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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

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Summary

Background Many patients with psychotic disorders have persistent paranoid ideation and avoid social situations because of suspiciousness and anxiety. We investigated the effects of virtual-reality-based cognitive behavioural therapy (VR-CBT) on paranoid thoughts and social participation.

Methods In this randomised controlled trial at seven Dutch mental health centres, outpatients aged 18–65 years with a DSM-IV-diagnosed psychotic disorder and paranoid ideation in the past month were randomly assigned (1:1) via block randomisation to VR-CBT (in addition to treatment as usual) or the waiting list control group (treatment as usual). VR-CBT consisted of 16 individual therapy sessions (each 1 h long). Assessments were done at baseline, after treatment (ie, 3 months from baseline), and at a 6 month follow-up visit. The primary outcome was social participation, which we operationalised as the amount of time spent with other people, momentary paranoia, perceived social threat, and momentary anxiety. Analysis was by intention to treat. This trial was retrospectively registered with ISRCTN, number 12929657.

Findings Between April 1, 2014, and Dec 31, 2015, 116 patients with a psychotic disorder were randomly assigned, 58 to the VR-CBT group and 58 to the waiting list control group. Compared with the control, VR-CBT did not significantly increase the amount of time spent with other people at the post-treatment assessment. Momentary paranoid ideation (b=–0·331 [95% CI –0·432 to –0·230], p<0·0001; effect size –1·49) and momentary anxiety (–0·288 [–0·438 to –0·1394]; p=0·0002; –0·75) were significantly reduced in the VR-CBT group compared with the control group at the post-treatment assessment, and these improvements were maintained at the follow-up assessment. Safety behaviour and social cognition problems were mediators of change in paranoid ideation. No adverse events were reported relating to the therapy or assessments.

Interpretation Our results suggest that the addition of VR-CBT to standard treatment can reduce paranoid ideation and momentary anxiety in patients with a psychotic disorder.

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Introduction

People with psychotic disorders often avoid public and social activities. Their social networks are generally small and they spend more time alone than people without a psychotic disorder.[1] Many people with psychotic disorders do not have romantic partners, and the unemployment rate is high.[2,3] As many as 90% of patients have paranoid ideation to some degree.[4] Often, such ideation is strong and manifests as paranoid delusions, which are characterised by unfounded anticipation of intentional harm inflicted by other people. The anxiety resulting from paranoid ideation strongly contributes to social avoidance. This conditioned avoidance is not always affected by use of antipsychotic medication.[4] Cognitive behavioural therapy (CBT) is the most effective psychological treatment for people with psychotic disorders.[5] The effect sizes of CBT on paranoid delusions and social functioning are small to medium, but can be

improved by more emphasis on behavioural rather than cognitive change, and by more person-specific exposure[5]—a key element of CBT.

Exposure-based therapeutic exercises for paranoid ideation have several limitations. First, the social environment and reactions of others cannot be controlled by the therapist—relevant events might not occur, or unwanted events can suddenly occur. Second, exposure takes place between therapy sessions, and thus therapist feedback is retrospective and based on patient reports, which could be inaccurate because of biases.[6] Finally, many patients are reluctant or unable to undergo exposure because of strong paranoid fears or negative symptoms.

These limitations could be overcome through virtual reality. The virtual social world is a controlled environment and exercises are done with the guidance of a therapist. Virtual reality is effective and safe for treating anxiety.[7]

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Research in context

Evidence before this study

Paranoid ideation is common in patients with psychotic disorders. The anxiety resulting from paranoid ideation strongly contributes to social avoidance. Cognitive behavioural therapy is the most effective psychological treatment for this symptom, but effects sizes are small to medium at best. The positive results of using virtual reality to treat anxiety disorders suggest that virtual reality might be used to improve treatment for anxiety and avoidance of social situations resulting from paranoid ideation. We searched MEDLINE with the terms (Virtual Reality) AND (Delus* OR Paranoi* OR Psychosis OR Psychotic OR Schizophren*) for articles published in any language before Sept 14, 2017. We identified 94 peer-reviewed papers. Research showed exposure of patients with a psychotic disorder to immersive virtual environments is safe and that virtual reality can be used to elicit paranoid ideation and anxiety in patients with a psychotic disorder, which suggests that the creation of virtual environments for treatment is feasible. Only one of the identified papers was a randomised controlled trial of virtual reality therapy for reducing paranoid

ideation. This small (n=30) experimental study showed large reductions in delusional conviction and real-world distress.

Added value of this study

We did the first randomised controlled trial (to our knowledge) of virtual-reality-based cognitive behavioural therapy with the aim of improving social functioning and reducing paranoid ideation in patients with psychotic disorders. We found that the addition of virtual reality cognitive behavioural therapy to standard therapy reduced paranoid ideation, anxiety, and use of safety behaviours in social situations compared with standard therapy alone. Results of the mediation analysis supported the importance of reducing safety behaviours and modifying social cognition in the treatment of paranoid delusions.

Implications of all the available evidence

Virtual-reality-based cognitive behavioural therapy is safe and effective in patients with psychotic disorders. Future research should compare virtual-reality-based cognitive behavioural therapy with standard cognitive behavioural therapy in terms of treatment effects and cost-effectiveness.

It is safe to use in people with psychotic disorders,[8] and studies suggest promising results for several virtual reality interventions, including for social skills training, auditory hallucinations, and paranoid ideation.[9,10] These findings suggest that virtual-reality-based CBT (VR-CBT) could be an effective, affordable, acceptable, and accessible form of treatment for patients with paranoid ideation and social withdrawal.

We did a randomised controlled trial to establish the effectiveness of VR-CBT, compared with treatment as usual, in improving the quantity and quality of social participation in patients with psychotic disorders who experience paranoid ideation and social avoidance. The primary hypothesis was that VR-CBT would lead to more time spent with other people, and a decrease in momentary paranoia, perceived social threat, and anxiety during real-life social activities. Our secondary hypotheses were that safety behaviours and paranoid ideation would be reduced by VR-CBT, that levels of social anxiety, depression, stigma, cognitive biases, and cognitive limitations would decline, and that social functioning, quality of life, and schematic beliefs would improve. Furthermore, we hypothesised that changes in safety behaviour and cognition (biases and mental schemas) would mediate the reduction in paranoia. Cost-effectiveness analyses will be reported in a separate paper.

Methods

Study design and participants

We did a single-blind randomised controlled trial of VR-CBT plus treatment as usual versus treatment as usual only in outpatients at seven Dutch mental health

centres. Details of the study protocol have been published.[11] Inclusion criteria were a DSM-IV diagnosis of a psychotic disorder based on the Mini-International Neuropsychiatric Interview,[12] the Schedules for Clinical Assessment in Neuropsychiatry,[13] or the Comprehensive Assessment of Symptoms and History[14] (varied by centre); avoidance of either shops, streets, public transport, or bars or restaurants; paranoid ideation in the past month (defined as a score greater than 40 on the Green et al Paranoid Thoughts Scale[15]); and age 18–65 years. Exclusion criteria were an IQ of 70 or lower (established by a valid instrument such as the Wechsler Adult Intelligence Scale or the Wechsler Intelligence Scale for Children); insufficient mastery of the Dutch language; and history of epilepsy. The protocol was approved by the medical ethical committee of VU University Medical Center Amsterdam (METC number NL37356.058.12). Patients were informed about the study by their treating psychiatrist, psychologist, or psychiatric nurse. If a patient was eligible and willing to participate, written informed consent was obtained.

Randomisation and masking

After a baseline assessment, patients were randomly assigned. Research assistants blinded to treatment allocation did the post-treatment and follow-up assessments. Assessors were instructed to stop the assessment in case of unblinding, and the assessment was repeated by another research assistant. (An assessor had to be replaced on three occasions.) Block random-isation was used to allocate patients (1:1) to the VR-CBT or control group. Each block had six assignments

per condition. If a centre had more patients, a second randomised block was allocated. Blocks were made with the scientific randomisation program Research Randomizer by the independent randomisation bureau of Parnassia, which also allocated patients to groups.

Procedures

The two groups were compared at baseline, after treatment (3 months after baseline), and at follow-up (6 months after baseline). Participants who dropped out of treatment were asked to complete the post-treatment and follow-up assessments. Instructions were given to psychiatrists not to change patients' medication during the study. When patients reported medication changes, these changes were checked with their clinician. No additional psychological treatments for paranoid ideation or social participation were allowed. Participants in the control group were offered VR-CBT after follow-up.

Four virtual social environments (a street, bus, café, and supermarket) were created with Vizard software (appendix). Within the environment, participants could move by operating a Logitech F310 Gamepad. They used a Sony HMZ-T1/T2/T3 Head Mounted Display with a high-definition resolution of 1280×720 per eye, with 51·6 diagonal field of view, and a 3DOF tracker for head rotation. Therapists could vary the number of human avatars (0–40), the characteristics of the avatars (including sex and ethnicity), and the avatars' responses to the patient (neutral or hostile, eye contact) to match the paranoid fears of the patient. Therapists could also make the avatars say pre-recorded sentences. Because these stimuli were directly controlled by the therapist, personalised treatment exercises were created for each patient.

VR-CBT consisted of 16 sessions over 8–12 weeks. Sessions lasted 1 h, 40 min of which comprised virtual-reality exercises. The remaining 20 min were used to plan and reflect on exercises. An individualised case formulation guided exposure to idiosyncratic social environmental cues that elicited fear, paranoid thoughts, and safety behaviours. Patients and therapists communicated during virtual-reality sessions to explore and challenge suspicious thoughts during social situations, drop safety behaviours during social situations (such as avoiding eye contact with, keeping distance from, and refraining from communication with avatars), and test harm expectancies. No homework exercises were given between sessions to test the effects of the in-virtuo exposure without the effects of structured in-vivo exposure. VR-CBT therapists were psychologists with at least basic CBT training. They received 2 days' training in VR-CBT. The VR-CBT manual described a structured treatment plan for all 16 sessions. Therapists were supervised in a group for 4 h every month. All therapy sessions were recorded on audiotapes. Experienced CBT psychologists anonymously rated a random selection of sessions (two per therapist) for treatment fidelity with the Cognitive Therapy Rating Scale.[16]

Patients in the waiting list control group received treatment as usual—antipsychotic medication, regular contact with a psychiatrist to control symptoms, and regular contact with a psychiatric nurse to improve self-care, daytime activities, and social and community functioning.

Outcomes

The primary outcome was social participation—a multidimensional construct with a behavioural, objective dimension and a subjective, experiential dimension. We operationalised objective social participation as the amount of time spent with others and subjective social participation as momentary paranoia, perceived social threat, and momentary anxiety in company.

The experience sampling method (ESM)—a structured diary method in which individuavls are asked in daily life to report their momentary thoughts, feelings, symptoms, social contexts, and appraisal of social contexts—was used to assess momentary outcomes. ESM has been used by patients with psychotic disorder, with or without symptoms.[17] The method used in this study, PsyMate, has high ecological validity.[18] All participants carried a PsyMate electronic device for assessments, which beeped at quasi-random moments ten times a day during 6 days. At each beep, the device collected self-assessments on a seven-point Likert scale, ranging from 1 ("not at all") to 7 ("very"). Reports had to be completed within 15 min of the beep. To be included in the analysis, participants had to complete diary entries for at least one-third of the beeps (ie, a minimum of 20 measurements).

For ESM, items from previous studies were used. Principal component analyses have been done previously for ESM affect items, and identified the following factors: negative affect, positive affect, momentary paranoia,[19] and perceived social threat.[17] A principal component analysis with oblique rotation and Kaiser normalisation for the person-centred data from our study identified these four factors according to the Kaiser criterion (eigenvalue >1). We used the momentary paranoia and perceived social threat subscales. The principal component analysis confirmed the perceived social threat factor for all four items (factor loadings ranging from 0·57 to 0·80) and partly confirmed momentary paranoia for three items (factor loadings ranging from 0·52 to 0·83). The three-item momentary paranoia subscale was used.

Time spent with others was measured by the proportion of beeps that participants reported to be in company of other people (not mental health professionals). Momentary paranoia was calculated as the mean score of the three items: "I feel that others might hurt me", "I feel that others dislike me", and "I feel suspicious". Perceived social threat was calculated as the mean score on the items "I like this company [reversed score]", "In this company, I feel accepted [reversed score]", "I would
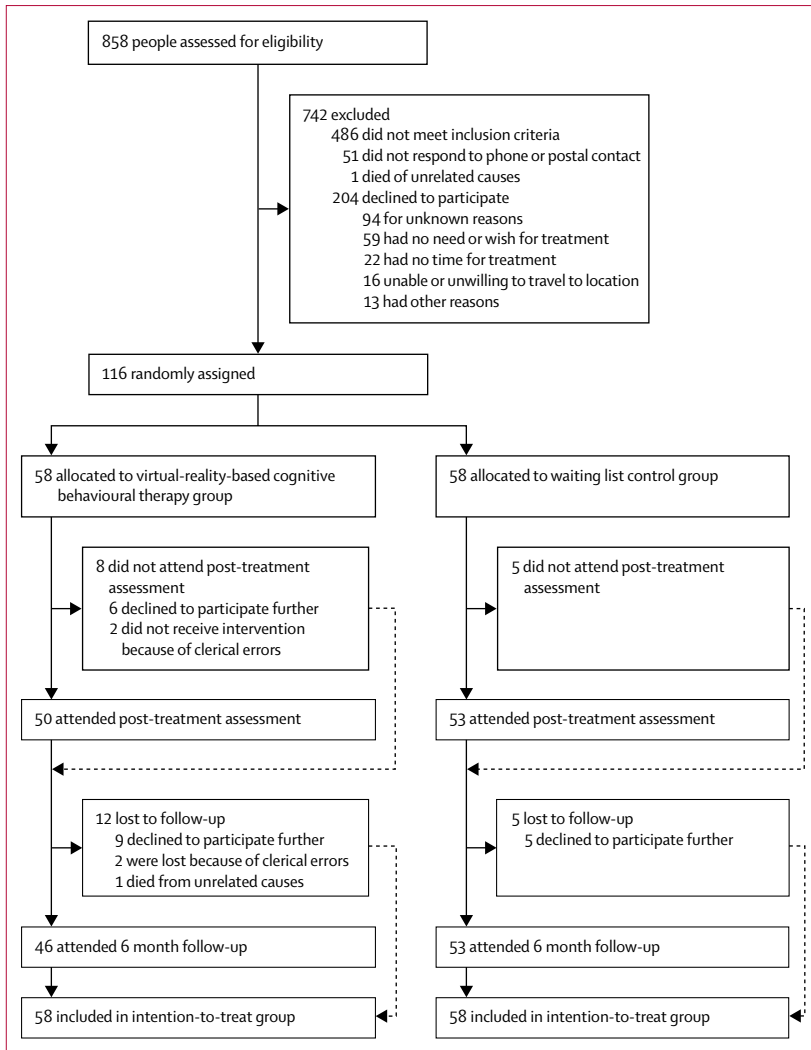
Figure: Trial profile

rather be alone", and "In this company, I feel threatened". Scores on the item "I feel anxious" when in the presence of other people were used to establish momentary anxiety.

Secondary outcomes for symptom measures were the Safety Behaviour Questionnaire-Persecutory Delusions,[20] the Green et al Paranoid Thoughts Scale,[15] the Social Interaction Anxiety Scale,[21] and the Beck Depression Inventory.[22] Functional outcomes were rated with the Social and Occupational Functioning Assessment Scale[23] and the Manchester Short Assessment of Quality of Life.[24] Stigma was assessed with the Internalized Stigma of Mental Illness questionnaire.[25] To examine putative working mechanisms of the therapy, cognitive constructs were assessed with the Brief Core Schema Scales[26] and the self-reported Davos Assessment of Cognitive Biases Scale.[27] Medication adherence was measured with the Brief Adherence Rating Scale.[28] After the fourth and eighth sessions, presence in virtual reality was assessed with the

Igroup Presence Questionnaire,[29] and cybersickness symptoms with the Simulator Sickness Questionnaire.[30]

Statistical analyses

Because, to our knowledge, VR-CBT has never been tested before and ESM had not previously been used as a primary outcome in intervention studies, we conservatively estimated sample size by assuming a moderate effect size of 0.5 with a power of 0.8, an α of 0.05 and a two-sided independent t test. The estimated sample size was 64 for each group. We postulated an attrition rate of 20%, and thus set 160 as the total sample size.

For primary outcomes, we applied the Bonferroni correction for four tests, with a significance level of 0.0125. For all other outcomes, the significance level was 0.05. Group characteristics were compared at baseline with t tests, non-parametric Mann-Whitney U tests, or χ^2 tests.

All data had a hierarchical structure, with repeated measurements (level 1) nested within individuals (level 2). Multilevel analyses were done to take into account that intra-individual observations are more similar than inter-individual observations. Logistic multi-level regression analyses were done for objective social participation; multilevel regression analyses were done for all other outcomes. All models included a random intercept for participant. We used the maximum-likelihood method and the covariance structure identity for estimation. All data were analysed by intention to treat. The treatment effect was established with the group by time interaction for the post-treatment and follow-up assessments separately. Post-treatment and follow-up data were each compared to baseline. In all analyses age, sex, ethnicity, and education were included as covariates. If baseline differences between groups were noted, this variable was included as a covariate in all analyses. We calculated effect sizes for group by time interaction effects with the z test statistics to determine r.[31] To facilitate interpretation, we transformed r into Cohen's d^{pp} (the superscript shows that the effect size was based on pre–post measures).[32]

Two parallel multiple mediation analyses were done to examine the mediating effects of VR-CBT on paranoid ideation at the post-treatment assessment. The analyses had different outcome measures—paranoid ideation (Green et al Paranoid Thoughts Scale total score) and momentary paranoia (ESM; appendix). Selection of potential mediators was based on the results of our multilevel analysis. We used a significance level of 0.10 for the post-treatment treatment effect variables as the cutoff for inclusion in the mediation analysis. Analyses were done with the PROCESS macro,[33] which uses linear regression to estimate indirect effects according to the methods recommended by Hayes and Rockwood for clinical studies.[34] This method is based on a modern framework, and, by contrast with the causal steps approach, in which a series of criteria are required

to establish mediation,[35] it focuses solely on quantification of indirect effects. Hayes and Rockwood also emphasise the value of mediation analysis for research if only two measurement moments are used. Post-treatment scores were added as mediators, and baseline scores for the outcome variables and mediators were added to the models as covariates. Least-square path analysis was used and the bootstrap confidence interval (5000 permutations) was applied to estimate indirect effects. We used Stata (version 13.1) and SPSS (version 24.0.0.0) for all analyses. Because of an oversight, prospective trial registration was overlooked, but the trial was registered retrospectively with ISRCTN, number 12929657. Details of our initial ethics approval and protocol are in the appendix.

Role of the funding source

The study funders had no role in the study design; data collection, analysis, or interpretation; or writing of the Article. RMCAP-K, CNWG, WV, PAEGD, and MvdG had full access to all study data, and RMCAP-K, the corresponding author, had final responsibility for the decision to submit for publication.

Results

Between April 1, 2014, and Dec 31, 2015, 116 patients with a psychotic disorder were randomly assigned (figure). Patients who were included in the study did not differ significantly in terms of frequency and severity of paranoid ideation from those who chose not to participate (we did separate analyses for patients who were eligible but did not consent to be contacted about study participation, those who had no wish, need, or time for treatment, those who were unable to travel to the treatment location, and those who gave permission for contact but did not respond; data not shown).

Sociodemographic characteristics were well balanced between groups (table 1). Participants who dropped out from VR-CBT did not differ from participants who completed VR-CBT in baseline paranoid ideation or safety behaviours (data not shown). We noted no differences in baseline paranoid ideation or safety behaviour between participants who refrained from follow-up measurements and those who completed all measurements (data not shown). Cybersickness was recorded (appendix), but only one participant dropped out because of nausea, rendering further statistical investigation irrelevant. No adverse events relating to either VR-CBT or the assessments were reported.

11 patients (19%) in the VR-CBT group dropped out of therapy (including four who never started treatment). Seven patients discontinued treatment: one was too afraid (completed one session), one had no time (one session), one was not willing to travel to therapy location (two sessions), one had nausea (two sessions), one was unable to attend sessions sober (three sessions), and two found the head-mounted display too uncomfortable to

	Virtual-reality-based cognitive behavioural therapy group (n=58)	Waiting list control group (n=58)
Age, years	36·5 (10)	39·5 (10)
Non-Dutch origin	15 (26%)	25 (43%)
Sex		
Male	40 (69%)	42 (72%)
Female	18 (31%)	16 (28%)
Education		
None or primary	16 (28%)	16 (28%)
Vocational	18 (31%)	24 (41%)
Secondary	9 (16%)	9 (16%)
Higher	15 (26%)	9 (16%)
DSM-IV diagnosis		
Schizophrenia	46 (79%)	49 (85%)
Schizoaffective disorder	1 (2%)	5 (9%)
Delusional disorder	1 (2%)	0 (0%)
Not-otherwise specified psychotic disorder	10 (17%)	4 (7%)
Duration of illness, years	13·3 (10·6)	14·9 (9·5)
Medication use		
Antipsychotics	54 (93%)	57 (98%)
Olanzapine equivalent of prescribed antipsychotic medication (mg per day)	10·5 (6·8)	11·0 (8·3)
Antidepressants	15 (26%)	17 (29%)

Data are n (%) or mean (SD).

Table 1: **Baseline characteristics**

tolerate (five and six sessions, respectively). Participants felt sufficiently present in the virtual environments on all three subscales of the Igroup Presence Questionnaire (range 0–6): spatial presence (mean 3·79), involvement (mean 3·16), and realness (mean 2·96). 28 sessions were rated for treatment fidelity. Therapists had "good" to "very good" adherence to the protocol and CBT quality (mean 4·5 [range 2·4–5·9]).

The VR-CBT group reported 17 changes of antipsychotics: ten doses were lowered, three doses were raised, and four patients changed medication. 18 changes were reported in the control group: 11 doses were lowered, six doses were raised, and one person changed medication. No significant differences were noted between patients who had any medication changes and those who had no changes at baseline, at 3 months after treatment, or at follow-up (data not shown).

At baseline, no significant differences were noted between the VR-CBT and control groups, except in use of safety behaviours (table 2), which was significantly lower in the control group (24·1) than in the VR-CBT group (28·8; $z=-2·09$; $p=0·036$). Baseline level of safety behaviours was thus included as a covariate in analyses. All participants completed ESM measurements at baseline (mean number of completed self-assessments 46·1 [SD 13·3]), 96 participants completed the

	Measurement instrument	Virtual-reality-based cognitive behavioural therapy group			Waiting list control group		
		Baseline	After treatment	Follow-up	Baseline	After treatment	Follow-up
Primary outcomes							
Time spent with others	Experience Sampling Method	0·416 (0·26)	0·404 (0·24)	0·419 (0·24)	0·364 (0·27)	0·323 (0·28)	0·340 (0·30)
Momentary paranoia	Experience Sampling Method	3·064 (1·39)	2·714 (1·38)	2·719 (1·37)	3·140 (1·43)	3·302 (1·60)	3·354 (1·56)
Perceived social threat	Experience Sampling Method	2·703 (0·86)	2·805 (1·01)	2·728 (1·04)	2·816 (0·91)	2·837 (0·98)	2·752 (0·99)
Momentary anxiety	Experience Sampling Method	2·986 (1·12)	2·586 (1·14)	2·645 (1·21)	3·259 (1·50)	3·221 (1·56)	3·218 (1·49)
Secondary outcomes							
Ideas of persecution	Green et al Paranoid Thoughts Scale	41·2 (18·9)	33·4 (17·1)	31·4 (17·9)	36·2 (16·3)	38·2 (17·9)	38·4 (18·7)
Ideas of social reference	Green et al Paranoid Thoughts Scale	43·6 (15·9)	35·4 (15·5)	34·0 (16·1)	40·4 (15·7)	38·7 (14·9)	39·1 (15·4)
Safety behaviours	Safety Behaviour Questionnaire—Persecutory Delusions	28·8 (14·2)	21·1 (16·0)	20·2 (16·2)	24·1 (15·0)	23·8 (16·5)	22·5 (13·5)
Social interaction anxiety	Social Interaction Anxiety Scale	43·8 (13·1)	36·8 (13·1)	36·2 (13·0)	43·1 (14·9)	39·2 (15·7)	40·3 (15·1)
Depression inventory	Beck Depression Inventory	17·2 (9·5)	16·0 (10·4)	13·3 (10·1)	17·6 (9·7)	15·0 (10·0)	15·8 (9·9)
Quality of life	Manchester Short Assessment of Quality of Life	4·3 (0·9)	4·3 (1·0)	4·4 (1·0)	4·2 (0·9)	4·3 (0·8)	4·3 (0·8)
Social functioning	Social and Occupational Functioning Assessment Scale	49·6 (8·0)	50·1 (8·7)	51·4 (10·7)	49·6 (8·3)	49·5 (8·6)	47·6 (8·6)
Stigma	Internalized Stigma of Mental Illness	2·4 (0·3)	2·3 (0·4)	2·2 (0·4)	2·4 (0·4)	2·4 (0·5)	2·4 (0·4)
Jumping to conclusions	DACOBS	26·8 (5·4)	25·4 (5·6)	25·4 (5·3)	25·0 (5·1)	25·2 (5·3)	24·8 (5·9)
Belief inflexibility	DACOBS	22·6 (5·6)	23·1 (6·6)	22·2 (6·2)	22·0 (5·2)	22·0 (5·3)	21·5 (4·7)
Attention for threat	DACOBS	29·6 (6·1)	27·7 (7·2)	27·6 (7·2)	28·0 (6·4)	28·5 (6·2)	27·9 (6·1)
External attribution	DACOBS	24·8 (6·8)	24·3 (6·7)	22·8 (6·3)	24·3 (7·0)	23·8 (6·4)	24·1 (6·7)
Social cognitive problems	DACOBS	29·7 (6·1)	27·4 (7·1)	26·6 (6·8)	27·5 (6·0)	27·5 (6·2)	27·6 (6·3)
Subjective cognitive problems	DACOBS	26·1 (5·5)	25·9 (6·3)	25·2 (6·4)	26·2 (6·7)	26·5 (6·1)	25·0 (5·6)
Safety behaviour	DACOBS	22·8 (6·5)	20·5 (6·5)	20·3 (7·1)	20·2 (7·4)	20·0 (7·8)	20·4 (7·1)
Negative self-core schema	Brief Core Schema Scales	5·8 (4·7)	4·8 (4·6)	4·6 (4·5)	5·6 (4·5)	4·8 (4·3)	5·1 (4·0)
Negative others core schema	Brief Core Schema Scales	6·6 (7·2)	5·1 (6·5)	5·0 (6·5)	5·6 (6·2)	5·3 (5·9)	5·8 (6·5)
Positive self-core schema	Brief Core Schema Scales	8·3 (5·3)	8·4 (6·1)	8·9 (6·0)	7·0 (4·2)	8·1 (5·1)	7·1 (4·5)
Positive others core schema	Brief Core Schema Scales	7·9 (5·3)	8·1 (6·1)	9·3 (6·5)	6·2 (5·2)	6·9 (5·9)	6·5 (4·6)

Data are mean (SD). DACOBS=Davos Assessment of Cognitive Biases Scale.

Table 2: Treatment efficacy for outcome measures in the intervention and control groups

post-treatment assessment sufficiently (43·1 [10·1]), and 87 participants completed the follow-up (43·2 [11·1]).

For amount of time spent with others, the treatment effect at the post-treatment visit compared with baseline was not significant (d^{pp} 0·25; p=0·178), but the treatment effect at follow-up compared with baseline was (d^{pp} 0·50; p=0·0090; table 3). Time spent with others decreased by 2·4% in the control group between baseline and the follow-up assessment, whereas the amount of time marginally increased by 0·3% in the VR-CBT group.

Between baseline and the post-treatment assessment, a large reduction was noted in momentary paranoia (–0·350) in the VR-CBT group, whereas a slight increase was noted in the control group (0·162; d^{pp} –1·49; p<0·0001; table 3). A significantly larger decrease in momentary anxiety was noted in the VR-CBT group than in the control (d^{pp} 0·75; p=0·0002; table 3). The effect sizes for momentary paranoia and anxiety remained significant at follow-up. When the mean of the original four-item subscale was used (instead of the three-item subscale), the pattern of results for momentary paranoia

was identical (data not shown). No significant interaction effects were noted for perceived social threat at the post-treatment (d^{pp} –0·33) or follow-up (d^{pp} 0·36) assessments (table 3).

Compared with the control group, use of safety behaviours decreased significantly in the VR-CBT group at both the post-treatment and follow-up assessment (table 3). The largest reduction at the post-treatment visit was for the in-situ safety behaviours subscale ($b^{interaction}$ –3·7 [95% CI –6·2 to –1·2]; z –2·93, p=0·0033).

Treatment effects on paranoid ideation were significant: at the post-treatment and follow-up assessments, levels of ideas of persecution and social reference were lower in the VR-CBT group than in the control group (table 3). Depression and anxiety were not significantly lower in the intervention than in the control group (table 3). The VR-CBT group had improvements in self-stigmatisation and social functioning at follow-up whereas the control group did not (table 3). Quality of life at the post-treatment or follow-up assessments did not differ significantly between groups (table 3).

	Measurement instrument	After treatment						6 month follow-up					
		b	95% CI	SE	z	p	Effect size	b	95% CI	SE	z	p	Effect size
Primary outcomes													
Time spent with others	Experience Sampling Method	0.140	-0.064 to 0.344	0.10	1.35	0.178	0.25	0.288	0.072 to 0.502	0.11	2.61	0.0090	0.50
Momentary paranoia	Experience Sampling Method	-0.331	-0.432 to -0.230	0.05	-6.44	<0.0001	-1.49	-0.287	-0.385 to -0.188	0.05	-5.69	<0.0001	-1.24
Perceived social threat	Experience Sampling Method	-0.099	-0.211 to 0.013	0.06	-1.73	0.084	-0.33	0.107	-0.004 to 0.219	0.06	1.89	0.059	0.36
Momentary anxiety	Experience Sampling Method	-0.288	-0.438 to -0.139	0.08	-3.78	0.0002	-0.75	-0.207	-0.358 to -0.057	0.08	-2.70	0.0070	-0.52
Secondary outcomes													
Ideas of persecution	Green et al Paranoid Thoughts Scale	-8.59	-13.32 to -3.85	2.42	-3.55	0.0004	-0.70	-9.68	-14.52 to -4.83	2.47	-3.91	0.0001	-0.78
Ideas of social reference	Green et al Paranoid Thoughts Scale	-5.53	-10.26 to -0.80	2.41	-2.29	0.022	-0.44	-6.25	-10.56 to -1.94	2.20	-2.84	0.0045	-0.55
Safety behaviours	Safety Behaviour Questionnaire—Persecutory Delusions	-6.13	-10.85 to -1.42	2.41	-2.55	0.011	-0.49	-5.19	-9.79 to -0.60	2.34	-2.21	0.027	-0.42
Social interaction anxiety	Social Interaction Anxiety Scale	-2.71	-6.93 to 1.51	2.15	-1.26	0.209	-0.24	-3.38	-7.18 to 0.43	1.94	-1.74	0.082	-0.33
Depression inventory	Beck Depression Inventory	1.32	-1.40 to 4.05	1.39	0.95	0.341	0.18	-0.85	-3.87 to 2.18	1.54	-0.55	0.582	-0.10
Quality of life	Manchester Short Assessment of Quality of Life	-0.01	-0.22 to 0.22	0.11	-0.07	0.942	-0.01	-0.00	-0.23 to 0.22	0.11	-0.04	0.966	-0.01
Social functioning	Social and Occupational Functioning Assessment Scale	1.22	-1.46 to 3.90	1.37	0.89	0.372	0.17	3.73	0.48 to 6.98	1.66	2.25	0.024	0.43
Stigma	Internalized Stigma of Mental Illness	-0.04	-0.16 to 0.08	0.06	-0.61	0.540	-0.11	-0.13	-0.25 to -0.02	0.06	-2.32	0.020	-0.44
Jumping to conclusions	DACOBS	-1.51	-3.16 to 0.13	0.84	-1.80	0.072	-0.34	-0.93	-2.66 to 0.80	0.88	-1.05	0.294	-0.20
Belief inflexibility	DACOBS	0.42	-1.38 to 2.22	0.92	0.46	0.646	0.09	0.34	-1.28 to 1.97	0.83	0.42	0.677	0.08
Attention for threat	DACOBS	-2.11	-3.97 to -0.26	0.95	-2.23	0.026	-0.42	-1.11	-2.97 to 0.74	0.95	-1.18	0.239	-0.22
External attribution	DACOBS	0.25	-1.70 to 2.20	0.99	0.25	0.803	0.05	-0.73	-2.74 to 1.29	1.02	-0.71	0.480	-0.13
Social cognitive problems	DACOBS	-1.84	-3.60 to -0.08	0.90	-2.04	0.041	-0.39	-2.35	-4.33 to -0.36	1.01	-2.32	0.021	-0.44
Subjective cognitive problems	DACOBS	-0.45	-2.17 to 1.27	0.88	-0.51	0.607	-0.09	-0.33	-2.42 to 1.74	1.06	-0.32	0.749	-0.06
Safety behaviour	DACOBS	-1.42	-3.29 to 0.45	0.95	-1.49	0.136	-0.28	-1.58	-3.53 to 0.37	1.00	-1.59	0.113	-0.30
Negative self-core schema	Brief Core Schema Scales	-0.25	-1.54 to 1.05	0.66	-0.37	0.710	-0.07	-0.13	-1.40 to 1.15	0.65	-0.19	0.845	-0.04
Negative others core schema	Brief Core Schema Scales	-1.09	-2.63 to 0.45	0.79	-1.39	0.165	-0.26	-0.88	-2.38 to 0.61	0.76	-1.15	0.248	-0.21
Positive self-core schema	Brief Core Schema Scales	-0.91	-2.48 to 0.66	0.80	-1.13	0.257	-0.21	0.20	-1.16 to 1.55	0.69	0.29	0.774	0.05
Positive others core schema	Brief Core Schema Scales	-0.73	-2.31 to 0.84	0.80	-0.92	0.360	-0.17	0.62	-1.03 to 2.28	0.84	0.74	0.459	-0.14

Treatment effects (ie, the interaction effect of time and treatment condition) are shown. The effect size is based on the pre-measure–post-measure difference. Separate multilevel regression models were estimated for baseline–post-treatment and baseline–follow-up data. Age, ethnicity, education, sex, and baseline safety behaviour were included as covariates in all analyses. b=beta coefficient. DACOBS=Davos Assessment of Cognitive Biases Scale.

Table 3: Primary and secondary outcome results

	Paranoid ideation* (n=101)			Momentary paranoia† (n=95)		
	Effect	p	95% bootstrap CI	Effect	p	95% bootstrap CI
Total effect	13·72	0·0024	..	0·38	0·012	..
Direct effect	6·83	0·060	..	0·28	0·042	..
Indirect effect safety behaviour	4·62	..	0·62 to 10·21	0·02	..	–0·01 to 0·26
Indirect effect attention for threat	–0·35	..	–3·86 to 1·71	0·06	..	–0·01 to 0·23
Indirect effect social cognitive problems	2·63	..	0·05 to 8·01	0·05	..	–0·03 to 0·25
Indirect effect jumping to conclusions	–0·01	..	–1·49 to 1·49	-0·03		–0·17 to 0·01

Mediation analysis was done by the method described by Hayes and Rockwood.[34] Baseline and post-treatment values were used. Baseline values of outcome and mediator variables were added as covariates to the model. *Measured with Green et al Paranoid Thoughts Scale. †Measured with Experience Sampling Method.

Table 4: Results of mediation analysis

Significant interaction effects were noted for attention for threat and social cognitive problems at the post-treatment assessment (table 3). No significant treatment effects were found for positive and negative beliefs of self or others (table 3).

Mediation analysis showed that part of the treatment effect on paranoid ideation (measured by the Green et al Paranoid Thoughts Scale) at the post-treatment assessment was mediated by change in safety behaviour (percentage mediated 33·7%) and change in social cognitive problems (percentage mediated 19·2%; table 3; appendix). Individuals who received VR-CBT used less safety behaviour and reported fewer social cognition problems than did those in the control group, and in turn experienced less paranoid ideation. Jumping to conclusions and attention for threat did not mediate the effect of treatment on paranoid ideation (table 4). The direct effect of the treatment on paranoid ideation was no longer significant after inclusion of the mediators in the model (p=0·060). The indirect effect of safety behaviour was not significantly larger than the indirect effect of social cognition problems (bootstrap CI of the contrast –3·4 to 7·5). None of the included mediators significantly mediated the effect of VR-CBT on momentary paranoia as measured with ESM (table 4). The total effect (independent of mediators) and direct effect (including the mediators) of treatment were both significant for momentary paranoia (table 4).

Discussion

To our knowledge, ours is the first randomised controlled trial of VR-CBT to treat paranoid ideation and social avoidance in patients with psychotic disorders. Although the amount of time spent with others did not increase after VR-CBT compared with the control, VR-CBT resulted in large reductions in momentary paranoia and anxiety during social interactions, not only at the post-treatment assessment, but also at the 6 month follow-up assessment. Significant improvements were also noted for ideas of persecution, ideas of social reference, and use of safety behaviour. The therapeutic effect of VR-CBT for paranoid ideation was mediated by improvements in safety behaviours and social cognition, but mediation effects were not noted for momentary paranoia.

Our findings suggest that VR-CBT does not immediately lead to spending more time with others, but helps patients to learn how to drop safety behaviours and to have social interactions more positively, with less anxiety and paranoia after therapy. In turn, these positive experiences seem to lead to fewer paranoid thoughts and fewer ideas of social reference in general. This interpretation was supported by the results of the mediation analysis, which showed that reductions in safety behaviour accounted for 34% of the change in paranoid ideation, and improvements in social cognition for 19%.

How do these mechanisms contribute to reductions in paranoid ideation? Safety behaviours interfere with the development of new associations and prevent gathering of social information. For example, during the first sessions, many participants looked at avatars from the neck down only, avoiding eye contact. When such safety behaviour is dropped, the patient receives more social information. Improvements in social cognition can result in more adequate interpretations of that information, thereby reducing the chance of incorrect paranoid appraisals. Safety behaviour was targeted explicitly during sessions, because people practised within virtual recreations of situations that they would usually avoid. Cognition was actively challenged and discussed during virtual reality exposures, although in a less structured fashion than safety behaviour, which could explain the absences of findings for several cognitive biases.

No mediating effects were identified for momentary paranoia as measured by ESM. Although this finding seems contradictory to the results for paranoid ideation on the Green et al Paranoid Thoughts Scale, it could be explained by the nature of the scales. The Green et al Paranoid Thoughts Scale assesses paranoia with 32 items, whereas momentary paranoia is composed of three items. Thus variation in ESM scores tends to be lower, and the ESM scale might be less sensitive to changes. Additionally, retrospectively measured paranoid ideation could capture different constructs from those captured by measurement of momentary state paranoia. ESM is ecologically valid, but also seems to be complementary to retrospective measures rather than a measurement of the same constructs.[36]

Overall, expansion of social activities and improvement of social functioning seem to require more time and are mainly accomplished in the period after therapy. Patients in symptomatic remission do not immediately spend more time with others.[37] When patients increasingly feel more comfortable in social situations and learn that other people are less threatening than anticipated, they might try and succeed to make and maintain social

contacts and find hobbies and jobs. At the follow-up assessment in our study, a positive effect of VR-CBT was noted for stigma and social and occupational functioning. Furthermore, resolution of symptoms might not automatically improve social functioning—negative symptoms and deficient social skills could get in the way. Additional training might be needed.

Our results are in line with a virtual reality pilot study[38] for treatment of ideas of persecution, in which significant reductions in delusional conviction and real-world distress were noted after one session. Similar to virtual reality interventions for social skills and job interview training for people with schizophrenia, our intervention was generalisable to everyday life.[9] Although many virtual reality studies have a high frequency of dropouts due to cybersickness,[39] in our study only one participant had cybersickness to the extent that he quit treatment. Cybersickness might become less of a problem as a result of improvements in technology.

Perception of social threat, as measured by ESM, was not significantly affected by VR-CBT. Collip and colleagues[17] noted that perceived social threat was more often reported in the company of less familiar people than in the presence of familiar people. However, the term social threat could be misleading, because the items on the ESM could also express the wish to enjoy company versus a preference for being alone. This scale thus needs further validation.

A strength of our study is the use of ESM to assess treatment effects in the flow of daily life. Another strength is the pragmatic effectiveness design of the study. The study was done in seven mental health centres, and treatment was delivered within standard services by regularly employed therapists. Therapists' experience with exposure therapy and CBT varied. Our results suggest the effectiveness of VR-CBT in real-world conditions in a sample of patients who are representative of standard clinical practice.

Our study also had several limitations. First, we did not use an active control group, such as CBT with exposure in vivo. Thus we cannot rule out a dose-effect of therapeutic contacts. Second, the long-term effects of VR-CBT remain unknown, because follow-up was restricted to 6 months. Third, technological limitations restricted conversational interaction possibilities between participants and avatars. Therefore VR-CBT could not sufficiently address conversational issues. Fourth, a potential limitation of VR-CBT is that patients are not exposed to unexpected surprises that can occur in life. Although this criticism is valid, many patients with psychosis become too frightened in real-life situations, preventing them from dropping safety behaviours or causing them to avoid exposure. To prevent the risk that the presence of the therapist becomes a safety signal, as therapy progresses the therapist should become less prominently present and should guide the patient less. Fifth, some eligible patients did not participate because they were too frightened to travel to the therapy location. Thus our sample might have been biased, because some of the most paranoid and avoidant patients could not participate. Additionally, little is known about the patients who seemed eligible on the basis of screening but did not consent to be contacted, or about the people who provided consent to be contacted, but did not respond. Furthermore, we could not recruit the aimed number of participants within our financial and time limits. The study is thus somewhat underpowered. Finally, the temporal order of the mediation analysis was based on the assumed mechanisms of VR-CBT, but reverse causality cannot be ruled out. That said, we agree with Hayes and Rockwood[34] that mediation analysis, despite limitations, provides useful insights into clinical research findings. Although no final conclusions can be drawn, our findings support the predetermined hypothesis.

In conclusion, in patients with a psychotic disorder, our findings support the hypothesis that VR-CBT strongly reduces paranoid ideation, momentary anxiety, and safety behaviours in real-life social situations. This study shows that targeting safety behaviour and social cognitive appraisals in psychotherapy with virtual reality can effectively reduce paranoid thoughts. Future research should compare VR-CBT with standard cognitive behavioural therapy in terms of both treatment effects and cost-effectiveness.

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