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BIOFEEDBACK, VIRTUAL REALITY AND MOBILE PHONES IN THE TREATMENT OF GENERALIZED ANXIETY DISORDER (GAD): A PHASE-2 CONTROLLED CLINICAL TRIAL

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Generalized Anxiety Disorder (GAD) is a psychiatric disease characterized by long-lasting anxiety that is not focused on a specific object or situation. Within the treatment of GAD, physical (relaxation and controlled breathing), behavioral (visualization and controlled exposure) and cognitive control strategies (challenging negative thoughts) represent a key part of the treatment, even if they difficult to learn. To overcome this limitation, the EU-funded INTREPID research project (IST-2002-507464) proposes improvement of exiting treatment for GAD through the use of a biofeedback-enhanced virtual reality (VR) system, used both for relaxation and controlled exposure. Furthermore, this experience is strengthened by the use of a mobile phone that allows patients to perform the virtual experience even in an outpatient setting. This approach was tested in a Phase II randomized controlled trial (NCT00602212), including three groups of four patients each, resulting in a total of 12 patients. The first group consisted of the VR and Mobile group (VRMB) including biofeedback, the second of the VR and Mobile group (VRM) without biofeedback, and the third the waiting list (WL) group.

This study provides initial evidence for better efficacy of treatment for the VRMB group. Subjects belonging to this group reported a higher decrease in some of the anxiety psychometric questionnaires after the treatment than both VRM and WL groups, even if the VRM group, too, reported some significant improvements at the end of therapy. Moreover, qualitative reports concerning outpatient use of mobile phones suggests that it can solve a classical problem of VR therapies–the impossibility of using a VR system in the real life context of the patient.

Keywords: Generalized Anxiety Disorder (GAD), Virtual Reality (VR), Biofeedback, Relaxation, Portable Devices

Introduction

Generalized anxiety disorder (GAD) is a common anxiety disorder that typically has an early age of onset, a chronic course and a high degree of comorbidity with other anxiety and mood disorders (Kessler et al., 1994). According to the DSM-IV-TR (APA, 2000) the essential feature of GAD is at least six months of "excessive anxiety and worry" about a variety of events and situations. Anxiety and worry are often accompanied by additional symptoms like restlessness, being easily fatigued, difficulty concentrating, irritability, muscle tension and disturbed sleep.
The lifetime prevalence of GAD in the general population

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is 4-7% (Allgulander et al., 2003), while among individuals seeing their physicians for psychological problems, 25% of them have a diagnosis of pure GAD. Indeed, in primary care facilities, GAD is the most frequent anxiety disorder and the second most frequent of all mental disorders (Wittchen, 2002; Barret et al., 1998). The high prevalence of GAD in the general population and the severe limitations it causes point out the necessity to find new strategies to treat it in a more efficient way.

GAD is usually treated with medications and/or psychotherapy. In particular, the two most promising treatments seem to be cognitive therapy and applied relaxation. As shown by numerous studies, both of these treatments are equally effective, (Siev & Chambless, 2007; Wittchen, 2002) immediately and over long-term periods. Cognitive treatment helps patients recognize and alter patterns of distorted thinking and dysfunctional behavior, while relaxation serves to reduce the increased physical arousal often strictly associated with this disorder. In fact, physical arousal can be voluntarily altered with training in relaxation skills that enables patients to shift physical functions voluntarily toward those that naturally occur in a relaxed state (Barlow et al., 1992). Progressive muscle relaxation and general imagery techniques can be used as therapy progresses since the ability to relax, in any place or situation, is vital to reduce anxiety levels.

Even if relaxation represents a useful approach for the treatment of GAD, it presents an important limitation–it is difficult to learn. Traditionally, relaxation techniques are verbally taught by a therapist or recorded on an audiotape. Recently, a series of CDs playing calming music have been used to help individuals relax, showing positive effects on anxiety reduction by achieving psychological benefits including distraction and sense of control over symptoms. Music interventions also have reported good results to reduce state and trait anxiety, to ease stress, and to increase relaxation (Guzzetta, 1989; Zimmerman et al., 1989). These CDs strengthened the positive effect of calm and sedative music with relaxation techniques to achieve enhanced effects. To increase effectiveness, commercial relaxation DVDs have also integrated visual stimuli. In such a delivery, the visual representation of the scenario supports the process of relaxation creating an isolated context in which the subject can feel comfortable.

Virtual reality (VR) can also be used to facilitate relaxation processes in stressed or anxious subjects (Manzoni et al., 2009; Ferrer-García et al., 2009; Manzoni et al., 2008; Gorini & Riva, 2008; Villani et al., 2007) by visually presenting key relaxing images (Freeman et al., 2004). The advantage of VR compared to CDs or DVDs is its ability to induce a sense of presence in the users, that can be defined as the "feeling of being in a world that exists outside of the self " (Riva et al., 2004; Riva, 2009).

The visual presentation of a virtual calm scenario can facilitate patients' practice and mastery of relaxation, making the experience more vivid and real than the one that most subjects can create using their own imagination and memory. This has the ability to trigger a broad empowerment process within the experience induced by a high sense of presence (Riva & Gaggioli, 2009; Villani & Riva, 2008; Villani et al., 2009). VR can be provided using desktops or laptops connected to a variety of peripheral devices, such as head-mounted displays and joysticks and even through different kinds of mobile devices, such as the new generation of portable audio-visual devices, cellular phones and hand-held personal digital assistants (PDA) equipped with enough raw horse power to deliver a believable 3D experience. Another area of continuing research interest has been the use of various biofeedback techniques for the treatment of anxiety disorders (Reiner, 2008; Rice et al., 1993; Rice et al., 1982). Biofeedback therapies use scientific instruments to measure, amplify and feedback physiological information to the patient being monitored. The information assists the patient in gaining self-regulation of the physiological process being monitored.

Biofeedback consists of the use of biosensors and electronic devices for monitoring human physiological reactions so that individuals can see their body functions and how they react to different anxious or stressful stimuli. The idea is that understanding these habitual patterns will allow the person to take steps to change them in order to reduce symptoms associated with different diseases and disorders. Biofeedback-based treatments show the patients their abnormal physiological response levels helping them to recognize when they are becoming abnormally anxious and, in turn, to help control their anxiety. Biofeedback has demonstrated value for hyperarousal reduction training in GAD (Walley et al., 1994), and represents an effective alternative to medications, particularly for patients who do not respond well, who have a potential for dependency, or who refuse to take, prescription drugs.

Unfortunately, one of the main limitations of traditional biofeedback is that subjects receive very simple audio and

video feedback information from a computer that processes their physiological data, such as blood pressure, heart rate, skin temperature, sweat gland activity, and muscle tension, in real time. This method is anti-intuitive for many patients, for two main reasons. First, the graphic display of physiological functions often is of little interest for the patient, who is concerned primarily with symptom relief, not physiology. Second, the interaction of the patient with the feedback environment primarily involves verbal communication with the therapist, who advises the patient on the relaxation techniques. This interaction is important from an educational perspective, but reduces the level of the patient's active and intuitive participation.

To overcome this limitation, the EU-funded INTREPID research project (IST-2002-507464) tried to improve the treatment of GAD through the use of a biofeedback enhanced VR system used both for relaxation and controlled exposure. One of the main advantages of VR in association with biofeedback is the possibility to create complex and fully controlled environments with specific features that can be adapted to the needs of any single subject (Riva, 2007; Freeman et al., 2004).

However, a critical issue related to the use of virtual exposure in the treatment of GAD is the lack of availability of a VR system in the real life context of the patient. Both the cost and the setting of the system limit its use to the health care center, hospital or therapist's office. To solve this issue, we included in the protocol the use of a mobile phone, enabling the patient to visualize a guided experiences in an outpatient setting.

Instruments and Methods

Goals

The main aim of the study was to test the approach proposed by the INTREPID project in a Phase II randomized controlled trial (NCT00602212) with GAD patients.

Subjects

One hundred and five consecutive patients seeking treatment in a public health-care institute in Italy were seen for screening interviews for admission to the study. Criteria for participation in the study included diagnosis of GAD following DSM-IV-TR criteria, age between 18 and 50 years, no psychotherapy treatment received for their GA, in case of taking pharmacotherapy, the type and amount of medication had to remain consistent during the experimental period, no history of neurological diseases, mental retardation, psychosis, alcohol or drug dependence, and no migraine, headache, or vestibular abnormalities. Women who were pregnant or breastfeeding were also excluded.

Of these, 91 either did not fulfil the inclusion criteria or were excluded for other reasons such as time constraints or involvement in other treatments. All patients meeting the inclusion criteria were then randomly assigned to the waiting-list group and to one of the two possible treatment conditions described below.

Thirteen patients were randomly assigned to one of the following groups (see Figure 1–Consort Flow Chart–for details)–the VR and Mobile group (VRMB) including biofeedback;, the VR and Mobile group (VRM) without biofeedback, or the waiting list (WL) group. The randomization scheme was generated using the Web site www.randomization.com. After randomization, a patient in the VRM group refused to participate in the study abandoning the trial for family and work reasons.
Finally, 12 patients, nine females and three males, (see Tables 2-3 for details about epidemiological and clinical variables of the sample) entered the treatment phase. The majority of them (70%) had graduated from upper secondary school, were employed at the time of the study and were married.

The study received ethical approval by the Ethical Committee of the Istituto Auxologico Italiano and was recorded in the Clinicaltrials.gov database with the official trial number "NCT00602212".

Clinical Assessment

A semi-structured interview was used in order to identify relevant DSM-IV-TR diagnostic criteria for GAD in the sample. The following psychometric questionnaires were also administered to each patient at pre-treatment and upon completion of the clinical trial:

- Generalized Anxiety Disorder -7 questions (GAD-7, Spitzer et al., 2006), a seven-item valid and efficient tool for screening for GAD and assessing its severity in clinical practice and research.
- Penn State Worry Questionnaire (PSWQ; Meyer at al., 1990), a 16-item self-report inventory designed to assess trait worry and to capture the generality, excessiveness, and uncontrollability characteristics of pathological worry.
- Beck Anxiety Inventory (BAI; Beck et al., 1993), a 21-item scale which covers cognitive, behavioral and physiological symptoms of anxiety. The BAI is a standardized and well-used assessment measure with good psychometric properties used to assess anxiety.

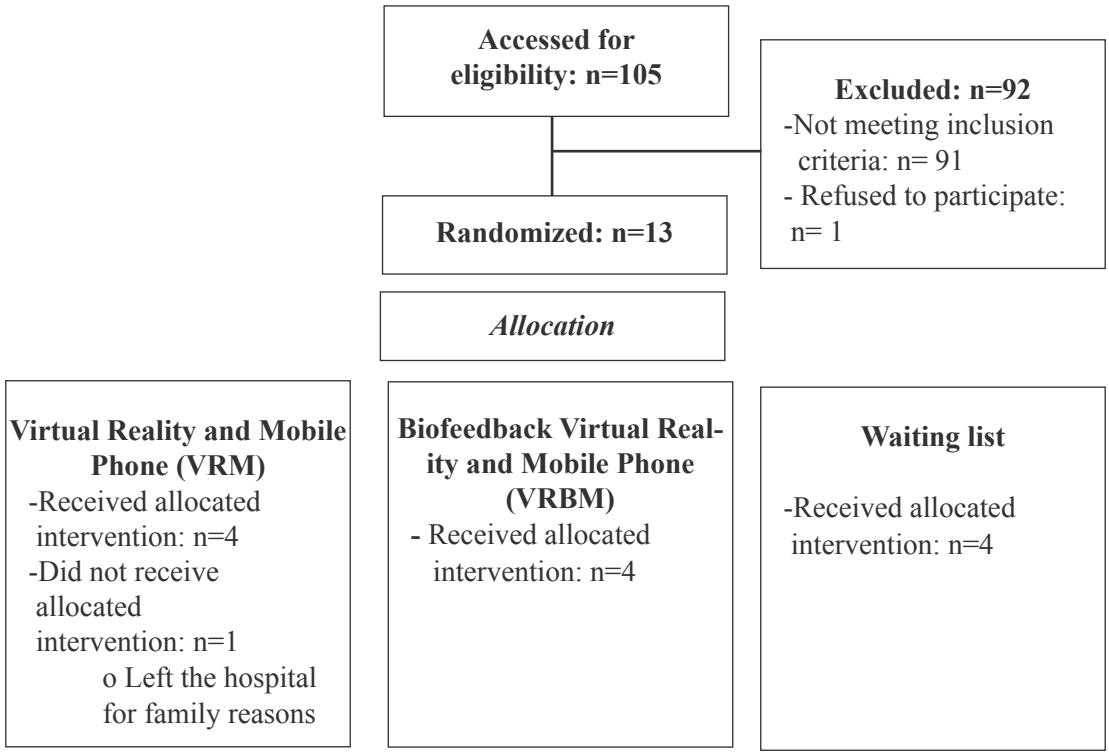

Figure 1. Consort Flowchart for Randomized Trial.

• State-Trait Anxiety Inventory Form Y-2 (STAI-Y, Spielberger et al., 1970), a two-scale questionnaire containing 20 items each that measure anxiety in adults. The STAI clearly differentiates between the temporary condition of "state anxiety" (STAY-Y1) and the more general and long-standing quality of "trait anxiety" (STAY-Y2).
• Hamilton Anxiety Rating Scale (HAM-A; Hamilton, 1959) was one of the first rating scales developed to measure the severity of anxiety symptoms and is still widely used today in both clinical and research settings. The scale consists of 14 items, each defined by a series of symptoms, and measures both psychic anxiety (mental agitation and psychological distress) and somatic anxiety (physical complaints related to anxiety).

The two experimental conditions that received treatment (VRM and VRMB) were also assessed at the beginning and at the end of each of the eight protocol sessions using the following questionnaires:
• State-Trait Anxiety Inventory Form Y-1 (STAI Y-1, Spielberger et al.,1970). The STAY Y-1 addresses state anxiety, which could be defined as a temporary emotional condition characterized by apprehension, tension, and fear about a particular situation or activity.
• Visual Analogue Scale for Anxiety (VAS-A) measures anxiety across a continuum. It is a horizontal line, 100 mm in length, anchored by word descriptors at each end (No anxiety; Very severe anxiety). The patient marks on the line the point that they feel represents their perception of their current state.

At the beginning and end of each training session (baseline and post treatment measures consisting in three minutes of rest condition with eyes opened) the Galvanic Skin Response (GSR) and the Heart Rate (HR) were also recorded. Psychophysiological data was obtained using the GSR/HR Sensor Module, developed by Aurelia Microelettronica Multisensor System during the INTREPID project. The module is a part of the Multisensor System, whose purpose is to obtain analog data from different physiological sensors and, after conditioning and digitalizing, send the data to a host PC using a wireless connec-

tion. The GSR/HR sensor module is composed of a GSR block that acquires and digitalizes raw analog skin conductance data, and of a HR block recording heart rate digital samples from a commercial NONIN iPOD Integrated Pulse Oximeter.

Finally, heart rate of the patients included in the VRMB group was also assessed during the treatment sessions, in order to obtain and monitor in vivo measures of their emotional state (biofeedback condition–see below for further details).

Experimental Protocol

To study the efficacy of the different protocols, a between subjects design was used with three experimental conditions and repeated measurements (pre and post-treatment). Specifically, the study compared the following conditions:

1. Virtual Reality + Mobile Phone without Biofeedback Condition (VRM). In this experimental condition patients received an eight-session VR-based treatment (see Table 1) including both relaxation and exposure and techniques supported by HR biofeedback. In sessions one through six, the patient explored a beautiful tropical island (developed by ESIEA using 3DVIA Virtools 4 - Figures 5 & 6) following a predefined path leading to different relaxing areas–Campfire, Beach and Waterfall. In these areas the patients started to relax by observing the flickering campfire, watching waves lapping gently on a shore, or looking at the waterfall and fish pond. Each experience was supported by an audio narrative based on progressive muscle relaxation and/or autogenic techniques. To improve the efficacy of the training and to increase the effects of relaxation, patients experienced at home, using a mobile phone, a non-navigable version of the same virtual reality environment experienced during the therapy. The patient was asked to train relaxation abilities at least once a day for the entire duration of the treatment following the treatment plan provided by the therapist. In sessions seven and eight the patients explored the island again, this time reaching a Gazebo in which they were exposed to pre-selected words or images related to their personal stressful events. The patients were then asked to use the learned relaxation techniques to cope with them.

2. Virtual Reality + Mobile Phone with Biofeedback Condition (VRMB). The patients experienced the same protocol described above, but with the biofeedback support. Specifically, in the sessions with the therapist, HR variations were used to modify specific features of the virtual environment:

Table 1
Clinical Protocol

1. Initial clinical evaluation of the patient's state; 2. The patient is connected with biosensors that record his/her physiological parameters (skin conductance, heart rates, respiration). A baseline measure of these parameters is registered for 3 minutes in rest condition; 3. The patient wears a head-mounted display connected with a pc and handles a joystick; 4. The patient starts exploring the virtual environment: a beautiful tropical island facing on the ocean. The patient, following the narrative recorded by the therapist, reaches the island by boat and explore it. Following a footpath that guides him/her through the island, the patient arrives to the starting point, where different panels indicate the directions to the different target areas. In each of these areas a relaxing exercise is provided; during this training, following the indications given by the voice-guide, the patient tries to relax him/herself. In the VRMB group only, some elements of the virtual environment are directly modified by the patient's heart rate variation recorded in real time. Thus, the patient receives an immediate feedback of his/her level of activation (as in the traditional biofeedback techniques), but with the extra value given by the "presence" experienced in the virtual environment. 5. Once completed the virtual reality session, physiological parameters are recorded again for 3 minutes in rest condition; 6. Final clinical evaluation of the patient's state. 7. Daily relaxation homework using the mobile phone.

a. Campfire (sessions 1-2). The physiological parameter controls the fire intensity–a reduction in the patient's physiological activation reduces fire intensity until it disappears;
b. Beach (sessions 3-4). The physiological parameter controls the movement of the waves: a reduction in the patient's physiological activation reduces the movement of the waves until the ocean becomes completely calm;
c. Waterfall (sessions 5-6): The physiological parameter controls the movement of the water: a reduction in the patient's physiological activation reduces the movement of the water until the water flow becomes completely still;
d. Gazebo (sessions 7-8): The physiological parameter controls the size of a stressful image or video: a reduction in the patient's physiological activation reduces the size of the stimulus until it disappears;
3. Waiting List Condition (WL). This was a control condition, in which patients were included in a waiting list and did not receive any kind of relaxation training.

Hardware (see Figure 2-4):
The hardware elements of the INTREPID system include
• A wireless (Bluetooth) multi-sensor module: GSR/HR Sensor Module including finger sensors that simultaneously measure heart rate and electrodermal activity (GSR).
• The Virtual Reality control unit: Asus G2S portable computer with Intel® Core™2 Extreme Processor X7800, Nvidia GeForce 8600 GT 256 MB DDR3 graphic card, Bluetooth support.
• A head-mounted display: Vuzix iWear VR920 with twin high-resolution 640x480 (920,000 pixels) LCD displays, iWear® 3D compliant.
• The therapist's netbook: (EEPC 100H - BK039X) used to control in real time the features of the virtual environment and to assess physiological parameters.
• A joystick (Xbox Controller)
• A crosscable between the portable computer and the therapist's netbook.
• A smartphone (HTC Touch Pro T7272) for relaxation homework.

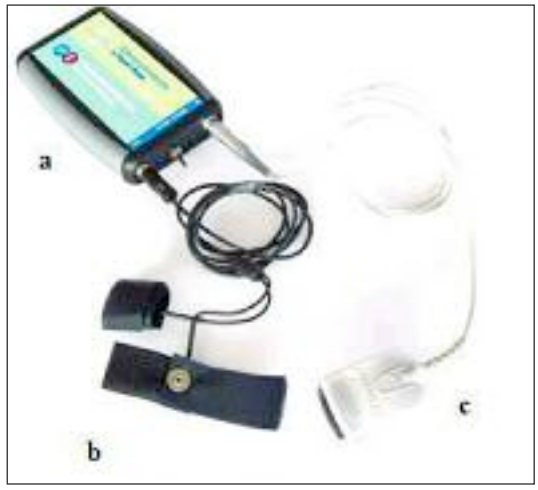

Figure 2. (above) GSR/HR Sensor Module:a) the control box; b) the Skin Conductance Response sensors; c) the Blood Volume Pulse sensor.

Figure 3. (above, right) The control unit: a)a personal computer (Asus G2S; Intel® Core™2 Extreme Processor X7800); b)a crosscable; c)a therapist's laptop (EEPC 100H - BK039X); d)A joypad (Xbox Controller); e)a head-mounted display (Vuzix iWear VR920).

Figure 4. (right) The smartphone given to the patients, in which they can experience a Homecare Scenario, achieved by presenting the same virtual environment of the therapist's office training session.

VIRTUAL ENVIRONMENT (PC version: 3DVIA Virtools by Dassault Systèmes - www.virtools.com; Mobile Version: Windows Mobile 6)
Developed by the ESIEA INTREPID team (J.L. Dautin, J. Ardouin, F. Crison and M. Le Renard -www.esiea.fr).

Figure 5. A screenshot from INTREPID in the VRM Group. The figure illustrates a campfire, one of the relaxing environments shown to the patients during the treatment.

Figure 6. A screenshot from INTREPID in the VRMB Group. During the relaxation exercise a bar in the right of the environment, connected with the patient's physiological parameter their emotional state.

RESULTS

Descriptive methods were used to demonstrate the consistency of the three groups, describing participants' characteristics. Analyses of variance were used to evaluate the baseline characteristics of the three groups involved in the study, and the overall significance of improvement across outcome measures. For each patient, change in psychometric and physiological measures were calculated and analysed using Wilcoxon Signed Ranks Test for matched groups for both intervention and control groups. The magnitude of change was estimated and the 95% confidence intervals given.

In order to obtain qualitative data about the usefulness of the portable device (PDA) subjective reports of participants at the experimental groups were used.

EPIDEMIOLOGICAL AND CLINICAL VARIABLES

Table 1 summarizes epidemiological data and clinical characteristics of the three groups of subjects. Non-parametric tests indicated that there were no significant differences in age and years of education of the subjects (Table 2). Similarly, no significant differences were found in their clinical characteristics (PSWQ, BAI, HAM-A, STAI-Y2 and GAD-7) (Table 3).

Table 2
Demographic details by study group

	Group				
	VRMB	**VRM**	**WL**	**F**	**p**
Variables	**Mean (SD)**				
Age	41.25 (13.24)	48.5 (12.662)	51.25 (9.845)	.746	.502
Years of Education	14.25 (2.5)	11.75 (4.787)	10.25 (3.594)	1.164	.355

Table 3
Pre-Treatment and post-Treatment Scores on Psychometric questionnaires of Anxiety for All Groups. As it is possible to see in this table there aren't significant differences in pre-treatment scores on psychometric questionnaires of Anxiety in All Groups

	Group				
	VRMB	**VRM**	**WL**	**F**	**p**
Variables	**Mean (SD)**				
PSWQ Pre	41.25 (13.24)	48.5 (12.662)	51.25 (9.845)	1.332	.311
Post	48.5 (12.396)	47.25 (8.732)	50 (5.292)		
BAI Pre	28.5 (14.059)	26.75 (20.37)	27.50 (13.204)	.012	.988
Post	15.50 (11.733)	18.25 (10.813)	17.75 (6.946)		
HAM-A Pre	25.00 (8.679)	19.50 (3.697)	25.00 (7.439)	.838	.464
Post	15.00 (4.802)	18.75 (9.743)	16.25 (6.702)		
STAI-Y2 Pre	53.25 (2.630)	50.75 (4.573)	58.50 (9.434)	.471	.639
Post	48.50 (12.396)	46.25 (9.912)	58.00 (5.831)		
GAD7 Pre	16.00 (8.367)	10.25 (5.560)	14.25(4.573)	.856	.457
Post	6.50 (4.509)	8.25 (3.948)	8.75 (6.185)		

Psychometric variables

Non-parametric analyses were conducted in order to analyze the treatment effects for pre versus post-treatment on the psychometric variables within the three groups. Results show a significant decrease in the BAI scores ($Z=-1.826$; $p<.05$), GAD-7 ($Z= -1.826$; $p<.05$) and STAI-Y2 ($Z=-1.826$; $p<.05$) in the VRMB group, a significant decrease in the PSWQ scores ($Z=-1.826$; $p<.05$) in the VRM group, and a significant decrease in the GAD-7 scores ($Z=-1.841$; $p<.05$) in the WL group (Table 4). Non-parametric K-Independent Tests were used to analyze differences between the subjects in the pre and post-treatment anxiety questionnaires. No significant differences were found for $p<.05$ (BAI: Chi-Square=1.385, p=.548; GAD-7: Chi-Square=4.720, p=.083; HAM-A: Chi-Square=2.192, p=.358; PSWQ: Chi-Square=.299, p=.868; STAI-Y2: Chi-Square=4.606, p=.093), but some differences emerged with $p<.1$ for GAD-7 (Chi-Square=4.720, p=.083) and STAI-Y2 (Chi-Square=4.606, p=.093).

Table 4
Non-parametric 2-Dependent Samples Test in Anxiety Questionnaires pre and post treatment for all groups

	Group		
Variables	**VRMB**	**VRM**	**BF**
STAI pre-STAI post			
Z	-1.826	-1.473	.000
p	.05	.11	.54
PSWQ pre-PSWQ post			
Z	-1.461	-1.826	-1.604
p	.12	.05	.11
HAM pre-HAM post			
Z	-1.604	-.365	-1.461
p	.05	.42	.11
GAD7 pre-GAD7 post			
Z	-1.826	-.921	-1.841
p	.05	.23	.05
BAI pre-BAI post			
Z	-1.826	-1.461	-1.604
p	.05	.13	.11

Psychometric variables, physiological responses and subjective reports in VRMB and VRM groups
The GSR, the HR, as well as the STAI-Y1 and the VAS-A were recorded at the beginning and at the end of each training session in the VRMB and in the VRM groups. Regarding the physiological responses, we observed that the mean of the differences of HR and GSR before and after each session tended to be higher in the VRMB group

than in the VRM group (Table 5). Nevertheless, the difference between the two experimental groups was not statistically significant. Regarding the psychometric variables, we observed that the mean of the differences of STAI-Y1 and VAS-A before and after each session tended to be higher in the VRMB group than in the VRM group (Table 6). Again, the difference between the two experimental groups was not statistically significant.

Table 5
Mean of HR differences between Pre and Post all sessions training

	Group	Mean	Standard Deviation
Mean of HR differences Pre-Post all sessions training	**VRMB**	4,67	3,327
	VRM	2,83	1,169

Table 6
Mean of STAI-Y1 and VAS-A differences between Pre and Post all sessions training

	Group	Mean	Standard Deviation
Mean of STAI-Y1 differences Pre-Post all sessions training	**VRMB**	6,7917	2,71761
	VR	5,2083	3,26886
Mean of VAS-A differences Pre-Post all sessions training	**VRMB**	7,7083	4,28782
	VR	6,4583	3,82563

At the end of the treatment a questionnaire about the usefulness of the PDA was given to all subjects included in the two experimental groups. Ninety-one precent of participants were very satisfied with the PDA, 6% were neutral about it, and 3% were completely unsatisfied. Participants who thought that the PDA was useful said that by using it they could consolidate the training received at the therapist's office, and also that they used it when they were very anxious at home to try to reduce anxiety. On the contrary, the reason for dissatisfaction was explained as the difficulty in using it or in the lack of immersion provided by the PDA compared with the VR environment.

Discussion

Research over the past three decades has shown that the use of virtual reality (VR) was quite effective in treating several psychological problems, especially anxiety disorders. As stated before, VR has been traditionally used to deliver graded exposure, as an adjunct to cognitive-behavioral therapy to treat pathologies such as phobias, post-traumatic stress disorder, and other disorders related to anxious stimuli management. In this study, we used VR in the treatment of GAD, an anxiety disorder characterized by excessive anxiety and worry about a variety of events and situations. Specifically, we tested the following hypotheses:

- The possible use of VR and mobile phones in the treatment of GAD. We used a specific virtual environment–a tropical island–both for controlled exposure and relaxation within an eight-session bi-weekly protocol. Moreover, this experience was strengthened by the introduction of a mobile phone used to visualize guided experiences, similar to the one experienced in VR, in an outpatient setting.

- The possibility of improving this protocol by adding biofeedback to it. Biofeedback therapies use scientific instruments to measure, amplify and feedback physiological

information to the patient being monitored. In the present study, the physiological data was used to modify specific features of the virtual environment in real time. For example, the physiological data controlled the movement of the waves: a reduction of the patient's physiological activation reduced the movement of the waves until the ocean becomes completely calm.

The study offered three interesting results. On one side, it confirmed the possibility of using VR in the treatment of GAD. Both experimental groups improved their clinical outcome after the end of the treatment. On the other side, it supports the clinical use of a mobile phone to re-experience and anchor the contents of the VR sessions at home. When interviewed about the usefulness of the PDA, the majority of patients (91%) answered that they were very satisfied with it because it helped them to consolidate the relaxation training in the absence of the therapist. Moreover, the portable device represents a useful instrument that can be used every time the patient needs it, not only at home, but also in every real-life situation in which he/she needs help to become relaxed, solving the problem of the lack of availability of a VR system in the real life context of the patient.

Finally, the study provided initial evidence of the added value offered by the use of biofeedback. Only in the VRMB group did we find a significant reduction in the GAD symptoms (GAD-7) and in the anxiety scores (STAI) from the beginning to the end of the treatment. Regarding the patients' physiological responses, we found a tendency indicating a decrease in HR and GSR between the pre and post-session measurements in the VRMB group, higher than in the VRM.

Even if characterized by some limitations (limited number of subjects, caution in generalizing the results, etc.) a Phase II controlled trial is necessary to understand if a new treatment can helps patients. Our results demonstrate that biofeedback used in combination with VR increases its effect helping patients to better control their physiological parameters and to gauge their success in a more efficient way.

In conclusion, this study represents the first experimental evidence that firstly, VR can also be used in the treatment of GAD, secondly, in a VR treatment, patients can take advantage of a mobile device that delivers guided experiences similar to those experienced in VR in an outpatient setting and lastly, the effectiveness of an immersive virtual relaxing environment that helps patients master the complex training of relaxation can be reinforced by using physiological data to modify specific features of the virtual environment in real time.

Since Phase II of the study has provided promising results, Phase III will be performed in order to consolidate and generalize this initial data.

Acknowledgments
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