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Research report

Haloperidol can increase responding to both discrete and contextual cues in trace conditioned rats

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Abstract

Haloperidol has been shown to enhance attentional selectivity in conditioning procedures. For example, in latent inhibition (LI) it improves animals' ability to treat as irrelevant, stimuli that have previously been presented without consequence. The present study tested whether this finding would generalize to other procedures that present animals with weak predictors. We therefore used a trace conditioning procedure to present rats with a conditioned stimulus (CS) weakened through temporal discontiguity (rather than preexposure in LI) and a flashing light background provided an alternative experimental stimulus.

In Experiment 1, a noise CS was paired contiguously (at '0 s') with food or at a 10 s trace interval. In Experiment 2, the trace interval was lengthened to 20 s. In both experiments, haloperidol treatment generally reduced responding in 0 s contiguous groups. By contrast, 0.03 mg/kg haloperidol enhanced conditioning, selectively, to the weakly predictive trace CS, though it was without effect on responding within the trace interval. In addition, again at 0.03 mg/kg, haloperidol significantly increased excitatory conditioning to contextual stimuli in trace groups relative to contiguous groups. At the shorter (10 s) Experiment 1 trace, this result was shown in the extinction test of conditioning to the background stimulus. At the longer (20 s) Experiment 2 trace, this result was shown in the acquisition of responding to the box context in the inter-trial-interval.

The demonstration that low dose haloperidol can increase conditioning is novel. This increase was seen selectively with stimuli (both trace-conditioned and contextual) that should have been treated as weak predictors so these results are contrary to what was expected on the basis of haloperidol effects on stimuli weakened through pre-exposure. The possibility that increased contextual conditioning could be relevant to the interpretation of haloperidol-induced enhancement of LI is discounted. However, it is suggested that this result could nonetheless reflect cognitive enhancement.

Keywords: Haloperidol; Trace conditioning; Contextual conditioning; Animal models; Schizophrenia

1. Introduction

Some of the symptoms of schizophrenia can be attributed to an attentional disorder that results in a reduced ability to select between informative and uninformative environmental stimuli. It has been suggested that such an attentional deficit leads to perceptual flooding and hence the positive symptoms associated with schizophrenia [12,37,38,40]. This kind of cognitive abnormality can be modelled in animals using associative learning procedures that require selection between competing environmental stimuli, together with tests of drug and lesion effects to allow the development of neuropsychopharmacological theories of this aspect of attention deficit.

Associative learning is normally restricted to the best predictors of motivationally significant outcomes such as food or foot shock (unconditioned stimulus, UCS). Thus animals demonstrate that they have learned to expect a UCS by anticipatory conditioned responses to the (best available) signal or conditioned stimulus (CS). The informativeness of the CS can be experimentally manipulated, for example, using stimulus preexposure to weaken learning. Thus, LI refers to the phenomenon whereby previous experience with a non-reinforced

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stimulus causes retarded conditioning to that stimulus when it is subsequently paired with a motivationally significant event or UCS [24]. Loss of LI results in conditioning to the uninformative pre-exposed stimulus.

Significantly, LI has been found to be absent in acutely ill schizophrenia patients [2]. Moreover, LI is affected by dopaminergic drugs, as would be predicted on the dominant psychopharmacological hypothesis of schizophrenia: that it results in part from a hyperdopaminergic state. Support for this hypothesis comes from the finding that the dopamine agonist amphetamine can produce psychosis in humans and hence amphetamine is used experimentally to model the putative neurochemical changes associated with schizophrenia [8]. Specifically, amphetamine disrupts LI in both rats [33,41,43] and humans [13,23]. Conversely, facilitation or enhancement of LI has been demonstrated by the typical neuroleptic haloperidol [39,42] as well as by the newer atypical neuroleptics sulpiride [11] and clozapine [32]. Aytpical antipsychotics also reinstate LI after its disruption by amphetamine [31]. Different drug doses and routes of administration may result in discrepant findings regarding the effects of haloperidol on LI in humans. However, consistent with the animal work, haloperidol can also enhance LI in humans ([45], but see [46]). Hence, experimental disruptions of LI that result in conditioning to uninformative, irrelevant stimuli model the widely described failure of schizophrenics to ignore irrelevant stimuli; and reversals of such effects by neuroleptics suggest that the model has predictive validity [12,26,38].

However, there is little consensus on the psychological mechanisms underpinning LI and these are obviously important in considering the construct validity of the model. In part, the complexity arises because LI is set-up in two stage procedures. The purpose of the first stage is to establish the to-be-conditioned stimulus as irrelevant (through stimulus preexposure). The purpose of the second stage is to determine the effect of stimulus preexposure on later associability. However, this introduces a role for associations between the to-be-conditioned stimulus and context in stage 1 [3,14]. Thus the level of contextual conditioning supported could in principle affect the magnitude of the observed LI. Moreover, there is also the possibility that when LI is reduced this may be because impairment in some aspect of retrieval or comparison (of the preexposure experience of the stimulus as irrelevant) improves later conditioning because the CS is treated as if it were novel [9].

Thus one way to develop this line of research is by the adoption of simpler (one stage) conditioning procedures. Usually, successful classical conditioning depends on the temporal contiguity of the CS and the UCS. In trace conditioning, the time interval between the termination of the CS and the onset of the UCS reduces conditioning to the CS [17]. Thus, this experimental paradigm, like LI, involves testing conditioning to a CS that is a less informative predictor of the UCS. Arguably, the same psychopharmacological mechanisms could underlie conditioning to poor predictors, irrespective of whether the CS has been weakened by nonreinforced prior exposure (as in LI) or (as here) by a trace interval [6].

In addition, there is evidence to suggest that, in the absence of temporal contiguity, associative strength should accrue to other stimuli present concurrently, e.g., to the contextual cues provided by the experimental chamber [29]. In other words, the greater the trace interval, the weaker the conditioning to the CS and the more likely it is that alternative stimuli will be associated with the reinforcing event.

Therefore, the experiments reported here used a trace conditioning procedure to allow between subjects' comparisons of conditioning to strong (contiguous CS) and poor (trace CS) predictors of the UCS. The procedure was appetitive so we could also measure anticipatory (nose poke) responses in the trace interval. In addition, a background stimulus was presented continuously throughout the conditioning trials. This provided an alternative stimulus and allowed measurement of conditioning to an experimental contextual stimulus, as well as to the discrete CS [30,34,35]. As this background stimulus was present throughout the conditioning trials, it also represented a relatively uninformative predictor of the UCS.

This procedure was used to test the effects of haloperidol because of its actions in LI (see above) and its known antipsychotic action. To allow comparison, the doses and route of administration of haloperidol were based on those found to be effective in LI [7,31,39,42]. There are two points of comparison with results obtained in the stimulus selection task provided by LI procedures. First trace conditioning provides an alternative means of presenting animals with a weakly predictive CS. Secondly, LI has been shown to be highly context dependent both in rats [3,15,25] as well as in humans [14] and this dependence on context has been argued to have an associative basis [9]. The trace conditioning procedure used here also provides measures of contextual conditioning, both to the experimental background stimulus and the cues provided by the conditioning chambers, together with a manipulation (the trace interval between CS and UCS) that should influence the level of contextual conditioning supported.

The normal selective learning effect is to show relatively increased contextual conditioning when the discrete stimulus is rendered less informative because of the use of a trace interval. If haloperidol generally improves selective attention it should promote the tendency to form associations with contextual stimuli in trace conditioned groups [29], particularly within the 'mini-context' that is defined temporally as responding within the trace interval itself [19].

2. Materials and methods

2.1. Subjects

Forty-eight Wistar rats of mean weight 303 g (ranging from 263 to 332 g) were allocated to experimental conditions, counterbalanced for their previous experimental experience.

These rats had previously been tested in an aversive conditioning procedure that does not interfere with the demonstration of the appetitive effects of interest here [27].

There was a 2 week gap between Experiments 1 and 2 during which one rat died. Thus, 47 of these rats progressed (in the same experimental conditions) to Experiment 2, by then of mean weight 359 g (ranging from 308 to 442 g). Throughout the experiment, the rats were housed in pairs (except for the singleton which was caged alone during Experiment 2) on a 12:12 light/dark cycle (lights on 08:00–20:00). Testing took place during the light phase. Water was available ad libitum in the home cage throughout, but food was restricted to a basic 5 g per 100 g of body weight, that was adjusted to allow further weight gain in rats of below average weight. All procedures were carried out in accordance with the United Kingdom Animals Scientific Procedures Act, 1986, Project Licence number PPL 40/2019.

2.2. Apparatus

Experimental testing was conducted within fully automated ventilated conditioning chambers, housed within sound-attenuated casings (Cambridge Cognition, Cambridge, UK). In total, six identical conditioning chambers were used. Each of the inner conditioning chambers comprised of a plain steel box (25 cm × 25 cm × 22 cm high) with a Plexiglas door (19 cm × 27 cm) at the front. The floor consisted of steel bars 1 cm apart and 1 cm above the lip of a 7 cm deep sawdust tray.

A recessed food magazine was located on a side-wall of each of the chambers. The magazine was constantly illuminated in all sessions during which food was delivered. Access to the magazine was via a magazine flap. Nose pokes were recorded by the breaking of the photo beam within the food magazine. The UCS consisted of two 45 mg sucrose pellets dispensed serially into the magazine (Formula F, Noyes Precision Food, New Hampshire, UK).

Two experimental stimuli were available as potential predictors of food delivery. The auditory stimulus (broadband noise CS) was presented via a loudspeaker inset on the roof of the chamber, set at 80 dB including background and of 5 s duration. The second stimulus was the background stimulus, which comprised three wall mounted stimulus lights and the house light flashing on (0.5 s) and off (0.5 s) continuously for the duration of the session. Stimulus control and data collection was by an Acorn Archimedes RISC computer programmed in Basic with additional interfacing using an Arachnid extension (Cambridge Cognition).

2.3. Procedures

Allocation to conditioning groups was counterbalanced by box. Each experiment was run in a single replication with rats remaining in the same experimental groups in Experiment 2 as were used in Experiment 1.

2.3.1. Pre-conditioning

In Experiment 1, there were 2 days shaping to accustom rats to eating from the magazine. This involved access to a preload of 10 reward pellets with an additional 5 rewards over 5 min to familiarise rats with the sound of the food deliveries. The tray flap was door propped open day 1 and closed on day 2 so the rats were then required to nose poke the door open to collect food. Then followed 2 days baseline sessions, during which there were 10 unsignalled rewards in 10 min, delivered on a variable interval around 3 min. The total number of nose pokes was recorded. Food deprivation was re-introduced 1 day prior to the start of Experiment 2 and there were 2 additional days of pre-conditioning (as above) to re-establish baseline response rates.

2.3.2. Conditioning under drug

Conditioning consisted of 10 signalled rewards in 30 min. Depending on the experimental group, the reward (UCS) was delivered directly (in the 0 s contiguous group) and either 10 s (Experiment 1) or 20 s (Experiment 2) after CS offset (in the trace groups). Conditioning trials were presented throughout the 30 min session, on a variable interval, with the constraint that the inter-trial-interval (ITI) was always at least 1.5 times longer than the inter-stimulus-interval (ISI) length. Throughout the 30 min of acquisition, the background stimulus (flashing lights) was presented continuously. This continuous presentation also continued into the ISI. In both Experiments 1 and 2, there were 12 days conditioning under drug.

2.3.3. Drug-free extinction tests

In order to test conditioning to both the CS and the background stimulus, extinction was conducted over 2 days, one for each type of stimulus. For both stimuli, there were 10 stimulus presentations of 5 s duration, delivered over the 30 min session with the same 'ITI' (there were no food deliveries) as was used in acquisition (variable but at least 1.5 times longer than the ISI). On day one, half the rats received the auditory stimulus (CS) and the other half the flashing lights (background stimulus). On the second day, the alternative stimulus was presented. The order of extinction was counterbalanced across experimental conditions.

The number of nose pokes was recorded 5 s prior to stimulus onset (pre-stimulus: noise and light), during the stimulus (stimulus: noise and light), and during the remainder of the session (residual responding).

2.4. Drugs

Haloperidol was dissolved in physiological saline to an injection volume of 1 ml/kg for administration by intraperitoneal injection. Two doses of haloperidol were used: a low dose of 0.03 mg/kg and a higher dose. This was 0.1 mg/kg in Experiment 1, taken down to of 0.05 mg/kg in Experiment 2, to reduce non-specific effects. Vehicle controls were injected with equivalent amounts of saline mixed with 10% lac-

tic acid to match the pH. Drug treatments were given 45 min prior to conditioning.

2.5. Design and analysis

There were six experimental groups run in a 3 × 2 factorial design for subsequent analysis of variance (ANOVA). The repeated measures factor was Days and between subject factors were Trace (at levels contiguous and trace) and Drug (at levels saline and two doses of haloperidol). The dependent variable was in each case the number of nose pokes.

Thus in the conditioning phases of the experiments, the dependent variables measured to distinguish effects on associative learning from motor or motivational effects were as follows: *Pre-CS responding* (the equivalent 5 s period immediately prior to CS presentations, as the best estimate of baseline differences that could arise from motor impairment under drug); *CS responding* (during the 5 s noise presentations, adjusted for pre-CS differences, as appropriate); *Trace interval responding* (where applicable, to measure anticipatory responding between CS offset and UCS delivery, adjusted for differences seen in the ITI that reflect more general contextual conditioning); *UCS responding* (during the 5 s after food delivery, as the best estimate of differences that could arise from motivational effects of the drug); and *Residual responding* (in the ITI, excluding responding in the aforementioned response bins and the trace interval, where applicable, to provide a measure of contextual conditioning). In each case, repeated measures analyses were conducted to check the stability of the observed effects over the course of acquisition.

To allow for drug effects on baseline responding in acquisition (e.g., reduced responding under the higher dose of haloperidol), both conditioning to the target CS stimulus and responding during the UCS deliveries were analysed using difference measures. These were calculated as CS responding minus responding during the equivalent pre-CS period and UCS responding (i.e. in the equivalent period after UCS delivery) minus responding during the pre-CS. Similarly, drug effects on responding in the inter-stimulus-interval (ISI) were assessed relative to those seen in the equivalent average of the inter-trial-interval (ITI $_{\text{average}}$), again by the use of a difference measure calculated as ISI minus ITI $_{\text{average}}$ responding.

In the extinction phases of the experiments, the dependent variables required were: (1) for target: *Pre-CS responding* (the equivalent 5 s period immediately prior to CS presentations, as the best estimate of baseline differences); and *CS responding* (during the 5 s noise presentations, now in the absence of food deliveries the drug-free extinction test of associative strength); and (2) for background: *Pre-stimulus responding* (the equivalent 5 s period immediately prior to presentations of the light background, as the best estimate of baseline differences); and *Stimulus responding* (during the 5 s light presentations, as an off-the-baseline test of associative strength to this component of the context).

ANOVAs use an alpha level of 0.05. Mauchly's test of sphericity was applied to all repeated measures ANOVAS and, where necessary, Greenhouse-Geisser corrections were performed. In view of the fact that comparisons were planned and multiple comparisons were not performed, significant main effects and interactions were explored with two-tailed *t*-tests based on the individual error term [16]. Where there was a clear a priori prediction, non-significant interactions were explored with planned comparisons [1]. In such cases, in view of the increase in Type 1 error rate, Bonferroni correction was applied (by dividing the prescribed alpha value by the number of comparisons made).

3. Results

3.1. Experiment 1: Acquisition with 10 s trace

3.1.1. Pre-experimental response rates

There were no significant effects of Drug or Trace or interactions, maximum $F(1, 41) = 2.7$. Thus the groups were evenly matched prior to conditioning. As would be expected there was only a significant effect of days, $F(1, 41) = 13.86$, $P < 0.001$, with greater responding on day 2 than day 1 (means: day 1 = 141, day 2 = 174).

3.1.2. Conditioning under drug

3.1.2.1. Pre-CS responding. There was a main effect of Drug on responding in the pre-CS period, $F(2, 41) = 9.92$, $P < 0.001$. This arose because of overall reduced responding in the 0.1 mg/kg haloperidol group, compared with both the

Table 1

Drug	Conditioning					
	0 s			10 s		
	Saline	0.03	0.1	Saline	0.03	0.1
Pre-CS	4.34 (0.74)	2.41 (0.53)	1.14 (0.16)	4.47 (0.93)	4.29 (1.10)	1.26 (0.29)
ISI-ITI $_{\text{10 s average}}$				28.73 (6.38)	26.12 (2.54)	5.06 (1.31)
Post-CS	18.40 (1.44)	15.33 (1.65)	13.43 (1.13)	21.79 (1.49)	17.64 (1.47)	15.85 (0.95)

Experiment 1 acquisition data pre- and post-presentation of the noise conditioned stimulus (CS): mean nose pokes (S.E.M.) in the contiguous (0 s) and trace (10 s) conditioning groups under one of three drug treatments (saline, 0.03 and 0.1 mg/kg haloperidol). For the trace group (10 s), ISI-ITI $_{\text{10 s average}}$ gives the elevation in responding in the inter-stimulus-interval (ISI) over the average for the equivalent time period in the inter-trial-interval (ITI $_{\text{10 s average}}$), again shown as mean nose pokes (S.E.M.), for each of the three drug treatments.

vehicle and 0.03 mg/kg haloperidol groups, $t(29) = 5.19$, $P < 0.001$ and $t(29) = 3.15$, $P < 0.01$, respectively (see Table 1). Responding in the vehicle and 0.03 mg/kg haloperidol groups did not differ significantly, $t(29) = 1.23$. There was an effect of Days, $F(11, 451) = 7.79$, $P < 0.001$ (overall means of 5.34 on day 1 and 3.17 on day 12). Thus nose pokes in this response bin tended to reduce over days whilst selective responding to the CS and during UCS deliveries increased (see below). However, there was no interaction of Days with Trace or Drug, maximum $F(11, 451) = 1.34$.

3.1.2.2. CS responding. As would be expected, there was an overall main effect of Trace, $F(1, 41) = 82.34$, $P < 0.001$, a main effect of Drug $F(2, 41) = 13.71$, $P < 0.001$, and a Trace × Drug interaction, $F(2, 41) = 5.28$, $P < 0.01$. As can be seen from Fig. 1, this interaction did not arise because of a loss of the conditioning advantage in 0 s over 10 s trace-conditioned groups. In each case, the 0 s conditioned responded more than the 10 s trace-conditioned in the corresponding drug condition. Rather, whilst in 0 s groups, responding (adjusted for differences seen also pre-CS) was decreased by treatment with haloperidol (significantly so at the higher dose, $t(13) = 4.56$, $P = 0.001$), in 10 s trace-conditioned groups, there was increased responding at the 0.03 mg/kg dose of haloperidol compared with both vehicle and 0.1 mg/kg haloperidol groups, minimum $t(14) = 2.20$, $P < 0.05$. This difference in the direction of effects on 0 and 10 s trace-conditioned groups means that the relative increase in responding over the 10 s trace interval, seen at the 0.03 mg/kg dose of haloperidol could not be attributed to a general increase in responding at this dose.

As would be expected acquisition was reflected in an effect of Days, $F(8, 326) = 26.04$, $P < 0.001$. This depended on trace group in that there was also a Trace × Days interaction, $F(8, 326) = 10.61$, $P < 0.001$. The *t*-tests demonstrated overall greater responding in 0 s than 10 s conditioning groups from

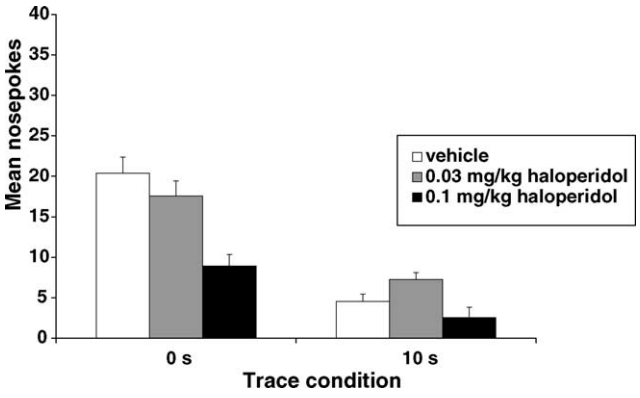

Fig. 1. Mean overall nose pokes for CS acquisition in Experiment 1 calculated as a difference measure (CS responding minus pre-CS responding, to adjust for variation in baseline response rates). 0 s = contiguously conditioned groups; 10 s = trace conditioned groups; shown separately for groups treated with vehicle, 0.03 and 0.1 mg/kg haloperidol. Bars show two standard errors of the mean for approximate between-groups comparisons.

day 3 onwards, minimum $t(45) = 3.14$, $P < 0.005$ (on day 3). The change in responding over days also depended on drug allocation, seen as a Drug × Days interaction, $F(16, 326) = 2.9$, $P < 0.001$, because the 0.1 mg/kg dose of haloperidol produced significantly lower responding (even allowing for its effect in the pre-CS) than both the 0.03 mg/kg dose and vehicle on some of the acquisition days. However, there was no significant Drug × Trace × Days interaction, $F(16, 326) = 1.51$, so (changes in) drug effects over the course of acquisition need not be considered further.

3.1.2.3. Trace interval responding. On the difference measure (ISI-ITI $_{10\text{ s average}}$), there was a main effect of Drug, $F(2, 21) = 10.35$, $P = 0.001$. This arose because (even adjusting for the general reduction in responding under this treatment) the 0.1 mg/kg haloperidol groups clearly responded overall less in the ISI than both the 0.03 mg/kg haloperidol and vehicle groups, minimum $t(14) = 3.64$, $P < 0.005$. The saline and 0.03 mg/kg haloperidol groups were not significantly different from each other, $t(14) = 0.38$. The overall mean difference scores are shown in Table 1. There was also an effect of Days, $F(11, 231) = 16.94$, $P < 0.001$, and a Days × Drug interaction, $F(22, 231) = 2.77$, $P < 0.001$. The interaction arose because whilst the difference scores show that responding in the vehicle and 0.03 mg/kg haloperidol groups was relatively increased over days (from 7.43 on day 1 to 43.27 on day 12, and from 11.41 on day 1 to 35.39 on day 12, in vehicle and 0.03 mg/kg haloperidol groups, respectively), there was much less of an increase in the 0.1 mg/kg haloperidol group (from 3.68 on day 1 to 7.51 on day 12).

3.1.2.4. UCS responding. Analysis of the difference scores for the period of food delivery showed no main effect of Trace, Drug or any interaction between these factors, maximum $F(2, 42) = 3.04$. There was some fluctuation in the efficiency with which rewards were collected in that there was an effect of Days $F(11, 451) = 4.33$, $P < 0.001$ that interacted with Drug, $F(22, 451) = 2.2$, $P < 0.01$. However, the mean responses for each group per day exceeded the minimum of 10 responses necessary to collect the 10 presentations of food reward (see Table 1 for the raw scores).

3.1.2.5. Residual responding. There was a main effect of Drug, $F(2, 41) = 14.78$, $P < 0.001$, that arose because of reduced responding under 0.1 mg/kg haloperidol compared with both the vehicle and the 0.03 mg/kg haloperidol groups, $t(29) = 6.23$, $P < 0.001$ and $t(29) = 3.28$, $P < 0.01$, respectively (overall means: vehicle = 158.84; 0.03 mg/kg haloperidol = 111.11; 0.1 mg/kg haloperidol = 45.92). The 0.03 mg/kg haloperidol dose resulted in a marginal reduction in responding compared with vehicles, $t(30) = 1.92$, $P = 0.065$ (see Fig. 2). There was neither a main effect of Trace nor any Trace by Drug interaction, maximum $F(1, 41) = 3.15$.

There was an effect of Days $F(7, 305) = 13.48$, $P < 0.001$ but no interaction with Trace or Drug, maximum $F(15, 305) = 1.39$. The effect of Days just arose because of some general

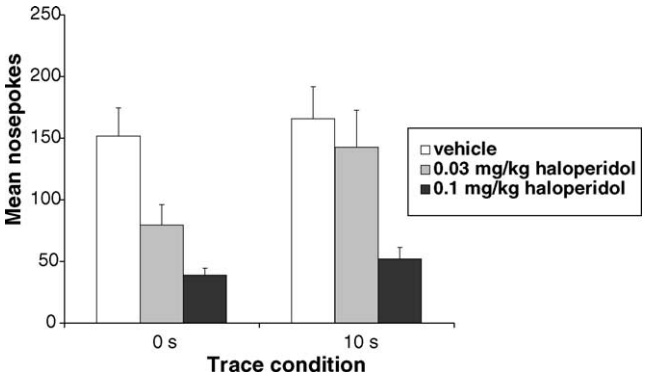

Fig. 2. Mean overall nose pokes during the remainder of the session ('residual responding') in Experiment 1. 0 s = contiguously conditioned groups; 10 s = trace conditioned groups; shown separately for groups treated with vehicle, 0.03 and 0.1 mg/kg haloperidol. Bars show two standard errors of the mean for approximate between-groups comparisons.

fluctuation in responding and a tendency to reduce over time, from 171.18 (on day 1) to 109.73 (on day 12).

3.1.3. Drug-free extinction tests

3.1.3.1. Target CS (noise) stimulus.

Pre-CS responding. There were no significant effects of Trace, Drug or the interaction on responding in the pre-stimulus period, maximum $F(1, 41) = 2.28$.

CS responding. In all drug conditions, 0 s responded more than 10 s trace-conditioned groups (see Table 2). As would be expected, there was a significant effect of Trace $F(1, 41) = 10.71$, $P < 0.01$. There was no effect of Drug, $F < 1$, and no Trace × Drug interaction, $F(2, 41) = 1.01$. However, planned comparison confirmed that, as in acquisition, there was relatively increased responding in the 0.03 mg/kg haloperidol 10 s trace-conditioned group compared with vehicle 10 s trace-conditioned group, $t(14) = 2.35$, $P < 0.05$.

3.1.3.2. Background (light) stimulus.

Pre-stimulus responding. There were no effects of Trace, Drug or the interaction, maximum $F(2, 41) = 2.51$.

Stimulus responding. There was a Trace × Drug interaction, $F(2, 41) = 3.35$, $P < 0.05$ in the absence of an effect of Trace or Drug, Fs < 1. In the 0 s groups, the 0.03 mg/kg haloperidol group respond less than vehicle and 0.1 mg/kg haloperidol, whereas in the 10 s groups the 0.03 mg/kg haloperidol group respond more than the other two groups (see Table 2). Thus this dose of haloperidol produced relatively greater conditioning to the background light stimulus in the trace conditioned group. Statistically, the difference between 0 and 10 s groups was significant in the 0.03 mg/kg haloperidol groups only, $t(14) = 3.07$, $P < 0.01$.

3.2. Experiment 2: Trace extended to 20 s

3.2.1. Pre-experimental response rates

There was no effect of Trace, Drug or the interaction, all Fs <1. There was only an effect of Days, $F(1, 41) = 13.86$, $P < 0.001$, because responding increased over the two days, from 141.43 on day 1 to 173.66 on day 2, consistent with the expected elevation in responding on reintroduction to experimental procedures.

3.2.2. Conditioning under drug

3.2.2.1. Pre-CS responding. There was no effect of Trace, either overall or in interaction with Days, maximum $F(1, 41) = 2.42$. There was, however, an overall effect of Drug, $F(2, 41) = 5.29$, $P < 0.01$. *T*-tests confirmed that the saline group responded overall more than both the 0.03 and the 0.05 mg/kg haloperidol groups, minimum $t(30) = 2.49$, $P < 0.05$, but there was no difference between the two drug groups (see Table 3). There was no overall effect of Days, $F(7, 302) = 1.92$, but there was a Days by Drug interaction, $F(11, 302) = 2.38$, $P < 0.01$. In both the saline and 0.03 mg/kg haloperidol groups there was a gradual increase in responding over days; whilst the 0.05 mg/kg haloperidol group tended to respond less over time.

The drug effects on pre-CS responding meant that it was appropriate to assess responding to CS and during UCS deliveries using difference measures, to allow for any generally depressant effects of drug.

3.2.2.2. CS responding. As would be expected, there was a significant overall effect of Trace, $F(1, 41) = 91.94$, $P < 0.001$), of Drug, $F(2, 41) = 9.70$, $P < 0.001$) and a significant two way interaction between Trace and Drug, $F(2, 41) = 6.66$, $P < 0.001$). The effect of Trace arose because responding to the CS in the 0 s conditions was overall greater (mean 21.50) than in the 20 s trace conditioned groups (overall mean 3.83). The only statistically significant difference to explain the main effect Drug was between the saline (mean 17.22) and 0.05 mg/kg haloperidol group (mean 7.02), $t(29) = 2.27$, $P < 0.05$ (see Fig. 3).

Table 2

Drug	Conditioning					
	0 s			10 s		
	Saline	0.03	0.1	Saline	0.03	0.1
Noise CS	13.88 (3.64)	13.38 (1.13)	12.00 (1.15)	4.50 (1.39)	9.63 (1.68)	7.63 (2.65)
Light Stim.	2.75 (1.53)	0.13 (0.13)	2.43 (1.21)	1.75 (0.65)	3.00 (0.93)	0.88 (0.52)

Experiment 1 extinction data for noise conditioned stimulus (Noise CS) and light background stimulus (Light Stim.): mean nose pokes (S.E.M.) for contiguous (0 s) and trace (10 s) conditioning groups under one of three drug treatments (saline, 0.03 and 0.1 mg/kg haloperidol).

Table 3

Drug	Conditioning					
	0 s			20 s		
	Saline	0.03	0.05	Saline	0.03	0.05
Pre-CS	3.92 (1.13)	1.31 (0.27)	1.39 (0.35)	4.35 (1.01)	2.92 (0.50)	2.32 (0.83)
ISI-ITI $_{20\,s\,average}$				73.74 (11.64)	49.01 (4.07)	20.15 (8.28)
Post-CS	17.5 (2.13)	11.45 (1.60)	10.42 (2.56)	22.19 (2.66)	19.55 (1.39)	15.70 (1.25)

Experiment 2 acquisition data pre- and post-presentation of the noise conditioned stimulus (CS): mean nose pokes (S.E.M.) for contiguous (0 s) and trace (20 s) conditioning groups under one of three drug treatments (saline, 0.03 and 0.05 mg/kg haloperidol). For the trace group (20 s), ISI-ITI $_{20\,s\,average}$ gives the elevation in responding in the inter-stimulus-interval (ISI) over the average for the equivalent time period in the inter-trial-interval (ITI $_{20\,s\,average}$), again shown as mean nosepokes (S.E.M.), for each of the three drug treatments.

Analysis of the Trace by Drug interaction showed that, as expected, the 0 and 20 s trace-conditioned saline groups differed significantly from each other, $t(14) = 6.49$, $P < 0.001$, as did the 0 and 20 s trace conditioned groups in both drug conditions, minimum $t(14) = 4.84$, $P < 0.001$. Thus in all drug groups there was significantly more responding to the CS in the 0 s compared to the 20 s trace condition. Fig. 3 shows that there was again a dose-related reduction in responding in 0 s conditioned groups: both the 0.03, $t(14) = 2.46$, $P < 0.05$, and the 0.05 mg/kg haloperidol groups, $t(13)=3.75$, $P < 0.005$, responding less than under saline.

By contrast, in the 20 s trace conditioned groups, the 0.03 mg/kg haloperidol group responded more than the saline group (means of 6.19 and 3.93, respectively). This difference was not, however, statistically significant, $t(14) = 1.07$. The only statistically significant difference was between the 0.03 and 0.05 mg/kg, 20 s trace conditioned haloperidol groups, $t(14) = 3.06$, $P < 0.01$.

Effects on conditioning were stable in that there were no significant effects involving days, maximum $F(4, 199) = 1.38$.

3.2.2.3. Trace interval responding. As might be expected given the persistent effects of Drug at other times in the session, there was an overall effect of Drug, $F(2, 21) = 9.78$, $P = 0.001$. This arose because (even after adjustment for general differences seen also in the ITI $_{20\,saverage}$) the 0.05 mg/kg haloperidol group responded less than both the saline and the 0.03 mg/kg haloperidol group, minimum $t(14) = 3.13$, $P = 0.01$. The reduction in the 0.03 mg/kg haloperidol relative to the saline group was not significant, $t(14) = 2.01$, $P = 0.065$.

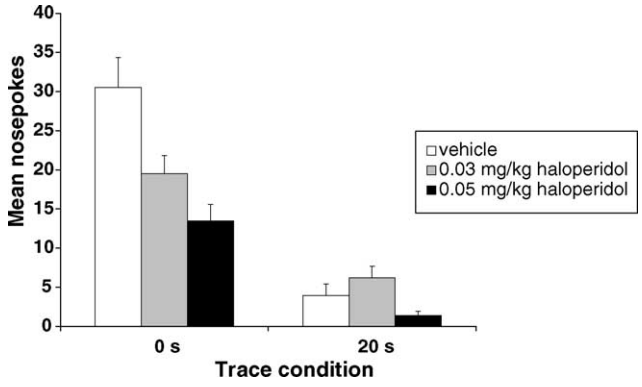

Fig. 3. Mean overall nose pokes for CS acquisition in Experiment 2 calculated as a difference measure (CS responding minus pre-CS responding, to adjust for variation in baseline response rates). 0 s = contiguously conditioned groups; 10 s = trace conditioned groups; shown separately for groups treated with vehicle, 0.03 and 0.1 mg/kg haloperidol. Bars show two standard errors of the mean for approximate between-groups comparisons.

Repeated measures analysis showed an effect of Days, $F(11, 231) = 2.06$, $P < 0.05$, because of some inconsistent fluctuation in overall response rates. This fluctuation was of little interest since there was no interaction between Days and Drug, $F(22, 231) = 1.06$. Therefore the overall means are shown in Table 3.

3.2.2.4. UCS responding. There was an overall effect of Trace, $F(1, 41) = 7.70$, $P < 0.05$, that arose because there was generally more responding in the 20 s trace compared to the 0 s condition. Table 3 (that shows the raw scores) suggests that this difference was little affected by drug and this conclusion is confirmed statistically by the absence of any effect of Drug, or Trace by Drug interaction, maximum $F(2, 41) = 2.04$. There was an effect of Days, $F(5, 234) = 5.33$, $P < 0.001$. Over the further conditioning days, rats tended to emit fewer responses after UCS delivery. This reduction in responding was, however, less obvious in the trace group reflected in a Days by Trace interaction, $F(5, 234) = 2.88$, $P < 0.01$.

3.2.2.5. Residual responding. There was an effect of Trace, $F(1, 41) = 5.26$, $P < 0.05$, and an effect of Drug, $F(2, 41) = 8.50$, <0.001). There was, however, no significant interaction, $F(2, 41) = 0.46$. Fig. 4 shows that while the trace conditioned groups showed relatively higher responding than the corresponding 0 s conditioned groups in the remainder of the session, irrespective of drug group, this difference was greatest in the 0.03 mg/kg haloperidol group. This was confirmed statistically in that only in the 0.03 mg/kg haloperidol group did the trace respond significantly more than the 0 s conditioned group, $t(14) = 3.81$, $P < 0.005$. In both the saline group, $t(14) = 0.57$, and in the 0.05 mg/kg haloperidol group, $t(14) = 1.67$, the increase in responding in 20 s trace relative to 0 s conditioned groups was not statistically significant. The main effect of Drug arose because the saline group (mean 147.86) responded significantly more than both the 0.03 (mean of 77.41), $t(30) = 2.54$, $P < 0.05$, and the 0.05 mg/kg haloperidol

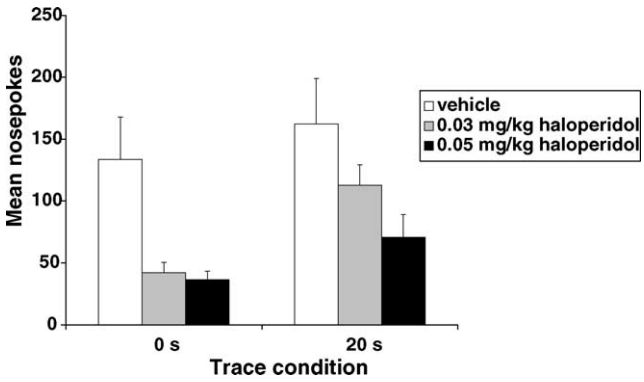

Fig. 4. Mean overall nose pokes during the remainder of the session ('residual responding') in Experiment 2. 0 s = contiguously conditioned groups; 10 s = trace conditioned groups; shown separately for groups treated with vehicle, 0.03 and 0.1 mg/kg haloperidol. Bars show two standard errors of the mean for approximate between-groups comparisons.

group (mean of 54.69), $t(29) = 3.38$, $P < 0.005$. The haloperidol groups did not differ significantly from each other, $t(29) = 1.34$.

The only other significant result was a main effect of Days, $F(5, 223) = 3.41$, $P < 0.01$, because over the course of conditioning the number of responses in the remainder of the session increased.

3.2.3. Drug-free extinction tests

3.2.3.1. Target CS (noise) stimulus.

Pre-CS responding. There was no effect of Trace, Drug or the interaction, maximum $F(2, 41) = 2.06$.

CS responding. There was an effect of Trace, $F(1, 41) = 69.45$, $P < 0.001$. As expected there was overall more conditioning to the CS in the 0 s compared to the 20 s trace group (see Table 4). Moreover, there was no overall effect of Drug or the Trace by Drug interaction, maximum $F(2, 41) = 1.19$. Thus there was a statistically significant difference between the 0 and 20 s trace conditions at each level of drug: saline, $t(14) = 5.39$, $P < 0.001$; 0.03 mg/kg haloperidol, $t(14) = 5.03$, $P < 0.001$; and 0.05 mg/kg haloperidol, $t(13) = 4.37$, $P = 0.001$. In other words, irrespective of prior drug treatment, there was less conditioning to the CS in the 20 s trace than in the 0 s condition. A further planned comparison confirmed that, as in Experiment 1, there was relatively increased responding in the 0.03 mg/kg haloperidol trace group compared with the vehicle trace group, $t(14) = 2.35$, $P < 0.05$.

3.2.3.2. Background (light) stimulus.

Pre-stimulus responding. There was no effect of Trace, Drug or their interaction, maximum $F(2, 41) = 1.58$.

Stimulus responding. There was an effect of Trace, $F(1, 41) = 6.61$, $P < 0.05$). Table 4 shows that there was overall more responding to the light in the 20 s trace than in the 0 s condition. This effect was not moderated by treatment with haloperidol as there was no effect of Drug, or Trace by Drug interaction, maximum $F(2, 41) = 1.89$. However, response rates were even lower than in Experiment 1 so there was a clear floor effect.

4. Discussion

These experiments tested the effects of haloperidol on the acquisition and expression of associative learning in an appetitive conditioning procedure. Importantly, the extinction tests were drug free to exclude direct effects of the drug on responding. Moreover, in the acquisition phase the range of measures taken allowed us to exclude any effects of haloperidol on motor responding or collection of the reward and to distinguish effects on contextual conditioning.

4.1. What did the results show?

One clear effect of haloperidol was a reduction in the apparent level of appetitive conditioning in contiguously conditioned groups. This effect was seen both during acquisition under drug and confirmed in drug free extinction. This means that any (further) reduction in conditioning over the trace interval would be difficult to demonstrate (because of a potential floor effect). However, in contrast to this general reduction in conditioning, 0.03 mg/kg haloperidol selectively increased conditioning to contextual stimuli in trace-conditioned groups, as well as to the trace CS, though this treatment was without effect on responding within the trace interval.

This finding that haloperidol can increase conditioning is novel and not what would be expected on the basis of the further reduction in conditioning that it produces in LI procedures [39,42,45], as well as the reduced conditioning that

Table 4

Drug	Conditioning					
	0 s			20 s		
	Saline	0.03	0.05	Saline	0.03	0.05
Noise CS	15.25 (2.23)	12.25 (1.41)	13.43 (2.72)	2.50 (0.80)	4.88 (0.40)	2.00 (0.63)
Light Stim.	1.25 (0.59)	0.00 (0.00)	0.00 (0.00)	2.50 (1.02)	0.88 (0.40)	2.63 (1.31)

Experiment 2 extinction data for noise conditioned stimulus (Noise CS) and background light stimulus (Light Stim.): mean nosepokes (S.E.M.) for contiguous (0 s) and trace (10 s) conditioning groups under one of three drug treatments (saline, 0.03 and 0.05 mg/kg haloperidol).

we observed in contiguously conditioned groups. Moreover, the specific 0.03 mg/kg dose of haloperidol (that increased conditioning to the trace stimulus and the contextual cues in the present study) was selected because of its known effects in an LI procedure in which (as here) higher learning was reflected in increased responding, and 0.03 mg/kg did not affect general task performance [31]. The other difference in our procedure was the number of drug injections required (because appetitive conditioning takes place over a number of days). Haloperidol has been little used in appetitive LI, but, in the more standard conditioned emotional response procedure, it enhanced LI after chronic treatment at 0.03 mg/kg [7].

Thus there is no obvious explanation as to why (the same dose of) haloperidol should improve selective learning in LI (in so far as this is measured by an increase in the effect of stimulus preexposure) but decrease selective learning as measured in a trace conditioning procedure. Like the preexposed stimulus, the trace conditioned stimulus would be expected to have reduced salience (see also below).

4.2. Baseline responding

Before offering any further interpretation of these results, we should consider the possibility that apparent effects on conditioning might arise from motor or motivational effects of treatment with haloperidol. Analysis of the Experiment 1 baseline data confirmed that groups were evenly matched prior to conditioning. However, over the course of conditioning, effects on baseline responding did emerge under drug. Fluctuations in responding (immediately pre-CS) were taken into account in analysis of responding to the experimental stimuli and UCS delivery (by the use of a difference measure). In addition, in Experiment 2, the higher dose in use was dropped (to 0.05 mg/kg). However, since the general depression in responding persisted, we again applied a difference measure in analysis of responding to the experimental stimuli and UCS delivery in Experiment 2.

Responding after UCS delivery was also lower under drug, perhaps reflecting reduced motivation. If collection of the reinforcer were impaired under drug, this could in principle reduce conditioning through a non-associative mechanism (in the same way that any ineffective reward will support less learning). This issue is also addressed by comparison between experimental and control groups (contiguously conditioned in the present study, non-preexposed in LI experiments) but only a direct measure of responding after UCS delivery can distinguish motivational from motor effects.

We found that the mean number of responses was always greater than the number of UCS presentations so any motivational effect of haloperidol should not have impeded learning by preventing drugged rats from collecting the reinforcer. Moreover, the critical results took the form of increased rather than decreased responding under drug.

4.3. Effects of repeated drug testing

Although in a different procedure, the 0.03 mg/kg dose of haloperidol that increased conditioning here enhanced LI after repeated injections [7]. This is the same as the acute effect of haloperidol on LI [39,42] suggesting that the repeated injection regime used here should not have presented a problem.

Treatment with haloperidol might in principle have carryover effects from 1 day to the next. However, since its half-life in the rat is relatively short [20] any such effects would presumably have to be mediated by enduring changes in receptor sensitivity. There were some interactions between days and drug that could reflect cumulative effects of drug (or the development of tolerance). However, all the important results were seen as overall effects rather than in interaction with Days.

4.4. Conditioning to the trace CS

A conditioning advantage in contiguous over trace conditioned groups was seen in both vehicle-injected and haloperidol-treated groups. Thus even though the higher doses of haloperidol clearly reduced responding, they did not prevent us from seeing a difference between groups depending on whether or not there was temporal contiguity between CS and UCS. In Experiment 1, 0.03 mg/kg haloperidol also produced a clear effect in the opposite direction: namely, an increase in responding to the trace conditioned stimulus relative to that seen in the vehicle group. This effect was seen in both acquisition and extinction. This tendency was also shown in the Experiment 2 acquisition phase, where again a significant interaction arose because the direction of the (low dose) drug effect was opposite in trace and contiguously conditioned groups, producing relatively decreased and increased responding, respectively. Moreover, the relatively increased trace conditioning in the 0.03 mg/kg haloperidol compared with the saline trace group was significant (as a planned comparison to test for replication) in the Experiment 2 extinction test. Thus there was overall good evidence that 0.03 mg/kg haloperidol could enhance conditioning, selectively, to a weakly predictive stimulus. Contrary to hypothesis [6], this is unlike the effect of haloperidol on stimuli rendered less salient through stimulus preexposure in LI (see also below).

4.5. ISI and ITI responding

The introduction of an ISI in trace conditioning raises the possibility that stimulus offset plus some elapsed time may become an effective CS, in which case any improvement in attentional learning should increase responding here. However, we saw no evidence for increased excitation in the ISI under haloperidol. In both experiments, the only consistent drug effect in the ISI was depressed responding at the higher dose. Notably, the fact that responding under the 0.03 mg/kg

haloperidol dose did not differ significantly from responding seen in the vehicle groups suggests that the lower dose did not affect conditioning across the trace as such. However, this treatment was not simply ineffective. Firstly, it increased conditioning to the trace conditioned CS (most obviously Experiment 1 and this pattern replicated in Experiment 2). Secondly, low dose haloperidol clearly increased conditioning to contextual stimuli within the ITI (in both experiments, though the way in which this effect was manifest changed depending on the length of training, see below).

4.6. Effects on contextual conditioning

Contextual conditioning was assessed in two ways: over the course of acquisition as responding to box context (measured as responding in the ITI); and at the end of acquisition as responding to the experimental background (measured as responding to light presentations in extinction tests).

In the Experiment 1 extinction tests, the 0.03 mg/kg haloperidol dose increased conditioning to the background stimulus in the trace relative to the contiguously conditioned group. By contrast, under vehicle and high dose treatments, the contiguous showed relatively greater responding to background than did the trace groups. This effect on conditioning to the flashing light background stimulus did not continue in Experiment 2. At this stage of testing, the trace group responded overall more to background (again on the extinction test) than the contiguous group but this effect was not moderated by drug, most likely because of a floor effect. In Experiment 2, 0.03 mg/kg haloperidol instead increased conditioning to the cues provided by the experimental chambers (as measured by ITI responding), again in the trace group. Thus the difference between the experiments in terms of which cues functioned as a competing background stands in need of explanation. Over the course of acquisition, conditioning to the experimental light stimulus is indistinguishable from that shown to box context. In the extinction tests, the experimental light stimulus needs in effect to stand out from the alternative cues provided within the experimental chambers in order to show any additional associative strength (over and above the background response rates). One possibility is that, with continued training, the increased exposure to the experimental background without any consequence rendered this stimulus differentially ineffective through LI. There is independent evidence that LI is readily produced by intermittent stimuli, such as the experimental light background as flashing the stimulus in effect generates a very high number of stimulus presentations [44].

4.7. Effects on attention?

Irrespective of the details of the measure on which the effect was demonstrated, the finding of increased contextual conditioning might be related to trace conditioned rats' uncertainty over when food might be delivered. On this account, it would seem to follow that there should be an inverse relationship between conditioning to the (trace) CS and that seen to context. This was not observed. On the contrary, there was evidence for the opposite direction of effect, namely increased conditioning to the CS presented at the trace interval (as well as to the background stimulus) under 0.03 mg/kg haloperidol. Thus there was no evidence that treatment with haloperidol improved attentional processes through any increase in selectivity. Rather, this pattern of effects could be interpreted post hoc in terms of increased breadth of attention.

Treatment with amphetamine can similarly increase conditioning to a number of available cues in an aversive trace conditioning procedure [28], though not in an appetitive variant as used here [18]. Effects on breadth of attention might well depend on the experimental parameters in use if they are mediated through changes in the level of arousal [10,22]. However, we have not directly tested this possibility as an account of the apparent difference between aversive and appetitive studies (in terms of amphetamine versus haloperidol effects) since the effectiveness of the UCS was not systematically manipulated in the appetitive studies as it was in the aversive procedure [28].

Finally, the present experiments allowed us to distinguish an effect of haloperidol on contextual conditioning in the ITI from an effect on responding in the ISI. This distinction between different components of the contextual conditioning matters because simply measuring responding to literal duration of the CS might underestimate trace conditioning if the effective CS is the discrete stimulus plus the ISI into which presentation of the background stimulus extends. However, in the ISI there was no elevation (and some sign of a reduction) in responding under low dose haloperidol. So functionally the ISI resembled neither the trace CS nor the ITI context in terms of the direction of the observed drug effects. Thus although, as expected, responding in the ISI was elevated over that seen in the ITI, there was no evidence that treatment with haloperidol promoted attention to the mini-context provided by the ISI [19]. This result also points towards the conclusion that we had no improvement in the selectivity aspect of attention in that the mini-context provided by the ISI was in principle a much better predictor of UCS deliveries than the trace CS or the cues in the remainder of the context (in the ITI).

4.8. Implications

The known role of DA in simple associative learning [36,47] would seem to suggest that a DA antagonist such as haloperidol should have the general effect of reducing associative learning and this effect was seen here. However, the results obtained also showed increased associative learning under some experimental conditions.

Treatment with haloperidol can increase LI but this effect takes the form of further reduced associative learning in the group given stimulus preexposure [39,42,45]. In principle, this effect of haloperidol could result from an effect on stimulus salience during the preexposure stage necessary to pro-

duce LI (more salient stimuli are known to produce stronger LI). In the present experiments, haloperidol increased the effective salience of potentially predictive stimuli in the trace condition where there was no clear CS (though not responding specifically within the ISI).

However, there is other evidence that haloperidol does not increase in fact LI through an effect on stimulus salience because the critical stage of the procedure at which haloperidol must be administered to enhance LI is in fact conditioning rather than preexposure [37,38,40,42].

Alternatively, could haloperidol effects on contextual conditioning account for its effects in LI? If haloperidol generally increases contextual conditioning, then this presumably should affect LI because LI is known to be highly context-dependent. If we take the view that LI arises because associations between context and CS formed at preexposure interfere with the later acquisition of the CS-UCS association at the conditioning stage of the procedure [3,14], then potentiation of contextual conditioning should enhance LI measured as the difference in learning between preexposed and non-preexposed groups. This is the effect typically seen after treatment with haloperidol. Thus, just as restored or enhanced LI under haloperidol could result from stronger CS-context associations being formed during CS-preexposure, disrupted LI in acute schizophrenics and animals under amphetamine could find some account in terms of weak CS-context associations being formed during CS-preexposure treatment. However, again the fact that the critical stage of the procedure at which haloperidol must be administered to enhance LI is in fact conditioning rather than preexposure would seem to undermine this account because it is in preexposure that the associations with context are formed and the critical stage at which haloperidol must be given to enhance LI is conditioning [37,38,40,42].

In more general terms, the finding that low dose haloperidol increased contextual conditioning nevertheless has implications for the mechanisms through which it might improve cognitive function in schizophrenia. There is both theoretical [4] and empirical [5] evidence that schizophrenics show impaired contextual processing. Moreover, increased contextual conditioning in the trace group is in line with the effect that can be demonstrated in normal animals with a weak discrete cue [29]. Thus this aspect of the results could be argued to reflect an improvement in the selectivity aspect of attention. Lower doses of haloperidol than those typically used experimentally (in rats 0.1–0.2 mg/kg) have been argued to more closely approximate those used clinically [20] and in the present study a still lower dose (0.03 mg/kg) produced an effect consistent with cognitive enhancement. In humans ill with schizophrenia, lower doses of haloperidol (producing 65–70% dopamine D2 occupancy) have recently been argued to produce a better clinical outcome with fewer extrapyramidal side effects [21]. The results of the present study show that there are dose-related effects of haloperidol on cognitive performance, so for patients lower doses could be more likely to improve cognitive function, as well as to reduce the general incidence of unwanted side effects. Though (paradoxically), in the present study, the increased conditioning to the trace CS (at the same low dose that increased contextual conditioning in the same trace conditioned group) could be argued to reflect an increase in breadth of attention to a relatively uninformative environmental stimulus, contrary to what would be expected based on haloperidol's effects in LI [7,31,39,42]. Taken together these results suggest that different ways of manipulating stimulus salience are not functionally equivalent.

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