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Virtual reality therapy for refractory auditory verbal hallucinations in schizophrenia: A pilot clinical trial

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ABSTRACT

Schizophrenia is a chronic and severe mental illness that poses significant challenges. While many pharmacological and psychosocial interventions are available, many treatment-resistant schizophrenia patients continue to suffer from persistent psychotic symptoms, notably auditory verbal hallucinations (AVH), which are highly disabling. This unmet clinical need requires new innovative treatment options. Recently, a psychological therapy using computerized technology has shown large therapeutic effects on AVH severity by enabling patients to engage in a dialogue with a computerized representation of their voices. These very promising results have been extended by our team using immersive virtual reality (VR). Our study was a 7-week phase-II, randomized, partial cross-over trial. Nineteen schizophrenia patients with refractory AVH were recruited and randomly allocated to either VR-assisted therapy (VRT) or treatment-as-usual (TAU). The group allocated to TAU consisted of antipsychotic treatment and usual meetings with clinicians. The TAU group then received a delayed 7 weeks of VRT. A follow-up was ensured 3 months after the last VRT therapy session. Changes in psychiatric symptoms, before and after TAU or VRT, were assessed using a linear mixed-effects model. Our findings showed that VRT produced significant improvements in AVH severity, depressive symptoms and quality of life that lasted at the 3-month follow-up period. Consistent with previous research, our results suggest that VRT might be efficacious in reducing AVH related distress. The therapeutic effects of VRT on the distress associated with the voices were particularly prominent ($d = 1.2$). VRT is a highly novel and promising intervention for refractory AVH in schizophrenia.

1. Introduction

Schizophrenia is a chronic and devastating severe mental illness that poses significant challenges. This disorder, affecting up to 1% of the population (Saha et al., 2008), is associated with long-lasting health, social and financial burden, not only for patients but also for families, caregivers and society. Notwithstanding the evidence-based efficacy of antipsychotics, the main reason for this heavy burden is that 25 to 30% of patients with schizophrenia will not respond well to antipsychotics and will suffer from persistent psychotic symptoms, particularly auditory verbal hallucinations (AVH) (Kane et al., 1988). Such symptoms are hallmark symptoms of schizophrenia (David, 1999), as their prevalence may reach up to 80% in these patients (Sartorius et al., 1986). Treatment-resistant schizophrenia (TRS) is associated with substance use disorders, suicidal ideations, lower quality of life and functioning, and higher rates of hospitalization (Elkis and Buckley, 2016). Unsurprisingly, it has been estimated that the direct healthcare costs are 3 to 11 times more elevated in TRS patients compared to treatment responders (Kennedy et al., 2014).

Clozapine is considered the gold standard treatment for this population (Taylor et al., 2015). However, 40 to 60% of TRS patients still do not respond to this medication (Lieberman et al., 1994) and many side effects undermine its efficacy (Siskind et al., 2016). Unfortunately, treatment alternatives are very limited for this suffering population. Therefore, to potentiate pharmacological interventions, psychosocial interventions have been utilized. Several clinical trials have shown that Cognitive Behavioural Therapy (CBT) is effective in reducing the positive symptoms (e.g., delusions, hallucinations) of schizophrenia (Turner et al., 2014). The Cognitive model of AVH suggests that the way a person appraises their voices will influence their emotional and

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behavioural responses. Thus, beliefs about voices regarding identity, intention, power and especially control will play a significant role in the development of distress and compliant behaviours (Chadwick and Birchwood, 1994). Nonetheless, the magnitude of the therapeutic effects of CBT is low to moderate (Jauhar et al., 2014). It may be possible that changes in AVH related distress cannot be addressed via voice appraisals alone (Mawson et al., 2011). Furthermore, only a few small-scale CBT trials have specifically targeted patients with well-defined treatment resistance (Burns et al., 2014). Consequently, the efficacy of CBT for this complex population is uncertain and treatment options continue to be very limited for TRS.

Interventions focusing on psychological key processes hypothesized to be associated with AVH distress, such as interpersonal relating, are likely to be promising (Thomas et al., 2014). The interpersonal dimension of AVH is increasingly acknowledged (Hayward et al., 2011). Most voice-hearers will report having some relationships with their voices (Chin et al., 2009; McCarthy-Jones et al., 2014). Personifying the voices is one of the most common characteristics of the experience (Nayani and David, 1996). Accordingly, preliminary clinical work has shown that encouraging patients to enter in a dialogue with their voices may help them develop a more constructive relationship with their voices and reduces their feelings of helplessness (Corstens et al., 2012; Hayward et al., 2016). Yet, one crucial explanation for the lack of efficacy of psychotherapeutic treatments may be that patients are not in direct relation with their persecutory voices. Typically, patients must imagine their persecutor and report the content of the voices to their therapist. To overcome this problem, Leff et al. (2013) used a computerized system enabling patients to create an avatar of their persecutor. In their pilot study comparing their system with treatment as usual in 16 treatment resistant voice hearers, patients were prompted to engage in a dialogue with their avatar animated by the therapist. The therapeutic objective was to help patients gain control over their symptoms.

Recently, they extended their results in a randomized controlled trial comparing their computerized therapy to an adapted supportive counselling with 150 voice hearers, 75 of whom were allocated to the therapy group (Craig et al., 2017). Results showed large effects of the therapy on distress associated with AVH (Cohen's $d = 0.8$) compared to supportive counselling. Given the important suffering associated with TRS, the promising results of their therapy deserve to be extended by an independent team.

The current study sought to achieve this main objective, while making significant modifications to the trials from Leff et al. (2013) and Craig et al. (2017). First, we opted to use *immersive* virtual reality (VR) rather than conventional computerized technology, as growing evidence suggests that greater immersion in a VR system increases both the feeling of presence and emotional arousal (Diemer et al., 2015). Second, unlike these prior studies, we delivered the therapy specifically to patients responding to the criteria of treatment resistance.

2. Methods

2.1. Participants

We recruited 19 patients (≥18 years old) with schizophrenia or schizoaffective disorder from the *Institut Universitaire en Santé Mentale de Montréal* and the community. Patients were diagnosed by AD using the criteria of the *DSM-5* (American Psychiatric Association, 2013). We recruited patients who had been hearing persecutory voices and did not respond to at least two antipsychotic trials. Exclusion criteria were: (a) any change in medication within the past 2 months; (b) concomitant substance use disorder (within the last 12 months), neurological disorder or unstable and serious physical illness; (c) highly unstable state (e.g., currently in psychiatric intensive care unit); and (d) CBT for psychosis within the last 12 months. All patients signed a detailed consent form. Additionally, the trial was approved by the local ethics committee.

2.2. Design

This is a 7-week phase-II, randomized, partial cross-over trial. Patients fulfilling inclusion criteria were randomly allocated (1:1 ratio) to either VR-assisted therapy (VRT) or treatment-as-usual (TAU). The group allocated to TAU consisted of antipsychotic treatment and usual meetings with clinicians. The TAU group then received a delayed 7 weeks of VRT. A follow-up was done 3 months after the last therapy session of VRT. The trial was registered on ClinicalTrials.gov (NCT03148639).

2.3. Virtual reality assisted therapy

Patients underwent 7 weekly sessions (one avatar creation session and six 45-minute therapeutic sessions). First, patients created an avatar best resembling the most distressing person or entity believed to be the source of the malevolent voice, which was designed to closely have both the face and the voice of the "persecutor". Patients hearing several voices were requested to select the most distressing voice or the most dominant one for the creation of the avatar. Patients created their avatar with the help of AD and a peer patient, who received VRT prior to the current trial. Idiosyncratic avatars were created using Unity 3D game engine with custom made assets and Morph3D Character System. The avatar's voice was simulated in real-time with a voice transformer Roland AIRA VT-3. Prosody and lip synchronization was performed via the SALSA with RandomEyes Unity 3D extension. Patients were immersed in VR through the Samsung GearVR head-mounted display and Samsung Galaxy S6 smartphone. The immersive virtual environment consisted of an avatar standing in the dark, seen from a first-person perspective.

In sessions 1 to 3, patients were confronted to the reproduced hallucinatory experience. The therapist induced a dialogue between patients and their avatar with the help of sentences they provided. They were encouraged to enter into a dialogue with the avatar to improve emotional regulation and assertiveness. Self-esteem was emphasized in session 4, which was reinforced by enabling the patients to express themselves and to consider their personal qualities. To ease this process, a list of qualities provided by the patient's personal surroundings was introduced in the avatar's dialogue. Over the course of VRT, the avatar's interaction with the patient became gradually less abusive and more supportive. The patient became progressively more empowered in interaction with the avatar as the former developed more assertiveness. In the final consolidation sessions, patients were encouraged to apply what they had previously learned in the experiential sessions and to follow-up on the initial objectives. Three patients received 1 to 4 additional consolidation sessions at the end of VRT, based on a mutual decision between the therapist and the participant when several novel learned strategies needed to be overviewed further. During the study, the therapy was delivered in French or in English by AD who has around 5 years of experience as a psychiatrist. In his clinical practice, he has evaluated and treated over one thousand patients with major psychiatric disorders, with a majority suffering from schizophrenia. Importantly, the therapy was manualized, and each therapy session was audio recorded. The assessment of the external validity of the delivery of the intervention was performed by KO, who has expertise in cognitive behavioural and dialogical therapies (Hallam and O'Connor, 2002; Morand-Beaulieu et al., 2015; O'Connor et al., 2009).

2.4. Clinical assessments

The clinical assessments were administered before and after TAU as well as VRT and at the follow-up by a trained psychiatric nurse. AVH and related beliefs of omnipotence and malevolence were measured with the *Psychotic Symptoms Rating Scale* (PSYRATS) (Haddock et al., 1999; Woodward et al., 2014) and the *Beliefs About Voices Questionnaire-Revised* (BAVQ-R) (Chadwick et al., 2000), respectively. Psychiatric

symptoms were assessed with the *Positive And Negative Syndrome Scale* (PANSS) (Kay et al., 1987) and the *Beck Depression Inventory-II* (Beck et al., 1996). Life satisfaction was evaluated with the *Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form* (Endicott et al., 1993; Ritsner et al., 2005). After the first encounter with their avatar, participants were asked how much they felt in presence with their persecutor on a scale from 0 (no feeling of presence) to 10 (very strong feeling of presence). Also, after each VRT session, patients rated their fear and their anxiety on a scale from 0 (no emotion) to 10 (very strong emotion).

2.5. Statistical analyses

Changes in psychiatric symptoms, before and after TAU, and before and after VRT, were assessed using a linear mixed-effects model. We analysed only the data of VRT completers (immediate and delayed VRT groups combined). The statistical threshold for significance was set at $p < 0.05$.

3. Results

3.1. Sample characteristics

The total sample comprised of 19 patients, with four patients having dropped out of VRT due to anxiety after the first therapeutic session and a lack of engagement into the therapy model. Also, we were unable to reach 3 patients at their follow-up. At baseline, the mean age was 42.9 ranging from 24 to 62 years old. The final sample included 15 patients, with a majority being men, single, Caucasian and diagnosed with treatment-resistant schizophrenia. Moreover, the mean duration of illness was of 18 years, with half of them being unresponsive to clozapine (see Table 1 for more details).

At baseline (before VRT), there were no significant differences between the two groups (immediate versus delayed VRT) in terms of psychiatric symptoms and socio-demographic data ($p < 0.05$). In terms of adverse events, no patients were re-hospitalized during the totality of the trial, however one patient did temporarily enter a counselling and support centre during the first weeks of the VRT. Noteworthily, the two first weeks are the most anxiogenic for patients.

Table 1
Sociodemographic and clinical characteristics of the sample at baseline.

VRT + TAU n = 15					
Sociodemographics			Clinical		
Gender			Diagnosis		
Male	10	(66.7)	Schizophrenia	12	(80.0)
Female	5	(33.3)	Schizoaffective disorder	3	(20.0)
Age	42.9	(12.4)	Duration of illness	17.8	(4.7)
Ethnicity			Medication		
Caucasian	13	(86.7)	Typical	3	(20.0)
Other minority	2	(13.3)	Atypical	14	(93.3)
Language			Clozapine	8	(53.3)
French	13	(86.7)			
English	2	(13.3)			
Civil status					
Single	12	(80.0)			
Married/common in law	1	(6.7)			
Divorced/separated	2	(13.3)			
Education	13.7	(4.5)			
Employment status					
Unemployed	11	(73.3)			
Employed	1	(6.7)			
Retired	3	(20.0)			

n (%) or mean (SD).
TAU = treatment as usual; VRT = virtual reality assisted therapy.

Regarding the range of avatars created, 9 participants described someone they personally knew, 5 portrayed a demon or an evil spirit and 1 caricatured a political figure. Among them, 5 were females and 10 were males. Moreover, participants rated their avatar credible enough (mean score of 7.5 on a scale of 10; SD = 1.5) to make them feel in presence of their persecutor.

3.2. Changes in psychiatric symptoms

Psychiatric symptoms remained unchanged throughout the TAU period (Table 2). Concerning VRT sessions, there was no significant relationship between the number of therapy sessions and clinical outcomes (all $p > 0.05$). As shown in Table 3, many improvements were observed during VRT from baseline to post treatment. First, there was a reduction of AVH symptoms ($p < 0.01$) as seen with the PSYRATS scores. Significant reductions were found most prominently for the distress related to AVH ($p < 0.001$). Also, beliefs about voices improved significantly both for the related beliefs of omnipotence and malevolence ($p < 0.05$). Second, general symptoms as measured with the PANSS and depressive symptoms were diminished ($p < 0.05$), while quality of life was ameliorated ($p < 0.05$). These improvements remained significant at the follow-up period. The effects of VRT on AVH and related beliefs were large (PSYRATS total: Cohen's d = 1.0; PSYRATS-distress d = 1.2; BAVQ-R: d = 0.7).

Regarding the subjective ratings conducted after each therapy session, significant decreases in anxiety as well as fear occurred during VRT beginning at Week 4 as seen in Fig. 1.

4. Discussion

In this pilot trial, VRT produced significant improvements in AVH severity, depressive symptoms and quality of life that remained stable at the 3-month follow-up period. This therapy enabled patients with TRS to directly enter in a dialogue with a virtual representation of their persecutory voices. This approach being both dialogical and experiential provided a unique opportunity to treat such a difficult population with whom every other prior treatment has failed.

Principally, our results showed that AVH symptoms mostly related to the distress associated with the persecutory voices diminished. Such therapeutic effects of VRT on the distress associated with the voices were particularly prominent, as indicated by a very large effect size estimate (d = 1.2). The putative benefits of VRT seem above those of other psychotherapeutic treatment alternatives, such as CBTp, which provide at best moderate benefits (Jauhar et al., 2014; Turner et al., 2014). It is worth highlighting that only a minority of these studies

Table 2
Changes in psychiatric symptoms during treatment-as-usual.

	T0 n = 7		T1 n = 7		T0/T1	
					t	p
PSYRATS	30.86	(4.67)	31.14	(2.97)	0.32	0.760
Distress	15.71	(3.59)	17.00	(2.58)	2.00	0.093
Frequency	7.14	(1.86)	6.14	(2.27)	−1.45	0.197
Attribution	5.71	(0.95)	6.14	(1.07)	2.12	0.078
Loudness	2.29	(1.38)	1.86	(1.22)	−1.00	0.356
BAVQ-R	24.29	(7.91)	22.47	(5.41)	−0.63	0.552
Omnipotence	11.14	(3.67)	11.14	(3.24)	0.00	1.000
Malevolence	13.14	(5.05)	12.14	(4.71)	−1.73	0.134
PANSS	79.57	(16.26)	81.57	(13.00)	0.62	0.558
Positive symptoms	18.57	(4.50)	19.43	(3.51)	1.07	0.325
Negative symptoms	19.14	(5.90)	19.57	(5.22)	0.32	0.760
General symptoms	41.86	(6.82)	42.57	(6.66)	0.43	0.682
BDI	26.29	(12.05)	25.43	(8.48)	−0.17	0.868
QLESQ-SF	45.86	(5.96)	44.14	(7.47)	−0.60	0.569

Mean (SD); T0 = baseline; T1 = after treatment-as-usual; PSYRATS = Psychotic Symptoms Rating Scale; BAVQ-R = Beliefs About Voices Questionnaire-Revised; PANSS = Positive And Negative Syndrome Scale; BDI = Beck Depression Inventory; QLESQ-SF = Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form.

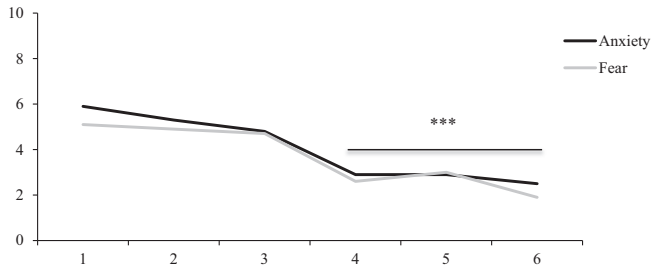
Table 3
Changes in psychiatric symptoms during the virtual reality assisted therapy.

	T1 n = 15		T2 n = 15		T3 n = 12		F	T1/T2 t	T1/T3 t
PSYRATS	30.47	(3.18)	23.33	(8.44)	21.92	(9.60)	7.43**	−3.20**	−3.39**
Distress	16.07	(2.92)	10.87	(4.69)	10.42	(5.33)	11.32***	−4.07***	−4.08***
Frequency	6.87	(1.96)	5.93	(2.96)	5.58	(3.06)	2.17	−1.96	−1.53
Attribution	5.60	(1.24)	4.87	(2.03)	4.08	(2.02)	2.51	−1.18	−2.23*
Loudness	1.93	(0.96)	1.67	(1.05)	1.83	(1.27)	0.28	−0.74	−0.29
BAVQ-R	22.47	(4.60)	16.36	(7.47)	17.00	(7.55)	5.07*	−2.91**	−2.46*
Omnipotence	10.53	(3.18)	7.14	(4.20)	8.18	(4.60)	3.64*	−2.64*	−1.69
Malevolence	11.93	(4.30)	9.21	(5.03)	8.82	(4.54)	4.20*	−2.31*	−2.60*
PANSS	76.67	(13.29)	71.47	(11.78)	67.25	(10.79)	3.36	−1.89	−2.45*
Positive symptoms	18.33	(3.85)	16.87	(3.83)	16.08	(3.40)	2.44	−1.93	−1.84
Negative symptoms	18.47	(4.72)	18.40	(5.07)	17.92	(5.20)	0.01	−0.06	0.09
General symptoms	39.87	(6.52)	36.20	(5.45)	33.25	(5.08)	6.37*	−2.31*	−3.48**
BDI	20.87	(9.69)	14.10	(13.14)	12.42	(10.80)	3.84*	−2.25*	−2.47*
QLESQ-SF	47.73	(7.12)	52.00	(8.09)	53.00	(8.11)	3.85*	2.24*	2.49*

m (SD); T1 = baseline; T2 = after the virtual reality assisted therapy; T3 = after the follow-up. PSYRATS = Psychotic Symptoms Rating Scale; BAVQ-R = Beliefs About Voices Questionnaire - Revised; PANSS = Positive And Negative Syndrome Scale; BDI = Beck Depression Inventory; QLESQ-SF = Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form.
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.

have specifically targeted AVH and most have included patients with residual symptoms who do not meet proper criteria for TRS (Burns et al., 2014). As such, our findings are consistent with the prior results from Leff et al. (2013) and Craig et al. (2017). It is however important to note that the clinical implications of our trial differ in many respects. The previous trials recruited chronic voice hearers who did not necessarily suffer from TRS, whereas the current trial used a clear definition of treatment resistance. Markedly, half of our sample consisted of ultra-resistant schizophrenia patients (i.e., unsuccessful response to clozapine). Consequently, our results add to the field by indicating that VRT holds a great promise even for the most difficult-to-treat patients with schizophrenia. The current trial also significantly differs from previous trials in that we used an *immersive* virtual environment (e.g., head-mounted display), whereas Leff et al. (2013) and Craig et al. (2017) used a laptop. In theory, *immersive* virtual environments are likely to enhance the feeling of presence and emotional arousal (Diemer et al., 2015). Most studies have not measured or reported this feeling as we have in our study. Noteworthily, we believe that the feeling of presence is an important prerequisite for VR therapies. We thereby found that the feeling of presence was satisfactory, and this may have enabled patients to experiment more meaningful emotions to better regulate them through the relationship with their persecutor.

While the main objective of the trial was not to clarify the mechanisms underlying the presumed efficacy of VRT, the results presented suggest that self-related emotional factors might play a key role as well. Not only did we observe the largest effects of VRT on AVH-related *distress*, we also observed a sharp decrease in negative emotions such as fear and anxiety beginning at session 4. As Leff et al. (2013) emphasized,



anxiety: F(5;69.26)=6.01***; fear: F(5;69.08)= 6.05***
post-hoc tests S1 vs S4, S5, S6; *** p < 0.001.

Fig. 1. Changes in self-reported anxiety and fear after each virtual reality assisted therapy session.

one of the core objectives of avatar based therapies is to improve patients' self-image. Interestingly, the fourth session of VRT is precisely the session during which this issue is addressed. Thus, patients gradually stand up to their voice and take control while building their self-esteem as their avatar begins to surrender. As an experiential therapy, VRT primarily focussed on how patients relate with and respond to their voices by tackling emotional regulation, enhancing self-esteem and promoting acceptance rather than directly challenging beliefs about voices. Emotion regulation has been proposed to be a central part in treating psychotic disorders such as schizophrenia (Khoury and Lecomte, 2012), which has been associated with greater levels of emotional deregulation (Trémeau, 2006). Craig et al. (2016) stressed the importance of the dialogue shifting with the avatar becoming progressively less threatening and more under control of the voice hearer. By enabling the patients to engage with their personified voice with an emphasis on altering their emotional experience, they may be able to show a shift in their distorted beliefs about their voices (Tai and Turkington, 2009). As seen in our results, beliefs about voices were significantly ameliorated. Voices appraised as malevolent and/or omnipotent have been positively associated with distress, anxiety and depressive mood (Mawson et al., 2010). While Craig et al. (2017) did not find a positive effect on voices' malevolence as we did, they did likewise observe a significant reduction on voice related distress and omnipotence obtained at post-treatment, which was maintained at the follow-up period. This difference in voice malevolence may likely be explained by the immersive virtual environment that enables patients to enter in a more profound relationship with their personified voice and to evoke stronger emotions. In doing so, beliefs about voices may more easily be altered to change their malevolent appraisal. Taken together, the preliminary results suggest that VRT might alleviate patients' distress by attenuating the threats to the Self of AVH. Though, this hypothesis will need to be formally tested in future investigations on the topic. The respective contribution of the technology (e.g., immersive VR) and of the specific content of VRT will need to be determined, as well as the role of self-esteem in the therapeutic process. Future studies will need to identify which VR parameters enhance the efficacy of VRT.

Moreover, focusing on emotional regulation and reductions in distress may influence affective symptoms. Contrary to prior results by Craig et al. (2017), we found a significant effect on depressive symptoms at post-treatment and at follow-up. Through our immersive VRT, depressive symptoms may be tackled by eliciting more intense emotions and better managing them, addressing negative beliefs about the self and improving patients' self-image. It has been speculated that distressing AVH with negative content may have an immediate and

powerful impact on mood, and low mood may in turn make an individual vulnerable to further AVH (Smith et al., 2006). These improvements in depressive symptoms contributed to a significant reduction in the severity of the general symptomatology of schizophrenia that lasted up to 3 months following the end of the therapy. In addition, we even observed certain changes in the overall symptomatology (i.e., total PANSS score) well beyond the end of the therapy noticed at the 3-month follow-up. This suggests that VRT continues to improve patients' symptomatology after the end of the therapy. Beyond the severity of symptoms, the quality of life of participants was improved with VRT, and even tended to increase thereafter. It would not be surprising that the effects of therapy gradually become manifested in the different spheres of patients' lives. AVH and their related distress cause patients with numerous consequences (i.e., depressed mood, anxiety) and interfere with their daily lives. VRT continues to have an impact on patients' symptomatology beyond the sessions, that is patients' may be able to consolidate their learnings into their daily lives. Accordingly, the benefit of VRT on these psychotic symptoms may explain the reduction in depressive symptomatology and enable patients to gain a better quality of life as seen in our results.

Our results propose that VRT is a highly promising intervention for refractory AVH in schizophrenia. Nevertheless, the current trial has a few limitations that are worth being acknowledged, namely the non-blinding to treatment allocation of the evaluator performing the clinical assessments and the non-inclusion of the data from dropouts. The latter factor may have contributed to an over-estimation of treatment effect. The choice of TAU as the control is another limitation that needs to be acknowledged, since TAU is a comparison condition that only controls for the effect of time, and does not allow to directly compare VRT to a proven efficient psychological intervention for TRS. Further head-to-head randomized-controlled trials involving larger samples of patients are warranted, comparing VRT to CBTp, as well as to a "control" VR-assisted therapy *lacking* the specific components of VRT (e.g., emotion regulation, self-esteem, etc.). Finally, careful attention will need to be paid to the training of future therapists, as the VRT requires a specific set of skills, principally "actor-like" qualities that are not traditional. Consequently, it will be crucial to determine if the efficacy of VRT remains constant across therapists.

To conclude, we found large therapeutic effects in TRS patients. This is interesting as very limited treatment options are available for this costly and suffering population. VRT may have implications for schizophrenia patients' health and quality of life that are potentially enormous. Schizophrenia is an extremely complex disorder associated with significant impairments in social and occupational functioning. Although preliminary, the benefits reported are clearly superior to the benefits of any other available psychological treatment at the moment for TRS, at least to our knowledge.

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Conflict of interest

AD is holder of a grant from Otsuka Pharmaceuticals. SP is holder or co-holder of grants from Otsuka and INSYS Pharmaceuticals.

Contributors

AD, SP and OL secured funding for the trial. SP, AD and PR conceived the trial. TB developed the virtual reality software and pipeline. AD administered the therapy. OL, PL and ML were involved in patient recruitment. ML, KP and OPS were involved in study assessments. JFP supervised the peer patient. Statistical analyses were performed by OPS and KP. SP, OPS and LD wrote the manuscript. All authors provided critical comments. All authors approved the final version of the manuscript.

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