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Research paper

Auditory and visual 3D virtual reality therapy as a new treatment for chronic subjective tinnitus: Results of a randomized controlled trial

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ABSTRACT

Background: Subjective tinnitus (ST) is a frequent audiologic condition that still requires effective treatment. This study aimed at evaluating two therapeutic approaches: Virtual Reality (VR) immersion in auditory and visual 3D environments and Cognitive Behaviour Therapy (CBT).
Methods: This open, randomized and therapeutic equivalence trial used bilateral testing of VR versus CBT. Adult patients displaying unilateral or predominantly unilateral ST, and fulfilling inclusion criteria were included after giving their written informed consent. We measured the different therapeutic effect by comparing the mean scores of validated questionnaires and visual analog scales, pre and post protocol. Equivalence was established if both strategies did not differ for more than a predetermined limit. We used univariate and multivariate analysis adjusted on baseline values to assess treatment efficacy. In addition of this trial, purely exploratory comparison to a waiting list group (WL) was provided.
Results: Between August, 2009 and November, 2011, 148 of 162 screened patients were enrolled (VR n = 61, CBT n = 58, WL n = 29). These groups did not differ at baseline for demographic data. Three month after the end of the treatment, we didn't find any difference between VR and CBT groups either for tinnitus severity (p = 0.99) or tinnitus handicap (p = 0.36).
Conclusion: VR appears to be at least as effective as CBT in unilateral ST patients.

1. Introduction

Subjective tinnitus (ST) is an illusory perception experienced in the absence of auditory stimulation. ST is a frequent symptom (Shargorodsky et al., 2010; Nondahl et al., 2011), affecting at least 10% of the general population, which may become incapacitating in a minority of patients (Gilles et al., 2012; Baigi et al., 2011). For such patients the, sometimes severe, negative impact on quality of life is linked to attention deficits (Delb et al., 2008), sleep problems (Cronlein et al., 2007) and mood disorders (Hebert et al., 2012) induced by ST perception. In the absence of causally oriented cure (Savage and Tinnitus, 2012), economic and social burden due to ST is huge (Maes et al., 2013). To date, pathophysiology of ST remains a matter of debate. Nevertheless, according to the most recent models, chronic disabling ST is supposed to result from the hyperactivity and/or functional reorganization of cortical and subcortical auditory and non-auditory networks (De Ridder et al., 2013). Hearing loss due to a peripheral auditory damage is considered to be the most common trigger of such maladaptive neuroplastic changes (Norena, 2011). ST shares then strong analogies with chronic pain following amputation (Moller, 2001). Moreover management of both conditions is based on the same pharmacological agents (review in Langguth and Elgoyhen (2012)) and analogous sound/tactile, electric and magnetic stimulations (review in Vanneste and De Ridder (2012)).

Recent psychological models have underlined the relevance of cognitive distortions or negative automatic thoughts ("I cannot

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help it", "I have lost silence forever"…) and consequent inappropriate behaviors (use of ear plugs, anxious or phobic reactions to ST perception) that promote the persistence of ST related discomfort (Anderson and McKenna, 2006). It is for this reason that Cognitive and Behavioural Therapies (CBT) have been widely and successfully included in the multidisciplinary therapeutic management of tinnitus patients (Caffier et al., 2006; Londero et al., 2006). Cognitive Behaviour Therapy is a form of psychological treatment, aimed at modification of dysfunctional beliefs and behaviors, that uses relaxation techniques, thoughts remodeling and in-vivo exposure, often in combination with mindfulness-based training, in order to improve patient's attitude towards challenging situations. The target of these short-term psychotherapies is to alter behavior and associated thoughts (deconditioning techniques and Socratic questioning) to modify the conditions that initiate and sustain the disorder and to modify the consequences of inappropriate behavior on the person's environment. Basically therapists use functional analysis, relaxation, and behavioral retraining. Through progressive training to appropriate behavioral techniques, it is possible to promote neglect of tinnitus which also loses its unpleasant cognitive significations. Patient is considered a protagonist in his/her proper management, as cognitive distortions and inappropriate behaviors are analyzed and sometimes criticized by the patient himself with the help of his therapist. Indeed, as well as for chronic pain (Williams et al., 2012), CBT has shown some efficiency in ST management (Cima et al., 2012; Hesser et al., 2011; Martinez-Devesa et al., 2010).

Following this analogy, and because techniques of immersion in virtual reality (VR) environments have demonstrated their usefulness in several anxious disorders (Viaud-Delmon et al., 2006) as well as for pain management (Cole et al., 2009; Shahrbanian et al., 2009; Keefe et al., 2012), we sought to apply VR to ST patients. Most often, VR integrates real-time computer graphics, body tracking devices and visual displays to immerse a user in a computer-generated virtual environment (VE). Other sensorial interfaces can also be used such as force or tactile feedback systems. All these interfaces enable the user to become an active participant within a virtual world and to give the user a sense of presence in the virtual environment (Loomis, 1992). The setting in which the user performs an action can be controlled by the experimenter, recorded and measured. The unique features and flexibility of VR give it extraordinary potential for use in health research. Regarding mental health applications, the goal to achieve immersion in a VE is to give to the user a compelling illusion that he actually moves in the VE and no longer in the physical world. The number of sensory modalities through which the user is coupled to the VE is a main factor contributing to the feeling of presence (Sheridan, 1992). Thus, "multisensory" involvement is a key for VR. In our study, the aim of the application is to offer to the tinnitus patient the possibility to manipulate an auditory–visual tinnitus avatar within a VE to gain control over the ST perception. Therefore, the application is based on the immersion in a visual VE coupled with accurate auditory spatial rendering, as well as a natural sensorimotor interaction provided Virtual Reality through the use of two trackers. The overall procedure comprises first, the creation of an auditory avatar of the patient's ST, and second, its inclusion in an interactive auditory–visual VE where the different audio components are spatialized according to the navigation and manipulation of the patient. The auditory avatar stimulus is created following the frequency patterns of the patient's ST. The "spatialization" process is based on binaural technology using a database of either generic or individual HTRFs. The task of the subject is to navigate in the VE and to steer the visual and auditory avatar to place it in different positions (either according to distance or according to directional localization). So, in this protocol, the expected success of the habituation process lies essentially on the principle of integration of visual, auditory, and proprioceptive information. The present study follows on a previously published theoretical framework for adaptation of VR techniques to this pathology (Londero et al., 2009).

The trial was designed as a two arms study, to clinically evaluate VR by comparing the efficacy of an exposure in a 3D environment in which the patients are given the ability to voluntarily manipulate a sound resembling their individual ST (ST avatar) to standard sessions of CBT.

2. Materials and methods

2.1. Study design and patients

We undertook an open, and randomized controlled two arms trial (RCT) comparing two juxtaposed therapeutic approaches: VR, rationale of this study, and CBT. Outside the RCT, a waitlist control group (WL) was used to evaluate the natural history of ST over the same period of time. The possible changes in WL would serve to help in understanding the results in the main analysis comparing VR to CBT. To avoid a bias of selection of the patients included in this WL group, a randomization was made, at the same level as for both arms of the study. The research hypothesis was that VR should at least be as effective as standard CBT for ST management. Patients were recruited at the Tinnitus Clinic of our ENT Department. This tertiary care clinic is staffed with otolaryngologists and physicians with special training in psychology. The protocol was proposed to any patient referred to our clinic presenting a stable, tonal and unilateral (or predominantly unilateral) ST. We chose to recruit unilateral ST patients for two main reasons. First, we thought that it would be easier for the patients to create a plausible avatar by comparing their tinnitus to a sound presented on the contralateral normal ear. This lessened the risk of confusion between two sounds overlapping on the same ear. This was in accordance with a methodology published previously by our team (Londero et al., 2009). Second, we theoretically assumed that these patients would be more prone to adhere to the VR given the ability to displace ST avatar (i.e. towards the contralateral normal ear) than the bilateral and symmetric ST patients. Before inclusion each patient underwent an ENT assessment to rule out any pathological condition requiring immediate medical care, a tonal audiometry (125–16 kHz), a customized ST matching session aimed at creating a sound resembling each individual ST. ST avatar recreation protocol has been previously described (Bertet et al., 2013): the method used was based on a combination of two complex stimuli respectively composed of a pure tone and a band-pass noise centered at an adjustable single frequency. This combination allowed the patient to tune between different tinnitus sensations, often reported in the literature as sounding "tonal" or "ringing", "hissing", or "whooshing". In this method, we used the contralateral ear to drive the tinnitus matching. The method was close to single pitch matching, as the patients were asked to span the frequency range to find the matching frequency.

A summary of the clinical trial protocol was previously published (Londero et al., 2009), and the whole protocol (see Tinnitus study protocol in supplements) was approved and registered by the ethical committee (number CPP:070208, N° IDRCB: 2007-A00015-48). One hundred and sixty two patients were eligible during the 15 months inclusion period. Inclusion criteria were defined by the age between 18 and 70 with informed consent signed, subjective tinnitus from peripheral etiology (middle ear, inner ear, auditory nerve), stable and chronic tinnitus being present for at least one year, good language skills (understanding, ability to answer questionnaires), unilateral or perhaps define predominantly unilateral tinnitus with normal or slightly impaired hearing,

tinnitus with a well defined spectrum that permits the fabrication of an exact copy that can be modulated in a virtual environment, and failure of the usual pharmacological agents (vaso-active drugs, anti-convulsants, etc.). Exclusion criteria were fluctuating tinnitus, poor frequency matching, active Meniere's disease, contraindication to virtual reality environment techniques (claustrophobia, vision impairment), on-going medical litigation, uncontrolled psychiatric pathologies, and pregnancy.

Nine patients were excluded because they had not been able to recreate a plausible auditory image of their individual ST, five other patients eventually refused to participate after ST avatar synthesis (see Fig. 1). Thus randomization process has been completed for 148 patients from whom we priorly obtained their written informed consent.

A few deviations from the initial protocol appeared during the study as the number of patients randomized lower than what was planned (148 vs 156), the questionnaire “hyperacusis” that wasn't distributed to the patients because of an IT problem, and the use of the THI questionnaire that was not planned initially. They are taken into consideration further on.

2.2. Procedures

VR and CBT were provided in two steps. The first step, similar for both groups, started approximately 2–6 weeks after randomization. It consisted of two 1-h sessions during which explanations regarding ST physiopathology and treatment modalities were presented, and short techniques of respiratory control and

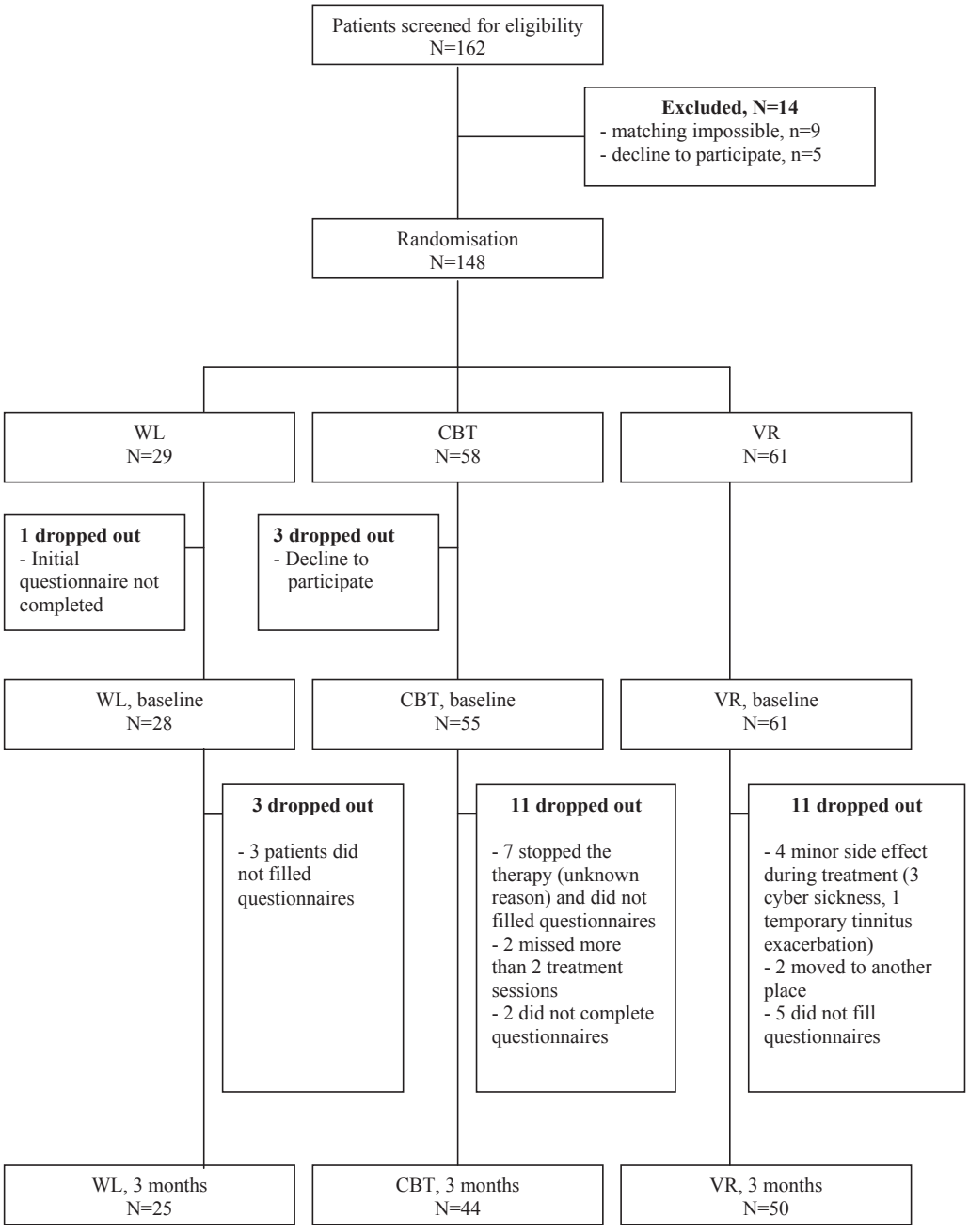


Fig. 1. Flow chart of the trial, with losses and reason when known.

relaxation were taught. These techniques are part of the CBT treatment and patients had the freedom to use them or not during VR sessions. The second step started 3 weeks after, and lasted for 8–12 weeks in both treatment approaches. Eight treatment sessions were scheduled for each patient, weekly for the best (sometimes every two weeks), monitored by an otolaryngologist for VR, and by a psychologist for CBT. Every treatment session lasted approximately 90 min for CBT, and 60 min for VR. VR technical set-up has been previously described (Bertet et al., 2013). Patients were equipped with a head-mounted display coupled with an infrared camera sensor system and immersed in the virtual scenes in which they could move forward by pressing a mouse button. Patients had to turn on their own vertical axis in order to change the direction of heading and displacement in the virtual environment (VE). The soundscape associated to the VE was updated in real time according to their movement and was delivered through the headphones. An additional marker attached to the tip of a rod allowed the patient to control the virtual position of the tinnitus avatar through the displacement of the rod around his head.

Treatment modalities:

In virtual reality protocol, the patient was immerged in a visual VE coupled with accurate auditory spatial rendering, as well as a natural sensorimotor interaction provided through the use of two trackers. The task of the subject was to navigate in the VE and to steer the visual and auditory avatar to place it in different positions (either according to distance or according to directional localization). So, in this protocol, the expected success of the habituation process lies essentially on the principle of integration of visual, auditory, and proprioceptive information.

The Virtual Reality protocol was directed by an ENT specialist, assisted by physicians specialized in VR, biophysicists and hearing physiologists. The sessions lasted an hour. Each patient had 1 session a week for 8 weeks.

During each session, the patients were given the ability to voluntarily and freely manipulate a sound resembling their individual ST in a 3D auditory and visual virtual environment. ST avatar sound was virtually attached to the tip of a rod and its audio components were real-time spatialized according to the navigation and manipulation of the patient. ST avatar was also materialized as a sparkling spot in the 3D head-mounted display in order to facilitate multi-sensory integration. Patients were asked to navigate in three different environments (countryside, urban, and indoor scenes) in each of which 10 different fixed sounds were present. Patients could then gain agency on ST by displacing, masking or unmasking it at will. After each session, patients had to fill a questionnaire assessing the quality of immersion (10 min).

In CBT protocol, all patients had the same therapist (clinical psychologist). CBT was given as a weekly 1-h in groups of 8–10 patients. A total of eight sessions (90 min per session) were given over 12 weeks, as it came impossible to perform a session each week for every patient.

Treatment consisted in cognitive behavior therapy, psychoeducation, cognitive restructuring, exposure techniques, mindfulness-based elements, stress relief, applied relaxation, extensive explanation of neurophysiological model, and fear avoidance discussion. Each session was ending with group discussion and remaining questions were answered. After each session, patients were asked to complete an evaluation form as a treatment feed-back for the therapist (10 min). After randomization and before the first step, patients were asked to answer French validated standardized questionnaires and visual analog scales (VAS) for baseline assessments. Follow up assessment were obtained at the end of treatment, one and three months after step 2. WL patients filled the questionnaires 4 and 6 months after the pre-treatment evaluation in order to match the timeline of both treated groups (see study protocol 6.1.1 in supplement).

2.3. Randomization

Randomization and treatment allocation took place between August, 2009, and July, 2011, and follow-up was completed in November, 2011. The randomization was performed with SAS system Version 9.2 (SAS Institute, Cary, NC, USA) by a statistician independent of the study. The allocation was done according a 2: 2: 1 ratio after screening and return of informed consent, i.e., twice as many patients VR and CBT groups than the control group (WL). The randomization was unstratified, and patients were randomized in blocks of five and ten patients randomly permuted.

2.4. Outcomes

The primary outcome measured for this study was the Subjective Tinnitus Severity Scale (STSS) developed by Halford and Anderson (1991). It has been translated and validated in French by Meric et al. (1996). STSS is based on 16 questions with a “yes” or “no” answer. After scoring, tinnitus severity is graded as “light” (score < 8), “moderate” ($8 >$ score < 11) or severe (score > 12). Despite the fact that it is not aimed at evaluating short term post treatment changes in tinnitus intrusiveness, STSS has been chosen as the main outcome measurement tool because it is the only questionnaire available in French which is not correlated to patients' psychological profile.

Three other questionnaires were used as secondary outcome measures to assess tinnitus induced handicap (Tinnitus Handicap Inventory (THI) and Tinnitus Handicap Questionnaire (THQ)) and associated anxiety and depression states (Hospital Anxiety-Depression scale (HAD)). THI is the most commonly used questionnaire in the ST literature worldwide (Bartels et al., 2008; Newman et al., 1996, 1998bib_Newman_et_al_1998; Landgrebe et al., 2012). It has been translated in many different languages but its French version has been validated after the redaction of initial protocol, shortly before the beginning of this study thus included in the analysis (Ghulyan-Bedikian et al., 2010). THI has 25 questions with answers rated as follows: yes (Score 4), sometimes (score 2) and no (Score 0) for a maximum score of 100. THI is sensitive to short-term changes but correlated to patients' psychological profile. THQ, developed by Kuk et al. (Kuk et al., 1990) translated in French by Meric et al. (Meric et al., 1997) is also commonly used to measure as patients' perceived handicap. This questionnaire has 27 questions scored from 0 to 100. The maximum total score is then 2700. Sub-scores can be extracted reflecting somatic repercussions of ST; auditory or emotional impairments, as well as, the consequences on social behavior. It shares the same benefits and limitation than THI.

Hospital Anxiety-Depression scale (HAD) is commonly used in ST studies because it provides an easy-to-perform tool for assessing the importance of anxiety and/or depression states in the clinical course of tinnitus patients. HAD has 14 questions (rated 0, 1, 2, 3), 7 to evaluate anxiety (HADa) and 7 to evaluate depression (HADd) for a maximum score of 21 for HADa and 21 for HADd (Zigmond and Snaith, 1983). Finally VAS, graduated from 0 to 100, was used to evaluate ST intensity (VASi) and ST discomfort (VASd). VAS provides a rapid and efficient tool to overall estimate ST perceived level and intrusiveness (Meikle et al., 2012).

2.5. Statistical analysis

This trial was designed as an equivalence trial. A 2-sided 90% confidence interval of the difference between treatment groups for the relative changes of STSS included in [−15.95%; +15.95%]

interval was our equivalence hypothesis. Assuming a power of 80% and a change in the STSS standard deviation of 31.91%, a sample size of 126 assessable patients (63 in each treatment group VR and CBT) was needed to conclude equivalence. However, because of the lack of available patients and the period of inclusion constraints we had to limit the study to 162 patients (see Fig. 1). However, the statistical results were powerful enough to detect equivalence between treatment groups.

All statistical analyses were carried out using SAS system Version 9.2 (SAS Institute, Cary, NC, USA). We followed the recommendations of the Consort statement for reporting trials (Hopewell et al., 2008). Eleven patients in each group were excluded from analysis after randomization due to major protocol violation (see Fig. 1 and Results). To describe the population at baseline we used the chi-square test for categorical parameters and Student's t test or Wilcoxon rank test for quantitative parameters, depending of the distribution of the parameters (normal or not normal distribution respectively). Analysis of covariance (ANOVA) was used to compare the groups, using the baseline value as cofactor.

3. Results

Among the 148 patients that were randomly selected, three of them were excluded (two did not want to participate any longer, one did not fill the questionnaires). Overall, 145 patients were eventually included, 116 in the trial (VR n = 61, CBT n = 55), and 28 in the WL group. For the whole sample, audiometry showed greater hearing impairment on ST side (24.87 dB ± 11.63 dB) compared to the contralateral side (18.40 dB ± 9.80 dB).

Fig. 1 displays the trial flow chart, including patients who dropped-out (with reason why when applicable), and those who did not undergo the total treatment course (missing two or more of the 8 treatment sessions or missing the last follow-up assessment). Participants choosing to quit the trial permanently while informing investigators were regarded as having dropped out. In each group, 11 patients were missing for follow up. They did not differ at baseline ($p > 0.05$) either for demographic characteristics (age, sex, ST duration, and hearing loss), and for ST intrusiveness. Among the 11 patients who dropped out during VR treatment, four had to stop because of minor side effects: three had cyber sickness (i.e. dizziness during VR immersion), a commonly described side effect of VR, and one experienced temporary (less than 24 h) after-session tinnitus exacerbation.

Every patient who missed less than two treatment sessions and filled at least the last follow-up questionnaire, was taken into consideration for statistical evaluation. Table 1 shows baseline values of the studied population. Baseline characteristics (age, sex, education, side and nature of tinnitus (permanent/intermittent), tinnitus severity), and initial scores on the STSS, the THI, the THQ (somatic) and the HAD did not differ between groups ($p > 0.05$). Comparison between VR and CBT at baseline and at the end of the study is shown in Table 2, with post treatment results adjusted on baseline findings, shown as $p^{£}$.

According to the primary outcome measurement (STSS) no statistical difference could be shown between the two treated groups (VR vs CBT) immediately post treatment (−0.36, 95% CI −8.36 to 7.63; effect size of Cohen's $d = -0.034$; $p = 0.0001$), at one month follow-up (−0.70, 95% CI −8.47 to 7.07; $d = -0.010$; $p = 0.0001$) and at three months follow-up (between group difference −3.78, 95% CI −10.57 to 3.00; $d = -0.145$; $p = 0.0003$, and Table 2). This equivalence was present for all secondary outcome measurements (THI, THQ, HAD or VAS), as shown on Table 2 where we provide the comparison between the two arms at three months.

The evolution of both arms VR and CBT for our secondary outcomes was also equivalent at immediate post treatment evaluations, apart from handicap measured with THI, and intrusiveness (THQ emotional and social sub-scores) as shown in Fig. 2. Moreover, in a pure descriptive way, without any statistical analysis, Fig. 2 also shows that the effect of treatment is obtained from the end of treatment in both arms (post tt). This effect remained stable over time after the end of therapies with statistical equivalence between groups especially for our primary outcome STSS, but also for all secondary outcome measurements apart from HAD depression sub-score.

When comparing final measurements (three months follow-up) to baseline values (Fig. 3), both treatments arms (VR and CBT) provided significant tinnitus improvement ($p < 0.05$) according to the primary outcome measurement (STSS). THI also showed significant improvement at three months follow-up in both treatment arms (VR and CBT). Similarly THQ showed a positive effect of VR and CBT on somatic impact of ST ($p < 0.05$). CBT but not VR showed a significant effect for emotional states (HAD), and for overall intrusiveness (VAS and THQ emotional and social sub-scores). Tinnitus intensity remains the same before and after treatment for both CBT and VR groups, according to VAS intensity scores.

In a purely descriptive way also, natural evolution of tinnitus with time was recorded using the evolution of the WL group in time (as shown in Fig. 3). It seemed that the positive and significant effect of the CBT for emotional states (HAD-depression, and THQ emotional and social sub scores) was not better than the natural course of ST. One must be aware that items used to calculate THQ social sub-score are not strongly intercorrelated. So far, THQ social sub-score is to be regarded with great caution, and every conclusion made to this sub-score needs careful interpretation.

4. Discussion and conclusions

According to these pioneering results, it can be stated that VR is equivalent to CBT, and effective both for the reduction of tinnitus severity and tinnitus handicap as measured by the STSS, THI and THQ inventories. Nevertheless when regarding other secondary outcome measurements, VR shows a non-significant outcome for both overall intrusiveness and emotional component of ST (VAS, THQ emotional and social sub-scores, HAD). These discrepancies could be explained by the fact that VR sessions were not aimed at addressing specifically the patients' psychological profile but rather the tinnitus perception per se. As expected, and because CBT is known to contribute positively to the management of ST (Cima et al., 2012) by improving both anxiety-depression and quality of life even if it has no effect on ST itself (i.e. does not improve ST loudness), CBT arm displayed significant psychological improvement as evaluated by VAS, THQ emotional and social sub-scores and HAD. Conversely there was no specific effect of VR on these sub-scales. VR could then have a specific effect on tinnitus itself independently of psychological aspect.

Nevertheless, and as a secondary analysis outside the RCT, one should note that the WL group also displayed a positive and significant effect for the emotional component of ST (HAD-depression sub-score and THQ emotional and social sub-scores) similar to the CBT (Fig. 3) revealing a possible role for a placebo effect. In contrast, the positive effects we got with both CBT and VR on the primary outcome STSS, on the THI, and on the THQ somatic sub-score seemed real therapeutic effects as we observed no positive effect on the WL group at the same time (see Fig. 3).

Thus, equivalence between both treatments VR and CBT proves the efficiency of our treatment, which may be used as an alternative or in combination to CBT. Indeed, VR seems to have some specific advantages: a shorter duration of treatment sessions,

Table 1
Baseline characteristics of the 2 arms included in the trial (CBT and RV groups) and of the group followed up on the waiting list without intervention. Numbers are means (SD) or numbers (%)).

	WL (n = 28)	CBT (n = 55)	RV (n = 61)	P
Gender (N, %men)	16 (57.14%)	36 (65.45%)	49 (80.33%)	0.053
Age	54.19 ± 12.62	49.14 ± 12.11	52.20 ± 12.64	0.219
Have you already consulted for the same motive ?; Yes	25 (89.29%)	50 (90.91%)	54 (88.52%)	0.257
Can you say that the tinnitus and/or the hyperacousis is your main concern of health at present ? (N, % yes)	19 (67.86%)	35 (63.64%)	41 (67.21%)	0.850
In what ear do you hear the tinnitus?				0.355
To the right	10 (35.71%)	24 (43.64%)	22 (36.07%)	
To the left	15 (53.57%)	21 (38.18%)	33 (54.10%)	
Whistle; Yes	20 (71.43%)	44 (80.00%)	46 (75.41%)	0.666
Is your tinnitus permanent or does it disappear completely sometimes?				
Permanent	22 (78.57%)	40 (72.73%)	51 (83.61%)	0.245
Occasional	3 (10.71%)	10 (18.18%)	5 (8.20%)	
Socioprofessional category				0.582
Upper	6 (21.43%)	18 (32.73%)	21 (34.43%)	
Middle	6 (21.43%)	16 (29.09%)	14 (22.95%)	
Lower	5 (17.86%)	5 (9.09%)	10 (16.39%)	
STSS	9.96 ± 1.82	10.09 ± 1.77	9.90 ± 1.60	0.834
Tinnitus intrusiveness ((N, % yes))	9 (32.14%)	18 (32.73%)	14 (22.95%)	0.424
THI	45.68 ± 22.10	45.96 ± 20.75	42.10 ± 19.69	0.562
HAD				
Depression	4.96 ± 4.05	5.81 ± 3.72	5.18 ± 3.79	0.557
Anxiety	8.84 ± 4.13	9.54 ± 4.13	8.49 ± 3.94	0.383
VAS				
Tinnitus intensity	77.31 ± 14.16	61.30 ± 21.02	62.38 ± 19.27	**0.001**
Tinnitus intrusiveness	74.81 ± 18.84	62.69 ± 20.13	61.72 ± 18.30	**0.011**
THQ				
THQ somatic score	263.20 ± 133.49	246.09 ± 138.44	198.51 ± 126.91	0.059
THQ emotional score	285.00 ± 163.36	237.46 ± 160.84	191.41 ± 144.13	**0.032**
THQ social score	212.80 ± 144.79	182.02 ± 133.37	174.03 ± 141.67	0.499

WL: Waiting list, TCC: RV: virtual reality.
The results for which three groups are statistically different at baseline are in bold.

Table 2
Baseline and post treatment results. Trail arms (CBT and RV) comparison at 3 months.

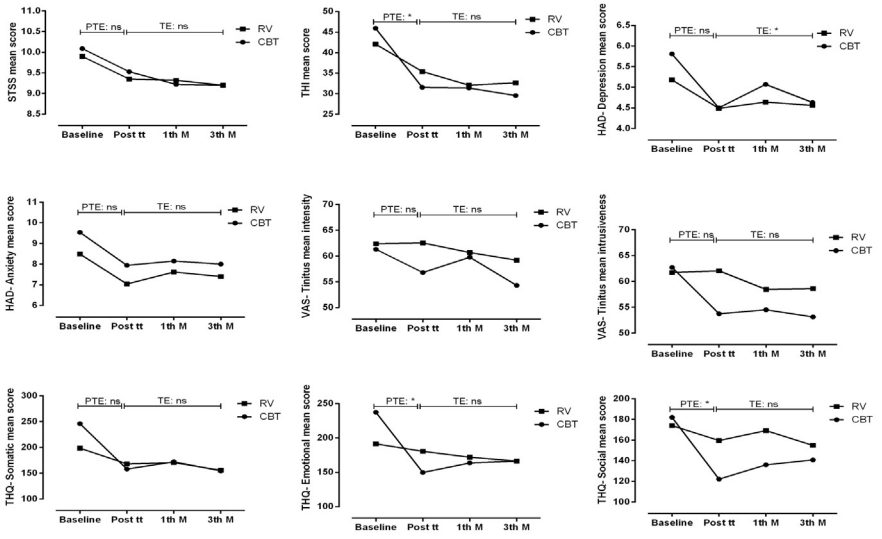
	Baseline			3 Months after treatment		
	CBT (n = 55)	RV (n = 61)	P†	CBT (n = 44)	VR (n = 50)	P£
STSS; mean ± SD	10.09 ± 1.77	9.90 ± 1.60	0.545	9.20 ± 1.87	9.20 ± 1.50	0.541
THI score; mean ± SD	45.96 ± 20.75	42.10 ± 19.69	0.123	28.93 ± 23.74	32.68 ± 15.66	0.062
HAD						
Depression score; mean ± SD	5.81 ± 3.72	5.18 ± 3.79	0.368	4.42 ± 4.14	4.56 ± 3.20	0.077
Anxiety score; mean ± SD	9.54 ± 4.13	8.49 ± 3.94	0.168	7.87 ± 4.42	7.40 ± 3.47	0.553
VAS						
Tinnitus intensity; mean ± SD	61.30 ± 21.02	62.38 ± 19.27	0.937	54.56 ± 22.18	59.20 ± 20.44	0.799
Tinnitus intrusiveness; mean ± SD	62.69 ± 20.13	61.72 ± 18.30	0.647	53.33 ± 23.52	58.60 ± 21.21	0.351
THQ						
Somatic score; mean ± SD	246.09 ± 138.44	198.51 ± 126.91	0.068	154.09 ± 141.36	155.68 ± 103.39	0.190
Emotional score; mean ± SD	237.46 ± 160.84	191.41 ± 144.13	0.121	160.71 ± 161.06	166.46 ± 126.58	0.170
Social score; mean ± SD	182.02 ± 133.37	174.03 ± 141.67	0.592	135.62 ± 149.95	154.88 ± 125.60	0.368

P†: Student-test/Wilcoxon test.
P£: Analysis of variance (ANOVA) adjusted on baseline value.

independence from the skills of the healthcare professional (psychologist, audiologist …) organizing the sessions, a playful aspect, and no psychiatric connotation.

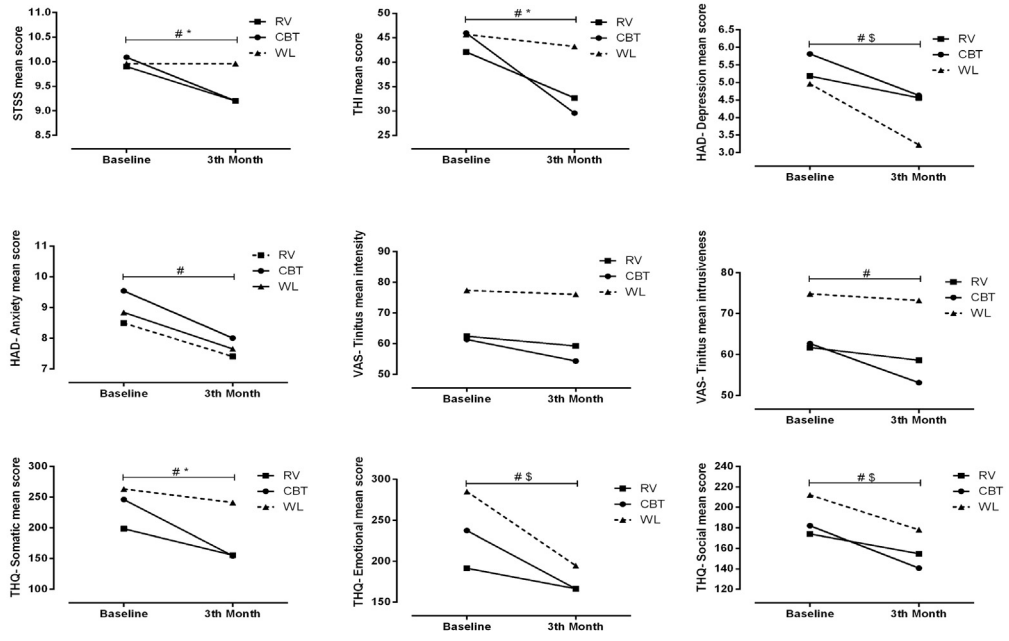
Another issue raised by this study is the pathophysiological mechanisms underlying VR efficiency. The first VR exposure experiments were published in 1992 and since then the number of studies has steadily increased taking advantage of technological developments. While most studies focus on anxiety, there is increasing research on eating and sexual disorders, addiction and pain control. In the treatment of phobia, many case studies have demonstrated the efficiency of VR with a significant improvement in anxiety and avoidance (Emmelkamp et al., 2002; Vincelli et al., 2003). Other relevant result concerns the positive effect on pain syndromes (Shahrbanian et al., 2009; Keefe et al., 2012). According to authors, VR exposure can reduce the sensory or emotional components of pain. VR is supposed to act by distracting attention (Keefe et al., 2012; Hoffman et al., 2004), an effect also demonstrated during dental care for toothache (Hoffman et al., 2001). Regarding ST, we anticipate that a plausible explanation of VR efficacy could be linked to the ability given to the patients to willingly manipulate and gain agency on their ST. This could elicit a multisensory effect on cortico-subcortical perception and on auditory attention. Then VR could act as a kind of recalibration or modulation tool based on neural plasticity. These predictions deserve further validation by assessing real-time cerebral activations (i.e. EEG, MEG) during VR immersions that could, in turn, be eventually used as a feedback marker to increase VR efficiency.

Moreover, we have been able to demonstrate that a subjective tinnitus percept can be fused with its avatar and then perceptually behave (at least in a VR environment) like a “real sound” with



PTE: post treatment equivalence: comparison between CBT and RV at post treatment adjusted on baseline value (ANOVA); TE: Time Effect: maintenance of effect overtime post treatment, 1 month, 3 months, repeated ANOVA; *: p-value<0.05; NS (not significant): p-value>0.05

Fig. 2. Evolution of parameters with time. Comparison at immediate post treatment (PTE) and comparison of the effects after treatment over three months of follow-up for the two arms of the study (TE). PTE are adjusted on baseline value (ANOVA).



#: p<0.05 Before-After CBT comparison; *: p<0.05 Before-After RV comparison; $: p<0.05 Before-After WL comparison.

Fig. 3. Difference between initial and final evaluations in each trial arm (CBT and VR) and in the waiting list group.

which it is possible to voluntarily interact. If confirmed by future research, this fact could have profound consequences in our understanding of tinnitus pathophysiology, including cortico-subcortical maladaptative plasticity in tinnitus patients. Here are some examples of theoretical audiological issues this study raises even if they cannot be proven by the data provided. We found that it was possible for the patients to control and move the position of tinnitus percept only by controlling the level of the tinnitus avatar displayed in the contralateral ear almost as this is done for a real sound. If confirmed, and not the mere consequence of masking, this would mean that the complex 3D localization processing for the frequencies matching tinnitus is preserved even for a longstanding symptom. The study of the multimodal integration (auditory, visual and sensory) in tinnitus patients which is uniquely enabled by VR techniques is also a possible target for future VR research. Another issue is the possibility to test, in a realistic setting, the masking effect induced by different controlled nature-like sounds displayed in VR settings. This could be of crucial importance for the development of individualized, and then more efficient, sound therapies. Moreover VR environments give a unique opportunity to test in a

totally controlled auditory (and visual) environment attention processes that seem to be crucially impaired in clinical tinnitus patients. This could, in a near future, contribute to a better understanding of the very intriguing, and so far almost unexplained, fact that the same (i.e.just above the threshold 4 kHz) tinnitus may lead to severe disturbance in some patients and to a total neglect in many others.

Our study has several strengths, the homogeneity of the recruitment (unilateral ST, no severe hearing loss), the homogeneity of treatment procedures, the high number of patients included in each arm (RV n = 60, CBT n = 55) for such an innovative procedure, the presence of a control group (WL) and an equivalent patient–therapist interaction (number of sessions, follow-up) in both treated arms. Additionally VR is a safe therapy: among 61 patients only four had to stop because of minor side effects (see Fig. 1).

We also acknowledge some limitations. First, the number of patients included did not fit exactly the pre-planned figures and, because of dropping out, the sample size was even more reduced. But drop-out patients were equivalent in both groups, and we showed that the study was powerful enough to detect equivalence between treatment groups. Second, we conducted this trial with a dedicated, very unique and innovative set-up. Even if, by doing so, this study establishes the proof of concept that a VR 3D visual and auditory navigation tool can be settled in a soundproof audiometric booth and used in the clinics, these preliminary results urgently call for replication and multicentric validation. Third, we only studied a specific sub-group of unilateral ST patients. Whether VR tools can be proposed to other ST patients cannot be extrapolated from these data. Upgrading of VR set-ups and scenarios are warranted to improve clinical efficiency and ultimately extend VR indications in the ST field.

As a conclusion these results provide the first evidence for VR to be a new feasible and effective approach in ST treatment.

Contributors

The trial project members AL (project leader and principal investigator) and PB (project co-leader) designed the study. DM (project member, and main author) and PB collected data and monitored data collection and integrity of randomization. IVD (VR principal investigator) conceived the VR treatment and assessment methodology in collaboration with AL. OW (VR project co-adviser) designed and developed the technical environment.

PhP (project member and CBT adviser) developed and performed CBT protocol.

The statistical analysis plan was set up by RN (adviser statistical analyses), GC (co-adviser statistical analyses) and PB. The statistical analyses were done by RN with support from GC.

Data interpretation was done by AL, DM, RN and PB. Trial treatments were coordinated and monitored by AL and PB. DM, AL, RN and PB were involved in the writing of the report, and the design of tables and figures. All authors contributed to drafts of this manuscript.

Conflicts of interest

We declare that we have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.heares.2015.12.023.

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