Status and Clinical Experiences from the Challenge Trial – A Randomized Controlled Trial Investigating Virtual Reality-based Therapy for Auditory Hallucinations

Vernal, Ditte Lammers; Nordentoft, Merete; Christensen, Mads Juul; Smith, Lisa Charlotte; Mariegaard, Lise; Mainz, Jan; Glenthøj, Louise Birkedal

Published in:
World Social Psychiatry

Publication date:
2023

Document Version
Publisher's PDF, also known as Version of record

Status and Clinical Experiences from the Challenge Trial – A Randomized Controlled Trial Investigating Virtual Reality-Based Therapy for Auditory Hallucinations

Abstract

Background: Auditory verbal hallucinations are a prevalent symptom in schizophrenia and other psychotic disorders, affecting around 70% of patients. A sizable proportion does not achieve adequate treatment response with current interventions, including antipsychotic medication. Virtual reality-based therapy (VRT) shows promise as a new intervention. **Methods:** The Challenge Trial is a randomized controlled study examining the efficacy of VRT compared to standard treatment for auditory hallucinations in patients with psychotic disorders. In the intervention arm, virtual reality software and voice modulation are used to design a visual representation of the patient's voice (an avatar) and to transform the therapist's voice to sound like the voice the patient hears. The aim is to foster a dialogue for the patient to strengthen their power, practice self-efficacy, and alter their relation to the voice. During therapy, the avatar becomes more compassionate and/or less powerful. **Results:** Quantitative data are currently unavailable as recruitment is ongoing. Instead, the design and intervention are presented along with recruitment data, retention rates, and case vignettes. Early clinical experiences are promising, with high acceptability and tolerance among patients. The trial has successfully enrolled a diverse patient population, including those with long-standing histories of hospitalization, medication use, and chronic hallucinations. The effectiveness of VRT varies, for example, some patients have reported significant reductions in the frequency of voices and associated distress, whereas others have primarily noted improvements in emotional responses to the voices. **Conclusions:** Based on the first 2 years of the Challenge Trial, VRT shows considerable promise as a potential treatment for auditory verbal hallucinations.

Keywords: *Hallucinations, schizophrenia spectrum and other psychotic disorders, virtual reality exposure therapy*

Ditte Lammers Vernal[1,2], Merete Nordentoft[3,4], Mads Juul Christensen[1], Lisa Charlotte Smith[3], Lise Mariegaard[3], Jan Mainz[1,5,6,7], Louise Birkedal Glenthøj[3,8]

[1]Department of Psychiatry, Aalborg University Hospital, [2]Department of Clinical Medicine, Aalborg University, [3]Copenhagen Research Centre for Mental Health (CORE), Mental Health Center Copenhagen, Copenhagen University Hospital, [4]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark, [5]Department of Clinical Medicine, Danish Center for Clinical Health Services Research, Aalborg University, Aalborg, [6]Department of Health Economics, University of Southern Denmark, Odense, [7]Department of Community Mental Health, University of Haifa, Haifa, Israel [8]Department of Psychology, University of Copenhagen University, Haifa, Israel

Address for correspondence:
Dr. Ditte Lammers Vernal, OPUS, Brandevej 5, 9220 Aalborg Ø, Denmark.
E-mail: dhl@rn.dk

Access this article online

Website: www.worldsocpsychiatry.org

DOI: 10.4103/wsp.wsp_4_23

Quick Response Code:

Introduction

Individuals diagnosed with schizophrenia-spectrum disorders often require a broad range of interventions to alleviate them from the most debilitating symptoms. Antipsychotic medication remains the first line of treatment, although cognitive behavioral therapy has also proven efficacy in recent times.[1-4] The optimal approach to reduce symptoms and distress is believed to involve a combination of pharmacological and psychosocial interventions, such as psychotherapy, family-based interventions, and psychoeducation, for example, as employed in early intervention services.[5]

Auditory verbal hallucinations ("voices") are among the most common symptoms of schizophrenia, affecting approximately 75% of patients.[6] Hearing voices is not necessarily indicative of mental disorders; in the general population about one in ten report such experiences at some point in their lives.[7,8] However, in patients with psychosis, hearing voices are associated with distress and may lead to isolation, decreased self-confidence and self-worth, impaired social functioning, and exhaustion. Despite our interventions, approximately 20%–30% continue to experience auditory verbal hallucinations even after many years,[9-11] highlighting the need for new strategies. Virtual reality-based therapy (VRT) may offer a promising approach for some of these patients.[12]

Research in the use of virtual reality (VR) for mental disorders is blooming: A search

Submission: 07-03-23 **Web Publication:** 26-04-23
Acceptance: 07-03-23

How to cite this article: Vernal DL, Nordentoft M, Christensen MJ, Smith LC, Mariegaard L, Mainz J, *et al*. Status and Clinical Experiences from the Challenge Trial – A Randomized Controlled Trial Investigating Virtual Reality-Based Therapy for Auditory Hallucinations. World Soc Psychiatry 2023;5:71-6.

in PubMed using the keywords "mental disorders" and "virtual reality" conducted on February 25, 2023, yielded 1933 articles, with the earliest dating back to 1991. Half of these articles were published in the last 5 years, indicating a rapidly growing field.

VR has been investigated as a tool for both assessment and treatment interventions in mental disorders,[13] for example, such as assessing psychopathology[14,15] or treatment compliance,[16] psychosocial vocational rehabilitation,[17] cognitive remediation,[18] social cognition training,[19,20] psychotherapy,[21,22] and even as an automated VR therapy to be used in the patients' homes without the assistance of a therapist.[23,24] VRT exists for various mental disorders, with most studies focusing on anxiety disorders,[25-27] addiction disorders,[28,29] posttraumatic stress disorder (PTSD),[26,30-32] or psychotic disorders.[12,33] The highest level of evidence for VRT is found for anxiety disorders and PTSD.[22]

Within the field of psychosis, VR seems to be a safe and well-tolerated tool for various purposes, including assessment of and interventions targeting, neurocognitive deficits, functional capacity, social cognition, social competence, paranoid ideation, and auditory hallucinations.[14] Especially, VR has been investigated in research on paranoia.[34-36] Presenting neutral social situations in a safe environment, VR enables the detection of unfounded paranoid ideation, and thus, therapeutic targets.[37] Conducting exposure-based exercises in VR has several advantages, for example, the social environment can be controlled and tailor-made, exercises can be conducted directly in sessions, and it might accommodate reluctance to undergo exposure due to paranoid fears or negative symptoms.[38] Usually, VR environments are inhabited by avatars that, according to the given purpose, can be manipulated into being hostile, neutral, or friendly.[14] Roleplays mimicking everyday experiences or worst-case scenarios with avatars can be integrated into the therapeutic process of facing one's fears.[39]

Julian Leff was the first to propose using avatars and voice modulation of the therapist's voice to make it correspond to the patient's auditory hallucinations as a means of fostering dialogue. This proof-of-concept pilot was published in 2013.[40] Subsequently, the UK-Avatar Trial by Craig *et al*., which tested this approach on a larger scale, was published in Lancet in 2017[41] and was widely regarded as a potential paradigm shift in the field of hallucinations, inspiring researchers worldwide to explore technological interventions.[42] In Denmark, this publication prompted the idea of conducting a replication study. We decided to employ VR technology to avoid the logistical challenge of having the computer set up in one room and the therapist in another and to enable easier implementation of the intervention in the future, as space can be a concern in Danish psychiatry. Moreover, we hypothesized that the utilization of VR could potentially augment treatment efficacy by facilitating a heightened level of exposure within a more immersive environment. The phase of fundraising for the study was initiated in 2018.

The Challenge trial enrolled the first patient in November 2020, and the design is described in detail in Smith *et al*.[43] Quantitative data is not yet available. The purpose of the present article is to share experiences from the trial after the first 2 years, including some case vignettes and clinical experiences from the first 233 participants.

Methods

The ongoing Challenge trial is a randomized, controlled, single-blind multicenter study comparing VRT with supportive counseling in patients with schizophrenia-spectrum disorders who hears voices. The trial has been approved by the Danish Ethical Committee on March 10, 2020 (journal number H-19086621) and is registered on clinicaltrials.org, identifier: NCT04661163.

Inclusion criteria

Adults (+18 years of age), schizophrenia-spectrum disorder (ICD-10 F20.x–F29.x) having experienced verbal hallucinations for at least 3 months and either currently on antipsychotic medication or having previously tried at least two compounds without sufficient effect on hallucinations.

Exclusion criteria

Brain-organic disorder, substance use disorder that hinders participation in therapy, hallucinations in a language not spoken by the therapist, or if the patient does not speak and understand Danish or English.

Three Danish regions participate in the trial; the Capital Region, North Denmark Region and the Southern Region, and patients in treatment in these regions are eligible for participation. Referrals are mostly received from case managers or doctors in the outpatient clinic, a few were self-referrals, in which case their treating psychiatrist was also contacted. Initially, patients are screened in a brief phone interview, afterwards written information is sent to the patient and a face-to-face meeting is scheduled in which informed consent is obtained and the baseline assessment is conducted. Randomization is done utilizing the program REDCap and stratified by site; each patient is either randomized to VRT (experimental group) consisting of seven sessions in the first 12 weeks, followed by two booster sessions in the next 12 weeks, or supportive counseling (control group) which is equivalent to a treatment as usual in most Danish outpatient clinics for psychotic disorders. The trial specifies that patients in the control group must receive at least seven contacts in the first 12 weeks and two contacts in the 12 weeks to follow. Follow-up assessment is conducted at 12 weeks and 24 weeks. The assessment battery contains semi-structured interviews focusing on the severity and presence of psychotic symptoms (The Psychotic Symptom Rating

Scales and Scale for the Assessment of Positive Symptoms), negative symptoms (Brief Negative Symptom Scale), level of functioning (the Personal and Social Performance) scale as well as questionaries exploring relation to the voices, self-efficacy, trauma history, etc. For further details, readers may consult the design article.[43]

The experimental group: Virtual reality-based therapy

The software employed in the Challenge trial was custom-built by Khora, a Danish VR company. To ensure a robust design, Khora collaborated with the researchers and individuals with lived experience of hearing voices. While the software is currently not CE-marked, the certification process is anticipated to be completed soon.

Fundamental in our VRT is the initial session, where the avatar is created collaboratively between the therapist and the patient. The session involves gathering comprehensive knowledge about the voice, including its content, onset, associated life events, and the patient's previous attempts to manage the voice. During this session, the patient expresses their goals for the treatment and what changes they expect in their daily living if these goals are met. The visual representation of the voice is developed using computer technology, which can be customized by the patient to resemble their perceptions of the voice based on factors such as age, gender, color of skin and facial hair, bone structure, and facial features. Voice modulation software is then utilized to modify the therapist's voice, including tone, age, masculinity/femininity, presence, and trembling.

During sessions two to seven, the therapist uses voice modulation software to switch between their own voice and the avatar's voice to facilitate a dialogue between the patient and their voice. The second and third sessions focus on empowering the patient to resist the voice's negative influence and assert themselves. In sessions four and five, the therapist works on improving the patient's self-efficacy and self-esteem by encouraging them to identify their personal strengths and receive positive feedback from significant others. The final two sessions concentrate on the patient's future and personal recovery, emphasizing the consolidation of therapeutic gains and the development of strategies to cope with future voice experiences. In addition, the therapist and the patient review the initial therapy goals, evaluate achievements, and identify areas for further work.

Results

The study's inclusion period was projected to last for 2 years, ending in November 2022. There has been a minor delay, probably due to a combination of factors, including COVID-related delays, clinician reluctance to refer patients to a trial with a new technology where they may be uncertain if it would destabilize their patients, and patients' fear of how their voice may react. As of now, 233 patients (equivalent to 88% of the total sample) have been enrolled, and enrollment is set to end in May 2023.

At present, we can say that the retention rate is acceptable and relatively high for trials focusing on psychotic disorder with drop-out rates below 20% at 12-week follow-up. In the intervention group, approximately 80% engaged in the full therapy course with seven sessions. The sample is heterogeneous on many accounts: Duration of psychotic disorder (from months to several decades), ages (from 18 to 65 years of age), family status (married, partnered, or single), vocational status (studying, working, early-retired or other types of public benefits), living situation (alone, institutionalized, with partners, friends, or parents) and comorbidities (e.g. substance use disorders, intellectual disabilities, autism spectrum disorders, depression, and anxiety), and medication history, with some patients being on clozapine or treated with several antipsychotics. Most patients have been enrolled from outpatient clinics, but patients are also referred and included from long-term intensive inpatient units.

Adverse events occurred during the trial. Particularly, some patients experience symptom exacerbation initially and there have been some instances of inpatient admissions due to this. Due to the blinding of allocation to the treatment group, it is yet unknown if adverse events are evenly distributed in the treatment arms.

In the following paragraph, three different cases are presented to illustrate possible outcomes and the heterogeneity of the sample.

Case vignettes

Dennis, a man in his fifties, had heard voices since he was 6 years old and had a diagnosis of schizoaffective disorder. Dennis was on antipsychotic medication and mood stabilizer, having previously tried several medications, received electroconvulsive therapy, and been admitted several times. He heard three voices non-stop and decided to work on the worst one of them, "Brian." The first five sessions of the VRT were hard, and Dennis often thought of backing out. In the sixth session, "Brian" started to listen and respond differently, and Dennis began to have 15 min of quiet time each day. Looking at the data, Dennis' symptoms at the end of treatment were only slightly reduced – he still heard voices almost constantly. However, from his point of view, the difference was massive and led to big changes in life. He started advocating for our trial when talking to other patients, often expressing his hopes for this intervention to become a standard option, and he joined the researchers at public talks where he would share his experiences. In Dennis' words, "*Avatar Therapy saved my life. And had you told me two years ago that I would stand here, in front of people and talk, I would have called you nuts!"*

Cille is a young woman suffering from schizophrenia. She joined the Challenge project in the pilot phase and allowed a Danish TV team to make a short documentary

of her experiences in therapy (titled "My New Life – How I conquered the voices,"[44] available in Danish at TV 2 Play). She quickly felt a change in the presence and content of the voices, and early in the course explained to the TV crew how it was strange that "*it's like my head is completely silent and I have no idea what's going on (...) I enjoy this, kind of calm, it's absolutely fantastic. But it's also weird.*" As part of the therapy, participants are encouraged to share a recording of the VR dialogue as well as a picture of the avatar with their close relations. This was a moving experience, to be able to share something that had previously been very private. Cille's self-esteem grew during therapy, and she would not believe the voice anymore. In the last session, the avatar apologized to her. Now, more than 2 years after her participation, she has continued to experience progress from her hallucinations, and the previous derogatory voice she worked with in therapy, is now her most friendly voice and a positive influence in her life.

Julia is a young woman suffering from schizophrenia. She was enrolled in Challenge after having been admitted for more than a year in a locked, long-term inpatient unit. She had heard voices for many years and believed she had little agency and the voices were in total control. The voices did not want her to take her medication which often led to her being restrained and medicated against her will. Initially, she was not able to stand up against the voices; she listened to the therapist and the voices but did not engage. Slowly, she gained more power and self-efficacy, became more involved, and even stood up to the voices on some accounts. She became more compliant with treatment, as indicated by a reduction in the need for physical restraints, and her acceptance of a switch to clozapine. At the end of the VRT, she was discharged to a less restrictive, open institution in the community where she still lives.

Discussion

The present article is written 2 years and 3 months into the Challenge trial. As the trial is ongoing, quantitative data are not available at present. We aimed at inclusion and exclusion criteria that would allow the inclusion of the patients that most clinicians see and treat on an everyday basis. Therefore, deliberately, the trial was not designed with elaborate and restrictive criteria that only the least complex and most high-functioning patients are able to meet. As described in the results, these endeavors have proven possible. Retention also seems promising.

The follow-up data in challenge at 12 and 24 weeks will show if the intervention is superior to treatment as usual and if the benefits seem sustainable after the end of treatment. It is possible that certain patient subgroups and/or symptom profiles may exhibit different treatment outcomes, providing valuable insight into the targeted application of the intervention. Finally, if the VRT is implemented in standard clinical practice, time will show if seven sessions plus two booster sessions are the optimal number or if some patients might need a more individualized approach to time, length, or possibly resumption of therapy after a break.

Conclusion

In general, our clinical experiences and the feedback we have received from patients indicate that VRT is a beneficial intervention. Therapists, colleagues, and patients have expressed hopes that the outcomes will demonstrate sufficient efficacy to establish our VRT as a potential treatment option for individuals with psychotic disorders. Concurrently, new trials investigating VRT continue to emerge, which is contributing to a generally positive outlook on the use of VR technology.

Acknowledgments

The challenge team wishes to thank the late Professor Julian Leff for his groundbreaking work and ideas which – along with the UK trial run by Professor Tom Craig and colleagues – served as inspiration for the Challenge trial. Furthermore, we thank our brave participants in the trial, the peers who helped us in the developmental phase, and the software firm Khora for their work in developing the virtual reality software.

Financial support and sponsorship

The Challenge trial is supported by: The Innovation Fund Denmark, Denmark, Independent Research Fund Denmark, Faculty of Health and Medical Sciences - University of Copenhagen, LifeScience, Health Innovation Fund North Denmark Region, The Fund for Clinical Psychiatric Research North Denmark Region, AP Møller Foundation, and ML Jørgensen and Gunnar Hansen's Foundation.

Conflicts of interest

Ditte Lammers Vernal has received speaking fees from Lundbeck Pharma. Ditte Lammers Vernal is the sub-investigator at Aalborg University Hospital in a medical trial run by Boehringer-Ingelheim, she does not receive a salary from Boehringer-Ingelheim. Ditte Lammers Vernal has attended a 1-day meeting on cognitive dysfunctions in schizophrenia held in Amsterdam, lodging and flight paid by Boehringer-Ingelheim. The co-authors report no conflicts of interest.

References

1. Agbor C, Kaur G, Soomro FM, Eche VC, Urhi A, Ayisire OE, *et al.* The role of cognitive behavioral therapy in the management of psychosis. Cureus 2022;14:e28884.
2. Ryan M, Sattenspiel D, Chianese A, Rice H. CE: Original research: Cognitive behavioral therapy for symptom management in treatment-resistant schizophrenia. Am J Nurs 2022;122:24-33.
3. Wood L, Burke E, Morrison A. Individual cognitive behavioural therapy for psychosis (CBTp): A systematic review of qualitative literature. Behav Cogn Psychother 2015;43:285-97.
4. Morrison AP, Law H, Carter L, Sellers R, Emsley R, Pyle M,

et al. Antipsychotic drugs versus cognitive behavioural therapy versus a combination of both in people with psychosis: A randomised controlled pilot and feasibility study. Lancet Psychiatry 2018;5:411-23.

5. Correll CU, Galling B, Pawar A, Krivko A, Bonetto C, Ruggeri M, *et al.* Comparison of early intervention services vs. treatment as usual for early-phase psychosis: A systematic review, meta-analysis, and meta-regression. JAMA Psychiatry 2018;75:555-65.
6. Waters F, Fernyhough C. Hallucinations: A systematic review of points of similarity and difference across diagnostic classes. Schizophr Bull 2017;43:32-43.
7. Beavan V, Read J, Cartwright C. The prevalence of voice-hearers in the general population: A literature review. J Ment Health 2011;20:281-92.
8. Sommer IE, Daalman K, Rietkerk T, Diederen KM, Bakker S, Wijkstra J, *et al.* Healthy individuals with auditory verbal hallucinations; who are they? Psychiatric assessments of a selected sample of 103 subjects. Schizophr Bull 2010;36:633-41.
9. Austin SF, Mors O, Budtz-Jørgensen E, Secher RG, Hjorthøj CR, Bertelsen M, *et al.* Long-term trajectories of positive and negative symptoms in first episode psychosis: A 10 year follow-up study in the OPUS cohort. Schizophr Res 2015;168:84-91.
10. Gotfredsen DR, Wils RS, Hjorthøj C, Austin SF, Albert N, Secher RG, *et al.* Stability and development of psychotic symptoms and the use of antipsychotic medication – Long-term follow-up. Psychol Med 2017;47:2118-29.
11. Wils RS, Gotfredsen DR, Hjorthøj C, Austin SF, Albert N, Secher RG, *et al.* Antipsychotic medication and remission of psychotic symptoms 10 years after a first-episode psychosis. Schizophr Res 2017;182:42-8.
12. Dellazizzo L, Giguère S, Léveillé N, Potvin S, Dumais A. A systematic review of relational-based therapies for the treatment of auditory hallucinations in patients with psychotic disorders. Psychol Med 2022;52:2001-8.
13. Wiebe A, Kannen K, Selaskowski B, Mehren A, Thöne AK, Pramme L, *et al.* Virtual reality in the diagnostic and therapy for mental disorders: A systematic review. Clin Psychol Rev 2022;98:102213.
14. Rus-Calafell M, Garety P, Sason E, Craig TJ, Valmaggia LR. Virtual reality in the assessment and treatment of psychosis: A systematic review of its utility, acceptability and effectiveness. Psychol Med 2018;48:362-91.
15. Geraets CN, Wallinius M, Sygel K. Use of virtual reality in psychiatric diagnostic assessments: A systematic review. Front Psychiatry 2022;13:828410.
16. Baker EK, Kurtz MM, Astur RS. Virtual reality assessment of medication compliance in patients with schizophrenia. Cyberpsychol Behav 2006;9:224-9.
17. Tan BL, Shi J, Yang S, Loh H, Ng D, Choo C, *et al.* The use of virtual reality and augmented reality in psychosocial rehabilitation for adults with neurodevelopmental disorders: A systematic review. Front Psychiatry 2022;13:1055204.
18. Perra A, Riccardo CL, De Lorenzo V, De Marco E, Di Natale L, Kurotschka PK, *et al.* Fully immersive virtual reality-based cognitive remediation for adults with psychosocial disabilities: A systematic scoping review of methods intervention gaps and meta-analysis of published effectiveness studies. Int J Environ Res Public Health 2023;20:1527.
19. Nijman SA, Pijnenborg GH, Vermeer RR, Zandee CE, Zandstra DC, van der Vorm D, *et al.* Dynamic interactive social cognition training in virtual reality (DiSCoVR) versus virtual reality relaxation (VRelax) for people with a psychotic disorder: A single-blind multicenter randomized controlled trial. Schizophr Bull 2023;49:518-30.
20. Vass E, Simon V, Csukly G, Fekete Z, Kis B, Simon L. Virtual reality-based theory of mind intervention in schizophrenia: Preliminary efficacy results. Compr Psychiatry 2022;119:152350.
21. Geraets CN, van der Stouwe EC, Pot-Kolder R, Veling W. Advances in immersive virtual reality interventions for mental disorders: A new reality? Curr Opin Psychol 2021;41:40-5.
22. Emmelkamp PM, Meyerbröker K. Virtual reality therapy in mental health. Annu Rev Clin Psychol 2021;17:495-519.
23. Freeman D, Lambe S, Galal U, Yu LM, Kabir T, Petit A, *et al.* Agoraphobic avoidance in patients with psychosis: Severity and response to automated VR therapy in a secondary analysis of a randomised controlled clinical trial. Schizophr Res 2022;250:50-9.
24. Freeman D, Lambe S, Kabir T, Petit A, Rosebrock L, Yu LM, *et al.* Automated virtual reality therapy to treat agoraphobic avoidance and distress in patients with psychosis (gameChange): A multicentre, parallel-group, single-blind, randomised, controlled trial in England with mediation and moderation analyses. Lancet Psychiatry 2022;9:375-88.
25. Carl E, Stein AT, Levihn-Coon A, Pogue JR, Rothbaum B, Emmelkamp P, *et al.* Virtual reality exposure therapy for anxiety and related disorders: A meta-analysis of randomized controlled trials. J Anxiety Disord 2019;61:27-36.
26. van Loenen I, Scholten W, Muntingh A, Smit J, Batelaan N. The effectiveness of virtual reality exposure-based cognitive behavioral therapy for severe anxiety disorders, obsessive-compulsive disorder, and posttraumatic stress disorder: Meta-analysis. J Med Internet Res 2022;24:e26736.
27. Meyerbröker K, Morina N. The use of virtual reality in assessment and treatment of anxiety and related disorders. Clin Psychol Psychother 2021;28:466-76.
28. Taubin D, Berger A, Greenwald D, Greenwald H, Burke C, Gongora DS, *et al*. A systematic review of virtual reality therapies for substance use disorders: Impact on secondary treatment outcomes. Am J Addict 2023;32:13-23.
29. Langener S, Van Der Nagel J, van Manen J, Markus W, Dijkstra B, De Fuentes-Merillas L, *et al.* Clinical relevance of immersive virtual reality in the assessment and treatment of addictive disorders: A systematic review and future perspective. J Clin Med 2021;10:3658.
30. Heo S, Park JH. Effects of virtual reality-based graded exposure therapy on PTSD symptoms: A systematic review and meta-analysis. Int J Environ Res Public Health 2022;19:15911.
31. Vianez A, Marques A, Simões de Almeida R. Virtual reality exposure therapy for armed forces veterans with post-traumatic stress disorder: A systematic review and focus group. Int J Environ Res Public Health 2022;19:464.
32. Eshuis LV, van Gelderen MJ, van Zuiden M, Nijdam MJ, Vermetten E, Olff M, *et al.* Efficacy of immersive PTSD treatments: A systematic review of virtual and augmented reality exposure therapy and a meta-analysis of virtual reality exposure therapy. J Psychiatr Res 2021;143:516-27.
33. Monaghesh E, Samad-Soltani T, Farhang S. Virtual reality-based interventions for patients with paranoia: A systematic review. Psychiatry Res 2022;307:114338.
34. Freeman D. Studying and treating schizophrenia using virtual reality: A new paradigm. Schizophr Bull 2008;34:605-10.
35. Freeman D, Bradley J, Antley A, Bourke E, DeWeever N, Evans N, *et al.* Virtual reality in the treatment of persecutory delusions: Randomised controlled experimental study testing how to reduce delusional conviction. Br J Psychiatry 2016;209:62-7.

36. Freeman D, Slater M, Bebbington PE, Garety PA, Kuipers E, Fowler D, *et al.* Can virtual reality be used to investigate persecutory ideation? J Nerv Ment Dis 2003;191:509-14.
37. Freeman D, Reeve S, Robinson A, Ehlers A, Clark D, Spanlang B, *et al.* Virtual reality in the assessment, understanding, and treatment of mental health disorders. Psychol Med 2017;47:2393-400.
38. Pot-Kolder RM, Geraets CN, Veling W, van Beilen M, Staring AB, Gijsman HJ, *et al.* Virtual-reality-based cognitive behavioural therapy versus waiting list control for paranoid ideation and social avoidance in patients with psychotic disorders: A single-blind randomised controlled trial. Lancet Psychiatry 2018;5:217-26.
39. Jeppesen UN, Due AS, Mariegaard L, Pinkham A, Vos M, Veling W, *et al.* Face Your Fears: Virtual reality-based cognitive behavioral therapy (VR-CBT) versus standard CBT for paranoid ideations in patients with schizophrenia spectrum disorders: A randomized clinical trial. Trials 2022;23:658.
40. Leff J, Williams G, Huckvale MA, Arbuthnot M, Leff AP. Computer-assisted therapy for medication-resistant auditory hallucinations: Proof-of-concept study. Br J Psychiatry 2013;202:428-33.
41. Craig TK, Rus-Calafell M, Ward T, Leff JP, Huckvale M, Howarth E, *et al.* AVATAR therapy for auditory verbal hallucinations in people with psychosis: A single-blind, randomised controlled trial. Lancet Psychiatry 2018;5:31-40.
42. Dellazizzo L, Potvin S, Phraxayavong K, Dumais A. Exploring the benefits of virtual reality-assisted therapy following cognitive-behavioral therapy for auditory hallucinations in patients with treatment-resistant schizophrenia: A proof of concept. J Clin Med 2020;9:3169.
43. Smith LC, Mariegaard L, Vernal DL, Christensen AG, Albert N, Thomas N, *et al.* The Challenge trial: The effects of a virtual reality-assisted exposure therapy for persistent auditory hallucinations versus supportive counselling in people with psychosis: Study protocol for a randomised clinical trial. Trials 2022;23:773.
44. Horn N, Buus C, Aarestrup R. Mit nye liv: Sejren over stemmerne. Denmark: TV2 Play; 2020.