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Gender and the nocebo response following conditioning and expectancy☆

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Abstract

Objective: To investigate the role of Pavlovian conditioning and expectancy and of gender on the nocebo effects. **Methods:** Conditioning experiment: Forty-eight healthy male and female volunteers were investigated for 3 days using a standard rotation procedure. Subjects in the experimental group received a salient oral stimulus prior to rotation; subjects in the control group received the stimulus 12 h after rotations on Days 1 and 2; on Day 3, all subjects received the stimulus prior to rotation. Expectancy experiment: Another 48 healthy subjects were rotated 5×1 min once only. All subjects received the same oral stimulus immediately prior to rotation; subjects in the experimental group were told that the symptoms might worsen with the stimulus; controls did not receive additional information. In both experiments, symptom rating (SR) and rotation tolerance (RT) were determined. **Results:** Conditioning significantly reduced RT (P=.015) and increased SR (P=.024). For both RT and SR, a significant "day×group×gender" effect was found (P=.044; SR: P=.011) indicating that conditioning was more effective in women. Expectancies lowered RT (P=.085) without affecting SR. There was a significant "rotation×gender" interaction on RT (P=.005) indicating that the expectancy was more effective in men. **Conclusion:** Women responded stronger to conditioning while men responded to expectancies, but to a lesser degree. It needs to be determined whether this is restricted to nausea-specific conditions or can be generalized across clinical and experimental conditions.

Keywords: Placebo; Nocebo; Conditioning; Suggestions; Gender

Introduction

The rising placebo response (PR) in clinical trials, e.g., in psychiatry [1], pain therapy [2], and functional bowel disorders [3], has raised concerns not only about future chances to test and approve drugs for various medical indications but also about the underlying mechanisms of the PR both in clinical trials and in everyday medicine.

We [3] and others [4,5] have postulated that—beyond methodological errors resulting in "regression to the mean"—the mechanisms that underlie the PR are twofold: Pavlovian conditioning on the one hand and expectancy on the other [6], i.e., suggestions by physicians and respective expectations by the patients, that manipulate the ability to perceive symptoms and their changes in a "noisy" environment, e.g., with variable symptom intensity and frequency.

Both mechanisms have been tested and approved to exist in specific experimental and clinical conditions such as in placebo analgesia [5,7], with motor control in Parkinson's disease [8], depression [1], mania [9], and functional bowel disorders [3,10]. However, these mechanisms have not been tested for the contribution of gender, despite the fact that Pavlovian conditioning, habituation, and other learning procedures are known to be more effective in women than in men [11–13]. Gender differences in placebo analgesia

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have, however, been noted [14]. It is also unknown whether both mechanisms are effective in similar clinical (or experimental) situations, and whether their effect size is comparable. Finally, ongoing discussion [15–17] has questioned whether the nocebo response follows the same rules as the PR, but experimental data on this issue is scarce.

For clinical trials, e.g., in functional bowel disorders, only a few factors contributing to placebo such as the number of study visits and the severity of the disease have been identified [3], and gender has not been among them. This may be due to the fact that in clinical trials, the amount of conditioning and expectancy elements is usually not known and may be highly variable, as may be the number of males and females included [16].

Therefore, we investigated the relative contribution of gender in two independent experiments—one on conditioning and one on expectancy of a nocebo response—with similar procedures and in identical experimental settings. We hypothesized that both procedures would elicit nocebo responses similar in size and would not be different between men and women.

Methods

Subjects

The studies were conducted at two institutions, the Institute of Medical Psychology, University Hospitals Düsseldorf, Germany, and the Department of Psychosomatic Medicine, University Hospitals Tübingen, Germany, and by independent female experimenters (SK, SB) in 2006. The ethics boards of both institutions had approved the experimental protocols prior to the studies being performed. All subjects gave written informed consent before participation.

All subjects were healthy volunteers recruited from the students of the universities and were selected from a larger cohort screened for motion sickness susceptibility using a paper–pencil test [18]. They were all naïve to the procedures applied and were only used once in one of the experiments.

The Motion Sickness Susceptibility Questionnaire [19] used to select subjects asks for previous experience with nausea and vomiting in a number of everyday situations (riding in a car, on a boat, in a merry-go-round, etc.) during childhood and adult life and scores these on a 0-to-150 point scale. It was validated for predictability of nausea in various clinical and nonclinical conditions [19].

Rotation procedure and data recording for both experiments

All investigations were performed in the morning between 8:00 a.m. and 12:00 p.m., and subjects were instructed to fast for 12 h prior to arriving to the laboratory. Consumption of noncaloric drinks was not limited provided they did not contain caffeine. Blood glucose was measured to assess compliance with the fasting instructions.

Subjects seated in a conventional rotation chair were rotated around the yaw axis at a constant speed of 120°/s with their eyes closed, and for 5×1 min with 1-min interruptions. They were instructed by audiotape to move their heads up and down every 6 s with a pitch of approximately 90°. Subjects could terminate each rotation sequence upon request but were asked to continue after a break of 1 min; the tolerated rotation times were added to produce a total rotation tolerance (RT) time (in seconds).

Symptom ratings (SR) were collected for seven symptoms associated with motion sickness (vertigo, headache, nausea, urge to vomit, tiredness, sweating, stomach awareness) on a scale of 0 (*not present*) to 5 (*very strong*), which has been shown to be responsive to experimental interventions and to be discriminative for experimental variations in previous studies [11–13,20]. The subjects selected usually responded with nausea, but not necessarily with vomiting during rotation; however, not all responded with the same type or cluster of symptoms: some with autonomic responses—sweating, stomach awareness—while others might show more of a stress response.

SR was performed at the beginning and immediately after the end of each rotation period. A total symptom score was computed as the sum of all ratings separately for each time point. The basal SR rating and the maximal SR noted during the five rotation procedures were evaluated.

Experiment 1: Pavlovian conditioning of nausea

Forty-eight subjects (24 males and 24 females, 26.3±0.8 years) were recruited. Each subject was exposed to rotation as described above, at 3 days 1 week apart, and at the same time of the day. Subjects were randomly assigned to the experimental group (n=24) or to the control group (n=24) with an equal number of males and females in each group.

After seating in the rotation chair, subjects in the experimental group received an inert and salient oral stimulus (Cinnamon Listerine PocketPaks breath strips, Pfizer, Morris Plains, NJ, USA) as the conditioning stimulus (CS) immediately prior to the first rotation (unconditioned stimulus) on each of the 3 days. Subjects in the control group were given this stimulus in the evening of the rotation day, approximately 12 h after rotation for Days 1 and 2. On Test day 3, all subjects received the CS immediately prior to rotation, followed by a baseline SR.

Experiment 2: Expectancy of nausea

Again, 48 subjects (24 males and 24 females, 23.8±0.5 years) were recruited. Each subject was exposed to rotation as described above, but only on 1 day. Subjects were randomly assigned to the experimental group ("nocebo") and control group (each n=24), with an equal number of males and females in each group.

After seating in the rotation chair, all subjects received the same salient oral stimulus (Listerine Cinnamon) immediately