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Virtual Reality Therapy for the Negative Symptoms of Schizophrenia (V-NeST): A pilot randomised feasibility trial

Matteo Cella a,b,*, Paul Tomlin a, Daniel Robotham c, Patrick Green a, Helena Griffiths a, Daniel Stahl a, Lucia Valmaggia a,b,d

a Institute of Psychiatry, Psychology and Neuroscience, King's College London, UK
b South London and the Maudsley NHS Trust, UK
c McPin Foundation, UK
d Katholieke Leuven Universiteit, Belgium

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ABSTRACT

Background: Negative symptoms are typically observed in people with schizophrenia and indicate a loss or reduction of normal function (e.g. reduced motivation and affect display). Despite obstructing people's recovery, intervention development has received limited attention. This study tests the feasibility and acceptability of a novel Virtual Reality Supported Therapy for the Negative Symptoms of Schizophrenia (V-NeST).

Method: A single (rater) blind randomised study with two conditions; V-NeST plus treatment as-usual (TAU) vs. TAU alone, recruiting people with schizophrenia experiencing debilitating negative symptoms. Assessment was at baseline and 3-month post-randomisation. The pre-specified primary outcome was participants' goal attainment, secondary outcomes were negative symptoms and functioning. The study assessed feasibility and acceptability parameters including recruitment, eligibility, treatment adherence and retention. Acceptability was also evaluated qualitatively using a post-therapy feedback interview. Explorative therapy effect on outcomes was estimated.

Results: The study recruited to its pre-specified target of 30 participants (15 randomised to V-NeST). Two participants in each trial arm disengaged and did not complete the study. Therapy engagement for those randomised to V-NeST was appropriate and research procedures were feasible. The experience with therapy and VR was described as positive and useful. Preliminary analysis suggested the therapy may have a large effect on participants goals and a possible effect on negative symptoms.

Conclusion: V-NeST is a feasible and acceptable intervention. This therapy has the potential to support people with schizophrenia achieving their recovery goals and may reduce negative symptoms. The efficacy results need to be evaluated in an appropriately powered efficacy study.

1. Introduction

Negative symptoms (NS) are common in people with schizophrenia with at least one in three experiencing debilitating and long-lasting NS (Bobes et al., 2010). These include poor motivation, social withdrawal, difficulties in experiencing pleasure, blunted affect and reduced communication (Marder and Galderisi, 2017). Extensive evidence points at the critical role NS play in negatively affecting people's recovery goals, quality of life and functioning levels (Galderisi et al., 2018).

Despite their importance to illness prognosis and functioning, the development of interventions for NS received only very limited attention (Aleman et al., 2017). Current guideline treatment recommendations for both pharmacological and psychosocial interventions centres on efficacy evidence for positive symptoms reduction (e.g., NICE, 2014). First line intervention for schizophrenia such as antipsychotic medication and Cognitive Behaviour Therapy (CBT) for psychosis are targeting prevalently positive symptoms and have a small effect on NS (Jauhar et al., 2014; Krause et al., 2018).

Psychosocial interventions have shown some promise in targeting NS (Cella et al., 2017a; Turner et al., 2018). However only a handful of

* Corresponding author at: Department of Psychology, Institute of Psychiatry, Psychology & Neuroscience, King's College London, De Crespigny Park, SES 8AF London, UK.
E-mail address: matteo.cella@kcl.ac.uk (M. Cella).

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approaches were designed and tailored to tackle these symptoms. An issue that has hampered therapy development is the absence of a clear therapy target or mechanisms. Adapted CBT approaches for NS have focussed on tackling clients’ defeatist beliefs (Grant et al., 2012), while cognitive remediation approaches have targeted the cognitive difficulties underpinning NS (Cella et al., 2017b; Ventura et al., 2019).

Research has shown a consistent association between reward processing abnormalities and negative symptoms in people with schizophrenia (Gold et al., 2008; Strauss et al., 2014). Studies found that difficulties in motivation and pleasure experience were associated with reduced sensitivity to feedback and reward learning (Whitton et al., 2015). Researchers have attempted to address this issue using contingency measures (e.g. financial incentives Noordraven et al., 2017); but these approaches circumvent reward processing difficulties by disproportionally increasing reward and may not allow the reward processing system to recalibrate. This may limit the potential for the benefit to generalise to other areas of life. There is evidence suggesting that changes in reward learning following therapy are associated with NS reduction (Cella et al., 2014), suggesting that a therapy targeting reward processing difficulties may be appropriate to reduce NS.

NS are a key barrier to therapy engagement (e.g. Browne et al., 2021). Motivational issues, flat affect and difficulties engaging with social contact may make attending therapy sessions difficult. Expressive and cognitive difficulties may also make it difficult for people with high levels of NS to engage with long sessions of talking therapy. Role-plays, in-vivo practice and behavioural work may be important to address NS (Velligan et al., 2015), but are often complicated to organise, time consuming for clinicians, and it may be challenging for clients due to extended withdrawal from activities.

Virtual reality (VR) technology allows the creation of virtual environments simulating real life and for participants to interact within these environments in a controlled and graded fashion. Previous research has shown that VR can be used as part of psychological intervention to allow effective exposure to simulated activities that participants may find challenging in real life (Counotte et al., 2017; Rus-Calafell et al., 2018). VR may be a useful tool for a therapy targeting NS due to its immersive and engaging properties, but it can also allow graded behavioural activation and real-time or “in the moment” reflections on the participant’s behaviour and enjoyment levels.

The overall aim of this project is to test the feasibility and acceptability of a novel virtual reality assisted therapy, called V-NeST (Virtual reality-NEGative Symptom Therapy), to reduce the impact of negative symptoms on recovery in people with schizophrenia. The results will inform a future efficacy trial by providing information on key parameters including recruitment, retention, acceptability and treatment protocol. The therapy aims of recalibrating feedback sensitivity by reducing oversensitivity to negative feedback and increase sensitivity to positive. As our aim is to make this therapy as useful as possible to those who may be taking advantage of it in the future, we have asked service users with negative symptoms to choose the primary outcome for this and future evaluations of this therapy. The primary outcome chosen reflected the importance of personal recovery goals.

2. Methods

2.1. 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 post randomisation (i.e. end of therapy for those randomised to V-NeST). The primary outcome was participant’s progress on personal recovery goals measured by the Goal Attainment Scaling (GAS) at week 12 post randomisation. Secondary outcomes were negative symptoms and functioning. Apart from the participants, the therapists and the trial principal investigator, all other study staff including outcome assessors were blind to trial arm allocation, including the trial statistician until primary analysis completion.

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

2.2. Randomisation

Consented participants were randomised using web-based randomisation service the UKCRC registered King’s Clinical Trials Unit (KCTU). Randomisation used variable block size with equal allocation.

2.3. Participants

Participants were recruited from community mental health teams part of the South London and Maudsley NHS trust. Inclusion criteria were: i) currently under the care of a community psychosis services; ii) aged over 18; iii) in a stable clinical condition with no recent medication change; iv) with a documented episode of psychosis (e.g., first episode psychosis) and/or a diagnosis of schizophrenia; iv) no current or history of epilepsy (as it is a contra-indication for VR); v) experiencing disabling NS as identified by care staff. This last criterion was operationalised by a member of the research team using a screening checklist with the referring clinicians enquiring about severe and enduring difficulties with task initiation, motivation and pleasure for everyday life activities, flat affect, reduced speech production and prosody when communicating and difficulties with social behaviour. Only participants presenting with at least one of these difficulties were approached directly and further screened for inclusion.

Exclusion criteria: i) having a co-morbid organic condition affecting their behaviour; ii) severe learning disability; iii) insufficient communication skills for consenting, undertaking the research assessment and therapy.

2.4. Protocol changes

The onset of the COVID-19 pandemic prompted the following protocol amendments which were approved by the Trial Steering committee. Participants with health conditions or characteristics associated with COVID-19 complications (e.g., diabetes, respiratory problem, cancer) were excluded from participation in the study. Research assessments were conducted primarily remotely. All therapy contact was conducted face-to-face but with COVID-19 risk mitigation measures in place in line with the UK NHS and academic institution host guidelines. All equipment was sterilised with UV light before and after each session.

2.5. Measures

The Goal Attainment Scaling (GAS) was the study primary outcome. This is a structured measure of personal recovery goal (Kiresuk and Sherman, 1968; Turner-Stokes, 2009). A positive value in GAS score at follow-up reflects partial-, complete- or over-achievement on the participants’ pre-selected goals while negative values represent degrees of underachievement. The GAS has been used widely to evaluate intervention in mental health (Clare et al., 2019; Hurn et al., 2006; Lee et al., 2021). The following measures were secondary outcomes. The Clinical Assessment Interview for Negative Symptoms (CAINS) an interviewer-based assessment of negative symptoms (Kring et al., 2013). The Self-evaluation of Negative Symptoms (SNS) (Dollius et al., 2016) providing an assessment of NS from the participant’s perspective. The work and social adjustment scale (WSAS) (Mauds et al., 2002) was used to assess functioning. For all these measures a decrease in score represents a reduction in NS or functioning difficulties. The mechanistic elements of the intervention were assessed using the Effort Expenditure for Reward Task (EERT) (Treadway et al., 2009), the Wisconsin Card Sorting Task WCST (Tien et al., 1996). The following were measures
used to characterise the sample. The Psychotic Symptom Rating Scales (PSYRATS) assessing the positive symptoms of psychosis (Haddock et al., 1999). The Hospital Anxiety and Depression Scale (HADS) (Snith, 2003). The Rosenberg Self-Esteem Scale (RSS) (Rosenberg, 1989). The digit span (Wechsler, 2011) assessing working memory and the Trail Making Test (A and B) assessing processing speed and executive function (Lezak et al., 2004).

Participants randomised to V-NeST were invited to take part in a feedback semi-structured interview assessing acceptability once therapy was completed (adapted from Reeder et al., 2016; Sedgwick et al., 2021). The interview asked questions in relation to the therapy and assessment procedures, use of VR and asked for suggestion for therapy and research improvements. All interviews were recorded and transcribed.

2.6. Intervention and VR equipment

V-NeST is a 12-session therapy using psychological intervention principles based on Cognitive Behavioural Therapy (e.g., the link between actions and emotion) and Cognitive Remediation (e.g., teaching metamemory and strategy use to help regulate behaviour) (Cella et al., 2015). Each therapy session involves therapist supported activities including psychoeducation, behavioural activation, developing insight on pleasure experience and emotions. Central to the therapy is developing awareness and recalibrate the way participants use feedback to improve goal-directed behaviour. This is achieved by psychoeducation activities (e.g., how feedback influences behaviour), the routine use of activity appraisal (e.g., enjoyment rating) and re-appraisal (e.g., outcome re-evaluation), promoting an errorless learning environment (e.g., excessive use of positive feedback), promoting successful and enjoyable everyday life activities.

The therapy is supported by the use of a purposefully designed and built VR software with five VR environments available. These environments present unique and tailored motivational challenges which participants are encouraged to approach while reflecting (and rating) their experiences. These are then discussed with the therapist. Environments requiring low motivation such as domestic rooms (e.g., lounge) where participants can engage in passive activities such as listening to music or watching TV and environments requiring higher level of motivation such as a factory like environment where participants are asked to perform tasks, a social space where participants are asked to take part in a conversation with other avatars and a game room with multiple activities available at different difficulty levels (see Appendix 1 for VR environments screenshots examples).

The VR environments were designed by the first and last author in collaboration with people with lived experience of negative symptoms and supported by Virtualware using Unity. The software run a VR ready laptop and the head mounted display used was the Oculus Rift-S. Ear covering headphones were used for sound. The experience was designed as a sitting experience. Therapists were graduate level psychologists with clinical experience with the target population. Therapists received tailored training and weekly supervision to monitor adherence to the manual.

2.7. Service users involvement

People with the experience of using mental health services were consulted at different stages of this study. For the initial discussion on study procedures, to revise wording on information sheet and consent, and for VR development feedback. Service users were part of the trial management group and supported the interpretation and dissemination of the results.

2.8. Sample size

Due to the feasibility and acceptability objectives of this study power calculations to determine sample size are not appropriate (Browne, 1995). Based on previous research and recommendations from our lead statistician, we have considered a sample size of 30 adequate for obtaining reliable feasibility parameter estimates. On the bases of previous similar studies conducted at our site we have estimated for a dropout rate of 20 % over the study period (e.g. Reeder et al., 2017). This will allow this study to have completed follow-up data for at least 24 participants.

2.9. Statistical analyses

Analyses were conducted using STATA 17 (StataCorp, 2007). Descriptive statistics were used to summarise the participants’ clinical and demographic characteristics.

2.10. Feasibility evaluation

The feasibility of trial procedures was examined using proportions and exact Clopper Pearson’s 95 % confidence intervals 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.

2.11. Explorative treatment effect estimate

These analyses followed the intention-to-treat principle, with data from all participants who entered the study included in the analysis. Clinical outcomes were analysed using a linear regression model with data collected from all participants whether or not they attended the intervention. A linear regression with clinical outcome at follow-up and treatment arm (Treatment or TAU) and baseline values of clinical outcomes as independent variables. Baseline values of the outcome were included as a covariate to control for potential baseline differences (ANCOVA approach). Treatment differences with 95 % confidence intervals at follow-up will be 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 % confidence intervals will be presented. Pilot and feasibility studies are generally not powered to formally assess treatment effects and do not provide robust parameter estimates for assessing efficacy (Leon et al., 2011). An additional aim was to estimate the likely range of intervention effects at post-treatment by assessing 95 % confidence intervals of the treatment effects.

2.12. Acceptability evaluation

Thematic analysis was used to analyse the post-therapy feedback interviews transcripts. This explored people’s experiences of receiving the therapy and take part in this research study. Emergent themes were identified by the one researcher and then the themes were reviewed and coded by two members of the team with the input from service-users.

3. Results

3.1. Feasibility

A total of 190 persons were assessed for eligibility of which 160 (84.2 %, 95 % C. I. 78.2 to 89.1 %) were excluded. Thirty-nine (20.5 %; 95 % C. I. 15.0 to 27.0 %) declined to participate and 44 (23.2 %, 95 % C. I. 17.4 to 29.8 %) were not contactable. The remaining 77 (40.1 % (95 % C. I. 33.5 to 47.9 %) people did not meet inclusion criteria due to not experiencing severe and disabling NS or having limited English language proficiency or not being considered clinically stable. A total of 30 (15.8 %, 95 % C. I. 10.9 % to 21.8 %) were assessed at baseline and randomised into V-NeST plus TAU (N = 15; 50 %) or TAU alone (15; 50 %). Twenty-nine out of 30 participants (96.7 %, 82.8 to 99.9 %) received
the allocated treatment (V-NeST plus TAU: 14 (93.3 %, 95 % C.I. 68.1 % to 99.8 %) and TAU 15 (100 %, 95 % C.I. 78.2 % to 100 %). The participant not receiving the intervention moved out of the area. Four participants (16.6 %, 95 % C.I. 5.6 % to 34.7 %) did not provide data at follow-up, either were “lost at follow-up” (V-NeST: 3.1 %, 95 % C.I. 0.07 % to 16.2 %; TAU: 6.3 %, 95 % C.I. 0.8 % to 20.8 %) or discontinued the study (V-NeST: N = 1 (3.1 %, 95 % C.I. 0.07 % to 16.2 %). See Fig. 1 for recruitment flow.

In the treatment arm 14 out of 15 participants attended at least 1 therapy session with an average of 9.7 (SD = 3.77, range 1 to 15) sessions. Two participants did not receive the minimum therapy dose of six session completing 1 and 4 therapy sessions respectively.

Participants characteristics for the participants randomised is presented in Table 1.

3.2. Acceptability

Nine out of fifteen participants (60 %, 95 % C.I. 32.3 % to 83.7 %) in the intervention arm of the trial were interviewed. Two participants did not want to be recorded and declined to be interviewed, two did not want to participate in this additional part of the study (i.e., one because of the time demand, the other did not want to provide a reason). Two did not complete the intervention (one relocated; one was not contactable any longer). Two thirds of the participants (6 of 9) were male.

The following themes emerged from the interview:

1. Therapy goals: Positive experiences of therapy often centred around the goals and activities set. Participants described specific goals from their sessions, and how the therapy had contributed to goals progress (see Table 2 for quotes examples).

2. Impact of the pandemic: In some cases, the pandemic infringed on participants’ abilities to practice what they had learnt in therapy in real life. This meant that certain goals could not be achieved because the places where participants could practice or see friends were closed.

3. Issues experienced with symptoms. Participants described how difficulties with motivation and “feeling low” made it difficult to attend therapy sessions. In some cases, the therapy was seen as making a positive contribution.

4. Using VR: Only one had tried VR before and most described it as their first experience. Most were curious about the VR and valued the chance to do something different. Responses were positive, most said they would recommend it to a friend (n = 7, none said that they would not). The combination of VR use and therapy allowed participants to ‘relax’, particularly at the end of the session.

5. VR relevance: Participants’ opinions varied in how important they saw the VR. Some saw it as integral to the therapy. The therapist provided structure and guidance; the VR added a chance to practice aspects of the therapy. These participants connected the practical aspects of the therapy with the chance to practice in VR. However, participants were not always able to vocalise whether or say why the intervention was helpful (e.g., participant #18, Table 2). The benefits of therapy could be more diffuse, and some found it difficult to understand how the VR fitted with the wider therapy.

6. Therapy procedures: There were different opinions about the optimal session length and number of sessions, likely reflecting participants

Fig. 1. Study recruitment flow.
Table 1

<table>
<thead>
<tr>
<th>Participants’ characteristics.</th>
<th>N</th>
<th>% or Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>21</td>
<td>70 %</td>
</tr>
<tr>
<td>Female</td>
<td>9</td>
<td>30 %</td>
</tr>
<tr>
<td>Age</td>
<td>30</td>
<td>37.1 10.8</td>
</tr>
<tr>
<td>Time since 1st episode</td>
<td>30</td>
<td>120 142.9</td>
</tr>
<tr>
<td>WSAS</td>
<td>30</td>
<td>28.33 7.54</td>
</tr>
<tr>
<td>CAINS</td>
<td>30</td>
<td>31.63 7.94</td>
</tr>
<tr>
<td>SNS</td>
<td>30</td>
<td>20.37 9.55</td>
</tr>
<tr>
<td>PSYRATS_H</td>
<td>30</td>
<td>9.23 13.55</td>
</tr>
<tr>
<td>PSYRATS_d</td>
<td>30</td>
<td>6.13 7.99</td>
</tr>
<tr>
<td>HADS_Anx</td>
<td>30</td>
<td>10.43 5.56</td>
</tr>
<tr>
<td>HADS_dep</td>
<td>30</td>
<td>10.53 5.06</td>
</tr>
<tr>
<td>RSS</td>
<td>30</td>
<td>27.27 3.16</td>
</tr>
<tr>
<td>TMT-a</td>
<td>23</td>
<td>42.52 13.83</td>
</tr>
<tr>
<td>TMT-b</td>
<td>23</td>
<td>111.31 45.35</td>
</tr>
<tr>
<td>Digit span</td>
<td>30</td>
<td>14.87 2.80</td>
</tr>
<tr>
<td>eEfr-h</td>
<td>25</td>
<td>11.60 11.18</td>
</tr>
<tr>
<td>N e trial completed</td>
<td>25</td>
<td>46.48 27.43</td>
</tr>
<tr>
<td>wcst-c</td>
<td>25</td>
<td>65.48 14.13</td>
</tr>
<tr>
<td>wcst-e</td>
<td>25</td>
<td>53.96 18.95</td>
</tr>
<tr>
<td>wcst-p</td>
<td>25</td>
<td>7.84 6.69</td>
</tr>
</tbody>
</table>

Note: WSAS = Work and Social Adjustment Scale; CAINS = The Clinical Assessment Interview for Negative Symptoms (CAINS); SNS = Self-evaluation of Negative Symptoms; PSYRATS = The Psychotic Symptom Rating Scales; HADS = The Hospital Anxiety and Depression Scale; RSS = The Rosenberg Self-Esteem Scale; TMT = Trail Making Test; EEFRT = Effort Expenditure for Reward Task; WCST = Wisconsin Card Sorting Task.

preferences. One participant mentioned that group sessions might be useful.

7. Suggestions for improvement: One of the challenges for people experiencing negative symptoms was leaving the house to attend therapy. Some welcomed the idea of doing the therapy remotely. Some practical difficulties were described with the VR aspects of the sessions. Some participants experienced mild discomfort when wearing the headset. There were occasional criticisms of both the hardware (e.g., hand controllers) and the software (e.g., avatar and environment appearance) while others struggled with the mechanical aspects of controlling the VR handset.

8. Research procedures: Most found the length of the assessment was appropriate and that they understood the process they were consenting to. There were comments from some participants about the length and repetitive nature of some of the assessments.

Interviewing participants with high levels of negative symptoms presents challenges. Maintaining a good engagement levels and conversation flow was not always easy. As a result, some of the answers to the interview questions were short and provided limited information.

3.3. Adverse events

There were 2 serious adverse events reported by participants randomised to TAU and 11 adverse events (7 in the V-NeST group and 4 in the TAU group). None of these was considered to be associated with study participation by the trial data monitoring and ethics committee.

3.4. Treatment effect estimate

Table 2 shows 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. The primary clinical outcome (i.e. the GAS) had a score of 0 for all participants and no baseline value was included. The results of the pairwise

Table 2

| Example quotes from participants' end of therapy acceptability interview. |
|-----------------------------|-----------------------------|
| **Therapy goals**           | Example quotes               |
| "I wanted to restart playing music and I sort of did... I still haven’t found a band but I now do practice a little at home." | (#3) |
| "It helped me (the therapy) with my weight, losing weight... for example, my homework was to do some exercise at home, or cook few meals a week." | (#4) |
| "just going to the sessions would make me passively reflect on what I experience and what could change my experience in life [...] I would reflect on the sessions it would push and drive me more to like to achieve and get things done, push my life forward. Push my life in the direction envisaged it to be." | (#23) |
| "the lockdown obviously is preventing a lot of things... A lot of things I would like to get done means being out of my house." | (#18) |

**Impact of the pandemic**

<table>
<thead>
<tr>
<th>Issues experienced with symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;My mood can be very low and I don't end up leaving the house for days. This [therapy] helped me. It helped with the mood, and I left the house to attend sessions.&quot;</td>
</tr>
<tr>
<td>&quot;It supposed to be action then gives motivation and that's how you change the cycle.&quot;</td>
</tr>
<tr>
<td>&quot;My motivation went up... only a little but it did go up&quot;</td>
</tr>
<tr>
<td>&quot;After a few sessions I thought this is boring, I didn't want to go back. But this was what the therapy was about.&quot;</td>
</tr>
<tr>
<td>&quot;I think the therapy in combination with the VR, was good. Sometimes like, when I have therapy I don't really like the constant back and forth thinking. It becomes a bit heavy after a while... So taking the VR time with it helped to break out the heaviness or tension. [...] everything was really well done. I felt like it was a good idea. Like, having a therapy session with a VR session where you can listen to music and have choice.&quot;</td>
</tr>
<tr>
<td>&quot;it relaxes you and it is helpful...&quot;</td>
</tr>
<tr>
<td>&quot;Having the sessions going into details about like, intense things. To have like, almost like a cool off at the end was really nice. [...] Like in the living room or tv room that was just like really relaxing, quite sombre, kind of zen.&quot;</td>
</tr>
<tr>
<td>&quot;without VR... I think it would be worse. [...] without the therapist you'd be lost... the therapist is telling me what to do.&quot;</td>
</tr>
<tr>
<td>&quot;How would you pull it off without VR? I think it will be less effective... it just adds the practical part to it.&quot;</td>
</tr>
<tr>
<td>&quot;It was like a video game, it was easy and also it took you somewhere else [...] you feel like being somewhere else, but you are not and you don't have to travel or do other things that can be difficult&quot;</td>
</tr>
<tr>
<td>&quot;I visited the pub and the factory. The factory I treated like a game. The pub was very useful. Very useful, because I was scared to go to the pub but after going into the pub, I was less scared. [...] I don't know if I have the vocabulary to describe how he was helpful, but he was helpful but even if he wasn't just as a sounding board as someone to talk to with my problems&quot;</td>
</tr>
</tbody>
</table>

**Therapy procedures**

(continued on next page)
“The first one [session] was erm, kind of long.” (#17)

“Twelve sessions was good but it definitely could be longer because you get to a point where you are finally getting that momentum. It takes a while if you have negative symptoms. It takes a while to even start the ball rolling. [ ...] I think it could be maybe a little bit longer, maybe by like I don’t know… 10, 15 minutes. So maybe have like a full-length session for maybe like an hour. And then a separate 15 minutes for the VR. Rather than putting it all into one.” (#25)

“rather than just continuously doing it 1–1. I feel like having one group session wouldn’t. Just to hear other people’s perspectives.” (#23)

“maybe if it could be done a bit more remotely. Because like, for me, one of the hardest things I think is physically getting there some days. Erm, because, once the anxiety or the depressive thought set in, it is very hard to physically get out of bed to leave the house, to physically go to that location.” (#25)

“…I needed more therapy, for depression rather than motivation. I know the two are linked but I think if I wasn’t depressed the therapy for the motivation would have been more helpful.” (#18)

“It wasn’t always comfortable to have on and the goggles view sometimes blurred” (#3)

“one thing I found a bit of a hindrance was the physical shape of the headset. Like I know, I think that was like the first gen of that. But this is more of a design thing. Like, my hair, is very voluminous... They have obviously designed it for people with flatter hair” (#25)

“I was little bit reluctant to use my right hand, doing the job (referring to factory environment). It wasn’t great, with my right hand but after a while it was ok.” (#33)

comparisons at follow-up controlled for baseline difference. Effect sizes d and 95 % confidence intervals are presented. Because of the small sample size, statistical techniques for handling missing data were not applied.

A large treatment effect was observed for the primary outcome GAS and assessment of the 95 % confidence intervals suggests that the treatment effect is at least d = 0.61. Treatment effects of the main secondary outcomes (CAINS, Negative symptoms, WSAS and Digit span) are smaller and the 95 % confidence intervals are too large to derive any conclusion (Table 3).

Only 6 participants were able to complete the trial mechanistic measures (i.e. EEIRT task and WCST) at follow-up due to face-to-face research assessment procedures restriction imposed by the pandemic. Statistical analyses were not conducted on these outcomes.

4. Discussion

Recent years have seen a renewed interest in the assessment and consideration of the negative symptoms of psychosis (Aleman et al., 2017). Unfortunately, this has not yet led to novel, effective and widespread interventions. Digital technology tools may be a way to improve intervention usefulness by improving adherence, reducing motivation difficulties and barriers to accessing therapy. In this study we developed and evaluated a novel therapy for negative symptoms using VR (called V-NeST). The primary aim of this study was to evaluate V-NeST acceptability and feasibility.

The therapy demonstrated good acceptability and feasibility parameters particularly considering this study involved participants with severe and disabling levels of negative symptoms. The therapy procedures were considered acceptable, and the VR aspects well tolerated and found engaging. A number of therapy features were suggested for revision including ways of interacting with the virtual environment (e.g., hands movements) and some therapy components (e.g., make psycho-education more engaging). Only one of the participants had tried VR before and many had limited digital technology skills. This was not a barrier to therapy use and the VR proved intuitive and easy to learn. However, independent use of the VR therapy may be complex for this group. The feasibility of the research procedure was also good with most research procedures well tolerated by all participants. The study recruited to target but considered 190 referrals to reach the 30 required to meet the study target. This is approximately 1 in 6 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 negative symptoms in research studies may be complex (Marder et al., 2013). However, we proved that it is possible and that once participants entered the trial, we were able to retain in excess of 80 % of those randomised to treatment. This is in line with other randomised controlled trials in people with psychosis (e.g. Craig et al., 2018; Morrison et al., 2018; Reeder et al., 2017).

The explorative analysis on the V-NeST pre-specified primary outcome suggested that the intervention may be helpful in supporting people’s recovery goals. We chose this outcome 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 support further development and evaluation of this therapy. One important caveat in considering the effect size is how pandemic related restrictions may have impacted therapy goals. It is likely that, as some participants expressed, restriction may have limited the ability of participants to achieve goals (e.g., limitation in social contact; gym being close). However, this would have impacted equally both groups. With most of the participants having been affected by pandemic restrictions, to some degree, teasing out its effects is complex. With studies suggesting that pandemic restrictions and COVID-19 have a negative effect on mental health (Hossain et al., 2020) accessing therapy it is likely to have been a positive experience to those who received it.

This study has limitations. We were not able to evaluate the mechanistic element of the therapy as planned. This was consequent to limitations imposed to research procedures during different period of social contact restrictions in the UK. While we were able to continue to deliver therapy sessions and assessment remotely many participants did not have a computer or were able to complete computer tasks at home. A further limitation of this study is the lack of a follow-up assessment to consider assessment completion level and evaluate exploratively how
treatment effect estimates may be retained over time. Future steps for developing V-NeST include the modification of the VR software and therapy procedures in line with the feedback received from participants and planning an appropriately powered trial to formally evaluate the therapy efficacy. Future evaluation should also consider the cost-efficacy of this intervention and how it may be implemented in clinical settings (e.g., therapist training, access to VR). The results of our thematic analysis also hinted at the difference in difficulties being related to mood, others to apathy, poor confidence or lack of skills. This further suggests, in line with recent recommendations and evidence, that NS are best represented by individual subtypes (e.g., anhedonia, amotivation) and that therapies targeting specific symptoms may be more successful in targeting distinct mechanisms (Ahmed et al., 2019; Galderisi et al., 2021; Mucci et al., 2019).

The development and evolution of digital therapies has enormous potentials to reduce the impact of negative symptoms 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. However, complex and often rooted difficulties such as severe negative symptoms are unlikely to be resolved by short and standalone interventions. Therapist training and supervision, other support and rehabilitation approached availability, service capacity to endure poor adherence are likely to contribute importantly to the long-term recovery prospect. As such digital interventions like V-NeST should be considered as part of an integrated model of care rather than single approach or solution.

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CRediT authorship contribution statement
MC, LV, DS designed the study. MC, LV designed the VR environments. MC, LV managed the study. DS conducted the quantitative analysis. PS, HG supported the qualitative analyses and trial management. PT supported data collection and recruitment. MC drafted the manuscript. All authors contributed and approved the final version of the manuscript.

Declaration of competing interest
None.

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Appendix. Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2022.07.013.

References
