

## Attention to Irrelevant Cues Is Related to Positive Symptoms in Schizophrenia

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**Many modern learning theories assume that the amount of attention to a cue depends on how well that cue predicted important events in the past. Schizophrenia is associated with deficits in attention and recent theories of psychosis have argued that positive symptoms such as delusions and hallucinations are related to a failure of selective attention. However, evidence demonstrating that attention to irrelevant cues is related to positive symptoms in schizophrenia is lacking. We used a novel method of measuring attention to nonpredictive (and thus irrelevant) cues in a causal learning test (Le Pelley ME, McLaren IP. Learned associability and associative change in human causal learning. *Q J Exp Psychol B*. 2003;56:68–79) to assess whether healthy adults and people with schizophrenia discriminate previously predictive and nonpredictive cues. In a series of experiments with independent samples, we demonstrated: (1) when people with schizophrenia who had severe positive symptoms successfully distinguished between predictive and nonpredictive cues during training, they failed to discriminate between predictive and nonpredictive cues relative to healthy adults during subsequent testing and (2) learning about nonpredictive cues was correlated with more severe positive symptoms scores in schizophrenia. These results suggest that positive symptoms of schizophrenia are related to increased attention to nonpredictive cues during causal learning. This deficit in selective attention results in learning irrelevant causal associations and may be the basis of positive symptoms in schizophrenia.**

*Key words:* associative learning/chronic schizophrenia/salience/learned relevance/causal learning

Associative learning theories assume the amount of attention to a cue depends on the “predictive value” of the cue, that is, how well that cue predicted important events in the past. Several theories assume that attention to the cue increases with the predictive value of the cue and decreases when the cue is a poor or unreliable predictor.<sup>1–3</sup>

Disturbances in attention are considered to be a key feature of schizophrenia. Various forms of attentional disturbances have been reported in schizophrenia including deficits in sensory-motor gating,<sup>4</sup> attentional set shifting,<sup>5</sup> response inhibition,<sup>6</sup> spatial cuing,<sup>7,8</sup> and signal detection.<sup>9</sup> These examples represent deficits in how attention determines performance, typically under conditions of instruction where participants are told which cue is the target or where to attend. However, attention itself can also determine how much is learned. For instance, tests of the preexposure effect (originally called latent inhibition)<sup>10</sup> and the Kamin blocking effect<sup>11</sup> indicate that people learn to ignore irrelevant stimuli. In the Kamin blocking procedure, a cue (A) is trained as a good predictor of the outcome. That cue is then trained alongside a new cue (B) and together these cues reliably predict the same outcome. Despite its reliable pairing with the outcome, little is learned about cue B in healthy participants. One explanation for this effect is that the initially trained cue A blocks learning about cue B because cue A is already a good predictor of the same outcome and hence captures selective attention at the expense of B, which is ignored. In contrast, people with schizophrenia essentially learn as much about the redundant cue B as they do about the initially trained cue A (albeit to a slightly lesser extent than healthy adults).<sup>12,13</sup> On this account, the absence of blocking is consistent with a failure of selective attention. However, an alternative view is the absence of blocking reflects a general failure in deductive reasoning or probabilistic inference.<sup>14,15</sup> It is possible, for example, that all participants attended equally to cue B but that healthy adults successfully deduced that this cue is redundant,<sup>15</sup> while the patient group failed to reach the same conclusion. Deductive reasoning processes have been implicated in blocking,<sup>16</sup> and reasoning and probabilistic inference are impaired in a large proportion of people with schizophrenia.<sup>17,18</sup> Consequently, prior demonstrations of a failure to learn to ignore

irrelevant stimuli in schizophrenia are ambiguous as to the cause being attention or reasoning deficits.

Le Pelley *et al.*<sup>19</sup> have developed a procedure to investigate attentional selection in learning, which addresses the alternative explanations of reasoning and inference contributions. In this “learned irrelevance” test, healthy volunteers learned that some cues (A, B, C, and D) consistently predict 1 of 2 outcomes (o1 and o2), while other cues (V, W, X, and Y) are irrelevant and predict neither outcome. In a second training stage, participants learned to predict 2 new outcomes (o3 and o4) using the same cues as in the first stage. Importantly, in this second stage, each cue (A–D and V–Y) was perfectly predictive of 1 of the 2 new outcomes. Thus, learning that a particular cue predicts outcome o1 in stage 1 tells a participant nothing about the effect of that cue in stage 2. A final test phase revealed that healthy participants had learned more about the previously predictive cues (A–D) than the previously nonpredictive cues (V–Y) during the second stage. Moreover, tests of eye-gaze revealed that healthy adults reduced overt attention to the previously nonpredictive cues during the second training stage.<sup>20</sup> Thus, learned irrelevance studies provide support for an attentional bias toward predictive cues and away from irrelevant cues in healthy adults, which is consistent with theories of learned attention.<sup>1–3</sup>

Current theories of psychosis<sup>21,22</sup> have emphasized the role of attention to irrelevant cues in the formation and experience of positive symptoms of schizophrenia. For instance, delusions may result from the formation of associations between irrelevant or unrelated events.<sup>23</sup> Furthermore, the beneficial effect of antipsychotic medications on positive symptoms may be related to improving attention and restoring the ability to discriminate between relevant and irrelevant cues. However, antipsychotic medication does not necessarily normalize abnormal dopamine signaling in chronic schizophrenia<sup>24</sup> and some patients continue to suffer persistent positive symptoms despite antipsychotic treatment. Therefore, current theories anticipate a relationship between attention deficits related to cue discrimination and positive symptoms, even for people with chronic schizophrenia who have been treated with antipsychotics.

We wished to determine whether the inability to discriminate between relevant and irrelevant cues, as measured by the amount of learning in a novel test of attention, is related to positive symptoms. The learned irrelevance test depends upon successfully learning which cues are predictive in stage 1 (as with blocking, described above). Given that a large proportion (up to 75%)<sup>17</sup> of people with schizophrenia displays a learning deficit and may be unable to learn the initial cue–outcome pairings during stage 1, it is necessary to assess people with schizophrenia who are able to learn in the initial stage of training. Previous demonstrations of a deficit in blocking in schizophrenia may be ambiguous because it is unclear if the

relevant cue (eg, cue A as described earlier) was established as a reliable predictor.<sup>25–27</sup> In the present study, equivalent stage 1 learning was attained in experiment 1 by selecting people with schizophrenia who showed learning in stage 1 that was comparable to healthy controls and in experiment 2 by adjusting the task difficulty so that learning was easily achieved in a group of people with schizophrenia who would normally show some learning impairment. Our hypotheses in both experiments were that people with schizophrenia will fail to discriminate between relevant and irrelevant cues, and in line with recent theories of psychosis, the amount of learning about the irrelevant cues will be related to the severity of positive symptoms. This could provide novel evidence of a deficit in selective attention in schizophrenia and potentially reveal how cognitive dysfunction relates to positive symptoms.

## Experiment 1

The aim of the first experiment was to establish whether learned irrelevance occurs in people with schizophrenia who were able to learn which cues were predictive in the initial stage of the experiment.

## Methods

### Participants

Fourteen healthy adults and 14 people with a diagnosis of schizophrenia or schizoaffective disorder participated. All volunteers provided informed consent according to procedures approved by the South Eastern Sydney and Illawarra Area Health Service and the University of New South Wales Human Research Ethics Committees. All participants spoke English as their first language. People with schizophrenia or schizoaffective disorder had no history of additional axis I disorders, head injuries with loss of consciousness, recent substance abuse or dependence within the past 5 years, seizures, or central nervous system infection. Healthy participants met the same criteria but also had no personal or family history of schizophrenia. Diagnosis was confirmed by a trained clinician using the Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*.<sup>28</sup> All people with schizophrenia were receiving second-generation antipsychotic medication with the most common medication being clozapine ( $n = 7$ ). All participants were administered 4 subtests of the Wechsler Adult Intelligence Scale–third edition: Picture Completion, Similarities, Arithmetic, and Digit-Symbol Substitution test to provide an estimate of current full-scale IQ.<sup>29</sup> The Wechsler Test for Adult Reading was administered to obtain a premorbid IQ estimate in people with schizophrenia.<sup>30</sup> Two research assistants administered the Positive and Negative Syndrome Scale (PANSS) to assess symptom severity,<sup>31</sup> interrater correlation

**Table 1.** Mean (SEM) Demographic Information for People With Schizophrenia and Healthy Adults

Experiment 1	Patients ( <i>n</i> = 14)	Controls ( <i>n</i> = 14)	<i>t</i> ( <i>df</i> )	<i>P</i>
Age	36 (2.0)	36 (2.8)	0.00 (26)	1.0
Females	5	6	X <sup>2</sup> 0.15 (1)	.70
Education years	13 (0.5)	15 (0.6)	2.32 (26)	.03
WAIS-III IQ	104 (3.4)	124 (4.5)	19.29 (26)	<.01
WTAR	108 (2.9)	115 (1.1)	2.02 (26)	.05
PANSS positive	18 (1.5)			
PANSS negative	14 (1.2)			
PANSS total	66 (5.5)			
Experiment 2	Patients ( <i>n</i> = 20)	Controls ( <i>n</i> = 15)	<i>t</i> ( <i>df</i> )	<i>P</i>
Age	33 (2.1)	32 (2.1)	0.51 (33)	.61
Females	8	7	X <sup>2</sup> 0.00 (1)	.96
Education years	14 (0.3)	15 (0.7)	1.40 (33)	.17
WAIS-III IQ	104 (3.3)	114 (4.0)	1.81 (33)	.08
WTAR	111 (1.8)	112 (1.5)	0.32 (33)	.75
PANSS positive	17 (1.1)			
PANSS negative	13 (0.8)			
PANSS total	60 (4.6)			

*Note:* The possible range of positive and negative PANSS scores in the 3-dimension model is 7–49. Kay et al.<sup>31</sup> reported 18 was the 50 percentile rank score for positive symptoms in a sample of chronic medicated inpatients; a mean positive symptom score of 17–18 would suggest mild to moderate symptom severity in our sample of medicated chronic outpatients. WTAR, Wechsler Test of Adult Reading; WAIS-III, Wechsler Adult Intelligence Scale (third edition); PANSS, Positive and Negative Syndrome Scale.

coefficient was 0.90. Table 1 presents a summary of the demographic data collected on each group.

### Design and Procedure

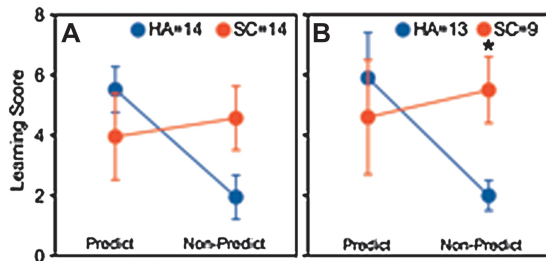
The procedure followed Le Pelley et al.<sup>32</sup> Participants acted as a horticulturalist developing new plant species at different hypothetical farms. The scenario was presented on a laptop computer. Instructions were provided describing the types of trees that grow at a hypothetical farm (Riverside Ranch). On each trial, participants had to predict the type of tree (outcomes o1 or o2) that would be created by combinations from 2 sets of seed varieties (cues A, B, C, or D with V, W, X, or Y), see Le Pelley et al.<sup>32</sup> Participants were told that feedback would be provided and that they would start out guessing but with feedback their choice would become more accurate. If participants chose the correct tree, the word “Correct” appeared; if they chose incorrectly, “Incorrect” appeared. Stage 1 comprised 10 blocks of trials, with 8 cue-outcome combinations (AV-o1, AW-o1, BV-o2, BW-o2, CX-o2, CY-o2, DX-o1, and DY-o1) occurring once per block in random order.

Stage 2 instructions stated that participants were now working at a new farm (Rural Retreat) at which new seed combinations produced new types of tree (outcomes o3 or o4). Stage 2 had 8 blocks of trials, with the 4 cue-outcome combinations (AX-o3, BY-o4, CV-o3, and DW-o4) appearing once per block in random order.

Participants were tested on what they had learned in stage 2 in a series of 2-choice tests involving outcomes o3 and o4. For each test, a seed combination was displayed (AC, BD, VX, or WY) and participants selected whichever of the 2 trees from stage 2 (o3 or o4) that they thought was most likely to result from the given seed combination. Because forced choice measures yield (relatively insensitive) categorical data, we also asked participants to rate their confidence in their decision on a scale from 0 (not confident) to 10 (very confident).<sup>19,20,32</sup> Each of the 4 test combinations was presented twice in random order. As a final test to ensure participants remembered the original relationships from stage 1, each person was also tested on their stage 1 knowledge in similar fashion: each of the stage 1 cue combinations was presented and participants had to choose and rate which outcomes (o1 or o2) were more likely to be produced. All participants were reimbursed \$20 for their time and travel expenses.

### Data Analysis

Confidence ratings provided a continuous variable on each decision, which was multiplied by 1 when the choice was correct and by –1 when the choice was incorrect to produce a measure of confidence accuracy hereafter termed “learning score.”<sup>19,20,32</sup> Thus, the learning score takes into consideration both accuracy and confidence with higher scores (maximum 10) indicating more confidence in correct decisions while lower scores (minimum –10) indicate more confidence in incorrect decisions. A score of 0 represents no confidence in a correct or incorrect decision. Scores were averaged for compounds AC and BD to produce an overall score for the previously predictive cues and scores for VX and WY were averaged to produce an overall score for the previously nonpredictive cues. Learned irrelevance in each group is indicated by lower scores for nonpredictive relative to predictive cues (VWXY < ABCD). Scores were analyzed in a 2 × 2 ANOVA with group and cue-type as independent variables. A deficit in learned irrelevance (and a failure of selective attention) in people with schizophrenia would be revealed by a significant group × cue interaction, reflecting a smaller difference between predictive and nonpredictive cues in people with schizophrenia compared with healthy adults. Planned *t* tests were used to confirm the occurrence of learned irrelevance in each group. Pearson’s correlation coefficient was used to assess the relationship between learning scores for previously nonpredictive cues and positive symptom scores as measured by the PANSS. Due to controversy regarding the number of factors that



**Fig. 1.** Mean learning scores of the stage 2 test for each group (A) and each subgroup of learners (B). Error bars show SEM. \*Significant between-group difference ( $P < .05$ ).

contribute to the PANSS and specific items that comprise each factor, we calculated the association between positive symptoms and predictive/nonpredictive cues based on the original 3-dimension model<sup>31</sup> and a 5-factor model<sup>33</sup>. Accordingly, the 3-dimension model included delusions, hallucinations, grandiosity, suspiciousness, conceptual disorganization, excitement, and hostility; while the 5-factor model included the first 4 items listed above plus unusual thought content.

## Results and Discussion

Percent accuracy during stage 1 was significantly higher among the healthy adults (mean = 82, SEM = 4.4) than the people with schizophrenia (mean = 59, SEM = 4.2),  $t_{26} = 4.15$ ,  $P < .01$ , demonstrating that healthy adults learned the initial predictive relationships better than people with schizophrenia. Learning scores from the test of stage 2 outcomes are shown in figure 1A. Crucially, a  $2 \times 2$  mixed ANOVA with factors of group (healthy vs schizophrenia) and cue-type (previously predictive vs previously nonpredictive) revealed a significant group  $\times$  cue-type interaction,  $F_{1,26} = 6.01$ ,  $P < .05$ . Planned  $t$  tests revealed that healthy adults showed significantly higher learning scores for previously predictive cues than for previously nonpredictive cues in stage 2,  $t_{13} = 4.72$ ,  $P < .01$ , demonstrating a learned irrelevance effect. In contrast, people with schizophrenia did not show a significant learned irrelevance effect,  $t_{13} = 0.82$ , nonsignificant. Thus, the results are consistent with a healthy attentional bias toward previously predictive cues,<sup>19,32</sup> which was not the case in schizophrenia. However, the absence of a learned irrelevance effect in schizophrenia cannot be unambiguously attributed to a failure of selective attention because some participants failed to learn the original predictive relationships in stage 1.

To determine whether a learned irrelevance effect occurred among people who learned and remembered the original predictive relationships, we selected the subset of participants from each group who showed a positive score in the final test phase, which assessed stage 1 learning. A positive score implies the participant learned and

remembered the stage 1 relationships throughout the experiment, thus any group differences cannot be due to a failure to remember the relevant cue-outcome contingencies. Thirteen healthy adults and 9 people with schizophrenia obtained a positive score in the final test phase showing stage 1 learning. The mean (SEM) stage 1 learning scores for healthy learners and learners with schizophrenia were 4.8 (0.8) and 3.3 (0.5), respectively,  $t_{20} = 1.41$ , nonsignificant. Scores for these learners from the test of stage 2 learning are shown in figure 1B. The important group  $\times$  cue interaction was significant,  $F_{1,20} = 4.36$ ,  $P < .05$ , indicating healthy learners displayed a greater learned irrelevance effect than learners with schizophrenia. Planned  $t$  tests confirmed a significant learned irrelevance effect among healthy learners ( $t_{12} = 4.84$ ,  $P < .01$ ), while learners with schizophrenia had similar scores for previously predictive and nonpredictive cues,  $t_8 = 0.82$ , nonsignificant. Furthermore, learners with schizophrenia learned significantly more about the previously nonpredictive cues than the healthy learners,  $t_{20} = 2.20$ ,  $P < .05$ , as if attention to irrelevant cues was abnormally increased among this subgroup.

The relationship between positive symptom score in the 3-dimension PANSS model and learning about nonpredictive cues was moderately strong, albeit nonsignificant in the small subset of learners with schizophrenia ( $n = 9$ ). Table 3 shows that the correlations of learning scores with IQ estimates, negative symptom scores, and drug dose (chlorpromazine equivalent<sup>34</sup>) were weak and nonsignificant.

## Experiment 2

Since several people with schizophrenia appeared to have difficulty learning the stage 1 predictive relationships in experiment 1, the first aim of experiment 2 was to examine whether learned irrelevance occurs in an independent sample of participants under easier stage 1 learning conditions. Thus, we reduced the task difficulty by decreasing the number of cues from 8 to 4 in stage 1 (see table 2, stage 1) and we introduced a criterion of 6 consecutive trials correct before participants could progress to stage 2. This criterion was added to ensure all the participants learned the relevant cue-outcome relationships to a similar extent in stage 1. The second aim of experiment 2 was to determine whether a relationship existed between the attention to irrelevant cues and positive symptoms in an independent sample.

## Methods

### Participants

Fifteen healthy adults and 20 people with a diagnosis of schizophrenia or schizoaffective disorder participated in experiment 2. Exclusion criteria for both groups were as described for experiment 1. Table 1 shows the demographic

**Table 2.** Cue-Outcome Pairs in Experiment 2

Stage 1	Stage 2	Test
AV—outcome 1	AV—outcome 3	A
AW—outcome 1	BW—outcome 4	B
BV—outcome 2		V
BW—outcome 2		W

Note: Cues (A–W) were different types of seeds (eg, Devlin). Outcomes (1–4) were different types of trees (eg, Pine). The predictive cues in stage 1 of experiment 2 were A and B, and the nonpredictive cues were V and W.

breakdown of participants. All people with schizophrenia were receiving second-generation antipsychotic medication with the most common medications being olanzapine (6) and clozapine (6).

### Design, Procedure, and Data Analysis

The procedure of experiment 2 was similar to experiment 1 with the following changes. Participants were initially trained with the 4 seed-tree (cue-outcome) combinations shown in table 2 (stage 1). Training continued until participants made 6 correct decisions in a row. Stage 2 consisted of 8 blocks of trials with each of the 2 cue-outcome combinations indicated in table 2 (stage 2) appearing once per block. After stage 2, participants were tested with individual cues (seeds) in a 2-choice test of the outcomes trained in stage 2 (o3 and o4) (table 2, test).

To ensure no group differences existed after learning the initial predictive relationships in stage 1, we compared the mean number of trials-to-criterion between groups in a *t* test. We also wished to determine whether the amount of learning about each cue-type was related to the severity of symptoms, so we correlated predictive and nonpredictive cue scores with positive and negative symptoms. Finally, to confirm the significant relationship between attention to irrelevant cues and positive symptoms resulted in abnormal learning relative to healthy adults, we divided people with schizophrenia into high- and low-positive symptom subgroups ( $n = 10$  per subgroup) according to the median positive PANSS score (median = 16) and compared each subgroup with the healthy adult group. A  $2 \times 2$  mixed ANOVA with 2 levels of cue (scores on previously predictive and nonpredictive cues) and 2 levels of group (eg, high-symptom subgroup vs healthy adults) was used to compare the amount of learning among the high-positive symptom subgroup with the healthy adults. The significant interaction between cue-type and group was tested to determine whether significant group differences in attentional bias existed. Planned *t* tests were used to confirm the source of any significant interaction. A similar ANOVA was performed to compare the low-positive symptom subgroup with healthy adults.

**Table 3.** Correlations of Learning Scores With IQ, Symptoms, and CPZ in Schizophrenia

	Positive Symptoms	Negative Symptoms	CPZ	WTAR	WAIS-III
Experiment 1 ( $n = 9$ )					
Predictive	0.32	-0.15	-0.21	-0.20	0.11
Nonpredictive	0.45	0.09	0.00	0.09	0.12
Experiment 2 ( $n = 20$ )					
Predictive	0.20	0.26	-0.28	0.32	-0.20
Nonpredictive	0.71**	0.48	-0.03	-0.33	-0.33

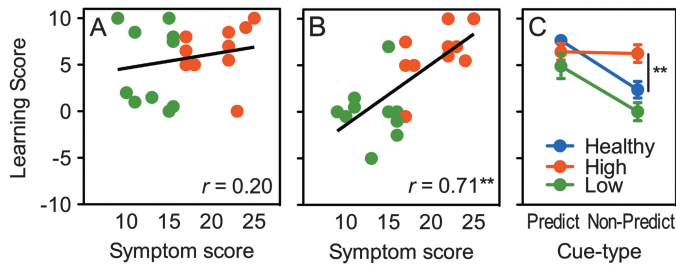
Note: CPZ, chlorpromazine equivalent dose; WTAR, Wechsler Test of Adult Reading; WAIS-III, Wechsler Adult Intelligence Scale (third edition).

\*\* $P < .01$ .

### Results and Discussion

There were no significant differences between the groups in the number of trials to criterion in stage 1; the mean (SEM) number of trials to criterion for the healthy adults and the people with schizophrenia were 36 (5.7) and 28 (4.2), respectively,  $t_{33} = 1.15$ , nonsignificant, verifying that both groups learned at a similar rate in stage 1. The stage 2 test revealed the mean (SEM) learning score for the previously predictive cues (A and B) and the previously nonpredictive cues (V and W) of the healthy adults were 8 (0.6) and 2 (0.9), respectively; while the scores of people with schizophrenia were 6 (1.2) and 3 (1.0), respectively. A  $2 \times 2$  mixed ANOVA with factors of cue-type and group revealed a significant main effect of cue-type,  $F_{1,33} = 16.55$ ,  $P < .01$ , but no significant group  $\times$  cue-type interaction. Thus, under easier task conditions and after comparable stage 1 learning, evidence of a normal bias toward predictive cues and a bias against nonpredictive cues existed in both groups.

We also obtained evidence that psychotic symptoms were positively related to attention to irrelevant cues, as predicted by current theories of psychosis.<sup>21,22</sup> The correlation between learning scores for the previously nonpredictive cues and positive symptoms using the 3-dimension PANSS model<sup>31</sup> was significant,  $r = .71$ ,  $P < .01$ , while the relationship between predictive cues and positive symptoms ( $r = .20$ ) was not significant. Figure 2 A and B shows that the relationships of positive symptoms with predictive and nonpredictive cues were clearly different. Fisher's *r*-to-*z* transformation confirmed the difference between these correlations was significant,  $t_{17} = 2.14$ ,  $P = .02$ . No other correlations among predictive/nonpredictive cues, negative symptoms, and drug dose (CPZ) were significant (see table 3). The correlation between the positive symptoms factor and nonpredictive cues using the 5-factor PANSS<sup>33</sup> model was  $r = .58$ ,  $P = .01$ , while the correlation with predictive cues was  $r = .11$ , nonsignificant.



**Fig. 2.** Correlation of Positive and Negative Syndrome Scale positive symptom scores with predictive (A) and nonpredictive cue performance (B); and mean learning scores of the stage 2 test for the high- and low-positive symptom subgroup and the healthy adults (C). Error bars show SEM.  $**P < .01$ .

To confirm the significant relationship between attention to irrelevant cues and positive symptoms resulted in abnormal learning relative to healthy adults, we compared stage 2 test scores of the high- and low-positive symptom severity subgroups with the healthy participants (see figure 2C). The  $2 \times 2$  mixed ANOVA comparing the high-positive symptom severity subgroup and healthy participants revealed a significant cue-type  $\times$  group interaction,  $F_{1,23} = 7.29$ ,  $P = .01$ , which was due to a significantly greater learned irrelevance effect in healthy adults than in the high-positive symptom severity subgroup. The high-symptom severity subgroup had significantly higher scores on the previously nonpredictive cues than healthy adults,  $t_{23} = 2.98$ ,  $P < .01$ , but no significant difference between the groups was seen for the previously predictive cues,  $t_{23} = 1.30$ . A separate ANOVA comparing the high- and low-positive symptom severity subgroups revealed a group  $\times$  cue interaction which approached but did not exceed conventional levels of significance,  $F_{1,18} = 4.13$ ,  $P = .06$ . The group  $\times$  cue interaction in an ANOVA comparing the low-positive symptom severity subgroup and healthy participants was nonsignificant,  $F_{1,23} = 0.04$ . Taken together, these data suggest that higher positive symptom severity is associated with increased attention to irrelevant cues.

## General Discussion

Experiment 1 confirmed that healthy adults learned more about previously predictive cues relative to nonpredictive cues, suggesting predictive cues attract more attention. Experiment 1 also found that people with schizophrenia did not show the normal bias toward predictive cues over nonpredictive cues, including in a subset of people who successfully learned the original predictive relationships. This provides novel evidence consistent with a failure of selective attention in schizophrenia obtained after controlling for learning deficits. Experiment 2 used an easier task, and in contrast to experiment 1, found that when all participants were able to learn the original predictive relationships in stage 1 both groups showed a bias toward

predictive cues. Thus, in comparison to the first experiment, experiment 2 suggests normal selective learning can occur in schizophrenia under easier task conditions. However, comparing high- and low-positive symptom severity patients to controls in experiment 2 showed that those with more severe positive symptoms failed to ignore the nonpredictive cues, suggesting the bias also varies with the severity of positive symptoms.

The bias toward learning about predictive cues observed in the healthy adults is consistent with theories of attention, which assume attention increases with “predictive value.”<sup>1–3</sup> Accordingly, when the different cues were trained in stage 1, cues more relevant to the outcome (ie, the predictive cues) attracted more attention. The increase in attention to the predictive cues resulted in better learning about these cues relative to the previously nonpredictive cues, when both sets of cues were recombined and predicted new outcomes equally well in stage 2. However, among people with schizophrenia, including people who learned and remembered the predictive relationships in stage 1 (experiment 1) and a subset of people with more severe positive symptoms (experiment 2), the normal bias toward predictive cues over nonpredictive cues was not present. The equivalent learning about predictive and nonpredictive cues, according to these theories,<sup>1–3</sup> is consistent with both sets of cues attracting equal attention in schizophrenia.

The absence of bias toward predictive cues among the subset of people with schizophrenia in each experiment was not likely due to a deficit in learning, reasoning, or memory for a number of reasons. First, deficits in deductive reasoning or probabilistic inference that may underlie the observed decrement in blocking seen in other studies would not produce the objectively superior performance for previously nonpredictive cues in the high-positive symptoms group. In stage 2, both the previously predictive and nonpredictive cues were equally predictive of the new outcomes. Thus, the optimal strategy is to learn about both sets of cues equally, which is what occurred among the subset of patients. Second, while group differences in IQ existed, subsets of the groups were matched on stage 1 performance: In experiment 1, we restricted an analysis to people who remembered the relevant stage 1 contingencies at the end of the experiment; in experiment 2, we reduced the number of relevant contingencies to remember in stage 1 which ensured each participant achieved the same level of accuracy before proceeding to stage 2. Thirdly, tests of eye-gaze using the same task have shown healthy adults reduce overt attention to the previously nonpredictive cue,<sup>20,35</sup> consistent with the role of attention in the present task. Thus, the present results are not easily explained by a deficit in learning, reasoning, or memory and are consistent with other evidence favoring an attentional interpretation; however, we cannot conclusively rule out the involvement of other processes, which may explain the apparent failure of bias toward predictive cues in schizophrenia.

The significant correlation between positive symptom severity and learning about nonpredictive cues suggests that the mechanism that leads to attention for irrelevant cues may underlie some positive symptoms. Consistent with this, the correlation of positive symptom severity with nonpredictive cue scores was significantly greater than with predictive cues in experiment 2. A preferential increase in the attention to irrelevant cues represents an inefficient form of learning in schizophrenia<sup>36,37</sup> and is an important precursor to the formation of delusions in some theories of psychosis, which view delusions as learned associations between unrelated events.<sup>21,23</sup> Other research has also found that people with psychosis, and delusions in particular, learn to respond faster to irrelevant or nonreinforced stimuli in reaction-time tasks.<sup>38–40</sup> Thus, the present results extend previous findings by showing that people with severe positive symptoms more readily learn causal relationships between irrelevant events.

The present results also provide evidence for a link between a deficit in selective attention and attenuated prediction-error signals in the brains of people with schizophrenia. Prediction error is the difference between anticipated and obtained outcomes and is related to attention such that good predictors attract more attention.<sup>1–3</sup> In other words, as people learn the predictive relationship between cues, cues that are good predictors elicit smaller prediction errors and attract more attention. Neuroimaging research using tasks similar to that employed here shows that activation in the right dorsolateral prefrontal cortex (DLPFC) tracks the magnitude of prediction-error signals in healthy adults.<sup>41</sup> Furthermore, prediction-error signals in the right DLPFC are attenuated in people with delusions during the same tasks.<sup>23</sup> An interesting prediction stemming from the present results is that the increased attention to poor predictors observed in schizophrenia may cooccur with an attenuated prediction-error signal in the right DLPFC. We have found the abnormal prediction-error signal in the right ventral striatum in schizophrenia was due to an increased response to well-predicted stimuli.<sup>42</sup> Future research determining the relationship between attenuated prediction-error signals and attention to irrelevant cues may clarify the role of altered neural function in selective attention in schizophrenia.

There are some limitations to the present study. All our patients were treated with second-generation antipsychotics, so it is possible that the abnormal cue salience we observed was due to chronic striatal dopamine binding antagonism. This would be consistent with the expected attenuating effect of antipsychotic treatment on prediction-error signaling in subcortical regions and their connections to the DLPFC.<sup>41,43</sup> However, we did not find any strong relationship between learning scores and chlorpromazine equivalent dose among patients (table 3). Furthermore, studies of learned irrelevance in healthy adults have found deficits among people with high levels of schizotypy.<sup>32</sup> In particular, a small but significant correla-

tion existed between scores on the “unusual experiences” subscale of the Oxford-Liverpool Inventory of Feelings and Experiences (thought to correspond to the positive symptoms of schizophrenia) and the amount of attentional bias, which is consistent with the correlation between positive symptoms and attention to irrelevant cues we found in experiment 2. Similar results across healthy adults (with high levels of schizotypy)<sup>32</sup> and medicated people with schizophrenia (with high-positive symptom severity, as in the present study) suggest antipsychotics may not be a factor in the current results.

In sum, the present results are consistent with models of attention, which assume that predictive cues attract more attention than nonpredictive cues.<sup>1–3</sup> Furthermore, this normal attentional bias is impaired in people with schizophrenia with high-positive symptom severity. The failure of these patients to distinguish between previously predictive and nonpredictive cues results in the formation of abnormal causal associations and suggests this deficit may be critical in the formation and experience of psychotic symptoms.<sup>21,23</sup> A broader implication of this research is that treatment of attention deficits and related positive symptoms may be achieved by new therapies which aim to restore prediction-error signaling in schizophrenia.

## Funding

This work was supported by the University of New South Wales School of Psychiatry, National Health and Medical Research Council (NHMRC) Project Grant #568807, Neuroscience Research Australia, and the Australian Schizophrenia Research Bank, which is supported by the NHMRC of Australia, the Pratt Foundation, Ramsay Health Care, the Viertel Charitable Foundation and the Schizophrenia Research Institute utilizing infrastructure funding from New South Wales Health.

## Acknowledgments

The authors have declared that there are no conflicts of interest in relation to the subject of this study.

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