Dopamine Dysfunction and Delusions, Hallucinations and Anhedonia

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Abstract
This article outlines theoretical arguments along with related empirical studies concerning the relationship between abnormal reward processing and the symptoms of schizophrenia. Patients with schizophrenia and other psychoses usually show behavioural and physiological abnormalities when learning about or anticipating rewards or other important events. Patients also show impaired ability to modulate behaviour in response to incentives. There are plausible theories to directly link these abnormalities to the manifestation of positive and negative psychotic symptoms, but to date these links remain theoretical.

Keywords
Reward, psychosis, schizophrenia, dopamine, learning

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In this article I will draw on a selection of recent evidence to advance an argument that attempts to relate dopamine dysfunction to both positive and negative symptoms of schizophrenia (and other mental illnesses) via disruption of its normal role in motivation and learning about rewards. The argument itself is not new, but very recent functional magnetic resonance imaging (fMRI) and behavioural neuropsychological evidence has emerged to support it; herein I will present this new evidence in relation to the previously established theoretical position.

Extensive evidence from molecular imaging studies implicates dysregulated striatal dopamine in schizophrenia, and very recent evidence suggests that such abnormalities may be generalisable to the earliest stages of psychotic illness. Although Laruelle and colleagues have shown that the degree of sensitisation of the dopamine system is linked to the severity of psychotic symptoms, it remains unclear how the subjective experience of illness emerges from this underlying biological disturbance. For example, we know that dopamine is important for movement, and perhaps also for mood. So, why does dopamine dysfunction in psychotic illness lead to paranoia and not to some other manifestations, such as motor disturbance or mood disturbance? We should aim to understand how brain disturbances lead to symptoms through intermediate psychological processes that are more clearly related to biology: only then will we be able to answer the question of how a neurotransmitter disturbance has anything to do with paranoia, hallucinations or anhedonia, and how and why a dopamine D2 receptor antagonist can improve such symptoms.

Dopamine’s Role in Health and Psychiatric Disease
In order to understand how dysfunction of a neurotransmitter system may lead to psychiatric manifestations, a straightforward strategy is to consider the role of the system in question in health. Evidence over the last 30 years has shown that ascending midbrain dopamine neurons (mesocorticolimbic or mesostriatal) play a key role in learning about reward, signalling errors in the prediction of reward and motivational processing. It is therefore not surprising that some authors have proposed that dopamine abnormalities lead to symptoms of schizophrenia because of disruptions in dopamine’s role in motivational and reward processing. Indeed, both motivational deficits and dysfunction of associative learning (closely related to reward learning) were proposed in schizophrenia long before the discovery of dopamine. For example, Bleuler described avolition and loosening of associations (due to a failure of any unifying concept of purpose or goal) as core features of schizophrenia.

In the early 1970s, Stein and Wise proposed that dysfunction of monoamine neurotransmission could explain both of the core schizophrenia deficits: avolition and loosening of associations. In advancing this argument, they drew on early evidence that noradrenalin (not dopamine) mediated these reward-related processes. They reasoned that because noradrenalin (as was thought at the time) is important in both motivation and learning of goal-directed associations, perhaps dysfunction of this one system could explain both of these features of the disorder. However, as the majority of evidence subsequently demonstrated the primacy of dopamine (as opposed to noradrenalin) in reward and motivational processing (and as extensive data accumulated implicating dopamine dysfunction in schizophrenia), the argument was subsequently re-formulated by a number of successive authors. Some scholars focused their arguments on delusions and hallucinations, some on stereotyped thought and behaviour and some on negative symptoms. In most of these re-formulated models, the emphasis is on dopamine instead of noradrenalin, although...
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some authors have incorporated both of these monoamines into their theories of psychosis.12,13

The first scientist to make the case clearly and repeatedly for relating the emergence of psychotic symptoms to dopamine-driven associative and reinforcement learning was Robert Miller.14–24 In his 1976 article he wrote: "The process of acquiring the associations necessary for learning a conditioned response in an experimental animal depends on the presence of dopamine. In human schizophrenic patients, an excessive supply of cerebral dopamine may facilitate the acquisition of associations between 'units of information', to the point where unrelated features are associated and treated as if they are meaningful combinations: this process can be terminated by administering dopamine antagonists."14 Since that time, several other authors have expanded and developed Miller’s ideas, most notably Shitij Kapur.

Behavioural Studies of Reward Processing in Psychotic Illness

Is there any evidence to support these claims? Until recently, there was little if any evidence to demonstrate that patients with schizophrenia and other psychoses have any problems learning about rewards. Admittedly, in the 1950s and 1960s a considerable number of studies (including a number by Skinner himself) examined the effects of either reward or punishment on patients with schizophrenia.20–22 However, in addition to these studies being conducted without the use of diagnostic criteria, the focus of these studies was rather different from that of studies in the modern era. In that time, the key question was whether cognitive deficits in schizophrenia were ‘real’ or simply secondary to lack of effort on behalf of patients, and the results were rather mixed.

In the following years, non-reward-related associative learning received prolonged and detailed study by Jeffrey Gray and his colleagues at the Institute of Psychiatry,23 but with the exception of a handful of publications, behavioural studies of reward learning in psychosis were largely abandoned. The last five years have seen a resurgence of research into reward-related processes in schizophrenia. For example, in one recent study Roiser and colleagues24 studied 20 medicated patients with schizophrenia and 17 controls on a test in which money was used as a reinforcer: adaptive responses (fast responses to a predictive cue) resulted in a financial reward. Patients demonstrated fewer adaptive responses to cues signalling a potential for reward compared with controls, and the degree of impairment was linked to both positive and negative symptoms.

Gold’s group at the University of Maryland has conducted extensive behavioural studies of reward processing in schizophrenia and examined the relationship between behavioural deficits in reward processing and negative symptoms. These studies have largely employed studies of patients with chronic schizophrenia, almost all of whom are taking antipsychotic medication. In a recent review of their work, Gold and colleagues describe eight studies in this area and conclude that patients show deficits in rapid learning on the basis of trial-to-trial feedback, such as reversal learning.25,26 This is consistent with previous studies of reversal learning in schizophrenia26 and with a recent study of mine examining reversal learning in first-episode psychosis. In early psychosis, deficits were subtle and significantly correlated with negative symptoms, although the strength of the correlation was modest.26 Gold’s studies point to evidence of comparatively intact sensitivity to reward, but at the same time document impairments in decision-making in relation to reward, which they argue is due to a failure to accurately represent reward value.27,28

One limitation of studies in patients with chronic schizophrenia is that nearly all of the patients are taking antipsychotic medication, and such dopamine antagonist medication has been shown to affect reward processing in healthy volunteers.29,30 Thus, it is important to study patients who are not taking antipsychotic medication to confirm (or refute) results in medicated samples. Relevant to this is a recent study of ours that documented a failure of patients with first-episode psychosis to modulate their behaviour by motivational manipulation;31 importantly, when the analysis was restricted to patients free from dopamine antagonist medication, the deficits persisted. In my view, Gold’s studies are consistent with the thesis advanced by Kring, Green, Barch and others that patients with schizophrenia have reasonably intact hedonic responses but impaired motivation.32–34 Interestingly, modern pre-clinical scientists have indicated that the consummatory (hedonic) reward system is at least partially separable from anticipatory and motivational reward systems; whereas hedonics may be driven by opioid or cannabinoid neurotransmission, motivation may be primarily dopaminergic.35

Functional Neuroimaging Studies of Reward Processing in Psychotic Illness

Although there is a very long tradition of studying how experimental animals learn about rewards, it has proved more difficult to find adequate behavioural tests with which to investigate this psychological domain in humans. However, the advent of functional neuroimaging has re-invigorated this area of research, as this technique allows the study of humans while they learn about and receive (or miss out on) rewards, but obviates the need to design tasks with very careful, accurate measures of behaviour, as the dependent measure of interest is brain activation. Paradigms employed in healthy human fMRI have proved fairly easy to utilise in patient studies; since 2006 there have been at least six fMRI studies of patients with schizophrenia or other psychoses while they learn about or receive rewards or punishments. Heinzel and colleagues examined 14 unmedicated schizophrenia patients as they performed the Monetary Incentive Delay Task, which in controls produces robust ventral striatal activation in the anticipation of reward compared with the anticipation of neural feedback. Patients recruited less ventral striatal activation than controls, and this failure correlated moderately and significantly with negative symptoms and moderately but non-significantly with positive symptoms. These researchers have gone on to show that the responses of patients are partially normalised after prescription of the second-generation antipsychotic olanzapine.36,37 Perhaps this helps to understand why, using a different reward processing task, Adler, Walter and colleagues showed that schizophrenia patients taking second-generation antipsychotic medication had striatal activations in anticipation of reward that could not be differentiated from controls.38

Following Kapur’s theoretical paper six years ago in which he set out an argument to relate dopamine’s role in producing psychotic symptoms to dysfunction of its normal role in motivational importance,39 he and his colleagues have conducted a number of studies to test the theory, examining in detail the time-course of the action of antipsychotic drugs and reporting how the delusions of patients change in response to this treatment.40 They have also conducted fMRI investigation in patients, employing an aversive
conditioning paradigm. They noted abnormal activation in the ventral striatum in schizophrenia patients, together in discriminating between motivational salient and neutral stimuli. Specifically, patients activated the ventral striatum more towards neutral (motivationally irrelevant) stimuli than healthy controls. These results are consistent with a recent fMRI study of reward learning by my colleagues and I conducted in first-episode psychosis patients with active psychotic symptoms at the time of the experiment. We showed that brain responses correlating with reward prediction error in the dopaminergic midbrain and associated dopamine neuron striatal and limbic target regions – in addition to cortical regions such as the temporal and dorsolateral prefrontal cortex – were abnormal in patients. Although some patients in the study were taking dopamine receptor antagonist medication, some were not, and the results also held in the unmedicated patients, showing that the results could not solely be explained by medication effects. The results were consistent with a companion study employing a complementary learning paradigms. Using a largely overlapping sample of patients in a study led by Phil Corlett, we examined causal learning as opposed to reward learning in early psychosis and, again, found abnormal activation in a network of midbrain, striatal andfrontal regions. Interestingly, the severity of the dysfunction of activation in the lateral prefrontal cortex correlated with the severity of delusions.

Conclusions

Could it be that the same neural (dopaminergic) system could be responsible for both positive and negative symptoms in psychosis? At first glance it would appear not. Hyperdopaminergic activity in the striatum has been linked to positive symptoms; motivational andhedonic theories of dopamine’s role would predict that hypodopaminergic activity would be related to negative symptoms. Thus, at first consideration, these possibilities seem inconsistent. Two possible solutions could be advanced. First, there could be subsystems that display different pathologies in psychotic illness: for example, a more ventro-medial system could be more implicated in negative symptoms, and this could be underactive, while a more dorsolateral system could be more related to positive symptoms, and this could be overactive. There is preliminary evidence to suggest that positive psychotic symptoms are linked specifically to abnormalities in the ‘associative’ striatum (i.e. the head of the caudate nucleus). Another possibility is that dopaminergic systems could be dysregulated; the dopamine neurons could be overactive inappropriately, resulting in aberrant assignment of motivational salience to irrelevant phenomena, or they could be underactive inappropriately, failing to fire to rewards or cues predictive of rewards.

In this article I have outlined theoretical arguments and empirical data relating abnormalities in reward processing to particular psychiatric symptoms. The imaging and behavioural studies that I have reviewed show that patients with schizophrenia and other psychoses show behavioural and physiological abnormalities when learning about or anticipating rewards or other important events. Patients also show impaired ability to modulate behaviour in response to incentives. There are plausible theoretical arguments to directly link these abnormalities to the manifestation of positive and negative psychotic symptoms, but, as yet, these links remain unproven. The key issues to investigate further will be the specificity of reward learning and motivational abnormalities to particular symptom expression, and the degree to which such abnormalities can be normalised by treatment.

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