

The emerging biology of delusions

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This article examines a model of how delusions may arise, not just in schizophrenia but also in a number of neurological and psychiatric conditions, through a combination of dysregulated dopamine release from ascending midbrain pathways and reasoning bias. Negative symptoms may also be related to dopamine dysregulation, with the precise mixture of positive and negative symptoms depending on the relative degree of dopamine dysregulation in particular mesocorticolimbic circuits. Evidence for this model is examined, and predictions arising from this model are described.

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Introduction

What do we know about the biology of delusions? Many theories have been advanced, and this article will address only a selected few. An important issue is that whilst the biology of delusions clearly relates to the biology of schizophrenia, the two are not identical or interchangeable. The biology of delusions, which tend to come and go in schizophrenia, must differ from the biological basis of the trait features of the disorder, and from the basis of the negative symptoms which tend to be longstanding (Makinen *et al.* 2008). We know a lot about brain abnormalities (Ellison-Wright *et al.* 2008; Glahn *et al.* 2008) and cognitive deficits in schizophrenia (Nuechterlein *et al.* 2004), for example, but this tells us very little about the biology of delusions.

Dopamine disturbance as a common pathway to psychosis, most proximal to the symptoms

Delusions occur in a variety of mental disorders: schizophreniform disorders, affective disorder (over 50% of bipolar disorder patients but under 15% in unipolar depression), Alzheimer's disease (20%), Parkinson's disease (13%) as well as in a number of rarer neurological conditions (Lyketsos *et al.* 2000; Ohayon & Schatzberg, 2002; Kennedy *et al.* 2005; Aarsland *et al.* 2007). Do these conditions have anything biological in common? Is there, for example, a 'final common pathway' to psychosis? If there is one, it is likely to involve dopamine pathology, because

there is overwhelming evidence from *in vivo* molecular imaging studies in patients that this is the neurotransmitter most closely associated with mental experience of psychosis. In a powerful series of experiments, Laruelle, Abi-Dargham and colleagues have shown that the degree of sensitization of the dopamine system is linked to the severity of psychotic symptoms (Parsey *et al.* 2001; Toda & Abi-Dargham, 2007). High presynaptic dopamine synthesis capacity is linked to the severity of psychotic symptoms not just in schizophrenia, but also in individuals with mild psychotic symptoms, such as hallucinations with preserved insight or suspicions (Abi-Dargham *et al.* 2000; Laruelle *et al.* 1996; Breier *et al.* 1997; Howes *et al.* 2009). Of course, other transmitter abnormalities may be involved in schizophrenia – for example, γ -aminobutyric acid (GABA), glutamate and endocannabinoids – but this evidence is less direct, and disruptions in some of these neurotransmitter systems may be more closely linked to cognitive rather than psychotic manifestations of illness (Lewis *et al.* 2008).

Influences on dopamine neurons

What could cause excessive dopamine synthesis or release in ascending midbrain systems? Some have speculated that the normal suppression of dopamine neuron firing by the frontal cortex is attenuated, but abnormality within the temporal lobe could also drive dopamine dysregulation. Schobel, Small and colleagues have recently shown that perfusion in the CA1 area of the hippocampus (which is important for recognizing salient, novel events), is increased in psychotic illness and in those with prodromal symptoms of psychosis (Schobel *et al.* 2009). We know, from work in experimental rodents by many scientists, including,

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notably, Grace, that hippocampal overactivity in CA1 can stimulate dopamine release from midbrain neurons via the hippocampal inputs to the striatum and from there to the dopamine neurons in the brainstem. The hippocampus, via GABAergic signals from the ventral pallidum, determines the number of dopamine neurons capable of responding to burst firing, and then glutamatergic afferents from cortical (prefrontal cortex) or subcortical structures, determine the degree of dopamine neuron firing (Lisman & Grace, 2005; Lodge & Grace, 2006; Goto *et al.* 2007; Grace *et al.* 2007). Preclinical models such as these have been extremely useful in suggesting how dopamine circuits might be disturbed in psychotic states, and how hippocampal pathology may drive this disturbance; nevertheless, it is critical that such models are eventually validated, refined or refuted by clinical studies.

A cross-level account of the biology of experience

If we accept a causal relationship between dopamine neurophysiology and psychosis, how can we understand the relationship between a molecule and mental experience? Miller has argued that the most powerful explanations in psychiatry are 'cross-level', in that they bridge scientific disciplines such as physiology and phenomenology (Miller, 2008). In this respect, our task is to find an 'experiential neuroscience' of psychosis. We know that dopamine is important for movement, and perhaps also for mood (Nestler & Carlezon, 2006). What is less clear is why dopamine dysfunction in psychotic illness leads to paranoia, or hallucinations, and not to some other manifestation, such as mood disturbance or motor disturbance? A full understanding of the biology of psychosis requires an account of how brain disturbances lead to symptoms through intermediate psychological processes (Frith, 1992; David, 2006). It is only through this approach that we will be able to answer the question of how a neurotransmitter disturbance provokes paranoid beliefs, and how and why a dopamine D₂ receptor antagonist can improve such symptoms.

A plausible strategy in attempting to understand how dopamine dysfunction leads to delusions is to appeal to the normative function of dopamine systems in health. Dopamine's role in associative and reinforcement learning (Robbins & Everitt, 1996; Schultz *et al.* 1997; Pessiglione *et al.* 2006) has potential relevance for the biology of psychosis. As Miller stated in 1976:

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. (Miller, 1976)

The argument has been subsequently developed by several scholars (Beninger, 1983; McKenna, 1987; Gray *et al.* 1991; Kapur, 2003), but until recently has there been little evidence for associative or reinforcement learning abnormalities in psychosis, let alone evidence to specifically link such processes to symptoms. However, we do now know that there are associative learning deficits in schizophrenia and first-episode psychosis, including deficits in causal learning, probabilistic learning and reversal learning (Corlett *et al.* 2007; Waltz & Gold, 2007; Murray *et al.* 2008a). Abnormalities in reward processing in schizophrenia can be exacerbated by medication (Schlagenhauf *et al.* 2008), but deficits are also present in patients who are not taking dopamine receptor antagonists (Murray *et al.* 2008b). Furthermore, in schizophrenia, learning about important events is linked with dysfunction in dopaminergic regions such as the striatum and midbrain (Jensen *et al.* 2008; Murray *et al.* 2008c). Frontal, temporal and parietal cortical abnormalities are also seen in such processes (Murray *et al.* 2008c, 2010), and recent evidence suggests that the degree of abnormality of cortical response is linked to the severity of delusional ideation (Corlett *et al.* 2007; Schlagenhauf *et al.* 2009).

How do delusions persist?

Is the biology of the genesis of a delusion the same as the biology of a longstanding delusion? Miller has called longstanding delusions 'cognitive habits'. Like many false beliefs, they can persist in the absence of any pathophysiology. This fact has major implications for studies of psychosis patients where researchers attempt to correlate delusional strength with a physiological measure. Many of us believe things that are false just because we made up our minds about them many years ago. In my view, we need a biology of the genesis of delusions, and a psychology of how they persist. The two processes may be at least partially separable. Kapur and colleagues have shown that administration of a dopamine receptor antagonist does attenuate the strength of psychotic symptoms with rapid onset, but that the process of complete resolution of delusions follows a slower course, with patients first being less captivated by their delusions, and then gradually being less and less bothered by them over time (Agid *et al.* 2003, 2008; Kapur *et al.* 2005; Mizrahi *et al.* 2005, 2006). Thus, delusions resolve in two related processes. There is an important cognitive and logical reasoning operation to perform in dismantling a delusional system, which inevitably

takes time and may not be closely related to any particular neuromodulatory chemical. However, given that patients with schizophrenia have reasonable logical reasoning (Owen *et al.* 2007) there is likely to be another factor involved which must be addressed before a delusion becomes amenable to logical scrutiny. This key factor is the motivational salience of the abnormal thought, and this factor can be addressed with medication (Kapur, 2003).

A two-factor account of delusions

The above conceptualisation relates to what is sometimes termed a 'two-factor' account of delusions. Coltheart (2007), whose work is mainly grounded in studies of patients with monothematic delusions secondary to brain lesions or dementia, identifies the two factors: how does the delusion arise, and how does it persist? A closely related model perhaps more relevant to psychosis in young adults at least (but possibly also relevant for psychosis in other groups of patients) is that one abnormality is required to generate perceptual abnormalities or unusual thoughts or experiences, such as feelings of paranoia, coincidence or significance, and another abnormality is required to move from unusual thoughts into delusions. Thus I would rephrase Coltheart's questions as 'how does the unusual idea/experience arise, and how does it change from an unusual thought to a delusion?' Having experienced something unusual, an individual can then interpret it in a number of ways. It is possible he may recognize that he has experienced something unusual, that his mind is playing tricks on him, and that he can seek help for this phenomenon. Such an individual would probably be diagnosed as having an 'at-risk mental state' if he presented to a 'prodromal' clinic (Yung *et al.* 2004). If he did not seek help and did not find the experiences distressing, he might never come to the attention of medical services but, if he also exhibited introverted anhedonia, then he might be considered to have a schizotypal personality (van Os, 2003).

An alternative possibility is that such an individual might draw bizarre conclusions to try and explain his strange experiences: he might deduce from repeatedly noticing policemen that he is under surveillance and is being persecuted, or deduce from hearing voices that there is a transmitter in his head. Not everyone who experiences hallucinations develops a psychotic illness or a delusional interpretation of their hallucination (Sommer *et al.* 2008). Studies of reasoning in schizophrenia and other psychoses have demonstrated intact logical reasoning but impaired probabilistic reasoning. A two-factor account of delusions states that one abnormality is required to

experience prodromal symptoms, and a deficit in reasoning is required to explain what has been termed the 'jump to conclusions' (Garety *et al.* 1991) exhibited by some patients with delusions. The two deficits may have some overlap in their biological basis, but this is not a necessary part of the account. The reasoning deficit could be in either logical or probabilistic reasoning, with the evidence favouring the latter (Garety *et al.* 1991, 2007; Owen *et al.* 2007).

This understanding yields the following predictions: individuals with longstanding stable delusional disorder will show less abnormal dopamine synthesis than individuals with prodromal symptoms of schizophrenia such as newly formed attenuated delusions (referential ideas). Patients with longstanding delusions which have been attenuated by dopamine antagonists may well no longer have any dopaminergic pathology [as could be examined *in vivo* with positron emission tomography (PET) or single photon emission computed tomography (SPECT) molecular imaging] but should show reasoning abnormalities. Thus, when conducting experiments that attempt to relate symptoms with physiological measures it is important to bear in mind whether patients are in the process of developing delusions, or whether their delusions are merely cognitive habits that persist in the context of a subsequently normalized physiology (Chouinard & Miller, 1999*a, b*).

An alternative to the two-factor model of delusions

Fletcher & Frith (2009) have argued that a two-stage theory of psychosis in schizophrenia is unnecessary, as both perception and belief rely on predictions and updating those predictions in the light of evidence (so-called prediction error). Frith has shown the importance in health of being able to monitor one's own thoughts and actions subconsciously, and of being able to predict the consequences of those actions using the so-called efference-copy or corollary discharge mechanism. He and others have shown that patients with schizophrenia do indeed have problems in predictive coding and monitoring of their actions (Feinberg, 1978; McGuire *et al.* 1995; Shergill *et al.* 2005; Mathalon & Ford, 2008). By linking this theory of abnormal predictive coding in psychosis to evidence that dopamine-driven prediction error signalling is also abnormal in psychosis, Fletcher and Frith argue that abnormal predictive coding at multiple levels of brain complexity could lead to both false perceptions and false beliefs in schizophrenia. This provides a unitary psychological process that could underlie all positive psychotic symptoms. This simplicity and parsimony is a very attractive aspect of the theory; a disadvantage is that this parsimony may not be

reflected at a biological level. For example, it is unlikely that a single neurotransmitter system could be responsible for predictive coding throughout the brain. Whilst predictive coding for rewards may be intricately linked to dopamine, it is unlikely that predictive coding for visual perception will have the same biological basis. Empirical work combining pharmacological, imaging and psychological studies is required to test this theory.

A possible link to negative symptoms

A longstanding problematic issue in schizophrenia is the paradox of how an individual can have both positive and negative symptoms at the same time. A full account of psychosis would explain how these symptoms co-occur in many, though not all, individuals. One possibility that has been previously suggested is that the same neural monoaminergic system could be responsible for both positive and negative symptoms. Stein & Wise (1971) argued that dysregulation of noradrenalin's role in reward processing could result in both positive and negative symptoms, but given the progress we have made in understanding dopamine's role in incentive motivation and in psychotic illness, their theory should perhaps now be reformulated in terms of dopamine dysregulation.

It is true that there is an apparent conflict in attempting to explain both positive and negative symptoms through disturbance of the same psychological construct of incentive motivation. If the incentive motivation system is down-regulated, the result should be an apathetic individual, without positive symptoms; if it is hyperactive, everything should be imbued with motivational importance (perhaps as in a manic state). Perhaps the resolution to this paradox is in the system's potential dysregulation, rather than simple over-activation or under-activation of the system. In a dysregulated system, a stimulus that should be an incentive may in fact lack motivational value, and stimuli that should be valueless may take on motivational significance.

At the biological level, there could be at least two possible explanations for how disruption of dopamine systems could lead to both positive and negative symptoms. One possibility is that the dopaminergic system could be temporally dysregulated; the dopamine neurons could be overactive inappropriately, resulting in aberrant assignment of motivational salience to irrelevant phenomena, and they could be underactive inappropriately, failing to fire to primary rewards or cues predictive of primary rewards. Another possibility is that there could be anatomical subsystems that display different pathologies in psychotic illness. The so-called 'limbic striatum', or

ventro-medial striatal system, has been especially linked to reward associations, and could be more implicated in negative symptoms if underactive, whilst the more dorsolateral ('associative') striatal system could be more related to positive symptoms, and this could be overactive. There is some evidence to suggest that positive psychotic symptoms are linked specifically to dopaminergic abnormalities in the head of the caudate nucleus, i.e. the 'associative' striatum (Kegeles *et al.* 2007; Howes *et al.* 2009). If it could be shown that patients with prominent negative symptoms but no positive symptoms have normal associative striatal dopamine function, but abnormal limbic striatal dopamine, then this would be strong evidence for the anatomical subsystem hypothesis.

Conclusion

Developments in preclinical science have paved the way for plausible explanatory models to link biological disturbances to disturbed experiences in psychosis (Corlett *et al.* 2009; Murray & Fletcher, 2009; Ziauddeen & Murray, 2010). How delusions arise, not just in schizophrenia but also in other disorders, can be accounted for by a combination of dysregulated firing in ascending midbrain dopamine neurons and reasoning bias. Negative symptoms may be related to dopamine dysregulation, perhaps especially in circuits involving the limbic or ventral striatum, with the precise mixture of positive and negative symptoms in an individual depending on the relative degree of dopamine dysregulation in particular mesocortico-striatal circuits. A more precise understanding of the relationship between biology and mental experience will not only prove immensely valuable in psycho-educational interventions with patients and carers, but it will also facilitate the development of better treatments for psychotic symptoms in a variety of disorders (Mallet *et al.* 2007, 2008; Murray & Fletcher, 2009).

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Declaration of Interest

None.

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