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.

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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