PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Effectiveness of a Projection-based Augmented Reality Exposure System in Treating Cockroach Phobia: Study protocol of a randomized controlled trial.
AUTHORS	Grimaldos, Jorge; Bretón-López, Juana; Palau-Batet, María; Díaz-Sanahuja, Laura; Quero, Soledad

VERSION 1 – REVIEW

REVIEWER	Dorothee Bentz University of Basel
REVIEW RETURNED	17-Nov-2022

GENERAL COMMENTS	The protocol describes a randomized controlled trial that investigates the effectiveness of a projection-based augmented reality (AR) exposure for cockroach phobia against the gold standard in vivo exposure therapy and a waiting list control group. Overall, the study is well designed and the research questions extend existing knowledge in the field. The novelty of the implemented AR makes it particularly timely. The protocol is sufficiently detailed in most parts, but lacks important information and clarity on outcomes and statistical procedure. To improve the quality of the study protocol, I recommend that the authors refrain from vague statements on the primary outcomes and use a strict predefined analysis strategy (including a strategy for multiple testing, such as Bonferroni correction). First, the study protocol defines two primary outcomes. For statistical rigor, I would suggest the authors define one of the primary outcomes as primary and subsume the remaining primary outcome under secondary outcomes. Second, I would suggest to define a strategy for alpha error cumulation that is based on the number of secondary outcomes explored. Third the primary outcomes are not clearly defined. Concerning the primary outcome BAT the following is mentioned “measuring the distance at which they are able to approach and to what extent they are able to interact with it, thus providing an objective measure of the behavioral response to the feared stimulus. During the BAT, fear, avoidance, and the maximum level of anxiety are also measured.” To me it remains unclear how the primary outcome is evaluated. Is approach behavior the primary ouctome. If yes, how is it measured? Are there any pre-defined steps (range)? Or is any of these three: fear, avoidance, and the maximum level of anxiety during the BAT the primary outcome? The details on how these outcomes are measured is also lacking and should be included in the protocol. Furthermore, the statement “In any case, to apply the most appropriate statistical analysis method, the state of the art in analytic methodology for RCTs will be reviewed

	before analyzing the data; thus, variations in the selection of the analytic procedures may occur." weakens the rigor of the protocol as it allows too much flexibility for possible a posteriori changes of the data analytics plan. Minor: Page 5 (line 50, 52): HDM is used instead of HMD Page 8: Please indicate who is on the clinical team, rather than just saying that the entire clinical team will evaluate the inclusion and exclusion criteria. Information about data management and the data management plan is not sufficient. Here, I recommend following the points mentioned in the SPIRIT guidelines.

REVIEWER	Arash Javanbakht Wayne State University
REVIEW RETURNED	15-Dec-2022

GENERAL COMMENTS	This is a protocol suggesting use of augmented reality (AR) technology for treatment of fear of insects. Although AR sounds very promising and possibly part of the future of the exposure therapy, there are multiple weaknesses in this project that reduce my enthusiasm. Introduction: the advantage of AR/VR over traditional exposure therapy is noted to be an issue of confidentiality. For sure there are easy ways to assure confidentiality in the clinic specially with fear of insects. There are many other advantages for AR/VR, the most important lack of access to feared objects in the clinic for traditional exposure therapy. Same applies to the advantages of AR over VR, as "comfort" is not a very important determining factor as are sense of control and the ability to navigate real world environment among others. Other issues such as reduced eye contact with the therapist are not a problem with advanced AR technologies such as the Microsoft Hololens where the HMD is like see-through sunglasses and the patient can comfortably see their real environment. The studies noted are older AR technologies, and addressing more advanced AR (Javanbakht et al, 2021) will be helpful. While AR has already shown to be an effective treatment in fear of insects/spiders, the argument in this work is that the specific method used in this RCT is superior to other AR methods. In that sense, comparing with traditional treatment will not help with addressing that hypothesis. I would argue if proven helpful, the major advantage of this technology over AR/VR would be lower cost as it uses a projector and not AR devices (good commercial technologies cost near $4000 a piece including shipping and tax). I still do not have a clear idea of how the technology works and how it looks in patient's view. Addition of diagrams and more images that clearly show the technology, especially in relation to the patient will be helpful. Overall, due to the above major concerns and lack of clarity, I recommend major revision to make a more clear paper. This should also include the rationale and the hypotheses driving the design.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1 comments:

Overall, the study is well designed and the research questions extend existing knowledge in the field. The novelty of the implemented AR makes it particularly timely. The protocol is sufficiently detailed in most parts but lacks important information and clarity on outcomes and statistical procedure. To improve the quality of the study protocol, I recommend that the authors refrain from vague statements on the primary outcomes and use a strict predefined analysis strategy (including a strategy for multiple testing, such as Bonferroni correction).

First, the study protocol defines two primary outcomes. For statistical rigor, I would suggest the authors define one of the primary outcomes as primary and subsume the remaining primary outcome under secondary outcomes.

First, we appreciate all the words of the reviewer 1, it has helped us to improve the general quality of the manuscript. Regarding the comments about the primary outcomes, we agree with them and, as we have explained above, we have defined the attentional bias task as a secondary outcome. We have made this change both in the manuscript and in the protocol registry.

Second, I would suggest to define a strategy for alpha error cumulation that is based on the number of secondary outcomes explored.

We thank this comment about alpha error cumulation related to the secondary outcomes. We tried to clarify this adding this explanation in the analysis section:

Page 13:

"To control the Type I error rate inflation, Bonferroni correction will be applied for all secondary outcome analyses."

Concerning the primary outcome BAT the following is mentioned "measuring the distance at which they are able to approach and to what extent they are able to interact with it, thus providing an objective measure of the behavioral response to the feared stimulus. During the BAT, fear, avoidance, and the maximum level of anxiety are also measured." To me it remains unclear how the primary

outcome is evaluated. Is approach behavior the primary ouctome. If yes, how is it measured? Are there any pre-defined steps (range)? Or is any of these three: fear, avoidance, and the maximum level of anxiety during the BAT the primary outcome? The details on how these outcomes are measured is also lacking and should be included in the protocol.

We agree with this comment, it helped us to explain deeply the primary outcome which could remain unclear. Following these suggestions, we have rewritten the description of the primary outcome (BAT) in the instruments section.

Page 10:

"The Behavioral Avoidance Test (BAT; adapted from [35]), will be used as a primary outcome. The BAT is an observational test that consists of the participants facing the feared stimulus, measuring the distance at which they are able to approach and to what extent they are able to interact with it, thus providing an objective measure of the behavioral response to the feared stimulus. During this test a cockroach will be presented inside a closed and transparent container, and the participant will be asked to get as close as possible, open the container, and interact with the cockroach using a piece of paper. The researcher will explain to the participant that it is an evaluation test and that they can end the test at any time. This test has been used in previous studies following the same procedure [13,15]. Specifically, "performance" is the dependent variable of this test. This variable is based on a 12-point scale which is based on the distance that the patient is able to approach (measured in meters marked on the floor) and ultimately interact with the cockroach. In this scale is ranged from "0", which represents that the participant does not want to enter the room and "12" represents that the participant is able to interact with the cockroach more than 2 minutes.

After the therapist have explained the instructions to the participant, he/she will be asked to what extent (from 0 to 10) they believe in the negative thoughts related to cockroaches. Additionally, fear, avoidance, and the maximum level of anxiety are also measured during this test on a scale ranging from 0 to 10."

Furthermore, the statement "In any case, to apply the most appropriate statistical analysis method, the state of the art in analytic methodology for RCTs will be reviewed before analyzing the data; thus, variations in the selection of the analytic procedures may occur." weakens the rigor of the protocol as it allows too much flexibility for possible a posteriori changes of the data analytics plan.

We appreciate this comment, and we agree that it could be ambiguous regarding possible posteriori changes of the data analytics plan. We stated that in order to be able to cope with some unexpected changes during the procedure that may occur in the future and following previous published protocols, but we agree that this can work against us and reduce the reliability of the trial. Finally, we decided to remove that statement following the recommendations of the reviewer 1.

Minor:

Page 5 (line 50, 52): HDM is used instead of HMD

Corrected.

Page 8: Please indicate who is on the clinical team, rather than just saying that the entire clinical team will evaluate the inclusion and exclusion criteria.

We agree that this statement was not clear. The clinical team of this project is composed by all the authors of this protocol. We have clarified this:

Page 8:

"The inclusion or exclusion of each case will be assessed by the entire clinical team in order to carry out a more objective and reliable selection process. This team is composed by all the authors of the present work. With the prior agreement of the participant, the audio of the diagnostic interview will be recorded and used to make an independent inter-rater assessment."

Information about data management and the data management plan is not sufficient. Here, I recommend following the points mentioned in the SPIRIT guidelines.

We appreciate this comment. Previously this information was described more briefly in the ethics section but, following the recommendations, we have decided to create a new section called "Data

collection and management" in which we have tried to explain with more detail all data management procedure:

Page 14:

"Data collection and management

Regarding data protection, this trial will comply with the existing guidelines in Spain and the European Union for the protection of patients in clinical trials. All the data collected from the evaluation interviews and the instruments included in the evaluation protocol of all the studies considered in this project will be kept under the data security conditions of the Emotional Disorders Clinic attached to Labpsitec, to which all the authors of the present work are linked as part of the research team. This clinic is governed by international and national ethical guidelines related to the practice and research in Clinical Psychology (64th World Medical Association General Assembly, Fortaleza, Brazil, October 2013; Code of Ethics of the Official College of Psychologists, 1987).

For ensuring data collection process, most of the instruments used in the evaluation protocol will be implemented through electronic means (www.qualtrics.com). Patients will receive a personal link in which they will be able to complete the questionnaires. Each participant will be linked to a code and all the data collected on paper (personal data, informed consent form and diagnostic interview) will be stored under key and will only be available to researchers responsible for the study, always protecting the right to privacy. All the clinical data (not personal data as name, telephone, etc.) will be transferred to a general database (with password protection) which will contain the corresponding codes of each participant, so that it is impossible to link this data to the participants. The primary use of the data is anonymous."

Reviewer 2:

Introduction: the advantage of AR/VR over traditional exposure therapy is noted to be an issue of confidentiality. For sure there are easy ways to assure confidentiality in the clinic specially with fear of insects. There are many other advantages for AR/VR, the most important lack of access to feared objects in the clinic for traditional exposure therapy. Same applies to the advantages of AR over VR, as "comfort" is not a very important determining factor as are sense of control and the ability to navigate real world environment among others. Other issues such as reduced eye contact with the therapist are not a problem with advanced AR technologies such as the Microsoft Hololens where the HMD is like see-through sunglasses and the patient can comfortably see their real environment.

The studies noted are older AR technologies, and addressing more advanced AR (Javanbakht et al, 2021) will be helpful.

We greatly appreciate the contribution of the reviewer 2, we believe that his experience in this field can greatly help improve our knowledge and the final quality of the manuscript.

Specifically, when in our manuscript we refer to other augmented reality systems that use a head-mounted display (HMD) system, we are referring to the one used in an RCT previously carried out by our research group. As explained in the introduction to the manuscript, this system turned out to be just as effective as the in vivo exposure treatment, but presented some problems such as dizziness, headache, or muscle discomfort due to wearing the glasses after a 3-hour session. As reviewer 2 very well comments, there are currently new augmented reality systems based on glasses (such as sunglasses) that are much more innovative and much more comfortable to use during long sessions, so these problems reported by patients in the commented study are solved. We want to thank the contribution of studies that use this type of more innovative technology, since our intention has never been to bias the information in favor of our system over others, we simply compared it with what we previously knew. We have decided to include this information in the introduction to provide the most up-to-date information and to be as honest as possible.

Pages 4 and 5:

"In the aforementioned RCT, some patients in the ARET group reported dizziness and back pain due to the use of the HMD [15]. In light of these issues, there is a need to continue to improve these systems and make them more natural and user-friendly. In this sense, the apparition of systems where the HMD consists of comfortable see-through glasses (such as sunglasses) that allow the patient to fully see the outside world and interact with it could offer an option to overcome these problems. A pilot parallel randomized controlled trial has tested an augmented reality exposure treatment based on an HMD using more innovative glasses for the treatment of patients suffering from arachnophobia. The results show that this system is effective for the treatment of arachnophobia both at post-treatment and at follow-up compared to the waiting list, thus offering a system that can be used in a simple and more friendly way for the user [19]."

While AR has already shown to be an effective treatment in fear of insects/spiders, the argument in this work is that the specific method used in this RCT is superior to other AR methods. In that sense, comparing with traditional treatment will not help with addressing that hypothesis. I would argue if proven helpful, the major advantage of this technology over AR/VR would be lower cost as it uses a projector and not AR devices (good commercial technologies cost near $4000 a piece including shipping and tax).

I still do not have a clear idea of how the technology works and how it looks in patient's view. Addition of diagrams and more images that clearly show the technology, especially in relation to the patient will be helpful.

Overall, due to the above major concerns and lack of clarity, I recommend major revision to make a more clear paper. This should also include the rationale and the hypotheses driving the design.

We appreciate these comments because it helped us for improving our manuscript, encouraging us to make it clearer regarding the objectives and the given background. Perhaps it was a mistake on our part, and we have not been able to adequately explain the objective of our work, which is not to prove that our projection-based augmented reality system is superior to other augmented reality systems. For this, as the reviewer points out, it would be appropriate to include a group that uses a different AR system to compare with. The main objective that we pursue with this work is not to belittle other AR systems, but to offer data about the effectiveness of a new, different AR system that does not use any type of wearable device. We seek to find out if this system is superior to the waiting list and at least as effective as traditional exposure, with the aim of being able to offer another possibility, based on evidence, effective and reliable, for the treatment of small animal phobia. We believe that the more options mental health professionals have for the treatment of mental disorders, the further and more patients we can reach, so beyond declaring this system superior to others, we want to evaluate its effectiveness, regardless of the existence of other effective AR systems.

The technology that we propose in this study is based on a different augmented reality system that completely dispenses with the use of any wearable device. In this sense, the augmented reality system that we present in this study is based on projection. That is, the stimuli are projected directly onto a table, in the same way that a small animal would do if it were in that place. In this way, the stimuli are not combined with the real world by means of software as is the case with the use of augmented reality glasses, but simply, in the eyes of the patient, the stimulus simply appears in the real world without having to use any complement. This system can be useful in different situations, such as when a patient who wears glasses to correct their vision cannot use the augmented reality glasses, for example. Or simply, this study can help to generate knowledge about different ways to implement augmented reality in psychological treatments without the use of technology based on wearable devices (like glasses).

We have made changes both in the introduction and discussion sections with the aim of clarifying these issues.

Pages 4 and 5:

“In light of these issues, there is a need to continue to improve these systems and make them more natural and user-friendly. In this sense, the apparition of systems where the HMD consists of comfortable see-through glasses (such as sunglasses) that allow the patient to fully see the outside world and interact with it could offer an option to overcome these problems. A pilot parallel randomized controlled trial has tested an augmented reality exposure treatment based on an HMD using more innovative glasses for the treatment of patients suffering from arachnophobia. The results show that this system is effective for the treatment of arachnophobia both at post-treatment and at

follow-up compared to the waiting list, thus offering a system that can be used in a simple and more friendly way for the user [19].

Our research group developed an AR system for small animal phobias that has been designed with the aim of offering a different AR alternative to the previously mentioned augmented reality systems."

Page 15:

"The implementation of AR technology in exposure treatments could have important advantages in solving some of the problems associated with more traditional ways of delivering exposure, such as in vivo exposure, highlighting access, acceptance, and adherence to the treatment [9]. The appearance of new AR systems has made possible to overcome some of the problems associated with this type of technology such as dizziness and discomfort caused by intensive use of a traditional HMD [15]. Currently some studies are already available that demonstrate the effectiveness of AR systems based on sunglasses-like HMD that greatly facilitate their use and reduce these associated problems [19].

In this study we present an alternative to HMD-based AR systems with the aim of increasing the availability of evidence-based tools for the treatment of small animal phobia in order to offer more tools that mental health professionals may have and thus be able to better adapt the treatment to each situation and specific case. In this line, the P-ARET offers a natural and friendly environment in which to carry out the treatment, and it is able to present the feared stimuli without the need to wear an HMD. This results in a very generalizable environment in which patients can behave completely naturally since the stimuli are projected on a physical surface. In addition, the P-ARET offers the possibility of interacting with the animals, which can respond immediately and naturally to the behavior of the patients, thus increasing the sense of presence and the judgment of reality, important key characteristics of virtual environments [58]."

We have also added images depicting the P-ARET system for facilitation how this technology looks.

End of the page 9:

Figure 2 shows an example of the P-ARET system.

Figure 2. *Images depicting the P-ARET system and an example of how the cockroaches looks like from the patient's view.*

VERSION 2 – REVIEW

REVIEWER	Dorothee Bentz University of Basel
REVIEW RETURNED	20-Feb-2023

GENERAL COMMENTS	The authors have addressed my points to my satisfaction.