine: recent findings indicate that patients with schizophrenia also show greater radiotracer displacement to a standard psychosocial stress challenge, providing evidence that the dopamine system, in these patients, is generally hyper-responsive [82]. Interestingly, the elevation appears to be most apparent in acutely psychotic patients, and much less marked in stable remitted patients [81].

Synaptic dopamine levels at rest can be assessed by depleting presynaptic dopamine stores using a drug such as alpha-methyl-*para*-tyrosine, which blocks dopamine synthesis and reduces extracellular dopamine levels. Studies using this dopamine depletion technique have found that baseline occupancy of D2/3 receptors by dopamine is elevated in schizophrenia, which suggests that extracellular dopamine concentrations are elevated at baseline [83]. Elevated dopamine synthesis capacity and stress-induced dopamine release have also been found in high risk subjects experiencing prodromal symptoms [84] prior to the onset of the full-blown illness [58,82,85,86], although studies in people at genetic risk are inconsistent [87,88]. Elevated dopamine synthesis capacity is not seen in people with long-term subclinical symptoms who have not developed schizophrenia, suggesting specificity to the development of the clinical disorder [89]. Furthermore, dopamine synthesis capacity has been found to increase with the onset of psychosis [90].

By contrast, findings on D2/3 receptor availability have been less consistent. Meta-analysis of the studies to date indicates that D2/3 receptor availability is elevated in schizophrenia, but the effect size is small [76]. Striatal dopaminergic transmission is predominantly terminated by dopamine transporters. Because meta-analyses of the studies of dopamine transporter availability indicates that this is unaltered in schizophrenia, there does not seem to be a compensatory increase in the capacity of the dopamine system to 'buffer' the effects of disordered dopamine neurotransmission in schizophrenia [76,91].

Studies to date have focussed on striatal dopaminergic neurotransmission [76]. Consequently, it remains to be determined how this reflects dopamine function in other regions, although findings on D2/3 receptor availability outside the striatum indicates that this aspect of dopamine neurotransmission is not consistently altered in schizophrenia [63,92]. Nevertheless, taken together, the molecular imaging studies provide compelling evidence that striatal dopaminergic neurotransmission is altered in schizophrenia, and linked to the onset of psychosis, in line with recent theories [57,93]. Furthermore, they indicate that nigrostriatal neurotransmission is overactive, both at rest and in response to stimulation, and there has been no compensatory increase in the capacity to terminate neurotransmission.

fMRI studies of salience in psychosis

fMRI studies allow the direct measurement of functional activation during salience processing in psychosis. fMRI has a temporal resolution of about 10 s and thus cannot be used to directly measure abnormalities relating to the phasic increase in dopamine firing, which ranges in the milliseconds scale [23]. However, it can address changes in neuronal network activation, which may result from a brief dopaminergic input. Early studies tested the hypothesis that the increase in dopaminergic activation of schizophrenic patients [75,91] would conceal the phasic increase in dopamine elicited by reward-predicting cues and thus obscure the fMRI signal.

Table 2. Functional magnetic resonance imaging (fMRI) studies investigating ventral striatal (VS) alterations in schizophrenia during monetary reward prediction tasks (published up to 2012)

Author	Year	SCZ				HC (*n*)	BOLD response in VS (SCZ vs. HC) during reward/error prediction			
		(*n*)	Diagnosis[a]	Illness stage and medication			Effect	Cohen's *d*[d]	Correlation with symptoms	Type of symptoms
Juckel *et al.* [96]	2006	20	DSM-scz	Chronic	A (10 FGA; 10 SGA)	10	↓ (for FGA) – (for SGA)	1.51	↙ (–)	PANSS neg
Juckel *et al.* [94]	2006	10	DSM-scz	First episode	7 DN, 3 DF	10	↓	1.50	↙ (–)	PANSS neg
Schlagenhauf *et al.* [120]	2008	10	DSM-scz	Chronic	A (10 FGA then 10 SGA)	10	↓ (for FGA) – (for SGA)	1.37	↙ (–)	PANSS neg
Murray *et al.* [100]	2008	13	DSM-scz[b]	First episode	5 DN, 8 A	12	↓	0.69		BPRS
Abler *et al.* [121]	2008	12[c]	DSM-scz/scf	Chronic	A (3 FGA, 9 SGA)	12	–	NA	NA	
Schlagenhauf *et al.* [95]	2009	15	DSM-scz	Mixed	8 DN, 7 DF	15	↓	0.84		PANSS pos
Walter *et al.* [122]	2009	16	DSM-scz	Chronic	A (SGA)	16	–	NA	NA	
Simon *et al.* [123]	2010	15	DSM-scz/scf	Chronic	A (SGA)	15	–	NA	↙ (–)	AES
Waltz *et al.* [97]	2010	17	DSM-scz/scf	Chronic	A (1 FGA; 16 SGA)	17	↓	1.37	↙ (–)	SANS
Koch *et al.* [124]	2010	19	DSM-scz	Chronic	A (18 SGA, 1 DF)	20	↓	0.64	NA	
Morris *et al.* [98]	2012	21	DSM-scz/scf	Chronic	A (SGA)	16	↓	1.39	↙ (–)	PANSS tot, neg
Nielsen *et al.* [99]	2012	31	ICD-scz/scf	First episode	DN	31	↓	0.57	↙ (–)	PANSS pos

[a]A, antipsychotic; AES, Apathy Evaluation Scale; BOLD, blood oxygen level dependent; BPRS, Brief Psychiatric Rating Scale; DF, drug free; DN, drug naive; DSM-scz/scf, schizophrenia or schizoaffective Diagnostic and Statistical Manual of Mental Disorders (DSM) diagnosis; ICD-scz/scf, schizophrenia or schizoaffective International Classification of Diseases (ICD) diagnosis; FGA, first generation antipsychotics; HC, healthy controls; NA, not applicable; PANSS, Positive and Negative Syndrome Scale (tot, total scores; neg, negative subscale; pos, positive subscale); SANS, Scale for the Assessment of Negative Symptoms; SCZ, patients with schizophrenia; SGA, second generation antipsychotics.

[b]Two patients were diagnosed with bipolar disorder and psychosis not otherwise specified.

[c]A third group of 12 manic patients was additionally investigated in this study.

[d]Cohen's *d* was computed as a measure of effect size only in case of significant differences between patients and controls.

It is not yet clear which is the most critical aspect of salience that is altered in psychosis; the concept of salience has been widely applied. Results of the frequently used monetary reward prediction task are summarized in Table 2. Most studies found that functional activation in the ventral striatum following reward-predicting stimuli is blunted in schizophrenia patients as compared to controls, with consistent findings in unmedicated first-episode schizophrenia patients [94,95]. More importantly, there is converging evidence indicating such alterations are associated with both negative symptoms [94–98] and positive symptoms [99] of schizophrenia (Table 2). Further fMRI reward task variants have clarified that schizophrenia is also associated with altered ventral striatal response to neutral stimuli, interpreted as a neural correlate of the aberrantly assigned motivational salience to irrelevant/neutral stimuli [100]. In another interesting variant that explicitly tests salience attributions [101], patients at high risk of psychosis attributed greater relevance to irrelevant cues, and ventral striatal fMRI signals to these cues were correlated with delusion scores [102].

As noted above, aspects of salience and dopamine function extend beyond reward although, to date, studies in patients are few. Increased responses to neutral stimuli analogous to those found in reward-based tasks have been found in salience paradigms relating to anticipation of aversive stimuli [103], viewing emotional scenes [104,105], and emotional words [106]. Also, functional connectivity between the brain areas implicated in salience processing is altered during reward conditioning in schizophrenic patients [107]. Overall, the above studies provide evidence that the brain regions implicated in salience processing are dysfunctional in psychosis from onset.

Can antipsychotics modulate reward learning?

All currently licensed antipsychotic drugs bind to D2/3 receptors to some degree [108]. Furthermore, the level of antipsychotic D2/3 occupancy in the striatum is related to therapeutic response [109,110], and although some antipsychotic drugs also bind to other receptors, they are no more effective than highly selective D2/3 receptor antagonists [108,111]. Taken together, this is strong evidence that blocking dopaminergic neurotransmission is central to the therapeutic response. Given this and the roles of dopaminergic neurotransmission in reward, aversion, and learning outlined above, one would anticipate that antipsychotic drugs would modulate these processes, and that this might underlie the treatment response [63,64]. A limited number of studies have employed reward and aversive learning-based paradigms in patients treated with antipsychotics (Table 2). However, the interpretation of these studies is complicated because alterations could be due to treatment or the underlying disorder (e.g., [96]). Studies in healthy volunteers have found that antipsychotics modulate the brain response to rewarding and aversive stimuli [112], reward and aversion prediction errors [104], and reward-based learning [113]. These findings indicate that antipsychotics modulate salience processing of stimuli, although the effects may depend on whether the drug is primarily acting presynaptically or postsynaptically at the dose used [113,114].

Specificity of salience dysregulation to schizophrenia or psychosis

Although psychosis is a cardinal feature of schizophrenia, it is also seen in a number of other psychiatric conditions, particularly bipolar affective disorders and severe depression. Psychosis is also seen in epilepsy, particularly temporal lobe epilepsy, and of course is associated with the use and abuse of drugs that alter dopamine neurotransmission, such as amphetamine and L-DOPA. Elevated dopamine synthesis capacity has been detected in patients with temporal lobe epilepsy who experienced psychosis compared to patients with temporal lobe epilepsy who did not experience psychosis and controls [71]. Thus the same dopaminergic abnormality seen in schizophrenia was associated with psychosis in temporal lobe epilepsy, suggesting that the same dopamine-mediated dysfunction underlies psychosis in both conditions. The link between psychosis and temporal lobe dysfunction, whether due to epilepsy or schizophrenia, fits with the preclinical evidence of the effects of damage to this brain region (see the discussion on the MAM model above) and preliminary data in people with prodromal signs of psychosis [115,116]. Moreover, the pilocarpine-induced temporal lobe epilepsy model in the rat involves an increase in the number of spontaneously active dopamine neurons [117]. However, it remains to be determined if dopamine dysfunction is associated with psychosis in bipolar affective disorder or severe depression. Nevertheless, observations dating back over four decades that amphetamine can induce psychotic symptoms in healthy volunteers [118,119] suggest that the link between dopamine dysfunction and psychosis is not specific to schizophrenia. Another complication is that processes other than the attribution of salience, such as stress and motor learning, may contribute to the dopamine release indexed by imaging studies, complicating the interpretation of studies of dopamine and salience regulation [77]. This notwithstanding, the animal findings discussed above suggest that irrespective of whether it is due to schizophrenia, temporal lobe epilepsy, or amphetamine, altered dopamine neurotransmission would lead to salience dysregulation. Therefore, this suggests that salience dysregulation is not specific to schizophrenia but a common mechanism underlying psychosis [63].

Concluding remarks

A substantial body of evidence indicates that there are dopaminergic abnormalities in psychosis and links these to the onset of the disorder. Preclinical studies in non-human primates and rodents have indicated that dopamine neurons signal unexpected stimuli, coding their salience, and respond to aversive and novel stimuli as well as rewarding stimuli. This involves midbrain dopamine neurons and their projections to the ventral and dorsal striatum and temporal and frontal cortical regions. Imaging studies using tasks that involve salience processing indicate that the same systems are involved in these processes in humans, and have begun to link *in vivo* measures of dopaminergic function to salience processing. Furthermore, imaging studies in people with psychotic disorders are beginning to identify alterations in these systems, linking them to the symptoms of psychosis. There are thus

converging lines of preclinical and clinical evidence that indicate both the central role of dopamine in salience processing, indicating that both dopamine and salience processing are abnormal in psychosis. However, although this evidence is consistent with the hypothesis that dopamine dysfunction leads to salience dysregulation and hence psychosis, there are some significant weaknesses and gaps in the current evidence (some of the key issues are summarised in Box 2). A particular limitation of the current evidence is that the associations between dopaminergic function and salience processing in humans do not prove a causal relationship. This caveat notwithstanding, the link between dopaminergic dysfunction and altered salience processing also remains to be investigated in people with psychosis. Finally, to establish that dopamine dysfunction underlies salience dysregulation and the onset of psychotic symptoms, longitudinal studies beginning prior to the onset of the first psychotic episode will be required.

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