Schizophrenia Research: Cognition 36 (2024) 100305

Contents lists available at ScienceDirect

Schizophrenia Research: Cognition

journal homepage: www.elsevier.com/locate/scog

Research Paper

Using virtual reality to improve verbal episodic memory in schizophrenia: A proof-of-concept trial

Bryce J.M. Bogie [a,b,c], Chelsea Noël [d], Feng Gu [c], Sébastien Nadeau [f], Cecelia Shvetz [c,e], Hassan Khan [g], Marie-Christine Rivard [f], Stéphane Bouchard [f,h,i], Martin Lepage [j,k], Synthia Guimond [b,c,e,f,l,*]

[a] MD/PhD Program, Faculty of Medicine, University of Ottawa, Ottawa, ON, Canada
[b] Department of Cellular and Molecular Medicine, Faculty of Medicine, University of Ottawa, Ottawa, ON, Canada
[c] The Royal's Institute of Mental Health Research, Royal Ottawa Mental Health Centre, Ottawa, ON, Canada
[d] Department of Psychology, Lakehead University, Thunder Bay, ON, Canada
[e] Department of Neuroscience, Carleton University, Ottawa, ON, Canada
[f] Department of Psychoeducation and Psychology, Université du Québec en Outaouais, Gatineau, QC, Canada
[g] School of Epidemiology and Public Health, University of Ottawa, Ottawa, ON, Canada
[h] Centre de recherche, Centre Intégré de Santé et de Services Sociaux de l'Outaouais, Gatineau, QC, Canada
[i] School of Psychology, University of Ottawa, Ottawa, ON, Canada
[j] Douglas Research Centre, Montréal, QC, Canada
[k] Department of Psychiatry, McGill University, Montréal, QC, Canada
[l] Department of Psychiatry, University of Ottawa, Ottawa, ON, Canada

A R T I C L E I N F O

Keywords:
Cognitive remediation therapy
Ecological treatment
Episodic memory
Semantic encoding
Schizophrenia
Verbal memory
Virtual reality

A B S T R A C T

Background: Schizophrenia is associated with impairments in verbal episodic memory. Strategy for Semantic Association Memory (SESAME) training represents a promising cognitive remediation program to improve verbal episodic memory. Virtual reality (VR) may be a novel tool to increase the ecological validity and transfer of learned skills of traditional cognitive remediation programs. The present proof-of-concept study aimed to assess the feasibility, acceptability, and preliminary efficacy of a VR-based cognitive remediation module inspired by SESAME principles to improve the use of verbal episodic memory strategies in schizophrenia.

Methods: Thirty individuals with schizophrenia/schizoaffective disorder completed this study. Participants were randomized to either a VR-based verbal episodic memory training condition inspired by SESAME principles (intervention group) or an active control condition (control group). In the training condition, a coach taught semantic encoding strategies (active rehearsal and semantic clustering) to help participants remember restaurant orders in VR. In the active control condition, participants completed visuospatial puzzles in VR. Attrition rate, participant experience ratings, and cybersickness questionnaires were used to assess feasibility and acceptability. Trial 1 of the Hopkins Verbal Learning Test – Revised was administered pre- and post-intervention to assess preliminary efficacy.

Results: Feasibility was demonstrated by a low attrition rate (5.88 %), and acceptability was demonstrated by limited cybersickness and high levels of enjoyment. Although the increase in the number of semantic clusters used following the module did not reach conventional levels of statistical significance in the intervention group, it demonstrated a notable trend with a medium effect size ($t = 1.48, p = 0.15, d = 0.54$), in contrast to the control group where it remained stable ($t = 0.36$, $p = 0.72$, $d = 0.13$). These findings were similar for the semantic clustering ratio in the intervention ($t = 1.61$, $p = 0.12$, $d = 0.59$) and control ($t = 0.36$, $p = 0.72$, $d = 0.13$) groups. There was no significant change in the number of recalled words in either group following VR immersion.

Discussion: This VR intervention was feasible, acceptable, and may be useful for improving the use of semantic encoding strategies. These findings support the use of more ecological approaches for the treatment of cognitive impairments in schizophrenia, such as VR-based cognitive remediation.

* Corresponding author at: 1145 Carling Ave, Ottawa, ON K1Z 7K4, Canada.
E-mail addresses: bryce.bogie@uottawa.ca (B.J.M. Bogie), synthia.guimond@uqo.ca, synthia.guimond@theroyal.ca (S. Guimond).

https://doi.org/10.1016/j.scog.2024.100305
Received 19 December 2023; Received in revised form 13 February 2024; Accepted 26 February 2024

1. Introduction

Cognitive performance significantly impacts functional outcomes in individuals with schizophrenia (SZ; Alptekin et al., 2005). One of the most common cognitive impairments implicated in SZ is verbal episodic memory (Bogie et al., 2023; Cirillo and Seidman, 2003; Guimond et al., 2016; Guo et al., 2019). Impairments in verbal episodic memory are a core feature of SZ during both the acute and non-acute phases of the illness, suggesting that this cognitive domain may represent an important target for treatment outcomes (Bogie et al., 2023; Molina and Tsuang, 2020). However, current pharmacological treatments have shown limited efficacy at improving the cognitive symptoms of SZ (Keefe et al., 2013; Tsapakis et al., 2015). There is therefore a need for improved non-pharmacological interventions to supplement current pharmacological treatments (Bowie et al., 2020; Harvey et al., 2019).

Cognitive remediation (CR) is the preferred treatment method for improving cognitive functioning in SZ (Medalia and Erlich, 2017; Vita et al., 2021). Although CR can help improve some of the cognitive symptoms of SZ, these interventions have limited generalizability and require long durations of treatment (Lejeune et al., 2021; Seccomandi et al., 2020; McCleery and Nuechterlein, 2019; Vita et al., 2021). Moreover, traditional CR interventions are often associated with high attrition rates and variable levels of transfer to real-world situations, suggesting that current approaches may not meet patients' needs nor preferences (Dickinson et al., 2010; Gomar et al., 2015; Wykes et al., 2011).

Virtual reality (VR) is an innovative tool that can help overcome some of the limitations of CR interventions (Park et al., 2019; Rus-Calafell et al., 2018; Schroeder et al., 2022). VR is an immersive experience which simulates three-dimensional environments, allowing for the development of novel treatments with increased ecological validity (Campbell et al., 2009; Freeman, 2008; O'Connor et al., 2016). Research has shown that immersive VR programs are superior to non-immersive approaches at promoting the transfer of learned skills to real-world situations (Dobrowolski et al., 2021; Wu et al., 2020). These findings highlight the potential therapeutic utility of immersive VR technology for the treatment of mental health conditions. Preliminary evidence has also demonstrated that CR interventions delivered using VR can lead to improvements in positive symptoms, attention, memory, spatial learning, and social skills in SZ (du Sert et al., 2018; Rus-Calafell et al., 2014; Spieker et al., 2012; Tsang and Man, 2013). Furthermore, research suggests that individuals with SZ perceive VR-based CR as enjoyable and engaging (Chan et al., 2010; Rus-Calafell et al., 2018; Schroeder et al., 2022). Hence, this technology may represent a more effective approach to the delivery of CR for individuals with SZ (Rothbaum et al., 1995; Rus-Calafell et al., 2018). Further investigation is needed to assess the utility of VR-based CR approaches for improving *specific* domains of cognition in individuals with SZ, such as verbal episodic memory.

The current proof-of-concept study employed a randomized controlled design with intervention and active control conditions. The aim was to assess the feasibility, acceptability, and preliminary efficacy of a VR-based CR module designed to improve the use of verbal episodic memory strategies in SZ compared to a VR-based control condition. We hypothesized that the VR-based CR module would be associated with a low attrition rate, positive feedback from participants, and minimal adverse side effects, demonstrating the overall feasibility and acceptability of the intervention. We further hypothesized that the module would improve the use of semantic clustering strategies and verbal episodic memory performance at post- versus pre-intervention assessments.

2. Methods

This research was approved by the Research Ethics Board at the Royal Ottawa Mental Health Centre (ROMHC; Ottawa, Canada) and was pre-registered on ClinicalTrials.gov (identifier: https://clinicaltrials.gov/study/NCT04251195?term=nct04251195&rank=1).

2.1. Participants

Participants were recruited from outpatient services in the Ottawa region affiliated with the ROMHC. Inclusion criteria were: (1) an established diagnosis of SZ or schizoaffective disorder (hereinafter considered together as "SZ"), confirmed by the Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1998); (2) aged 20–60 years; (3) a score $\leq$ 95 on the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987); (4) a stable medication regimen for at least one month prior to study participation; and (5) the ability to read and speak fluent English. Exclusion criteria were: (1) uncorrected vision problems; (2) a significant comorbid medical disorder that may produce cognitive impairment; (3) history of alcohol and/or substance use disorder within the past three months; (4) lifetime history of migraines, seizures, epilepsy, or cybersickness; and (5) decisional incapacity requiring a guardian. All participants provided written informed consent prior to participation.

2.2. Study design

The study followed a single-blind (participants blind to condition), parallel groups, randomized controlled trial design. Participants were randomized in a 1:1 ratio to either the intervention or active control group according to a predetermined randomization sequence. Both the intervention and active control conditions were delivered in VR. We chose to deliver the active control condition in VR to ensure that: (1) participants were blind to condition; and (2) any differences observed following the VR session were not simply due to the experience of VR immersion alone.

2.3. Measures

2.3.1. Clinical assessments

2.3.1.1. Mini International Neuropsychiatric Interview. The MINI was used to confirm current and past psychiatric diagnoses (Sheehan et al., 1998).

2.3.1.2. Positive and Negative Syndrome Scale. The severity of psychosis-related symptoms was evaluated using the PANSS (Kay et al., 1987; see Supplementary Material 1).

2.3.2. VR feasibility assessments

The primary measure of feasibility was the attrition rate (proportion of enrolled participants who failed to complete the trial).

2.3.2.1. Exclusion VR Criteria Questionnaire. The Exclusion VR Criteria Questionnaire (EVCQ), a 4-item questionnaire developed by our research team to assess participants' eligibility to use the VR equipment on the day of participation, was administered to examine the presence and severity of any physiological discomfort after trying the VR technology following a one-minute trial. Participants who experienced severe physiological discomfort following one-minute of VR immersion were terminated from the trial. The EVCQ was also used as a primary measure of feasibility. Further details about the EVCQ can be found in Supplementary Material 1.

2.3.3. VR acceptability assessments

The following two assessments were the primary measures of acceptability.

2.3.3.1. Simulator Sickness Questionnaire. The Simulator Sickness Questionnaire (SSQ) was administered to both groups after the full VR session to assess their experience with VR immersion (Kennedy et al., 1993).

2.3.3.2. VR Experience Questionnaire. To further assess the acceptability of the VR sessions, our research team designed a 5-item VR Experience Questionnaire (VEQ). The VEQ was administered to both groups after the full VR session.

Further details about the VR acceptability assessments can be found in Supplementary Material 1.

2.3.4. Assessment of preliminary efficacy

The primary measure of the preliminary efficacy of the VR-based CR module was the Hopkins Verbal Learning Test – Revised (HVLT; Benedict et al., 1998). The HVLT was administered to both groups before and after the VR session (different version forms were used at each time point). Participants were assessed on one trial of immediate recall per version form to avoid interference. The post-intervention assessment was administered within five minutes of the VR session, allowing time for participants to readapt to reality following the VR immersion.

The number and ratio of semantic clusters were used as primary outcome measures of preliminary efficacy. The raw total number of recalled words was used as a secondary outcome measure (see Supplementary Material 1).

2.3.5. Trial design outcomes

Participant enrollment rate was used as a general marker of trial design feasibility. This variable was defined as the proportion of invited participants who enrolled in the trial, all of whom previously expressed interest in participating in research and met basic pre-screening eligibility criteria.

2.3.5.1. Blinding question. At the conclusion of the study, participants rated the likelihood with which they believed they were assigned to the intervention group (see Supplementary Material 1).

2.4. VR Interventions

Both VR conditions were delivered using an Oculus Rift head mounted display, handheld controllers, and sensors.

2.4.1. Intervention group

The CR training followed the Strategy for Semantic Association Memory (SESAME) training principles (Guimond et al., 2018). The training coached participants how to use semantic information to organize items (i.e., semantic clustering), followed by cues to apply these strategies within a restaurant order-taking memory task. The training encouraged participants to use the semantic clustering strategy in combination with active rehearsal strategies. The training manual is available in Supplementary Material 2.

Following the CR training, participants in the intervention group completed a 15-minute verbal episodic memory task in a three-dimensional VR restaurant environment, developed by our research team (Fig. 1). Participants played the role of a waiter/waitress. While using the VR equipment, participants walked around the virtual restaurant environment and took “orders” from customers. The avatars at each table verbalized their orders aloud. Participants were instructed to remember the orders using semantic clustering and active rehearsal, walk to the cashier in the VR environment, and verbally recall the items. Outside of the VR environment, the experimenter interacted with the participant and tracked their progress. If the participant did not correctly recall all items from the order, the experimenter instructed

Fig. 1. Images from the virtual reality environment delivered to the intervention group.
Note. The participant took on the role of a waiter/waitress in this restaurant environment. Using the handheld controllers, the participant walked to a pre-determined table (e.g., top right image), listened to the customers' orders, and walked back to the cashier (bottom right image) to recall the orders from memory. Participants were encouraged to engage the semantic encoding strategies coached during the CR training throughout this task.

them to return to the table and repeat the level. Participants proceeded to the next level once all items were correctly recalled.

The verbal episodic memory task included four levels (i.e., tables), including a total of ten customers. Each table increased in the level of difficulty (i.e., number of customers at the table, number of items ordered, number of possible semantic categories). The VR session was considered complete after 15 minutes had elapsed or once the participant correctly recalled the orders from all four levels.

2.4.2. Control group

Participants in the control group played a 15-minute three-dimensional puzzle game in VR called "Cubism" (https://www.cubism-vr.com/). This game was moderately cognitively challenging and did not require the use of verbal memory processes (Fig. 2). Instead, the game engaged spatial reasoning processes. Participants were tasked with assembling progressively more complex puzzles using colorful blocks (see Fig. 2). Participants manipulated the blocks using the handheld controllers. No CR was administered in this condition; instead, the experimenter provided active encouragement throughout the session (see Supplementary Material 2). The session was considered complete after 15 minutes had elapsed.

2.5. Procedure

See Fig. 3 for a schematic summary of the study procedure. Participants were compensated CAD$30.00 for their participation.

2.6. Statistical analyses

Differences in age, years of education, symptom severity, and

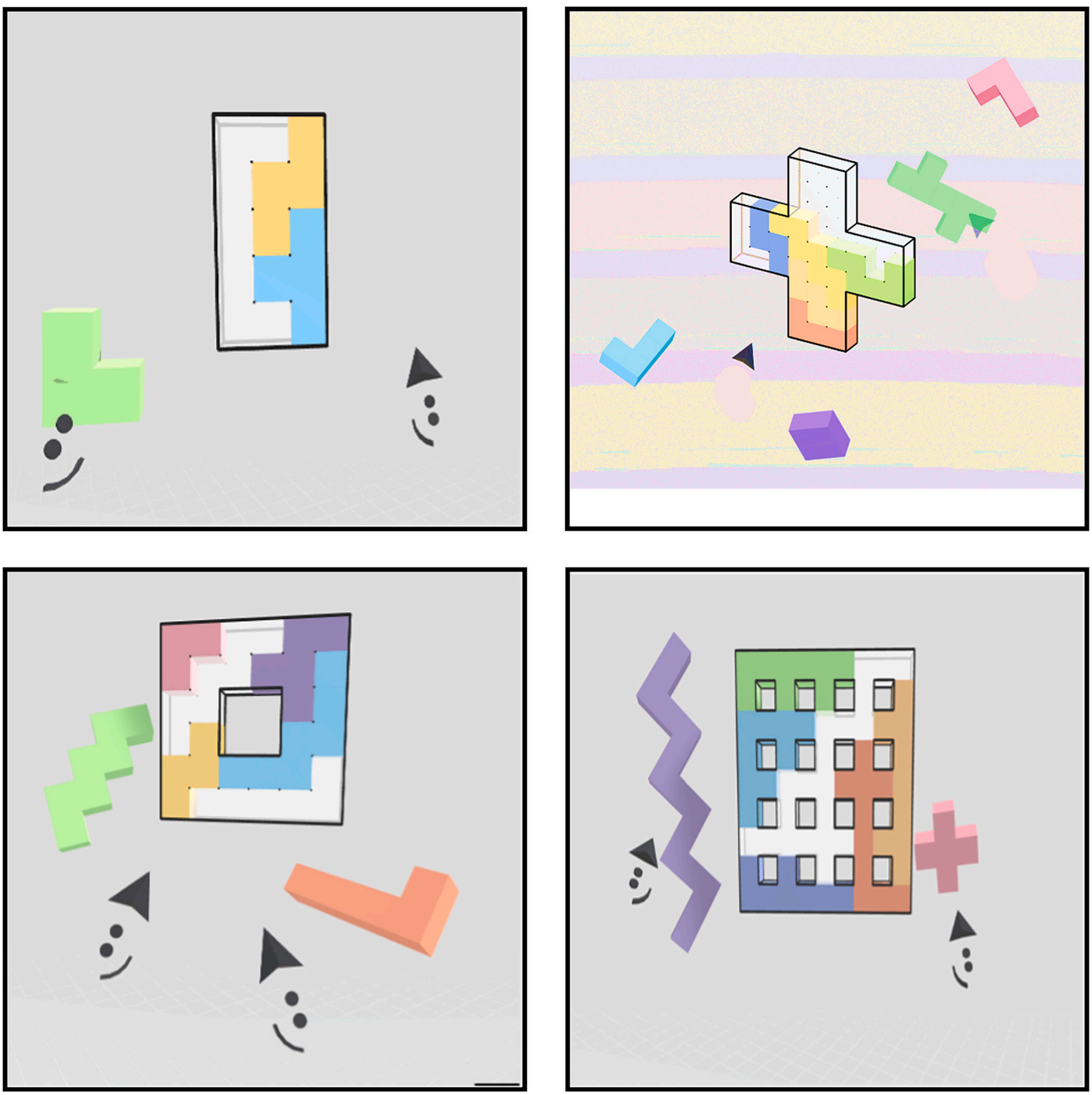


Fig. 2. Images from the virtual reality environment delivered to the control group.
Note. In each level, the participant used the handheld controllers to manually retrieve and manipulate colorful geometric shapes to complete a puzzle board. Each level was progressively more difficult than the previous level. The black arrowheads represent the participant's left and right hands. Images reproduced with permission from the owner of *Cubism*.

antipsychotic dosage (chlorpromazine equivalents, in mg) were compared between groups using *t*-tests. Difference in the distribution of sex between groups was compared using a Chi-squared test.

t-Tests were used to compare results from the SSQ, VEQ, and blinding question between groups. Changes in the use of semantic clustering strategies and overall verbal episodic memory performance were analyzed across time points within each group using *t*-tests due to the small sample size.

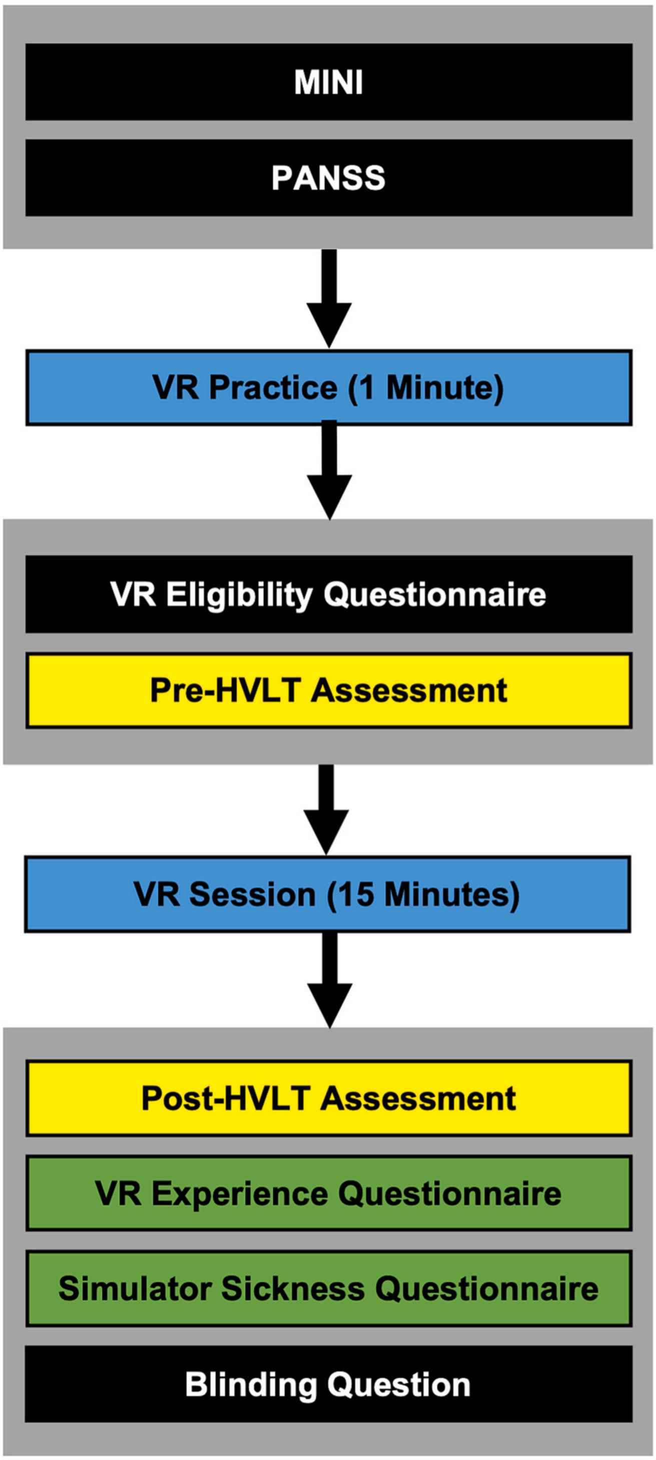


Fig. 3. Schematic summary of study procedures.
Note. The assessments surrounded by the gray boxes occurred outside of the VR environment.
Abbreviations: HVLT: Hopkins Verbal Learning Test – Revised; MINI: Mini International Neuropsychiatric Interview; PANSS: Positive and Negative Syndrome Scale; VR: virtual reality.

Cohen's *d* effect sizes were calculated to characterize the magnitude of change in the use of semantic clustering strategies and overall verbal episodic memory performance across time points. Given the small sample size, Cohen's *d* effect sizes were considered when drawing conclusions about preliminary efficacy.

Statistical significance was set at $p < 0.05$ and trending towards significance was set at $p < 0.15$. All analyses were performed in R (version 4.2.2).

3. Results

3.1. Demographic and clinical characteristics

The final sample comprised 30 participants equally divided between the two groups. Table 1 summarizes the demographic and clinical characteristics of the participants. The groups did not significantly differ in age (range: intervention = 24–48; control = 20–51), sex, years of education, psychosis-related symptom severity, nor dosage of antipsychotic medications.

3.2. Feasibility

A total of 34 participants were enrolled in this study, of which two were excluded due to reasons unrelated to the feasibility of the VR technology (current alcohol use disorder and distraction due to noise outside of the assessment room; both were assigned to the intervention group).

Two additional participants were excluded due to difficulties

Table 1
Demographic and clinical characteristics of the intervention ($n = 15$) and control ($n = 15$) groups.

	Intervention Group		Control Group		t/X^2	p
	Mean	SD	Mean	SD		
Demographics						
Age	36.60	7.58	34.07	11.13	0.73	0.47
Sex (Male/Female)	12M/3F		13M/2F		0.00	1.00
Years of Education	15.20	3.93	15.53	2.90	0.26	0.79
Clinical Characteristics						
PANSS Total Score	60.40	11.69	59.87	12.45	0.12	0.90
Current Medications						
Antipsychotic Dose[a]	198.93	543.78	302.77	844.24	0.40	0.69
Range[a]	0.00–2142.86		0.00–3333.33			
Co-morbid Diagnoses[b]						
Major Depressive Disorder (Recurrent)	$n = 4$		$n = 1$			
Suicide Behaviour Disorder	$n = 1$					
Panic Disorder	$n = 1$					
Agoraphobia	$n = 2$		$n = 1$			
Social Anxiety Disorder	$n = 2$					
Generalized Anxiety Disorder			$n = 2$			
Obsessive Compulsive Disorder	$n = 2$		$n = 3$			
Alcohol Use Disorder (Past Year)			$n = 1$			
Substance Use Disorder (Past Year)			$n = 1$			

Note. The two groups did not significantly differ in: age, sex, years of education, PANSS total score, nor antipsychotic dose.
Abbreviations: PANSS: Positive and Negative Syndrome Scale.
[a] Chlorpromazine (CPZ) equivalent (in mg).
[b] Co-morbid diagnoses confirmed through the Mini International Neuropsychiatric Interview.

experienced during VR immersion: (1) discomfort following the VR practice session (i.e., according to the EVCQ; control group); and (2) anxiety reported during the full VR session (intervention group). It is noted that the latter participant subsequently disclosed significant pre-appointment anxiety which almost caused them to postpone the appointment. This participant had also rescheduled this appointment once before due to significant anxiety. This corresponded to a low attrition rate of 5.88 %.

Of the 30 participants who were included in the final sample, two provided positive responses to the EVCQ question, *Are you feeling dizzy?* One participant reported that the dizziness was a result of VR immersion, while the other reported that it was unrelated. Follow-up questioning revealed that the level of dizziness was minimal, and both participants wanted to continue. Both participants were assigned to the intervention group.

3.3. Acceptability

The results of the SSQ and VEQ are presented in Table 2. Generally, participants reported low levels of cybersickness. While the intervention group showed increased sub-scale and total SSQ scores compared to the control group, these differences were not statistically significant. Per the VEQ, both groups judged the VR experience as highly enjoyable and realistic. Both groups also endorsed wanting to try the VR activity again and that they would recommend it to a friend. The total VEQ scores did not significantly differ between groups. The qualitative feedback was also mostly positive, with many respondents commenting that the VR immersion was fun and realistic (see Supplementary Material 3).

3.4. Preliminary efficacy

3.4.1. Number of semantic clusters

The mean number of semantic clusters used by the intervention and control groups across time points is presented in Fig. 4A. The intervention group showed a moderate increase in the mean number of semantic clusters used between time points. This change trended towards statistical significance ($t = 1.48$, $p = 0.15$, CI: −0.31, 1.91) and was associated with a medium effect size ($d = 0.54$). In comparison, participants in the control group did not show a significant nor trending significant change between time points ($t = 0.36$, $p = 0.72$, CI: −0.94, 1.34, $d = 0.13$).

3.4.2. Semantic clustering ratio

The mean semantic clustering ratios for the intervention and control groups across time points are presented in Fig. 4B. The intervention group showed a slight increase in the mean semantic clustering ratio between time points. Similar to the previous findings, this change trended towards statistical significance ($t = 1.61$, $p = 0.12$, CI: −0.03, 0.24) and corresponded to a medium effect size ($d = 0.59$). The control group similarly showed a slight increase in the mean semantic clustering ratio between time points, but this change was not statistically significant and was of small effect size ($t = 0.36$, $p = 0.72$, CI: = −0.12, 0.17, $d = 0.13$).

3.4.3. Raw total HVLT scores

The raw total HVLT scores for the intervention and control groups across time points are presented in Fig. 4C. The intervention group showed a slight increase in the raw total HVLT score across time points. However, this change was not statistically significant ($t = 0.36$, $p = 0.73$, CI: −0.95, 1.35). This difference corresponded to a small effect size ($d = 0.13$). In comparison, the control group showed a slight decrease in the total HVLT score between the time points. This change was similarly not statistically significant and reflected a small effect size ($t = -0.17$, $p = 0.86$, CI: −1.71, 1.44, $d = -0.06$).

Table 2
Acceptability of the virtual reality environments according to the intervention ($n = 15$) and control ($n = 15$) groups.

	Intervention Group		Control Group		*t*	*p*
	Mean	SD	Mean	SD		
SSQ						
Scaled Scores						
Sub-scale Scores						
Nausea Symptoms	20.35	24.15	13.99	12.42	0.91	0.38
Oculomotor Symptoms	19.20	20.03	17.18	16.57	0.30	0.77
Disorientation Symptoms	32.48	48.69	20.42	20.29	0.89	0.39
Total Score	18.20	22.74	14.21	10.21	0.62	0.54
Raw Scores						
Sub-scale Scores						
Nausea	4.07	3.06	3.60	1.59	0.52	0.61
Nausea (−Anxiety)	3.93	2.74	3.27	1.16	0.87	0.40
Oculomotor	2.40	3.18	2.00	1.89	0.42	0.68
Oculomotor (−Anxiety)	1.93	2.46	1.60	1.59	0.44	0.66
Total Scores						
Total Raw	4.87	6.08	3.80	2.73	0.62	0.54
Total Raw (−Anxiety)	4.27	5.11	3.07	2.37	0.83	0.42
VEQ						
Statement Scores						
1 – Enjoyment	4.80	0.41	4.60	0.63	–	–
2 – Realistic	4.27	0.70	3.67	1.00	–	–
3 – Try Again	4.53	0.64	4.40	0.91	–	–
4 – Recommend	4.33	0.72	4.33	0.90	–	–
Total Score	17.93	1.87	17.00	2.67	1.11	0.28

Note. The results of the SSQ are presented using two scoring methods: the traditional scaled scoring method (Kennedy et al., 1993) and the more recent method which accounts for anxiety symptoms (Bouchard et al., 2021; see Supplementary Material 1). Each item is rated on a 4-point Likert scale (anchors: *0 = Not At All, 1 = Mild, 2 = Moderate, 3 = Severe*). Possible (unscaled) scores on the SSQ range from 0 to 48, with higher scores representing stronger perceptions of cybersickness (Bimberg et al., 2020). Possible total scores on the VEQ range from 4 to 20 (response anchors: *1 = Strongly Disagree, 3 = Neutral, 5 = Strongly Agree*; see full individual statements in Supplementary Material 1).
Abbreviations: SSQ: Simulator Sickness Questionnaire; VEQ: Virtual Reality Experience Questionnaire.

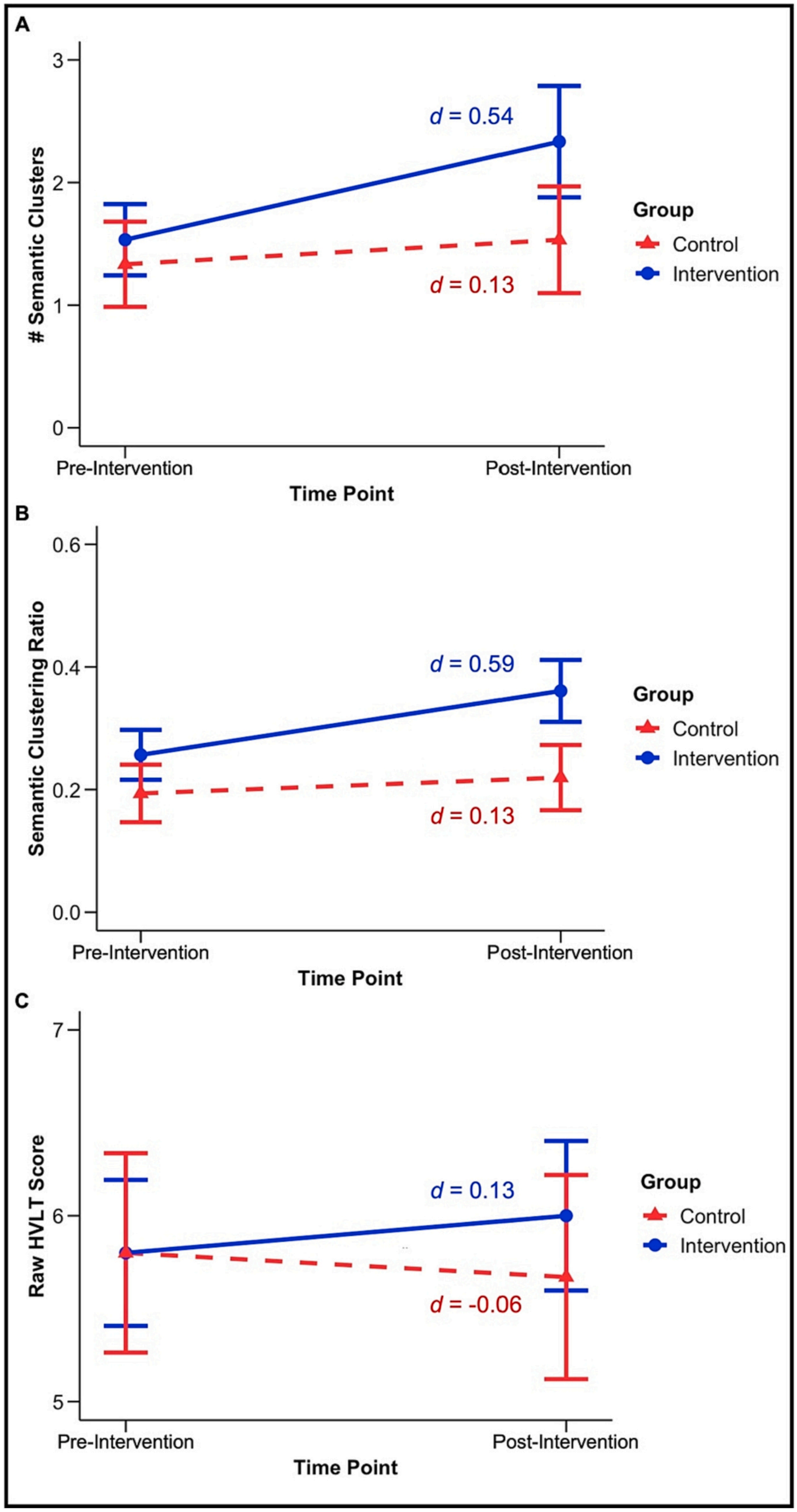
3.5. Trial design outcomes

A total of 41 participants who met basic pre-screening eligibility criteria were invited to participate in the current trial. Of these, seven declined to participate, representing an enrollment rate of 82.93 %.

In response to the blinding question, all participants in the intervention group thought it was likely that they were assigned to the intervention condition, while the majority of participants in the control group reported feeling neutral or likely that they were assigned to the intervention condition (see Supplementary Material 3).

4. Discussion

Overall, this single, brief VR-based CR module targeting verbal episodic memory in SZ was found to be feasible (attrition rate: 5.88 %), acceptable, and demonstrated medium effect sizes for the improvement of semantic clustering strategies. These findings add to emerging evidence suggesting that the use of VR-based interventions in SZ are feasible, acceptable, and efficacious at treating cognitive outcomes (Jespersen et al., 2023; Schroeder et al., 2022). The current research is the first to evaluate these outcomes for a VR-based CR module *specifically* targeting verbal episodic memory in SZ, which could be incorporated into future interventions.



(caption on next page)

Fig. 4. Pre- vs. post-intervention HVLT performance for the intervention (n = 15) and control (n = 15) groups.
Note. **A.** Mean number of semantic clusters used across the pre-intervention (intervention group: M = 1.53, SD = 1.13; control group: M = 1.33, SD = 1.35) and post-intervention (intervention group: M = 2.33, SD = 1.76; control group: M = 1.53, SD = 1.68) time points. **B.** Mean semantic clustering ratios across the pre-intervention (intervention group: M = 0.26, SD = 0.16; control group: M = 0.19, SD = 0.18) and post-intervention (intervention group: M = 0.36, SD = 0.20; control group: M = 0.21, SD = 1.68) time points. **C.** Raw total HVLT scores across the pre-intervention (intervention group: M = 5.80, SD = 1.52; control group: M = 5.80, SD = 2.08) and post-intervention (intervention group: M = 6.00, SD = 1.56; control group: M = 5.67, SD = 2.13) time points. All data are presented as mean ± standard error. Cohen's d effect sizes for both groups are displayed on each figure.
Abbreviations: HVLT: Hopkins Verbal Learning Test – Revised.

4.1. Feasibility

Of the 34 enrolled participants, most completed the VR session with no cybersickness. Only two participants were excluded from the trial due to poor tolerability of the VR technology. The overall attrition rate (5.88 %) was therefore low, indicating that the use of the VR technology was feasible and well tolerated. It is important to acknowledge that the current intervention involved only a single session, so it is difficult to compare this attrition rate to that of longer, multi-session studies (Wykes et al., 2011). Nevertheless, only one of the excluded participants failed to pass the one-minute VR practice session (control condition), indicating poor tolerance of the VR technology irrespective of condition. The second excluded participant experienced anxiety during the full VR session (intervention group). However, at the end of the appointment, the participant disclosed that they considered postponing the appointment due to high anxiety. Thus, it is possible that this poor tolerance was a reflection of significant pre-existing clinical symptoms and not a direct result of the VR technology.

4.2. Acceptability

The VR-based intervention was well accepted, with both groups demonstrating minimal cybersickness and high enjoyment per the SSQ and VEQ, respectively (see Table 2). Importantly, the intervention and control groups did not significantly differ in their scores on the SSQ and VEQ, suggesting that perceptions of cybersickness and VR experience were similar between conditions. Given that the intervention condition was more immersive than the control condition (i.e., more movement and social interaction), these findings suggest that the increased level of immersiveness did not significantly contribute to increased levels of cybersickness.

Overall, the measures of feasibility and acceptability used in the current study all suggest that the VR-based CR module was feasible and acceptable.

4.3. Preliminary efficacy

The intervention group showed an increase in the use of semantic clustering strategies following the VR-based CR module which trended towards statistical significance. These changes highlight the potential for this VR intervention to yield clinically meaningful increases in the use of semantic clustering. In comparison, the control group showed no statistically significant differences between the pre- and post-intervention assessments of verbal episodic memory nor the use of semantic clustering (see Fig. 4).

In their original study, Guimond and Lepage (2016) evaluated the efficacy of the full SESAME training in participants with SZ with confirmed deficits in the self-initiation of semantic encoding strategies (n = 13). Following the training, participants displayed a significant increase in verbal episodic memory performance (d = 1.27) and the number of semantic clusters used (d = 1.20). In a more recent and slightly larger study (n = 15), Guimond et al. (2018) again showed that the full SESAME intervention led to significant improvements in the number of semantic clusters used by participants with SZ (d = 0.62). However, change in the number of recalled words only trended towards statistical significance (p = 0.09, d = 0.46).

The adapted module used in the current study involved a single, much shorter version of the original full SESAME training intervention. Moreover, the participants in the current study did not have confirmed deficits in the self-initiation of semantic encoding strategies. Nevertheless, our results align with the behavioural findings from these two previous studies, showing a statistical trend towards significant improvements in the use of semantic clustering strategies.

4.4. Trial design outcomes

The majority of invited participants agreed to be enrolled in the current trial (34/41, 82.93 %). This high enrollment rate reflected a strong interest among individuals with SZ to participate in VR-based interventions. The seven individuals who declined to participate in the trial did not disclose the reason(s) for their decision. However, it is important to note that these individuals were invited because they previously disclosed a general interest in participating in research. These individuals only met basic pre-screening eligibility criteria; their full eligibility to participate, determined through the MINI and PANSS, was not yet established.

Finally, both groups provided high likelihood ratings concerning their assignment to the intervention group, demonstrating that the blinding procedures employed in the current trial were effective (see Supplementary Material 3).

4.5. Limitations

The main limitation of the current study was the relatively small sample size. However, given the pilot nature of this study, this sample size was sufficient to test the feasibility, acceptability, and preliminary efficacy of the module.

Second, the intervention and control conditions were delivered in VR and both engaged cognitive processes. Given that there was no control group which did not include a VR-based intervention, it is difficult to isolate the potential effect of the VR component on verbal episodic memory performance. Future research should contrast a VR-based CR program with a more traditional, non-VR approach. Nevertheless, the protocol used in the current proof-of-concept trial was rigorous, allowing us to reject the hypothesis that any changes in behavioural performance following the intervention were due to the VR immersion alone or repeated HVLT assessments.

Third, given the single-blind study design, the experimenter who conducted the cognitive assessments was unblinded to group assignment, introducing a potential risk of experimenter bias.

Fourth, the observed and self-reported semantic encoding strategies used by participants in the intervention group were not documented. During the intervention, the experimenter frequently asked participants, "*What strategies did you use, and do you think they helped you?*", while also encouraging the use of active rehearsal and semantic clustering strategies (see Supplementary Material 2). It is possible, however, that differences in the use of these strategies influenced subsequent performance on the HVLT. It is also possible that participants engaged semantic encoding strategies outside of those that were taught in the CR intervention. Future research should report the observed and self-reported use of the target encoding strategies among participants, as well as their influence on the primary outcome measure(s).

Finally, considering the brief duration of VR immersion used in the current study, along with concerns that pre-intervention assessments might prime higher post-intervention ratings, the SSQ was administered at the post-intervention time point alone to assess acceptability (Brown et al., 2022). Future studies should consider pre- and post-immersion SSQ administrations per Bouchard et al. (2021).

5. Conclusion

The VR-based CR module used in the current study was found to be feasible and acceptable by users with SZ. The results also suggest that the module may have a positive impact on semantic encoding strategies. These findings have implications for the conceptualization, development, and delivery of non-pharmacological treatments for cognition in SZ.

VR-based CR offers a more realistic and ecological approach to treating cognitive impairments in SZ. The current module could be used as part of future CR interventions targeting improvements in verbal episodic memory for individuals with SZ. Further research in larger samples involving a greater number of sessions and extended durations is warranted.

Funding

This work was supported, in part, by the Canadian Institutes of Health Research (Doctoral Award: Frederick Banting and Charles Best Canada Graduate Scholarship; BB); the Dr. Charles W. MacLeod Fellowship (BB); the Ontario eSports Scholarship Program (BB); the Canada Research Chairs Program (SB); the Emerging Research Innovators in Mental Health (eRIMh) Award from the Royal's Institute of Mental Health Research (SG); and the Chercheur Boursier Junior 1 from the Fonds de Recherche du Québec en Santé (FRQS; PI: SG).

CRediT authorship contribution statement

Bryce J. M. Bogie: Writing – review & editing, Writing – original draft, Visualization, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Chelsea Noël:** Writing – review & editing, Writing – original draft, Investigation, Conceptualization. **Feng Gu:** Writing – review & editing, Writing – original draft, Project administration, Investigation, Conceptualization. **Sébastien Nadeau:** Writing – review & editing, Writing – original draft, Software, Methodology, Investigation. **Cecelia Shvetz:** Writing – review & editing, Software, Investigation, Conceptualization. **Hassan Khan:** Writing – review & editing, Conceptualization. **Marie-Christine Rivard:** Writing – review & editing, Software, Conceptualization. **Stéphane Bouchard:** Writing – review & editing, Software, Methodology, Funding acquisition, Conceptualization. **Martin Lepage:** Writing – review & editing. **Synthia Guimond:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Software, Resources, Project administration, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

ML reports grants from Otsuka Lundbeck Alliance, personal fees from Otsuka Canada, personal fees from Lundbeck Canada, grants and personal fees from Janssen, grants from Roche, and personal fees from Boehringer-Ingelheim, all outside the submitted work. SB is President of, and owns equity in, Cliniques et Développement In Virtuo, a spin-off from the university that distributes virtual environments. The terms of these arrangements have been reviewed and approved by the Université du Québec en Outaouais in accordance with its 'Conflict of Interest' policies. SG has received financial compensation for consulting services from Boehringer Ingelheim, outside the submitted work.

Appendix A. Supplementary Materials

Supplementary Materials associated with this article can be found online at https://doi.org/10.1016/j.scog.2024.100305.

References

Alptekin, K., Akvardar, Y., Akdede, B.B.K., Dumlu, K., Işık, D., Pirinçci, F., Kitiş, A., 2005. Is quality of life associated with cognitive impairment in schizophrenia? Prog. Neuro-Psychopharmacol. Biol. Psychiatry 29 (2), 239–244. https://doi.org/10.1016/j.pnpbp.2004.11.006.

Benedict, R.H.B., Schretlen, D., Groninger, L., Brandt, J., 1998. Hopkins Verbal Learning Test - Revised: normative data and analysis of inter-form and test-retest reliability. Clin. Neuropsychol. 12 (1), 43–55. https://doi.org/10.1076/clin.12.1.43.1726.

Bimberg, P., Weissker, T., Kulik, A., 2020. On the usage of the simulator sickness questionnaire for virtual reality research. In: 2020 IEEE Conference on Virtual Reality and 3D User Interfaces Abstracts and Workshops (VRW). March.

Bogie, B.J.M., Noël, C., Alftieh, A., MacDonald, J., Lei, Y.T., Mongeon, J., Mayaud, C., Dans, P., Guimond, S., 2023. Verbal memory impairments in mood disorders and psychotic disorders: a systematic review of comparative studies. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 110891. https://doi.org/10.1016/j.pnpbp.2023.110891.

Bouchard, S., Berthiaume, M., Robillard, G., Forget, H., Daudelin-Peltier, C., Renaud, P., Fiset, D., 2021. Arguing in favor of revising the simulator sickness questionnaire factor structure when assessing side effects induced by immersions in virtual reality. Front. Psychol. 12, 739742 https://doi.org/10.3389/fpsyt.2021.739742.

Bowie, C.R., Bell, M.D., Fiszdon, J.M., Johannesen, J.K., Lindenmayer, J.P., McGurk, S. R., Medalia, A.A., Penadés, R., Saperstein, A.M., Twamley, E.W., Ueland, T., Wykes, T., 2020. Cognitive remediation for schizophrenia: an expert working group white paper on core techniques. Schizophr. Res. 215, 49–53. https://doi.org/10.1016/j.schres.2019.10.047.

Brown, P., Spronck, P., Powell, W., 2022. The simulator sickness questionnaire, and the erroneous zero baseline assumption. Frontiers in Virtual Reality 3, 118. https://doi.org/10.3389/frvir.2022.945800.

Campbell, Z., Zakzanis, K.K., Jovanovski, D., Joordens, S., Mraz, R., Graham, S.J., 2009. Utilizing virtual reality to improve the ecological validity of clinical neuropsychology: an fMRI case study elucidating the neural basis of planning by comparing the tower of London with a three-dimensional navigation task. Appl. Neuropsychol. 16 (4), 295–306. https://doi.org/10.1080/09084280903297891.

Chan, C.L.F., Ngai, E.K.Y., Leung, P.K.H., Wong, S., 2010. Effect of the adapted virtual reality cognitive training program among Chinese older adults with chronic schizophrenia: a pilot study. Int. J. Geriatr. Psychiatry 25 (6), 643–649. https://doi.org/10.1002/gps.2403.

Cirillo, M.A., Seidman, L.J., 2003. Verbal declarative memory dysfunction in schizophrenia: from clinical assessment to genetics and brain mechanisms. Neuropsychol. Rev. 13 (2), 4377. https://doi.org/10.1023/A:1023870821631.

Dickinson, D., Tenhula, W., Morris, S., Brown, C., Peer, J., Spencer, K., Li, L., Gold, J.M., Bellack, A.S., 2010. A randomized, controlled trial of computer-assisted cognitive remediation for schizophrenia. Am. J. Psychiatry 167 (2), 284–290. https://doi.org/10.1176/appi.ajp.2009.09020264.

Dobrowolski, P., Skorko, M., Pochwatko, G., Myśliwiec, M., Grabowski, A., 2021. Immersive virtual reality and complex skill learning: transfer effects after training in younger and older adults. Frontiers in Virtual Reality 1, 604008. https://doi.org/10.3389/frvir.2020.604008.

Freeman, D., 2008. Studying and treating schizophrenia using virtual reality: a new paradigm. Schizophr. Bull. 34 (4), 605–610. https://doi.org/10.1093/schbul/sbn020.

Gomar, J.J., Valls, E., Radua, J., Mareca, C., Tristany, J., Del Olmo, F., McKenna, P.J., 2015. A multisite, randomized controlled clinical trial of computerized cognitive remediation therapy for schizophrenia. Schizophr. Bull. 41 (6), 1387–1396. https://doi.org/10.1093/schbul/sbv059.

Guimond, S., Lepage, M., 2016. Cognitive training of self-initiation of semantic encoding strategies in schizophrenia: a pilot study. Neuropsychol. Rehabil. 26 (3), 464–479. https://doi.org/10.1080/09602011.2015.1045526.

Guimond, S., Chakravarty, M.M., Bergeron-Gagnon, L., Patel, R., Lepage, M., 2016. Verbal memory impairments in schizophrenia associated with cortical thinning. NeuroImage: Clinical 11, 20–29. https://doi.org/10.1016/2Fj.nicl.2015.12.010.

Guimond, S., Béland, S., Lepage, M., 2018. Strategy for semantic association memory (SESAME) training: effects on brain functioning in schizophrenia. Psychiatry Res. Neuroimaging 271, 50–58. https://doi.org/10.1016/j.pscychresns.2017.10.010.

Guo, J.Y., Ragland, J.D., Carter, C.S., 2019. Memory and cognition in schizophrenia. Mol. Psychiatry 24 (5), 633–642. https://doi.org/10.1038/2Fs41380-018-0231-1.

Harvey, P.D., Strassnig, M.T., Silberstein, J., 2019. Prediction of disability in schizophrenia: symptoms, cognition, and self-assessment. J. Exp. Psychopathol. 10 (3) https://doi.org/10.1177/2043808719865693, 2043808719865693.

Jespersen, A.E., Røen, I.S., Lumbye, A., Nordentoft, M., Glenthøj, L.B., Miskowiak, K.W., 2023. Feasibility and effect of an immersive virtual reality-based platform for cognitive training in real-life scenarios in patients with mood-or psychotic disorders: a randomized, controlled proof-of-concept study. Neuroscience Applied 2, 101120. https://doi.org/10.1016/j.nsa.2023.101120.

Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr. Bull. 13 (2), 261–276. https://doi.org/10.1093/schbul/13.2.261.

Keefe, R.S.E., Buchanan, R.W., Marder, S.R., Schooler, N.R., Dugar, A., Zivkov, M., Stewart, M., 2013. Clinical trials of potential cognitive-enhancing drugs in schizophrenia: what have we learned so far? Schizophr. Bull. 39 (2), 417–435. https://doi.org/10.1093/schbul/sbr153.

Kennedy, R.S., Lane, N.E., Berbaum, K.S., Lilienthal, M.G., 1993. Simulator sickness questionnaire: an enhanced method for quantifying simulator sickness. Int. J. Aviat. Psychol. 3 (3), 203–220. https://doi.org/10.1207/s15327108ijap0303_3.

Lejeune, J.A., Northrop, A., Kurtz, M.M., 2021. A meta-analysis of cognitive remediation for schizophrenia: efficacy and the role of participant and treatment factors. Schizophr. Bull. 47 (4), 997–1006. https://doi.org/10.1093/schbul/sbab022.

McCleery, A., Nuechterlein, K.H., 2019. Cognitive impairment in psychotic illness: prevalence, profile of impairment, developmental course, and treatment considerations. Dialogues Clin. Neurosci. https://doi.org/10.31887/DCNS.2019.21.3/amccleery.

Medalia, A., Erlich, M., 2017. Why cognitive health matters. Am. J. Public Health 107 (1), 45–47. https://doi.org/10.2105/AJPH.2016.303544.

Molina, J., Tsuang, M.T., 2020. Neurocognition and treatment outcomes in schizophrenia. In: Schizophrenia Treatment Outcomes: An Evidence-Based Approach to Recovery. Springer International Publishing, pp. 35–41. https://doi.org/10.1007/978-3-030-19847-3_5.

O'Connor, S., Hanlon, P., O'Donnell, C.A., Garcia, S., Glanville, J., Mair, F.S., 2016. Understanding factors affecting patient and public engagement and recruitment to digital health interventions: a systematic review of qualitative studies. BMC Med. Inform. Decis. Mak. 16, 1–15. https://doi.org/10.1186/s12911-016-0359-3.

Park, M.J., Kim, D.J., Lee, U., Na, E.J., Jeon, H.J., 2019. A literature overview of virtual reality (VR) in treatment of psychiatric disorders: recent advances and limitations. Front. Psychol. 10, 505. https://doi.org/10.3389/fpsyt.2019.00505.

Rothbaum, B.O., Hodges, L.F., Kooper, R., Opdyke, D., Williford, J.S., North, M., 1995. Effectiveness of computer-generated (virtual reality) graded exposure in the treatment of acrophobia. Am. J. Psychiatry 152 (4), 626–628. https://doi.org/10.1176/ajp.152.4.626.

Rus-Calafell, M., Garety, P., Sason, E., Craig, T.J.K., Valmaggia, L.R., 2018. Virtual reality in the assessment and treatment of psychosis: a systematic review of its utility, acceptability and effectiveness. Psychol. Med. 48 (3), 362–391. https://doi.org/10.1017/S0033291717001945.

Rus-Calafell, Mar, Gutiérrez-Maldonado, J., Ribas-Sabaté, J., 2014. A virtual reality-integrated program for improving social skills in patients with schizophrenia: a pilot study. J. Behav. Ther. Exp. Psychiatry 45 (1), 81–89. https://doi.org/10.1016/j.jbtep.2013.09.002.

Schroeder, A.H., Bogie, B.J., Rahman, T.T., Thérond, A., Matheson, H., Guimond, S., 2022. Feasibility and efficacy of virtual reality interventions to improve psychosocial functioning in psychosis: systematic review. JMIR Mental Health 9 (2), e28502. https://doi.org/10.2196/28502.

Seccomandi, B., Tsapekos, D., Newbery, K., Wykes, T., Cella, M., 2020. A systematic review of moderators of cognitive remediation response for people with schizophrenia. Schizophrenia Research: Cognition 19, 100160. https://doi.org/10.1016/j.scog.2019.100160.

du Sert, O.P., Potvin, S., Lipp, O., Dellazizzo, L., Laurelli, M., Breton, R., Lalonde, P., Phraxayavong, K., O'Connor, K., Pelletier, J.F., Boukhalfi, T., Renaud, P., Dumais, A., 2018. Virtual reality therapy for refractory auditory verbal hallucinations in schizophrenia: a pilot clinical trial. Schizophr. Res. 197, 176–181. https://doi.org/10.1016/j.schres.2018.02.031.

Sheehan, D.V., Lecrubier, Y., Sheehan, K.H., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., Dunbar, G.C., 1998. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J. Clin. Psychiatry 59 (20), 22–33.

Spieker, E.A., Astur, R.S., West, J.T., Griego, J.A., Rowland, L.M., 2012. Spatial memory deficits in a virtual reality eight-arm radial maze in schizophrenia. Schizophr. Res. 135 (1–3), 84–89. https://doi.org/10.1016/j.schres.2011.11.014.

Tsang, M.M.Y., Man, D.W.K., 2013. A virtual reality-based vocational training system (VRVTS) for people with schizophrenia in vocational rehabilitation. Schizophr. Res. 144 (1–3), 51–62. https://doi.org/10.1016/j.schres.2012.12.024.

Tsapakis, E.M., Dimopoulou, T., Tarazi, F.I., 2015. Clinical management of negative symptoms of schizophrenia: an update. Pharmacol. Ther. 153, 135–147. https://doi.org/10.1016/j.pharmthera.2015.06.008.

Vita, A., Barlati, S., Ceraso, A., Nibbio, G., Ariu, C., Deste, G., Wykes, T., 2021. Effectiveness, core elements, and moderators of response of cognitive remediation for schizophrenia: a systematic review and meta-analysis of randomized clinical trials. JAMA Psychiatry 78 (8), 848–858. https://doi.org/10.1001/jamapsychiatry.2021.0620.

Wu, B., Yu, X., Gu, X., 2020. Effectiveness of immersive virtual reality using head-mounted displays on learning performance: a meta-analysis. Br. J. Educ. Technol. 51 (6), 1991–2005. https://doi.org/10.1111/bjet.13023.

Wykes, T., Huddy, V., Cellard, C., McGurk, S.R., Czobor, P., 2011. A meta-analysis of cognitive remediation for schizophrenia: methodology and effect sizes. Am. J. Psychiatry 168 (5), 472–485. https://doi.org/10.1176/appi.ajp.2010.10060855.