Virtual reality-based cognitive remediation versus virtual reality control in people with mood or psychosis spectrum disorders in Denmark: a single-centre, double-blind, randomised controlled trial

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Summary

Background There is a paucity of real-life-like cognitive training programmes to bolster the transfer of treatment-related cognitive gains to daily-life functioning. We aimed to investigate the effects of 4-week, intensive virtual reality-based cognitive remediation therapy (VR-CRT) involving daily-life challenges versus an active virtual reality control treatment on cognition and functioning in patients with mood or psychosis spectrum disorders.

Methods This was a single-centre, double-blind, parallel-group, randomised controlled trial at the Psychiatric Centre Copenhagen in Denmark. Clinically stable outpatients aged 18–55 years with an ICD-10 diagnosis of unipolar disorder, bipolar disorder, or a psychosis spectrum disorder, and with clinically relevant objective and subjective cognitive impairment were included. Participants were randomly assigned (1:1) to 4 weeks of VR-CRT or virtual reality control treatment and assessed at baseline, treatment completion (5 weeks) and follow-up (17 weeks). Randomisation used the REDCap module with block randomisation (block sizes four to eight), stratified by age (<35 *vs* ≥35 years) and diagnosis (mood disorder *vs* psychosis spectrum disorder), with allocation concealed from the enrolling author. The primary outcome was a global functional cognitive capacity score on the Cognition Assessment in Virtual Reality test at week 5. This trial was registered with ClinicalTrials.gov, NCT06038955, and is completed.

Findings Between Oct 10, 2022, and Aug 9, 2024, 103 candidates were assessed for eligibility, of whom 62 participants were enrolled and randomly assigned (VR-CRT group n=31 and control group n=31). Of the 30 participants commencing VR-CRT, 28 (93%) completed treatment per protocol. At week 5, the mean Z score improvement in the global functional cognitive capacity score was 1·5 (SD 0·6) in the VR-CRT group and 0·4 (0·8) in the virtual reality control group (treatment effect 0·98 [95% CI 0·65–1·32]; p<0·0001; *d*=1·55). This effect was maintained at follow-up at week 17 (mean Z score improvement 1·6 [0·5] *vs* 0·6 [0·7]; treatment effect 0·91 [0·61–1·21]; p<0·0001; *d*=1·53). The intervention was well tolerated with no treatment-related serious adverse events.

Interpretation Improvement in functional cognitive capacity was significantly greater in the VR-CRT group than the control group, and the intervention was well tolerated. Our findings suggest that embedding cognitive strategy training in immersive virtual reality can enhance transfer to real-world functioning, offering a feasible, engaging solution for cognitive rehabilitation in psychiatry.

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Introduction

Cognitive impairment is a prevalent and disabling feature of mood disorders and psychosis spectrum disorders, affecting approximately 50% of individuals with unipolar depression,[1] 50–70% with bipolar disorder,[2] and up to 80% with schizophrenia.[3] Although the severity and cognitive profiles vary across diagnoses, accumulating evidence points to a shared clinical vulnerability that transcends traditional diagnostic boundaries.[4] Studies identifying subgroups with overlapping neuropsychological profiles across mood disorders and psychosis spectrum disorders support the conceptualisation of cognitive impairment as a transdiagnostic symptom domain, in line with the Research Domain Criteria framework.[5] These impairments are closely linked to poorer daily functioning and reduced quality of life,[6] underscoring cognition as a key therapeutic target across severe psychiatric disorders.[7]

Emerging evidence suggests potential pro-cognitive effects of several treatments,[8,9] including cognitive remediation therapy (CRT), which produces small-to-moderate

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Research in context

Evidence before this study

We searched PubMed, PsycINFO, and Embase for English-language articles published from database inception to April 1, 2025, using the following MeSH and free-text terms: "cognition", "cognitive impairment", "cognitive remediation", "virtual reality", "mood disorders", "depression", "bipolar disorder", "schizophrenia", and "psychotic disorders". We prioritised meta-analyses, systematic reviews, and randomised controlled trials evaluating cognitive remediation or virtual reality-based cognitive interventions with cognitive or functional outcomes. Cognitive impairments are well established across mood and psychosis spectrum disorders and are closely associated with poorer social and occupational functioning. Meta-analyses show that cognitive remediation therapy (CRT) produces small-to-moderate cognitive improvements, yet its effects on real-world functioning are limited, particularly in people with mood disorders, for whom functional gains remain difficult to achieve. This highlights the need for interventions with stronger transfer to daily-life functioning. Virtual reality offers an immersive, ecologically valid platform for cognitive training, and systematic reviews suggest that virtual reality-based interventions are feasible and potentially beneficial in populations with neurological or psychiatric disorders, including early evidence of functional improvements. However, high-quality randomised controlled trials in people with mood disorders are scarce, and existing studies are constrained by small samples, lack of active control conditions, and limited assessment of real-world functional outcomes.

Added value of this study

To our knowledge, this is the first double-blind, randomised controlled trial to evaluate the efficacy of virtual reality-based CRT (VR-CRT) against an active virtual reality control condition in a transdiagnostic sample of clinically stable individuals with mood or psychosis spectrum disorders. The intervention led to significant improvements in functional cognitive capacity (primary outcome; large effect size), with sustained gains at the 17-week follow-up. Treatment adherence was high, with 93% of participants in the VR-CRT group completing treatment per protocol, and participants reported high acceptability and satisfaction. No intervention-related serious adverse events occurred. These findings provide the first rigorous evidence supporting the feasibility and efficacy of VR-CRT in improving cognitive functioning in adults with mood or psychosis spectrum disorders, addressing a crucial gap in current treatment options.

Implications of all the available evidence

The improvements in functional cognitive capacity observed in this trial build on emerging evidence for immersive virtual reality as a transformative tool in cognitive remediation. By embedding cognitive strategy training directly in interactive, ecologically valid environments, VR-CRT appears uniquely positioned to bridge the long-standing gap between performance on cognitive tests and real-world functioning. This approach offers a scalable, engaging, and transdiagnostic solution to cognitive rehabilitation in people with serious mental illness, with the potential to improve treatment outcomes and reduce disability.

cognitive improvements across psychosis spectrum disorders[10,11] and mood disorders.[12,13] A key limitation of CRT interventions is the limited transfer of cognitive gains into daily-life functional improvements,[12,13] possibly because interventions rarely involve direct training of cognitive skills within real-world settings.[8] Indeed, meta-analytic evidence suggests that integrating structured psychosocial rehabilitation in CRT interventions enhances transfer effects.[10] However, direct real-world exposure and rehabilitation might be challenging and costly in clinical practice, highlighting the potential of virtual reality to enable more accessible, real-life-like treatment in controlled, engaging, and ecologically valid environments.[14] In virtual reality, users can be immersed in relevant scenarios simulating daily-life cognitive challenges while receiving real-time support and guidance from their therapist.[14,15] This enables safe practice of cognitive skills and strategies necessary for carrying out real-world tasks (eg, household chores and holding down a job) in line with the domain of activity and participation in WHO's International Classification of Functioning, Disability, and Health.[16]

See Online for appendix

Meta-analytic evidence suggests that fully immersive virtual reality, such as with head-mounted displays, is more effective than less immersive approaches for learning outcomes.[17] According to the Cognitive Affective Model of Immersive Learning, immersive virtual reality increases perceived presence and agency, which facilitates a more enjoyable and meaningful learning experience that boosts motivation and engagement.[18] Similar effects in CRT programmes using virtual reality platforms could help increase transfer effects and treatment adherence.[19] Several systematic reviews have provided preliminary evidence supporting the feasibility and potential cognitive and functional benefits of virtual reality-based interventions in people with neurological or psychiatric disorders.[19–22] However, few studies have investigated fully immersive virtual reality-based cognitive remediation programmes in people with mood disorders or psychosis spectrum disorders (for details of previous studies and comparison to the current study, see appendix pp 1–5). Randomised controlled trials investigating virtual reality-based cognitive interventions in these populations are scarce and have various methodological challenges, such as an absence of active control groups, blinding procedures, real-world functional outcomes, and measurements of long-term effects.[19–22]

Our group developed an immersive virtual reality prototype simulating daily-life cognitive challenges and

showed in a proof-of-concept randomised controlled trial that short-term (1 week) virtual reality-based cognitive training was feasible, well tolerated, and improved cognitive performance in virtual reality.[23] Therefore, the virtual reality prototype was expanded into a comprehensive training programme featuring multiple daily-life scenarios based on interviews with individuals with lived experience.[24] In this study, we aimed to investigate the effect of 4-week, intensive, virtual reality-based CRT (VR-CRT) versus an active virtual reality control treatment on cognition and functioning in a transdiagnostic sample of clinically stable patients with mood disorders or psychosis spectrum disorders. In contrast with previous virtual reality trials, this treatment programme involved strategy presentations and training embedded directly within the virtual reality simulations, potentially enhancing transfer of strategy use to daily-life situations. We hypothesised that VR-CRT would improve functional cognitive capacity—ie, the capacity to apply cognitive functions in challenging real-world activities—measured in virtual reality, and that this effect would transfer to activities of daily living (ADL) process ability (secondary outcome). We also aimed to investigate if improvements were durable at the 3-month follow-up and explore effects on secondary and tertiary outcomes of cognition and functioning. Finally, we aimed to explore the neuronal underpinnings of treatment effect with functional MRI, reported in a separate publication.

Methods

Study design and participants

This was a single-centre, double-blind, parallel-group, randomised controlled trial conducted at the Psychiatric Centre Copenhagen, Bispebjerg and Frederiksberg Hospital (Frederiksberg, Denmark) with participants referred from different outpatient clinics in the Capital Region of Denmark. Participants were aged 18–55 years, fluent in Danish, and had clinically relevant objective and subjective cognitive impairment at the time of inclusion in line with recommendations.[24] Participants with mood disorders had an ICD-10 diagnosis of unipolar disorder or bipolar disorder and were in full or partial remission (scores $\leq$14 on the Hamilton Depression Rating Scale 17 items and Young Mania Rating Scale). Participants with psychosis spectrum disorder had an ICD-10 diagnosis within the F20-spectrum and were assessed to be relatively symptom-stable by their treating clinician on study referral. Diagnoses were verified with the Schedules for Clinical Assessment in Neuropsychiatry interview. Objective cognitive impairment was assessed using the Screen for Cognitive Impairment in Psychiatry and subjective impairment was assessed using the Cognitive Complaints in Bipolar Disorder Rating Assessment (COBRA) and the Cognitive Difficulties in Everyday Life (CODEL).[24,25] Data from age, sex, and IQ-matched healthy control participants were included to standardise cognitive test scores. Healthy controls were recruited through websites or blood banks in the Capital Region of Denmark and had no personal history of psychiatric illness requiring treatment. General exclusion criteria were dyslexia, current alcohol abuse or substance abuse, neurological illness, previous severe head trauma, severe somatic illness, daily benzodiazepine use above cutoffs for doses with limited cognitive side-effects, and electroconvulsive therapy within the previous 3 months. Additional functional MRI-specific exclusion criteria included pregnancy, claustrophobia, and having a pacemaker or other metal implants inside the body. However, because functional MRI was an exploratory outcome, otherwise eligible individuals unable to undergo scanning were still included to ensure adequate power for the primary cognitive outcome. Data on participants' sex were obtained from medical records, whereas data on race and ethnicity were not systematically collected.

The study was approved by the Committee on Health Research Ethics (H-22004153) and the Danish Data Protection Agency (P-2022–411) in the Capital Region of Denmark. The study was conducted in compliance with existing laws on data protection and in accordance with the recommendations of the Declaration of Helsinki. All participants received written and verbal study information and provided written informed consent. The study was preregistered at ClinicalTrials.gov, NCT06038955, and CONSORT reporting guidelines were used. The trial was registered retrospectively due to some initial delay in confirming that we had the logistical and financial capacity to carry out all the planned outcome assessments across the full study period (appendix p 6). The trial protocol has been published previously.[24] Further details on the study design and methods are in the appendix (pp 7–25).

Randomisation and masking

Participants were randomly assigned (1:1) to VR-CRT or virtual reality control after full completion of the baseline assessment. Randomisation was done using the randomisation module in the REDcap system[24] with block randomisation (block sizes four to eight), stratified by age (<35 years *vs* $\geq$35 years) and diagnosis (mood disorder *vs* psychosis spectrum disorder).[24] The randomisation sequence was generated by a member of the NEAD Centre who was not otherwise involved in the trial and kept concealed from the enrolling author (AEJ).

Participants and outcome assessors were blinded to group allocation. Participants were told they would be assigned to one of two types of virtual reality training programmes involving weekly therapy sessions, but specific details were withheld until after randomisation. To maintain blinding, participants were only informed after the trial (week 17) that one group was a control. At this point, they guessed their allocation and were then debriefed. Outcome assessors were not informed of the treatment allocation or any details regarding treatments to ensure masking.

Procedures

The baseline assessment was conducted by a trained psychology student and comprised a virtual reality test of functional cognitive capacity, a set of neuropsychological tests, interviewer-based and performance-based measures of functioning, self-reported cognition, and symptom ratings.[24] Assessments were repeated at treatment completion (week 5) and after 3 months (week 17). Participants were also assessed on their ADL ability by a blinded occupational therapist at baseline and treatment completion (week 5). However, due to financial constraints, the ADL assessment was omitted at the 3-month follow-up, deviating from the original trial protocol.[24] Participants continued treatment-as-usual but were requested to avoid any changes in medication between baseline and treatment completion. Information on adverse events was collected and reported to the local ethics committee.

The VR-CRT intervention followed a prespecified treatment manual and involved strategy-based, individualised CRT, combining psychoeducation with cognitive skill training in virtual reality daily-life scenarios to help participants practise and implement learned cognitive strategies in their lives.[24] The programme was short-term (4 weeks) and intensive, with two weekly, 2 h, in-person sessions (eight in total) with a therapist (clinical psychologist) accompanied by between-session virtual reality training at home and homework assignments consisting of cognitively challenging real-life tasks to aid transfer (eg, cooking or grocery shopping). The main component of the programme was the immersive virtual reality training platform administered on a Meta Quest 2 head-mounted display featuring four scenarios: (1) a kitchen focusing on preparing a meal; (2) a supermarket focusing on grocery shopping; (3) a restaurant focusing on remembering names and personal information; and (4) an office focusing on structuring work assignments. Various CRT strategies embedded directly in the virtual reality environment were presented to the participant before and during task completion. The intervention primarily aimed to strengthen the strategic component of cognitive functioning across various domains by focusing on enhancing participants' general ability to apply CRT strategies in real-world situations. Each scenario included three to six difficulty levels, with difficulty adapting at the individual level based on performance. Participants advanced to a higher level when achieving 85% or more correct responses, ensuring an appropriate level of challenge to maintain motivation without exceeding the capacity of the individual participant. Positive auditory and visual stimuli were presented on completion of a training level to reinforce a sense of reward. The virtual reality training was supported by a psychoeducational programme focusing on applying learned cognitive strategies in daily life. Further details on the intervention are in the appendix (pp 8–15). Treatment completion was defined in the protocol as full completion of six of eight in-person training sessions.

Participants in the control group attended weekly 2 h individual sessions for 4 weeks. These sessions involved playing freely available virtual reality games that included training of simple reaction time in entertaining virtual reality environments (appendix pp 16–17). Participants also completed alternative versions of the virtual reality training scenarios (ie, the kitchen, supermarket, restaurant, and office) in which the active training elements (ie, strategy presentations, adaptive difficulty level, and feedback) were removed. The control sessions served three purposes: to establish if effects on the virtual reality functional cognitive capacity test reflected a therapeutic effect rather than habituation to virtual reality, to control for the therapeutic effects of weekly therapist meetings, and to mask participants to the training condition.

Outcomes

The predefined primary outcome was change from baseline to treatment completion (week 5) in a global functional cognitive capacity score on the Cognition Assessment in Virtual Reality (CAVIR) test. Follow-up assessment of the primary outcome was also conducted at week 17. Results are reported as model-estimated mean differences with 95% CIs, alongside observed mean (SD) at each timepoint (baseline, week 5, and week 17). The CAVIR assesses participants' functional cognitive capacity related to preparing a meal in a virtual reality kitchen scenario (different from the kitchen scenarios used in the interventions; see appendix pp 18–19).[25,26] The CAVIR was chosen as the primary outcome because the VR-CRT intervention specifically aimed to improve participants' ability to tackle typical daily-life challenges in line with the domain of activity and participation in WHO's International Classification of Functioning, Disability, and Health framework.[16] The CAVIR has previously shown high feasibility, validity, and sensitivity for cognitive assessment in individuals with mood disorders and psychosis spectrum disorders,[26] and shown a closer association with real-world ADL ability than traditional neuropsychological tests.[25]

The co-secondary functional outcome was change from baseline to week 5 in ADL process ability measured with the gold-standard Assessment of Motor and Process Skills (AMPS) in a test apartment. The co-secondary neuropsychological outcome was change from baseline to week 5 in a composite of verbal learning and memory on the Rey Auditory Verbal Learning Test (RAVLT), with a follow-up assessment at week 17. Results for both secondary outcomes are reported as model-estimated mean differences with 95% CIs, alongside observed mean (SD) at each timepoint.

All tertiary outcomes were assessed at baseline, week 5, and week 17. Tertiary cognitive outcome measures were CAVIR subtask 1 (memorising ingredients; learning and memory), subtask 2 (planning meal preparation; executive functioning), subtask 3 (selecting correct ingredients on time; processing speed), subtask 4 (remembering location of kitchen utensils; working memory), subtask 5

(monitoring food to prevent burning; sustained attention), global and domain-specific neuropsychological performance, and self-rated cognition measured with the COBRA and CODEL questionnaires. Tertiary functional measures were the University of California San Diego Performance-based Skills Assessment Brief and clinician-rated interview Functioning Assessment Short Test (FAST) assessing autonomy, occupational functioning, cognitive functioning, financial issues, interpersonal relationships, and leisure time.

Finally, self-reported treatment tolerability and satisfaction were included as exploratory measures of treatment feasibility, assessed at treatment completion (week 5) (see appendix pp 18–23 for details).

Statistical analysis

A power calculation performed using data from the proof-of-concept study[23] showed that 54 participants (27 per group) would achieve more than 80% power for detection of a greater improvement of 0·6 or more in Z scores (a moderate effect size) in the VR-CRT group versus the control group for the primary outcome at an α level of 0·05.[24] To accommodate an expected 20% dropout rate, we aimed to recruit 66 participants.

Baseline group comparisons for demographic and clinical data were performed using independent *t* tests or Mann–Whitney tests for normally distributed and non-parametric data, respectively (normality was assessed using Shapiro–Wilk's test). A χ^2 test was applied to investigate group differences in sex distribution (male or female as assigned at birth). All participants with baseline data were included in the intention-to-treat analyses. To investigate the effect of VR-CRT versus control, all outcomes were analysed using linear mixed-effect models with an unstructured covariance pattern. Model factors were time, stratum (age and diagnoses), and treatment (with control treatment as the reference category for baseline correction). Fixed effects were time, stratum, time × stratum, and time × treatment (appendix pp 24–25). The α level was set to $p \leq 0{\cdot}05$ (two-tailed). The Benjamini–Hochberg method was applied to adjust for multiple comparisons for secondary and tertiary outcomes. The false discovery rate was set at 5%, and adjusted p values $\leq 0{\cdot}05$ were considered significant. Post-hoc linear-mixed models analyses were conducted to explore treatment effects on clinical symptoms, as well as treatment effects on the primary and secondary outcomes in participants with mood disorders or psychosis spectrum disorders separately. All statistical analyses were carried out using SPSS version 29.0.1.0.

Role of the funding source

The funders of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

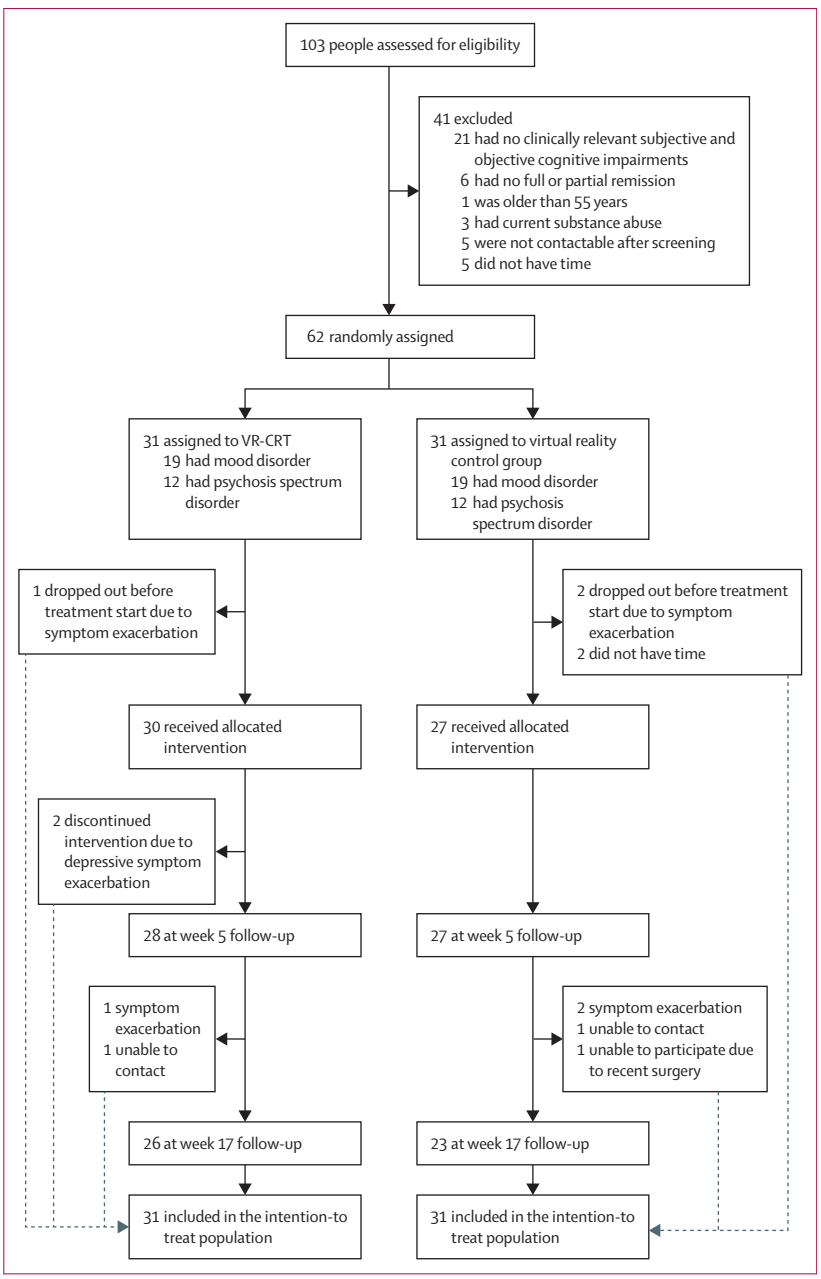

Figure 1: **Trial profile**
Of the 103 screened participants, 82 (80%) presented with clinically meaningful objective and subjective cognitive impairments. VR-CRT=virtual reality-based cognitive remediation therapy.

Results

Between Oct 10, 2022, and Aug 9, 2024, 103 candidates were assessed for eligibility, of whom 62 participants were enrolled and randomly assigned (VR-CRT group n=31 and control group n=31) with the final follow-up completed on Dec 13, 2024 (figure 1). There was a lower than expected dropout rate (seven [11%] of 62 *vs* 20% expected), which ensured a minimum of 27 participants per treatment group with complete data at baseline and treatment completion as

	VR-CRT group (n=31)	Virtual reality control group (n=31)
Sex assigned at birth		
Female	21 (68%)	22 (71%)
Male	10 (32%)	9 (29%)
Age, years	27 (23–39)	31 (24–44)
Years of education	13 (13–16)	14 (12–16)
Estimated premorbid verbal IQ*	111 (109–114)	112 (108–115)
HDRS-17	4 (2–5)	3 (1–5)
YMRS	0 (0–1)	0 (0–0)
BNSS†	19 (7)	18 (11)
SAPS psychotic‡	0 (0–3)	0 (0–4)
SAPS disorganised	0 (0–0)	0 (0–0)
Age at illness onset, years	18 (4)	18 (5)
Illness duration, years	10 (7–19)	12 (7–24)
Hospitalisations	0 (0–2)	1 (0–1)
Depressive episodes	3 (2–5)	2 (2–5)
Hypomanic episodes	5 (0–10)	4 (0–7)
Manic episodes	0 (0–0)	0 (0–0)
Mixed episodes	0 (0–0)	0 (0–0)
Total number of mood episodes	7 (2–14)	6 (3–9)
Occupational status		
Employed or studying	16 (52%)	12 (39%)
Unemployed or sick leave	11 (35%)	15 (48%)
Retired	3 (10%)	3 (10%)
Other	1 (3%)	1 (3%)
Diagnoses		
Bipolar disorder	14 (45%)	14 (45%)
Unipolar disorder	5 (16%)	5 (16%)
Psychosis spectrum disorder§	12 (39%)	12 (39%)
Comorbid ADD or ADHD¶	7 (23%)	4 (13%)
Medication		
Antidepressants	7 (23%)	9 (29%)
Antipsychotics	16 (52%)	16 (52%)
Anticonvulsants	10 (32%)	6 (19%)
Lithium	10 (32%)	8 (26%)
Psychostimulants	6 (19%)	2 (7%)
No medication	1 (3%)	5 (16%)
Number of medications	1 (1–2)	1 (1–2)
Cognition and functioning		
CAVIR global score, Z score	−0·8 (0·7)	−0·6 (0·9)
Verbal learning and memory, Z score	−0·6 (1·2)	−0·3 (1·2)
AMPS ADL process ability, Z score‖	−0·8 (0·6)	−0·8 (0·6)

Data are n (%), median (IQR), or mean (SD). ADD=attention deficit disorder. ADHD=attention deficit hyperactivity disorder. ADL=activity of daily living. AMPS=Assessment of Motor and Process Skills. BNSS=Brief Negative Symptom Scale. CAVIR=Cognition Assessment in Virtual Reality. HDRS-17=17-item Hamilton Depression Rating Scale. SAPS=Scale for the Assessment of Positive Symptoms. VR-CRT=virtual reality-based cognitive remediation therapy. YMRS=Young Mania Rating Scale. *Premorbid verbal IQ was estimated from the error score on Danish Adult Reading Test. †Data for BNSS were only collected for patients with psychosis spectrum disorders. ‡Data for SAPS were only collected for patients with psychosis spectrum disorders. §Of the participants with psychosis spectrum disorders, ten were diagnosed with schizophrenia (five in the VR-CRT group and five in the control group), 11 with schizotypal disorder (six in the VR-CRT group and five in the control group), and three with unspecified non-organic psychosis (one in the VR-CRT group and two in the control group). ¶21 participants (12 in the VR-CRT group and nine in the control group) had current comorbid psychiatric disorders: ADD or ADHD (seven in the VR-CRT group and four in the control group), anxiety disorder (three in the VR-CRT group and four in the control group), post-traumatic stress disorder (two in the VR-CRT group and one in the control group), and unspecified eating disorder (two in the VR-CRT group). ‖Missing data for AMPS at baseline: one in the VR-CRT group and three in the control group. Data on participants' race or ethnicity were not collected in the current study.

Table 1: **Baseline characteristics**

per the power calculation. Data were analysed for all 62 randomly assigned participants with baseline data as per the intention-to-treat principle.

At baseline, the VR-CRT and control groups were well balanced regarding demographic and clinical characteristics, including cognition and functioning (table 1). 43 (69%) of 62 participants were female and 19 (31%) were male. 62 healthy control participants were recruited and group comparisons between randomly assigned participants and healthy controls are reported in the appendix (p 26).

Of the 30 participants who started VR-CRT, 28 (93%) completed treatment per protocol, corresponding to completion of six or more sessions. Participants in the VR-CRT group, including two who discontinued the intervention, completed a mean of 7·1 (SD 1·0) in-person sessions of a possible eight with a mean of 18·0 h (SD 2·4) of a possible 20 h spent on training across the in-person sessions and the virtual reality home training. Of these hours, a mean of 10·7 h (1·5) were spent in virtual reality and a mean of 7·3 h (1·2) were spent on psychoeducation and reflection. Of the 10·7 h spent in virtual reality, a mean of 2·4 h (0·8) of the scheduled 4 h were completed as virtual reality home training. Any missed virtual reality home training was instead made up during the in-person sessions. In addition, participants completed a mean of 6·3 (SD 0·7) of the scheduled eight cognitively challenging real-life homework assignments. The participants in the virtual reality control group completed a mean of 7·2 h (1·0) of a possible 8 h of virtual reality control training. There was no significant difference in the overall attendance rate between the two groups (p=0·93).

The primary analysis using linear mixed models showed a significantly greater improvement in the VR-CRT group compared with the virtual reality control group in the CAVIR global functional cognitive capacity score at treatment completion at week 5 (treatment effect 0·98 [95% CI 0·65–1·32]; p<0·0001; d=1·55; figure 2A, table 2). Participants receiving VR-CRT showed a mean Z score improvement of 1·5 (SD 0·6) compared with 0·4 (0·8) in the virtual reality control group. This treatment effect was also evident at the week 17 follow-up (treatment effect 0·91 [0·61–1·21]; p<0·0001; d=1·53; mean Z score improvement VR-CRT 1·6 [SD 0·5] *vs* virtual reality control 0·6 [0·7]).

At treatment completion (week 5), there was a significantly greater improvement in the VR-CRT group compared with the virtual reality control group in ADL process ability assessed with the AMPS (treatment effect 0·57 [95% CI 0·14–1·00]; p=0·0088; d=0·80; table 2, figure 2B). There was also a significantly greater improvement in the VR-CRT group versus the virtual reality control group in the neuropsychological verbal learning and memory domain (RAVLT) score at treatment completion (treatment effect 0·66 [0·35–0·97]; p<0·0001; d=0·99), which was also evident at the week 17 follow-up (treatment effect 0·67 [0·29–1·05]; p=0·0009; d=0·76; table 2, figure 2C). These findings remained significant after adjustment for multiple testing (table 2).

Treatment effects and mean scores for tertiary outcomes are shown in table 3 and the appendix (p 27). Analyses showed significant effects of VR-CRT versus virtual reality control at treatment completion (week 5) on CAVIR subtask 3 (processing speed; p<0·0001), subtask 4 (working memory; p=0·0034), and subtask 5 (sustained attention; p=0·031). These effects remained significant at the week 17 follow-up for CAVIR subtask 3 (p<0·0001), subtask 4 (p=0·0042), and subtask 5 (p=0·0015). For neuropsychological outcomes, there were significantly greater improvements in the VR-CRT group compared with the virtual reality control group at treatment completion (week 5) in global neuropsychological performance (p=0·0002) and in the processing speed (p=0·012) and working memory domains (p=0·017). The effect on global neuropsychological performance was durable at follow-up (p=0·013). VR-CRT versus virtual reality control significantly improved interviewer-rated functioning on the FAST at treatment completion (week 5), including the total score (p=0·0076) and the subdomains of autonomy (p=0·040), cognitive functioning (p<0·0001), and interpersonal relationships (p=0·050), with sustained effects for autonomy (p=0·030) and cognitive functioning (p=0·0039) at the week 17 follow-up. Participants' subjective cognitive complaints were also significantly reduced at treatment completion (week 5) following VR-CRT versus control on both the COBRA (p=0·047) and CODEL (p=0·019), but these effects were not significant at the week 17 follow-up. The effects on CAVIR subtasks 3 and 4, global neuropsychological performance, processing speed, working memory, FAST total and cognition subdomain scores remained significant after adjustment for multiple testing (table 3). By contrast, the effects on COBRA, CODEL, FAST autonomy and interpersonal relationship, and CAVIR sustained attention were no longer significant after adjustment (table 3).

The VR-CRT and virtual reality control groups reported no or only mild simulation sickness and high user-friendliness and engagement in the virtual reality scenarios with no differences between groups (appendix p 29). In the VR-CRT group, 18 (64%) of 28 completers thought they had received VR-CRT, two (7%) thought they were in the virtual reality control group, and eight (29%) said they were unsure. In the control group, five (19%) of 27 believed they had received VR-CRT, nine (35%) thought they had received virtual reality control treatment, and 12 (46%) were unsure.

In the post-hoc analyses using linear mixed models, there were no treatment effects on mood, negative symptoms, or positive symptoms across timepoints (appendix p 30), and groups showed no differences in symptom severity at treatment completion or follow-up (data not shown). Exploratory analyses in participants with mood disorders and participants with psychosis spectrum disorders separately showed significantly greater improvements in primary and secondary outcome measures in the VR-CRT group than the virtual reality control group in both diagnostic subgroups (appendix pp 31–32). There were no

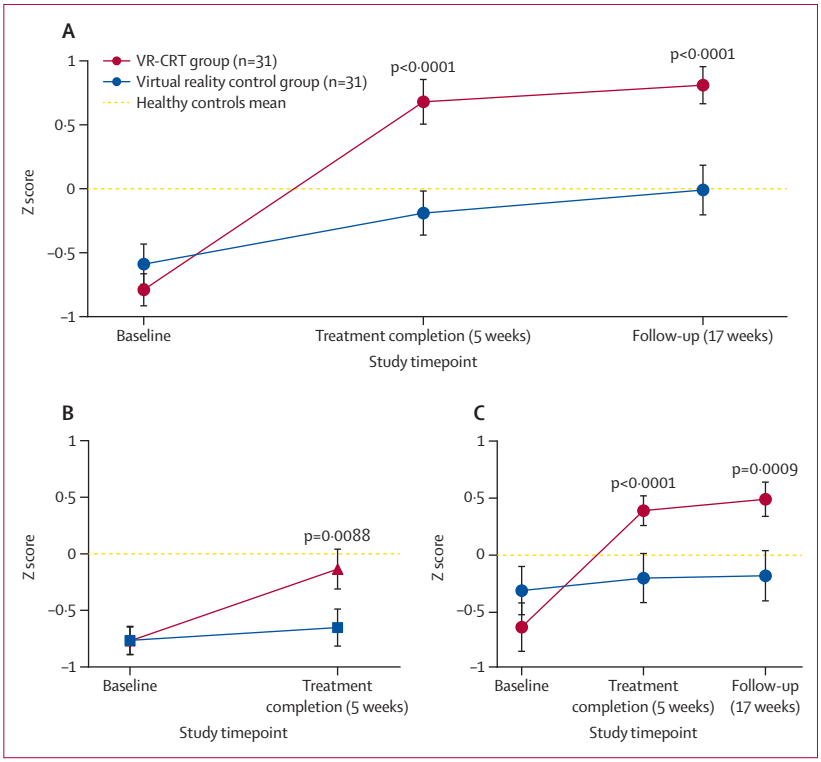

***Figure 2*: Treatment effects on the primary and secondary outcomes**
(A) Change in Z score for Cognition Assessment in Virtual Reality global cognitive composite score (primary outcome). (B) Change in Z score for Assessment of Motor and Process Skills activities of daily living process ability measure (secondary functional outcome). (C) Change in Z score for the standard neuropsychological verbal learning and memory domain score on the Rey Auditory Verbal Learning Test (secondary cognitive outcome). In each chart, the y-axis shows the mean Z scores based on the mean (SD) of healthy controls (healthy control mean 0 [SD 1]). Error bars show standard error of the mean. p values are reported unadjusted. VR-CRT=virtual reality-based cognitive remediation therapy.

significant differences between the VR-CRT and virtual reality control groups in the total number of medications at any timepoint, and medication status (type and dosage) remained unchanged in 49 (89%) participants from baseline to endpoint (week 5).

Two participants in the VR-CRT group discontinued the intervention due to exacerbation of depressive symptoms, whereas no participants discontinued in the virtual reality control group. Both participants who discontinued in the VR-CRT group reported that the depressive symptoms exacerbation was related to external personal circumstances and not to the intervention. One participant in the virtual reality control group had hypomanic symptom exacerbation, resulting in omission of the final session. No other participants required treatment changes or dose reductions, and no other serious adverse events were observed (table 4). The most frequent adverse events in both groups were virtual reality-related symptoms, including mild cybersickness (four [13%] of 30 in the VR-CRT group and six [22%] of 27 in the virtual reality control group), eye strain (six [20%] and five [19%]), and mild anxiety or discomfort during the tasks (two [7%] and one [4%]) but none led to treatment changes or discontinuation (table 4).

	Baseline, mean (SD)	Treatment completion (week 5)*				Follow-up (week 17)†			
		Mean (SD)	Treatment effect (95% CI)	Unadjusted p value (adjusted p value)	*d*	Mean (SD)	Treatment effect (95% CI)	Unadjusted p value (adjusted p value)	*d*
Primary outcome									
CAVIR global cognitive composite score	..	..	0·98 (0·65–1·32)	<0·0001	1·55	..	0·91 (0·61–1·21)	<0·0001	1·53
VR-CRT Z score	–0·8 (0·7)	0·7 (0·9)	..	..	..	0·8 (0·7)	..	..	..
Virtual reality control Z score	–0·6 (0·9)	–0·2 (0·9)	..	..	..	–0·0 (1·0)	..	..	..
Secondary neuropsychological outcome									
Verbal learning and memory domain score (RAVLT)	..	..	0·66 (0·35–0·97)	<0·0001 (0·0002)‡	0·99	..	0·67 (0·29–1·05)	0·0009 (0·0013)‡	0·76
VR-CRT Z score	–0·6 (1·2)	0·4 (0·7)	..	..	..	0·5 (0·8)	..	..	..
Virtual reality control Z score	–0·3 (1·2)	–0·2 (1·1)	..	..	..	–0·2 (1·0)	..	..	..
Secondary functional outcome§									
AMPS ADL process ability Z score	..	..	0·57 (0·14–1·00)	0·0088 (0·011)‡	0·80	..	..	..	..
VR-CRT Z score	–0·8 (0·7)	–0·1 (0·8)	..	..	..	..	..	..	..
Virtual reality control Z score	–0·8 (0·7)	–0·7 (0·8)	..	..	..	..	..	..	..
AMPS ADL process ability logit score	..	..	0·23 (0·06–0·40)	0·0088 (0·011)‡	0·80	..	..	..	..
VR-CRT logit score	1·3 (0·3)	1·5 (0·3)	..	..	..	..	..	..	..
Virtual reality control logit score	1·3 (0·2)	1·3 (0·3)	..	..	..	..	..	..	..

Adjusted p values in parentheses are based on the Benjamini-Hochberg procedure. ADL=activities of daily living. AMPS=Assessment of Motor and Process Skills. CAVIR=Cognition Assessment in Virtual Reality. RAVLT=Rey Auditory Verbal Learning Test. VR-CRT=virtual reality-based cognitive remediation therapy. *Missing CAVIR and neuropsychological data at treatment completion (week 5) for three participants in the VR-CRT group and four in the virtual reality control group; missing AMPS data at treatment completion (week 5) for seven in the VR-CRT group and five in the virtual reality control group. †Additional missing CAVIR and neuropsychological data at follow-up (week 17) for two participants in the VR-CRT group and four in the virtual reality control group. ‡Adjusted p value ≤0·05. §AMPS ADL measures and treatment effects are reported in both Z scores and logit scores (log-odds probability units) derived from the assessment. Due to budgetary constraints, AMPS was only assessed at baseline and treatment completion. Also, four participants did not complete the AMPS at any assessment times, and data for this outcome were therefore analysed for only 30 participants in the VR-CRT group and 28 in the virtual reality control group with baseline data.

Table 2: **Primary and secondary outcomes in the VR-CRT group versus the virtual reality control group**

Discussion

To our knowledge, this is the first double-blind, randomised controlled trial to investigate the effect of VR-CRT versus a virtual reality control treatment on cognition and functioning in clinically stable patients with mood disorders or psychosis spectrum disorders. Consistent with the primary hypothesis, there was a significant large effect of VR-CRT on the primary virtual reality-based functional cognitive capacity outcome at treatment completion (week 5) and follow-up (week 17). Moderate treatment effects were also observed on both co-secondary outcomes, ADL ability and verbal learning and memory, which remained significant at follow-up for verbal learning and memory. For tertiary outcomes, there were significant moderate treatment effects on global neuropsychological performance and interview-based functioning at treatment completion and follow-up. In the VR-CRT group, 28 (93%) participants completed treatment per protocol, and participants reported high treatment tolerability and satisfaction.

The findings are clinically important, given that meta-analyses of CRT in people with mood disorders report only small-to-moderate cognitive benefits and no significant effects on functioning.[12,13] Indeed, only one other proof-of-concept CRT trial in people with bipolar disorder showed a significant effect on functioning.[27] Although CRT is more established in psychosis spectrum disorders, recent meta-analyses show only moderate effects on cognition and small effects on functioning.[10,11] These limitations highlight the need for new CRT approaches that both strengthen cognitive gains and improve the bridging to functioning.[8,11] The significant treatment effects on ADL ability and interview-based functioning shown in our study support evidence in people with schizophrenia that integrating CRT with more direct psychosocial rehabilitation and functional skill training is important for bolstering the transfer of cognitive gains to functioning.[10] Our results also converge with findings that functional remediation, an intervention emphasising real-world skill training, improves functioning in people with bipolar disorder.[28] The virtual reality platform likely contributed substantially to the observed cognitive and functional improvements. The training integrated elements of psychosocial rehabilitation and functional remediation, including ADL and vocational skill exercises, within simulations delivered through relatively affordable virtual reality hardware (approximately €300). Practising cognitive strategies in realistic, engaging, and safe simulations might help reduce avoidance of challenging real-life activities, which could be particularly relevant for individuals with mood disorders who often underestimate their cognitive abilities.[29] This negative bias can impede engagement in cognitively demanding tasks that would otherwise enhance skills. Consistent with this interpretation, participants in the VR-CRT group completed a high proportion of the real-world home assignments (approximately 75%), suggesting that virtual reality training helped enhance confidence in managing cognitively challenging tasks. These findings align with the theory that training in immersive virtual reality positively affects learning and self-efficacy by providing an increased feeling of agency.[18] They also corroborate preliminary

	Treatment completion (week 5)*			Follow-up (week 17)†		
	Treatment effect (95% CI)	Unadjusted p value (adjusted p value)	*d*	Treatment effect (95% CI)	Unadjusted p value (adjusted p value)	*d*
CAVIR subtask						
Task 1: verbal learning and memory	0·44 (–0·28 to 1·17)	0·23 (0·32)	0·27	0·21 (–0·40 to 0·82)	0·49 (0·55)	0·10
Task 2: executive functions	0·14 (–0·37 to 0·65)	0·58 (0·63)	0·09	0·18 (–0·32 to 0·68)	0·47 (0·54)	0·14
Task 3: processing speed	2·47 (1·81 to 3·14)	<0·0001 (<0·0001)‡	1·90	2·20 (1·49 to 2·91)	<0·0001 (<0·0001)‡	1·57
Task 4: working memory	0·85 (0·30 to 1·41)	0·0034 (0·021)‡	0·87	0·79 (0·26 to 1·32)	0·0042 (0·023)‡	0·82
Task 5: sustained attention	0·70 (0·07 to 1·33)	0·031 (0·084)	0·62	1·06 (0·43 to 1·70)	0·0015 (0·012)‡	0·98
Neuropsychological performance						
Executive functions domain score	0·16 (–0·41 to 0·10)	0·22 (0·32)	0·35	0·18 (–0·44 to 0·08)	0·18 (0·28)	0·32
Processing speed domain score	0·61 (–0·14 to 1·08)	0·012 (0·049)‡	0·77	0·40 (–0·10 to 0·90)	0·12 (0·22)	0·52
Working memory domain score	0·37 (0·07 to 0·68)	0·017 (0·050)‡	0·68	0·26 (–0·13 to 0·66)	0·19 (0·29)	0·42
Attention domain score	0·13 (–0·12 to 0·38)	0·29 (0·38)	0·45	0·25 (–0·10 to 0·60)	0·16 (0·26)	0·51
Global neuropsychological composite score	0·35 (0·17 to 0·53)	0·0002 (0·0023)‡	1·14	0·31 (0·07 to 0·55)	0·013 (0·046)‡	0·77
Functional measures						
FAST total score	–5·65 (–9·72 to –1·57)	0·0076 (0·034)‡	0·73	–3·59 (–8·23 to 1·05)	0·13 (0·23)	0·42
Autonomy	–1·07 (–2·09 to –0·05)	0·040 (0·10)	0·58	–1·19 (–2·26 to –0·12)	0·030 (0·085)	0·55
Occupational functioning	0·80 (–1·11 to 2·72)	0·40 (0·47)	0·27	1·12 (–0·90 to 3·14)	0·27 (0·37)	0·37
Cognitive functioning	–3·18 (–4·40 to –1·95)	<0·0001 (<0·0001)‡	1·46	–2·14 (–3·56 to –0·73)	0·0039 (0·022)‡	0·83
Financial issues	–0·50 (–1·08 to –0·09)	0·092 (0·19)	0·36	–0·45 (–1·04 to 0·15)	0·13 (0·23)	0·24
Interpersonal relationships	–1·41 (–2·82 to 0·00)	0·050 (0·11)	0·49	–0·71 (–2·26 to 0·85)	0·37 (0·44)	0·25
Leisure time	–0·28 (–0·81 to 0·25)	0·29 (0·38)	0·13	–0·07 (–0·71 to 0·57)	0·83 (0·85)	0·08
UPSA-B total score	0·45 (–4·02 to 3·13)	0·80 (0·84)	0·09	0·06 (–4·57 to 4·68)	0·98 (0·98)	0·12
Questionnaires						
Subjective cognition, COBRA total score	–2·64 (–5·24 to –0·04)	0·047 (0·11)	0·62	–1·75 (–5·07 to –1·57)	0·29 (0·37)	0·39
Subjective cognition, CODEL total score	–3·16 (–5·78 to –0·54)	0·019 (0·058)	0·73	–2·93 (–6·57 to 0·70)	0·11 (0·22)	0·56

Adjusted p values in parentheses based on the Benjamini–Hochberg procedure. CAVIR=Cognition Assessment in Virtual Reality. COBRA=Cognitive Complaints in Bipolar Disorder Rating Assessment. CODEL=Cognitive Difficulties in Everyday Life. FAST=Functioning Assessment Short Test. UPSA-B=Brief Performance-Based Skills Assessment of the University of California, San Diego. VR-CRT=virtual reality-based cognitive remediation therapy. *Missing CAVIR, neuropsychological, COBRA, and CODEL data at treatment completion (week 5) for three participants in the VR-CRT group and four in the virtual reality control group; missing FAST data at treatment completion (week 5) for four participants in the VR-CRT group and five in the virtual reality control group; missing UPSA-B data at treatment completion (week 5) for eight in the VR-CRT group and eight in the virtual reality control group. †Additional missing CAVIR, neuropsychological, COBRA, and CODEL data at follow-up (week 17) for two participants in the VR-CRT group and four in the virtual reality control group; additional missing CAVIR subtask 5 data at follow-up (week 17) for two participants in the VR-CRT group and one in the virtual reality control group due to technical issues; additional missing FAST data at follow-up (week 17) for two participants in the VR-CRT group and four in the virtual reality control group; additional missing UPSA-B data at follow-up (week 17) for three participants in the VR-CRT group and five in the virtual reality control group. ‡Adjusted p≤0·05.

Table 3: **Tertiary outcomes in the VR-CRT group versus the virtual reality control group**

evidence that virtual reality-based interventions can improve cognitive and functional skills in populations with psychiatric disorders,[19,20,22] especially if the virtual reality training focuses on realistic ADL scenarios.[19] Indeed, participants received automated strategy guidance and practised these directly while immersed in realistic ADL-focused virtual reality scenarios, a novelty of the current trial (appendix pp 1–5), which likely helped enhance the transfer of strategy use to daily-life situations. Although a significant moderate treatment effect was observed on the ADL process ability score, this did not reach the clinical relevance threshold (0·2 *vs* ≥0·3 logits),[24] although the confidence interval did encompass a clinically relevant difference (table 2). This might be because the tasks trained in virtual reality were not fully aligned with the spectrum of ADL tasks addressed with the AMPS (eg, cleaning). Nevertheless, the treatment-related 0·2 logits increase (from 1·3 to 1·5) in ADL process ability from baseline to week 5 suggests that participants were lifted out of the defined risk zone for requiring assistance with ADL tasks, highlighting the promising potential of VR-CRT for improving daily-life functioning. However, the AMPS was not re-assessed at the week 17 follow-up due to financial constraints, rendering the durability of this effect uncertain. On the FAST, a significant effect was observed at treatment completion, with only the large effect on the cognition subscale retained at follow-up, suggesting that VR-CRT produced durable improvements in the FAST cognition domain but did not normalise global functioning. Importantly, functional impairments in individuals with mental health conditions stem from multifactorial causes beyond cognition alone.[8] Given this complexity, we consider it promising that short-term VR-CRT alone showed significant effects for ADL performance and interviewer-rated functioning. However, achieving more substantial and lasting functional improvement likely requires longer treatment or more comprehensive biopsychosocial interventions.[8,12] Pending further investigation, VR-CRT could potentially serve as an accessible and scalable therapeutic component within multimodal treatment aimed at improving functioning in individuals with mood disorders or psychosis spectrum disorders.

	VR-CRT group (n=30)	Virtual reality control group (n=27)
Psychiatric symptom exacerbation during treatment		
Depressive symptom exacerbation	2 (7%)	0
Hypomanic symptom exacerbation	0	1 (4%)
Positive symptom exacerbation	0	0
Negative symptom exacerbation	0	0
Discontinued intervention due to symptom exacerbation	2 (7%)	0
Virtual reality-related symptoms during treatment		
Mild cybersickness (nausea, dizziness, or headache)	4 (13%)	6 (22%)
Eye strain	6 (20%)	5 (19%)
Mild anxiety or discomfort during tasks	2 (7%)	1 (4%)
Discontinued intervention due to virtual reality-related symptoms	0	0

Data are n (%). Data are only shown for events that occurred during the active treatment period. VR-CRT=virtual reality cognitive remediation therapy.

Table 4: **Adverse events**

In contrast to previous virtual reality cognition trials,[19,20] this study included a control group exposed to virtual reality, including the same daily-life scenarios as the intervention group but without the training elements.[24] The control group was slightly less exposed to virtual reality than the treatment group (mean 7·2 h *vs* 10·7 h), which was due to practical and ethical considerations. This was deemed the best possible trade-off to ensure that participants in the control group were masked and exposed to virtual reality without losing them to attrition, as they did not receive any real cognitive training. However, as the treatment group had greater exposure to virtual reality, we cannot exclude the possibility that the large effect on the primary outcome was related to greater intensity, habituation to virtual reality, or teaching the test in the VR-CRT group rather than improvements in functional cognitive capacity per se. Nevertheless, this seems unlikely, because the CAVIR and the virtual reality training scenarios differed substantially (appendix p 19). Hence, the virtual reality training provided little advantage for completing CAVIR (administered in alternate versions) unless participants actively employed learned CRT-strategies such as strategically encoding kitchen items. Importantly, the additional treatment-related improvements in neuropsychological performance, ADL ability, and FAST corroborate an active use of strategies in the treatment group that effectively transferred beyond the virtual reality environment and were useful in daily life. This aligns with the growing recognition that strengthening strategy use across cognitive domains is a core component for increasing cognitive and functional benefits of CRT.[11] The observed improvements likely reflect enhanced recruitment of prefrontal brain regions through the strong emphasis on training strategies to improve memory and problem-solving. Indeed, our previous randomised controlled trial showed that similar strategy training increased dorsal prefrontal activation during memory tasks.[30]

Strengths of the trial include preregistration, an active virtual reality control condition, double-blinding procedures, measurements of transfer to functioning, follow-up assessment, and intention-to-treat analyses. The masking was successfully kept in the virtual reality control group but only partially kept in the VR-CRT group, as indicated by nine (34%) and 18 (64%) correctly guessing their treatment allocation in these groups, respectively. The limited success of the masking in the VR-CRT group could have inflated treatment effects, particularly for tertiary outcomes involving self-reporting, although treatment adherence and satisfaction were equally high in both groups. Since the primary cognitive outcome was virtual reality-based, it could be argued that the observed effects primarily reflect near-transfer from virtual reality-based training. However, this seems unlikely, as we also observed robust treatment-related improvements in standard neuropsychological measures and functional outcomes, suggesting broader transfer beyond the virtual reality environment. Another limitation was the modest sample size. However, the study was adequately powered for the primary outcome[24] and post-hoc power calculations showed sufficient power (≥80%) for the secondary outcomes and global neuropsychological performance (appendix p 33). Although the inclusion of both participants with mood disorders and participants with psychosis spectrum disorders allowed for a preliminary transdiagnostic perspective, the study was underpowered to assess diagnostic subgroups separately. Nonetheless, significant treatment effects on primary and secondary outcomes were observed in both subgroups, suggesting transdiagnostic potential. The relatively young, symptomatically stable sample recruited primarily within the Capital Region of Denmark—with few hospital admissions but moderate baseline impairment—might partly explain the treatment effects and limit the generalisability of the results. Data on race and ethnicity were not systematically collected because the recruitment setting was relatively homogeneous; approximately 95% of participants were White, reflecting local population characteristics and the requirement for Danish language proficiency. Future studies are therefore warranted to investigate VR-CRT in larger multicentre trials, including older, more symptomatic, ethnically diverse, and comorbid populations with more severe illness trajectories. Other limitations include the short follow-up period and possible medication effects; however, medication status was unchanged between baseline and week 5 in 49 (89%) participants, tested at endpoint, with no group differences in total medication load at any timepoint (data not shown).

In conclusion, short-term, intensive VR-CRT versus virtual reality control had a significant, large, durable effect on virtual reality-assessed functional cognitive capacity in individuals with mood disorders or psychosis spectrum disorders, which also transferred to neuropsychological performance and functioning with moderate effects. The intervention had a high completion rate and acceptability. Future studies should investigate the efficacy and cost-effectiveness of VR-CRT in larger, diagnosis-specific samples with long-term follow-up (≥6 months), assess objective functional outcomes (eg, occupational status and

health-care utilisation), examine predictors of treatment response to support personalisation (eg, diagnosis, baseline cognition, age, and neural correlates), evaluate the effect of session attendance and home training duration, compare VR-CRT with traditional CRT, and explore integration of technologies such as biofeedback-driven difficulty modulation and artificial intelligence-based task personalisation. The perspective is a VR-CRT with transdiagnostic potential to bolster treatment engagement, cognitive improvements, and transfer of cognitive gains to real-world functioning.

Contributors

AEJ was responsible for data curation, formal analysis, investigation, project administration, software development, visualisation, and drafting the original manuscript, as well as reviewing and editing the manuscript. AL contributed to software development and manuscript review and editing. MV contributed to methodology development, provision of resources, and manuscript review and editing. LBG contributed to the provision of resources and manuscript review and editing. MN contributed to the provision of resources and manuscript review and editing. CFB contributed to project administration and manuscript review and editing. CvB contributed to data curation, investigation, methodology, provision of resources, and manuscript review and editing. GM contributed to methodology development, provision of resources, supervision, and manuscript review and editing. EJW contributed to data curation, investigation, methodology, supervision, provision of resources, and manuscript review and editing. KWM was responsible for conceptualisation and funding acquisition, and contributed to data curation, formal analysis, investigation, methodology, project administration, provision of resources, software development, supervision, validation, visualisation, drafting the original manuscript, and manuscript review and editing. All authors had full access to all data in the study, including the raw data, and had final responsibility for the decision to submit for publication. All authors had access to the final dataset, and the data were accessed and verified by AEJ and KWM.

Declaration of interests

KWM has received honoraria from Lundbeck, Angelini, Gedeon Richter, and Janssen-Cilag and funding from the European Research Council, Innovations Fund Denmark, Independent Research Fund Denmark, Svend Andersen Foundation, and KID Foundation within the past 3 years. MV has received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Lundbeck, Eli Lilly, and Johnson & Johnson; received support for attending meetings or travel from Johnson & Johnson; participated on a data safety monitoring board or advisory board for Johnson & Johnson; and served as chair for the Danish Psychiatric Society Research Chapter (unpaid), the Danish Chapter International Society for Bipolar Disorders (unpaid), and Member of European College of Neuropsychopharmacology (ECNP)'s Bipolar Network and ECNP's Poster Board (unpaid) all within the past 3 years. LBG has received payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events from Lundbeck, Heka-VR, and the mental health services in the Capital Region of Denmark for providing specialist level training in adult psychiatry and teaching a cognitive behavioural therapy course; received consulting fees from Boehringer Ingelheim; and received funding from the Independent Research Fund Denmark, Lundbeck Foundation, Danish Life Science Strategy, Danish Parliament budget law, Sofus Carl Emil Friis and Wife Foundation, and EIT Health Grant all within the past 3 years. CvB has received royalties or licences from Munksgaard Publishing for writing textbooks within health-care science within the past 3 years. Munksgaard Publishing had no role related to the project, including publications. EJW has received funding from the Oak Foundation (grant number OFIL-24–07); received royalties or licences from Munksgaard Publishing for writing textbooks within health-care science; and served on the REHPA (Knowledge Centre for Rehabilitation and Palliation) advisory board all within the past 3 years. Munksgaard Publishing and REHPA had no role in the project, including publications. AEJ has received honoraria from Lundbeck within the past 3 years. All other authors declare no competing interests.

Data sharing

Although full open access is restricted due to General Data Protection Regulation, anonymised participant data may be shared on request to researchers who provide a methodologically sound proposal, beginning 6 months after publication. Study protocols and statistical analysis plans will also be available. Proposals should be directed to kamilla.woznica.miskowiak@regionh.dk to gain access and data requestors will need to sign a data access agreement.

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