

## Dopamine and the aberrant salience hypothesis of schizophrenia

Decades of investigation have established a central role for pre-synaptic mesostriatal dopamine dysfunction, in particular elevated dopamine synthesis and release capacity, in the pathoaetiology of psychosis<sup>1,2</sup>. The question of exactly *how* increased striatal dopamine synthesis and release capacity causes the symptoms and signs of psychosis, however, remains unresolved<sup>2,3</sup>.

Dopamine's role in the basal ganglia was first thought of purely in terms of motor function. Subsequent electrophysiological studies in animals established a role in reward processing and motivation<sup>4</sup>. Recent preclinical studies have demonstrated that mesostriatal dopamine signaling has a much more nuanced role in cognition, and in particular a critical role in processing the salience of stimuli<sup>5</sup>. These insights may bridge the explanatory gap between neurobiology and phenomenology, explaining how dopamine dysfunction might underlie psychotic symptoms.

Several lines of evidence indicate that schizophrenia is a disorder of abnormal dopamine signalling. Drugs which increase striatal dopamine release may cause psychosis, and the potency of an antipsychotic medication is proportional to its ability to antagonize D2/3 receptors<sup>6</sup>. Studies using positron emission tomography (PET) provide robust evidence that dopamine synthesis and release capacity are elevated in patients with schizophrenia compared to control subjects, both in the striatum<sup>1</sup> and in the midbrain origin of the neurons<sup>7</sup>. Furthermore, these elevations are also seen in patients at high risk of developing schizophreniform psychosis<sup>8</sup> and are specifically linked to those who later develop psychosis<sup>9</sup>. Striatal dopaminergic dysfunction has thus been proposed as a final common pathway leading to psychosis in schizophrenia<sup>6</sup>. To answer the question of how this neurochemical abnormality is related to the symptoms and signs of psychosis, it is instructive to consider what is known about the function of mesostriatal dopamine signalling in the healthy brain.

Early electrophysiological studies in animals showed that activity in the dopaminergic mesolimbic pathway increases transiently after the presentation of unexpected rewards or reward-predicting stimuli, but decreases when an expected reward is omitted. This activity has been construed as a marker of incentive salience, underpinning motivated action selection<sup>4</sup>. Midbrain dopamine neurons, however, are not homogeneous: whilst a proportion encode motivational *value* for positive outcomes such as food, engendering seeking behaviour and value learning<sup>4</sup>, others respond to salient but non-rewarding (e.g., aversive) stimuli, encoding a motivational *salience* signal that triggers orienting and exploration behaviour<sup>5</sup>.

Early articulations of the aberrant salience hypothesis of schizophrenia proposed that disordered mesostriatal dopamine release results in an over-attribution of meaning and motivational value (incentive salience) to irrelevant environmental events<sup>2</sup>. Evidence supporting the heterogeneous character of phasic dopamine signalling<sup>5</sup>, however, suggests that dopaminergic dysfunction may contribute to a more multifaceted mis-

attribution of salience involving both rewarding and aversive signalling. This could lead to the world seeming pregnant with significance, generating feelings of apprehension and a sense that the world has changed in some as yet uncertain way. These experiences are characteristic of the prodromal phase of schizophrenia<sup>2,3</sup>. Jaspers<sup>10</sup> referred to this as the *delusional atmosphere*, in which “there is some change which envelops everything with a subtle, pervasive and strangely uncertain light”.

Although the aberrant salience account of delusional atmosphere is appealing, it is less intuitive how anomalous experiences lead to positive psychotic symptoms. Cognitive theories of psychosis offer an explanation. Patients experiencing paranoid delusions tend to exhibit a “pessimistic” and “externalizing” thinking style, which may develop after exposure to social adversity and childhood trauma<sup>11</sup> (see also Peters et al<sup>12</sup> in this issue of the journal). Perplexing experiences, when interpreted through this biased appraisal process, may be seen as threatening and uncontrollable, giving rise to persecutory ideas, ideas of reference and delusions of control<sup>11</sup>. By extension, when salience is misattributed to internal representations and self-generated actions, these phenomena may be interpreted as externally generated<sup>3</sup>, giving rise to auditory verbal hallucinations and passivity phenomena. As childhood adversity may also sensitize the dopaminergic system, cognitive theories of psychosis provide an important link between the socio-developmental risk factors, neurobiological substrate and subjective experience of schizophrenia<sup>11</sup>.

More recent formulations of the salience hypothesis of schizophrenia have been informed by computational accounts of brain function, that highlight the role of cortical-subcortical interactions in integrating incoming sensory information with existing internal models of the world. From this perspective, sensory information is salient when it violates the brain's predictive model of the world, represented in cortical regions. Persistent mis-matches between predicted and actual sensory stimuli drive adaptive changes to the brain's world-model<sup>3</sup>. This process is finely modulated by subcortical dopamine transmission, such that even subtle abnormalities in dopamine signalling may result in radical maladaptive changes to brain's world model, which may manifest clinically as false beliefs and perceptions<sup>3</sup>.

Investigation of salience attribution in schizophrenia has mainly focussed on reward-anticipation tasks. In functional magnetic resonance imaging (fMRI) studies, patients with schizophrenia generally show reduced activation in the mesolimbic pathway (ventral tegmental area and ventral striatum) upon presentation of reward-predicting stimuli, and exaggerated neuronal responses to “neutral” stimuli, compared to control subjects<sup>13</sup>. These changes are present in unmedicated and first-episode patients. Furthermore, there is a correlation between mesolimbic signalling abnormalities and both positive and negative symptoms.

In studies that have operationalized salience attribution, medicated patients with schizophrenia demonstrate impaired adaptive salience attribution, and delusional patients exhibit more aberrant salience attribution than non-delusional patients. Moreover, aberrant salience attribution is higher in individuals at ultra-high risk of psychosis compared with healthy volunteers, and both aberrant salience attribution and ventral striatal fMRI responses to irrelevant stimuli are correlated with severity of delusion-like symptoms<sup>14</sup>.

Despite the intuitive appeal of the aberrant salience model, a number of issues remain. To date there has been no direct demonstration of aberrant phasic dopaminergic activity in patients with schizophrenia, because of inherent methodological challenges. Different experimental approaches measure different aspects of neuronal function. The relationship between electrophysiological activity (measured by single-unit recordings) and transmitter release (in voltammetry, microdialysis and PET studies) is incompletely understood, and confounded by modulatory neurotransmitters and autoreceptor feedback. These experimental approaches also have vastly different spatial and temporal resolution.

In humans, the most commonly used tool for investigating the neuronal correlates of aberrant salience attribution is fMRI, which neither directly measures neuronal activity nor dopamine release, but rather regional changes in the blood oxygen level on a time-scale of seconds. PET, which does allow non-invasive measurement of dopaminergic activity, has a temporal resolution that is several orders of magnitude larger than the animal electrophysiological studies on which the aberrant salience hypothesis is based.

Finally, it remains an open question whether aberrant salience attribution is sufficient to explain the full spectrum of symptoms in psychosis, and whether this abnormality is specific to schizophrenia. The hypothesis may account for delusional atmosphere and delusion formation, but it is less clear how it extends to thought alienation and hallucinations. Moreover, recent evidence suggests that ventral striatal fMRI responses to anticipatory reward are also reduced in alcohol dependence and major depressive disorder<sup>15</sup>, and further comparative studies are needed to understand the specific nature of aberrant salience processing in schizophrenia.

The aberrant salience hypothesis has the potential to bridge the explanatory gap between biological, psychological and behavioural features of schizophrenia<sup>2,3</sup>. In order for the hypothesis to be rigorously tested, however, the gap between animal and human studies must be bridged. Preclinical studies that employ electrophysiological recordings and neuroimaging in the same animals, undertaking clinically relevant

behavioural tasks, will be critical to this endeavour. Human studies that combine multiple imaging modalities (e.g., fMRI, PET) with behavioural and physiological markers of salience attribution are needed to explore how inter-individual differences in dopamine synthesis and salience-related neuronal activity are related<sup>14</sup>. Finally, longitudinal studies investigating patients at multiple stages of the disease process, from the prodrome to established psychosis and relapse, will test whether aberrant salience attribution is causally implicated in psychosis.

If it can be shown that aberrant salience attribution, caused by dopaminergic dysfunction, is the final component in the causal pathway leading to psychosis, then the most effective therapeutic approach is likely to involve medication targeting the presynaptic dopaminergic dysfunction to dampen aberrant salience attribution, followed by a programme of psychotherapy to help the patient reappraise his/her model of the world, and reinterpret his/her place within it. Ultimately, studies directly modulating the dopamine system and measuring associated changes in psychological appraisal will provide the final proof that the aberrant salience hypothesis bridges the explanatory gap from neurobiology to symptoms of psychosis.

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