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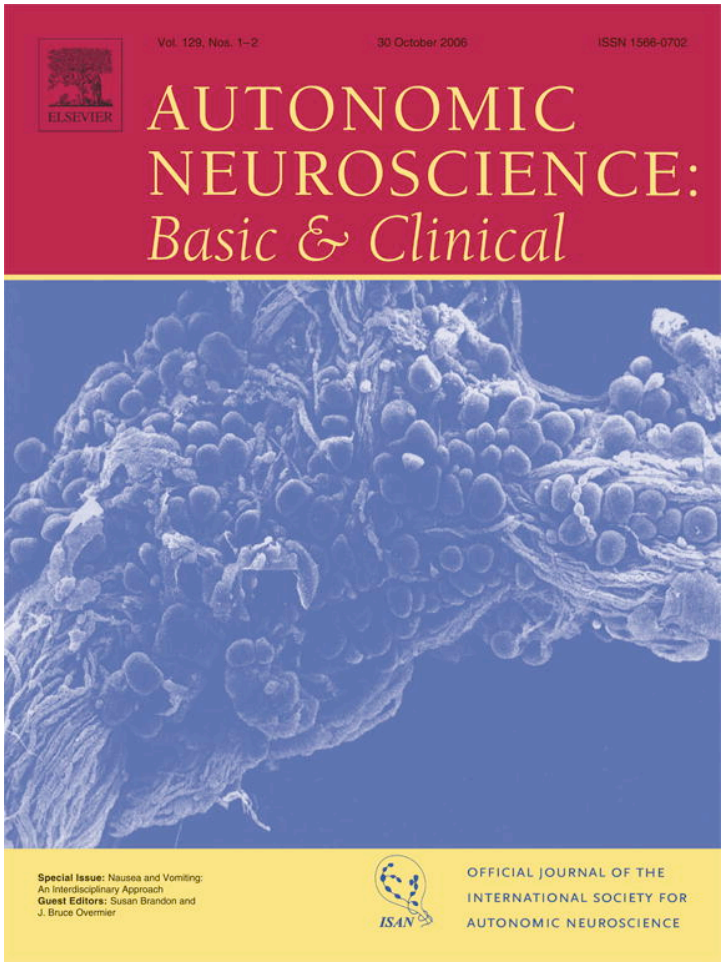

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Review

Overshadowing and latent inhibition of context aversion conditioning in the rat

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Abstract

A review is presented of experimental studies, using rats as the subjects, that were designed to establish an animal model of the clinical phenomenon of anticipatory nausea. Experiments 1 and 2 demonstrated that pairing a distinctive context with an illness-inducing injection of lithium chloride endowed the context with new properties, consistent with the proposal that classical conditioning had established an association between the context as the conditioned stimulus and nausea as the unconditioned stimulus. The conditioned response to the context constitutes a form of anticipatory nausea. Experiment 3 examined *overshadowing*, showing that the presence of a novel salient cue (a flavour) during context conditioning reduced the magnitude of the aversion conditioned to the context. Experiments 4–7 examined the effects of giving exposure to the context prior to conditioning. They demonstrated a *latent inhibition* effect, that is, a reduction in the magnitude of the aversion in pre-exposed animals. It is suggested that these ways of modulating conditioned aversions could form the basis of interventions for use in the chemotherapy clinic. Anticipatory nausea is assumed to be a consequence of the formation of an association between the cues that constitute the clinic and the drug-induced nausea experienced in their presence. By restricting the development of this association, latent inhibition and overshadowing procedures should be effective in alleviating the problem of anticipatory nausea.
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Keywords: Rats; Conditioning; Context; Aversion; Nausea; Overshadowing; Latent inhibition

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1. Introduction

One of the effects produced by ingestion or an injection of a lithium salt is activation of cells in the area postrema of the hindbrain that are sensitive to distension of the stomach (Tsukamoto and Adachi, 1994). Whether or not the state induced by this means can legitimately be equated with that described by human subjects as "nausea" is a matter for debate (and will be debated subsequently in this article). What is firmly established, however, is that animals given an injection of lithium chloride (LiCl) following consumption of a substance with a novel flavour, will show evidence of having acquired an aversion to that flavour by refusing to consume the flavour when it is presented subsequently. This phenomenon is usually taken to be an instance of classical conditioning in which an association is formed between the conditioned stimulus, the flavour, and the unconditioned stimulus, some aspect of the state induced by the injection (e.g., Domjan, 1980). Even those who question the identification with classical conditioning (e.g., Garcia et al., 1989) accept that this rejection response occurs because the flavour has itself acquired aversive properties.

The cytotoxic drugs used in chemotherapy (even when combined with modern antiemetics) frequently induce nausea. Patients who experience such nausea in a clinic may also come to develop it in an anticipatory form, that is, they may begin to feel nauseous simply when re-exposed to the sights, sounds, and smells of the clinic in which the treatments are given (Andrykowski and Redd, 1987). The parallel with the experimental procedure of flavour aversion learning is obvious, and it has been suggested (e.g., Carey and Burish, 1988; Stockhorst et al., 1998a) that anticipatory nausea is a product of classical conditioning, with contextual cues as the conditioned stimulus and chemotherapy-induced nausea as the unconditioned stimulus. But although this suggestion seems eminently plausible, to accept it requires us to reject the "belongingness" analysis of nausea-induced learning advanced by Garcia and others (e.g., Seligman, 1970; Garcia et al., 1989). According to this analysis, such learning shows a special selectivity so that, although flavour cues can readily come to function as conditioned stimuli, exteroceptive cues (such as contexts) cannot. If we are to pursue the conditioning account of anticipatory nausea, a necessary first step would be to disprove the belongingness assertion by means of an appropriate experimental test. This was the starting point for the programme of research that is reviewed here.

All our experiments used laboratory rats as the subjects and an intraperitoneal injection of LiCl as the nausea-inducing agent (the unconditioned stimulus). Our initial studies (described in the first major section below) were designed to show that experience of this unconditioned stimulus in conjunction with exposure to a novel context would endow that context with new properties and would render the context aversive. We found, to anticipate, that this procedure was successful in producing conditioning, and that the conditioned responses elicited were consistent with the interpretation that the contextual cues had acquired the capacity to evoke nausea. Armed with this paradigm as an animal model of anticipatory nausea, we went on to investigate the effects of (procedurally) simple behavioural manipulations that, on the basis of orthodox conditioning studies, might be expected to attenuate or prevent the formation of context-unconditioned stimulus associations. The results of these studies are described in subsequent sections. They give grounds for hoping that the procedures employed, with suitable modification, might be used as interventions in the chemotherapy clinic that will serve to limit the degree to which patients develop anticipatory nausea.

2. Demonstrating context aversion conditioning

The basic conditioning procedure that we have used in all our experimental work on this topic (e.g., Symonds and Hall, 1997, 1999, 2000, 2002) is exceedingly simple: it merely involves giving the rat an injection of LiCl in association with exposure to a novel context (a cage different from that used as the home cage). The challenge (particularly acute for a species that lacks a vomiting reflex) was to devise a test capable of revealing that a context treated in this way evokes a state akin to nausea. In the majority of out studies we have made use of one or other of two test procedures: the *consumption* test, and the *blocking* test.

2.1. The consumption test

Our first test procedure is based on observation (e.g., Symonds and Hall, 2002) of the direct effects of an injection of LiCl (i.e., the nature of the unconditioned response, UR, evoked by this unconditioned stimulus). Rats given access to a novel-flavoured solution (we have used a sucrose solution) immediately after such an injection, drink little of it — an outcome plausibly interpreted as a response to the nausea induced by the injection. It follows that if conditioned contextual cues are capable of evoking this same state, they too should be capable of suppressing consumption of the sucrose solution.

The design and results of an experiment (Rodriguez et al., 2000, Experiment 1) intended to assess this possibility, are presented as Experiment 1 in Table 1. The experiment had two phases. In the first (context conditioning) phase, rats received four 30-min exposure trials in each of two distinctive contexts (one was a big white box, the other a smaller dark box, both were different from the home cage). Exposure to one of these (labelled A in the table) was preceded by an intraperitoneal injection of the LiCl; exposure to the other (control) context (B in the table) was preceded by an injection of saline[1]. After a rest period, in which they were allowed to recover from the

[1] In some of our earlier work (e.g., Symonds et al., 1998) we gave the injection after exposure to context A. In this experiment we gave the injection just before the rat was put into context A. This latter procedure has proved to be more effective (presumably because the animal experiences the ill-effects of the injection in the presence of the contextual cues) and we have used it in all of our subsequent experiments (with the exception of that described here as Experiment 3, in which the original procedure was used).

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Table 1
Tests for context aversion conditioning

Experiment 1: Consumption test			
	Context conditioning	Test	
E	A+Li & B	Suc in A	12.0 ml
C	A+Li & B	Suc in B	16.2 ml

Experiment 2: Blocking test				
	Context conditioning	Compound conditioning	Test (in home cage)	
E	A+Li & B	Suc→A+Li	Suc	8.6 ml
C	A+LI & B	Suc→B+Li	Suc	1.9 ml

E and C are experimental and control groups; A and B are distinctive contexts; Suc refers to sucrose solution; Li, an injection of lithium chloride. Context conditioning consisted of four trials in each context. Full details are given in Rodriguez et al. (2000).

immediate effects of the injections, the rats were tested for their consumption of sucrose solution. Subjects in the E group received this test in the conditioned context, A; subjects in the C group were tested in context B. As the table shows, consumption was suppressed in the E group, a result consistent with the proposal that these contextual cues are capable of evoking, as a conditioned response, some aspect of the state induced by the unconditioned stimulus itself.

2.2. The blocking test

Table 1 (Experiment 2) presents the design and results of a study that made use of the blocking test procedure (Rodriguez et al., 2000, Experiment 3). In this, the rats received an initial phase of context conditioning like that described for Experiment 1. The next stage of the experiment was designed to demonstrate that context A had acquired aversive properties whereas context B had not. For this the rats were divided into two groups. Both received flavour aversion conditioning in which a sucrose solution was used as the conditioned stimulus and a lithium injection as the unconditioned stimulus; the only departure from the standard flavour-aversion procedure was that, having received the injection, the E group spent 30 min in context A and the C group spent 30 min in context B. Both groups thus experienced a compound conditioned stimulus consisting of the flavour plus the context. It is well established, for a wide range of conditioning procedures, that when one element of a compound conditioned stimulus has been pretrained as a signal for a given unconditioned stimulus, its presence in the compound will *block* conditioning to the other. Thus the aversive properties of the context can be assessed in terms of the extent to which the context blocks the acquisition of a conditioned aversion by the flavour.

No blocking is to be expected for animals in the C group and acquisition of the aversion to sucrose should proceed normally. But if context A has become associated with the unconditioned stimulus as a result of the first stage of training it should be able to block conditioning to sucrose and limit the development of the aversion in the E group. Table 1 shows the results of test trials in which the rats were given access to the sucrose solution in the home cage. Group C drank little of this, usually readily accepted, substance, indicating that an aversion had been formed. Group E drank substantially more, indicating that blocking had occurred. To the extent that flavour aversion learning may be taken to depend on an association between the flavour and nausea, we may conclude that the ability of context A to block this learning reflects an association between the context and nausea.

2.3. The taste reactivity test

The experimental results summarized in Table 1 were enough to convince us that, in spite of seemingly authoritative assertions to the contrary, an injection of LiCl will support conditioning in which the conditioned stimulus is a context. A sceptic might still doubt, however, that the conditioned response established by our conditioning procedure truly reflects a state of nausea. And grounds for this scepticism might be found in the analysis of drug-induced conditioning developed by Parker (2003). According to Parker, injection of LiCl has two major effects — not only does it produce a state of nausea, it also produces a novel change in physiological state that signals danger to the rat. Both these effects can support conditioning. A taste associated with nausea will acquire conditioned aversiveness that will be evident in the rat's consummatory behaviour when it encounters that taste again. This is made apparent by the taste reactivity test in which a small amount of the conditioned substance is introduced into the rat's oral cavity by means of a cannula and the orofacial reactions of the animal are noted. In these circumstances the rat shows a characteristic rejection response: an open-mouthed "gaping," which is perhaps as close to vomiting as this species can get. But this effect is not held to be responsible for the suppression of intake observed in a standard consumption test for flavour aversion learning. This latter effect is attributed to taste *avoidance* (as opposed to taste *aversion*); the conditioning (akin to fear conditioning) is supported by an association between the taste and the dangerous change of physiological state.

A possible implication of this analysis is that the learning produced by our context conditioning procedures might be based on avoidance rather than aversion in that the context comes to signal potential danger but does not actually evoke a state of conditioned nausea. A context with these properties might be expected to block subsequent taste avoidance learning (thus explaining the results obtained in our blocking test procedure); and rats might be expected to be reluctant to consume an otherwise palatable substance when it is presented in a fear-evoking context (the results of our consumption test). Proof that our conditioning procedure does indeed endow the context with the power to evoke nausea requires a different sort of test; and to this end we have conducted a further study using a version of the taste reactivity test.

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In this recent, unpublished, experiment (Limebeer et al., 2005) we gave one group of rats the standard conditioning regime: exposure to a distinctive context when suffering the effects of an injection of LiCl. (Control subjects experienced the context and the injection equally often, but on separate occasions.) In this experiment, the context was a box specially adapted for video-recording of the rat's orofacial responses. After conditioning, the rats were put back in the box and a saccharin solution was infused through an intraoral cannula. Control subjects that had not experienced pairings of the context and LiCl showed ingestion responses during the infusion, but those that had undergone context conditioning showed the gaping response. This direct test confirms that the conditioned context is capable of evoking nausea and restores our confidence in the assumption that our standard test procedures (i.e., the blocking and consumption tests) reflect the consequences of such conditioning.

3. Attenuating context aversion conditioning

Equipped with this experimental paradigm as an animal model of anticipatory nausea, we set about the investigation of procedures that might be expected to restrict the formation of context-unconditioned stimulus associations, and that might thus have potential as clinical interventions for the control of anticipatory nausea. Experimental study of more orthodox animal conditioning preparations has shown that, in some circumstances, learning may fail to occur in spite of the fact that the organism experiences a pairing of the conditioned stimulus and unconditioned stimulus. Given that the chemotherapy regime necessarily implies a conditioned stimulus-unconditioned stimulus pairing, these procedures are of special interest for our present concern. Two will be discussed: those known as *overshadowing* and *latent inhibition*.

3.1. Overshadowing

The phenomenon of overshadowing was first observed by Pavlov (1927) and has been amply confirmed in subsequent work. It is obtained when the conditioned stimulus is a compound consisting of two separable elements, one more salient than the other. The presence of the more salient element is commonly found to restrict the acquisition of associative strength by the less salient element (even though the latter, when trained on its own, may be learned about perfectly well). The potential relevance of overshadowing for the case of anticipatory nausea will be apparent. A novel salient cue presented during chemotherapy sessions might act to overshadow the context and thus prevent the development of anticipatory nausea. The cue itself might acquire aversive properties, but this will not be a problem if we choose, for the overshadowing cue, a novel-flavoured drink that the patient will never encounter again (see Stockhorst et al., 1998b).

There is, however, one major problem associated with this proposal. It has been found, for certain training procedures, that the presence of the salient cue, rather than producing overshadowing, can act to potentiate learning about the other element of the compound. If context aversion is susceptible to potentiation (and some early experiments e.g., Best et al., 1984, gave reason to suspect it might be), then an intervention designed to alleviate anticipatory nausea might make matters worse. Symonds and Hall (1999) reviewed the available literature on this topic and concluded that the evidence for potentiation in context aversion learning was inconclusive. But in a matter as important as this, it is clearly necessary to have direct evidence that overshadowing does indeed occur, and Symonds and Hall conducted a series of further experiments designed to look for it.

The design of one of these experiments is presented in Table 2 as Experiment 3. The procedure made use of a version of the blocking test procedure of Experiment 2. Two groups of rats received initial conditioning in which the target context A was paired with the unconditioned stimulus, prior to conditioning with the compound of sucrose presented in context A. Blocking can therefore be expected in both groups; that is, for both groups the aversion established to A in the first phase of training should interfere with the acquisition of the aversion to sucrose, and both should be willing to consume sucrose on the final test. The groups differed, however, in that the E group was allowed to consume a salient flavour (the sour taste of a weak acid solution) in context A during the first stage of training, whereas the C group was given only water in this stage. To equate the groups in other respects, the C group was given the sour solution in a different context, B; the E group received water in this second context. If the presence of the salient taste stimulus overshadows context conditioning, then the aversion to A will be less well formed in the E group than in the C group; context A will be less effective in blocking conditioning to sucrose in the E group, and they will thus consume less of it on the test than the C group. As Table 2 shows, this was just the pattern of results that was obtained. We conclude that conditioning of aversions to context is susceptible to overshadowing by a more salient proximal stimulus.

3.2. Latent inhibition

Extensive prior exposure to the event that is to be used as the conditioned stimulus in classical conditioning will severely

Table 2

Experiment 3: Overshadowing of context aversion conditioning

	Context conditioning	Compound conditioning	Suc (in home cage)	
			Test 1	Test 2
E	A(H)+Li & B(W)+Li	Suc→A+Li	4.6 ml	5.3 ml
C	A(W)+Li & B(H)+Li	Suc→A+Li	6.2 ml	8.1 ml

E and C are experimental and control groups; A and B are distinctive contexts; Suc refers to sucrose solution; H to an acid solution; Li, an injection of lithium chloride. Context conditioning consisted of three trials in each context; compound conditioning of two trials. Full details of this experiment are given in Symonds and Hall (1999).

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retard acquisition of the conditioned response. This effect, known as latent inhibition, is one of the best-established phenomena in classical conditioning (see Lubow, 1989). Could simple pre-exposure to the context provide a useful intervention for the alleviation of anticipatory nausea? We present next, preliminary reports of a series of previously unpublished studies, that were designed to investigate this issue.

As a first step, it is necessary to demonstrate that the latent inhibition effect can be obtained with our training procedure. Although latent inhibition has been observed in a wide range of experimental paradigms, these have usually been ones in which a discrete simple event has been used as the conditioned stimulus, and the result may be different when the conditioned stimulus is a set of contextual cues. Such studies of context conditioning as are available (studies of contextual fear conditioning in the rat, using shock as the unconditioned stimulus) have found that, in some circumstances, pre-exposure to the context can facilitate learning (Fanselow, 2000; Kiernan and Westbrook, 1993; Rudy and O'Reilly, 1999). Although accounts of this differ in details, all attributed this 'reverse latent inhibition' effect to the special nature of the context as a conditioned stimulus. Specifically they have suggested that exposure to such a complex and multifaceted set of cues engages a perceptual learning process that allows the formation of an integrated representation of the context, which is something that promotes the later acquisition or performance of conditioned responses.

3.2.1. Demonstrating latent inhibition

The occurrence of perceptual learning does not preclude the possibility of latent inhibition. Once formed, the integrated representation might be expected to be as susceptible to the effects of pre-exposure as any simple cue. The results reported by Kiernan and Westbrook (1993) support this view. Pre-exposure to the context was found to enhance conditioning when its duration was restricted to just a few minutes; but when exposure was extended to more than an hour, the outcome was a retardation of subsequent learning. In the light of this observation, we elected, in our preliminary study (which was intended simply as a demonstration of the latent inhibition effect in our training paradigm) to give very extensive context pre-exposure. The design of this experiment is presented in Table 3 (Experiment 4). Two groups of rats received context conditioning followed by a consumption test in which sucrose was presented in the experimental context. The groups differed only in that the E group had, on each of the eight days prior to conditioning, been placed in the experimental context for 30 min. Animals in the C group remained in their home cages on these days. On the test (see Table 3), the E group consumed significantly more than the C group, $F(1, 14)=5.98$, $p<0.05$, suggesting that the context aversion was weaker in the E than the C group.

The results of Experiment 4 encourage the view that prior exposure to the context will produce a latent inhibition effect. But other interpretations are possible. It might be argued, for instance, that the pre-exposure procedure enhances consumption on the test simply because it renders the test context more familiar — that the context evokes conditioned nausea in both groups, but that that C group consumes less because it is distracted by the novel features of the relatively unfamiliar context. To address this point, we carried out a further study of latent inhibition using the blocking test procedure, in which the test is conducted in the home cage rather than the experimental context. In addition, we took the opportunity of investigating the effect of reducing the amount pre-exposure. Prolonged pre-exposure to the context would not be practical in a the clinic, and if latent inhibition is to be a useful intervention in this setting we need to be able to show that the effect can be obtained with fewer pre-exposures.

The design and results of this study are shown as Experiment 5 in Table 3. Different groups of rats received either eight or four pre-exposure trials (Groups E(8) and E(4)) or no pre-exposure (Group C), prior to conditioning in which the context was paired with LiCl. Context conditioning was assessed by determining the extent to which the presence of the context cues blocked subsequent learning when the sucrose conditioned stimulus was paired with LiCl. When tested over two days with sucrose in the home cage, the C group drank readily, indicating that blocking had occurred (and thus that the context conditioning had occurred). But consumption on test was reduced in both of the E groups; that is, blocking was less evident, indicating that pre-exposure had restricted the acquisition of associative strength by the context. An analysis of variance conducted on the data presented in the table showed a significant difference among the groups, $F(2, 21)=11.92$. $p<.01$; pairwise comparisons using Tukey's test revealed that the C group differed significantly ($p<0.05$) from each of the E groups. These findings confirm that pre-exposure to the context will produce latent inhibition; and that the effect can be

Table 3
Latent inhibition of context aversion conditioning

Experiment 4: Consumption test

	Pre-exposure	Context conditioning	Test (Suc in A)
E	8 A→0	A+Li	9.8 ml
C	–	A+Li	7.3 ml

Experiment 5: Blocking test

	Pre-exposure	Context conditioning	Compound conditioning	Suc (in home cage)	
				Test 1	Test 2
E(8)	8 A→0	A+Li	Suc→A+Li	1.8 ml	4.5 ml
E(4)	4 A→0	A+Li	Suc→A+Li	3.9 ml	6.5 ml
C	–	A+Li	Suc→A+Li	8.4 ml	13.0 ml

E and C are experimental and control groups ($n=8$); A is a distinctive context, different from the home cage. Suc refers to a 3.4% sucrose solution; Li, to an intraperitoneal injection of 0.15 M lithium chloride, at 10 ml/kg of body weight. There were two context conditioning trials and one compound conditioning trial. In Experiment 4 the E group received eight 30-min pre-exposure trials in context A; in Experiment 5 different groups received either four, labelled E(4), or eight, E(8), pre-exposures.

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obtained, albeit to a lesser extent, when the number of pre-exposure trials is reduced from eight to four.

3.2.2. Enhancing latent inhibition

The usefulness of latent inhibition as a clinical intervention will be limited if it is necessary to give extensive pre-exposure to the context (the clinic) in order to produce a sizeable effect. Is there any way in which we can enhance the impact of any given pre-exposure session (thus reducing the number of sessions required)? One possibility emerges from the theoretical account of latent inhibition developed by Hall (1991) on the basis of the Pearce and Hall (1980) model of conditioning. According to this account, latent inhibition is taken to be a consequence of a reduction in the *associability* (very roughly, the attention paid to) the preexposed cue. This reduction depends on an associative learning process by which the organism learns what the cue signifies (which, the case of latent inhibition, will be nothing of consequence): the stronger the association the lower the associability. What we need, therefore, is a way of speeding this associative learning, and the theory suggests one. If a salient stimulus is presented along with the target cue, the compound as a whole will be learned about readily and, according to the theory, the associability of both elements of the compound (and, critically, that of the target cue) will decline rapidly.

In a previous test of this possibility, Honey and Hall (1988) found that compounding two flavours during pre-exposure reduced rather than enhanced the extent to which latent inhibition developed to one of them when subsequently it was conditioned on its own. They pointed out, however, stimuli of this sort are likely to interact at the sensory or perceptual level, something that might obscure the effect we are looking for. If the pre-exposed stimulus is perceived as being different from that presented in conditioning, we cannot expect latent inhibition to transfer from one stage to the next. But the situation may be different when the critical cue is a context. In this case it seems unlikely that the presence of a novel flavour during pre-exposure would radically disrupt the animal's perception of the contextual cues, and an enhancement of latent inhibition might be observable. This thinking was enough to encourage us to try the preliminary experiments described below.

Table 4, Experiment 6, shows the design of a latent inhibition experiment using the consumption test. Two groups of rats received four pre-exposure sessions in the context, followed by two context conditioning trials. The groups differed only in that the E group received access to a salient flavour (an acid solution was made available) during pre-exposure. (Rats in the C group were given equivalent access to this solution in their home cages.) For some unknown reason, levels of consumption during the test phase with sucrose in the conditioned context were rather elevated in both groups. Critically, however, the E group drank somewhat more than the C group, $F(1, 14)=3.90$, $05>p>.10$. This is the outcome that would be expected if the presence of the flavour during pre-exposure had enhanced the latent inhibition effect.

The results of Experiment 6 were encouraging, but are by no means conclusive, and may be open to other explanations. Perhaps, for example, rats that have learned to expect a sour taste in a context show some form of contrast effect that increases their consumption when a sweet taste is subsequently presented in that context. We decided, therefore, to investigate the matter further using a different technique, the blocking test.

Experiment 7 (conducted in collaboration with J. Wills) is outlined in the lower section of Table 4. As before, the rats received four pre-exposure sessions (with the acid solution presented in the context for the E group), followed by two context conditioning trials. They then received a single compound conditioning trial in which consumption of sucrose in the home cage was followed by experience of illness in the presence of the contextual cues. We can expect, on the basis of Experiment 5, that pre-exposure to the context will attenuate context conditioning and thus reduce the ability of the context to block the development of the aversion to sucrose in both groups. But if the presence of the added cue enhances latent inhibition for the E group, blocking will be even less effective, and the aversion to sucrose should be more substantial than in the C group. The results of the test phase, in which sucrose was presented in the home cage (Table 4), show just this effect. The E group drank less than the C group (i.e., showed a stronger aversion) and the difference between the groups proved to be statistically reliable, $F(1, 14)=7.58$, $p<0.05$.

The results presented in Table 4 are recent and preliminary, and more work will be needed to confirm their reliability. In particular, we need to repeat the experiments including nonpreexposed control conditions that will allow us to see the basic latent inhibition effect itself, alongside the

Table 4
Enhancement of latent inhibition of context aversion conditioning

Experiment 6: Consumption test

	Pre-exposure	Context conditioning	Suc in A	
			Test 1	Test 2
E	4 A(H) & 4 HC(W)	A+Li	18.0 ml	26.7 ml
C	4 A(W) & 4 HC (H)	A+Li	16.5 ml	22.5 ml

Experiment 7: Blocking test

	Pre-exposure	Context conditioning	Compound conditioning	Suc (in home cage)	
				Test 1	Test 2
E	4 A(H)	A+Li	Suc→A+Li	4.9 ml	8.3 ml
C	4 A(W)	A+Li	Suc→A+Li	8.9 ml	13.2 ml

E and C are experimental and control groups ($n=8$); A is a distinctive context, different from the home cage. Suc refers to a 3.4% sucrose solution; H to a .01 M solution of HCl; W to water; Li, to an intraperitoneal injection of 0.15 M lithium chloride, at 10 ml/kg of body weight. There were two context conditioning trials and one compound conditioning trial. In both experiments there were eight 30-min pre-exposure trials in context A, with the acid solution available for the E groups but not for the C groups.

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effect produced by a procedure designed to enhance it. And we want to investigate the effects produced by an added cue other than the acid solution — theoretically enhancement of latent inhibition should be produced by the addition of any salient cue, and it would be nice to obtain the effect with a more pleasant one. What we can say at this stage, however, is that some version of the procedure used in Experiments 6 and 7 appears to have potential as a technique for heightening the efficacy of latent inhibition.

4. Summary and implications

The experiments outlined here have established, for the laboratory rat, that pairing a distinctive novel context with lithium-induced illness will endow that context with new properties. Specifically, the context acquires the power to evoke responses consistent with the interpretation the rat is experiencing a state of conditioned nausea. But although the contiguous occurrence of the relevant events is usually thought to be necessary for conditioning to occur, it is not a sufficient condition, and modern learning theory has devoted a good deal of effort to the analysis of these failures of conditioning (see Hall, 1994). Two such phenomena have been demonstrated for the present case. The development of a context aversion will be restricted if a salient cue (a novel flavour) is presented in the context during conditioning (the overshadowing effect). Context conditioning is susceptible to latent inhibition: prior exposure to the context will reduce the impact of subsequent context-illness pairings.

As we have noted, both these procedures, overshadowing and latent inhibition, have potential as clinical interventions for the alleviation of anticipatory nausea. They would require only minimal changes to the standard chemotherapy regime, and they are non-invasive and simple to apply. But it is a big jump from the animal conditioning laboratory to the clinic, and some preliminary validation with human subjects would be worthwhile. In collaboration with colleagues at the Universities of Düsseldorf and Tübingen we have attempted this in studies with healthy human subjects who volunteered to undergo the nausea-inducing experience of rotation in a specially constructed rotation chair. This treatment can induce anticipatory nausea; that is, after one or two rotations, the subjects report feelings of nausea when returned to the experimental set-up. To investigate overshadowing all that is needed is to give some subjects a novel-flavoured drink prior to each rotation session; for latent inhibition we can simply place them in the chair one or a few times prior to the first rotation. Will these procedures attenuate this form of anticipatory nausea?

Results have recently been published for our latent inhibition study (Klosterhalfen et al., 2005), and they are encouraging. At least for female subjects (who tend to be more prone to reporting symptoms of nausea than are males), three pre-exposures to the context prior to the rotation procedure produced a significant reduction in the degree of anticipatory nausea evoked by the context in a final test session. The time seems right for a move to the clinic for a direct test of the efficacy of this sort of behavioural intervention.

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