Video Article

How to Study Placebo Responses in Motion Sickness with a Rotation Chair Paradigm in Healthy Participants

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Abstract

Placebo responses occur in every medical intervention when patients or participants expect to receive an effective treatment to relieve symptoms. However, underlying mechanisms of placebo responses are not fully understood. It has repeatedly been shown that placebo responses are associated with changes in neural activity but for many conditions it is unclear whether they also affect the target organ, such as the stomach in motion sickness. Therefore, we present a methodology for the multivariate assessment of placebo responses by subjective, behavioral and objective measures in motion sickness with a rotation chair paradigm. The physiological correlate of motion sickness is a shift in gastric myoelectrical activity towards tachygastria that can be recorded with electrogastrography. The presented study applied the so-called balanced placebo design (BPD) to investigate the effects of ginger compared to placebo and the effects of expectations by verbal information. However, the study revealed no significant main or interactional effects of ginger (as a drug) or information on outcome measures but showed interactions when sex of participants and experimenters are taken into considerations. We discuss limitations of the presented study and report modifications that were used in subsequent studies demonstrating placebo responses when rotation speed was lowered. In general, future placebo studies have to identify the appropriate target organ for the studied placebo responses and to apply the specific methods to assess the physiological correlates.

Video Link

The video component of this article can be found at https://www.jove.com/video/52471/

Introduction

The overall goal of the described methodology is the multivariate assessment of placebo responses by subjective, behavioral and objective measures in motion sickness with a rotation chair paradigm in healthy participants.

Placebo effects and responses play a role in every medical intervention when patients or participants expect to get an effective treatment to relieve symptoms in everyday medical practice or in clinical trials [1]. In the latter, placebo groups are included to control for placebo effects and all unspecific effects that could occur during the study, such as the natural course of disease (spontaneous remission, fluctuation of symptoms, regression to the mean, habituation), observer and patient biases (scaling biases, social desirability, conditioned answers), or "real" placebo responses [2]. Placebo responses are symptom improvements in individuals that occur only because of patients' or participants' expectancy or learned responses to a specific treatment. While learning is multi-faceted, it is assumed that all aspects of learning result in an expectancy concerning the treatment – whether by conscious expectations or unconscious conditioned reactions [1,3].

Studies with the primary aim to investigate placebo responses have to include additional groups to control for the above mentioned unspecific effects in comparison to the pure placebo response. For example, a group with positive expectancy concerning the treatment is compared with a group with no expectancy concerning the treatment while both groups receive the same inert substance. One possible study design is the so-called balanced placebo design (**Table 1**) in which half of the participants receive the real drug and the other half receives a placebo, and half of the participants of each drug group receive the correct information and the other half receives the wrong information about the drug received. Participants will be randomly assigned to one of the four groups to assess the differential effects of the drug received and the information given in a between-groups design. Therefore, the four groups are real drug/drug information, real drug/placebo information, placebo/drug information, placebo/placebo information [4].

A further question in placebo research is whether patients or participants "only" feel better subjectively or whether there is an objectively measurable change in physiology [5,6]. Imaging studies, especially in experimental pain studies, have shown repeatedly that placebo responses are associated with changes in neural activity, *e.g.* in the somatosensory cortex [7] or in the rostral anterior cingulated cortex (rACC) that is also involved in opioid analgesia [8,9]. Therefore, it is clear that placebo responses are not only subjective response biases by participants. However,

there is the remaining question whether placebo responses also occur in the target organ such as the stomach in motion sickness. To investigate this question it is necessary not only to ask for subjective symptom reports but also to assess objective organ specific measures.

Inducing motion sickness in a rotation chair paradigm in healthy subjects is a useful and easy to establish methodology to investigate placebo responses in a multivariate way. According to the neural mismatch theory [10,11], motion sickness occurs because of a mismatch between actual and expected perceptions from different sensory systems such as the vestibular and the visual system. This mismatch leads to a series of vegetative symptoms like nausea, vertigo, sweating, or tiredness but also to changes in gastric myoelectrical activity [12,13], and can be evoked in most healthy participants depending on the strength of the stimulus [14]. We have already repeatedly employed this rotation chair paradigm to induce motion sickness to investigate mediators [15] and placebo and nocebo responses [16-18]. In this paradigm, healthy participants are seated in a rotating chair, have to wear an eye mask and earphones to reduce the ability to orientate themselves during the rotation procedure, and to move their head slowly up and down. Particularly, the head movements induce the so-called Coriolis effect, the experience of an illusionary tumbling movement that leads to symptoms of nausea [11]. Participants can be asked to rate a list of subjective symptoms that typically occur during motion sickness, behavioral measures such as the number of head movements and the total rotation time tolerated can be assessed, and gastric myoelectrical activity can be objectively recorded with electrogastrography (EGG).

To record EGG data, three cutaneous electrodes are placed on the skin above the stomach and connected to a recording device [19,20]. As myoelectrical signals of the stomach are weaker than those from the heart, it is recommended to use an active electrodes technique that amplifies signals directly at the electrodes' side before sending them to the recording device. Although the EGG is sensitive to movement artifacts by speaking or deep breathing, it provides the advantage that it is a non-invasive technique and does not affect the studied physiological reactions of the stomach. In comparison, techniques such as implanted serosal electrodes [21] or fluoroscopies [22] are more invasive and could affect the studied behavior in an unforeseen way. To analyze EGG data, the data are screened visually for artifacts and are analyzed with a time series analysis such as a Fast Fourier Transformation (FFT). A predominance of the frequency range around three cycles per min (cpm) is regarded as normal gastric activity (normogastria) and a range from 4 to 10 cpm as tachygastria. A shift from normogastria in a baseline assessment to tachygastria has repeatedly been associated with nausea induced by rotation chair or vection drum [19,23,24].

There are only a few studies that have investigated placebo responses in motion sickness by manipulating expectations only, but these have lacked successful induction of a placebo response in any outcome measure [25,26]. When participants were exposed to a motion sickness inducing stimulus after being given a placebo pill along with the information that it will either: decrease symptoms (placebo information); increase symptoms (nocebo information); or have no effect; participants who received the nocebo information reported fewer symptoms and showed less tachygastria compared to the other groups [26]. A possible explanation by the authors was that participants who were given the positive information were disappointed that they had strong symptoms although they received the drug, but participants who were given the negative information were surprised that the procedure was not as strong as they expected. In a study by our own group, only male participants who were told that an orally delivered medication would increase symptoms (nocebo effect) compared to participants who did not receive any information showed lowered rotation tolerance without an effect on symptom ratings [16].

In conclusion, placebo responses through positive information given along with a placebo treatment have not been demonstrated on motion sickness with a rotation chair paradigm, except latter studies of our own group [18] (Weimer, K., Horing, B., Klosterhalfen, S., & Enck, P., 2012). Furthermore, placebo responses have rarely been investigated with multiple outcome measures in one study. The focus of this article is, therefore, to describe a methodology to assess placebo responses in a multivariate way by subjective, behavioral and objective outcome measures in an experimental paradigm for studying motion sickness.

Protocol

Ethics statement

The study protocol was approved by the Ethical Review Board of the University Medical School Tübingen, Germany. Participants gave written informed consent prior to inclusion, and complete disclosure of the study purpose was offered to all participants after completion of the study [17].

1. Study Preparation

1. Prepare the "drugs" used: fill similar looking, tasting and smelling capsules with a) ginger powder, and b) a "placebo powder" such as starch. The capsules should be prepared and stored in a numbered envelope by a third person to keep the experimenter blind to the condition.
2. Randomly assign participant to one of the four study groups of the balanced placebo design as described above (**Table 1**).
3. Preparations to assess outcome measures.
   1. Prepare a questionnaire to fill in symptom ratings of participant. Seven symptoms (vertigo, headache, nausea, urge to vomit, tiredness, sweating, stomach awareness) will be rated on a scale from 0 (no symptom) to 5 (maximal symptom) six times during the experiment.
   2. Prepare a table to fill in rotation times and the number of head movements during five runs of the rotation procedure, and use a stopwatch to assess rotation times.
   3. Prepare the equipment for recording the EGG: three cutaneous electrodes, EGG device with Fetrode technology (active electrodes).

2. Preparing Participants

1. Prepare the EGG recordings.
   1. Place three cutaneous electrodes on the skin above the stomach of the participant as described by Miller and Muth (2004) [24]. Place the first electrode on the lower third of the midline between the umbilicus and sternum. Place the second electrode in a 45° angle upwards from the first electrode but under the lowest rip on the left side. Place the third electrode (reference electrode) in a 45° angle downwards from the first electrode to the right side.

2. Connect the electrodes to the EGG device and start the recording software.

2. Seat the participant in the rotation chair and store the EGG device in a bag at the backside of the chair.

3. Baseline Assessments and Drug Intake

1. First baseline assessment before drug intake.
    1. Record at least 15 min of EGG previous to any intervention. Instruct participant not to move, speak or take deep breaths during this period of time.

2. Drug administration.
    1. According to group assignment, the participant takes the pills (drug or placebo) without receiving any information about their content.

3. Second baseline assessment after drug intake.
    1. Record at least 15 min of EGG after drug intake. Instruct participant not to move, speak or take deep breaths during this period of time.
    2. Afterwards, ask participant for seven symptoms of motion sickness (see above) on a scale between 0 (not symptom) to 5 (severe symptom).

4. Optional: Depending on the assumed time until onset of action of the tested drug, perform further baseline assessments as described above.

4. Inform Participant about Group Assignment

1. Immediately before the rotation procedure, inform the participant about his/her group assignment according to the balanced placebo design, *i.e.* if he/she received the real drug or the placebo.
    NOTE: The participant receives this information in a closed envelope to keep the experimenter blind to the condition.

5. Rotation Procedure

1. Give instructions to the participant.
    1. The rotation procedure consists of 5 runs, each with 2 min of rotation at a constant speed of 120 degrees/sec (20 rounds per min) and a 1 min break in-between the runs.
    2. The participant will wear an eye mask and earphones and hear a beep every 10 sec. During rotations, the participant is instructed to move his/her head up and down when he/she hear the beep tone from the earphones.
    3. Participants should not vomit during the procedure and can skip head movements or tell the experimenter to stop the rotation in time if they strongly feel an urge to vomit. They are encouraged to proceed with the next run until all 5 runs have at least been started. However, the runs can be interrupted immediately, or the entire procedure can be stopped if necessary.
    4. During the breaks in-between the runs and after the last run, participants will be asked to rate seven symptoms of motion sickness on a scale from 0 (no symptom) to 5 (maximal symptom).

2. Start the rotation procedure.
3. During the rotation procedure, note the actually done head movements and the rotation time of each run.
4. During the breaks and after the last run, ask the participant to rate symptoms and note the rating on the questionnaire.

6. Post Assessments

1. After the last run has finished and the subjective symptoms have been rated, record another 15 min of EGG during which participants should not move, speak, or take deep breaths.

7. Calculate Outcome Variables

1. Calculate subjective symptom ratings by adding the scores of each symptom for each of the six time points (at baseline and after each run) separately. Take the highest symptom rating during the rotation procedure and subtract the baseline symptom rating to get the final maximum symptom rating during the rotation procedure (SR).
    NOTE: Choosing the maximum symptom score as an outcome measure provides the advantage that in can also be used for participants who cannot tolerate the entire procedure - in contrast to the calculation of a sum or a mean value that are influenced by the number of runs tolerated.
2. Add up rotation times for the total rotation tolerance in seconds (RT).
3. Add the number of head movements during the rotation procedure for the total number of head movements (HM).

8. Analyze EGG Data

1. Visually screen the raw EGG data for artifacts and select at least 5 min of artifact-free recording during the recording periods. As a rule of thumb, artifacts are defined as signals with fast and sudden onset and signals stronger than +/- 1,000 µV because such signals are improbable gastric myoelectrical activities.
2. Use a Fast Fourier Transformation software to analyze the frequency domain of the EGG signal. As definition, signals between 2.5 and 3.75 cpm are regarded as normal gastric activity (normogastria) and between 4.0 and 9.75 cpm are regarded as tachygastria.

3. Calculate the percentage spectral power of the normogastria and tachygastria bands from the total range of 0.75 to 15.0 cpm [23], and compute the ratio between the percentage of the normogastria and the tachygastria band (EGG ratio). A shift towards tachygastria (*i.e.*, the ratio decreases) has repeatedly been associated with nausea in motion sickness induced by rotation chair or vection drum [19,23,24].

Representative Results

This study protocol has been used to investigate the effects of ginger and expectations on symptoms of motion sickness with a rotation chair paradigm in healthy participants [17]. Variants of this protocol have also been used in other studies of our work group to investigate placebo effects by expectations and conditioning procedures [16,18].

To analyze results, the four groups of the balanced placebo design should be compared concerning the subjective (SR), behavioral (RT, HM), and objective (EGG ratio) outcome measures with 2 x 2 analyses of variances (ANOVA) (drug x information). Including all variables at once in a multivariate ANOVA reduces alpha-error accumulation. However, we decided not to include EGG ratio in this analysis because of data drop outs due to movement artifacts as this would reduce participant numbers for the whole analysis. Furthermore, the EGG ratios should be included in a repeated measure ANOVA to assess whether there is a significant shift towards tachygastria during the experiment.

The conducted study [17] revealed an effect of ginger on gastric myoelectrical activity that attenuated a decrease of the normo-to-tachy EGG ratio before the rotation procedure but did not prevent a decrease in the ratio during the rotation procedure (**Figure 1**). The information given did not significantly affect the EGG ratio but results provide hints that the information could have had an effect as the placebo/placebo group had the lowest EGG ratio and the ginger/ginger group had the highest EGG ratio (**Table 2**). The non-significance of this result could be due to the strong stimuli applied as discussed below.

The differences between groups for SR, RT and HM were also not significant. However, the study revealed an additional interactional effect with sex of participants and experimenters: a placebo response was detected when male participants were given placebo pills with the ginger information by the female experimenter. Furthermore, subjective (SR) and behavioral (RT, HM) measures were associated in women (SR-RT: r = -0.524, p <0.001, and SR-HM: r= -0.465, p =.002), but not in men [17]. The interactional effect of sex of participants and experimenters is not part of the methodology, and is, therefore, not discussed in detail at this point (for further discussion of this result please see Weimer *et al.*, 2012 [17]).

This study design provides the possibility to assess the main and interactional effects of drug and information, and the multivariate assessment of placebo responses: A significant difference between the pills given reveals that the drug has an effect on one of the outcome measures, whereas a significant difference between the information given reveals that the information affects the outcome measures. A significant interactional effect between drug and information reveals that the information given differentially affects the drug effect. According to the literature about the balanced placebo design [4], the biggest difference is expected between the group that is given the real drug along with the correct information (drug plus high expectation) and the group that is given the placebo along with the correct information (placebo plus no expectation). A significant difference between groups in SR only means that participants feel better but this is not mirrored in their behavior (longer RT, more HM) or in the objective measure (higher EGG ratio). A significant difference between groups in RT only means that participants probably try to show socially desirable behavior but do not really feel better (SR, EGG ratio). A significant difference in EGG ratio means that the information given and/or the drug have an effect on gastric myoelectrical activity.
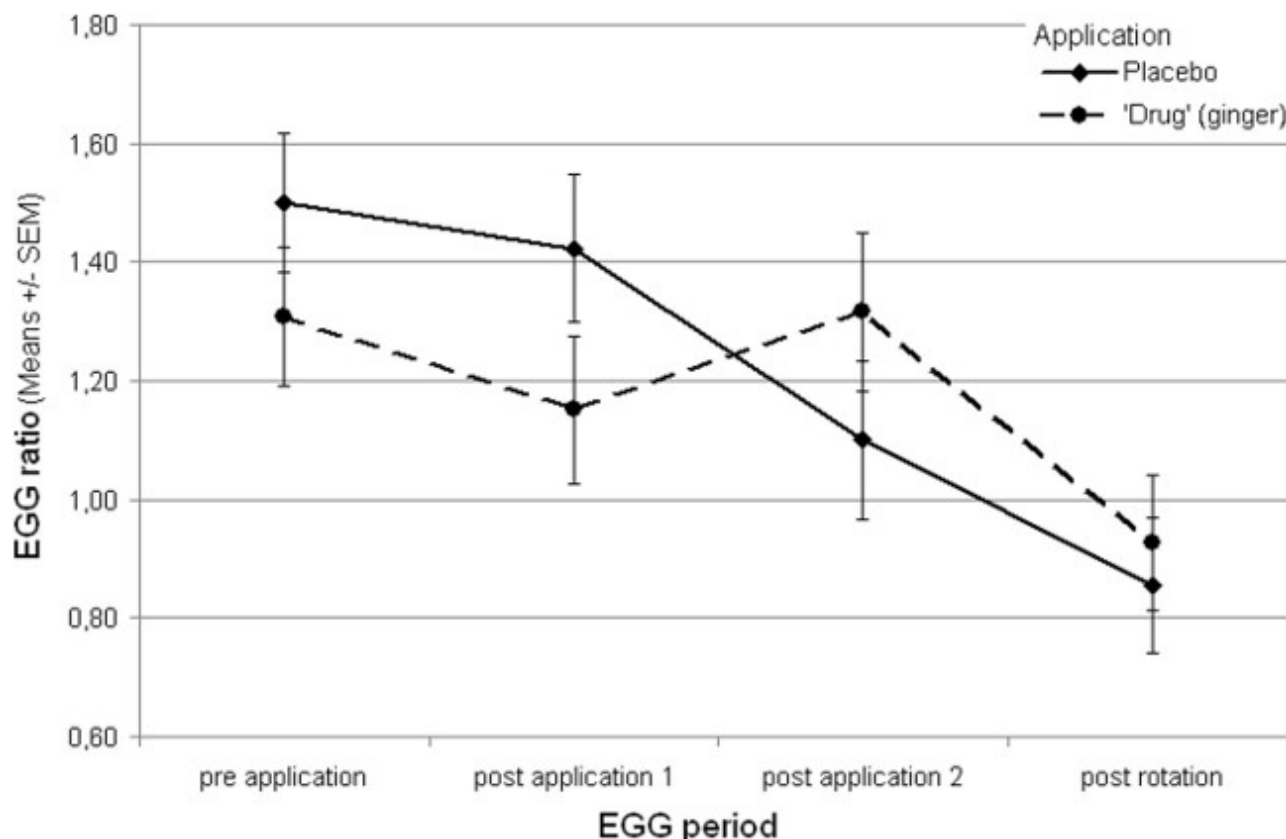
Figure 1: Electrogastrogram (EGG) in participants that received ginger or placebo. Legend text: EGG was evaluated as the ratio between normal activity (2.5 to 3.75 cycles per minute, cpm) and activity in the tachygastria band (4.0 to 9.75 cpm). With increasing nausea, this ratio decreases. Data segments were recorded at baseline, twice after drug application, and after rotation. The constant fall of the ratio from baseline to post rotation is interrupted in the ginger group but ginger was not able to prevent nausea to occur with rotation (Modified with permission from Weimer *et al.* 2012).

		Information	
		Drug	Placebo
Application	Drug	true positive	false negative
	Placebo	false positive	true negative

Table 1: The balanced placebo design.

Application (drug)	Placebo	Placebo	Ginger	Ginger	
Info	Placebo	Ginger	Placebo	Ginger	Statistics
HM	46.1 ± 17.2	48.1 ± 13.9	38.3 ± 19.0	45.1 ± 13.9	n.s.
RT (sec)	497 ± 163	482 ± 142	436 ± 182	466 ± 152	n.s.
SR	20.2 ± 5.8	20.5 ± 6.3	18.9 ± 6.8	20.8 ± 6.1	n.s.
EGG (n)	12	14	13	13	n.s.
EGG normo (%)	16.8 ± 5.5	18.2 ± 8.3	21.7 ± 7.2	20.8 ± 9.3	n.s.
EGG tachy (%)	25.8 ± 9.2	23.6 ± 7.7	27.9 ± 7.9	24.0 ± 6.9	n.s.
EGG ratio	0.78 ± 0.45	0.92 ± 0.63	0.90 ± 0.59	0.96 ± 0.64	n.s.

Table 2: Data between groups during and after rotations.

Legend text: HM = head movements, RT = rotation tolerance, SR = maximum symptom rating during rotations, EGG (n) = number of participants with all 4 measures available, EGG normo (%) = percentage of activity in the normogastric band, EGG tachy (%) = percentage of activity in the tachygastria band, EGG ratio = ratio between normogastria and tachygastria band (adapted with permission from Weimer *et al.* 2012).

Discussion

The methodology described provides the possibility to assess placebo responses in motion sickness in a multivariate way and appropriate timing of drug intake and administration of information. However, it was difficult to detect placebo responses in the conducted study [17]. This could be due to various facts, critical steps and limitations.

First, women could be more susceptible to stimuli eliciting motion sickness [15]. Also, women and men could be differentially susceptible to placebo inducing methods. For example, women were more susceptible to Pavlovian conditioning procedures to worsen symptoms and men were more susceptible to suggested symptom increases [16]. Furthermore, there could be interactional effects with participant's and experimenter's sex [27,28]. This must be taken into account and studies must be powered to detect such interactions.

Second, we assume that the stimuli of 5 runs with 2 min duration at a speed of 120 degrees/sec (20 rounds per minute) were too strong and could not be affected by a weak herbal remedy like ginger or information only. All of the 64 participants reported moderate to strong symptoms although not all of them reported to have ever been motion sick before, e.g. during rides in cars, on boats, or funfair rides, as assessed with the Motion Sickness Susceptibility Questionnaire (MSSQ) [29]. Furthermore, the assessed motion sickness susceptibility did not influence any of the outcome measures in this or the subsequent study [17,18]. For the subsequent experiment investigating an enhanced placebo instruction, we used a pilot study to assess appropriate speeds: With lower speeds of 10 and 15 rounds per minute, we found significant differences between groups [18].

Third, the most critical step is the assessment of the physiological outcome measure with an EGG in this study. This method is very sensitive to artifacts; consequently data loss due to dropouts is frequent. Therefore, the preparation of equipment, study design and careful participant instruction are crucial to reduce artifacts due to movements, speaking, or deep breaths. This not only applies to EGG recordings but also to recordings of electrocardiograms (ECG) or other physiological methods.

For future applications of the multivariate assessment of placebo responses, these critical points must be taken into consideration not only when investigating motion sickness but also for other symptoms such as pain or depressions. Participants could be differentially susceptible to different kinds of stimuli and symptoms, e.g. due to gender differences [30], or because of different symptom histories and treatment experiences [31]. Furthermore, the severity of induced symptoms plays a role in experimental placebo research on motion sickness where strong symptoms could lead to unexpected results [17,18,25,26]. We have recently shown that a lower baseline severity of symptoms could be a predictor for higher placebo responses in the placebo arm of clinical trials for the treatment of depression and other psychiatric disorders, neurological disorders and pain (Weimer, K., Colloca, L. & Enck, P., in press). In contrast, effect sizes of placebo analgesia in experimental studies were higher with long-lasting stimuli compared to painful stimuli of short duration [32]. Therefore, the kind and intensity of stimuli must be considered thoroughly when planning an experimental study to facilitate placebo effects.

Finally, for the assessment of multivariate outcome measures it is important to find the appropriate physiological correlate of the placebo response that will be investigated as an objective marker, such as the gastric myoelectrical activity in motion sickness that can be assessed with electrogastrography. In some conditions the target organ and the according physiological measure are easy to find and assess, e.g. heart function with ECG and blood pressure measurement when investigating placebo responses that accompany drugs for hypertension [6], but can be more complex in conditions like pain and depression. For example, Eippert and colleagues found that placebo analgesia can act on the level of the spinal cord as the earliest stage of pain processing in the central nervous system [33] that can be detected with high-resolution functional magnetic resonance imaging (fMRI) only. Future studies should investigate which conditions will activate and modulate this mechanism. Objective assessments are also important in conditions mainly monitored by patient reported outcomes, such as questionnaires in depression, that can considerably deviate from expert rated outcomes [34] and may be subject to biases. Despite this fact, objective outcomes such as the assessment of reward-related neural activation is only seldom used [35]. In conclusion, assessing placebo responses by multivariate outcomes will improve our understanding of predictors and mediators of placebo effects and their underlying psychological and physiological mechanisms.

Disclosures

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Acknowledgements

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