

# Do patients with schizophrenia exhibit aberrant salience?

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**Background.** It has been suggested that some psychotic symptoms reflect ‘aberrant salience’, related to dysfunctional reward learning. To test this hypothesis we investigated whether patients with schizophrenia showed impaired learning of task-relevant stimulus–reinforcement associations in the presence of distracting task-irrelevant cues.

**Method.** We tested 20 medicated patients with schizophrenia and 17 controls on a reaction time game, the Salience Attribution Test. In this game, participants made a speeded response to earn money in the presence of conditioned stimuli (CSs). Each CS comprised two visual dimensions, colour and form. Probability of reinforcement varied over one of these dimensions (task-relevant), but not the other (task-irrelevant). Measures of adaptive and aberrant motivational salience were calculated on the basis of latency and subjective reinforcement probability rating differences over the task-relevant and task-irrelevant dimensions respectively.

**Results.** Participants rated reinforcement significantly more likely and responded significantly faster on high-probability-reinforced relative to low-probability-reinforced trials, representing adaptive motivational salience. Patients exhibited reduced adaptive salience relative to controls, but the two groups did not differ in terms of aberrant salience. Patients with delusions exhibited significantly greater aberrant salience than those without delusions, and aberrant salience also correlated with negative symptoms. In the controls, aberrant salience correlated significantly with ‘introverted anhedonia’ schizotypy.

**Conclusions.** These data support the hypothesis that aberrant salience is related to the presence of delusions in medicated patients with schizophrenia, but are also suggestive of a link with negative symptoms. The relationship between aberrant salience and psychotic symptoms warrants further investigation in unmedicated patients.

Received 23 January 2008; Revised 28 April 2008; Accepted 8 May 2008; First published online 30 June 2008

**Key words:** Aberrant salience, dopamine, psychosis, reinforcement, salience attribution test, schizophrenia.

## Introduction

Together with direct evidence for dopamine dysregulation in medicated and unmedicated patients with schizophrenia (Laruelle *et al.* 1996; Abi-Dargham *et al.* 2000; Abi-Dargham, 2004; McGowan *et al.* 2004), recent advances in understanding the role of dopamine in reward learning (Wise, 2004; Berridge, 2007) have rekindled interest in the hypothesis that psychotic symptoms reflect the formation of abnormal stimulus–reinforcement associations, secondary to aberrant neurotransmission in the ventral striatal dopamine pathway (Snyder, 1976). Studies in experimental animals have demonstrated that stimuli that

are repeatedly associated with reward, termed conditioned stimuli (CS+), are able to elicit phasic dopamine firing in the midbrain when presented alone, while stimuli that do not predict reward (CS−) do not elicit such a response (Schultz *et al.* 1997). Presentation of a CS+ has also been shown to increase the speed of responding relative to the presentation of a CS−, an effect that is modulated by ventral striatal dopamine (Wyvell & Berridge, 2000). This effect has been interpreted as reflecting adaptive ‘motivational salience’, meaning that a neutral stimulus becomes imbued with an emotional quality due to its association with primary reinforcement, and consequently can influence behaviour and command attention (Berridge & Robinson, 1998; Milstein & Dorris, 2007).

A number of theorists have hypothesized that positive psychotic symptoms may be related to abnormal learning of stimulus–reinforcement associations (King *et al.* 1984; Miller, 1993; Shaner, 1999).

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Most recently, Kapur (2003) proposed that the positive symptoms of schizophrenia may arise out of 'the aberrant assignment of salience to external objects and internal representations', and that antipsychotic medications reduce positive symptoms, by attenuating aberrant motivational salience, via blockade of the dopamine D2 receptor. A corollary of this is that antipsychotic medications will also necessarily attenuate adaptive motivational salience, that is the correct assignment of salience. This may result not only in positive symptom remission, but also negative side-effects related to loss of motivation, such as apathy and anhedonia.

Despite the implications for understanding the neurobiological basis of schizophrenia, few studies have investigated reward learning in schizophrenia. Studies investigating Pavlovian conditioning in medicated patients found a deficit in learning stimulus–reinforcement associations (Garmezy, 1952; Cohen, 1956; Waltz *et al.* 2007) and reduced ventral striatal responses to CS+ predictive of monetary reward (Juckel *et al.* 2006). A recent study reported that medicated patients with delusions were not only impaired at learning the predictive value of a CS+ associated with an aversive noise, but also showed a tendency towards higher galvanic skin responses, uneasiness ratings and haemodynamic response in the ventral striatum following the presentation of a neutral stimulus (Jensen *et al.* 2008), consistent with aberrant salience hypothesis.

In order to extend these findings, here we employed a novel paradigm, the Salience Attribution Test (SAT), to quantify adaptive and aberrant salience in patients with schizophrenia and controls. It has been hypothesized that dopamine antagonists reduce both adaptive and aberrant salience, and that in the absence of effective treatment patients with schizophrenia exhibit aberrant salience (Kapur, 2003). Therefore, our first prediction was that that medicated patients with schizophrenia would exhibit reduced adaptive salience relative to controls, representing an undesirable side-effect of anti-psychotic medication. Our second prediction was that medicated patients with schizophrenia would exhibit equivalent aberrant salience to controls, representing the beneficial effect of anti-psychotic medication, which is hypothesized to normalize aberrant salience from a previously elevated level (Kapur, 2003). Our third prediction was that those patients with persistent positive symptoms, in whom medication is not entirely effective, would exhibit greater aberrant salience than patients without positive symptoms. Our fourth prediction was that in the controls, individual differences in aberrant salience would be related to the personality trait of schizotypy, considered to be an index of psychosis

proneness (Chapman *et al.* 1994; Claridge, 1994; Stefanis *et al.* 2004).

## Method

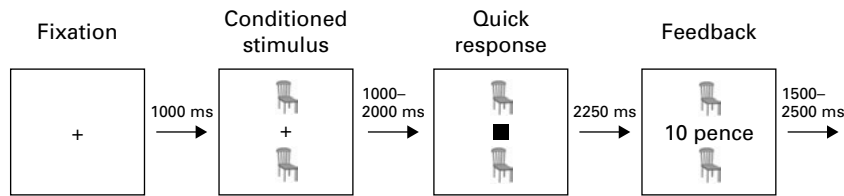
### Participants

Twenty patients were recruited from a prospective, longitudinal study of first-episode psychosis in West London, UK (Joyce *et al.* 2005). Patients were screened using the World Health Organization Psychosis Screen (Jablensky *et al.* 1992) and were recruited if they were aged 16–50 years. The diagnosis was ascertained using a structured interview, the diagnostic module of the Diagnostic Interview for Psychosis (Jablensky *et al.* 2000). In this longitudinal study, participants are contacted 1 and 3 years after presentation for repeat assessments, at which time the diagnosis is reviewed. The patients in the present study all presented with a schizophreniform psychosis and DSM-IV diagnoses were established or confirmed at initial assessment ( $n=1$ ), 1-year ( $n=14$ ) or 3-year ( $n=5$ ) follow-up. The final diagnoses were schizophrenia in 19 patients and schizoaffective disorder in the remaining patient.

Three patients were unmedicated at the time of testing, two were taking first-generation drugs (haloperidol, flupenthixol), and 15 second-generation drugs (five olanzapine, four aripiprazole, two quetiapine, two risperidone, one clozapine and one a combination of aripiprazole and quetiapine). Symptom type and severity were assessed in patients at the time of the study 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).

These patients were compared with 17 healthy volunteers, who were recruited by advertisement. Exclusion criteria were: known psychiatric or neurological disorder; medical disorder likely to lead to cognitive impairment; intelligence quotient (IQ) <70; recent illicit substance use and first-degree relatives diagnosed with a psychotic illness. The absence of axis-I psychopathology and alcohol- or substance-abuse/dependence was confirmed with the Mini International Neuropsychiatric Inventory (Sheehan *et al.* 1998). Healthy volunteers completed 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 Wandsworth, Ealing and West London Mental Health Trust, and National Hospital for Neurology and



**Fig. 1.** The Saliency Attribution Test. Participants were required to respond to the black square as quickly as possible. On 50% of trials, participants won more money for quicker responses. The conditioned stimuli appearing before the response are coloured either red or blue.

Neurosurgery and Institute of Neurology Research Ethics Committees. All participants provided written informed consent, were compensated £20 for their time and travel expenses, and could win up to another £20 on the SAT.

### SAT

On the SAT, participants made a speeded response to the onset of a probe (a black square) in order to earn money (see Fig. 1). Pictures that appeared just before the onset of the probe signalled the probability that the participant would win money on a given trial, which occurred on 50% of trials. However, participants were not informed of the contingencies between the different pictures and reward. Hence, the SAT is relatively straightforward to perform for patients, since it simply requires participants to respond as quickly as they can when the probe appears on the screen. Participants could earn a maximum of £20 on the test (minimum £5).

Prior to the main test, participants completed a computerized tutorial, which featured example displays, written instructions and test trials (see supplementary online materials). Two practice sessions were embedded into the tutorial to familiarize participants with the test and provide a measure of baseline response time (RT). On these practice sessions, a fixation cross appeared at the beginning of each trial. Following a variable interval (minimum 0.5 s, maximum 1.5 s) the probe appeared, and participants responded by pressing a button as quickly as possible. Participants were instructed to try to respond as quickly as they were able to, and before the box disappeared. During the first practice session the probe was on the screen for randomized variable periods, with a maximum duration of 1.5 s, minimum duration 0.5 s and mean duration 1 s. Feedback was provided after 2 s as 'Good' if the participant responded before the box disappeared, 'Try to respond faster' if they responded after the box disappeared, 'Too early' if they responded before the box appeared, and 'No key pressed' if they did not make a response. On the second practice session, the mean probe duration was

set to be the mean RT from the first, ensuring participants were responding as quickly as possible and to yoke task difficulty to individual performance. The standard deviation (s.d.) of the fastest half of the trials (SDF) was also calculated, and was used to set the minimum and maximum probe durations for the second practice session (mean from first practice session  $\pm 2 \times$  SDF). For the main test, the mean, minimum and maximum probe durations were calculated from the second practice session in the same way. No monetary reinforcement was provided during the practice sessions.

Participants then completed two blocks of 64 trials on the main test, where money was available on 50% of trials. The likelihood that money was available on a trial was signalled by one of four CS that appeared at the top and bottom of the screen before the onset of the probe. CSs varied on two different visual dimensions: colour (blue or red) and shape (animal or household object). Therefore, there were four different types of CS: blue animals; red animals; blue household objects and red household objects. One of these dimensions (e.g. colour) was task-relevant so that one level of the dimension was reinforced on 28 out of 32 (87.5%) of the trials while only four out of 32 (12.5%) trials of the other were reinforced. For example, if 'colour' was the reinforced dimensions, 14 out of 16 blue animals and 14 out of 16 blue household objects would be reinforced, compared with only two out of 16 red animals and two out of 16 red household objects. The other dimension, in this example 'shape', was task-irrelevant, so that 16 out of 32 (50%) of both levels were reinforced. The contingencies were identical on the first and second blocks of the game. Participants were not informed of these contingencies, but instead learned them over the course of the game.

At the beginning of each trial a fixation cross appeared; after 1000 ms, while the fixation cross remained on-screen, one of the four CSs was displayed at the top and bottom of the screen and remained on-screen until the end of the trial. After a variable period of time (between 0.5 and 1.5 s) the probe appeared and participants attempted to respond before it disappeared. The probe duration was calculated

according to the participant's responses on the second practice block, as described above. After 2.25 s, auditory and visual feedback was presented for 1.5 s (see Fig. 1). Four different versions of the SAT were used, each with a different stimulus feature (blue, red, animal or household object) reinforced with high probability. Each participant was administered the same version for both blocks of the SAT.

If the trial was not reinforced, the message 'Sorry – no money available' was displayed. If the trial was reinforced, participants won between 5 and 100 pence, depending on the latency of their response. On reinforced trials where participants either made no response or responded after the probe had disappeared, the message 'Missed: 5 pence' was displayed. If participants responded prematurely (<100 ms after the onset of the probe), the message displayed was 'Too early: 5 pence'. On reinforced trials where participants responded before the probe disappeared, but slower than their mean RT, the message 'Hit – good: 10 pence' was displayed. When participants responded more quickly than their mean RT, the message 'Quick – very good: X pence' was displayed (for responses up to 1.5 SDFs faster than their mean RT) and 'Very quick – excellent: X pence' (for responses faster than their mean RT by at least 1.5 SDFs). The reward was scaled according to  $X = 10 + 90 \times (\text{mean RT} - \text{trial RT}) / (3 \times \text{SDF})$ , up to a maximum of 100 pence. For example, a response 1 SDF faster than the mean was reinforced with 40 pence, a response 2 SDFs faster was reinforced with 70 pence, and any responses 3 SDFs or faster than the mean were reinforced with 100 pence. The money won on each trial was added to the participant's running total for that block, Y, which was displayed underneath the feedback: 'Total – £Y'. On reinforced trials, a 0.5 s tone sounded, frequency:  $(300 + (10 \times X))$  Hz. At the end of each block, participants indicated, using 10 mm visual analogue scales (VAS), their estimate of the reinforcement probabilities for each of the four different CSs.

Two measures of motivational salience were calculated for each block. Adaptive salience was defined in two ways (behaviourally or implicit and subjectively or explicit). RT adaptive salience (implicit) was defined as the speeding of responses on high-probability-reinforcement trials relative to low-probability-reinforcement trials (collapsing across the task-irrelevant stimulus dimension), and VAS adaptive salience (explicit) was defined as the increase in probability rating for high-probability-reinforcement trials relative to low-probability reinforcement trials (again, collapsing across the task-irrelevant stimulus dimension). Aberrant salience was defined as the absolute difference in RT (implicit) or VAS rating

(explicit) between the two levels of the task-irrelevant stimulus dimension (collapsing across the task-relevant stimulus dimension). Since aberrant salience is defined as any deviation from equal reaction time or subjective reinforcement probability rating for the two levels of the task-irrelevant stimulus dimension, the sign is unimportant. Therefore aberrant salience was always positive, whereas adaptive salience could be positive or negative. The number of premature responses and omissions were also recorded for each stimulus type on each block.

### Other cognitive tests

To assess whether any abnormalities on the SAT might be related to neurocognitive impairments in the patient group, pre-morbid IQ was estimated using the Wechsler Test of Adult Reading (WTAR; Wechsler, 2001) and working memory with the forwards and backwards digit-span (Wechsler, 1981). To assess whether aberrant salience might be related to the 'jumping to conclusions' bias previously reported in schizophrenia (Garety *et al.* 1991), a 60:40 version of the Beads Task (Garety *et al.* 1991) was included. Data on the Beads Task were not collected for one control.

### Statistical analysis

All data were analysed using the Statistical Package for the Social Sciences, version 15 (SPSS Inc., Chicago, IL, USA). Demographic data and data from the Beads Task were analysed using independent samples *t* tests and  $\chi^2$  tests. SAT and digit-span data were analysed using repeated-measures analysis of variance. For digit-span, stage (forwards/backwards for digit-span) was the within-subjects variable, while on the SAT block (1/2) was the within-subjects variable. Group (patient/control) was the between-subjects variable in both analyses. RT and VAS aberrant salience scores from the SAT were square root-transformed prior to analysis to reduce skew, though untransformed values are presented in the text, figures and tables for clarity. To determine whether participants consistently assigned aberrant salience to any particular stimulus feature,  $\chi^2$  tests were employed.

To investigate the hypothesis that aberrant salience was related to positive symptoms of schizophrenia, we divided the patients into those with and without positive symptoms when analysing SAT data. This grouping was performed on the basis of the sum of the global scores on the SAPS, either zero (no positive symptoms) or greater than zero (positive symptoms). We carried out a similar procedure using the SANS to investigate the effect of negative symptoms. In both

**Table 1.** Demographic measures

|                                       | Controls    | Patients    | Statistic              |
|---------------------------------------|-------------|-------------|------------------------|
| Age, years                            | 25.2 (7.4)  | 27.0 (7.0)  | $t(35) < 1$            |
| Gender (male/female)                  | 7/10        | 11/9        | $\chi^2(1) < 1$        |
| Estimated full scale IQ (WTAR)        | 97.8 (10.3) | 92.7 (12.1) | $t(35) = 1.4, p > 0.1$ |
| O-LIFE unusual experiences            | 3.1 (2.8)   |             |                        |
| O-LIFE cognitive disorganization      | 3.5 (2.9)   |             |                        |
| O-LIFE introverted anhedonia          | 1.6 (1.9)   |             |                        |
| O-LIFE impulsive non-conformity       | 1.8 (1.6)   |             |                        |
| SAPS sum of global subscale scores    |             | 4.9 (5.3)   |                        |
| SANS sum of global subscale scores    |             | 5.4 (6.0)   |                        |
| Calgary depression rating scale score |             | 4.2 (5.5)   |                        |
| Young mania rating scale score        |             | 1.4 (4.1)   |                        |

IQ, Intelligence quotient; WTAR, Wechsler Test of Adult Reading; O-LIFE, Oxford–Liverpool Inventory of Feelings and Experiences; SAPS, Scale for the Assessment of Positive Symptoms; SANS, Scale for the Assessment of Negative Symptoms.

Values are given as mean (standard deviation).

cases, symptom group was entered as the between-subjects variable.

Correlations with O-LIFE subscales and clinical variables were performed using Pearson's  $r$ , or Spearman's  $\rho$  if the residuals from the parametric correlation were not normally distributed. For all analyses a  $p$  value of  $< 0.05$  was considered significant while  $0.05 < p < 0.1$  was considered as a trend towards significance.

## Results

### Demographic data

Patients and controls were well matched for gender distribution, age and pre-morbid IQ (see Table 1). Within the patients, the symptom subgroups were well matched for demographic variables (data not shown).

### SAT

#### Reaction time (implicit salience)

Behavioural data are presented in Table 2. Participants responded more quickly on high- relative to low-probability-reinforced trials [RT adaptive salience:  $F(1, 35) = 9.5, p = 0.004$ , partial  $\eta^2 = 0.213$ ]. Consistent with our first prediction, controls exhibited greater RT adaptive salience than patients [group  $\times$  probability interaction:  $F(1, 35) = 4.8, p = 0.035$ , partial  $\eta^2 = 0.121$ ]. Controls exhibited significant RT adaptive salience [ $F(1, 16) = 9.8, p = 0.007$ , partial  $\eta^2 = 0.379$ ], but patients did not ( $F < 1$ , partial  $\eta^2 = 0.030$ ) (see Fig. 2). There was no main effect of block or group on RT, and no other

interactions approached significance ( $p > 0.1$ ). Patients and controls did not differ in terms of RT aberrant salience ( $F < 1$ , partial  $\eta^2 < 0.001$ ), and the main effect of block and group  $\times$  block interaction were both non-significant ( $p > 0.1$ ). Participants did not reliably respond more quickly in the context of any particular irrelevant stimulus feature relative to the other ( $p > 0.05$  for all).

#### VAS (explicit salience)

Participants rated high-probability-reinforced trials as more likely to yield reward than low-probability-reinforced trials [VAS adaptive salience:  $F(1, 35) = 54.3, p < 0.001$ , partial  $\eta^2 = 0.608$ ]. Again, consistent with our first prediction, controls exhibited greater VAS adaptive salience than patients [group  $\times$  probability interaction:  $F(1, 35) = 10.9, p = 0.002$ , partial  $\eta^2 = 0.238$ ], though VAS adaptive salience was significant in both groups [controls:  $F(1, 16) = 71.9, p < 0.001$ , partial  $\eta^2 = 0.818$ ; patients:  $F(1, 19) = 7.3, p = 0.014$ , partial  $\eta^2 = 0.279$ ] (see Fig. 3). There was no main effect of block or group on VAS rating, and no other interactions approached significance ( $p > 0.1$ ).

Consistent with our second prediction, patients and controls did not differ in terms of VAS aberrant salience ( $F < 1$ , partial  $\eta^2 = 0.005$ ), though controls reduced aberrant salience from block 1 to block 2 [ $F(1, 16) = 7.8, p = 0.013$ ] while patients did not ( $F < 1$ ) [group  $\times$  block interaction:  $F(1, 35) = 7.0, p = 0.012$ ]. RT and VAS aberrant salience were uncorrelated across subjects ( $p > 0.2$ ). Participants did not reliably rate any particular irrelevant stimulus feature as more

**Table 2.** Behavioural data

| Test                                    | Measure                                 | Controls                 | Patients     |
|---|---|--------------------------|--------------|
| Salience Attribution Test               |   |                          |              |
| Block 1                                 | RT high probability (ms)                | 247.5 (22.4)             | 281.4 (82.0) |
|   | RT low probability (ms)                 | 262.9 (28.9)             | 285.3 (86.6) |
|   | RT adaptive salience (ms) <sup>a</sup>  | 15.4 (24.7)              | 3.9 (18.7)   |
|   | RT irrelevant 'high' (ms) <sup>b</sup>  | 247.0 (23.3)             | 276.3 (83.4) |
|   | RT irrelevant 'low' (ms) <sup>b</sup>   | 263.5 (22.9)             | 290.4 (85.9) |
|   | RT aberrant salience (ms) <sup>c</sup>  | 16.5 (10.3)              | 14.2 (12.4)  |
|   | VAS high probability (mm)               | 65.1 (15.4)              | 53.5 (15.7)  |
|   | VAS low probability (mm)                | 26.2 (16.6)              | 35.3 (20.4)  |
|   | VAS adaptive salience (mm) <sup>a</sup> | 38.9 (28.5)              | 18.2 (32.8)  |
|   | VAS irrelevant 'high' (mm) <sup>b</sup> | 55.1 (10.6)              | 51.2 (12.0)  |
|   | VAS irrelevant 'low' (mm) <sup>b</sup>  | 36.1 (8.9)               | 37.7 (9.6)   |
|   | VAS aberrant salience (mm) <sup>c</sup> | 19.0 (13.2)              | 13.5 (15.2)  |
|   | Block 2                                 | RT high probability (ms) | 246.6 (23.4) |
| RT low probability (ms)                 |   | 254.6 (31.0)             | 289.1 (85.3) |
| RT adaptive salience (ms) <sup>a</sup>  |   | 8.2 (18.6)               | 0.1 (19.4)   |
| RT irrelevant 'high' (ms) <sup>b</sup>  |   | 243.4 (23.9)             | 278.8 (81.8) |
| RT irrelevant 'low' (ms) <sup>b</sup>   |   | 257.9 (30.3)             | 299.3 (91.4) |
| RT aberrant salience (ms) <sup>c</sup>  |   | 14.5 (14.9)              | 20.5 (24.2)  |
| VAS high probability (mm)               |   | 70.0 (14.1)              | 51.7 (21.2)  |
| VAS low probability (mm)                |   | 18.9 (15.7)              | 35.5 (18.7)  |
| VAS adaptive salience (mm) <sup>a</sup> |   | 51.0 (21.2)              | 16.1 (32.8)  |
| VAS irrelevant 'high' (mm) <sup>b</sup> |   | 49.9 (11.1)              | 51.5 (13.6)  |
| VAS irrelevant 'low' (mm) <sup>b</sup>  |   | 39.1 (11.6)              | 35.9 (13.6)  |
| VAS aberrant salience (mm) <sup>c</sup> |   | 10.8 (8.7)               | 15.6 (14.7)  |
| Digit span                              |   | Forwards                 | 8.8 (2.1)    |
|   | Backwards                               | 5.4 (2.6)                | 5.4 (1.8)    |
| Beads test                              | Number of beads viewed                  | 9.3 (2.9)                | 8.9 (5.3)    |
|   | Confidence rating (%)                   | 69.1 (11.6)              | 55.1 (27.9)  |
|   | Correct guess (% of sample)             | 87.5                     | 65.0         |

RT, Reaction time; VAS, visual analogue scale.

Values are given as mean (standard deviation).

<sup>a</sup> We defined adaptive salience as quicker responding to or higher subjective reinforcement probability rating for 90% (high) probability-reinforcement trials relative to 10% (low) probability-reinforcement trials. For RT, adaptive salience is computed as: low reinforcement probability mean RT – high reinforcement probability mean RT. For VAS, adaptive salience is computed as: high reinforcement probability VAS rating – low reinforcement probability VAS rating.

<sup>b</sup> We defined, for each subject, 'high' and 'low' irrelevant levels on the task-irrelevant stimulus dimension based on their responses: for RT, 'high' denotes whichever level participants responded faster to; for VAS, 'high' denotes whichever level participants rated as more likely to result in reinforcement. This calculation was performed separately for each block.

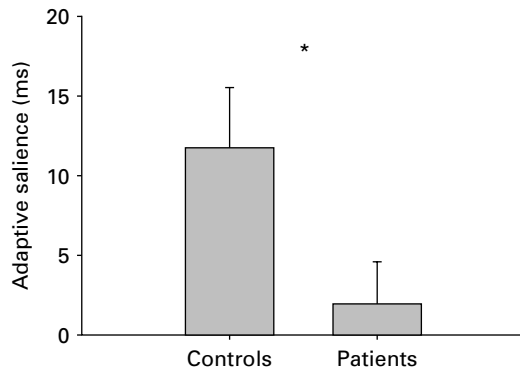
<sup>c</sup> We defined aberrant salience as quicker responding to or higher subjective reinforcement probability rating for one level of the task-irrelevant stimulus dimension relative to the other level (see <sup>b</sup> above). For RT, aberrant salience is computed as: irrelevant 'low' RT – irrelevant 'high' RT. For VAS, aberrant salience is computed as: irrelevant 'high' VAS rating – irrelevant 'low' VAS rating.

likely to be associated with reward relative to the other ( $p > 0.05$  for all).

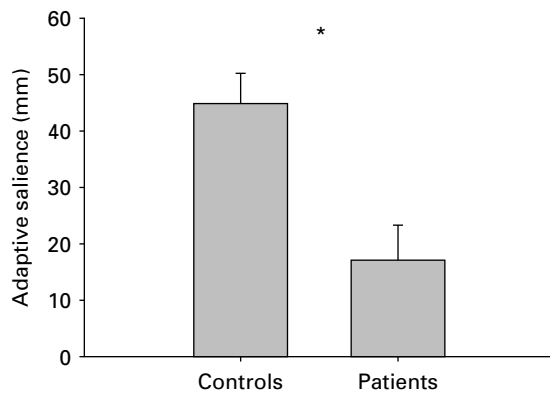
#### *Effect of symptoms of schizophrenia and schizotypy on aberrant salience*

Consistent with our third prediction, patients with positive symptoms [ $n = 13$ , mean sum of SAPS global

scores 7.5 (s.d. = 4.8)] exhibited significantly greater VAS aberrant salience than those without ( $n = 7$ ) [ $t(18) = 3.2$ ,  $p = 0.005$ , Cohen's  $d = 1.6$ ]. Positive symptoms showed a trend towards correlating with VAS aberrant salience ( $\rho = 0.40$ ,  $p = 0.085$ ). This effect appeared to be driven by the presence of delusions and not hallucinations. Delusional patients [ $n = 13$ , mean SAPS global delusions score 3.2 (s.d. = 1.0) out



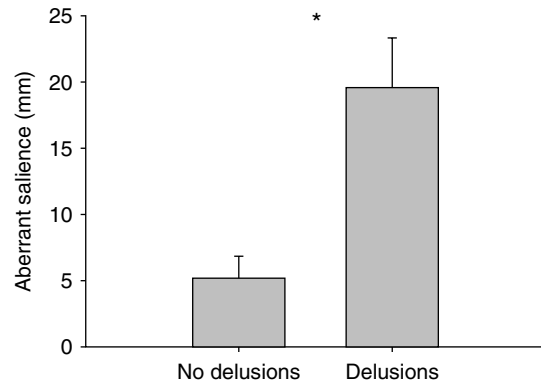
**Fig. 2.** Adaptive salience based on latency in patients with schizophrenia and controls. \* Patients exhibited reduced adaptive salience relative to controls ( $p=0.035$ ). Values are means and standard errors.



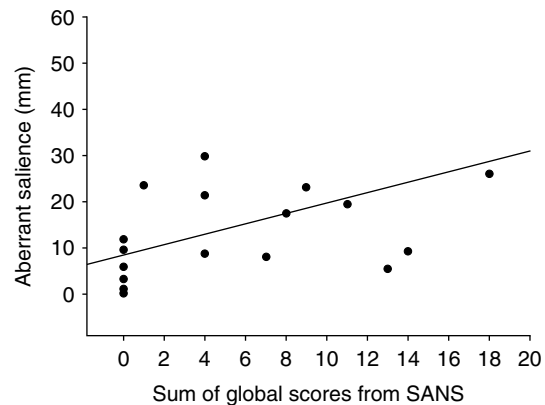
**Fig. 3.** Adaptive salience based on subjective reinforcement probability ratings in patients with schizophrenia and controls. \* Patients exhibited reduced adaptive salience relative to controls ( $p=0.002$ ). Values are means and standard errors.

of a maximum score of 5] exhibited significantly greater VAS aberrant salience than those with no delusions ( $n=7$ ) [ $t(18)=3.2$ ,  $p=0.005$ , Cohen's  $d=1.6$ ] (see Fig. 4). VAS aberrant salience correlated significantly with SAPS global delusions score ( $r=0.5$ ,  $p=0.025$ ). Interestingly, patients with no delusions actually exhibited significantly less VAS aberrant salience than controls [ $t(22)=3.0$ ,  $p=0.007$ ]. However, there was no difference in VAS aberrant salience between patients with hallucinations [ $n=9$ , mean SAPS global hallucinations score 3.9 (s.d.=1.4)] and those without ( $n=11$ ) ( $t=1.3$ ,  $p=0.21$ , Cohen's  $d=0.6$ ). Patients with positive symptoms did not differ from those with no positive symptoms on VAS adaptive salience [delusions: 16.7 (s.d.=28.4 mm); no delusions: 17.3 (s.d.=29.4 mm),  $t(18)=0.05$ ,  $p=0.96$ ].

Surprisingly, patients with negative symptoms [ $n=12$ , mean sum of SANS global scores 8.9



**Fig. 4.** Aberrant salience calculated from subjective reinforcement probability ratings in patients with schizophrenia. \* Patients with delusions exhibited significantly greater aberrant salience than those without delusions ( $p=0.005$ ). Values are means and standard errors.



**Fig. 5.** Relationship between the sum of global scores from the Scale for the Assessment of Negative Symptoms (SANS) and aberrant salience (calculated from subjective reinforcement probability ratings). Aberrant salience correlated significantly with negative symptoms in patients with schizophrenia ( $r=0.51$ ,  $p=0.020$ ).

(s.d.=5.1)] exhibited significantly greater VAS aberrant salience than those without ( $n=8$ ) ( $t(18)=3.5$ ,  $p=0.003$ , Cohen's  $d=1.6$ ). Interestingly, patients with no negative symptoms exhibited significantly less VAS aberrant salience than controls [ $t(23)=3.1$ ,  $p=0.006$ ]. Negative symptoms correlated significantly with VAS aberrant salience ( $r=0.51$ ,  $p=0.020$ ) (see Fig. 5). Negative symptoms also showed a trend towards correlating negatively with VAS adaptive salience ( $r=-0.42$ ,  $p=0.068$ ), though patients with negative symptoms did not differ significantly from those without negative symptoms on VAS adaptive salience [no negative symptoms: 28.6 (s.d.=25.2 mm); negative symptoms: mean 9.5 (s.d.=28.5 mm),  $t(18)=1.5$ ,  $p=0.14$ ].

Positive and negative symptoms were correlated in the patients ( $r=0.50$ ,  $p=0.027$ ). However, the difference in VAS aberrant salience between patients with and without positive symptoms remained significant when negative symptoms were included as a covariate [ $F(1,17)=5.5$ ,  $p=0.032$ ], and the difference in VAS aberrant salience between patients with and without negative symptoms remained significant when positive symptoms were included as a covariate [ $F(1,17)=10.5$ ,  $p=0.005$ ]. YMRS and CDRSS score were not correlated with either adaptive or aberrant salience.

Consistent with our fourth prediction, within the controls, score on the introverted anhedonia subscale of the O-LIFE correlated negatively with RT adaptive salience ( $r=-0.63$ ,  $p=0.007$ ) and VAS adaptive salience ( $r=-0.62$ ,  $p=0.008$ ), positively with VAS aberrant salience ( $r=0.49$ ,  $p=0.045$ ) and showed a trend towards correlating positively with RT aberrant salience ( $r=0.42$ ,  $p=0.092$ ). The cognitive disorganization subscale of the O-LIFE also showed a trend towards correlating with RT aberrant salience ( $r=0.45$ ,  $p=0.073$ ).

#### *Premature responses and omissions*

Other than trends towards making more premature responses [ $F(1,35)=3.0$ ,  $p=0.092$ ] and fewer omissions [ $F(1,32)=3.9$ ,  $p=0.057$ ] on high-probability-relative to low-probability-reinforcement trials, analysis of errors identified no main effects or interactions approaching significance.

#### *Other behavioural data*

Analysis of Beads Test and digit-span data revealed no group differences or interactions with group ( $p>0.1$ ), other than a trend towards greater confidence ratings on the Beads Test in controls than patients [ $t(26.5)=2.1$ ,  $p=0.052$ ]. Across all participants, VAS adaptive salience correlated significantly with WTAR ( $r=0.36$ ,  $p=0.030$ ), forwards digit-span ( $r=0.42$ ,  $p=0.010$ ) and backwards digit-span ( $r=0.43$ ,  $p=0.009$ ). RT aberrant salience was negatively correlated with WTAR ( $r=-0.341$ ,  $p=0.039$ ). However, Beads Task performance was uncorrelated with adaptive or aberrant salience on the SAT.

## **Discussion**

To our knowledge, this is the first study to demonstrate a relationship between the presence of delusions and abnormal attribution of salience in schizophrenia. Thus, although the schizophrenia group as a whole exhibited equivalent aberrant salience to controls, patients with delusions demonstrated significantly

more aberrant salience than those without. In concordance with other studies (Waltz *et al.* 2007; Jensen *et al.* 2008), we also found impaired learning of stimulus-reinforcement associations (indexed by a reduction in adaptive salience) in medicated patients with schizophrenia, which we hypothesize is related to dopamine D<sub>2</sub> receptor blockade (Cutmore & Beninger, 1990).

#### *Aberrant salience and positive symptoms of schizophrenia*

One explanation of increased aberrant salience in patients with positive symptoms concerns aberrant dopamine signalling. Contemporary accounts of reward learning suggest that phasic dopamine firing codes reward prediction errors (Schultz *et al.* 1997), for example, those arising from temporal difference models of reinforcement learning (Dayan & Balleine, 2002). Such models elegantly account for changes in both the firing patterns of ventral tegmental area dopamine neurons in monkeys (Schultz, 1997), and ventral striatal responses in humans (Pessiglione *et al.* 2006; Seymour *et al.* 2007), as reward-learning progresses. If phasic dopamine release signals reinforcement prediction errors, any large stochastic fluctuation in dopamine release may disrupt learning about stimulus-reinforcement associations, generating a state in which motivational salience could be misattributed to neutral stimuli, or what might be termed a 'false-positive' phasic dopamine signal; such events have been proposed to result in positive symptoms (Kapur, 2003).

In the present study, patients for whom medication had effectively eliminated positive symptoms actually exhibited significantly less aberrant salience than controls, supporting the hypothesis that the beneficial effects of antipsychotic medications on positive symptoms are related to their ability to dampen-down aberrant salience (Kapur, 2003). However, independent of symptoms at the time of testing, the patients with schizophrenia exhibited significantly less adaptive salience than controls. Antipsychotic medication has long been considered to exacerbate negative symptoms in schizophrenia, which may be related to reduced adaptive salience [see discussion below and Schooler (1994)]. Our findings support the suggestion of Kapur (2003) that this may be a necessary corollary to the beneficial effect of antipsychotic medication on positive symptoms.

Previous studies suggest that antipsychotic medication does not necessarily normalize abnormal dopamine signalling in psychotic patients. For example, functional neuroimaging studies have shown dopamine dysregulation in both medicated and



unmedicated patients (Hietala *et al.* 1995; Abi-Dargham, 2004; McGowan *et al.* 2004). Therefore persistent symptoms in medicated patients might still be related to aberrant salience. Furthermore, the only other study investigating stimulus–reinforcement learning for appetitive outcomes in psychosis found that both medicated and unmedicated patients responded more quickly to a CS– than controls, a finding interpreted as aberrant salience (Murray *et al.* 2008). This study also reported that patients exhibited reduced haemodynamic correlates of reward prediction errors in the ventral striatum relative to controls, consistent with other findings in medicated patients (Juckel *et al.* 2006; Jensen *et al.* 2008). Nevertheless it will be important to confirm our findings in unmedicated patients.

#### *Aberrant salience and negative symptoms of schizophrenia*

Although positive symptoms were associated with increased aberrant salience, our data also suggest a link between aberrant salience and negative symptoms. Aberrant salience correlated not only with negative symptoms in the patients, but also with O-LIFE introverted anhedonia, which relates to reduced interest and social withdrawal, in the controls. If dopamine transmission is dysregulated in psychosis (Abi-Dargham, 2004), it is possible that ‘false negatives’ in the phasic dopamine signal might occur, i.e. a reinforcement-related stimulus fails to elicit a sufficiently large phasic dopamine response. False negatives would decrease the value of motivationally salient stimuli, possibly leading to symptoms such as avolition, apathy and social withdrawal. Consistent with this explanation, other studies that investigated responses to emotionally salient images in medicated patients with schizophrenia reported decreased responding for (Heerey & Gold, 2007) and ventral striatal responses to (Taylor *et al.* 2005) positive emotional stimuli relative to controls.

This explanation is also consistent with data from a functional magnetic resonance imaging study investigating the effects of d-amphetamine on reward processing in healthy volunteers. Knutson *et al.* (2004) found that amphetamine administration paradoxically decreased the magnitude of phasic ventral striatal haemodynamic responses in response to a CS+ that signalled reward (i.e. increasing the potential for a false negative). In the same study, amphetamine administration caused significant phasic haemodynamic responses in the ventral striatum following CS+ that signalled potential monetary loss, an effect that was absent under placebo, possibly reflecting a loss of specificity of dopamine signalling (i.e. increasing the

potential for a false positive). The aberrant salience model might therefore explain both positive and negative symptoms by appealing to a common neurobiological mechanism, namely a loss of signal:noise ratio in the mesolimbic dopamine system, possibly as a result of increased tonic dopamine activity (Grace, 1991; Winterer & Weinberger, 2004).

#### *Study limitations and potential improvements*

Though these results broadly support the aberrant salience hypothesis, some limitations of the study merit comment. We tested a relatively small sample of patients with schizophrenia and performed multiple statistical comparisons, raising the likelihood of type I error. Therefore, these results should be treated with caution until replicated. Further, it is possible that the finding of reduced adaptive salience in the patients might simply reflect a learning deficit independent of reward, or perhaps a difficulty in using informative cues to guide speeded responses (Robbins, 2005), which could be related either to the illness or the effects of antipsychotic medication (Pessiglione *et al.* 2006). However, such explanations cannot explain differences in our measure of aberrant salience between symptom subgroups, or the correlation with schizotypy in the healthy volunteers.

It is possible that the differences in aberrant salience between the patients with and without delusions might also be explained by non-specific cognitive impairments in symptomatic patients, since such impairments might result in a failure to understand the task, difficulty in representing probabilities or a general tendency to respond more randomly. However, we consider this explanation unlikely for two reasons. First, the patients with and without delusions did not differ in terms of VAS adaptive salience, suggesting that they were equally able to learn and report the difference in reinforcement probability between the two levels of the task-relevant stimulus dimension, albeit to a lesser extent than controls. Second, the patients with and without delusions performed similarly on WTAR IQ, forwards and the backwards digit-span tasks and the Beads Task, making an explanation in terms of non-specific deficits less likely.

#### **Summary**

In summary, these data are consistent with the hypothesis that schizophrenia patients with delusions exhibit aberrant salience. However, negative symptoms were also correlated with our measures of both adaptive and aberrant salience. The aberrant salience hypothesis warrants further investigation in unmedicated patients with schizophrenia.

## Acknowledgements

The work was done at the Wellcome Trust Centre for Neuroimaging, Institute of Neurology (London, UK). This study was funded by the Raymond Way Fund, University College London, and the Wellcome Trust (grant number 064607/Z/01/Z). J.P.R. and E.M.J. were supported by the Raymond Way Fund. K.E.S. and K.J.F. were supported by the Wellcome Trust. H.E.M. was supported by a Wellcome Trust Ph.D. studentship. The authors acknowledge the assistance of Elizabeth Matheson in recruiting participants and Isobel Harrison and Stan Mutsatsa in assessing symptoms. The authors thank all of the participants for their involvement in this study.

## Note

Supplementary material accompanies this paper on the Journal's website (<http://journals.cambridge.org>).

## Declaration of Interest

None.

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