Journal of CyberTherapy & Rehabilitation
Spring 2012, Volume 5, Issue 1

VIRTUAL REALITY EXPOSURE THERAPY VERSUS COGNITIVE BEHAVIOR THERAPY FOR PANIC DISORDER WITH AGORAPHOBIA: A RANDOMIZED COMPARISON STUDY

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Our objective was to compare the effects of Virtual Reality exposure therapy (VRET), cognitive behavior therapy (CBT), and a waitlist control condition in patients with panic disorder with agoraphobia (PDA). Ninety two out-patients were initially randomized in three arms, 29 treated with VRET, 31 with CBT, and 32 assigned to the waitlist. At the end of a 12-week period, the patients assigned to the waitlist were re-randomized in VRET or CBT groups. No between-group significant differences appeared at the end of the first phase, however a lower responder rate was observed in the waitlist group. After the second randomization, response rates were not different in the VRET and CBT groups (respectively 38.7% and 48.5%; p=0.46). During the 9-month follow-up period, the response rates remained stable without differences between groups. Thus, VRET seems to be an effective treatment for PDA with short-term and long-term therapeutic results equivalent to those obtained with CBT.

Keywords: **Agoraphobia, Cognitive Behavior Therapy, Panic Disorder, Virtual Reality, Randomized Controlled Trial**

Introduction

Panic disorder with agoraphobia (PDA) is a chronic and recurrent psychiatric illness with a lifetime prevalence of about 2% in Europe and a well-known negative impact on the quality of life of suffering subjects (Alonso et al., 2004; Candilis et al., 1999; Goodwin et al., 2005). Drug treatments (specific antidepressants) and cognitive behavior therapy (CBT) are recognized as effective treatments with response rates varying between 40 and 80% according to studies and measures (Mitte, 2005; Otto & Deveney, 2005).

Virtual Reality exposure therapy (VRET), using real-time computer graphics, body tracking devices, visual displays and other sensory input systems, has been developed and proposed as an alternative therapeutic method useful in psychiatric illnesses, especially anxiety disorders (Gorini & Riva, 2008; Pull, 2005; Riva, 2008; de Carvalho, Freire, & Nardi, 2010). VRET is based on the gradual presentation of phobic stimuli to the patient via a computer-generated virtual environment that is synchronized with head and body motion (Wiederhold & Wiederhold, 2005). This desensitization through virtual immersion has been successfully used in most anxiety disorders (Coelho, Waters, Hine, & Wallis, 2009; Gorini & Riva, 2008; Pull, 2005). VRET may have some advantages when compared to standard exposure (Côté & Bouchard, 2008) as it takes place in the privacy of the therapist's office, can be repeated or prolonged easily, is less time-consuming for the therapist and more acceptable by the patients (Garcia-Palacios, Botella, Hoffman, & Fabregat, 2007; Garcia-Palacios, Hoffman, See, Tsai, & Botella, 2001).

Two meta-analyses of VRET in anxiety disorders have been published (Parsons & Rizzo, 2008; Powers & Emmelkamp, 2008). Both showed marked positive effects of VRET, with mean effect sizes of 0.95 and 1.11 on anxiety measures, which were equal or even superior to those of in vivo exposure techniques. Nevertheless, all these studies were conducted on small samples and a limited numbers of subjects: 13 trials (n=397) (Powers & Emmelkamp, 2008) and 21 trials (n=300) (Parsons & Rizzo, 2008).

To date, there is only limited evidence for VRET use in PDA. Case studies have been reported (Jang, Ku, Shin, Choi, & Kim, 2000; Wiederhold & Wiederhold, 2005). North et al (North, North, & Coble, 1996) showed the efficacy of VRT in 30 agoraphobic students versus a non-treated control group of the same size. Vincelli et al. (Vincelli et al., 2003) developed a specific

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VRET program for panic disorder and agoraphobia named the experiential-cognitive therapy (ExCT): a package integrating a CBT program with four VR environments (elevator, supermarket, subway and a large open square). A preliminary investigation randomly allocated 12 consecutive patients to ExCT (eight sessions), CBT (12 sessions), and a waitlist (Vincelli et al., 2003). Both CBT and ExCT significantly reduced the number of panic attacks. Another study was conducted by the same group, comparing four sessions of ExCT to 12 sessions of CBT in two samples of 20 patients each (Choi et al., 2005). Results were similar in post-test assessments, but long-term effectiveness of ExCT was relatively inferior to standard CBT. Botella et al. (Botella et al., 2007) reported a controlled study comparing VRET and CBT programs, each including nine weekly sessions, in panic disorder with or without agoraphobia. In post-treatment and follow-up assessments nine months later, VRET and CBT showed the same therapeutic results both being significantly superior to those obtained in the waitlist group. However this study was conducted on a relatively small sample size (12 subjects per group).

A recent study showed that a computer simulation of a simple 3-D computer animation of a short bus trip, from a first person perspective, may induce anxiety, and electrodermal and respiratory alterations in patients with PDA (Freire, De Carvalho, Joffily, Zin, & Nardi, 2010). The use of VRET in PDA is also encouraged by the knowledge of the role of vestibular dysfunctions in anxiety and by the potent impact of VR exposure on this phenomenon (Jacob, Whitney, Detweiler-Shostak, & Furman, 2001; Redfern, Furman, & Jacob, 2007; Viaud-Delmon, Ivanenko, Berthoz, & Jouvent, 2000; Viaud-Delmon, Warusfel, Seguelas, Rio, & Jouvent, 2006). These data need to be completed with a controlled research designed to clarify the process and outcome of "pure" CBT and "pure" VRET in PDA. In the present study, our primary objective was to compare pure VRET and a standard CBT program on a short- and long-term period. Our secondary objective was to compare both therapies with the absence of treatment (waitlist) on a short-term scale.

Subjects and Design

The sample was made up of outpatients referred to three centers for specialized treatment in Lyon, Paris, and Luxembourg university hospitals. They were screened by the principal investigator of each center using a structured interview based upon the DSM-4 (American Psychiatric Association, 1996), the MINI (Lecrubier et al., 1997), and several anxiety and depression scales. To be included, subjects had to meet the DSM-IV (American Psychiatric Association, 1996) criteria for PDA. Patients with current major depression, or a score greater than 18 on the Hamilton rating scale for depression (Hamilton, 1960) at the screening visit were excluded. Patients with bipolar disorder, schizophrenia or other psychotic disorders, alcoholism, or street drugs use were not eligible. A history of CBT for PDA, or a current psychotherapy, was also an exclusionary factor. Patients who had received treatment with antidepressants, neuroleptics, anxiolytics or mood stabilizers within the two weeks preceding the entry were also excluded. Eligible patients were not allowed to take any psychotropic medication, with the exception of low doses hypnotics, and could not receive psychotherapy during the study.

After the first evaluation, subjects were randomized either to VRET (12 sessions), CBT (12 sessions) or a waitlist control condition for three months (see the flow chart of the study, Figure 1). An assessment was done at the end of this first three-month period to compare the three groups. Then, the waitlist patients were re-randomized into VRET or CBT groups for three months of treatment (12 sessions). Hence, the whole sample was analyzed at three months and nine months after treatment. Patients received a two-page information leaflet about the trial and signed an informed consent. An ethic committee approved the protocol. Randomization was kept secret and delivered by the biostatistics department of the CHU of Lyon through a phone call to the secretary of each center.

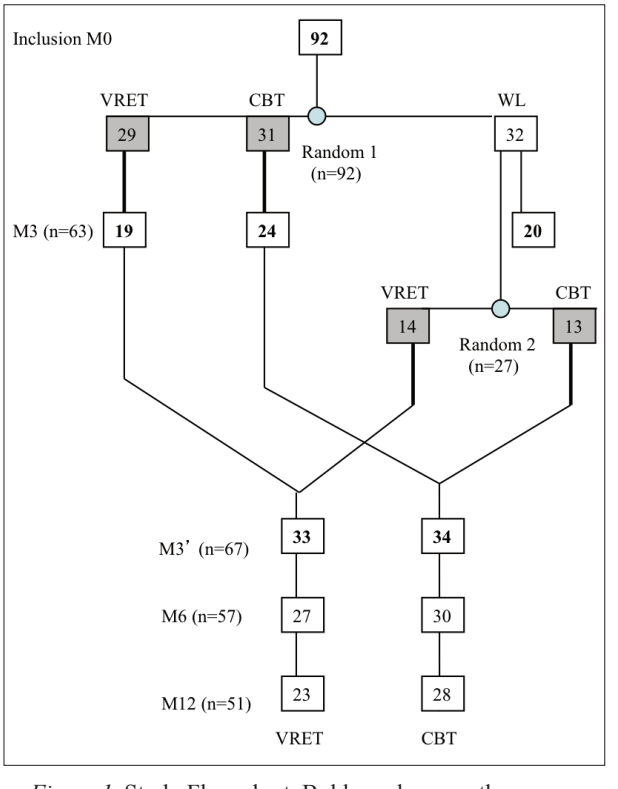

Figure 1. Study Flow chart. Bold numbers are the groups taken into account in the two main analyzes (M3 and M3'), and gray boxes indicate the total final population after the second randomization (n=87). Seven subjects initially randomized in the WL group had no assessment at M3 owing to availability problems, but continued the study (random 2).

Treatment

Both treatments comprised 12 one-hour therapeutic sessions and were applied by the same pool of therapists to control for the therapist effect. The therapists were post-graduate psychologists or psychiatrists, had practiced CBT for at least five years, and had an intensive training in VRET before starting the study.

CBT Methods

Cognitive and behavior methods used were those classically recommended for PDA (Cottraux et al., 1995; Landon & Barlow, 2004), and were highly structured and reproducible. Detailed manuals with guidelines for each session and checklists of the techniques were provided to the therapists and information sheets were given to the patient.

The treatment aimed at reducing both avoidant agoraphobic behavior, and the frequency of panic attacks. Session 1 comprised functional analysis of the relationships between emotions, behavior and cognition, and relaxation teaching. Patients received written information about panic attacks and agoraphobia, and a tape-recorded relaxation program. They were advised to practice relaxation 10 minutes every day. Cognitive and behavioral components were implemented from session 2 to 12. The cognitive component used respiratory control with provoked hyperventilation and cognitive restructuring. The subjects were taught to reattribute their symptoms to hyperventilation and/or tachycardia induced by stressful stimuli. Prolonged exposure in imagination to anxiety provoking scenes and interoceptive exposure to anxiety-related physical sensations were used. Misinterpretations of bodily sensations are discussed in a Socratic manner. A further step was the elicitation and disputing of automatic negative thoughts (e.g., becoming crazy or having a heart attack) and danger schemata. Questioning of automatic catastrophic thoughts and basic danger schemata were maintained outside the sessions through a daily five-column recording form discussed with the therapist. The behavioral component consisted of graduated exposure tasks agreed on by the therapists and patients and evaluated with a behavioral avoidance test form. Homework completion was discussed and cognitive techniques were implemented to facilitate subsequent exposure. During the last session, patients were advised to generalize these techniques to any situation that triggers anxiety.

Virtual Reality Exposure Therapy

The VRET program included 12 sessions using virtual environments developed specifically for this research at the Collège de France (Paris, France) institute. The choice of 12 environments was made by a panel of four experts in CBT for anxiety disorders taking into account the Fear Questionnaire ratings of panic with agoraphobia patients, and their clinical experience: subway scenes; tunnels (walking); elevator and tunnels; shopping in a supermarket; car driving on a road in a lonely countryside or near a ravine; travelling on a plane; entering and sitting in a movie theatre; car driving in a lonely town; car driving in a tunnel and stopped by an accident; travelling by bus in a lonely town; being caught in a sensorial conflict (derealization inducing VRET scenario); and street scenes and crowded subways. For example, the subway scenes included navigating in the stations' tunnels, a subway ride and a moving train (Figure 2a and 2b). According to the subjects' anxiety level, the tasks gradually included walking in the station, getting on the ride, staying in the train while it's at a stop, and finally riding for one or more stops. In the supermarket scene (Figure 2c), the subject was supposed to walk progressively in the shop, look at various items in the shelves, and when possible checking out at the cash register. In all the scenarios, the subject had the ability and was encouraged to explore visually the scene all around him in order to create an immersion effect and to enhance presence in the virtual world.

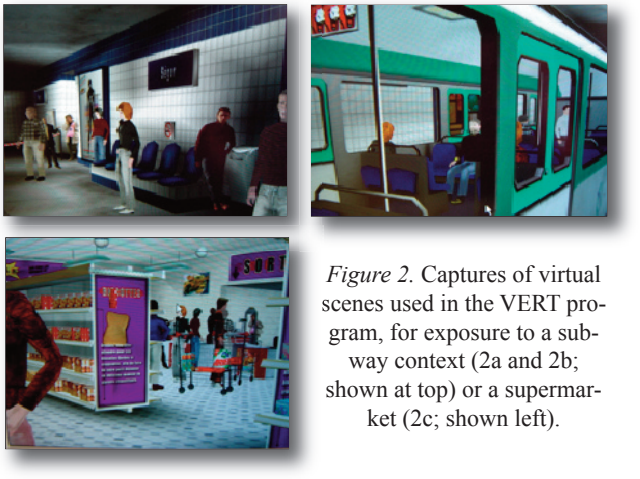

Figure 2. Captures of virtual scenes used in the VERT program, for exposure to a subway context (2a and 2b; shown at top) or a supermarket (2c; shown left).

All VR scenes were presented through a head mounted display (HMD) which provided a 60° diagonal field of view (Kaiser Pro view 60™), tracked head movement and was connected to a PC running the VR program developed with Virtools software.

In the first session, the patient was familiarized with the technique and gave four ratings while he or she was confronted briefly with the images of each of the 12 scenarios:

- Does the scenario represent a significant problem?

- Rating on the 0-100 Subjective Unit of Disturbance (SUD) the level of anxiety that would be felt in real life.

- Rating on the SUD the level of anxiety created by the VR images.

- Classification of the 12 scenarios along a hierarchy (fear thermometer): from the less disturbing (=1) to the most disturbing (=12). This allowed a progressive immersion into more and more fearsome scenarios.

The therapists conducted the computer program while taking into account the verbal and non-verbal reactions of the patients. Some patients, familiar with computer management, were able to carry out the navigation into VR on their own. Each scenario was of graded complexity according to the general difficulties encountered in agoraphobia. The therapists interacted verbally with the patient to enhance the illusion of presence. VRET was presented in blocks of 10 minutes. Patients received the general instruction to expose themselves in real-life situations, but had no formal written and structured exposure homework whereas the CBT group subjects did. They were informed that the therapy included only the VRET sessions and that this method could

be effective to treat their disorder. Detailed manuals with guidelines for each session and checklist of the techniques were provided to the therapists and information sheets were given to the patient.

Measures

In order to assess the impact of the intervention on the phobic symptoms, all patients completed the Fear Questionnaire (FQ) (Marks & Mathews, 1982) at baseline and at each visit. The other phobia measures were the Panic Disorder Severity Scale (PDSS) (Shear, Rucci et al., 2001), the Chambless Agoraphobic Cognitions (CAS) scale (Chambless, Caputo, Bright, & Gallagher, 1984), and the Panic, Phobia and Generalized Anxiety Scale (PPGAS) (Cottraux, Bouvard, & Légeron, 1985). Anxiety and depression were assessed through the State and Trait Anxiety questionnaire (STAI) (Spielberger, 1983), the Hamilton Anxiety Rating Scale (HARS) (Hamilton, 1959), and the 21-item Beck Depression Inventory (Beck, Steer, & Garbin, 1988). The Sheehan Disability Scale (SDS) (Sheehan, Harnett-Sheehan, & Raj, 1996) was also used at baseline and at each visit, as well as the Global Assessment of Functioning scale (GAF) (American Psychiatric Association, 1996) the Dissociative Experience Scale (DES) (Bernstein & Putnam, 1986) and the Work and Social Adjustment scale (WSA) (Mataix-Cols et al., 2005). At the first therapeutic session only, both the therapist and the patient filled out the Expectancies Rating Scale (ERS), rating the expectancies of improvement from zero to eight; the higher the score the worse the expectations of improvement. French validated versions of all the scales were used (Bouvard & Cottraux, 2005). At the end of the treatment, the Therapeutic Relationship Evaluation Scales (TRES) were filled in (the therapists evaluated the patients and the patients their therapists). These scales (Cottraux et al., 1995; Hoogduin, De Haan, & Schaap, 1989) consisted of 12 pairs of bipolar adjectives presented ranging from one (agreeable) to six (disagreeable). The higher the scores, the less favorably the relationship was evaluated.

Statistical Analyses

Values were expressed as mean and standard deviation (SD) or frequency and percentage. For socio-demographic and clinical scales, baseline comparisons of CBT, VRET and WL groups were done with Fisher's exact test for categorical variables and with Kruskal-Wallis test for dimensional variables. The response criterion was a 50% or more decrease of the FQ agoraphobia sub-score between baseline and post-treatment visits. The three groups were compared on this response rate at M3, and subsequently the two groups three months and nine months after treatment. The response rates were also compared using the Fisher's exact test, and the course of response rates over time in VRET and CBT were compared using two-level hierarchic models: logistic regressions with random intercepts. Secondary outcome criteria were FQ and other scales' means comparison between VRET and CBT groups at M3, M6 and M12 with the Kruskall-Wallis test. All statistical analyses performed with SAS software Version 9.1.3., $p < 0.05$, were considered statistically significant for all tests (two-tailed).

Results

Ninety two outpatients (30 males and 62 females) were randomized in three arms: 29 in VRET, 31 in CBT, and 32 in the waitlist (WL) group (see Figure 1). At the end of the first 12-week period (M3), 27 patients from the WL group were randomized in the two treatment arms: 14 in the VRET group, and 13 in the CBT group (five subjects stopped the trial before the second randomization). After three months of treatment (M3'), 33

Table 1

Baseline Characteristics of the Total Sample and of the Three Treatment Groups (n=92)

	VRET	CBT	WL	Comparison
	n=29	n=31	n=32	p value
Sex				0.64
Males	8 (27.6 %)	12 (38.7 %)	10 (31.3 %)	
Females	21 (72.4 %)	19 (61.3 %)	22 (68.8 %)	
Age	37.7 (7.3)	36.6 (10.6)	37 (11.3)	0.89
FQ				
Agoraphobia	18.2 (11.7)	21.2 (9.7)	24.25 (10.3)	0.11
Social Phobia	11.6 (9.0)	12.65 (7.9)	12.8 (10.2)	0.83
Blood-injury phobia	13.0 (9)	14.2 (9.8)	16.3 (9.1)	0.38
Anxiety-depression	18.8 (10.1)	20.4 (7.55)	19.75 (8.2)	0.70
Disturbance	6.1 (1.6)	6.1 (1.9)	6.7 (1.45)	0.26
PDSS	17.8 (5.6)	18.0 (5.1)	17.3 (6.0)	0.9
HARS				
Total	27.7 (11.4)	28.8 (10.7)	28.4 (9.9)	0.97
Psychological anxiety	13.7 (6.15)	14.35 (5.5)	14 (5.7)	0.92
Somatic anxiety	14 (6.1)	14.4 (6.5)	14.4 (4.75)	0.97
SDS	14.9 (8.8)	16.5 (7.2)	15.1 (6.7)	0.73
GAF	50.6 (8.2)	52.1 (11.1)	51.6 (10)	0.95

FQ=Fear Questionnaire; PDSS=Panic Disorder Severity Scale; HARS=Hamilton Anxiety Rating Scale; SDS=Sheehan Disability Scale; GAF=Global Assessment of Functioning

Table 2
Mean Scores (and SD) of Anxiety and Other Scales in VRET and CBT Groups at the Four Visits of the Study (n=87)

	Baseline		M3'		M6		M12	
	VRET	CBT	VRET	CBT	VRET	CBT	VRET	CBT
FQ scores								
- agoraphobia	20.6 (11.6)	21.6 (10.2)	12.8 (10.0)	12.5 (9.2)	13.6 (9.8)	10.5 (10.0)	11.6 (10.2)	10.0 (10.1)
- social	11.6 (8.6)	13.1 (8.5)	9.2 (8.7)	8.2 (7.4)	8.9 (8.4)	6.0 (5.1)	10.6 (8.8)	6.9 (7.1)
- blood/injury	14.1 (9.2)	14.2 (9.8)	11.7 (9.5)	9.7 (7.9)	11.4 (8.6)	7.7 (7.5)	11.9 (10.2)	7.4 (7.7)
- anxiety/dep.	19.6 (9.4)	19.2 (7.5)	14.4 (10.3)	13.2 (9.2)	11.7 (9.7)	9.4 (8.9)	10.9 (8.3)	8.5 (7.4)
- disturbance	6.3 (1.5)	6.0 (1.9)	4.39 (2.2)	3.8 (2.2)	4.4 (2.5)	3.0 (2.3)*	3.6 (2.5)	3.0 (2.8)
PDSS total	18.2 (5.5)	18.2 (5.2)	11.7 (6.3)	9.1 (5.3)	9.3 (6.5)	8.0 (6.5)	8.8 (6.3)	7.7 (8.0)
CAS	34.0 (10.6)	33.6 (9.0)	27.5 (7.7)	26.0 (6.8)	25.4 (9.7)	23.4 (6.5)	20.8 (7.5)	20.9 (8.1)
STAI trait	55.6 (10.8)	55.4 (9.2)	49.4 (11.3)	47.2 (10.6)	48.2 (13.0)	42.5 (11.3)	47.5 (12.0)	43.4 (11.3)
STAI state	46.1 (12.5)	43.7 (11.4)	41.0 (11.8)	37.3 (9.0)	38.6 (12.3)	35.3 (10.4)	40.3 (13.3)	36.9 (13.6)
HARS total	27.7 (10.8)	26.9 (10.6)	20.0 (13.1)	15.9 (10.7)	19.3 (14.9)	14.3 (11.7)	17.2 (13.7)	12.8 (13.1)
-psychological anxiety	13.6 (5.8)	13.6 (5.5)	10.2 (6.9)	7.8 (5.3)	7.9 (5.7)	7.4 (5.5)	7.9 (6.4)	6.5 (6.5)
-somatic anxiety	14.1 (5.9)	13.4 (6.2)	9.4 (6.7)	8.1 (5.8)	7.8 (6.2)	6.8 (6.4)	7.2 (6.1)	6.3 (6.8)
BDI-21	16.5 (10.2)	16.1 (6.8)	10.1 (8.2)	9.8 (7.5)	10.3 (9.4)	8.8 (7.7)	9.2 (7.3)	9.1 (9.7)
DES total	13.6 (11.6)	11.6 (10.3)	10.1 (8.7)	7.5 (7.2)	8.8 (8.5)	6.4 (8.0)	8.2 (11.3)	6.2 (8.7)
PPGAS								
- Phobia 1	7.1 (1.6)	6.9 (1.4)	5.2 (2.5)	4.2 (2.7)	5.0 (2.8)	3.5 (2.3)*	4.2 (2.7)	3.5 (2.7)
- Phobia 2	5.7 (2.6)	6.2 (2.1)	4.1 (2.5)	3.8 (2.5)	4.2 (2.5)	3.5 (2.5)	3.5 (2.4)	3.4 (2.6)
- Panic attacks	2.4 (2.6)	2.6 (2.4)	1.4 (2.6)	1.0 (2.0)	0.7 (1.6)	0.9 (1.5)	1.1 (1.8)	1.4 (2.2)
- Nb symp.	6.8 (4.1)	7.4 (3.5)	3.6 (4.5)	3.0 (3.7)	3.0 (4.4)	3.0 (3.7)	4.1 (4.5)	3.0 (3.8)
- Gen. Anx	4.9 (2.2)	5.1 (2.1)	3.3 (2.4)	3.2 (2.5)	3.3 (2.6)	3.1 (2.1)	2.7 (1.9)	3.2 (2.6)
WSA scale	17.5 (10.3)	18.4 (8.5)	11.6 (8.2)	10.3 (8.2)	12.2 (8.4)	9.1 (8.5)	10.9 (9.0)	8.5 (8.5)
SDS	15.2 (8.7)	15.6 (6.6)	10.2 (7.4)	8.5 (6.7)	10.0 (7.1)	7.3 (7.3)	8.4 (6.6)	7.7 (7.5)
TRES								
- patient	-	-	17.3 (4.0)	18.2 (10.8)	-	-	-	-
- therapist	-	-	23.1 (8.6)	22.2 (9.4)	-	-	-	-
ERS								
- patient	1.9 (1.3)	1.6 (1.5)	-	-	-	-	-	-
- therapist	2.5 (1.1)	1.5 (1.1)*	-	-	-	-	-	-

FQ=Fear Questionnaire; PDSS=Panic Disorder Severity Scale; CAS=Chambless Agoraphobic Cognitions; STAI= State and Trait Anxiety questionnaire ; HARS=Hamilton Anxiety Rating Scale; BDI=21-item Beck Depression Inventory; DES=Dissociative Experience Scale; PPGAS=Panic, Phobia and Generalized Anxiety Scale; WSA=Work and Social Adjustment Scale; SDS=Sheehan Disability Scale; TRES=Therapeutic Relationship Evaluation Scales; ERS= Expectancies Rating Scale

VRET subjects were compared with 34 CBT subjects, and then 27 versus 30 at M6, and 23 versus 28 at M12.

Demographic and baseline clinical characteristics of the three groups found no significant between-group differences (see Table 1). The mean PDSS and FQ scores indicated relatively severe disorders. The mean scores of the ERS-therapist were significantly more pessimistic in the VRET group than in CBT (p=0.01), while ERS-patient scores were not different.

At M3, no between-group significant difference appeared on the response criterion even if a lower responder rate was observed in the WL group: 35% versus 45.8% in the CBT group and 42.1% in the VRET group (p=0.77). At M3', no different response rates were observed between VRET and CBT groups, respectively 38.7% and 48.5% (p=0.46). During follow-up, no difference emerged between both groups concerning response rates at M6 (VRET 44% versus CBT 56.7%; p=0.42) and M12 visits (VRET 47.6% versus CBT 60.7%; p=0.40), and the response rates remained stable or tended to slightly increase. In the two-level hierarchic mixed model, with visits (M3', M6, M12) and visit deviations (months) in level 1, and group (VRET versus CBT) in level 2, no difference appeared in the response rates between both groups, taking into account the visit x groups interactions (OR=0.58; 0.21-1.61) or not (OR=0.58;0.21-1.62).

The mean Agoraphobia FQ sub-scores showed similar courses in both groups, with a decrease between M0 and M3' and a stability between M3' and M12, without any statistical difference during any visit (see Table 2). The mean of other scales' scores at each visit are presented in Table 2, which shows no significant difference between the VRET and CBT final groups after the second randomization, except for FQ disability sub-score at M6 (p=0,05), for Phobia 1 sub-score of the PPGAS scale also at M6 (p=0.04), and for ERS-therapist score (p=.0001), all measures being higher in the VRET group.

Discussion

The main result is the equivalent effect obtained with VRET and CBT in post-treatment assessment and during the nine-month follow-up. This is the first report of a controlled comparative trial of pure VRET in PDA conducted on a sample of more than 80 patients. Previous studies were open or controlled but with smaller sample sizes (Botella et al., 2007; Choi et al., 2005; North et al., 1996; Price & Anderson, 2007; Vincelli et al., 2003; Wiederhold & Wiederhold, 2005).

Response rates obtained in both active groups (45.8% for CBT and 42.1% for VRET at M3), using a relatively stringent criteria of a reduction of 50% or more on the FQ agoraphobia sub-scale, were satisfying and in accordance with those observed in reference studies for CBT. For example, in the Barlow et al. (Barlow, Gorman, Shear, & Woods, 2000) study on panic disorder, while using the same type of treatment methods, 48.7% of the patients receiving CBT alone were responders. However, we could not find a significant difference between both active groups and the WL control group. This unusual result may be partially explained by a lack of statistical power, due to unexpected high attrition rates (see below). Another explanation could be the relatively elevated response rate obtained in the WL group (35%), which could be related to therapeutic expectancies in either treatment. This was higher than the 21.7% obtained in the Barlow et al. (Barlow et al., 2000) study in the placebo group. The reasons for this phenomenon are unclear. Our sample exhibited a severe intensity of agoraphobia and panic: mean baseline PDSS score of 18.2, compared to about 12-13 in the Barlow et al. (Barlow et al., 2000) and Shear et al. (Shear, Houck, Greeno, & Masters, 2001) studies, with similar trends for FQ scores (Ost, Thulin, & Ramnero, 2004). Methodological factors should probably be implicated in the high response rates obtained in our control group and in the lack of statistical difference between active and WL group results. The choice of the response criteria can be one of the critical methodological factors as shown in the Barlow et al. (Barlow et al., 2000) study in which both imipramine and CBT were significantly superior to placebo for the acute treatment phase as assessed by the PDSS (with a 21.7% placebo response rate), but were not significantly different on the Clinical Global Impression scale (response rate 37.5%). The FQ-based outcome criteria chosen in our study is, however, one of the more widely used in studies of CBT in agoraphobia (Bandelow, Seidler-Brandler, Becker, Wedekind, & Ruther, 2007; Ost et al., 2004; Roy-Byrne et al., 2005; Shear, Houck et al., 2001; Vincelli et al., 2003).

The main limitation of this study is the elevated attrition rate during the trial (27.2%) although not exceptional; in a meta-analysis of therapeutic studies on panic disorder, Mitte found mean drop-out rates of 15.1% ± 12.8 for CBT trials, and of 20.4% ± 15.3 for pharmacotherapy trials (Mitte, 2005). Despite the relatively important sample size at inclusion (n=92), the final comparisons concerned two groups of restricted size (33 versus 34 subjects at three months after treatment). This high attrition rate limits the statistical power of the analyses. However, the numbers of missing subjects were about the same in CBT and VRET groups, respectively 22.7% and 23.2%, resulting in well-balanced final groups. The reasons for dropping out seemed unrelated to the randomly attributed treatment and beliefs in the effectiveness of VRT or CBT. An explanation might be the high severity of the majority of our patients compared to similar studies (Barlow et al., 2000; Shear, Houck et al., 2001). In France and Luxembourg the patients referred to university hospitals are generally severe cases.

The follow-up assessment of efficacy nine months after the end of the treatment showed that the response rates were maintained in both groups throughout this long-term period. The therapeutic effect size was stable with a mean reduction of about 50% of the FQ agoraphobia sub-score and of the PDSS score in comparison with values at inclusion (Table 2). This observation is of importance as agoraphobia and panic disorder are known to be chronic disorders with a natural course lasting many years according to epidemiological studies (Goodwin et al., 2005). The long-term efficacy of CBT has been well established in these conditions unlike what is generally observed after drug treatment ending (Furukawa, Watanabe, & Churchill, 2007). The fact that the same stable therapeutic effects were obtained with VRET is an asset considering the brevity (12 weeks) of the program. To date, only a few studies of VRET application in psychiatric disorders have shown stable outcomes on a comparable follow-up length (Pull, 2005).

Although not significant for primary outcome variables, there is a trend towards a slight superiority of CBT on several secondary measures when compared with VRET (see Table 2). Significant differences were observed at M6 on the FQ disturbance sub-score and PPGAS phobia scale. However, the levels of significance were low and disappeared after corrections for multiple comparisons. This finding is clearly at variance with a meta-analysis comparing VRET and CBT in anxiety disorders and concludes that VRET was "slightly, but significantly, more effective than exposure in vivo, the gold standard in the field" (Powers & Emmelkamp, 2008). Nevertheless, some limitations to VRET efficacy could exist in our program and some technical or psychotherapeutic components could be optimized. An important issue in this domain is to ascertain whether the VRET program should contain only pure VR exposure without any other therapeutic component such as relaxation, cognitive restructuring, and exposure instructions, or if a combination could be more efficient as suggested by some positive results obtained through combined CBT-VRET programs for panic disorder (Vincelli et al., 2003). This issue merges with the more general question, which is unresolved to this date, about the decisive therapeutic elements of CBT in anxiety disorders (Barlow & Allen, 2004).

The phenomenon called illusion of presence (the feeling of being in an environment although virtual) has been shown to be highly variable and unpredictable among subjects (Draper, Kaber, & Usher, 1999; Price & Anderson, 2007; Riva, 2008; Robillard, Bouchard, Fournier, & Renaud, 2003). We initially planned to measure this dimension during the VRET sessions,

but too much data was missing. This point needs to be explored in future research.

Another factor explaining the slight superiority of CBT to VRET could be the more pessimistic expectancies of the therapists regarding VRET compared with CBT, which was statistically significant. A recent study comparing VRET and CBT in fear of flying showed that higher positive expectancies can predict a better acute therapeutic response (Price, Anderson, Henrich, & Rothbaum, 2008). However, only the expectancies of the patients were measured in that study.

Other parameters may mediate the therapeutic response to VRET. For example, Côté and Bouchard (Côté & Bouchard, 2009) showed that changes in perceived self-efficacy and dysfunctional beliefs were the best predictors of change in general outcome of VRET for arachnophobia.

On a wider perspective, the place of VRET in PDA treatment still needs clarification. Some advantages of this method have been underlined: acceptability, confidentiality, feasibility for some exposures such as driving or flying, and time-consumption for the therapist, etc. (Côté & Bouchard, 2008). Another therapeutic interest may be the association of VRET with cognitive enhancers, such as d-cycloserine, especially in anxiety disorders (Meyerbröker & Emmelkamp, 2010). However, two important aspects could for the moment limit its use when compared to CBT: an insufficient knowledge of its specific efficacy on the various symptoms and forms of PDA and the cost of the equipment. The complete apparatus to perform VRET costs at least about 3000 dollars (with a need for a specific long-term maintenance), which is accessible for specialized and research centers, but not for front line therapists.

From a technical point of view, we used a HMD with relatively poor field of vision (60°). It was, at the time of the research, the best compromise between 3-D glasses and auto-stereo screens in order to create a good immersion effect, limit distractors in the field of vision, and be spatially and materially compatible with a hospital context. Recent progress in HMD devices (e.g., larger field of vision) provide higher immersion effects and, probably, would enhance some exposure and therapeutic effects. In conclusion, our primary objective was to show that "pure" VRET could be effective to treat PDA. This study, despite some limitations, suggests that the acute and long-term efficacy of "pure" VRET and "classical" CBT are similar in PDA. Further studies should now determine the optimal combination of the therapeutic components belonging to each method in order to optimize the outcomes.

Acknowledgements
This study has been supported by a grant from the French ministry of health: PHRC 2002 # 02-106, Hospices Civils de Lyon, and by a grant of the Luxembourg Hospital. We thank Chantal De Mey Guillard, Annie Duinat, Marie-Claire Erpelding-Pull, Frédéric Fanget. Virginie Genouilhac, Evelyne Mollard, Panagiota Panagiotaki, Manuela Tomba, Lidwine Wouters, and Feryel Znaidi for their participation to the study, and Albert Moukheiber for proofreading the manuscript.

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