Author's response to reviews

Title: Interreality for the management and training of psychological stress: study protocol for a randomized controlled trial

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Version: 3 Date: 30 May 2013

Author's response to reviews: see over
Dear Editor,

We really appreciated your careful evaluation of our manuscript entitled “Interreality for the management and training of psychological stress: study protocol for a randomized controlled trial” (MS: 6100045078638389)

In the following pages we have itemized the suggestions from the reviewer and we have presented our responses following each comment.

We have addressed each of the points raised by the reviewer in the revised manuscript and the responses are further elaborated upon below in the specific comments to the reviewer.

Sections that we revised in the papers following the reviewer suggestions are highlighted in a green color.

The article was re-formatted according to the journal style and in particular:

- The ethics statement was relocated to the methods sections;
- Table 1 and Table 2 were inserted at the end of the document text file;
- Figure legends were moved at the end of the document;
- All the text now is double line spacing;
- Now only the first word of the title is capitalized.

Moreover, we noticed and corrected some mistakes in the References Section.

Finally, we added a new author (Morganti Luca), since he strongly helped us in the revision of the paper.

We are grateful for your important contribution to our work, and we hope you can appreciate our effort in improving the quality of the article.

I look forward to hearing from you,

Best Regards,

Federica Pallavicini
Response to Reviewer

Major Compulsory Revisions

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1) On the last paragraph of page 4, I would use another word for “Objective”, as biosensors and behavioural analyses, although being more objective than self-reports, rely on inferential procedures

We agree with the reviewer that the term “Objective” is not the best one to describe this type of measure.

In general terms, there are several ways to assess the user's stress level. In general terms, it is possible to use three different assessment strategies: 1) a direct assessment of the individual's perceived subjective stress; 2) an indirect assessment of factors that mediate the stress response, such as anger, anxiety, and coping abilities; 3) and a psychophysiological assessment of stress indexes, such as breathing rate, heart rate, heart rate variability, skin conductance and skin temperature.

In the INTERSTRESS clinical protocol, we proposed an integrated and quantitative approach to assess individual’s stress by combining pervasive biosensors and behavioral analysis to monitor the individual’s stress level and both his/her general and psychological status.

Thanks to the reviewer’s meaningful suggestion, we corrected the article as following (page 6, last paragraph):

- “Integrated and quantitative assessment of the user’s stress level using biosensors and behavioral analysis: the level of stress will be continuously assessed in the virtual and in the real world by recording the participant's behavioral and emotional status”.

2) Page 4, paragraph 4: please delete the first is on the following sentence “The aim of this is proposal is to create” and a space between in and vivo is required on the sentence “current real-life (invivo) limitations of psychological”

Thanks to the reviewer for having point out these errors in the text. Typos have been corrected (page 6, paragraph 2).

3) Page 6, paragraph 3: are you expecting that some of the teachers and nurses to be mental retarded? Do you mean chronic headaches?

We apologize for this mistake in the text that the reviewer properly underlined. Clearly, given the complexity of the professions of individuals of our samples, we excluded the hypothesis that both teachers and nurses that we are recruiting could suffer from mental retardation. We did not notice to having include this criteria and we thank the reviewer to have point it out. We corrected this error, deleting “absence of mental retardation” in the inclusion criteria (see page 8 last paragraph).

4) Page 8: How confident are the authors on the new system for acquiring HR and respiratory data? Was the system validated?

The new system for acquiring HR and respiration data was tested and published in two papers:
Moreover, the authors have a huge expertise on psychophysiological signal processing and indexes interpretation in term of emotions, stress and affective states.

5) Page 10: Are mobile (psychologist office) versus home setting (participant home) training going to be compared? These are two completely “stressful” environments...

We agree with the reviewer that the clinical, mobile and home setting are very different training environments and they will be not be compared in our analyses.

In this section of the paper (see page 14-15) we simply describe technological devices that are used in the three settings of the INTERSTRESS training, that are:

1. **The Clinical setting** (psychologist’s office) where participants meet the therapist for cognitive restructuring and relaxation training (see also page 19, Clinical setting Section for more details).
   
   In this setting the hardware elements used are:
   - A cardiovascular belt, developed by Pisa National Centre of Research, to measure heart rate and respiration activity.
   - The Virtual Reality control unit: ACER ASPIRE portable computer with CPU Intel® Core™i5, graphic processor Nvidia GeForce GT 540M and Bluetooth support;
   - A head-mounted display: Vuzix VR Bundle with twin high-resolution 640x480 (920,000 pixels) LCD displays, iWear® 3D compliant;
   - A joypad (Xbox Controller)

2. **The Mobile setting** (participants’ daily life, out of the therapist’s office) where participants are able to rehearse/relax outside the psychologist’s office during their daily life everytime they using a Smartphone app developed for this specific purpose (see also page 20, Mobile setting Section for more details)
   
   In this setting the hardware elements used are:
   - A shimmer, developed by University of Pisa, a small wireless sensor platform that will record and transmit psychophysiological (ECG) and kinematic data in real-time.
   - A Smartphone (iPhone 4S).

3. **The Home setting** (participant’s home): individuals have the possibility to access the contents useful for stress management logging via PC in Second Life and visiting the INTERSTRESS Learning Island (see also page 20, Home setting Section for more details).
   
   In this setting the hardware elements is:
   - A portable computer (ACER ASPIRE 5742G-484G64MNKK) with internet connection
6) Page 8: can the authors discuss why was not skin conductance level assessed as it measures sympathetic activation, that is also involved in the stress response?

The reviewer pointed out a crucial question about psychophysiological parameters. Actually, we strongly agree with this observation. The main problem with biosensors used to measure skin conductance level is about the positioning. Since most of them are to be placed on the fingers, it’s almost impossible to use such type of biosensors in daily life situations or in laboratory sessions, where individuals use a joypad.

For this reason, we tried to find biosensors contemporary comfortable for the participants, with an acceptable signal, and not affected by hands use.

According to these criteria, we identified the wrist as the best position and “Empatica” resulted the best biosensor to detect signals.

Even if the platform has been adapted to accept an index of skin conductance level, we decided to not take this signal into consideration for several reasons.

1) First of all, according to our previous studies, we have been able to model stress basing on cardiovascular indexes and questionnaires. The results of these researches have been published in the following paper:


2) On the other hand, being able to model stress basing on cardiovascular indexes and questionnaires allow us to build a stress model based on just one sensor, electrocardiogram. To use only this signal allow us to be unobtrusive rather than using other biosensors.

3) Another consideration is that measures of sympathetic activation is already taken by using the electrocardiogram. Even if this signal is not a direct measure of the sympathetic activation, such as
skin conductance level, electrocardiogram offers a number of indexes related to sympathetic activation and also to sympathovagal balance.

7) Page 12, paragraph 3: it seems that the stressful scenarios were validated before they were developed. I would move this sentence to the end of paragraph 3. Where the relax scenarios also pre-tested?

We completely agree with the reviewer and now we have moved the sentence “The efficacy of these selected “stressful scenarios” in eliciting negative emotional responses was preliminary tested on a sample of ten teachers” to the end of the paragraph (see page 17, paragraph 1).

Regarding relaxing virtual environments (as reported on page 18, first paragraph), relaxing audio narratives were based on Guided Imagery procedures and developed according to emotive engineering’s principles. Differently from our previous version of the paper, in this revised version we added some literature in this field (Tusek et al., 1997; Rossman, 2009).

Moreover, we created the INTERSTRESS scenarios on the basis of similar virtual environments that were used and validated in a lot of previous studies (Manzoni et al., 2008; Gorini & Riva, 2008; Ferrer-García et al., 2009; Pallavicini et al., 2009).

Since in our first draft of the paper this fact was not clearly reported, we changed the sentence “The relaxation environments were created especially for INTERSTRESS and they include, for example, a beach, a lake, a campfire, a mountain summit and a desert.”

We corrected the phrase and we added literature of mentioned previous studies.

The text is now as follows (see page first, last paragraph):

- “The INTERSTRESS relaxation environments were created on the basis of similar virtual relaxing environments that were used and validated in previous studies [45, 52-54] and they include, for example, a beach, a lake, a campfire, a mountain summit and a desert”.

8) STAI-Y1 will be filled in by each participant 20 times. Is this not excessive? How are you going to deal with the learning effect? Why not use just the VAS-A, before and after?

We agree with the reviewer that filling STAI-Y1 20 times could be excessive.

Actually, in the INTERSTRESS trial STAI-Y1 will be filled only 10 times by each participant: once at the baseline and once after each of the 9 scenario.

We did not explain clearly this fact in the previous version of the paper and so we modified the sentence “In order to measure the psychological variations occurring during the different stressful environment exposure, subjects will complete the VAS-A and the STAI-Y1 immediately before and after each scenario” as it follows (see page 22, Assessment Session Section):

- “In order to measure the psychological variations occurring during the different stressful environment exposure, subjects will complete the VAS-A and the STAI-Y1 at the baseline and after each scenario”.

Moreover, in order to clear our methodology, we added text (baseline + after each environment) in Table 1 and Table 2 (page 32-33) Session I Section, after the sentence “Give STAI-Y1 and VAS-A”. 


**Minor Essential Revisions**

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9) **Page 5, paragraph 4: DSS (Decision Support System)**

Typo has been corrected (page 7, paragraph 3).

10) **Page 7: as mentioned previously stress maybe related to depression. On the other hand, depressive symptoms are not uncommon on these professionals. Should not a depression scale be included?**

We totally agree with the reviewer that depression and stress are two very interconnected phenomena. We will not include in the INTERSTRESS training individuals suffering from depression, according to DSM-IV-TR (see also page 9 Clinical Assessment Section) in order to exclude stress condition related to clinical depression.

We will consider the reviewer’s suggestion to add a depression scale to assess sub-clinical depression in our sample. Such type of scale, in fact, could give us interesting data about the relationship between individuals’ stress levels and their experienced negative emotional symptoms.

11) **Page 7: after last paragraph: include which scale will be used to assess technological abilities.**

Following the suggestion of the reviewer, we inserted in the papers (see page 9) the description of the self-assessment scale used to assess technological abilities.

The added text follows:

- “**Technological Skills Assessment**

  At the beginning of the training a self-assessment scale will be used to evaluate patients’ technological abilities. The 4-item questionnaire was created in order to assess individuals’ perceived technological skills in the use of Personal Computer and Smartphone”.

Moreover, we revised the initial sentence of the Section “Clinical Assessment” (page 9) and the text is now as following:

- “**Clinical assessment**

  In order to not include participants suffering from DSM-IV-TR Axis I disorders, individuals will be assessed before the start of the training by a Master-level charted psychologist or a PhD-level psychotherapist with the following semi-structured interview”

12) **Page 10: “Virtual scenarios for stress exposition” Do you mean exposure?**

Thanks to the reviewer’s note. We corrected the typo (page 16).

13) **Page 12, paragraph 4: it would be nice to have a glimpse on what the nurses stressful scenarios will consist on.**

Following the reviewer’s suggestion, we added a short description on what nurses stressful scenarios will consist on (see page 17, paragraph 2):
- “Virtual environments that will be created will include stressful situations that could be experienced by nurses at work, such as to be reproached by colleagues, to manage an emergency and to cope with patient’s criticism.”

14) Page 12, paragraph 5: the phrase “the participants have to imagine precisely how stress arises including respective thoughts and emotions” is a bit strong, as it is not possible to precisely assess imagination. How can the authors guaranty this?

The reviewer is right to highlight this sentence, that could confuse the reader.

In the Control Group, Guided Imagery has the same aim of Virtual Reality adopted in the Experimental Group, that is to induce stress in individuals.

In particular, we hypothesize that Virtual Reality will be more effective than Guided Imagery in inducing stress, since in previous studies (Borst & Kosslyn, 2010) some patients report difficulties when asked to imagine specific situations and furthermore, emotions have been shown to modulate visual imagery, impairing visualization of detailed scenes.

In order to be clearer, we changed the sentence “The imagination exercises should be as realistic as possible; the participants have to imagine precisely how stress arises including respective thoughts and emotions” as following (see page 17, paragraph 3):

- “Participants will be asked to close their eyes and to imagine themselves as vivid as possible during the situations described, following an audio narrative matching the VR experiences.”

15) Is it possible to further explain “INTERSTRESS will focus on modifying them through a more contextualized experiential process.”?

What we would underline through this sentence is the fact that the INTERSTRESS training, differently from more traditionals CBT based approaches, seeks the patient’s change through not a passive but an active and experiential learning.

In order to clarify this concept, we inserted in this section of the paper (page 6, paragraph 4) a small sentence, that follows:

- “In the INTERSTRESS training, in fact, individuals will be actively involved in the learning process, experiencing stressful situation reproduced in virtual environments and reflecting on their daily life stress level with the help of advanced technology, such as smartphone and unobtrusive biosenors”.

**Discretionary Revisions**

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16) Is stress one of the sources of anxiety and depression as pointed in the text or can trace anxiety be, as well, a source of stress? This bimodal path could also be discussed. Eventually, this relation is tangentially addressed on the 2nd paragraph of page 4: “These disorders depend a great deal on how the person experiencing a stressor is put together —psychologically and physically”.
We completely agree with the reviewer that trait anxiety could be a source of stress. In fact, it has been demonstrated by a lot of studies that individuals with high level of dispositional anxiety are very sensitive to stress and that they show strong physiological responses to stressor.

Following the suggestion of the reviewer we add a sentence and some literature references in order to underline this fact (page 4, first paragraph):

- “Repeated and early exposure to stress, above all in persons with a particular genetic disposition, as well as high level of trait anxiety, may result in a decreased threshold for developing anxiety [6-8]”.

17) As stated on the third paragraph of page 4, it might seem that INTERSTRESS is going to solve the problem of “the poor quality of trials, considerable heterogeneity observed between trials and evidence of significant publication bias make the pooled findings insecure.” Please, reformulate the paragraph.

We agree with the reviewer that this paragraph was not very clear. The sentence underlined by the reviewer is simply referring to what has been stated by the Cochrane Database, that is that CBT based stress treatments findings are still insecure and that further clinical research is needed to tune existing protocols and fully exploit its clinical potential.

What we would like to underline in the sentence that follows is that the INTERSTRESS project, since stress is very personal, will adopt a new paradigm for e-health – Interreality – in order to develop a stress assessment, prediction and treatment situated in the experience individuals.

In order to clear this concept, we separated these two paragraphs and we deleted the initial part of the sentence at page 5, paragraph 4 (“To overcome the above limitations”).

We changed the text as it follows:

- “For this aim, the INTERSTRESS..”.

18) Page 4, paragraph 3: It would be useful to have further explanations on what the Interreality paradigm is all about.

In order to further explain on what the Interreality paradigm is all about, we added in the paper (page 5, last paragraph) the following sentence:

- “The Interreality claim is that bridging virtual experiences (fully controlled by the therapist, used to learn healthy behaviors and coping skills) with real experiences (the therapist can identify critical situations and assess clinical change) – using advanced technologies (virtual worlds, advanced sensors and smartphones) is a feasible way to address the complexity of a lot of mental disorders, including psychological stress.

On one hand, patient are continuously assessed in the virtual and real worlds by tracking their behavioral and emotional status in the context of challenging tasks (customization of the therapy according to the characteristics of the patient). On the other hand, feedback is continuously provided to improve patients’ skills through a conditioned association between performance and execution of assigned tasks (improvement of self efficacy).”

For more details it is possible also to see related references [20-24].

In addition, in order to be not repetitive, we deleted the following sentence (page 6):
- “To reach this goal, the project will use a completely new concept for e-realtà – Interreality – that integrates assessment and treatment within a hybrid, closed-loop empowering experience bridging physical and virtual worlds.”

19) Page 13, paragraph 4: asking the participants to fill a short online questionnaire after the “home experience” would help to assess if they really have learned from the experience.

We thank the reviewer for the suggestion and we will consider to add a short questionnaire after the home experience.