

## Neural and Behavioral Correlates of Aberrant Salience in Individuals at Risk for Psychosis

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The “aberrant salience” model proposes that psychotic symptoms first emerge when chaotic brain dopamine transmission leads to the attribution of significance to stimuli that would normally be considered irrelevant. This is thought to occur during the prodromal phase of psychotic disorders, but this prediction has not been tested previously. In the present study, we tested this model in 18 healthy volunteers and 18 unmedicated individuals at ultra-high risk of psychosis. Subjects performed the Salience Attribution Test, which provides behavioral measures of adaptive and aberrant motivational salience, during functional magnetic resonance imaging to assess neural responses to relevant and irrelevant stimulus features. On a separate occasion, the same subjects were also studied with [<sup>18</sup>F]fluorodopa positron emission tomography to measure dopamine synthesis capacity. Individuals at ultra-high risk of psychosis were more likely to attribute motivational salience to irrelevant stimulus features ( $t(26.7) = 2.8, P = .008$ ), and this bias was related to the severity of their delusion-like symptoms ( $r = .62, P = .008$ ). Ventral striatal responses to irrelevant stimulus features were also correlated with delusion-like symptoms in the ultra-high risk group ( $r = .59, P = .017$ ). Striatal dopamine synthesis capacity correlated negatively with hippocampal responses to irrelevant stimulus features in ultra-high risk individuals, but this relationship was positive in controls. These data are consistent with the hypothesis that aberrant salience processing underlies psychotic symptoms and involves functional alterations in the striatum, hippocampus, and the subcortical dopamine system.

**Key words:** psychosis/aberrant salience/salience attribution test/functional magnetic resonance imaging/positron emission tomography/dopamine

### Introduction

Contemporary models of psychosis<sup>1–3</sup> propose that the development of psychotic symptoms, such as delusions, is driven by the inappropriate processing of stimuli that would normally be considered irrelevant, due to “aberrant salience.”<sup>2</sup> In the context of this model, “salience” refers to the motivational properties of a stimulus, which can cause it to attract attention and drive behavior.<sup>4</sup> Aberrant salience refers to the tendency for irrelevant stimuli to be attributed motivational salience and thus to attract attention and influence behavior inappropriately.

This aberrant salience is thought to generate a distorted model of the environment founded on erroneous inference<sup>5</sup> and is proposed to occur during the prodromal phase preceding frank psychosis. Data from experimental animals suggest that aberrant motivational salience attribution results from out-of-context dopamine signaling in the ventral striatum,<sup>2,3</sup> which may in turn be driven by abnormal regulation of subcortical dopamine transmission by the prefrontal cortex (PFC)<sup>5</sup> and hippocampus.<sup>6,7</sup> This is consistent with robust evidence of abnormal dopamine transmission in psychotic patients, as indexed by increased striatal dopamine synthesis and release,<sup>8</sup> though, interestingly, the most reliable effects have been identified in the dorsal, not the ventral, striatum. Moreover, elevated striatal dopamine synthesis capacity is evident in individuals with prodromal signs of psychosis,<sup>9</sup> especially those who subsequently develop psychosis,<sup>10</sup> and may increase during the transition to psychosis.<sup>11</sup>

The same regions implicated in aberrant motivational salience processing in experimental animals also participate in adaptive (appropriate) motivational salience processing in humans. Thus, in healthy volunteers, reward anticipation elicits activation in the striatum, hippocampus, and

PFC, as well as striatal dopamine release.<sup>12</sup> There is also evidence that motivational salience processing<sup>13,14</sup> and associated neural responses<sup>15–19</sup> are perturbed in psychotic patients. However, most previous studies included patients treated with antipsychotic medication, which blocks dopamine transmission and may thereby attenuate normal motivational salience processing, complicating the interpretation of these results.<sup>2,20</sup> Although 2 studies reported attenuated reward-related striatal responses in unmedicated psychotic patients,<sup>18,21</sup> this abnormality was related to negative—and not positive—symptoms, a pattern also described in medicated patients.<sup>22,23</sup>

Previous studies of motivational salience in psychosis focused on the processing of relevant stimuli in patients with established illnesses. However, the aberrant salience model posits that it is the response to *irrelevant* stimuli that is critically disrupted in psychosis<sup>2</sup> and that this drives the emergence of psychotic symptoms during the prodrome. Therefore, we examined this model of psychosis and tested these predictions in individuals at ultra-high risk (UHR) of developing psychosis, who had experienced attenuated psychotic symptoms but were unmedicated. Motivational salience-related responses were assessed using the Salience Attribution Test (SAT),<sup>13,24</sup> which features both relevant and irrelevant stimuli, during functional magnetic resonance imaging (fMRI). The aberrant salience model also proposes that aberrant motivational salience processing is driven by elevated subcortical dopamine transmission. To test this aspect of the model, we measured dopamine synthesis capacity with 6-[<sup>18</sup>F] fluoro-L-3,4-dihydroxyphenylalanine positron emission tomography (<sup>18</sup>F-DOPA PET) in the same subjects. Our primary prediction was that symptomatic UHR individuals would show aberrant motivational salience behaviorally, as previously described in first-episode psychosis.<sup>13</sup> We also tested the prediction that aberrant motivational salience processing would be associated with altered activation in the striatum, PFC and hippocampus, and with the level of subcortical dopamine synthesis capacity.

## Methods

Detailed methods are provided in the online [supplementary material](#).

### Participants

We studied individuals presenting to a specialized clinical service for people at risk for psychosis who met the Comprehensive Assessment of At-Risk Mental State (CAARMS)<sup>25</sup> criteria ( $N = 18$ ). All UHR individuals confirmed having experienced attenuated psychotic symptoms, and the majority scored at least 3 (moderate severity) on the CAARMS “thought content” (delusion-like symptoms) or “perceptual abnormalities” (hallucination-like symptoms) scales at the time of testing. Healthy volunteers

( $N = 18$ ) with no history of psychiatric illness (confirmed with the Mini International Neuropsychiatric Inventory)<sup>26</sup> were recruited by advertisement from the same geographical area. This represented a subset of subjects included in our previous study.<sup>10</sup> All participants were right-handed native English speakers and free of antipsychotic medication at the time of scanning. Two UHR subjects had developed a first episode of psychosis between presentation and scanning and had received antipsychotic medication, but they had been unmedicated for at least 6 months by the time of scanning. Excluding these participants did not change the results. Ethical approval was obtained from the London–Harrow Research Ethics Committee. All participants provided written informed consent.

### Salience Attribution Test

The SAT is a speeded-response game, rewarded with money, which measures responses to task-relevant and task-irrelevant cue features.<sup>13,24</sup> During the game, participants responded to a probe after seeing 1 of 4 categories of cues (blue animals, red animals, blue household objects, and red household objects), which varied along 2 dimensions (color and form; see online [supplementary figure 1](#)). Participants received monetary reward (5–100 pence) on 50% of trials, with more money for faster responses. The probability of reward varied along one of the cue dimensions (task-relevant dimension, eg, color—blue stimuli: 87.5% rewarded; red stimuli: 12.5% rewarded), but not for the other (task-irrelevant dimension, eg, form—animal and household stimuli: both 50% rewarded). The contingencies between category and reward probability were counterbalanced across participants and remained constant throughout the task. Two experimental sessions (64 trials each) were performed during fMRI. The SAT provides measures of adaptive (relevant) and aberrant (irrelevant) motivational salience on the basis of visual analogue scale ratings (VAS: explicit salience) and reaction times (RTs: implicit salience; see online [supplementary methods](#)).

### Clinical Scales and Other Cognitive Measures

Psychotic symptoms were assessed using the CAARMS<sup>25</sup> and the Positive and Negative Syndrome Scale (PANSS).<sup>27</sup> Symptom data were excluded for 1 UHR participant who denied any past or present psychopathology, despite having suffered from a psychotic episode. Intelligence quotient (IQ) was assessed using the National Adult Reading Test (NART),<sup>28</sup> and the Digit-Span test was used to index working memory.<sup>29</sup>

### Behavioral and Clinical Data Analysis

Behavioral data were analyzed using the Statistical Package for the Social Sciences (SPSS 16: SPSS Inc., Chicago, IL). Acquisition of reward contingencies was

assessed using a 1-sample  $t$  test against 0 on the SAT adaptive salience measures. RT measures were square-root transformed prior to analysis to reduce skew. Correlations were performed using Pearson's  $r$ . For all tests,  $P < .05$  was considered significant and  $.05 < P < .1$ , a trend toward significance.

### fMRI Procedure

MRI data could not be collected for 1 UHR participant due to the presence of a metal implant. Hemodynamic responses were measured using echo-planar images (EPIs), acquired with a General Electric (Milwaukee, Wisconsin) 3-Tesla HDx system. The first 4 images in each series were discarded to allow for signal stabilization.

EPI data were analyzed with Statistical Parametric Mapping (SPM5: [www.fil.ion.ucl.ac.uk/spm](http://www.fil.ion.ucl.ac.uk/spm)) in the context of the general linear model (GLM).<sup>24</sup> EPIs were initially realigned, spatially normalized, and smoothed before being entered into a GLM that included the 4 cue regressors, an outcome regressor, and its parametric modulation by reward magnitude. Two contrast images were generated per participant, representing (1) adaptive reward prediction and (2) aberrant reward prediction. The contrast of primary interest was aberrant reward prediction: This yields differential neural responses between cue features that the participant erroneously indicated (through VAS ratings) were different predictors of reward. First-level contrast images were combined at the second level to identify group differences. Relationships between neural responses and behavior on the SAT and dopamine synthesis capacity were identified by including parameters from the SAT and <sup>18</sup>F-DOPA PET analyses as covariates.

Group-level maps were initially thresholded at  $P < .005$  (uncorrected). We defined 3 regions of interest (ROIs) for our fMRI analyses. (1) Bilateral striatum: 15-mm-radius spheres centered on maxima from our previous study (right [ $x = 12$ ;  $y = 12$ ;  $z = -3$ ]; left [ $x = -12$ ;  $y = 9$ ;  $z = -3$ ]). This region was chosen on the basis of the aberrant salience hypothesis<sup>2</sup> and our earlier study,<sup>24</sup> which identified motivational salience-related responses in this region. (2) Right dorsolateral prefrontal cortex (DLPFC): a 15-mm-radius sphere, centered on a maximum from our previous study ( $x = 45$ ;  $y = 27$ ;  $z = 33$ ). This region was chosen on the basis of the hypothesized role of the right DLPFC in psychosis<sup>16</sup> and our earlier study.<sup>24</sup> (3) Bilateral hippocampus: defined using the Automated Anatomical Labeling Atlas.<sup>30</sup> This region was chosen on the basis of the hypothesized role for the hippocampus in psychosis through its regulation of dopamine signaling, as suggested by the methylazoxymethanol acetate (MAM) model of psychosis,<sup>6</sup> and prior work indicating a relationship between dopamine and motivational salience processing in this region.<sup>12</sup> Note that the ROI definitions for the fMRI analyses differ from those used for the PET analyses: The latter were performed on

individual participants, whereas the former were applied to group-averaged voxel maps.

We corrected for multiple comparisons, controlling the family-wise error adjusted for small volume ( $P_{\text{SVC}}$ ) across each of our ROIs at the voxel level. We then applied Bonferroni correction for our use of 3 ROIs ( $P_{\text{SVCB}}$ ). We use the latter, more conservative  $P$  values to make inferences but still report the former for completeness because we had strong a priori hypotheses and because such strict correction risks elevating the Type II error rate.<sup>31</sup> For the exploratory correlations with <sup>18</sup>F-DOPA Ki values only, we additionally discuss effects surviving whole-brain cluster-level correction ( $P_{\text{WBC}}$ ). For post hoc analyses of group interactions, we report uncorrected  $P$  values for illustrative purposes (indicated by the suffix “uncorrected”). For completeness, for all analyses, we list all clusters at the  $P < .005$  (uncorrected), 30-contiguous-voxel threshold in online [supplementary tables 1–4](#).

### <sup>18</sup>F-DOPA PET Procedure

Participants completed an <sup>18</sup>F-DOPA PET scan on a separate occasion, using an ECAT/EXACT3D PET scanner (Siemens/CTI), as described previously.<sup>9</sup> ROI analyses were performed blind to group status using the HamNet probabilistic atlas.<sup>32</sup> The striatum was divided to yield ventral (limbic) and dorsal (associative subdivision) subregions, reflecting its functional organization.

## Results

The groups did not differ on demographic measures, IQ, or working memory ([table 1](#)).

### *Salience Attribution Test Behavioral Data*

UHR individuals scored significantly higher than controls on SAT explicit aberrant salience [ $t(26.7) = 2.8$ ,  $P = .008$ ; [figure 1A](#); [table 1](#)], indicating a greater tendency to rate 1 irrelevant cue feature as more associated with reward than the other. The groups did not differ on SAT implicit aberrant salience (defined using absolute RT differences:  $t < 1$ ). We also tested whether participants responded more quickly to irrelevant stimuli that they (erroneously) rated as being more associated with reward. There was no evidence for this in either group (controls: mean RT difference = 3.1 ms, SD = 31.5 ms,  $t < 1$ ; UHR: mean RT difference = -3.7 ms, SD = 21.5 ms,  $t < 1$ ).

In UHR subjects, SAT explicit aberrant salience showed a particular association with the severity of abnormal beliefs. In a multiple regression model including the CAARMS thought content subscale together with each of the PANSS subscales (positive, negative, general), which was significant overall [ $F(4,12) = 4.66$ ,  $P = .017$ ], only the thought content subscale was a significant predictor of SAT explicit aberrant salience ( $t = 2.2$ ,  $P = .048$ ). Further

**Table 1.** Clinical and Behavioral Data

	Controls ( <i>N</i> = 18)	UHR ( <i>N</i> = 18) <sup>a</sup>	Statistic
Age, years	26.5 (6.0)	25.7 (4.3)	<i>t</i> (33) = .45, <i>P</i> = .658
Gender			
Male	10	7	$\chi^2_1 = .70$ , <i>P</i> = .402
Female	8	11	
Estimated full-scale IQ (NART)	104.6 (9.3)	101.8 (15.3)	<i>t</i> (33) = .64, <i>P</i> = .524
Digit span			
Forward	8.9 (1.7)	8.1 (2.1)	<i>t</i> (33) = 1.21, <i>P</i> = .236
Backward	6.9 (3.1)	6.7 (2.8)	<i>t</i> (33) = .24, <i>P</i> = .239
CAARMS			
Thought content (severity)	.0 (.0)	2.6 (2.0)	<i>t</i> (16) = 5.25, <i>P</i> < .001
Perceptual abnormalities (severity)	.2 (.5)	2.0 (2.0)	<i>t</i> (18) = 3.67, <i>P</i> = .002
Disorganized speech (severity)	.1 (.3)	1.2 (1.8)	<i>t</i> (17) = 2.39, <i>P</i> = .029
PANSS			
Total	30.6 (1.1)	43.5 (21.5)	<i>t</i> (16.1) = 2.47, <i>P</i> = .025
Positive	7.1 (.5)	11.5 (5.1)	<i>t</i> (16.3) = 3.58, <i>P</i> = .002
Negative	7.1 (.5)	8.9 (4.2)	<i>t</i> (16.4) = 1.75, <i>P</i> = .099
General	16.3 (.8)	22.7 (13.2)	<i>t</i> (16.1) = 2.01, <i>P</i> = .061
SAT			
Implicit adaptive salience (ms)	43.7 (51.8)	17.7 (32.8)	<i>t</i> (34) = 1.74, <i>P</i> = .091
Implicit aberrant salience (ms)	24.6 (21.9)	20.9 (11.5)	<i>t</i> (26) = .072, <i>P</i> = .943
Explicit adaptive salience (VAS %)	53.8 (35.6)	45.4 (32.1)	<i>t</i> (34) = .74, <i>P</i> = .320
Explicit aberrant salience (VAS %)	6.3 (5.1)	12.8 (9.1)	<i>t</i> (26.7) = 2.66, <i>P</i> = .008
Premature responses	.28 (.57)	.56 (1.9)	<i>t</i> (34) = .60, <i>P</i> = .55
Omissions	7.2 (9.8)	6.3 (5.4)	<i>t</i> (34) = .34, <i>P</i> = .74

Note: M, Male; F, Female; UHR, Ultra-high risk for psychosis; IQ, Intelligence quotient; NART, National Adult Reading Test; CAARMS, Comprehensive Assessment of At-Risk Mental State, scored from 0 (no symptom) to 6 (psychotic level of symptom); PANSS, Positive and Negative Syndrome Scale; SAT, Salience Attribution Test; VAS, Visual Analogue Scale. Values indicate means (standard deviations).

<sup>a</sup>*N* = 17 for symptom scores.

analysis confirmed a significant correlation between these measures ( $r = .62$ ,  $P = .008$ ; [figure 1C](#)). A second multiple regression model including the CAARMS thought content, perceptual abnormalities, and disorganized speech subscales showed a trend toward significance overall [ $F(3,13) = 2.949$ ,  $P = .072$ ], with only the thought content subscale showing a trend toward predicting SAT explicit aberrant salience ( $t = 2.0$ ,  $P = .075$ ).

The groups did not differ on SAT explicit adaptive salience [ $t(34) = 1.0$ ,  $P = .32$ ; [figure 1B](#); [table 1](#)], indicating that the ability of UHR individuals to discriminate between high- and low-probability cue features was unimpaired. There was a trend for a group difference on SAT implicit adaptive salience [ $t(34) = 1.74$ ,  $P = .091$ ], but both groups responded significantly faster on high-probability, relative to low-probability, trials [controls:  $t(17) = 3.58$ ,  $P = .002$ ; UHR:  $t(17) = 2.28$ ,  $P = .036$ ; [table 1](#)]. Within the UHR sample, multiple regression models examining the relationship between explicit adaptive salience and CAARMS scores [ $F(3,13) < 1$ ] and PANSS scores [ $F(3,13) = 1.49$ ,  $P = .26$ ] did not approach significance.

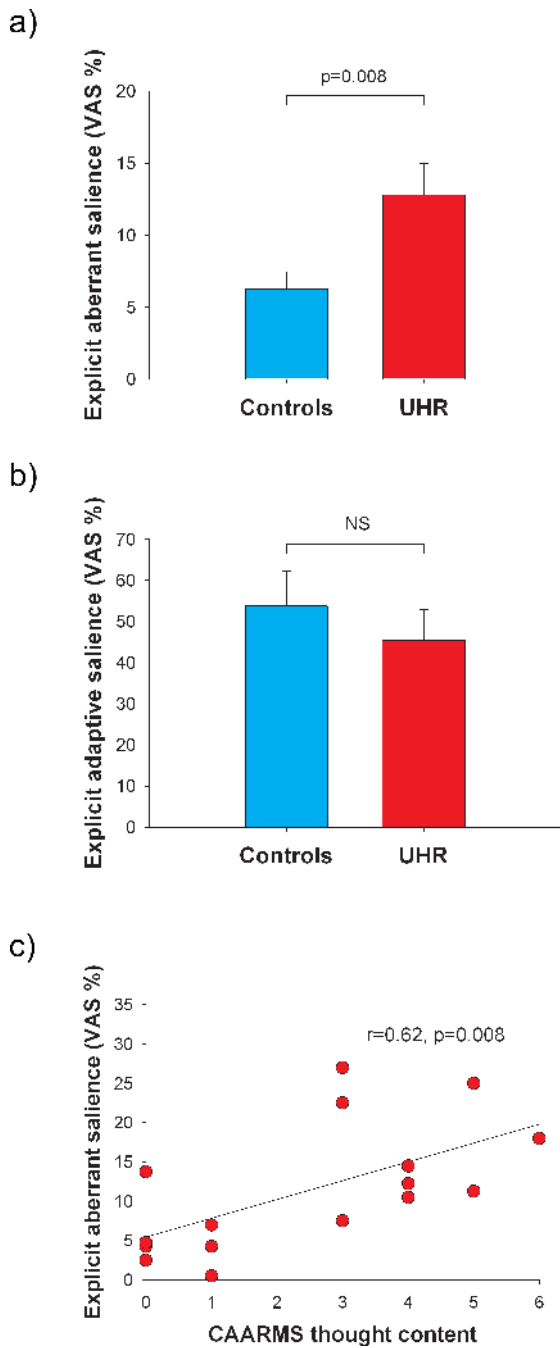
The group difference in explicit aberrant salience attribution remained significant when the explicit adaptive salience measure was included as a covariate in the analysis [ $F(1,33) = 7.0$ ,  $P = .012$ ]. This result, and the similar working memory and IQ scores in the 2 groups, indicates that the

elevated aberrant salience scores in UHR individuals were unlikely to be secondary to some general cognitive deficit.

### fMRI Data

Full fMRI results are presented in the online [supplementary tables 1–4](#).

**Aberrant Reward Prediction.** The groups differed in their right DLPFC responses to irrelevant cue features, but this result did not survive Bonferroni correction for multiple ROIs ( $Z = 3.50$ ,  $P_{SVCB} = .12$ ,  $P_{SVC} = .042$ ). Across all subjects, there was a positive relationship between aberrant reward prediction responses in the ventral striatum and SAT explicit aberrant salience ( $Z = 4.08$ ,  $P_{SVCB} = .018$ ,  $P_{SVC} = .006$ ; [figure 2A](#)). However, the slope of the regression line was significantly flatter and nonsignificant in UHR subjects (explicit aberrant salience  $\times$  group interaction:  $F(1,31) = 9.39$ ,  $P = .004$ ; [figure 2B](#)). Within the UHR group, in a multiple regression model including the CAARMS thought content subscale together with each of the PANSS subscales, which was significant overall [ $F(4,11) = 3.77$ ,  $P = .036$ ], both the thought content subscale ( $t = 2.9$ ,  $P = .016$ ) and the PANSS positive subscale ( $t = 2.3$ ,  $P = .042$ ) were significant predictors of ventral striatal responses to irrelevant cue features. Further



**Fig. 1. Behavioral data.** Ultra-high risk (UHR) individuals exhibited (a) elevated explicit aberrant salience but (b) equivalent explicit adaptive salience relative to controls. (c) Explicit aberrant salience was positively correlated with delusion-like symptoms in the UHR group. Error bars indicate standard errors of the mean (SEM). VAS, Visual Analogue Scale; CAARMS, Comprehensive Assessment of At-Risk Mental State.

analyses confirmed that the CAARMS thought content scale was correlated with ventral striatal responses ( $r = .59, P = .017$ ; [figure 2C](#)). A model including each of the CAARMS subscales showed a trend toward significance overall [ $F(3,12) = 3.46, P = .051$ ], but none of the individual subscales approached significance.

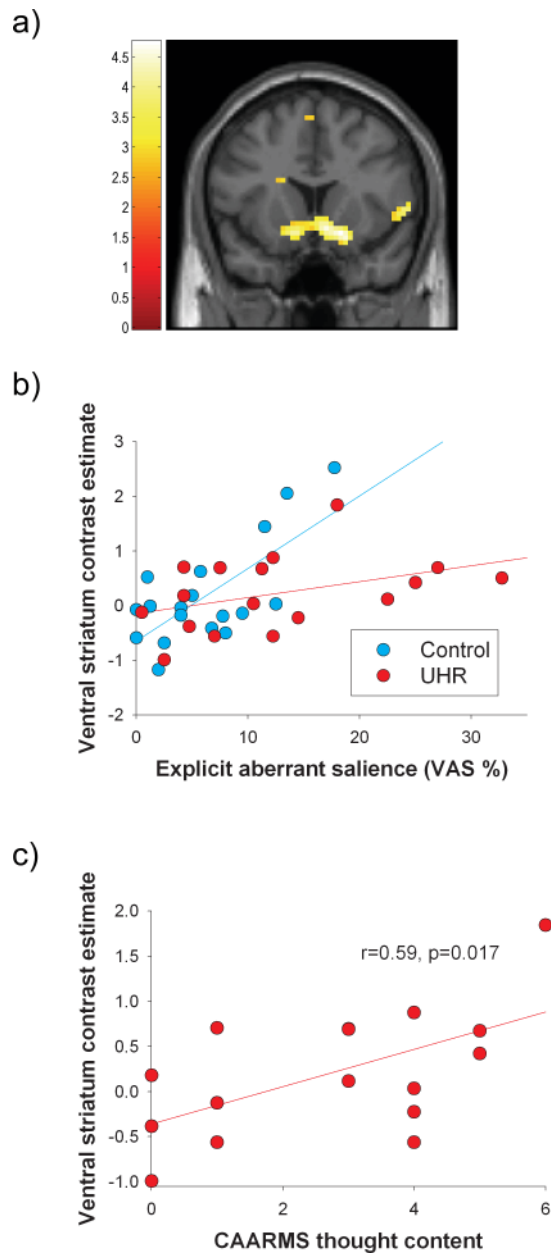
**Adaptive Reward Prediction Responses.** Across all subjects, presentation of high-probability, relative to low-probability, cue features elicited responses in the ventral striatum (right:  $Z = 5.60, P_{SVC} < .001, P_{SVCB} < .001$ ; left:  $Z = 5.92, P_{SVC} < .001, P_{SVCB} < .001$ ; [online supplementary figure 2A](#)). Mirroring the behavioral results, there were no group differences in adaptive (appropriate) reward prediction responses, even at a very liberal threshold (see [online supplementary table 1](#)). In the right ventral striatum, there was a trend toward responses being positively associated with SAT explicit adaptive salience, but this did not approach significance following Bonferroni correction for the 3 ROIs ( $Z = 3.31, P_{SVCB} = .19, P_{SVC} = .069$ ; [online supplementary figure 2B](#)). In contrast to the correlation with explicit aberrant salience, this relationship was similar in the 2 groups (explicit adaptive salience  $\times$  group interaction:  $F(1,31) < 1$ ; [online supplementary figure 2C](#)). Within the UHR sample, multiple regression models examining the relationship between ventral striatal response to relevant cue features and CAARMS scores [ $F(3,12) < 1$ ] and PANSS scores [ $F(3,12) = 1.11, P = .38$ ] did not approach significance.

*Relationship Between Reward Prediction Responses and Dopamine Synthesis Capacity*

**Comparison of Dopamine Function Between Groups.** The groups did not differ on any measure of dopamine synthesis capacity, in either the whole striatum or its subregions ( $t < 1$  for all regions).

**Aberrant Reward Prediction Responses.** There was a significant group  $\times$  dorsal striatal  $^{18}\text{F}$ -DOPA Ki interaction for aberrant reward prediction responses in the right hippocampus, which approached significance following Bonferroni correction for multiple ROIs ( $Z = 3.92, P_{SVCB} = .087, P_{SVC} = .030$ ; [figure 3A](#)). In controls, there was a positive correlation between the hippocampal response to irrelevant cue features and striatal dopamine synthesis capacity ( $r = .65, P = .004$  [uncorrected]). However, the opposite relationship applied in the UHR group ( $r = -.52, P = .035$  [uncorrected]; [figure 3B](#)). A similar interaction was evident in the motor cortex (left:  $Z = 4.42, P_{WBC} < .001$  [cluster level]; right:  $Z = 4.13, P_{WBC} = .006$  [cluster level]) and in the left occipital/parietal cortex, although in the latter region, the differential relationship was with dopamine synthesis capacity in the ventral striatum ( $Z = 4.28, P_{WBC} = .002$  [cluster level]).

**Adaptive Reward Prediction Responses.** There was a significant group  $\times$  ventral striatal  $^{18}\text{F}$ -DOPA Ki interaction for adaptive reward prediction responses in a large cluster comprising ventrolateral bilateral occipital gyri, right inferior temporal gyrus, right medial PFC, right supramarginal gyrus, and the planum temporale



**Fig. 2. Aberrant neural reward prediction signals in UHR individuals.** (a & b) The magnitude of aberrant salience attribution was positively correlated with ventral striatal response to irrelevant cue features (peak voxel: [ $x = -12; y = 18; z = -12$ ]), with a significantly steeper slope [ $F(1,31) = 9.39, P = .004$ ] in controls ( $r = .74, P < .001$  [uncorrected]) than UHR subjects ( $r = .40, P = .11$  [uncorrected]). (c) Aberrant reward prediction signals in the ventral striatum (peak voxel from the above analysis) correlated positively with the severity of delusion-like symptoms in the UHR group ( $r = .59, P = .017$ ). Error bars indicate SEM.

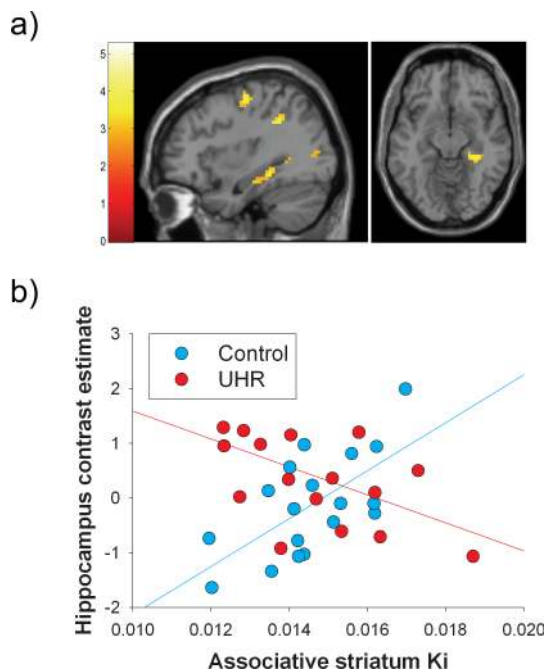
( $Z = 4.32; P_{WBC} < .001$  [cluster level]; online [supplementary figure 3A](#)). Similar interactions were also evident in the left putamen/thalamus extending to the parietal cortex ( $Z = 3.55, P_{WBC} = .036$  [cluster level]) and the right caudate/inferior frontal gyrus ( $Z = 3.84, P_{WBC} = .024$  [cluster level]). The peak in the right caudate was selected for

post hoc analysis (see online [supplementary figure 3](#)). In this region, higher dopamine synthesis capacity predicted greater adaptive reward prediction responses in controls ( $r = .63, P = .006$  [uncorrected]), whereas the opposite relationship applied in the UHR group ( $r = -.63, P = .007$  [uncorrected]; online [supplementary figure 3B](#)).

## Discussion

Collectively, our findings are consistent with several predictions of the aberrant salience model of psychosis.<sup>2</sup> At the behavioral level, UHR individuals scored higher on the SAT explicit aberrant salience measure than controls. This tendency was correlated with the severity of their abnormal beliefs, as were the ventral striatal responses to stimulus features inappropriately assigned motivational salience. It is unlikely that these effects reflect some general cognitive deficit, because the SAT incorporates a positive control, the adaptive (appropriate) salience contrast, which did not differentiate the groups at either the behavioral or the neural level. Additionally, though not predicted by the aberrant salience hypothesis, we identified several striking opposite relationships in the 2 groups in terms of the relationship between presynaptic dopamine synthesis capacity and motivational salience-related neural responses, both adaptive and aberrant. However, we were unable to confirm all aspects of the aberrant salience hypothesis: Presynaptic dopamine synthesis capacity did not differ significantly between UHR subjects and controls in this sample; and no group differences in neural responses during aberrant reward prediction survived stringent correction for multiple comparisons. Further studies in larger samples are required to test these aspects of the aberrant salience hypothesis.

Our fMRI data are consistent with the proposal that the ventral striatum plays a key role in processing both aberrant and adaptive motivational salience.<sup>2</sup> There was a direct relationship between both the aberrant and the adaptive explicit salience measures derived from the SAT, and the associated ventral striatal responses ([figure 2A](#) and online [supplementary figure 2](#)). The relationship between ventral striatal responses and aberrant motivational salience was significantly attenuated in the UHR group ([figure 2B](#)). Moreover, ventral striatal responses to irrelevant cue features correlated positively with the severity of positive symptoms in the UHR subjects ([figure 2C](#)). This is consistent with the putative role of the ventral striatum in the aberrant salience model<sup>2</sup> and in the pathophysiology of psychosis more generally. The UHR group additionally showed increased right DLPFC responses to stimulus features that were erroneously inferred to be poorer predictors of reward, though this finding did not survive stringent Bonferroni correction for multiple ROIs and, therefore, this result should be treated with caution until independently replicated. Nonetheless,



**Fig. 3. Relationship between striatal dopamine levels and aberrant neural reward prediction signals.** (a & b) In controls, aberrant reward prediction signals in the hippocampus (peak voxel:  $[x = 33; y = -36; z = -9]$ ) correlated positively with  $^{18}\text{F}$ -DOPA Ki in the dorsal striatum ( $r = .65, P = .004$  [uncorrected]), but the same relationship was negative in UHR individuals ( $r = -.52, P = .035$  [uncorrected]).

it is consistent with other work that found that patients with psychosis inappropriately engage the right PFC during the processing of irrelevant stimuli.<sup>16</sup>

The attenuated relationship between ventral striatal responses and aberrant motivational salience in the UHR group is unlikely to reflect a generalized blunting in this region, because the relationship between ventral striatal responses and adaptive motivational salience in UHR subjects was very similar to that in controls. Moreover, the adaptive reward prediction contrast did not differentiate the groups even at a very liberal threshold. These null results contradict several prior studies that have reported that adaptive reinforcement processing and associated hemodynamic responses are disrupted in psychotic disorders.<sup>15,17–19,21</sup> Importantly, these studies included patients treated with antipsychotic medication, which may impair reward processing,<sup>20</sup> in addition to reporting greater deficits in patients with pronounced negative symptoms.<sup>18,22,23</sup> By contrast, the subjects we tested were all unmedicated and relatively free of negative symptoms (table 1). Instead, we speculate that the weaker relationship between ventral striatal response and aberrant motivational salience in UHR subjects may reflect inconsistent phasic (ie, stimulus-evoked) dopamine signaling related to stimuli whose association with reward is relatively uncertain (see also the following paragraphs). Future studies should examine the relationship between

phasic dopamine transmission—eg, that measured using  $^{11}\text{C}$ -raclopride displacement—and motivational salience processing in individuals at risk for psychosis.<sup>33</sup>

In both groups, aberrant reward prediction signals in the hippocampus were associated with presynaptic dopamine synthesis capacity in the dorsal striatum. The nature of this relationship in UHR subjects was opposite to that observed in controls, though this interaction only showed a trend toward significance following stringent Bonferroni correction for multiple ROIs and should therefore be interpreted with caution. In healthy subjects, the hippocampus is central to the processing of novelty salience<sup>34</sup> and is thought to modulate dopamine release in the striatum.<sup>12,35</sup> The hippocampus has been consistently implicated in the pathophysiology of psychosis: Its structure and function are altered in schizophrenia and in subjects at UHR for psychosis.<sup>36,37</sup> However, our finding of an opposite relationship between dopamine synthesis capacity and hippocampal responses to irrelevant stimuli in the 2 groups is surprising and requires further clarification.

One possible explanation relates to the role that the ventral hippocampus plays in regulating phasic and tonic (baseline) dopamine neuron firing, via a circuit including pallidal gamma aminobutyric acid-secreting projections to the ventral tegmental area (VTA). Following *N*-methyl-D-aspartate infusion into the ventral hippocampus, Lodge and Grace<sup>38</sup> reported that the number of “spontaneously active” dopamine neurons (the subset of neurons with the potential to exhibit a phasic response) was doubled, an effect thought to be caused by disinhibition of the pallidum-VTA projection.<sup>39</sup> A similar elevation in dopamine system responsivity, accompanied by ventral hippocampus hyperactivity, was also identified in the MAM rodent model of psychosis,<sup>6</sup> consistent with findings of elevated hippocampal resting-state perfusion in schizophrenia,<sup>40</sup> which is reduced by effective treatment.<sup>41</sup>

This abnormal hippocampal modulation of dopamine neuron firing, maximizing the “gain,” or responsivity to excitatory inputs to the VTA from other regions, might increase the number of dopamine neurons firing following the presentation of irrelevant stimuli<sup>38,39</sup> and could contribute to the out-of-context dopamine signaling hypothesized to cause aberrant salience experiences.<sup>2</sup> Alternatively or additionally, an increase in tonic dopamine neuron firing, another consequence of decreased pallidum-VTA inhibitory tone,<sup>39</sup> might impair the discrimination of “signal” (phasic release) from background “noise” (tonic release) in projection sites such as the striatum.

Either of these effects of heightened dopamine system responsivity could conceivably be exacerbated in UHR individuals with high dopamine synthesis capacity, because each action potential would be expected to release proportionately more dopamine. In other words, the impact of high dopamine synthesis capacity on

motivational salience signaling may depend on the baseline state of the dopamine system, modulated by ventral hippocampus activity. In healthy volunteers, high dopamine synthesis capacity may facilitate the transmission of motivational salience, potentiating appropriate phasic signals against a background of relatively low gain or tonic dopamine release. In UHR individuals, in whom inappropriate dopamine firing may occur more frequently, high dopamine synthesis capacity might impair the transmission of appropriate motivational salience signals, equally potentiating inappropriate signals. This interpretation remains speculative, though, because (1) elevated tonic dopamine neuron firing has only been demonstrated in animal models of schizophrenia, not in human patients; (2) we could not identify any significant relationship between dopamine synthesis capacity and behavioral measures of aberrant motivational salience in our sample; and (3) the dissociation we identified was with dopamine synthesis capacity in the dorsal not the ventral striatum; interestingly, this is also the region in which abnormal dopamine transmission has been observed most frequently in psychosis.<sup>8</sup>

We also identified an opposite relationship in the 2 groups between dopamine synthesis capacity in the ventral striatum and striatal hemodynamic responses during the processing of relevant cue features. Although we did not predict (or find) significant group differences in adaptive reward prediction responses, there was a trend toward a reduction on the SAT implicit adaptive salience measure in UHR individuals. These observations raise the possibility that both adaptive and aberrant motivational salience processing operate abnormally in UHR individuals and are consistent with previous studies that reported that psychosis is associated with impaired reward-related speeding.<sup>13,14</sup>

Some limitations of our study merit comment. First, the small sample in which we were able to acquire both PET and fMRI data limits the generalizability of our findings and the sensitivity of our analyses. This may have accounted for the absence of significant group differences in striatal dopamine synthesis capacity.<sup>9</sup> With 18 subjects in each group, we had only 59% power to detect an effect size of .75 between the groups, as reported in our previous study.<sup>9</sup> Hence, for this comparison, which our study was not designed to address, the chance of Type II error was relatively high. Second, only a small number of the sample we tested have transitioned to a full psychotic episode, precluding a definitive examination of whether aberrant motivational salience predicts future psychosis in UHR individuals. Third, although most of the UHR individuals we studied were medication-naïve participants, 2 subjects had developed frank psychotic symptoms after first presenting and had received antipsychotic medication, although this had been discontinued by the time of scanning for at least 6 months. Importantly, excluding these 2 participants did not

change the results. Fourth, we did not measure socioeconomic state in our study, raising the possibility that the subjective value of the monetary incentives we provided may have differed between the groups. However, we consider that this is unlikely to have affected the results, because none of the behavioral and neuroimaging measures reflecting adaptive motivational salience differed significantly between the groups. Finally, our study only assessed motivational salience; beyond the scope of the present investigation, it would be interesting to determine whether other aspects of salience processing (eg, novelty, perceptual abnormalities) operate abnormally in UHR individuals.

### Supplementary Material

Supplementary material is available at <http://schizophreniabulletin.oxfordjournals.org>.

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