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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Keywords: psychosis; schizophrenia; dopamine; reward; salience.
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0166-2236/$ – see front matter
 http://dx.doi.org/10.1016/j.tins.2013.11.003

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

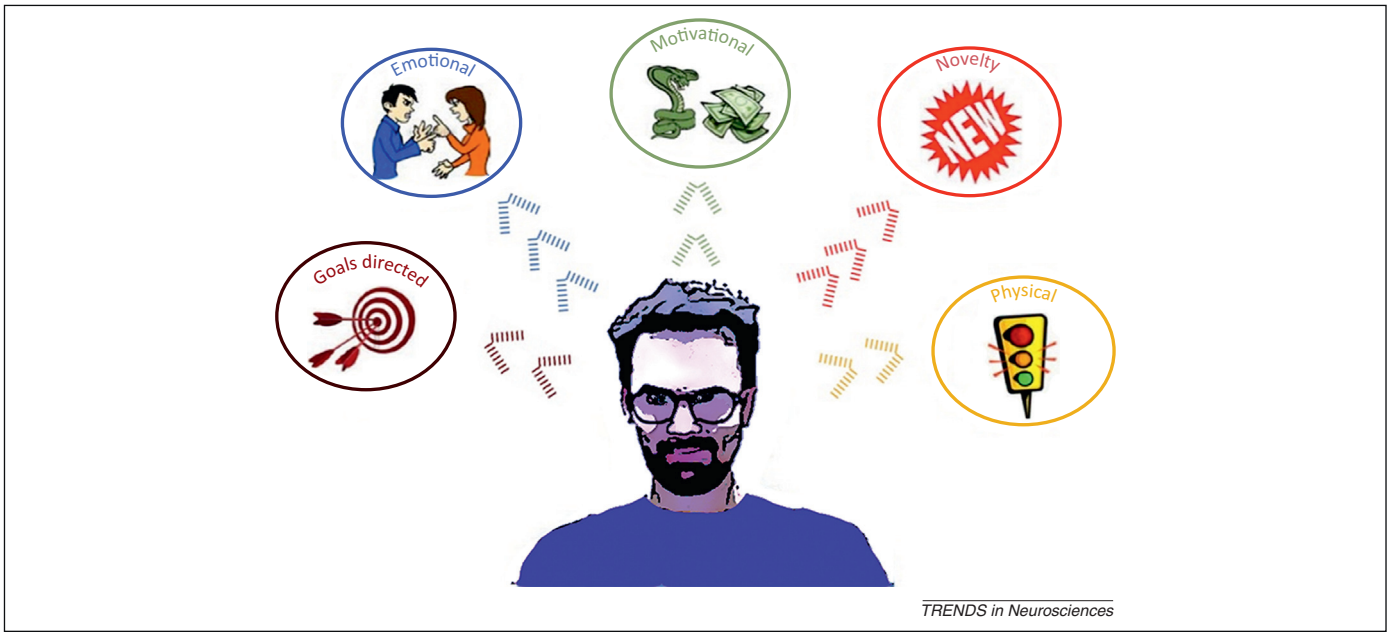

Figure 1. Salience is multifaceted and signalled (in part) by dopamine.