Virtual reality supported therapy for the negative symptoms of schizophrenia: the V-NeST feasibility RCT

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Scientific summary

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Scientific summary

Background

Schizophrenia is one of the most severe and debilitating mental health conditions. Full recovery rates are low, and the illness burden is huge for those affected. Negative symptoms (NS) are typically observed in people with schizophrenia and indicate a loss or reduction in normal functioning. NS include poor motivation, social withdrawal, difficulty in enjoying activities and reduced communication. These symptoms influence patients' day-to-day functioning, and reports of patient groups have highlighted this as a key area for new treatment development. Despite obstructing people's recovery, intervention development has received limited attention. Main barriers that have hampered development are the lack of clear therapy targets and poor adherence to interventions because of lack of motivation. In recent years research showed that people with NS are more sensitive to negative feedback and less sensitive to positive feedback. This may be a mechanism maintaining NS. Further, the use of digital technology in therapy delivery has the potential to make therapies more engaging and improve adherence. Virtual reality (VR), a form of computer-simulated immersive reality, may offer opportunities to improve engagement and therapy experience and reduce therapy motivational needs.

Objectives

1. Develop a novel virtual reality supported therapy [called Virtual Reality Supported Therapy for the Negative SympToms of Psychosis (V-NeST)] targeting the NS of schizophrenia with the overall aim of improving recovery.
2. Evaluate V-NeST for ease of use, acceptability and safety and estimate its potential benefits.

Methods

Design

This is a two-arm randomised controlled trial comparing V-NeST plus treatment as usual (TAU) to TAU alone. Participants were assessed at baseline and at 12 weeks postrandomisation (i.e. end of therapy for those randomised to V-NeST). The primary outcome was participants' progress on personal recovery goals measured by the Goal Attainment Scale (GAS) at 12 weeks postrandomisation. Secondary outcomes were NS and functioning. Apart from the participants, the therapists and the trial principal investigator, all other study staff including outcome assessors and the trial statistician were blind to trial arm allocation, until primary analysis completion.

Ethical approval and protocol registration

Study procedures were reviewed and approved by the London Camberwell and St. Giles NHS ethics committee (approval number 19/LO/0830). The study protocol was pre-registered on ClinicalTrials.gov (identifier: NCT03995420).

Randomisation

Consented participants were randomised using a web-based randomisation service at the UKCRC registered King's Clinical Trials Unit. Randomisation used variable block size (i.e. 2, 4 and 6) with equal allocation.

Participants
Participants were recruited from community mental health teams, which are part of the South London and Maudsley NHS Foundation Trust. Inclusion criteria: (1) currently under the care of a community psychosis services; (2) older than 18 years; (3) in a stable clinical condition; (4) with a documented episode of psychosis (e.g. first-episode psychosis) and/or a diagnosis of schizophrenia; (5) no current episode or history of epilepsy (as it is a contraindication for VR); (6) experiencing disabling NS as identified by care staff. Exclusion criteria: (1) having a comorbid organic condition affecting their behaviour; (2) severe learning disability; (3) insufficient communication skills for consenting and undertaking the research assessment and therapy.

Measures
The primary outcome of this study was GAS, which is a structured measure of personal recovery goals. The following measures were secondary outcomes: The Clinical Assessment Interview for Negative Symptoms, which is an interviewer-based assessment of NS. The self-evaluation of negative symptoms, which provides an assessment of NS from the participant's perspective. The Work and Social Adjustment Scale was used to assess functioning. The mechanistic elements of the intervention were assessed using the Effort Expenditure for Reward Task and the Wisconsin Card Sorting Task. The following measures were used to characterise the sample: The Psychotic Symptom Rating Scales to assess the positive symptoms of psychosis. The Hospital Anxiety and Depression Scale to assess anxiety and depression. The Rosenberg Self-Esteem Scale to assess self-esteem. The digit span to assess working memory and the Trail Making (A and B) to assess processing speed and executive function.

Acceptability
Participants randomised to V-NeST were invited to participate in a feedback semistructured interview assessing acceptability. The interview asked questions in relation to the therapy and assessment procedures, use of VR and asked suggestions for therapy and research procedures improvements. All interviews were recorded and transcribed.

Service users involvement
People experienced in using mental health services were consulted at different stages of this study, including the initial discussions on study procedures, to revise wording on the study information sheet and consent forms and for feedback on VR development. Service users were part of the trial management group and supported the interpretation and dissemination of the results and are also authors on this report.

Sample size
On the basis of previous research and recommendations from our lead statistician, we have considered a sample size of 30 participants to be adequate for obtaining reliable feasibility parameter estimates. And on the basis of previous similar studies conducted on our site, we have estimated for a dropout rate of 20% over the study period.

Feasibility evaluation
The feasibility of the trial procedures was examined using proportions and exact Clopper Pearson's 95% confidence intervals (CIs) for assessments of feasibility and acceptability in terms of recruitment, consent and availability for screening, eligibility, availability for baseline assessment and randomisation, treatment retention and follow-up assessments, and availability and consent to be approached by a research therapist.

Explorative treatment effect estimate
These analyses followed the intention-to-treat principle, with data from all participants who took part in the study considered. Clinical outcomes were analysed using a linear regression model with data collected from all participants irrespective of whether they attended the intervention or not. Treatment differences with 95% CIs at follow-up are presented. In addition, standardised effect sizes (Cohen's *d* calculated as the adjusted mean difference between treatment arms estimates divided by the

within-groups pooled standard deviation) with 95% CIs will be presented. Our main aim was to estimate the likely range of intervention effects at post-treatment by assessing 95% CIs of the treatment effects.

Acceptability evaluation

Thematic analysis was used to analyse the post-therapy feedback interview transcripts. This explored participants' experiences of receiving the therapy and taking part in this research study. Emergent themes were identified by one researcher and then the themes were reviewed and coded by four members of the team including service users with relevant lived experience.

Results

Recruitment and retention

A total of 190 people were assessed for eligibility of which 160 were excluded: 39 people declined to participate, 44 were not contactable and the remaining 77 people did not meet inclusion criteria. Thus 30 participants were assessed at baseline and randomised into V-NeST plus TAU (*N* = 15; 50%) or TAU alone (*N* = 15; 50%). Out of these 30 participants, 29 received the allocated treatment (14 participants received V-NeST plus TAU and 15 participants received TAU alone). Four participants did not provide data at follow-up; they either were 'lost at follow-up' (V-NeST: *N* = 1 and TAU alone: *N* = 2) or discontinued the study (V-NeST: *N* = 1). All 30 participants were considered for the primary analyses.

In the treatment arm, 14 out of 15 participants attended at least 1 therapy session with an average of 9.7 (standard deviation = 3.77, range 1–12) sessions. Two participants did not receive the minimum therapy dose of six sessions and completed one and four therapy sessions, respectively.

Assessment completion

All participants completed all clinical outcome measures (primary and secondary) at the baseline, while 76% of the participants completed the mechanistic outcomes. At follow-up, data completion for the primary and secondary outcome ranged between 86% and 100%. The completion rate for the mechanistic measure was 26%.

Adverse events

There were two serious adverse events (from two participants) and 11 adverse events (AEs) recorded in this study. AEs were not considered linked to the therapy or the research procedures.

Acceptability evaluation

Nine out of fifteen participants in the intervention arm of the trial were interviewed. Themes emerging from the interview were as follows: (1) therapy contributing to personal goals; (2) impact of pandemic-imposed restrictions on recovery; (3) debilitating nature of NS; (4) value of using virtual reality; (5) feedback on therapy procedures and suggestions for improvements.

Treatment effect estimate

The results of linear regression model analyses with the clinical outcome as the dependent variable, group as categorical independent variables and baseline value of outcome as a covariate showed that V-NeST had a large treatment effect on therapy goals [Cohen's *d* = 1.48 (95% CI 0.61 to 2.35)]. The treatment effects of main secondary outcomes were smaller and all favouring V-NeST but with large CIs.

Conclusions

V-NeST demonstrated good acceptability and feasibility parameters particularly considering this study involved participants with severe and disabling levels of NS. The therapy procedures were considered acceptable, and the VR aspects were well tolerated and found to be engaging. Several therapy features

were suggested for revision, including ways of interacting with the virtual environment (e.g. hands movements) and some therapy components (e.g. making psychoeducation more engaging). Only one participant had tried VR before, and most had limited digital technology skills. This was not a barrier to therapy use and the VR proved intuitive and easy to learn. The feasibility of the research procedure was also good with most research procedures being well tolerated by all participants. The study recruited to target (30 participants) but considered 190 referrals to meet its target. This means approximately one in six of the people referred was able to take part in the trial. While this study had comprehensive inclusion criteria, there is consensus that recruiting people with NS in research studies may be complex. However, we proved that it is possible and that once participants entered the trial, we retained more than 80% of those randomised to treatment.

The explorative analysis on the prespecified primary outcome suggested that the intervention may be helpful in supporting people's recovery goals. This outcome was chosen as this was what service users suggested to be the most valuable. This result is encouraging and taken together with the acceptability and feasibility findings supports further development and evaluation of this therapy.

Future steps for developing V-NeST will include the modification of the VR software and therapy procedures in line with the feedback received from participants. A formal evaluation of efficacy will also require an appropriately powered trial. A future evaluation should also consider the cost-efficacy of this intervention and how it may be implemented in clinical settings (e.g. therapist training or access to VR).

The development and evolution of digital therapies has enormous potential to reduce the impact of NS on recovery in people with schizophrenia. There is the promise of better and more engaging therapies coupled with the prospect of these being easier to deliver for services.

Study registration

The study protocol was pre-registered on ClinicalTrials.gov (identifier: NCT03995420).

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