

CONDITIONED TASTE AVERSION IN HUMANS USING MOTION-INDUCED SICKNESS AS THE US*

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(Received 22 July 1988)

Summary—The purpose of the experiment was to demonstrate conditioned taste aversion (CTA) and latent inhibition (LI) of CTA in humans using rotation-induced motion sickness as the unconditioned stimulus. To accomplish this, flavour familiarity (familiar vs unfamiliar) and rotation (rotation vs no rotation) were manipulated in a 2 × 2 factorial design. Subjects consumed either a familiarly flavoured carbonated beverage or a novel one after which half of each group was rotated or not rotated. Two hours later the subjects were re-presented with the flavoured drink that they had previously drunk. The groups receiving rotation consumed less of the drink than the non-rotated groups, thus demonstrating CTA. The rotated group pre-exposed to the novel flavoured drink consumed less than the rotated group pre-exposed to the familiar drink, thus demonstrating LI. The effectiveness of the rotation procedure in producing motion sickness was confirmed by self-reports of general feelings and by symptom rating scales. In addition, it was found that, at the time of consuming the test drink the rotation groups' motion-sickness symptom scores were reduced to the level of the nonrotated groups. Applications of these data to the prophylactic treatment of chemotherapy-induced food aversions were discussed.

In comparison to the extensive research concerning conditioned taste aversion (CTA) in animals (see Riley and Tuck, 1985, for a recent bibliography), relatively few such studies have used human Ss. Nevertheless, based on several surveys (Garb and Stunkard, 1974; Logue, Logue and Strauss, 1983; Logue, Ophir and Strauss, 1981; Midkiff and Bernstein, 1985; Rozin, 1986), it is possible to draw a fairly good picture of the nature of human CTA. CTA appears to be a common event in everyday life, and it follows, to a large extent, the basic principles which define this phenomenon among animals.

Information regarding human CTA has also been derived from CTA therapy for alcoholism. As the conditioned response of CTA is, typically, a strong aversion which results in a long lasting avoidance of the flavour (CS) that preceded the nauseogenic experience (US), CTA offers a potentially attractive method for treatment of alcoholics (Nathan, 1985, for review). Insofar as this treatment is concerned, CTA represents the desired outcome. However, in regard to a population of cancer patients undergoing chemotherapy, CTA may promote a negatively desired effect. These therapy procedures commonly produce nausea, and a common side-effect is anticipatory nausea and vomiting. The frequency of this reaction among such patients is high, cited at 71% by Pratt, Lazar, Penman and Holland (1984). It is reasonable to expect that following such gastrointestinal reaction, CTA would be established toward food products consumed some hours prior to the treatment. Indeed, as the chemotherapy treatment is usually of long duration and the number of exposures to the nauseogenic drugs is high, patients often exhibit aversions to items of their normal diet (Bernstein, 1978, 1982, 1985; Bernstein and Borson, 1986; Bernstein and Webster, 1980; Bernstein, Webster and Bernstein, 1982; Burish and Carey, 1986; Morrow, 1985; Morrow and Morrell, 1982; Pratt *et al.*, 1984).

The formation of food aversions as a consequence of chemotherapy has also been demonstrated in several experimental studies. Bernstein (1978) found that CTA was established to a novel tasting ice-cream in children undergoing chemotherapy. Similarly, a conditioned aversion was formed among adult patients (Bernstein and Webster, 1980). Bernstein, *et al.*, (1982) also documented the formation of CTAs to patients' customary diet.

*This study was conducted by S. Arwas in partial fulfilment of the requirements for a Master's degree at Bar Ilan University. Requests for reprints should be sent to R. E. Lubow, Department of Psychology, Tel-Aviv University, 69978 Ramat-Aviv, Israel.

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As 25% of patients fail to be helped by antinauseogenic drugs (Morrow and Morrell, 1982), the chemotherapy-induced CTA represents a severe and widespread problem. One way to reduce these undesirable CTAs may be by using a latent inhibition (LI) procedure. LI represents a decrement in stimulus associability which results from the nonreinforced pre-exposure of the to-be-conditioned stimulus (Lubow, 1973a). Thus, if one is familiarized with a particular flavour, and then that flavour is paired with illness-inducing experience, the *S* will not form the association between flavour and illness as strongly as will a *S* who has not been pre-exposed to the flavour. Such LI of CTA has been repeatedly demonstrated with animal *Ss* (Lubow, 1989, for review). Evidence supporting LI for naturally acquired human CTAs is available from retrospective survey data which indicate that common food products produce a disproportionately lower number of CTAs than relatively more novel foods (Logue, 1985; Logue *et al.*, 1981; Midkiff and Bernstein, 1985; de Silva and Rachman, 1987).*

The possibility of utilizing LI prophylactically to attenuate undesirable conditioned responses and maladaptive behaviour patterns has already been suggested (Lubow, 1973b, Poser, 1970). Indeed, there is one study that has demonstrated LI in human CTA (Cannon, Best, Batson and Feldman, 1983).

In summary, retrospective survey data and the clinical chemotherapy observations strongly suggest that conditioned taste aversion is a genuine learning phenomenon in humans which parallels the same very robust effect in animals. Furthermore, such aversion learning may have undesirable consequences in various treatments that produce nausea as a side effect. As a result of these considerations, it was decided to study CTA in humans under controlled laboratory conditions, particularly since there are very few such formal accounts of human CTA. In addition, it was decided to use motion-produced illness as the US. If such a US can be shown to be effective, it would be very useful in this research area, as it avoids major ethical and practical problems that accompany the use of drug-induced illness. Finally, the major question asked concerns the effectiveness of flavor familiarity in reducing CTA. Such a latent inhibition effect is consistently found in the animal literature (Lubow, 1989). Its presence in human CTA would help confirm the identity of process in animals and humans, and would provide a possible procedure for reducing the undesirable food aversions that often accompany chemotherapy in humans.

METHOD

Subjects

Forty-nine healthy males, between 18–19 yr of age, recruits in the Israeli navy, initially agreed to participate in an experimental procedure designed to measure their susceptibility to motion sickness. *Ss* were made aware of the possibility of becoming motion sick and signed a statement consenting to participate in this type of experiment. In addition, the symptoms of motion sickness were described and the *Ss* were told that they could withdraw at any time during the course of the experiment. The *Ss* received no further information in regard to the goals of the experiment. Four *Ss* refused to participate in the experiment, while three other *Ss* were excluded later for other reasons (two did not taste the CS drink and one was completely nonresponsive to the illness producing procedure), thus leaving 42 *Ss* in the experiment.

Materials

(1) *Apparatus*. The *S* was rotated by a motor-driven "Contraves" chair, governed by a 403-D "Contraves" servocontroller. Since rotation by itself rarely induces motion sickness, the rotating *Ss* were presented with a "Visual Vestibular Interaction Test" (VVIT). This test, together with directed head movements during rotation, produces moderate levels of sickness within several minutes, and has established norms (Lentz, Holtzman, Hixon and Guedry, 1977). The VVIT is a visual search task in which the *S* has to find a digit according to its corresponding *x* and *y* coordinates. The digit matrix dimensions were 17.5 × 17.5 cm. The matrix was placed on a board mounted on the rotating chair at a distance of 50 cm from the *S*'s forehead. The VVIT and head

*Indeed, this poses a problem for alcohol aversion therapy, in which, by definition, the alcoholic has received many pretreatment exposures to the to-be-conditioned alcoholic beverages.

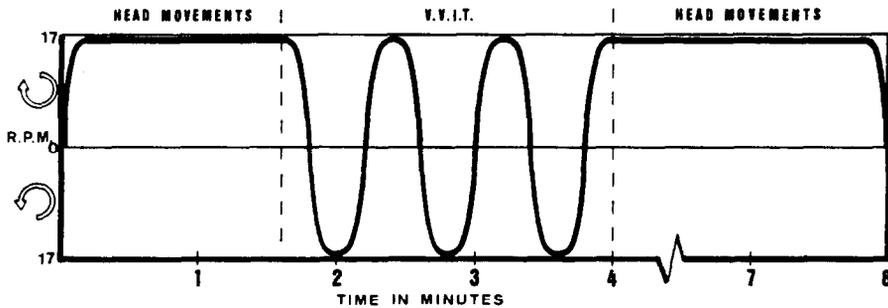


Fig. 1. Profile of 8 min rotation period showing changing rates of rotation in revolutions per minute (r.p.m.), direction of rotation, and phases during which head movements and target detections were required.

movement commands were taped and presented to the *S* via a loud-speaker mounted on the back of the rotation chair.

(2) *Rating scales.* Motion sickness was assessed with a set of rating scales which tapped each of the most common symptoms as described by Reason and Brand (1975): upset stomach, cold sweat, nausea, dizziness, near-vomiting, fatigue and general malaise. The *Ss* ranked each symptom on a five point scale, from "weak" (1) to "strong" (5). The rating scales were administered at two separate times, once immediately after rotation, and once 2 hr later. Each scale referred to four points of time, reported on retrospectively, four during the rotation as well as four following rotation. However, only the reports of two points of time were analyzed, one just after getting off the chair, and one 2 hr later during the second drinking period.

(3) *CS drinks.* Four soft drinks were selected for the study: Coca Cola and Sprite as familiar drinks and tonic and ginger-ale (both Schweppes) as unfamiliar drinks. The choice of drinks was based on a survey of 25 men and women who were asked to list all of the soft drinks with which they were acquainted. Coca Cola and Sprite were named by 25 and 20 persons respectively, while tonic and ginger-ale were noted only once each.

Design and procedure

The *Ss* were randomly divided into 4 groups. Two groups received the illness producing procedure (rotation groups) while the other 2 groups served as controls (nonrotation). The *Ss* of one rotation group and one control group were presented with a familiar drink. The other rotation and control groups were presented with an unfamiliar drink. (Within each familiar drink group, half the *Ss* received Coca Cola and half, Sprite; within each unfamiliar drink group, half received tonic and half, ginger-ale.) Thus, 4 groups were formed in a 2×2 factorial design, with rotation and familiarity as the main factors: rotation-familiar drink, rotation-unfamiliar drink, nonrotation-familiar drink, and nonrotation-unfamiliar drink.

CS administration. Prior to the motion sickness manipulation, each *S* was offered a 250 ml sealed bottle of one of the four drinks. The *S* was encouraged to consume the drink by pointing out that as a result of the procedure he was expected to perspire and lose body fluid. After the *S* left the table, the amount of fluid consumed was recorded.

US procedure. This procedure, combining rotation, head movements and VVIT performance, was designed to provoke a moderate level of motion sickness. The control groups were treated identically as the rotation groups, except for the rotation itself, which they did not experience.

During the first 70 sec, the chair was rotated at a constant velocity of 17 rpm and the *S* was instructed, via a synchronized recording, to lower and to raise his head between a head rest and a movement limiter (about a 15° movement). The second rotation period involved 2.5 min of VVIT activity. The *S* performed 21 search tasks with the VVIT matrix, according to 21 recorded search commands. In this stage, the chair went through 3 cycles of sinusoidal motion with varied velocity and constant acceleration and deceleration. The chair decelerated from 17 rpm to 0 rpm, then accelerated in the opposite direction to 17 rpm and so on. The cycle period was 50 sec. The third rotation stage was identical to the first one. Its duration was, however, 4 min, and it included 10 up and down head movements. The pattern of chair motion is illustrated in Fig. 1.

During the motion stimulation procedure, the *S* was asked (through the recording) once per minute to rank his general feeling. According to an explanation given to the *S* prior to rotation, the possible responses could range between 100–40%, with 40% indicating that the *S* was about to vomit and that rotation should be stopped. At the end of the rotation phase, the *S* left the chair and filled out the first set of motion sickness rating scales.

Drinking test. The *S* was requested to return to the laboratory in 2 hr. On arriving, the second set of the motion sickness rating scales was administered. At the same time, he received the second drink. The type of drink was identical to the previous one and it was offered, again, in a 250 ml sealed bottle. While filling out the inventory, the *S* drank as much as he wished. Unlike in the first drinking phase, the *S* did not receive any encouragement to drink. After the *S* exited the room, the amount of fluid consumed was measured.

RESULTS

First drink consumption

The mean level of fluid consumption of the CS drink, prior to rotation, was 98 ml for the unfamiliar drinks, and 144.5 for the familiar drinks. Separate *t*-tests failed to show significant differences between the two drinks within the same familiarity category ($t < 1.0$). A 2×2 analysis of variance, of the to-be-treated groups, on the amounts of fluid consumed (collapsing across the different flavours within the same category) showed no significant differences, neither an effect of rotation group [$F(1,38) = < 1.0$] nor of flavour familiarity group assignments. [$F(1,38) = 1.61$, $P > 0.05$]. Thus, the four groups were not different in their initial levels of fluid consumption prior to the administration of the rotation treatment.

Effectiveness of rotation in producing motion sickness. Nine out of 20 *Ss* in the motion condition requested that the rotation be terminated before the end of the test due to the onset of strong nausea. Three of these *Ss* vomited. Figure 2 shows *Ss*' responses to the question concerning their general feeling that was posed once every minute during the rotation phase. None of the non-rotated *Ss* ranked overall feeling less than 100%. A 2×8 analysis of variance (rotation vs nonrotation and the eight reports of general feeling) revealed a significant interaction [$F(1,7) = 16.48$, $P < 0.001$]. As can be seen in Fig. 2, both groups of *Ss* began the rotation phase of the experiment without discomfort. However, the rotation group, with increased time of motion, proceeded to feel worse, while the *Ss* in the nonrotated group maintained their high level of comfort. The two groups also differed in performance on the VVIT, with significantly more errors for the rotation group ($\bar{X} = 3.5$) than for the nonrotation group ($\bar{X} = 1.8$), $t(41) = 3.04$, $P < 0.01$, one tailed.

The efficacy of the rotation procedure for producing motion sickness is also reflected in the seven retrospective symptom rating scales. Table 1 presents the mean ratings on the seven scales for the rotated and nonrotated groups for the two critical comparison periods—immediately after rotation, when symptom reports were the highest, and 2 hr later, when symptom reports should have abated. A $2 \times 2 \times 2$ ANOVA on the overall mean scores with the main factors of rotation vs nonrotation, familiar vs unfamiliar drink (a repeated measure) and immediate vs delayed

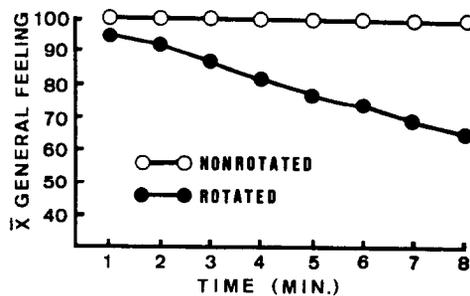


Fig. 2. Mean score of general feeling for rotated (●—●) and nonrotated (○—○) groups as a function of time in rotation phase of the experiment.

Table 1. Mean symptom scores on seven motion sickness scales for rotated (R) and nonrotated (NR) groups immediately after rotation phase and 2 hr later

Symptom	Just after rotations phase		2 hr after rotation phase	
	Group		Group	
	R	NR	R	NR
Stomach upset	1.55	1.05	1.15	1.00
Perspiration	2.85	1.10	1.10	1.00
Nausea	2.20	1.05	1.15	1.00
Dizziness	2.00	1.20	1.00	1.00
Near vomiting	1.95	1.05	1.15	1.00
Fatigue	1.90	1.25	1.15	1.00
General feeling	2.20	1.10	1.20	1.00
Mean	2.01	1.11	1.13	1.00

indicated significant main effects for rotation [$F(1,36) = 19.17$, $P < 0.001$], and period of report [$F(1,36) = 22.07$, $P < 0.001$]; no effect of drink familiarity [$F(1,36) < 1.0$] and the expected interaction between rotation and period of report [$F(1,36) = 12.06$, $P < 0.002$]. From Table 1, it is clear that significant motion sickness symptoms were barely present at any time in the nonrotated group, and were only present in the rotated group immediately after the rotation phase. In contrast to those *Ss* who were clearly affected by the motion stimulation procedure, nine *Ss* did not show any signs of motion sickness, either on the retrospective symptom questionnaire or on the 1-min *in situ* reports.

Evidence for conditioned taste aversion and latent inhibition. For the second drinking period, as for the first, there were no differences in the amount of fluid consumed between the two types of drinks within each of the familiarity categories; for ginger-ale vs tonic, $t(20) < 1.0$, and for Coca Cola vs Sprite, $t(18) = 1.27$, $P > 0.10$ (two tailed). On this basis, the subsequent analyses were conducted with the pooled data from the specific flavours within the two familiarity categories.

The fluid consumption data from the second drinking period were converted into suppression ratios, a commonly used index of conditioned aversion in animal CTA research. The suppression ratio is defined as the amount of the second drink consumed divided by the sum of the amount of first and second drink consumed. The means of the suppression ratios for the 4 groups are presented in Fig. 3. The 2×2 rotation by familiarity analysis of variance of the suppression ratios indicated an absence of main and interaction effects: rotation, [$F(1,38) < 1.0$]; familiarity, $F(1,38) < 1.0$; interaction; $F(1,38) = 1.39$, $P > 0.20$.

After examining the motion sickness data, it was decided to reject the drinking data of the nine *Ss* who were clearly unaffected by the rotation procedure (four *Ss* from the rotation-familiar drink group and five from the rotation-nonfamiliar drink group). Figure 3 presents the mean suppression ratios for this new classification. The 2×2 analysis of variance of the new suppression ratios failed to produce significant main effects of rotation [$F(1,29) < 1.0$] and familiarity [$F(1,29) = < 1.0$]. However, there was a significant interaction between familiarity and rotation, $F(1,29) = 5.04$,

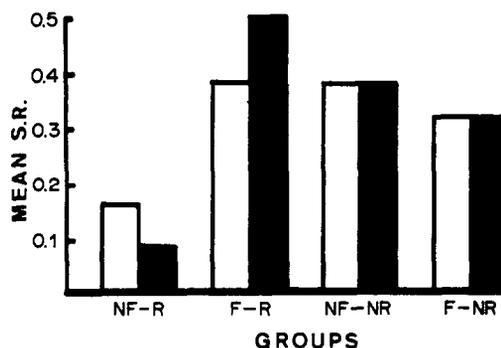


Fig. 3. Mean suppression ratios for the four conditions (NF-R, nonfamiliar drink-rotation; F-R, familiar drink-rotation; NF-NR, non-familiar drink-nonrotation; F-NR, familiar drink-nonrotation), for all *Ss* completing the procedure □, and for all *Ss* excluding those that showed no motion illness ■.

Table 2. Mean consumption (ml) of drinks, before rotation and after rotation, as a function of drink familiarity and rotation condition for all *Ss* and for *Ss* reporting motion sickness symptoms

Treatment	Unfamiliar drink				Familiar drink			
	Rotation		No rotation		Rotation		No rotation	
	pre-	post-	pre-	post-	pre-	post-	pre-	post-
Drinking period								
All <i>Ss</i>	92.8	26.1	102.3	110.4	150.0	88.1	138.9	115.5
Affected <i>Ss</i>	94.6	17.2	—	—	120.7	89.3	—	—

$P < 0.05$. *A posteriori* *t*-tests (one tail) indicated that the nonfamiliar flavour-rotated group suppressed drinking more than the nonfamiliar flavour-nonrotated group, $t(29) = 1.89$, $P < 0.05$, thereby demonstrating conditioned taste aversion; and the nonfamiliar flavour-rotated group suppressed drinking more than the familiar flavour-rotated group, $t(29) = 2.38$, $P < 0.01$, thereby demonstrating latent inhibition. No other comparisons reached an acceptable level of significance ($P > 0.05$).

DISCUSSION

The experiment was designed to attain two goals: (1) to demonstrate that rotation-induced motion sickness can serve as a sufficient condition for producing an effective US for conditioned taste aversion; (2) to demonstrate that familiarity of the to-be-conditioned flavour reduces the magnitude of conditioned taste aversion.

In regard to the first goal, it is obvious that a pre-requisite for establishing an effective US for CTA is that the procedure actually produces malaise and illness. In this regard, it was clearly demonstrated that rotation elicits feelings of general discomfort which increase with prolonged time of rotation (see Fig. 2). Measures of the strength of specific symptoms, even though reported retrospectively, similarly reflect the effectiveness of the rotation procedure in producing discomfort (see Table 1). Indeed, there is some evidence to suggest that these ratings are an underestimate of the effectiveness of the rotation. It will be noted in Table 1 that the highest symptom score was for perspiration, the only symptom that the experimenter could possibly observe directly. It may well be that male navy *Ss*, when being tested for motion sickness in a naval laboratory, would tend, with or without awareness, to report lower severity of sickness symptoms, at least for those symptoms which cannot be overtly verified. Nevertheless, in spite of the general effectiveness of the rotation procedure, 9 out of 20 *Ss* failed to report any ill-effects from rotation. As indicated, the presence of these symptoms is a pre-requisite for the procedure to serve as an effective US in the conditioning taste aversion paradigm. It is likely that most of these *Ss* could have been made ill by increasing the speed and/or duration of the rotation (Reason and Brand, 1975). However, for purposes of experimental design it was desirable to adopt a standard procedure for all *Ss*, and for reasons of *Ss*' convenience, one that minimized the actual number of vomiting incidents. An increase in the severity of the rotation conditions would reduce the number of nonresponding *Ss*, but at the same time it would increase the number of vomiting *Ss*.

Since rotation was not effective for these nine *Ss*, it was reasonable to omit them in a second analysis of the drinking suppression scores. This second analysis confirmed that *Ss* who were adversely affected by rotation did, indeed, show CTA. It is important to note that the reduced drinking in the nonfamiliar flavour-rotated groups represents conditioned suppression and not just a nonspecific side-effect of the symptoms. This point is confirmed by the fact that the suppressed drinking occurred 2 hr after rotation, when the reported symptoms were at the same level for the rotated and nonrotated groups (1.13 and 1.00, respectively).

In addition, it should be recalled that in the analysis of the data from the motion sickness symptom rating scales, the flavour familiarity variable had no reliable effect on symptom strength. This finding precludes the otherwise possible interpretation of the greater suppression in the nonfamiliar flavour-rotated group compared to the familiar flavour-rotated group as resulting from differences in unconditioned response strength. This type of independent assessment of the assumed equality of malaise-producing manipulations is absent in virtually all conditioned taste aversion experiments.

Further evidence that the suppressed drink consumption in the nonfamiliar flavour-rotated group represents conditioned taste aversion comes from the demonstration of LI itself. In the present study, LI was clearly demonstrated when the rotated group that consumed the familiarly flavoured drink showed significantly less suppression of the same post-rotation drink than did the nonrotated group. Since pre-exposure of a to-be-conditioned stimulus reduces the ability of that stimulus to enter into a new association, and this LI phenomenon is a characteristic of all mammalian conditioning preparations (see Lubow, 1989, for a review), the presence of the phenomenon in the present study also supports the contention that the procedures produced CTA.

The demonstration of CTA and LI in healthy human Ss under controlled laboratory conditions supports the contention that food aversion and anorexic effects of chemotherapy and radiation treatments of cancer patients are, indeed, mediated by conditioning processes, as already suggested by a number of writers (e.g. Bernstein and Borson, 1986). However, while the familiar flavours acquire immunity against entering into new associations, in this case conditioned taste aversions, in practice the repeated application of the cancer therapeutic procedures may overcome such resistance. Indeed, Riley, Jacobs and Mastropaolo (1983) have shown that rats may acquire a conditioned aversion to something as familiar as water, although only after many pairings of water and the toxicosis-producing US. Once it is accepted that the food aversion symptoms of patients on chemotherapy are, in fact, conditioning effects, and even though this conditioning is weakened by flavour familiarity, a tactic for reducing the pervasive undesirable side-effects is suggested. During the period of time that patients are receiving chemotherapy, they should avoid eating those foods that are part of their regular home or hospital diet. This pre-emptive avoidance should be adhered to even more stringently as the time interval between food consumption and therapy session is shortened.

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