Latent Inhibition of Rotation Chair-Induced Nausea in Healthy Male and Female Volunteers

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Objectives: Pre-exposure to an environment in which a nausea-inducing body rotation will subsequently be given constitutes a latent inhibition procedure that might act to reduce anticipatory and postrotation nausea. **Methods:** This was tested in 24 healthy subjects randomly assigned to receive no pre-exposure (group 0), a single pre-exposure (group 1), or three pre-exposures (group 3). Rotation was standardized as 5 × 1 minute rotation, but the subjects could terminate it on request. Nausea was determined on a 7-item symptom rating scale before, during, and after rotation on days 3 and 4, whereas anticipatory nausea was measured before presumed rotation on day 5. Saliva cortisol and tumor necrosis factor α (TNF-α) levels were determined at baseline before, directly, and 15 and 30 minutes after rotation every day, and before presumed rotation on day 5. **Results:** Pre-exposure significantly reduced the degree of anticipatory nausea on day 5. Cortisol levels increased with rotation and were higher at baseline on days 4 and 5, but subjects habituated from day 3 to day 4; levels were lower in women than in men. In contrast, TNF-α decreased with rotation but showed no habituation. For both cortisol and TNF-α, no effects on postrotational nausea were found. **Conclusion:** It is concluded that repetitive pre-exposure (latent inhibition) reduces anticipatory but not postrotation nausea; behavioral measures (rotation time) and measures of acute stress (cortisol, TNF-α) do not respond to latent inhibition. Thus, Pavlovian conditioning rules are effective in healthy humans with anticipatory nausea but not with postrotation nausea. Hormonal responses—TNF-α decrease with stress, compensatory cortisol increase—and gender-related effects on learning and habituation are discussed with regard to psychophysiological and psychoimmunological processes. **Key words:** latent inhibition, Pavlovian conditioning, nausea, motion sickness, gender.

AN = anticipatory nausea; **CS** = conditioned stimulus; **US** = unconditioned stimulus; **CR** = conditioned response; **PN** = posttreatment nausea; **UR** = unconditioned response; **TNF-α** = tumor necrosis factor α; **RT** = rotation tolerance; **MSSQ** = motion sickness susceptibility questionnaire; **SR** = symptom rating; **ANOVA** = analysis of variance.

INTRODUCTION

In spite of the advent of modern antiemetics, the cytotoxic drugs used in the treatment of cancer chemotherapy can still induce a state of nausea and attacks of vomiting that are severe and protracted in some patients (1). Over the course of treatment, the intensity and duration of posttreatment-nausea and vomiting is sometimes found to increase. In addition, some patients also develop anticipatory nausea (AN): after one or two sessions of treatment, simply being present in the clinic is enough to evoke nausea, vomiting, or both (2). These side effects can be sufficiently severe that they induce patients to withdraw from treatment (3); to understand their source and to alleviate them is a matter of clinical importance. The aim of this study was to explore the viability of a simple behavioral procedure (latent inhibition) as a technique for alleviating the side effects of chemotherapy.

It is now widely accepted (4–7) that anticipatory nausea and vomiting are (at least in part) a consequence of classical (or Pavlovian) conditioning, with the clinic in which treatment is given serving as the conditioned stimulus (CS) and the drug infusion as an unconditioned stimulus (US). After a number of treatment sessions, the formation of a CS-US association will mean that the complex of stimuli that constitute the clinic becomes capable of evoking a conditioned response (CR) of nausea and vomiting that is similar to the response directly evoked by the US. Support for this interpretation comes from laboratory studies of conditioning in the rat, showing that nausea can indeed function as a US and contextual cues as a CS (8,9), and from a detailed survey of the conditions in which ANV occurs showing that it obeys the standard laws of associative learning (2). Furthermore, conditioning processes may also contribute to the intensity of posttreatment nausea (PN). If the clinic becomes a CS capable of eliciting some degree of nausea, this CR could summate with the direct effects of drug infusion (the unconditioned response, UR), producing an enhanced net response (10).

What follows from this interpretation is that a procedure that restricts the development or expression of a CS-US association should alleviate the unwanted side effects of chemotherapy treatments and might be developed as an intervention for use in the clinic. One possibility is provided by the phenomenon of latent inhibition (9): the observation that pre-exposure to the event to be used as the CS reduces the readiness with which classical conditioning subsequently occurs. Giving patients exposure to the clinic before the initiation of a course of treatment could limit the acquisition of the context-nausea association and thus attenuate AN and the enhancement of PN. However, before advocating this proposal with any confidence, it is necessary to investigate two possible problems.

First, although the latent inhibition effect is very well established in experimental studies of conditioning with laboratory animals, the position for humans is less clear (11). Latent inhibition can certainly be obtained with humans, but

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the pre-exposed event has usually been a discrete stimulus, and it has often been found necessary to give the pre-exposure when the subjects are engaged in some other (masking) task (12). Therefore, we need direct evidence that simple exposure to a set of contextual cues will generate the effect in people. Second, latent inhibition is best obtained after extensive exposure to the to-be-conditioned stimulus. However, prolonged pre-exposure to the context would not be practical in the clinical setting, and accordingly, we need to determine whether the effect can be obtained with just one or a few pre-exposure sessions.

This last point raises a further issue. Experiments with laboratory rats by Fanselow (13) and Kiernan and Westbrook (14) have shown that very brief pre-exposure to the CS may not simply fail to generate latent inhibition; rather, it may actually produce the opposite effect: an enhancement of conditioning. This outcome has been attributed to a form of perceptual learning, referred to as *unitization*, which is particularly likely to occur with complex, multifaceted stimuli (15). With extended pre-exposure, unitization will give way to latent inhibition, but this finding raises the alarming possibility that brief pre-exposure to a complex set of contextual cues (such as those that define a clinic) might make matters worse rather than better. Clearly it is necessary to determine that the sort of exposure durations that might be used in the clinical setting do not fall into the range that generates the unitization effect.

These various considerations make it premature to move directly to a study of the latent inhibition procedure in the chemotherapy clinic. What is needed is an experimental study in which volunteer subjects can be exposed to a relatively mild and harmless nausea-inducing procedure in a distinctive context. The motion-sickness paradigm as used by Klosterhalfen et al. (16) is ideal for these purposes. Susceptible healthy volunteers, when given experience of a rotation-chair, reliably develop nausea, the severity of which can be measured according to well-established standard procedures. Previous work has demonstrated that rotation can serve as an effective US for classic conditioning of a taste aversion (16); and the observation (17) of elevated ratings of nausea in anticipation of rotation after a first experience 2 days earlier is consistent with the suggestion that contextual cues associated with the experience can come to serve as CSs. As was shown before, this may affect not only affect subjective and behavioral measures of nausea but eventually also endocrine and immunological correlates of nausea and acute stress (2,7,10,16,17).

Among the many biological indicators of rotation-induced nausea, release of stress hormones has been shown to be consistently increased under clinical and experimental conditions (18,19); other hormones such as vasopressin (20) known to be associated with severe motion sickness (18) are less responsive in psychophysiological experiments, eg, in anticipation to a motion procedure, where subtle stimuli may be insufficient to trigger its release (16). In addition, nausea is a frequent symptom of severe illness and infection (21); hence, inducing nausea experimentally may activate defense actions of the body's immune system, which would lead to increases of cytokines such as tumor necrosis factor α (TNF-α) and interleukin-6 (22). We therefore included the assessment of the stress hormone cortisol and the immunologic response of TNF-α in the analysis.

Finally, we wished to study gender differences in nausea susceptibility and for learning, because it had been shown before that women show normal susceptibility to motion but respond with a higher symptom rating than men (25–27). Gender differences are also well established for a variety of animal learning paradigms, whereas data on humans are inconclusive: significant gender effects have been seen for PN, and usually women respond more strongly with nausea (28–30).

METHODS

The study was conducted at the Institute of Medical Psychology, University Hospitals Düsseldorf, Germany. The protocol for both the screening procedure and the latent inhibition study had been approved by the Ethical Board of the Medical Faculty of the Heinrich-Heine University Düsseldorf, Germany, and all subjects had given written informed consent before participation. All tests and recordings were performed by one (female) investigator (S.Ke.), and subjects were instructed to keep their diet and other conditions as stable as possible during the week.

Screening of Subjects

A screening test to identify subjects susceptible to developing nausea during a body rotation procedure has been described previously for a Pavlovian conditioning study (16). In short, subjects seated in a conventional rotation chair were rotated around their vertical axis at a constant speed of 120°/s, and for 5 × 1 minute with 1-minute interruptions, while they were instructed by tape to move their heads up and down every 6 seconds in a nodding motion, with their eyes closed. Subjects tolerating less then the full length of 5 minutes of rotation and asking for premature termination because of the occurrence of nausea symptoms were recruited for the present study.

Twenty-four subjects (12:12 males:females; 25.1 [19–34] years; 175.7 ± 7.6 cm height; 70.9 ± 10.6 kg weight; 22.9 ± 2.9 BMI; nonsmokers) fulfilling the susceptibility criteria were recruited for the present study; selection was based on availability only. They were randomly assigned to one of three groups, but randomization was balanced for gender and rotation tolerance during screening.

Experimental Design

All subjects had to come to the laboratory on 5 consecutive days, and always at the same hour of the day. All investigations were performed in the morning between 8:00 and 12:00 hours, and subjects were instructed to fast for 12 hours before arrival but could drink noncaloric drinks ad libitum. Blood glucose sticks were used to control for compliance to the fasting instructions.

As can be seen in Figure 1, subjects in group 0 (control, no pre-exposure) were brought into a neutral environment (office room) on days 1 to 3, where they remained for approximately 60 minutes for baseline assessments. Subjects of group 1 (one pre-exposure on day 3) stayed in the neutral room on days 1 and 2 but were seated in a rotation chair different from the one for the screening procedure, and baseline assessments were made but without a rotation performed. Subjects in group 3 (3-fold pre-exposure) were seated in the rotation chair on days 1 to 3 for baseline assessment, again without rotation.

On day 3 (at least 1 hour after pre-exposure or the control treatment) and at the same time on days 4 and 5, subjects were seated in the rotation chair again and were rotated as described below, except on day 5, where they expected to be rotated again but were not. Before, during, and after rotation, and before expected rotation, assessments were collected as described below; they lasted approximately 60 minutes.

		Day 1 Monday	Day 2 Tuesday	Day 3 Wednesday	Day 3 Wednesday	Day 4 Thursday	Days 5 Friday
Group 0	n=8	neutral	neutral	neutral	rotation	rotation	baseline
Group 1	n=8	neutral	neutral	rotation chair	rotation	rotation	baseline
Group 3	n=8	rotation chair	rotation chair	rotation chair	rotation	rotation	baseline

Figure 1. Experimental design of the study on latent inhibition (LI). Subjects were investigated on 5 consecutive days. Pre-exposure was on 1 day (group 1) or on 3 days (group 3) in the rotation chair (but without rotation), or in a neutral environment on all three occasions (group 0). On days 3 and 4, all subjects were rotated in the chair; on day 5, all subjects were seated in the rotation chair but not rotated.

Rotation Procedure

Rotation was performed similar to the screening procedure but in a different chair in a different room, as previously described (17). The chair was rotated 5 ± 1 minute at the speed of 120°/s while the subjects were instructed to bend their heads every 6 seconds with their eyes closed. Subjects could terminate each rotation sequence on request but were asked to continue after a break of 1 minute; the tolerated rotation times were added to produce a total rotation tolerance (RT, in seconds).

Baseline and Test Assessments

Before the first session, usually during recruitment, subjects had to fill out a motion sickness susceptibility questionnaire (MSSQ) translated into German from a published and validated instrument (29) and used here for the first time.

At days 1 to 3 (pre-exposure and control) and at days 3 to 5 (rotation and presumed rotation), a sequence of assessments were performed in a standardized fashion.

This included the rating of nausea-associated symptoms (SR) on a 7-item symptom scale (vertigo, headache, nausea, urge to vomit, tiredness, sweating, stomach awareness) between 0 (not present) and 5 (very strong) that had been used previously (16). SR was performed at the beginning, immediately after the end of each rotation/control seating, and 15 and 30 minutes later.

At the same times as recording the SR (except during the rotation sequences, but in this case immediately afterward), saliva samples were taken. Four hundred microliters of saliva were immediately pipetted in 2-ml Eppendorf caps, centrifuged for 5 minutes at 3000 rpm, and stored at −80°C for later TNF-α analyses following a protocol previously described (7); 1000 μl saliva was pipetted in salivettes (Sarstedt, Nuremberg, Germany), stored at −20°C, and centrifuged for 5 minutes at 2000 rpm before salivary free cortisol analyses as described previously (31).

Statistics

A symptom score was computed as the sum of all symptom ratings at each time point; thus, a minimum of 0 and a maximum of 35 points could be scored. For the five ratings immediately after each rotation procedure, the maximum of all five was used as the rotation SR. The maximum of the two ratings 15 and 30 minutes after rotation was used as the postrotation rating.

For the analysis of cortisol data, rotation-induced changes from baseline rather then raw values were used, because cortisol decreases significantly during the day from morning peak values without stress, but this varies between subjects. In contrast, TNF-α levels are much more stable without stimulation and do allow the analysis of raw data.

To assess comparability of conditions between groups, all baseline measures on day 1 were first compared between groups by single-factor analysis of variance (ANOVA).

To test the main hypothesis (anticipatory responses), data were then analyzed by single measure ANOVAs (baseline SR, cortisol, and TNF-α levels on day 5) with the between-factors "group" (0, 1, 3) and "gender" (males, females).

To test the secondary hypothesis that pre-exposure would also affect postrotation responses, responses to rotation on days 3 and 4 were analyzed by multivariate repeated ANOVAS with within-factors "stress" (before and after rotation, 2 to 4 repeated measures depending on the measurement variable), and "time" (day 3 and 4) with the between factors "group" (0, 1, 3) and "gender" (males, females).

Post hoc analysis included paired and unpaired *t*-tests, when appropriate. A significance level was set at 5% for all tests. All analyses were performed with the SPSS (Version 11) software package on a personal computer.

RESULTS

Baseline Measures

At baseline (day 1, before all exposure procedures), no group differences were found for any of the following dependent variables: MSSQ, SR, and cortisol. A higher baseline value of TNF-α was found for group 0 (control; effect of group: $F[2,23] = 3.76$; $p = .041$). Consequently, baseline TNF-α values were used as covariates in the analysis of TNF-α for subsequent analyses.

Anticipatory Nausea

As can be seen in Figure 2, pre-exposure to the environment associated with a nauseogenic stimulus significantly reduced the SR before expected rotation on day 5, when rotation had been experienced before (days 3 and 4). This AN was reduced in groups 1 and 3 compared with group 0 (main effect of group: $F[2,23] = 4.093$; $p = .034$).

Post hoc testing showed that the effect was stronger in group 1 (one pre-exposure) than in group 3 (three pre-exposures), but the difference did not reach significant levels.

Women tended to have higher SR than men (main effect of gender: $F[1,23] = 3.949$; $p = .062$), but the effect did not reach significant levels.

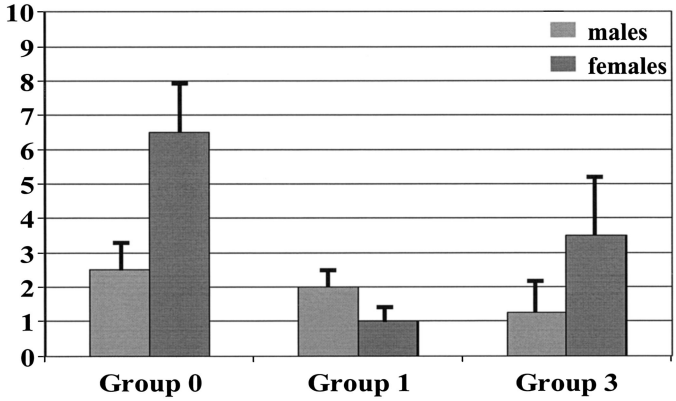

Figure 2. Baseline symptom rating (mean ± SEM) in groups 0, 1, and 3 by gender on day 5. Independent effects of group and gender ($F = 3.356$; $p = .082$; and $F = 3.478$; $p = .051$, respectively) were observed for AN.

Baseline cortisol and TNF-α levels on day 5 were not affected by the factor "group" (data not shown).

Rotation and Postrotation Nausea

Symptom rating on days 3 and 4 (before, during, and after rotation) was unaffected by pre-exposure (groups 1 and 3 vs. group 0); SR increased in all groups significantly with rotation (main effect of rotation: $F[2,23] = 45.4$; $p < .001$). RT was also not affected by pre-exposure (Table 1).

Baseline cortisol levels rose significantly from day 3 (first rotation) to day 4 irrespective of pretreatment (main effect of days: $F[2,23] = 10.66$; $p = .001$).

Cortisol increased with rotation in all subjects and under all conditions (ANOVA, main effect of rotation: $F[1,23] = 29.22$; $p < .001$). As can be seen in Figure 3, rotation-induced increases on days 3 and 4 were significantly affected by days and gender (main effect of days: $F[1,23] = 8.02$; $p = .01$; days $\times$ rotation: $F[1,1,23] = 7.06$; $p = .015$; rotation $\times$ gender: $F[1,1,23] = 6.07$; $p = .018$): the effect was stronger on day 3 compared with day 4, and women responded to rotation with lower increases than men, irrespective of the day.

Figure 4 shows that TNF-α decreased with acute rotation in all groups but was lower on day 4 compared with day 3 and in women compared with men. It was also higher in group 0 (no pre-exposure) compared with both pre-exposure groups: main effects of group ($F[2,23] = 6.68$; $p = .006$), of day ($F[1,23] = 4.89$; $p = .04$), and of rotation ($F[1,23] = 22.31$; $p < .001$). When these effects were adjusted for baseline values, all effects except the rotation induced TNF-α reduction were no longer significant (main effect of rotation: $F[1,23] = 4.49$; $p = .048$; Figure 4).

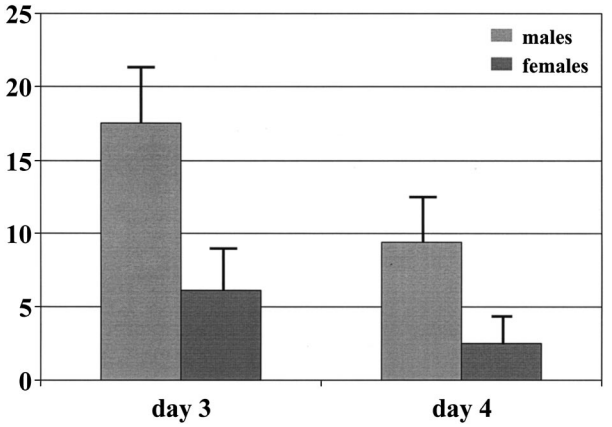

Figure 3. Rotation-induced cortisol increases (μmol/l, mean $\pm$ SEM) by gender on days 3 and 4. Cortisol rose in all subjects on both days (main effects of rotation: $F = 29.22$; $p < .001$), but the effect also depended on days and gender (main effect of days: $F = 8.02$; $p = .01$; days $\times$ rotation: $F = 7.06$; $p = .015$; rotation $\times$ gender: $F = 6.07$; $p = .018$).

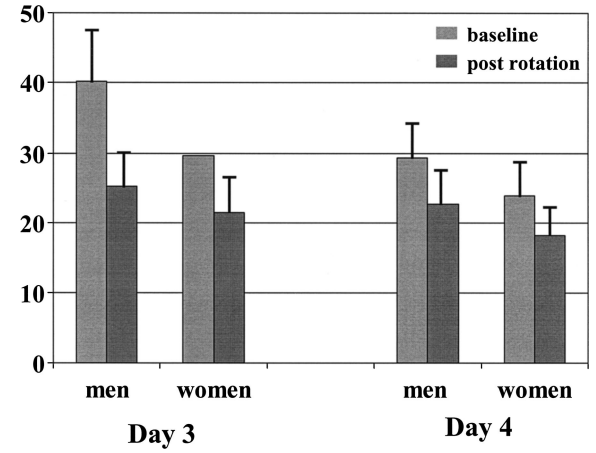

Figure 4. Baseline and postrotation TNF-α values (μmol/l, mean $\pm$ SEM) by gender on days 3 and 4. The rotation-induced decrease was significant (main effect of rotation: $F = 4.49$; $p = .048$), whereas apparent gender and day effects were not significant any longer when controlled for baseline differences.

DISCUSSION

This experiment has shown that subjects who have experienced nausea-inducing rotation in a given context report symptoms of nausea (in the absence of rotation) when they return to that context. This was seen with subjective, nausea-associated symptoms, but also with objective measures of rotation-induced stress such as saliva cortisol levels.

The occurrence of this anticipatory nausea is consistent with a classical conditioning analysis: rotation constitutes a US and the contextual cues a CS, and the formation of an association between them allows the CS to evoke a CR that

TABLE 1. Rotation and Postrotation Nausea (SR) and Rotation Tolerance (RT) (in Seconds) on Days 3 and 4 (Mean + SEM)*

		Groups		
		0	1	3
Day 3	SR baseline	3.75 + 1.1	2.13 + 0.58	1.88 + 0.74
	SR max	16.5 + 2.16	16.5 + 1.25	15.75 + 1.61
	SR post	7.25 + 1.25	8.85 + 1.59	5.75 + 0.70
	RT	126 + 17	98 + 9	129 + 27
Day 4	SR baseline	4.5 + 1.61	2.13 + 0.48	2.63 + 1.08
	SR max	17.75 + 2.04	15.63 + 1.56	18.5 + 1.69
	SR post	6.31 + 1.36	6.88 + 1.68	4.88 + 0.7
	RT	130 + 22	87 + 16	112 + 21

*None of the differences was significant.

has some of the properties of the UR evoked by US. The question of central interest was whether the magnitude of this CR might be reduced by giving subjects pre-exposure to the context (latent inhibition training) before experience of rotation. The results obtained demonstrate the existence of such an effect: ratings of nausea symptoms were reduced for subjects given pre-exposure. This reduction was somewhat more marked for female than for male subjects, and for subjects given one pre-exposure as opposed to three, but it was present in all cases. That a latent inhibition effect can be found with just a single pre-exposure is of particular significance. If the latent inhibition procedure is to be used in a clinical setting, practical considerations preclude the possibility of giving prolonged pre-exposure; but to use very brief pre-exposure entails the risk that unitization might occur and, consequently, an enhancement rather than an attenuation of the anticipatory CR. It is encouraging, therefore, to note that in the present procedure, even a single pre-exposure was effective in producing latent inhibition.

Because our experimental protocol involved two sessions of rotation, our results also provided information about how the direct effects produced by rotation might change with experience. We observed changes from the first session to the second both in the physiological measures (levels of cortisol and TNF-α) and on a behavioral measure (rotation tolerance). That the subjects were less tolerant of rotation in the second session than in the first suggests that its nausea-inducing effect had been enhanced. (As was noted in the Introduction, the severity of PNV produced by chemotherapy also tends to increase over successive sessions.) One possible interpretation of this change over trials is that the first trial allows conditioning to occur, so that the response evoked on the second trial is a composite of the UR to rotation and the CR conditioned to the contextual cues. A direct implication of this account is that the pre-exposure procedure, which, we have argued, attenuates the development of the CR, should also attenuate the enhancement of the direct response to rotation. Our results failed to show any such effect—the pattern of responding was much the same in pre-exposed and in control subjects—leading to the conclusion that the changes in the response to rotation observed here must have some source other than (or in addition to) conditioning effects.

Anticipatory, conditioned responses were seen not only with nausea-associated symptoms (on day 5) but also with objective measures such as the saliva cortisol after a first rotation on day 3. This may indicate that conditioned hormone release may have occurred after a single experience of a stressful, nausea-inducing body rotation, and re-exposure to the nausea-associated environment. This has not been observed previously with similar procedures (16).

However, the relationship between nausea symptoms and hormone levels may be more complex. It has been shown that nausea intensity is inversely related to the level of (urinary) cortisol before chemotherapy in cancer patients, in that patients with high nighttime cortisol levels respond with less nausea during and after chemotherapy injection (19). These authors argue that this phenomenon may be a consequence of the direct antiemetic effects of cortisol, or a blocking of the ability of the emetic drug to cross the blood-brain barrier, or a metabolic effect of cortisol on the serotoninergic pathway via its anti-inflammatory properties (30,32). In any case, the underlying physiological mechanism of cortisol release may act via a feedback loop to limit the nauseogenic action of the drug. In our study, therefore, the anticipatory increases of baseline cortisol may reflect a conditioned, compensatory mechanism that acts to prevent or reduce the rotation-induced cortisol increase. This interpretation would also fit data from a previous experiment (17), in which we had observed not only increased anticipatory nausea ratings but also a negative correlation of nausea experience on day 1 with baseline levels of adrenocorticotrophic hormone on day 2, similar to the observation by Fredrikson et al. (19).

The fact that TNF-α did not show a conditioned (anticipatory) response with repetitive rotation pre-exposure on day 5 is indicative of the fact that this response is mediated in quite a different way. Proinflammatory immunological mediators of an acute infection such as the cytokines TNF-α and interleukin-6 usually respond to (chronic) stress exposure with downregulation, especially in the absence of an acute inflammation (33); this is consistent with the decrease observed here on days 3 and 4 after repetitive exposure to rotation. It serves to prevent illness behavior (upregulation of temperature, downregulation of appetite, and so forth) from occurring in an acute stress situation without life-threatening or health-threatening circumstances (34). Hence, a conditioned response would have to overcome this downregulation and would induce signs and symptoms of acute inflammation. Probably, the rotation stress applied here was insufficient to allow acquisition of such a CR with only two pairings of the stressor with environmental cues, when other (immunological) signs of an acute infection are absent.

A second aspect of the results requires further comment: the higher responsiveness of women compared with men, both for conditioning of (anticipatory) nausea and for its latent inhibition. Two mechanisms may account for this: a higher susceptibility to motion and to the development of motion sickness in women, and/or a higher competence of women for learning (acquisition and inhibition) compared with men. The first aspect has been extensively discussed in the past, and it has been shown that women show normal susceptibility to motion but respond with higher SR than men (23–25); this can only partially explain our findings. With regard to learning, sex differences have been well established for a variety of animal learning paradigms. Data on humans are, however, inconclusive: significant gender effects have been seen for PN, and usually women respond more strongly with nausea (26–28). Data indicating gender differences in conditioned AN are both negative (35,36) and positive (37,38). However, preliminary evidence has been gathered that women are more prone to Pavlovian conditioning of sexual arousal (39), diffuse noxious inhibition of pain (40), and fear conditioning (41). Gender differences were also found for gating of auditory

evoked potentials (42), where women showed higher and faster responsiveness. Finally, higher placebo responses were shown to a CS evoking coughs in women compared with men; at the same time, women habituated faster to the US (43). The underlying mechanism for these gender differences in learning remain to be studied but requires specific attention to the contribution of gender effects in the design of learning experiments in the future; this is specifically true for behavioral interventions using Pavlovian conditioning paradigms, such as latent inhibition and overshadowing.

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