Latent inhibition reduces nocebo nausea, even without deception

V.F.Quinn (PhD), E.J.Livesey (PhD) & B.Colagiuri (PhD)

The University of Sydney, School of Psychology, Australia

Running head: Latent inhibition in nocebo nausea

Corresponding author:

Ms Veronica Quinn
School of Psychology, A18
The University of Sydney
NSW 2006, Australia.
T +61 430501250
E vqui6056@uni.sydney.edu.au

Acknowledgements

V.F.Quinn was supported by an Australian Postgraduate Research Award. B. Colagiuri was supported by an Australian Research Council Discovery Early Career Research Award (DE160100864).

COI and Ethical Adherence

The authors have no conflicts of interest to declare. Ethical standards set out by the declaration of Helsinki were adhered to. The project received ethical approval from the University of Sydney Human Research Ethics Committee, and all participants provided informed consent and were advised they could withdraw from the study at any time without repercussion.

Abstract

Background: Nocebo nausea is a debilitating and prevalent side effect that can develop after conditioning occurs between cues present in the treatment context and the experience of nausea. Interventions that retard conditioning may therefore be able to reduce nocebo nausea.

Purpose: To test whether 'latent inhibition', where pre-exposing cues in the absence of an outcome retards subsequent learning about those cues, could reduce nocebo nausea in healthy adults.

Methods: We examined this possibility using a Galvanic Vestibular Stimulation (GVS) model of nausea in healthy participants, with pre-exposure to the treatment cues achieved using a placebo version of GVS.

Results: In Experiment 1 we found clear evidence of conditioned nocebo nausea that was eradicated by latent inhibition following pre-exposure to placebo stimulation. Experiment 2 tested whether deception, which may be unethical in clinical settings, was necessary to produce latent inhibition by including an open pre-exposure group informed they were pre-exposed to placebo stimulation. Experiment 2 replicated the latent inhibition effect on nocebo nausea following deceptive pre-exposure from Experiment 1 and found that open pre-exposure was just as effective for reducing nocebo nausea. In both experiments, there was an interesting discrepancy found in expectancy ratings whereby expectations appeared to drive the development of conditioned nocebo nausea, but were not responsible for its retardation through latent inhibition.

Conclusions: These findings have significant clinical implications. Applying open pre-exposure in clinical settings may effectively and ethically reduce the development of nocebo effects for nausea and other conditions via latent inhibition.

Key words: Placebo, Nocebo, Nausea, Conditioning, Latent Inhibition

Latent inhibition reduces nocebo nausea, even without deception

Nausea is a pervasive problem in both clinical (e.g. chemotherapy, anaesthesia) and non-clinical settings (e.g. aviation, maritime). In its extreme, it impairs quality of life (1-3) and can lead to malnutrition and food aversions (4). Even in its moderate form, it is inherently unpleasant and can interfere with daily functioning. Importantly, evidence indicates that non-pharmacological factors can significantly contribute to nausea via the nocebo effect (see 5, 6 for reviews). Yet, there have been surprisingly few attempts to date to develop interventions to reduce nocebo nausea.

The nocebo effect is when treatment cues, in and of themselves, lead to adverse outcomes, and has been used to explain why so-called 'non-specific' side effects occur in many patients, i.e. adverse effects which are not a direct result of the pharmacological action of a drug (7). Classical conditioning is a key source of the nocebo effect (8). In the case of nocebo nausea, cues signaling treatment, for example the sensations of injection or ingesting a pill, can become associated with a nauseating agent such that these cues themselves become capable of eliciting nausea. A number of laboratory studies clearly demonstrate the contribution of conditioning to nocebo nausea. For example, it has been found that if an oral stimulus (a Listerine strip) is paired with rotation-induced nausea then this oral stimulus subsequently enhances nausea (9), and that re-exposure to placebo galvanic stimulation after nauseating galvanic stimulation leads to nocebo nausea (10). Furthermore, the contribution of conditioning to nocebo nausea is not confined to the laboratory. Patients receiving chemotherapy can experience increased nausea as a function of the number of treatment cycles, and treatment cues previously paired with nausea can give rise to nausea even before the chemotherapeutic agent has been delivered (see 11 for a

review).

Given the role of conditioning in the development of nocebo nausea, any intervention that impairs conditioning should inhibit nocebo nausea. Latent inhibition is one such procedure. It is the learning phenomenon whereby pre-exposure to a cue in the absence of any outcome impairs future learning about that cue. For example presenting a light alone before pairing it with a shock increases the time it takes an animal to learn the light-shock pairing (12). Latent inhibition is a well-documented and robust effect in non-human animals, having been observed for a wide range of cues and outcomes (for a review, see 13). Interestingly, this includes animal nausea conditioning studies in which cue pre-exposure to a to-be-conditioned cue has been found to reduce conditioned taste (e.g. 14) and place aversions (15). While the exact mechanisms of latent inhibition continue to be debated, it has been suggested that the initial unreinforced pre-exposure of a cue reduces its novelty or salience. This is proposed to lead the organism to direct less attention towards it when it is later encountered, hence reducing the extent of conditioning when it is subsequently reinforced (16).

To date, only two studies have examined whether latent inhibition can reduce conditioned nausea in humans, both of which involved pre-exposing healthy participants to a rotation chair prior to their experience of nauseating rotation. These studies tested the hypothesis that the pre-exposure to the chair would inhibit the participants learning to associate the chair with nausea when they were later rotated in it. The first study found evidence that pre-exposing healthy participants to a the rotation context may have reduced anticipatory nausea, i.e. nausea when the participants were placed in the rotation context but not rotated (17). Conversely, the second also using rotation found evidence that pre-exposure may have actually

facilitated the development of anticipatory nausea (18).

However, these two abovementioned studies have some potentially important limitations. First, both lacked "no conditioning" controls. In the absence of direct evidence that this paradigm would ordinarily lead to conditioned nausea compared with no conditioning, it is difficult to determine whether the addition of pre-exposure retarded conditioning via latent inhibition. Second, the studies focused on pre-exposing environmental cues to reduce nocebo nausea in the anticipatory period. Indeed, neither study found that pre-exposure reduced nausea in response to actual rotation (i.e. 'reactive' nausea). This limited focus is consistent with the historical emphasis in this area on anticipatory nausea (e.g. 11, 19, 20), which may be because anticipatory nausea is easier to isolate from toxicity-induced nausea than its reactive counterpart as it occurs before treatment has been administered. However, there are at least three reasons that nocebo factors may be *more* important in reactive nausea: a) the reactive period involves all cues that could be conditioned, whereas the anticipatory period necessarily involves fewer cues because it occurs *before* treatment, b) the cues specific to the reactive period may be more salient, as they are often more distinctive and tactile (e.g. infusion apparatus) than environmental cues present during both anticipatory and reactive periods, and c) the reactive cues are also more likely to be cognitively associated with nausea, since patients will know that they are the vehicle for the nauseating agent. All of these factors are known to facilitate conditioning, and may diminish or even prevent learning about less salient (e.g. environmental) cues (21). Third and related, the use of rotation chairs is limiting because there is no "placebo" setting in which the nocebo cues can be presented in the absence of the unconditioned stimulus that produces nausea. This means that every time a participant is rotated, their reactive response is a combination of the

unconditioned and conditioned nauseous response, which prevents a pure test of nocebo nausea.

The current study therefore tested whether pre-exposure could reduce nocebo nausea via latent inhibition using a new model of nocebo nausea based on Galvanic Vestibular Stimulation (GVS) that we recently developed (10). Through mild stimulation of the vestibular system, GVS causes a mismatch between visual and vestibular cues that produces nausea in most healthy adults. GVS is ideal because it has both 'active' and 'placebo' settings. This allows pre-exposure of cues normally specific to the reactive period and provides a critical test of the pure conditioned nocebo nausea in the reactive period, without the nauseating agent, but with all treatment cues present. Given that the applicability of any such intervention to applied settings rests on its ethicality, Experiment 2 also tested whether the latent inhibition effect required deception, which to our knowledge has never previously been tested. In another novel extension of previous studies of nocebo nausea, participants' expectancies were also assessed throughout to determine the extent that they predicted nocebo nausea and whether it was sensitive to latent inhibition.

Experiment 1

Experiment 1 first aimed to establish whether latent inhibition could reduce anticipatory and/or reactive nocebo nausea, with the appropriate control. Specifically, it tested whether participants who were pre-exposed to placebo GVS (group PreX) would experience less nocebo nausea than those who did not (group NoPreX) and, critically, compared this with a control group who never experienced active GVS to verify that conditioning had occurred.

Method

Participants

Participants were 45 undergraduates from the University of Sydney, who were awarded partial course credit for their participation or reimbursed at a rate of AUD$15/ hour for their time. Participants had to be aged 18 or over and not suffering from a known medical condition to participate. They had an average age of 21.1 years (SD= 4.1) and 24 were female, with 8 females allocated to each group after stratification of randomization separately for each gender. The project received approval from the University of Sydney Human Research Ethics Committee.

Design

The experimental design is displayed in Table 1. The control group received no experience with active stimulation, whereas the two experimental groups experienced equivalent active stimulation during acquisition. Within the two experimental groups, the PreX group received pre-exposure prior to placebo GVS during training, whereas the NoPreX group did not. During the test phase on Day 3, all groups received placebo stimulation, and therefore any differences would be as a result of either pre-exposure or conditioning. Nausea was assessed using numerical ratings before and after stimulation.

[Table 1 about here]

Apparatus

Nausea was induced using Galvanic Vestibular Stimulation; see Quinn, MacDougall and Colagiuri (10) for a more detailed description of the apparatus. In both types of stimulation, the wave sent was a pseudorandom sum of sines signal with

peak amplitude ±4mA. The type of stimulation was set by varying whether both sides of the vestibular system received the same stimulation, termed monopolar or 'placebo' stimulation, or whether one wave was sent to one side, and the additive inverse to the other, known as bipolar or 'active' stimulation. In the former there tends to be little perception of movement, whereas there is a large motion mismatch in the latter that has been shown to lead to nausea (10, 22). During both types of stimulation the individual will experience a mild prickling or itching sensation at the electrode site, and often the perception of a metallic taste due to the incidental stimulation of taste buds (23), making them difficult to distinguish. The stimulator was attached to participants using three 10cm² electrode pads (one behind each ear over the mastoid bone, and one centered on the v5 vertebra) and copper wires.

Procedure

Participants were instructed before attending the experiment to eat a small meal approximately two hours before their session, and were assessed individually at the same time of day across three days, with no more than two days between sessions. On the first day 'pre-exposure', participants were given the cover story that the experiment was exploring the effect of vestibular stimulation on spatial awareness to reduce demand characteristics. Described in more detail previously (10), participants were told that the researchers were using galvanic stimulation to understand how experiencing motion mismatch may affect their ability to make sophisticated spatial discriminations, and that unfortunately motion sickness sometimes resulted from this stimulation. Participants then filled out a demographics questionnaire and were told that for their safety during the experiment they would also be asked to fill out a 'symptom questionnaire' which asked them to rate six nausea-related symptoms (urge to vomit, stomach awareness, nausea, headache, fatigue and dizziness) and two

unrelated symptoms on a numeric rating scale from 0= not at all to 10= severe. An expectancy question was embedded within the questionnaire, which asked participants how much they expected to experience motion sickness during the day's session (0= not at all to 10 = very much so), as well as a bogus expectancy question about their cognitive performance. The control and NoPreX groups were then informed that the day's session would be a baseline assessment of their spatial awareness, with no GVS, and completed a 25 minute computerized visual search task where they had to repeatedly find a 'T' hidden in among 'L' distractors. The PreX group were instead attached to the GVS and received 25 minutes of placebo stimulation while undertaking the same spatial task. All three groups then filled out a second symptom questionnaire.

On the second 'acquisition' day, the baseline symptom questionnaire was repeated, after which GVS was administered to all participants. The control group had placebo stimulation, whereas the two conditioning groups (NoPreX and PreX) had active stimulation. All participants did a series of bogus spatial tasks (ball toss, balance, dot-to-dot, pattern completion) as per Quinn et al. (10) until they had received 25 minutes of stimulation. These tasks were administered both to uphold the cover story, as well as enhance the perception of motion mismatch by inducing movement. After this, participants completed the post symptom questionnaire.

On the last day, 'test', all participants had the same baseline questionnaire, received placebo stimulation while undertaking the same 25 minute computerized task as on Day 1, and then had the same post questionnaire. The computerized task was used on Day 1 and 3 as being seated minimizes participants' ability to discern the difference between placebo and active stimulation. They then underwent a manipulation check which was an open response question asking them what they

thought the aims of the experiment were. They were then thanked and fully debriefed.

Analysis

A participant's nausea rating score was calculated by summing the rating of each of the six nausea-relevant symptoms.

Anticipatory nausea

First, an assessment of anticipatory nausea was performed by comparing the baseline nausea ratings between the three groups. To determine whether there were any changes across the experiment as a result of the conditioning manipulations, a mixed 3 x (2) ANOVA was undertaken comparing the three groups on their Day 1 and Day 3 baseline nausea ratings.

Reactive nausea

Provided no baseline differences were found, a participant's nauseous response score was calculated as the difference between their post and baseline nausea ratings, with a possible range from -60 to 60, and analysed in a between subjects ANOVA separately for each day.

Expectancies

Baseline (Day 1) expectancies were assessed using a between-subjects ANOVA to ensure randomization had been successful and that no baseline differences were present. Expectancies were then compared across groups using a between-subjects ANOVA separately for Day 2 and Day 3.

Manipulation check

Responses to the manipulation check "Please describe the aims of the

experiment in your own words" were coded for 0= "no mention of nausea/ motion sickness", 1= "mention of nausea/motion sickness but in its effect on spatial awareness (ie. as an independent variable rather than dependent variable), and 2= "mention of nausea/ motion sickness as some form of dependent variable". A Pearson's chi-square analysis was then undertaken comparing the frequencies of these answers across groups.

In all ANOVA for between group differences (other than those computed only to compare baseline levels), planned pairwise comparisons (where each possible pair of means is compared) were undertaken using the Tukey's Honest Significant Difference (HSD) procedure. Analysis was conducted using SPSS (V20) and results were considered statistically significant when $p < .05$.

Results

Raw baseline and post-stimulation symptom mean ratings for the three groups across the three days are reported in Table 2. Prior to analysis, three participants were excluded due to equipment failure, one withdrew consent before study completion, and one did not complete the study and was not contactable. Recruitment was continued until n=15 in each group, resulting in a final N=45 included in analyses.

[Table 2 about here]

Anticipatory nausea

There were no differences in baseline nausea ratings between groups on any of the days, indicating, as expected, no evidence of failure of randomization or anticipatory nausea (smallest p= .699). Averaged across the three groups, there was no significant difference between baseline scores on Day 1 and Day 3, η_p^2 =.053,

F(1,42)= 2.35, *p*=.133, with the means actually suggesting a reduction in baseline nauseas by Day 3, no main effect of group averaged across the two times, η_p^2 = .005, *F*(2,42)= 0.09, *p*=.909, and no interaction between them, η_p^2 =.034, *F*(2,42)= 0.73, *p*=.486.

Reactive nausea

As there were no differences in baseline ratings on any day, nauseous response scores were calculated for each day separately and are depicted in Figure 1. On the pre-exposure day (Day 1), Tukey's HSD revealed no significant differences in nauseous response scores between any group (smallest *p*=.327). During acquisition on Day 2, the NoPreX group had significantly higher nauseous response scores than the control group, η_p^2 =.417, *F*(1,42)=29.99, *p*<.001, and the PreX group, η_p^2 =.136, *F*(1,42)=6.59, *p*=.036, and that the PreX group also had significantly higher nauseous response scores than the control group, η_p^2 =.168, *F*(1,42)=8.46, *p*=.016. On test (Day 3), the NoPreX group again had significantly higher nauseous response scores than the control group, η_p^2 =.127, *F*(1,42)=6.09, *p*=.046, indicating conditioned nocebo nausea. Further, the PreX group had significantly lower nauseous response scores than the NoPreX group, η_p^2 =.138, *F*(1,42)=6.74, *p*=.034, and did not differ significantly from controls, η_p^2 <.001, *F*(1,42)=.02, *p*=.991, indicating a significant latent inhibition effect.

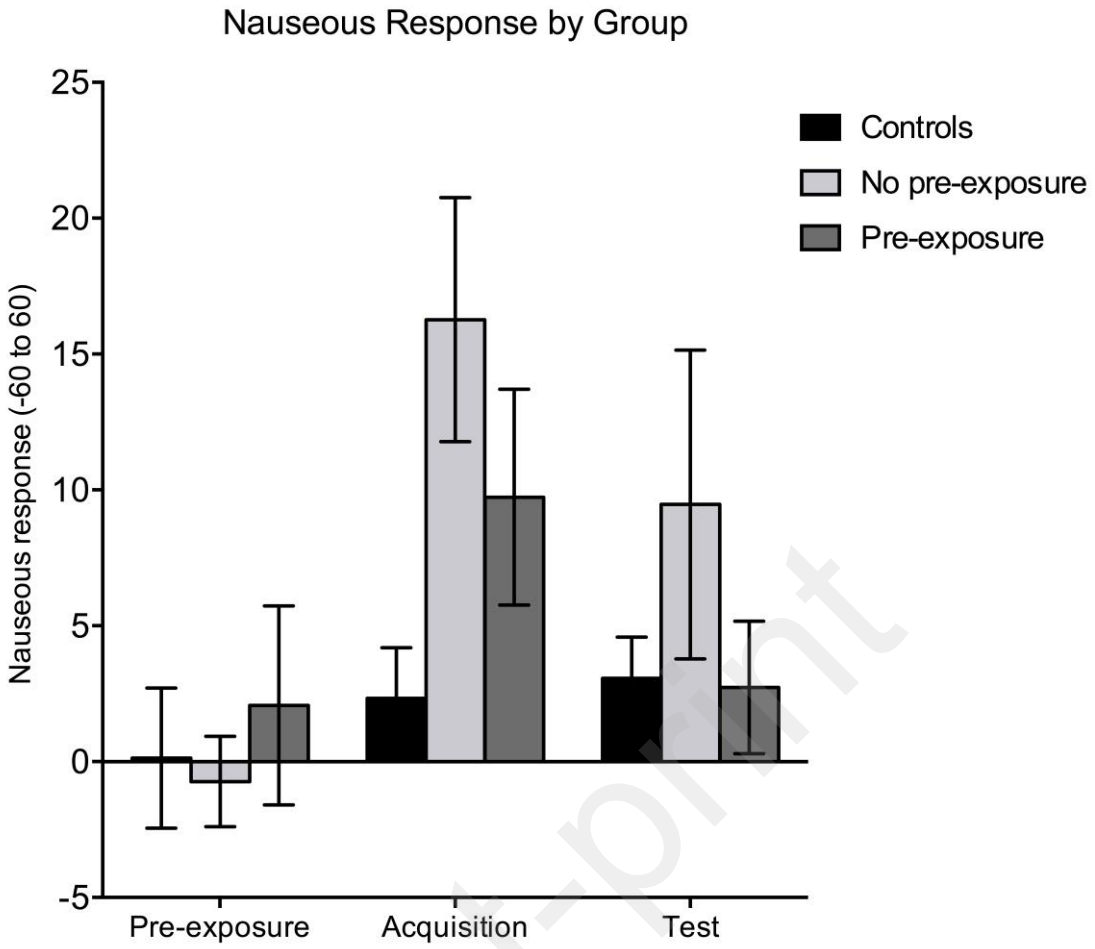

Figure 1. Mean nauseous response scores with 95%CI for the three groups during pre-exposure (Day 1), acquisition (Day 2) and test (Day 3).

Expectancies

Expectancy ratings are depicted in Figure 2. On Day 1 Tukey's HSD did not reveal any differences between groups at baseline (smallest p=.592), or on Day 2 before acquisition (smallest p=.717). On test (Day 3) the NoPreX group reported significantly higher expectancies than the control group, η_p^2 =.282, $F(1,42)$=13.72, p=.002, the PreX group reported numerically but non-significantly higher expectancies than the control group, $F(1,42)$=4.38, η_p^2 =.111, p=.103, and the NoPreX and PreX groups did not differ significantly, $F(1,42)$=2.59, η_p^2 =.069, p=.254.

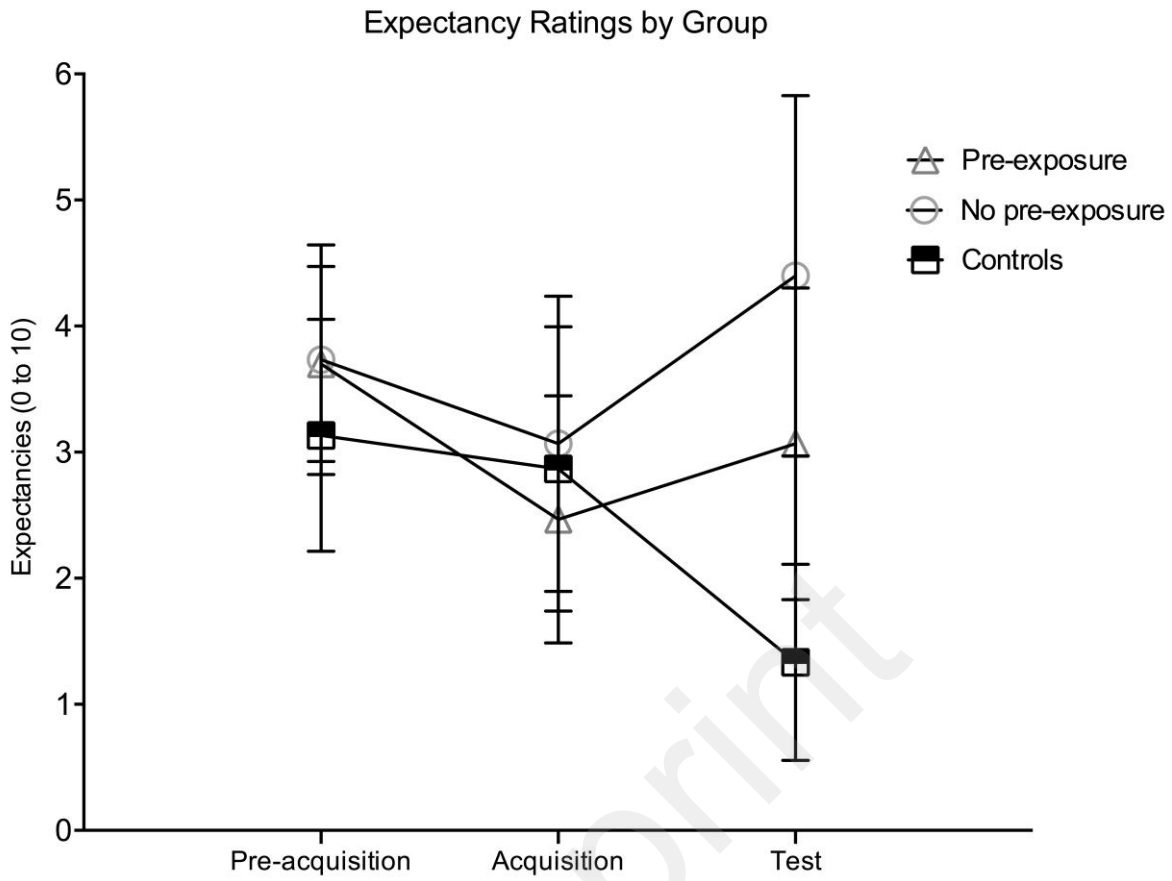

Figure 2. Mean with 95%CI expectancy ratings for the three groups prior to pre-exposure on Day 1, prior to acquisition on Day 2 and before test on Day 3.

A post hoc, exploratory regression was also undertaken to determine the extent to which expectancies actually *predicted* the nauseous response, and it was found that controlling for baseline expectancies, expectancy on Day 3 predicted a significant amount of the variance in Day 3 nauseous response score, with a one unit increase in expectancy leading to a 1.4unit higher nauseous response score, $t(42)=2.94$, $p=.005$.

Manipulation check

Of the 45 participants tested, none correctly identified nausea as the dependent variable. There were 11 participants who did mention nausea but who thought it might be an independent variable along with the experience of motion rather than

realising it was a dependent variable; 2 controls, 4 in the NoPreX group and 5 in the PreX group. The likelihood of mentioning nausea as an independent variable did not differ significantly between the groups, $\chi^2 = 1.68$, p=.430.

Discussion

Experiment 1 found clear evidence of conditioned reactive nocebo nausea and its latent inhibition through pre-exposure. On the test day on Day 3, although all groups received the placebo stimulation, the NoPreX group reported more nausea than controls, suggesting that conditioning had developed, and most interestingly, also reported more nausea than the PreX group, suggesting that pre-exposure had attenuated this effect. In fact, the latent inhibition effect was so strong that there was no evidence any nocebo nausea developed in the PreX group at all. It was also interesting to observe that the latent inhibition effect was present by the end of acquisition on Day 2. This suggests that participants were already learning about the stimuli during this acquisition session (see General Discussion for further discussion of this possibility).

On test (Day 3) those without pre-exposure reported stronger expectancies for nausea than controls, but the difference between the PreX and NoPreX groups did not reach significance. This suggests that reported expectancies were affected by conditioning, but not by latent inhibition. This may be because the expectancy question was carefully embedded within a larger questionnaire and asked about "motion sickness" rather than nausea. This was done purposefully to avoid alerting participants to nausea as a dependent variable, but it may also have reduced the conclusions that can be drawn from this question in terms of the importance of expectancies. However, taken at face value the expectancy data suggest that explicit

reasoning about the likelihood of nausea occurring may facilitate the development of conditioned nausea, but may not be as strongly involved in the retardation of this conditioning.

Experiment 1, therefore, suggests that pre-exposure to reactive cues may be able to prevent nocebo nausea from developing in clinical settings, e.g. in chemotherapy. However, this procedure concealed the real purpose of pre-exposure; an equivalent clinical application would presumably involve deceiving patients into thinking that they were actually receiving their first treatment during pre-exposure, whilst really delivering an inert agent. As a clinical treatment, this would raise serious ethical concerns. Thus it is also important to determine whether the latent inhibition effect persists when patients know the pre-exposure is pharmacologically inactive.

Experiment 2

Experiment 2, therefore, tested whether deception was required to produce latent inhibition. In Experiment 1, participants were not told that the device had two different settings, and those in the PreX group would most likely have assumed that the stimulation they received on the first day was representative of what they would receive on all three days. In Experiment 2, we included a new 'open' pre-exposure group who were informed about the two different settings of the device and explicitly told that they were receiving placebo stimulation during pre-exposure on Day 1. Such a procedure avoids any of the ethical concerns associated with standard pre-exposure.

Method

Participants

Participants were 45 undergraduates from the University of Sydney, none of

whom had participated in the first experiment, who were awarded partial course credit for their participation or reimbursed at a rate of AUD$15/ hour for their time. Participants had to be aged 18 or over and healthy to participate. They had an average age of 19.82 (SD= 3.4) and 24 were female, with 8 females allocated to each group after stratification of randomization separately for each gender. The project received approval from the University of Sydney Human Research Ethics Committee.

Design

The experimental design is displayed in Table 3. The control group was omitted as both Experiment 1 and a previous experiment in our laboratory (Quinn et al. 2015) demonstrated that placebo GVS does not unconditionally induce nausea, and therefore that any evidence of nausea in the conditioning groups reflects conditioning-induced nocebo nausea. The design included the same NoPreX and PreX groups as Experiment 1, with the addition of the Open PreX group. The Open PreX group were informed that the device has both monopolar and bipolar settings, and that participants would be receiving monopolar on Day 1 and then bipolar on the second two days. They were told that while bipolar stimulation can lead to nausea, monopolar usually does not, and that starting with monopolar stimulation usually reduces the individual's response to the bipolar stimulation they would get on the last two days (they were not provided with an explanation for how this might occur). The design still required deception with respect to Day 3 stimulation to allow an assessment of purely conditioned nausea, and so all participants on the test day were told that they were receiving bipolar stimulation, when in fact they were all receiving the placebo. But this simply served as the test of the nocebo effect.

[Table 3 about here]

Procedure

The procedure of Experiment 2 was identical to that of Experiment 1, except for the different instructions about the GVS settings, which was delivered immediately after the first baseline questionnaire.

Analysis

The analysis was the same as for Experiment 1, except that rather than pairwise comparisons, planned mutually orthogonal contrasts were conducted as these better reflected the design of Experiment 2, i.e. two latent inhibition groups versus a no-prexposure group. This first contrast compared the NoPreX group to the two pre-exposure groups (PreX and Open PreX), and the second compared the two pre-exposure groups themselves.

Results

Raw baseline and post nausea mean ratings for the three groups across the three days are reported in Table 4. Prior to analysis, two participants were excluded for insufficient English, one due to equipment failure, two withdrew consent before study completion, and one did not complete the study and was not contactable. Recruitment was continued until n=15 in each group, resulting in a final N=45 included in analyses.

[Table 4 about here]

Anticipatory nausea

As with Experiment 1, there were no differences in baseline nausea ratings between groups on any of the days, indicating, as expected, no evidence of failure of

randomization or anticipatory nausea (smallest p= .295). Averaged across the three groups baseline nausea ratings were lower on Day 3 than Day 1, η_p^2 =.244, F(1,42)= 13.57, p=.001. There was no main effect of group averaged across the two times, η_p^2 =.023, F(2,42)= 0.49,p=.619, and no interaction between them, η_p^2 =.043, F(2,42)= 0.935, p=.401.

Reactive nausea

As there were no differences in baseline ratings on any day, nauseous response scores were calculated for each day separately and are depicted in Figure 3. On Day 1 during pre-exposure, contrast analysis revealed no difference between the NoPreX and pre-exposure groups, η_p^2 =.044, F(1,42)=1.92,p=.173, but that the PreX group reported higher nauseous response scores than the Open PreX group, η_p^2 =.121, F(1,42)=5.76, p=.021. On Day 2, during acquisition the nauseous response scores were numerically lower in the two pre-exposure groups compared with the NoPreX group as in Experiment 1, but this did not quite reach statistical significance, η_p^2 =.078, F(1,42)=3.56, p=.066, and there was no difference between the two pre-exposure groups themselves, η_p^2 =.006, F(1,42)=0.24, p=.63. On Day 3 contrast analysis revealed that the two pre-exposure groups reported lower nauseous response scores than the NoPreX group F(1,42)=5.86, η_p^2 =.122, p=.020, indicating a significant latent inhibition effect. Further, there was no difference between the two pre-exposure groups, η_p^2 =.003, F(1,42)=0.11, p=.677, indicating that they were equally effective at inducing latent inhibition.

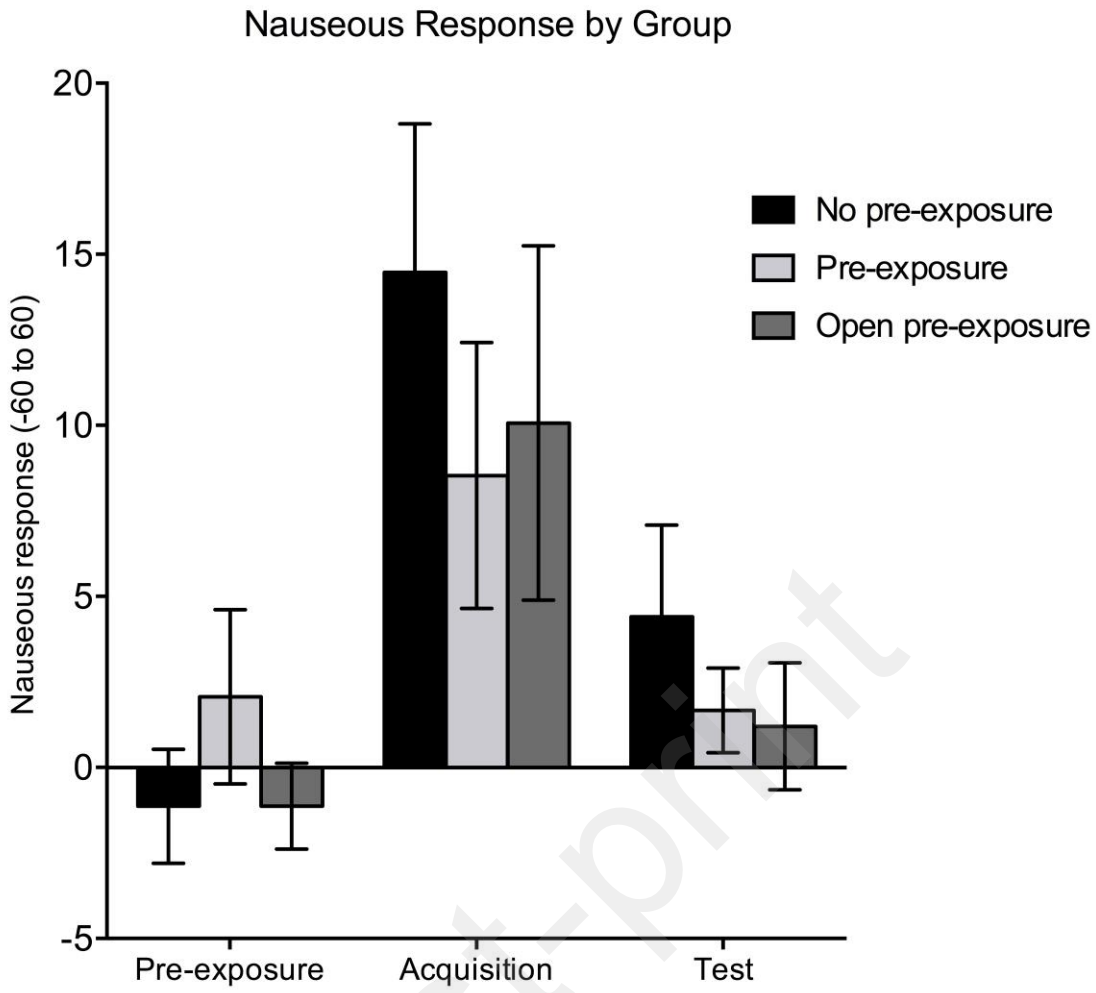

Figure 3. Mean nauseous response with 95%CI for the three groups during pre-exposure (Day 1), acquisition (Day 2) and test (Day 3).

Expectancies

Expectancy ratings are depicted in Figure 4. On Day 1 at baseline, there were no between-subject differences in reported expectancies η_p^2 =.018, $F(2,42)$= 0.38, p =.687. On Day 2, controlling for baseline expectancies, contrasts found that there was no difference between the NoPreX and two pre-exposure groups on average, η_p^2 =.032, $F(1,42)$= 1.38, p=.248, but that the Open PreX group reported numerically higher expectancies than the PreX that did not reach statistical significance, η_p^2 =.080, $F(1,42)$=3.64, p=.064. On Day 3, controlling for baseline expectancies there was no difference between the NoPreX and pre-exposure groups, η_p^2 = .004, $F(1,42)$= 0.15,

p=.70, and no difference between the two pre-exposure groups themselves, η_p^2 =.014, F(1,42)= 0.58, p=.451. A post hoc regression on the relationship between expectancies and nausea at test controlling for baseline expectancy, found that expectancies on Day 3 did not predict a significant amount of the variance in Day 3 nauseous response scores, t(42)=1.15, p=.258.

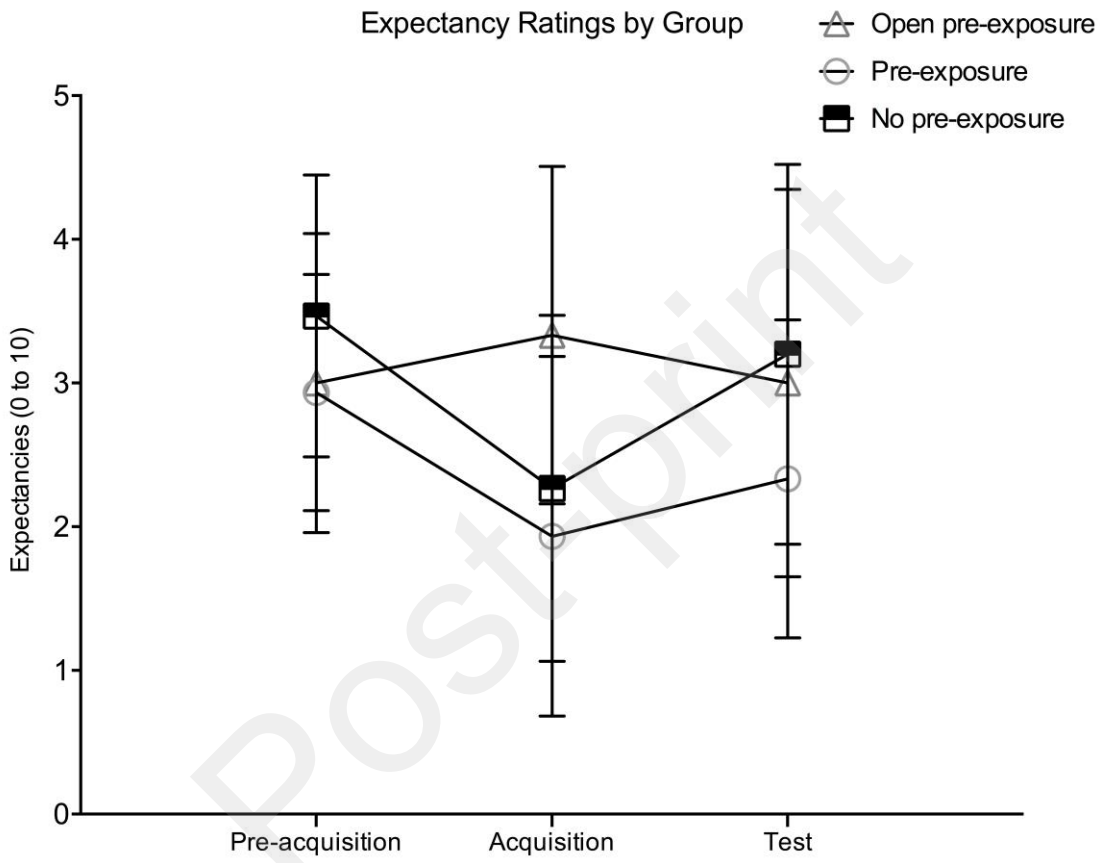

Figure 4. Mean with 95%CI expectancy ratings for the three groups prior to pre-exposure on Day 1, prior to acquisition on Day 2 and before test on Day 3.

Manipulation check

Following the criteria set out in the analysis section of Experiment 1, of the 45 participants, one participant (from the PreX group) was classified as reporting that nausea was a dependent variable. There were nine participants who mentioned nausea

but who referred to it as an independent variable that might affect spatial awareness rather than reporting it was a dependent variable; two in the NoPreX group, two in the PreX group and give in the Open PreX group. The rates of mentioning nausea as an independent variable, dependent variable or not mentioning it at all in their description of the aims did not differ significantly between the groups, $\chi^2 = 4.400, p>.250$.

Discussion

Experiment 2 replicated the latent inhibition effect of Experiment 1, finding that on average the two pre-exposure groups reported less nausea than the NoPreX group on test (Day 3). Most interestingly, informing participants that the stimulus they were pre-exposed to was not active did not reduce the efficacy of latent inhibition. This finding has significant clinical implications, as it suggests that an application of an open pre-exposure intervention in clinical settings may be able to produce a latent inhibition effect and reduce the development of nocebo nausea.

The pattern of expectancies on test in Experiment 2 again did not show latent inhibition, and in training on Day 2 the expectancies appeared to be in the opposite direction to the nausea ratings, with the Open PreX group reporting higher expectancies for nausea. Experiment 2 did not include a no-conditioning control, but these data are broadly consistent with the expectancy data from the conditioning groups in Experiment 1.

General Discussion

The two experiments presented here provide new evidence that nocebo nausea can be reduced through cue pre-exposure and critically, that deception is not required

to produce this effect. That is, latent inhibition of nocebo nausea was still observed even when individuals knew the pre-exposure was to inactive stimulation. The study, therefore, demonstrates that latent inhibition may be an effective technique to reduce nausea in both clinical and other applied settings.

In terms of applying latent inhibition procedures, it appears that reactive nausea will benefit the most. Neither experiment here showed any evidence of anticipatory nausea developing. In fact in Experiment 2 there was a significant *decrease* in nausea reporting in the anticipatory period on test relative to the beginning of the experiment. This is consistent with our previous research using this paradigm (10) as well as the prediction that anticipatory cues are less likely to be conditioned than reactive cues. This means that any attempt to use latent inhibition to reduce nocebo nausea should focus on reactive cues. In particular, pre-exposing patients to the sensations and stimuli that are usually only present while the treatment is actually being administered will be key. Critically, the fact that open pre-exposure is just as effective as standard pre-exposure ensures that such interventions can be used ethically, without impinging on patient autonomy.

The use of "open-label" placebos, where no deception is provided regarding the placebo administered is an emerging area of research. Reviewed in more detail elsewhere (8), some studies have observed placebo improvement following open-label placebo treatment, such as in reducing gastrointestinal distress (24). The current study extends this evidence by showing that an open-intervention can also inhibit development of a nocebo effect. It is worth noting that in other open-label placebo studies, the placebo treatment was accompanied by information about how placebo effects can reduce responding. This is similar to the information provided to participants in our open group regarding the potential of pre-exposure to reduce

nausea. As such, positive instructions during pre-exposure may be a necessary component of the intervention to produce symptom improvement. In the current study, it is conceivable that the symptom improvement in the open group was facilitated by a placebo effect. This explanation also predicts that the open pre-exposure group should have reported less nausea and lower expectancy for nausea than in the hidden pre-exposure group on Day 2, and so does not fully account for the observed results. Nevertheless, it may be the case that in the absence of deception, latent inhibition requires enhancement from positive instructions. Although this does not reduce the clinical applicability of our intervention, determining whether this feature of the instructions is necessary for the effect to occur is important to aid understanding of the reasoning processes that lead to latent inhibition.

In a novel extension, this study also assessed patient expectancies. Expectancies are often not directly assessed in studies of placebo and nocebo effects, but rather are just inferred from the information that participants had been provided with. The expectancy data revealed an interesting finding consistent across both experiments, where it appeared that explicit expectancies drove the development of conditioning, but not its retardation through latent inhibition. Although both of our expectancy assessments are vulnerable to methodological criticisms previously described, these data do question an account of placebo or nocebo effects that sees expectancies as entirely responsible for responding (see 25 for an example). It may be that there is a non-conscious or non-expectancy based component of the latent inhibition effect that drives the group differences observed, such as reduced attention towards the reactive cues or lower levels of anxiety due to their pre-exposure. This may also explain why the Open PreX group still experienced latent inhibition even when they knew that their experience during pre-exposure would not be predictive of

their likelihood for nausea during the experiment. Of course, one would need more sensitive indicators of learning outside awareness to claim definitively that non-conscious learning or placebo responding in the absence of expectancy occurred (26). Further, the correlation between expectancies and nauseous response on test in Experiment 1 would suggest that they play a role. However, this evidence does suggest that if they do play a role, they are likely not the only factor doing so.

The current study also has important implications for the theories of latent inhibition. There has been debate about whether it is possible to observe what has been labelled "unmasked" latent inhibition. Le Pelley and Schmidt-Hansen (27) argue that many of the human studies that have purported to observe latent inhibition are actually observing learned irrelevance, as the stimulus is not being merely pre-exposed, but is pre-exposed while the attention of participants is deliberately diverted. It has been argued that this deliberate 'masking' of the cue may be required to produce latent inhibition in humans (28), but this would make the effect inconsistent with those observed in the animal literature, where animals are free to attend to the pre-exposed stimulus, and has important implications for the mechanisms underpinning latent inhibition and associative learning more generally. The current experiments provide two examples of unmasked latent inhibition in humans, as participants were free to attend to the reactive cues during pre-exposure. This, along with another recent example of unmasked latent inhibition(29), suggests that in contrast to that which Lubow and Kaplan (28) argued, under certain conditions it is possible to observe unmasked latent inhibition in human learning.

There are some limitations to the current experiments worth noting. First, the GVS device was novel to participants, with participants unlikely to have even heard of it prior to the experiment. Although in our studies individuals were informed that

GVS could lead to nausea, given its novelty they may have held weaker beliefs that it may cause nausea than would be expected in a clinical setting with a well-known treatment (e.g. chemotherapy). One could speculate that latent inhibition would be less effective at reducing nocebo nausea in patients with more strongly held beliefs. On the other hand, it is also possible that pre-exposure may be even *more effective* in highly expectant patients as there would be larger violation of expectation. This would certainly be interesting to explore in future studies. Second, it is possible that the Open pre-exposure group realised on test (Day 3) that they were actually receiving monopolar stimulation, which then artificially produced a latent inhibition-like effect. However we screened for this during the manipulation check, and the trend towards a latent inhibition effect during acquisition in this group suggests that conditioning may already have been reduced before this. It is also important to note that the researcher was not blinded to participants' group allocation in the current study, and while the procedure was systematised to minimise any potential impact of this knowledge, it cannot be ruled out entirely. Further research is required to define the parameters of the latent inhibition effect, such as how the number and duration of pre-exposures should be configured to accommodate longer 'conditioning' or treatment sessions than the single session used in the present study.

In summary, the current study provides new evidence that pre-exposing reactive cues prior to pairing them with nausea reduces nocebo nausea, and critically that this can occur even when presented as an open intervention. Pre-exposing reactive cues may, therefore, be a novel and exciting new method of reducing maladaptive conditioning in the clinic and would be ethical in the sense that it does not require deception.

References

1. Bloechl-Daum B, Deuson RR, Mavros P, Hansen M, Herrstedt J. Delayed nausea and vomiting continue to reduce patients' Quality of Life after highly and moderately emetogenic chemotherapy despite antiemetic treatment. *J Clin Oncol.* 2006; *24:* 4472 - 4478.
2. Colagiuri B, Roscoe JA, Morrow GR, Atkins JN, Giguere JK, Colman LK. How do patient expectancies, quality of life and postchemotherapy nausea interrelate? *Cancer.* 2008; *113:* 654 - 661.
3. Hilarius DL, Kloeg PH, van der Wall E, van den Heuvel JJG, Gundy CM, Aaronson NK. Chemotherapy-induced nausea and vomiting in daily clinical practice: a community hospital-based study. *Support Care Cancer.* 2012; *20:* 107 - 117.
4. Davidson Q, Teleni L, Muller J, Ferguson M, McCarthy AL, Isenring E. Malnutrition and chemotherapy-induced nausea and vomiting: Implications for practice. *Oncol Nurs Forum.* 2012; *39:* 340 - 345.
5. Colagiuri B, Zachariae R. Patient expectancy and post-chemotherapy nausea: A meta-analysis. *Ann Behav Med.* 2010; *40:* 3 - 14.
6. Quinn VF, Colagiuri B. Placebo interventions for nausea: a systematic review. *Ann Behav Med.* 2015; *49:* 449 - 462.
7. Barsky AJ, Saintfort R, Rogers MP, Borus JF. Nonspecific medication side effects and the nocebo phenomenon. *JAMA.* 2002; *287:* 622 - 627.
8. Colagiuri B, Schenk LA, Kessler MD, Dorsey SG, Colloca L. The placebo effect: From concepts to genes. *Neuroscience.* 2015; *307:* 171 - 190.
9. Klosterhalfen S, Kellermann S, Braun S, Kowalski A, Schrauth M, Zipfel S, Enck P. Gender and the nocebo response following conditioning and expectancy. *J Psychosom Res.* 2009; *66:* 323 - 328.
10. Quinn VF, MacDougall HG, Colagiuri B. Galvanic Vestibular Stimulation: A new model of placebo-induced nausea. *J Psychosom Res.* 2015; *78:* 484 - 488.
11. Bovbjerg DH, Redd WH, Jacobsen PB, Manne SL, Taylor KL, Surbone A, Crown JP, Norton L, Gilewski TA, Hudis CA, Reichman BS, Kaufman RJ, Currie VE, Hakes TB. An experimental analysis of classically conditioned nausea during cancer chemotherapy. *Psychosom Med.* 1992; *54:* 623 - 637.
12. Lubow RE, Moore AU. Latent inhibition: The effect of nonreinforced pre-exposure to the conditional stimilus. *J Comp Physiol Psychol.* 1959; *54:* 415 - 419.
13. Lubow RE. Latent inhibition. *Psychol Bull.* 1973; *79:* 398 - 407.
14. Revusky SH, Bedarf EW. Association of illness with prior ingestion of novel foods. *Science.* 1967; *13:* 219 - 220.
15. Hall G, Symonds M. Overshadowing and latent inhibition of context aversion conditioning in the rat. *Auton Neurosci.* 2006; *129:* 42 - 49.
16. Holmes NM, Harris JA: Latent inhibition. In C. J. Mitchell and M. E. Le Pelley (eds), *Attention and associative learning: From brain to behaviour*. Oxford: Oxford University Press, 2010, 99 - 130.
17. Klosterhalfen S, Kellermann S, Stockhorst U, Wolf J, Kirschbaum C, Hall G, Enck P. Latent inhibition of rotation chair-induced nausea in healthy male and female volunteers. *Psychosom Med.* 2005; *67:* 335 - 340.
18. Hall G, Stockhorst U, Enck P, Klosterhalfen S. Overshadowing and latent inhibition in nausea-based context conditioning in humans: Theoretical and practical implications. *Q J Exp Psychol (Hove).* 2015; *69:* 1227 - 1238.
19. Andrykowski MA, Jacobsen PB, Marks E, Gorfinkle K, Hakes TB, Kaufman RJ, Currie VE, Holland JC, Redd WH. Prevalence, predictors and course of

anticipatory nausea in women receiving adjuvant chemotherapy for breast cancer. *Cancer.* 1988; *62:* 2607 - 2613.
20. Montgomery GH, Bovbjerg DH. Specific response expectancies predict anticipatory nausea during chemotherapy for breast cancer. *J Consult Clin Psychol.* 2001; *69:* 831 - 835.
21. Mackintosh NJ. Overshadowing and stimulus intensity. *Anim Learn Behav.* 1976; *4:* 186 - 192.
22. Quinn VF, Colagiuri B. Sources of placebo-induced relief from nausea: The role of instruction and conditioning. *Psychosom Med.* 2016; *78:* 365 - 372.
23. Dilda V, MacDougall HG, Curthoys IS, Moore ST. Effects of Galvanic Vestibular Stimulation on cognitive function. *Exp Brain Res.* 2012 275 - 285.
24. Kaptchuk TJ, Friedlander E, Kelley JM, Sanchez MN, Kokkotou E, Singer JP, Kowalczykowski M, Miller FG, Kirsch I, Lembo AJ. Placebos without deception: A randomized controlled trial in Irritable Bowel Syndrome. *PLoS One.* 2010; *5:* e15591.
25. Kirsch I. Response expectancy theory and application: A decennial review *Appl Prev Psychol.* 1997; *6:* 69 - 79.
26. Lovibond PF, Shanks DR. The role of awareness in Pavlovian conditioning: Empirical evidence and theoretical implications. *J Exp Psychol Anim Behav Process.* 2002; *28:* 3 - 26.
27. Le Pelley ME, Schmidt-Hansen M: Latent inhibition and learned irrelevance in human contigency learning. In R. E. Lubow and I. Weiner (eds), *Latent inhibition: Cognition, Neuroscience and Applications to Schizophrenia*. Cambridge: Cambridge University Press, 2010.
28. Lubow RE, Kaplan O. The visual search analogue of latent inhibition: Implications for theories of irrelevant stimulus processing in normal and schizophrenic groups. *Psychon Bull Rev.* 2005; *12:* 224 - 243.
29. Forrest DL, Mather M, Harris JA. Unmasking Latent Inhibition in Humans. *Q J Exp Psychol.* 2016 10.1080/17470218.17472016.11249894.

Table 1.

Design of Experiment 2 showing type of stimulation for each group across the experiment.

Group	Pre-exposure Day 1	Acquisition Day 2	Test Day 3
Control	-	Placebo	Placebo
NoPreX	-	Active	Placebo
PreX	Placebo	Active	Placebo

Table 2.

The mean (SD) nausea symptom ratings of the three groups across the three days of the experiment.

	Day 1		Day 2		Day 3	
Group	Baseline	Post	Baseline	Post	Baseline	Post
Controls (n = 15)	5.20 (4.09)	5.33 (5.90)	4.07 (5.09)	6.4 (5.78)	4.73 (5.98)	7.80 (7.12)
NoPreX (n = 15)	5.80 (6.73)	5.07 (5.55)	4.47 (4.70)	20.87 (11.57)	5.27 (4.80)	14.74 (13.48)
PreX (n = 15)	6.8 (4.39)	8.87 (5.66)	5.6 (5.74)	15.33 (7.20)	4.40 (3.33)	7.13 (4.84)

Table 3.

Design of Experiment 2 showing type of stimulation for each group across the experiment.

	Pre-exposure	Acquisition	Test
	Day 1	Day 2	Day 3
NoPrex	-	Active	Placebo
Prex	Placebo	Active	Placebo
Open PreX	Placebo	Active	Placebo

Table 4.

The mean (SD) nausea symptom ratings of the three groups across the three days of the experiment.

	Day 1		Day 2		Day 3	
Group	Baseline	Post	Baseline	Post	Baseline	Post
NoPreX (n = 15)	6.90 (8.02)	5.67 (6.52)	5.07 (5.32)	19.53 (11.64)	3.93 (4.56)	8.33 (8.40)
PreX (n = 15)	4.53 (3.56)	6.60 (6.22)	3.07 (2.94)	11.60 (8.79)	3.33 (4.50)	5.00 (4.57)
Open PreX (n = 15)	5.67 (4.97)	4.53 (4.15)	3.20 (2.78)	13.00 (9.78)	2.33 (2.97)	3.53 (3.81)