

# Real-world versus Virtual Reality Treatment Simulations

Lisa Evelyn Rombout

Graduation Thesis, August 2015

Media Technology MSc program, Leiden University

Thesis advisors: Maarten Lamers (LIACS) and Bernhard Hommel (FSW)

LisaEvelynR@gmail.com

**Abstract**—Placebo treatments are commonly used in scientific research as a comparison baseline for the actual treatment under study. Due to ethical considerations placebos alone are seldom used in clinical practice, although all treatments have placebo elements due to expectations and conditioning of the patient. In recent years, the mechanisms behind the placebo-response have been elucidated further, showing which factors influence the effect size and how the effect is psychologically and biologically mediated. With this greater understanding of what modulates the placebo-response, the possibilities of open-label placebo treatments can be explored. Studies show that the placebo-response can occur even when the patient is aware of the treatment being a placebo. While this is a potential solution for the ethical problems of placebo treatments, these ‘treatment simulations’ still require a real-life clinical setting and a health care provider. This study focuses on open-label placebo treatment in a virtual setting. A real-world and a virtual treatment simulation were compared to a control condition. The treatment simulations did not have major significant effects on the heart-rate, reaction-time and subjective experience of the participants. Some differences between the conditions indicate that the virtual reality experience may interact with treatment in as of yet unexpected ways. Further study, focused on the specific areas where open-label placebo treatments have been shown to be effective, may clarify whether virtual reality treatment simulations can be used as effective open label placebos.

## I. INTRODUCTION

The placebo is such an accepted part of modern scientific research that it sometimes slips the mind that its most common definition is a *contradictio in terminis*: a treatment containing no active substance, that nonetheless has measurable effects on the receiver [1]. For an individual subject, these effects are called their placebo-response. The average placebo-response to a treatment is called the placebo-effect of that treatment. The placebo-effect is often divided into placebo and nocebo—desired effects and side-effects or ‘negative’ effects—but both are essentially the same mechanism.

It is important to note that most active treatments also have a placebo component. The factors thought to be mainly involved with the placebo mechanism are most often present in ‘real’ treatment as well—unless hidden treatment is given [2]. The placebo can therefore take the form of a simulation of active treatment and be re-conceptualized as a ‘context mediated effect’ [3]—a psychosocial context where the surroundings of the patients, their expectations, prior experience

and beliefs, sensory effects of the treatment, and the patient-doctor relationship all play an important role [4].

### A. History of placebo research

The placebo-response has been known and studied for hundreds of years. Hippocrates already wrote in 400 BC that “the patient, though conscious that his condition is perilous, may recover his health simply through his contentment with the goodness of the physician” [5]. Though more commonly used in clinical practice in the past, more recently ethical considerations have limited the placebo. In pharmaceutical research, placebos are used mainly as a baseline comparison for active, ‘real’ treatment [6].

In the past few decades, our knowledge on the placebo-response has grown extensively. Many new considerations for the use of placebos have arisen. An important factor is the discovery of the biological components of the placebo response. First thought to be ‘only’ a psychological response resulting in just subjective changes, research has shown that biological systems like the immune and endocrine system exhibit objective placebo responses that can even occur unconsciously [7].

Furthermore, genetic differences are thought to play a role in the difference of magnitude of the placebo-response in distinct individuals [8]. This is an added explanation for the existence of so called placebo responders and non-responders—going beyond personality traits [9].

Research is also focusing on the neurological components of the placebo effect. Certain types of placebo responses can be blocked with antagonistic drugs, for instance targeting opioid receptors [10]. This points to the neurological pathways activated by these particular types of treatment simulations. One interesting aspect is that the placebo response may utilize the same pathways as the actual treatment, leading to interaction effects [11]. Research into this interaction is still in its infancy.

### B. Psychological components

The placebo effect has long been seen as a prime example of the mind-brain-body interaction. The two main psychological influences can be described as expectancy [12] and conditioning [13]. Expectancy is a conscious process and is influenced by the patients beliefs and desires. As stated, the placebo can be seen as the simulation of active treatment.

Indeed, it has been shown on several occasions that active treatment is less effective when the patient is not aware of receiving it. For example, a hidden dose of morphine can be less effective than an administration of a saline solution in full view of the patient [14]. This shows that in some situations, the conscious expectancy of treatment effects is sufficient (and sometimes even necessary) for any effects to occur.

Classical conditioning, on the other hand, can be an unconscious process that involves training the body to respond in certain ways to certain procedures. Patients receiving medicine that caused a low and by the patient unnoticeable pulmonary capacity suppression experienced the same effect when later treated with a placebo [15]. A similar mechanism has been shown to occur in non-human animals [16].

It has been suggested that the success of some alternative medicine treatments can be attributed to the placebo effect, as these procedures are often (intentionally or not) designed in such a way that they optimize the successful elements of a treatment simulation [17]. There is often more intensive therapeutic contact, strengthening the bond between the patient and the health care provider. There is almost always a diagnosis, and the health care provider is generally positive about the effects of the treatment. The treatment simulation or therapeutic ritual is often elaborate, with the use of many symbolic props and a lot of opportunity for reflection of and concentration on the procedure. These are elements that have been shown to increase the likelihood and magnitude of placebo effects [18].

### C. *Clinical practice*

Explicit use of the placebo effect in conventional medicine is not widespread. Ethical considerations do not allow the prescription of a placebo-only treatment. As one of the key elements in the doctor-patient relationship is trust, dishonesty about a prescribed treatment could potentially damage this relationship considerably, and by extension the patient's trust in all health-care providers [19].

Surveys of health care providers show that although some acknowledge the possible positive effects of placebo-only treatments, most think the disadvantages of being dishonest to their patients outweigh the benefits [20]. Surveys of patients show similar results, with patients often not fully understanding what placebos are or whether they could have any effects at all [21]. However, patients are in general more pragmatic than expected towards receiving limited or incorrect information from their physician [22].

### D. *The future of the placebo*

If the goal of health care is to provide the strongest positive effect on patient health as possible, brushing the placebo effect aside is a waste of a perfectly valid method of producing these results [23]. Several efforts have been made to re-contextualize the placebo and its use [24]. Below I propose three possible solutions to the ethical problem posed by using the placebo effect in clinical practice.

The first option is to train health care providers to utilize the placebo response as effectively as possible during actual, primary treatment. This has the advantage of combining 'real' treatment with a strong treatment ritual, arguably providing the best of both worlds for the patient. Disadvantages are the individual differences and time constraints of health care providers that make it difficult to utilize the placebo effect in full [25]. Moreover, ethical dilemmas do persist: what if the treatment ritual calls for optimism but the patient actually has very little chance of getting better?

The second solution is to leave conventional medicine as it is and let alternative and complementary medicine fulfill the need for more elaborate treatment rituals. Obvious disadvantages to this are that it excludes many patients from these treatment simulations (requiring them to seek it out themselves) and that there is little control on the practices of non-conventional medicine. This makes it hard to differentiate between 'harmless' procedures [26] and ones that can actually damage the patient's health.

Apart from these two options, there is also a third, slightly counter-intuitive one that puts the power back in the hands of the patient and gives the patient control over their own treatment ritual: the open-label placebo.

### E. *Open-label placebos*

Open-label or non-deceptive placebos could be the solution to the ethical problems that clinical placebo treatments face. Prior research shows that a placebo treatment can work even when subjects have been informed about its nature.

Already in 1969, a study into non-blind placebo treatment of neurotic patients found that 'sugar-pills' had an effect on some patients after only one week, even though the patients knew the pills were inert. In-depth interviews revealed that patients used many different rationalizations of the treatment: some did not believe the treatment was actually inert, others found it calming that they at least could not overdose on them. Patients noted that the very act of taking a pill regularly functioned as a therapeutic ritual that helped their symptoms. However, some patients were more skeptical about the treatment, exhibiting the common idea that placebo-responders are easily fooled and not wanting to belong to that group [27].

Other studies have looked at conditioning as a suitable substitute for expectations—as the latter arguably disappears once the patients know about the placebo treatment—finding that effects persisted after longer periods of conditioning in analgesic treatments [28] and ADHD [29]. In contrast, placebos that are open-label from the very beginning have also been shown to have the desired effect on patients, as well as some undesired ones, as patients can experience side-effects from a placebo treatment [30]. Although many studies focus on psychological conditions and effects on the mental state, there has also been some promising open-label placebo research into pain and irritable bowel syndrome [31].

Interesting about all these studies is how the control over the treatment simulation is shared by the patient and the health care provider: the latter stresses the effectiveness

of the placebo multiple times, but patients develop their own model of ‘how it works’ [32]. Although the results seem promising, the problem arises again that conventional health care providers often do not have much time available per patient and results may vary widely between different providers due to individual differences in communication skills. Not all health care providers can thus offer optimal patient-doctor interaction. An interesting question is thus how much actual interaction with a professional caregiver is needed for a treatment ritual to elicit a placebo response. Can people help themselves by conscious self-deception? This would dissolve the ethical considerations that currently limit the applicability of the placebo in clinical practice. With appropriate education on what placebos are and what they can do, common misconceptions that hinder the placebo response [33] could possibly be removed, allowing patients to seek out their own treatment rituals more effectively.

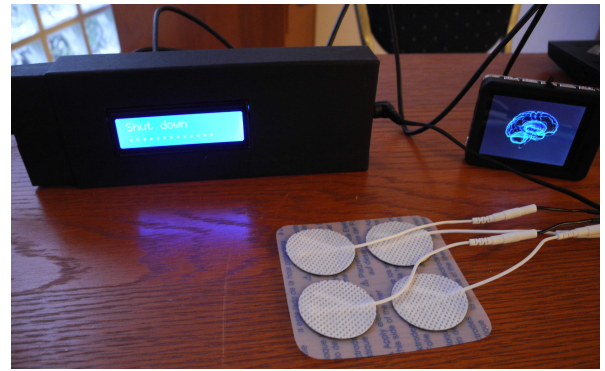
#### F. Virtual reality treatment

Virtual reality (VR) is already used in clinical practice in the form of training simulations, usually targeting PTSD, BDD or phobias [34] [35]. VR provides an interesting treatment tool because of the complex yet very controllable treatment environment. Often, the exercises are more interesting to patients than traditional ones, leading to greater motivation for therapy compliance [36]. They can also allow patients to work on their own pace. As such, VR environments seem ideal for open-label placebo treatment. The patient has control over the ritual—when it happens and how often. The treatment rituals can be as finely constructed as possible, providing the patient among other things with the ideal interaction with the (virtual) health care provider and other optimized context cues. Research seems to indicate that a virtual therapist can, in some circumstances, be an acceptable replacement of a real one [37]. This will arguably only increase with technological advances in artificially intelligent virtual agents.

It remains to be seen whether open-label placebo effects are strong enough to transfer to the virtual realm, as well as whether the loss of certain sensory experiences makes a significant difference on the effects. There is very little research available on the possible interaction effects caused by a virtual reality experience of a conventional treatment. It seems logical to assume that distinct treatment simulations and context manipulations translate differently from the real to the virtual world. No clear guidelines for this process are currently defined.

#### G. Real-world versus virtual reality placebos

This study therefore concentrates on the basic requirements of a treatment simulation within the open-label placebo framework. Does the treatment have to be a physical interaction and the health care provider physically present, or can a treatment ritual also be completely experienced in virtual reality? Our expectation is that the placebo effects of a virtual treatment simulation will be noticeable but reduced as compared to a real-world treatment simulation, because



(a) The fake electrical brain stimulation device with electrodes (front) and remote control (upper right)



(b) Placement of the electrodes



(c) During fake stimulation

Fig. 1. The experimental setup of the real-world treatment simulation

of a loss of certain variables such as smell and taste, and the removed possibilities of interaction with the virtual health care provider.

A basic virtual reality treatment simulation was compared to a real-world treatment simulation and a no-treatment condition. Additionally, participants were asked about their personal requirements and wishes regarding open-label placebos in clinical practice and treatment rituals in general.

## II. METHODS

### A. Participants

Healthy participants were recruited using online enlistment. Participants were asked to abstain from nicotine, caffeine, alcohol and other drugs directly before the experiment, and notify the experimenter of any mental health medication or severe heart problems. Apart from preventing or filtering out interaction effects of active substances this was done to promote the notion of a serious treatment procedure and thus enhance the strength of the placebo treatment.

### B. Electrical brain stimulation

On signing up online and at the start of the experiment participants were given written information explaining the effects of the proposed electrical brain stimulation, ‘EBS at 60Hz’. This treatment method was chosen because it is non-invasive—making it easier to replicate in virtual reality—but at the same time a novel and high-tech procedure, which could enhance the effect size [38]. The effects were described as similar to the effects of caffeine, with enhanced concentration, focus, elation, excitement and alertness. Mentioned side effects were a higher heart-rate, a tingling or itching sensation on the forehead and temples (just under the electrodes in the real-world treatment simulation), and a dry mouth. Caffeine was chosen as an effects template because most people are familiar with the substance. Expectation of caffeine consumption has been shown to affect cognitive task performance [39]. All effects and side-effects were said to subside after about 5 to 10 minutes.

### C. Conditions

Participants participated in all 3 conditions, using a counterbalanced measures design. After a general questionnaire and a practice round of the two reaction-time tasks, participants were told they were part of the ‘open-label placebo group’. They were informed about the nature of open-label placebos and asked to ‘play along’ in the simulated treatment conditions as if the treatment was real. It was implied that there were other groups receiving actual treatment and closed label placebos, to retain the notion that the research was about actual EBS. Additionally, before each condition participants read a short written explanation of the nature of that specific condition.

The first condition was a real-world treatment simulation. For this condition the experimenter wore a white lab coat. Four sticky electrodes were applied to the forehead and temples after cleaning the skin with a disinfectant (providing both tactile and olfactory feedback)(Fig. 1b). During the application, the experimenter explained again what was being done and what the participant could expect from the ‘treatment’ in a clear and optimistic manner. Then, an official-looking but fake ‘EBS device’ (Fig. 1a) was activated, providing visual and auditory feedback (respectively through an LCD-screen and a piezoelectric speaker) for a stimulation period of around one minute, plus a ‘ramp up’ and a ‘ramp down’ time indicated by sound and a message on the LCD screen (Fig. 1c). During the ramp up, the experimenter asked



(a) Participant wearing virtual reality glasses and headphones



(b) Still image of the 360° movie shown to the participants (here distorted due to depiction as a flat image)

Fig. 2. The experimental setup of the virtual reality treatment simulation

shortly whether the stimulation was still comfortable for the participant. After the ‘stimulation’ ended, electrodes were removed by the experimenter.

The second condition, a virtual reality treatment simulation, was similar to the first one with the exception that the participants watched the same scenario play out in a virtual environment, via virtual reality glasses showing a 360 degree movie (allowing for responsive head motion) of the same experimenter following the same procedure (Fig. 2). The simulation thus only had visual and auditory feedback, missing the tactile and olfactory components. Before the movie started, participants saw a still image of the virtual environment and could look around until they were used to the scene and the mechanisms of VR-glasses.

The third condition acted as a control: no simulation of treatment was given. The participants watched a short animated movie on a computer screen instead. Between conditions, participants had a short break of 5 minutes in which they were seated in a different environment with water and magazines provided. The tasks and questionnaire after a treatment/control, the break and the briefing on the next condition together took more than 10 minutes, which was the expected time-period for the effects to subside.

### D. Subjective experiences and expectations

Participants were asked for their prior experiences with VR and EBS, as well as their expectations for EBS and (virtual)



Fig. 3. General experimental setup - participant doing reaction-time task with heart rate sensor attached to the earlobe

open-label placebos. Questionnaires after each condition collected subjective ratings of differences in task-performance and treatment-response. After conditions with treatment simulations, participants answered additional questions on the believability of the simulation and the difficulty of pretending it was real.

After all three conditions, participants were debriefed on the true goal of the study, and filled in a questionnaire on the perceived value and feasibility of these types of treatment simulations and ethical considerations. Lastly they filled in a short personality test focusing on opinions on mind-body control, skill in convincing self and others, and personal use of treatment rituals.

### E. Performance measurements

Before and after each condition, participants did several iterations of two small tasks (Fig. 3). The first was a classic reaction-time task where they had to react with a mouse-click when an on-screen red circle turned green. The second task was a reaction-inhibition task where they had to react when the circle turned green, but not when it turned blue. Reaction times as well as mistakes (clicking too early or clicking when the circle turned blue) were recorded for each task separately.

### F. Physiological measurements

Participants were fitted with a heart-rate sensor for each condition, recording the time between heartbeats every few milliseconds and keeping a running average (Fig. 3). Heart rate was measured during the reaction time tasks and during the condition itself, giving data for before, during and after a condition.

After each condition, a pitcher with water was provided in the break, together with a glass (Fig. 4). The water consumption was then afterwards measured without the participants knowledge, to account for the listed side-effects having a dry mouth.



Fig. 4. Break setup - participant has access to magazines and water

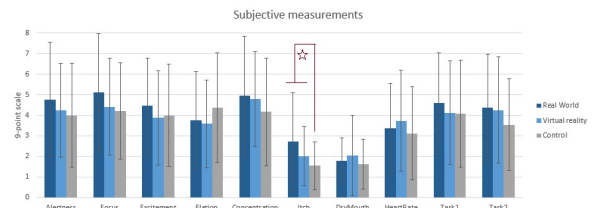


Fig. 5. After each condition, subjective experiences were indicated by the participants on a nine-point scale. A higher value corresponds with a positive change in the feature due to the treatment/control.

## III. RESULTS

### A. Participants

24 participants (13 female, 11 male, ages 23-75) were recruited. All participants gave informed consent to participate in a study involving electrical brain stimulation (EBS) and were debriefed fully at the conclusion of the study. None of the participants suffered from color-blindness, allowing normal participation in the reaction-time tasks.

### B. Missing data

One task performance for one participant was lost due to accidental overwriting of the file. Water consumption data on one subject had to be discarded due to the patient bringing their own water bottle. All heart rate segments where the sensor malfunctioned (returning pulse times < 10 ms and > 2000 ms and heart rate < 10 bpm and > 200 bpm) for more than 10% of the time were discarded (8 of 216 segments). These missing data points were not expected to have a notable effect on the outcome of the analysis.

### C. Subjective experiences

The subjective experiences of difference in alertness, focus, excitement, elation and concentration were not signif-

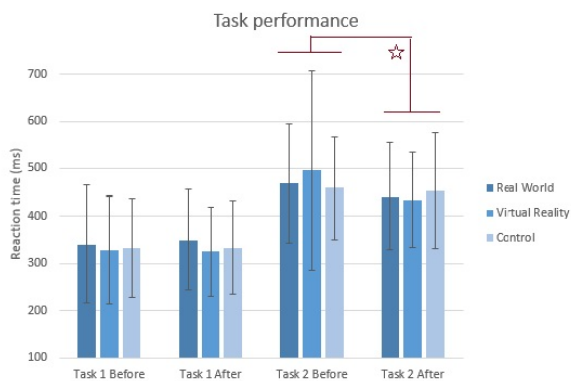


Fig. 6. Average performance on task 1 (simple reaction-time) and task 2 (inhibition test), before and after the treatment/control

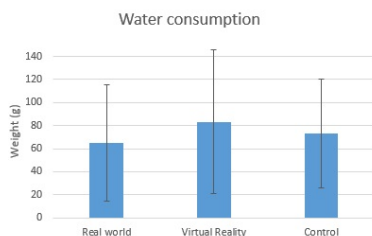


Fig. 7. After each condition, participants had a short break during which water was available to them. Their water consumption was subsequently measured by weighting the container and calculating the difference with before the condition.

icantly different over conditions (one-way repeated measures ANOVA). The same was true for subjective experience of differences in physiological effects—heart rate and dry mouth. Itching on forehead and temples was however found to be significantly influenced by condition (one-way repeated measures ANOVA with Greenhouse-Geisser correction:  $F(1.31,30.06) = 4.80$ ,  $p < 0.05$ ), being higher in the treatment-conditions as compared to control (post-hoc Fisher’s LSD,  $p < 0.05$ )(Fig. 5).

#### D. Task performance

The average number of mistakes on the reaction-time tasks (whether early clicks in both tasks or clicks when the red dot turned blue instead on green in task 2) were not significantly different over time (before versus after the treatment/control) or conditions. The average reaction time and variance on task 1 (the simple reaction-time test) were likewise not significantly different over time or conditions (two-way repeated measures ANOVA).

The average reaction time on task 2 (the inhibition reaction-time test) was significantly influenced by time (two-way repeated measures ANOVA with Greenhouse-Geisser correction:  $F(1,22) = 6.98$ ,  $p < 0.05$ ). Post-hoc tests using Bonferroni correction revealed that the participants were slower before the treatment/control than after ( $p < 0.05$ )(Fig. 6).

#### E. Physiological measurements

No significant differences on water consumption between conditions were found (one-way repeated measures ANOVA, Fig. 7). Heart rate however was significantly influenced by the interaction between condition and time (two-way repeated measures ANOVA:  $F(4,76) = 5.08$ ,  $p < 0.001$ )—during the virtual reality treatment simulation, heart rate was higher than before ( $p < 0.05$ ) or after ( $p < 0.05$ ) the treatment (Fisher’s LSD). There was also a significant difference between the average heart rate during the virtual reality treatment simulation and during the real world treatment simulation ( $P < 0.05$ , LSD) (Fig. 8a). Additional, the heart rate variability was higher during all conditions as compared to before ( $P < 0.001$ , LSD) and after ( $P < 0.001$ , LSD) (two-way repeated measures ANOVA:  $F(2,38) = 16.01$ ,  $p < 0.001$ ) (Fig. 8b).

#### F. Experiences and expectations

No participants had experience with any kind of real electronic brain stimulation before. The average expectation of EBS effectiveness was 5.71 on a nine-point scale ( $\sigma = 1.63$ ). The expectations of open-label placebos were not significantly different over type, where the type is specified as real-world, virtual reality, or in general (one-way repeated measures ANOVA). The average expectation of an open-label placebo was 5.14 ( $\sigma = 2.24$ ). The average prior experience with virtual reality was fairly low at 3.42 ( $\sigma = 2.89$ ).

#### G. Strength of treatment rituals

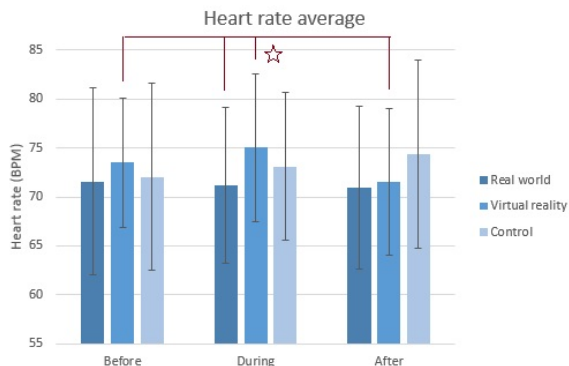
Participants found it easier to pretend towards the experimenter that the real-world treatment simulation was real than towards themselves (two-way repeated measures ANOVA:  $F(1,23) = 5.26$ ,  $p < 0.05$ , post-hoc Bonferroni:  $p < 0.05$ ). On average, participants found it also significantly harder to pretend that the virtual treatment simulation was real (two-way repeated measures ANOVA:  $F(1,23) = 7.20$ ,  $p < 0.05$ , post-hoc Bonferroni:  $p < 0.05$ ).

There was no significant difference between how convincing participants rated the real versus the virtual experimenter ( $\mu = 7.17$ ,  $\sigma = 1.69$  vs  $\mu = 6.42$ ,  $\sigma = 2.02$ ). The same was true for real versus virtual equipment ( $\mu = 7.04$ ,  $\sigma = 1.90$  vs  $\mu = 5.96$ ,  $\sigma = 2.42$ ) and surroundings ( $\mu = 7.00$ ,  $\sigma = 1.62$  vs  $\mu = 6.63$ ,  $\sigma = 1.95$ ) (two-way repeated measures ANOVA).

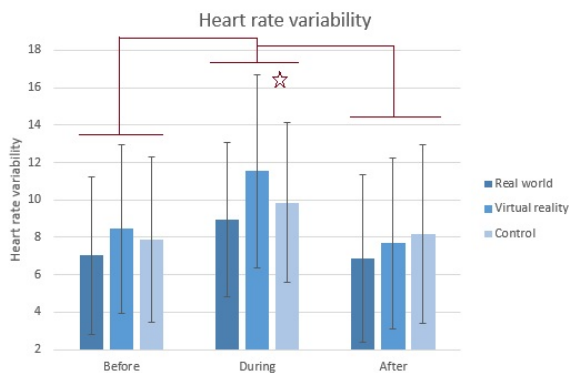
#### H. Correlations

In the real-world treatment simulation, a positive correlation was found between how participant rated their difficulty in pretending the treatment was real and their average improvement in task performance ( $r = 0.463$ ,  $p < 0.05$ ).

The correlation between how convincing the treatments were rated and the average heart rate increase caused by them was positive for the real-world treatment ( $r = 0.635$ ,  $p < 0.05$ ), but negative for the virtual reality treatment ( $r = -0.559$ ,  $p < 0.05$ ).



(a) Average Heart rate in beats-per-minute before, during and after the treatment/control



(b) Average heart rate variability before, during and after the treatment/control

Fig. 8. Heart rate measures

### I. Clinical feasibility of treatment rituals

On average, participants did not strongly suspect before debriefing that the study was about placebos ( $\mu = 3.25$ ,  $\sigma = 2.63$ ). The trust in the experimenter was on average not greatly damaged after the debriefing ( $\mu = 1.38$ ,  $\sigma = 1.06$ ). The average level of comfort with being prescribed a placebo was 5.22 on a nine-point scale ( $\sigma = 2.64$ ). The differences between the level of comfort with self-prescribed placebos, physician prescribed placebos without the patient knowing and physician prescribed placebos with the patient knowing were not significant (one-way repeated measures ANOVA). Participant largely indicated having personal ‘illness rituals’ ( $\mu = 5.91$ ,  $\sigma = 2.19$ ), with the most common examples being doing particular activities or eating particular food when ill.

### J. Preferred simulation and additional comments

11 participants preferred the real-world treatment simulation and 3 preferred the virtual one, the remainder was undecided or gave no answer. Common reasons given for real-world treatment preference were that the real human contact is appreciated, and that it is easier to pretend the treatment is not a placebo. The participants who preferred the virtual reality treatment noted that it was more exciting and fun to do, and reminded them of a game.

It is interesting to note that several participants believed that they were being ‘double-crossed’ in the real-world condition: they thought they were told that they would receive a placebo but actually got a real treatment.

## IV. CONCLUSION

The results show very little effect of the different conditions. As the real-world treatment simulation did not cause significantly different effects from the control, it is not possible to say much about the effectiveness of the virtual reality treatment simulation. Results indicate that the average heart-rate went up during the virtual reality treatment, but the most logical conclusion would be that this is due to the excitement that many participants felt about the VR experience. As prior experience levels of VR were fairly low, most subjects had probably never or seldom experienced VR glasses before, causing a novelty bias.

The results further indicate that heart rate variability was significantly higher during all conditions (real-world, virtual reality and control) when compared to before and after. This is most likely due to the different circumstances during this time segment: before and after the conditions participants were concentrated on doing the reaction time task, and likely this activity provided less variation than the treatments themselves.

It should be noted that the subjective evaluations are very prone to conscious or unconscious manipulation by the participant in this type of non-blind study. Subjects can quite easily deduce what the experimenter wants to happen, so subjective experiences should always be backed up by objective measurements to be certain that it is not just the participants being compliant. In this study, the significant effect of the treatments on forehead itching was most likely caused by the fact that in the real-world and virtual reality conditions the participants were wearing something on their heads (electrodes and VR glasses respectively), while in the control condition they were not.

The same caution applies when analyzing task performance level—it is possible that subjects intentionally perform bad before treatment to make the treatment look good. The correlation between the ease of pretending the treatment was real and improvement on task performance could have been caused by this effect (it is however not certain that it was caused by a conscious effort). Perhaps this can be subverted by making subjects perform the task before disclosure of the open-label condition. The fact that the inhibition task performance was significantly influenced by time could indicate a simple learning effect, or a dulling effect of the break on the performance in the task.

It could be that the effect expectancy for EBS was too low to elicit a measurable placebo response. As effects were described as fairly mild (over quickly and mimicking a well known mild stimulant), maybe participants were not expecting too much. A necessary effort when prescribing open-label placebos seems to lie in educating the patient on placebos and what they can do—although expectancy levels were not very low, it is still very likely that participants had

specific ideas about what could and could not be treated with a placebo and what sort of people reacted to them. This is perhaps also reflected in how comfortable people are in being prescribed placebos—the level of knowledge or control they have does not seem to make a significant difference on their comfort. It could be that other factors, like not wanting to be the type of person that responds to placebos or believing that placebos only work on the subjective level, contributed to the results.

Multiple participants mentioned the suspicion that the real-world treatment simulation was not a simulation at all, a mental model for 'why it works' that has been seen in prior research as well. For future research studying open-label placebos it might be important to look into this suspicion and what its effects are, or how they are influenced by education on placebos or the offer of competing mental models.

It is important to note that the virtual reality treatment simulation was not ideal in this experiment. If the VR simulation is performed in the health care provider's office, the patient still encounters an unfamiliar environment and a physician before going into the virtual world. It would therefore be interesting to see what effects a VR treatment simulation would have when used by patients themselves in their homes, for a longer period of time.

The made-up effects of the 'EBS treatment' in this study were chosen both for their prior use in placebo research but also for the convenience of recruiting healthy participants. Further research into VR treatment simulations might focus on the specific conditions and contexts where open label placebo effects have already been shown, such as analgesic treatments, anxiety, ADHD or irritable bowel syndrome. Recurring treatment simulations, where the patient returns to the VR environment each day, can also be considered, as they might establish a stronger ritual.

Another interesting possibility is the use of VR to tailor the treatment rituals to the patients individual wishes. This requires that the patient is aware of what 'works' for them as a placebo (a virtual visit to the doctor, an alternative procedure). Virtual reality offers many options for customization and giving the control of treatment back to the patient. It could therefore potentially be used as a tool to reinforce the patients own 'illness rituals' and make constructive use of this common attribute.

The results show unexpected effects of the virtual reality experience on the heart rate, seemingly caused by the interaction with how convincing participants rated the treatment. If physiological effects are indeed influenced by context-mediated elements, placebo effects should be seriously considered in this new therapeutic tool, whether as interaction effects on the 'actual' treatment or as the actual treatment itself.

Virtual reality remains a promising technique that is likely to influence context-mediated effects in novel ways due to how the human brain handles this new environment. Research into the direct effects and side-effects could not only strengthen active treatment in VR, but potentially provide beneficial interactions with a highly controlled context.

## ACKNOWLEDGMENTS

The author would like to thank Maarten Lamers and Bernhard Hommel for their advice, Kaya Peerdeman and Robin de Lange for their feedback, Ot de Wiljes for technical support, and Marcello Gomez Maureira for the lending of equipment.

## REFERENCES

- [1] D. D. Price, D. G. Finniss, and F. Benedetti, "A comprehensive review of the placebo effect: recent advances and current thought," *Annu. Rev. Psychol.*, vol. 59, pp. 565–590, 2008.
- [2] F. Benedetti, G. Maggi, L. Lopiano, M. Lanotte, I. Rainero, S. Vighetti, and A. Pollo, "Open versus hidden medical treatments: The patient's knowledge about a therapy affects the therapy outcome." *Prevention & Treatment*, vol. 6, no. 1, p. 1a, 2003.
- [3] F. Olesen, "Beyond the placebo: understanding the therapeutic context," *British Journal of General Practice*, vol. 65, no. 630, pp. 6–7, 2015.
- [4] D. E. Moerman and W. B. Jonas, "Deconstructing the placebo effect and finding the meaning response," *Annals of Internal medicine*, vol. 136, no. 6, pp. 471–476, 2002.
- [5] D. H. Novack, "Therapeutic aspects of the clinical encounter," *Journal of General Internal Medicine*, vol. 2, no. 5, pp. 346–355, 1987.
- [6] M. D. Sullivan, "Placebo controls and epistemic control in orthodox medicine," *Journal of Medicine and Philosophy*, vol. 18, no. 2, pp. 213–231, 1993.
- [7] D. G. Finniss, T. J. Kaptchuk, F. Miller, and F. Benedetti, "Biological, clinical, and ethical advances of placebo effects," *The Lancet*, vol. 375, no. 9715, pp. 686–695, 2010.
- [8] K. T. Hall, J. Loscalzo, and T. J. Kaptchuk, "Genetics and the placebo effect: the placeboome," *Trends in molecular medicine*, vol. 21, no. 5, pp. 285–294, 2015.
- [9] T. Furmark, L. Appel, S. Henningson, F. Åhs, V. Faria, C. Linnman, A. Pissioti, Ö. Frans, M. Bani, P. Bettica *et al.*, "A link between serotonin-related gene polymorphisms, amygdala activity, and placebo-induced relief from social anxiety," *The journal of neuroscience*, vol. 28, no. 49, pp. 13 066–13 074, 2008.
- [10] J. Levine, N. Gordon, and H. Fields, "The mechanism of placebo analgesia," *The Lancet*, vol. 312, no. 8091, pp. 654–657, 1978.
- [11] E. Frisaldi, A. Piedimonte, and F. Benedetti, "Placebo and nocebo effects: A complex interplay between psychological factors and neurochemical networks," *American Journal of Clinical Hypnosis*, vol. 57, no. 3, pp. 267–284, 2015.
- [12] W. A. Brown, "Expectation, the placebo effect and the response to treatment," *Rhode Island Medical Journal (2013)*, vol. 98, no. 5, p. 19, 2015.
- [13] S. Stewart-Williams and J. Podd, "The placebo effect: dissolving the expectancy versus conditioning debate." *Psychological Bulletin*, vol. 130, no. 2, p. 324, 2004.
- [14] J. D. Levine, N. C. Gordon, R. Smith, and H. L. Fields, "Analgesic responses to morphine and placebo in individuals with postoperative pain," *Pain*, vol. 10, no. 3, pp. 379–389, 1981.
- [15] F. Benedetti, M. Amanzio, S. Baldi, C. Casadio, and G. Maggi, "Inducing placebo respiratory depressant responses in humans via opioid receptors," *European Journal of Neuroscience*, vol. 11, no. 2, pp. 625–631, 1999.
- [16] R. Ader and N. Cohen, "Behaviorally conditioned immunosuppression." *Psychosomatic Medicine*, vol. 37, no. 4, pp. 333–340, 1975.
- [17] T. J. Kaptchuk, "The placebo effect in alternative medicine: can the performance of a healing ritual have clinical significance?" *Annals of internal medicine*, vol. 136, no. 11, pp. 817–825, 2002.
- [18] Z. Di Blasi, E. Harkness, E. Ernst, A. Georgiou, and J. Kleijnen, "Influence of context effects on health outcomes: a systematic review," *The Lancet*, vol. 357, no. 9258, pp. 757–762, 2001.
- [19] P. Fugelli, "James mackenzie lecture. trust-in general practice." *The British Journal of General Practice*, vol. 51, no. 468, p. 575, 2001.
- [20] M. Fässler, M. Gnädinger, T. Rosemann, and N. Biller-Andorno, "Placebo interventions in practice: a questionnaire survey on the attitudes of patients and physicians," *British Journal of General Practice*, vol. 61, no. 583, pp. 101–107, 2011.
- [21] F. L. Bishop, L. Aizlewood, and A. E. Adams, "When and why placebo-prescribing is acceptable and unacceptable: A focus group study of patients' views," *PLoS one*, vol. 9, no. 7, p. e101822, 2014.



- [22] N. Kisaalita, R. Staud, R. Hurley, and M. Robinson, "Placebo use in pain management: The role of medical context, treatment efficacy, and deception in determining placebo acceptability," *PAIN*, vol. 155, no. 12, pp. 2638–2645, 2014.
- [23] F. Benedetti, "Placebo and the new physiology of the doctor-patient relationship," *Physiological reviews*, vol. 93, no. 3, pp. 1207–1246, 2013.
- [24] U. Nitzan, Y. Bloch, and S. Fennig, "Using placebo medications in the clinical setting—an intellectual game or a possible reality?" *Israel Journal of Psychiatry and Related Sciences*, vol. 51, no. 3, pp. 182–187, 2014.
- [25] H. Spiegel, "Nocebo: the power of suggestibility," *Preventive medicine*, vol. 26, no. 5, pp. 616–621, 1997.
- [26] A. Vickers, "Why aromatherapy works (even if it doesn't) and why we need less research?" *British Journal of General Practice*, vol. 50, no. 455, pp. 444–445, 2000.
- [27] L. C. Park and L. Covi, "Nonblind placebo trial: An exploration of neurotic patients' responses to placebo when its inert content is disclosed," *Archives of General Psychiatry*, vol. 12, no. 4, pp. 336–345, 1965.
- [28] S. M. Schafer, L. Colloca, and T. D. Wager, "Conditioned placebo analgesia persists when subjects know they are receiving a placebo," *The Journal of Pain*, vol. 16, no. 5, pp. 412–420, 2015.
- [29] A. Sandler and J. Bodfish, "Open-label use of placebos in the treatment of adhd: a pilot study," *Child: care, health and development*, vol. 34, no. 1, pp. 104–110, 2008.
- [30] J. Aulas and I. Rosner, "Efficacy of a non blind placebo prescription," *L'Encephale*, vol. 29, no. 1, pp. 68–71, 2002.
- [31] T. J. Kaptchuk, E. Friedlander, J. M. Kelley, M. N. Sanchez, E. Kokkotou, J. P. Singer, M. Kowalczykowski, F. G. Miller, I. Kirsch, and A. J. Lembo, "Placebos without deception: a randomized controlled trial in irritable bowel syndrome," *PloS one*, vol. 5, no. 12, p. e15591, 2010.
- [32] F. L. Bishop, E. E. Jacobson, J. R. Shaw, and T. J. Kaptchuk, "Scientific tools, fake treatments, or triggers for psychological healing: How clinical trial participants conceptualise placebos," *Social Science & Medicine*, vol. 74, no. 5, pp. 767–774, 2012.
- [33] R. Tandjung, H. Tang, M. Fässler, C. A. Huber, T. Rosemann, R. Fent, and N. Badertscher, "The patient's perspective of placebo use in daily practice: a qualitative study," *Swiss medical weekly*, vol. 144, 2014.
- [34] G. Riva, "Virtual reality in psychotherapy: review," *Cyberpsychology & behavior*, vol. 8, no. 3, pp. 220–230, 2005.
- [35] M. M. North, S. M. North, and J. R. Coble, "Virtual reality therapy: An effective treatment for psychological," *Virtual Reality in Neuro-Psycho-Physiology: Cognitive, Clinical and Methodological Issues in Assessment and Rehabilitation*, vol. 44, p. 59, 1997.
- [36] C. Bryanton, J. Bosse, M. Brien, J. Mclean, A. McCormick, and H. Sveistrup, "Feasibility, motivation, and selective motor control: virtual reality compared to conventional home exercise in children with cerebral palsy," *Cyberpsychology & behavior*, vol. 9, no. 2, pp. 123–128, 2006.
- [37] S. van Vuuren and L. R. Cherney, "A virtual therapist for speech and language therapy," in *Intelligent Virtual Agents*. Springer, 2014, pp. 438–448.
- [38] T. J. Kaptchuk, P. Goldman, D. A. Stone, and W. B. Stason, "Do medical devices have enhanced placebo effects?" *Journal of clinical epidemiology*, vol. 53, no. 8, pp. 786–792, 2000.
- [39] M. Fillmore and M. Vogel-Sprott, "Expected effect of caffeine on motor performance predicts the type of response to placebo," *Psychopharmacology*, vol. 106, no. 2, pp. 209–214, 1992.