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Are persistent delusions in schizophrenia associated with aberrant salience?

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ABSTRACT

Objective: It has been suggested that positive psychotic symptoms reflect 'aberrant salience'. Previously we provided support for this hypothesis in first-episode schizophrenia patients, demonstrating that delusional symptoms were associated with aberrant reward processing, indexed by the Salience Attribution Test (SAT). Here we tested whether salience processing is abnormal in schizophrenia patients with long-standing treatment-refractory persistent delusions (TRS).
Method: Eighteen medicated TRS patients and 31 healthy volunteers completed the SAT, on which participants made a speeded response to earn money in the presence of cues. Each cue comprised two visual dimensions, colour and form. Reinforcement probability varied over one of these dimensions (task-relevant), but not the other (task-irrelevant).
Results: Participants responded significantly faster on high-probability relative to low-probability trials, representing implicit adaptive salience; this effect was intact in TRS patients. By contrast, TRS patients were impaired on the explicit adaptive salience measure, rating high-probability stimuli less likely to be associated with reward than controls. There was little evidence for elevated aberrant salience in the TRS group.
Conclusion: These findings do not support the hypothesis that persistent delusions are related to aberrant motivational salience processing in TRS patients. However, they do support the view that patients with schizophrenia have impaired reward learning.

1. Introduction

Advances in understanding the role of dopamine in reward learning support the hypothesis that psychotic symptoms reflect the formation of abnormal stimulus-reinforcement associations (Kapur, 2003). It is well established that mesolimbic dopamine transmission is involved in predicting rewarding events and coding outcome expectancies (Berridge, 2007; Wise, 2004). Stimuli that are repeatedly paired with a reward, termed conditioned stimuli (CS+), are able to elicit phasic dopamine firing in the midbrain when presented alone, while unconditioned stimuli (CS−) that do not predict reward do not elicit such a response (Schultz et al., 1997). It has been shown, in humans and in animals, that presentation of a CS+ leads to increased response vigour compared to the presentation of a CS− (Cools et al., 2008; Roiser et al., 2006; Talmi et al., 2008; Wyvell and Berridge, 2000), an effect that is modulated by ventral striatal dopamine (Wyvell and Berridge, 2000). This effect has been interpreted as reflecting 'motivational salience' (Berridge and Robinson, 1998; Milstein and Dorris, 2007).

A number of theorists have suggested that the formation of abnormal stimulus-reinforcement associations in schizophrenia might be related to dysregulated dopamine transmission in the ventral striatum (Gray et al., 1991; King et al., 1984; Shaner, 1999; Snyder, 1976). Disrupted motivational salience processing has been proposed to contribute to the development of abnormal beliefs in psychotic disorders, and in particular in patients with schizophrenia (Corlett et al., 2007; Hemsley, 1993; King et al., 1984; Maher, 1974; Miller, 1976; Shaner, 1999). Kapur (2003) proposed the aberrant salience hypothesis of psychosis, suggesting that the positive symptoms of schizophrenia may arise from the aberrant assignment of salience to external objects and internal representations, via context-independent stimulus-

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reinforcement signalling, driven by chaotic dopamine neuron firing (Seeman and Kapur, 2000). This model also proposes that antipsychotic medications contribute to the resolution of positive symptoms by attenuating aberrant motivational salience, via blockade of the dopamine D2 receptor (Kapur, 2003). However, a necessary corollary of this is that antipsychotic medication will also necessarily attenuate adaptive (appropriate) motivational salience which may result in negative side-effects related to loss of motivation, such as apathy and anhedonia.

Consistent with this model, numerous studies have demonstrated reinforcement learning deficits in schizophrenia (Gold et al., 2008; Murray et al., 2008b; Waltz et al., 2007; Waltz and Gold, 2007), although the patients included in these studies were mostly receiving medication; important because anti-psychotic medication is known to disrupt reward processing in healthy volunteers (Pessiglione et al., 2006). Findings of abnormal haemodynamic response patterns in regions strongly innervated by dopamine during reward processing in patients with psychosis, including in unmedicated patients, provide convergent support for the aberrant salience hypothesis (Jensen et al., 2008; Juckel et al., 2006; Murray et al., 2008a); though interestingly a recent longitudinal neuroimaging study demonstrated relatively normalised haemodynamic responses during the anticipation of uncertain rewards following 6 weeks' treatment with an atypical antipsychotic (amisulpride) in initially treatment-naïve patients (Nielsen et al., 2012).

Roiser et al. (2009) provided the first evidence linking aberrant reward learning with delusions, as predicted by the aberrant salience hypothesis, using a novel behavioural paradigm, the Salience Attribution Test (SAT), designed specifically to assess processing pertaining to irrelevant stimuli. First-episode schizophrenia patients with delusions scored higher on the SAT "explicit aberrant salience" measure (task-irrelevant reward learning) than those without such symptoms. Consistent with the above-mentioned studies they also identified impaired "adaptive salience" (task-relevant reward learning) in these predominantly medicated patients with first-episode schizophrenia. More recently, Roiser et al. (2013) reported elevated aberrant salience in "prodromal" individuals, who are at high risk of the development of psychosis because they experience attenuated psychotic symptoms (for example, suspicious ideas or unusual perceptual experiences), but do not (yet) meet criteria for psychosis. Interestingly, the degree of aberrant salience measured by the SAT correlated positively with delusion-like symptoms in that sample.

Importantly, Roiser et al. (2009) did not demonstrate a significant difference in aberrant salience between healthy volunteers and patients with first-episode schizophrenia. However, that study included a heterogeneous sample with only 65% of patients actually reporting delusions at the time of testing, with moderate severity. If a relationship between aberrant salience and delusions does indeed exist, it was anticipated that selecting a symptomatically homogeneous sample of patients with severe delusions would reduce variability and thereby increase the chance of finding a difference between patients with schizophrenia and healthy volunteers. Hence, the patients recruited for the present study were receiving medication but still exhibiting florid positive psychotic symptoms, specifically delusions.

1.1. Aims of the study

The aim of the current study was to test whether motivational salience processing was abnormal in schizophrenia patients experiencing persistent delusions. On the basis of the aberrant salience hypothesis we made the following predictions:

1. Patients experiencing persistent delusions would exhibit greater aberrant salience than healthy volunteers, reflecting a pathological neurobiological mechanism maintaining their delusions;
2. Patients experiencing persistent delusions would exhibit reduced adaptive salience relative to healthy volunteers, reflecting a corollary of anti-psychotic medication.

2. Methods

2.1. Participants

Eighteen patients with schizophrenia who had long-standing treatment-refractory persistent delusions (TRS) were recruited from five mental health rehabilitation units within an inner city UK National Health Service Trust. Eligible patients were invited to participate following review of their clinical notes and discussion with their psychiatrist. This Trust serves a population with one of the highest levels of psychiatric morbidity in the UK and provides a full range of inpatient and community based services. People receiving inpatient mental health rehabilitation (who were the target of recruitment for the present study) are those with especially complex psychosis (treatment resistant positive and/or negative symptoms, often with mental and physical health comorbidities) who require specialist treatment due to the severity of their illness.

Patients were recruited if they were aged 18–65 years. The inclusion criteria were a DSM-IV diagnosis of schizophrenia and the presence of persistent delusions despite adequate treatment with at least two antipsychotic drugs at therapeutic doses for at least 6 weeks (Table 1). Patients of these rehabilitation services had been in contact with mental health services from 15 to 30 years, with a mean of five previous admissions to hospital and had spent between five months and five years in their current unit (Killaspy et al., 2008). Symptom type and severity were assessed in patients at the time of testing using the Scales for the Assessment of Positive Symptoms – SAPS (Andreasen, 1983) and Negative Symptoms – SANS (Andreasen, 1981), the Calgary Depression Rating Scale for Schizophrenia – CDRSS (Addington et al., 1990) and the Young Mania Scale – YMRS (Young et al., 1978).

All patients were medicated at the time of testing. Total antipsychotic medication load was computed as a percentage of the maximum recommended British National Formulary (BNF: www.bnf.org) dose, summing percentages for different antipsychotics where appropriate. Eight patients were taking one atypical antipsychotic, two were taking two atypical antipsychotics, three were taking one atypical antipsychotic and one mood stabiliser (e.g. sodium valproate), four were taking two atypical antipsychotics and one mood stabiliser, and one patient was taking one atypical antipsychotic, one typical antipsychotic (haloperidol), and one mood stabiliser. In total eight patients were taking clozapine.

Patients were compared with thirty-one healthy volunteers, recruited via advertisement. Exclusion criteria were: known psychiatric or neurological disorder; medical disorder likely to lead to cognitive impairment; intelligence quotient (IQ) <70; and recent illicit substance use. The absence of axis-I psychopathology and alcohol- or substance-abuse/dependence was confirmed with the Mini International Neuropsychiatric Inventory (Sheehan et al., 1998). Dimensions of schizotypy were measured in the healthy volunteers using the short form of the Oxford-Liverpool Inventory of Feelings and Experiences schizotypy questionnaire – O-LIFE (Mason et al., 2005). Ethical approval was obtained from the Ealing & West London Mental Health Trust Research Ethics Committee. All participants provided written informed consent, and were compensated £40 for their time and travel expenses.

2.2. Experimental paradigm – Salience Attribution Test (SAT)

The SAT is a speeded reaction time task in which participants respond to a probe (a black square) following presentation of a cue in