

Effect of Virtual Reality on Cognitive Impairment and Clinical Symptoms Among Patients with Schizophrenia in the Remission Stage: A Randomized Controlled Trial

Shangda Li

Zhejiang University School of Medicine First Affiliated Hospital

Bin Sun

Ningbo Psychiatric Hospital

Ning Wei

Zhejiang University School of Medicine First Affiliated Hospital

Zhe Shen

Zhejiang University School of Medicine First Affiliated Hospital

Kangyu Jin

Zhejiang University School of Medicine First Affiliated Hospital

Haoyang Zhao

Zhejiang University School of Medicine First Affiliated Hospital

Yaping Chen

Ningbo Psychiatric Hospital

manli Huang

Zhejiang University School of Medicine First Affiliated Hospital

Yi Xu (✉ xuyizju@zju.edu.cn)

Zhejiang University School of Medicine First Affiliated Hospital <https://orcid.org/0000-0002-8773-8264>

Research

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Abstract

Background: This is an intervention study which explores the effect of using virtual reality supermarket training system (VRSTS) to improve cognitive function deficiency and clinical symptoms in Han Chinese patients with schizophrenia in the remission stage.

Methods:

68 patients with schizophrenia in the remission stage were recruited for the interventional study and were randomly allocated to either virtual reality training (VRT) group or treatment-as-usual (TAU) group. For VRT group, patients received training with VRSTS for two weeks and antipsychotic treatment as usual while TAU group only received antipsychotic treatment as usual. Cognitive function and clinical symptoms before and after intervention were assessed by MATRICS Consensus Cognitive Battery (MCCB), Positive and Negative Syndrome Scale (PANSS), and the Personal and Social Performance Scale (PSP).

Results:

Results showed (1) VRSTS could improve MCCB composite scores and 4 out of 7 cognitive domains: speed of processing, working memory, visual learning, reasoning and problem solving, and (2) VRSTS could alleviate general psychopathology symptoms of PANSS but did not exert effects on positive and negative symptoms among patients with schizophrenia in the remission stage

Conclusion:

A therapeutic effect of VRSTS was observed in patients with schizophrenia in the remission stage. It may improve cognitive impairment and general psychopathology symptoms.

Trial registration: China Clinical Trial Registry, ChiVTR1800016121. Registered 13 May 2018, <http://www.chictr.org.cn/showproj.aspx?proj=27233>

Background

Schizophrenia is a complex, heterogeneous behavioral and cognitive syndrome characterized by positive symptoms, negative symptoms and cognitive impairment (1, 2) with a global lifetime prevalence of 0.3%-0.7%(3, 4). Patients with schizophrenia exhibit damaged cognitive function, including reduced attention and memory, and difficulties with executive functioning(5). Schizophrenia in the remission stage often defined a mild or less symptoms assessed by scales, such as Brief Psychiatric Rating Scal(BPRS), the Scale for the the Assessment of Positive Symotoms (SAPS) and the Scale for the Assessment of Negative Symptoms (SANS) or Positive and Negative Symdrome Scale (PANSS), maintain for a period of 6 months at least with cognitive dysfunction remains(6). As schizophrenia is a chronic, frequently disabling mental disorder, clinically, many patients ultimately turned to the remission stage.

Although symptoms like delusions and hallucinations are reduced in remission stage, the functional recovery are usually not optimistic. Impairment of cognitive functions still existed in schizophrenia patients in remission stage(7) and disability of schizophrenia is largely due to cognitive deficits in this stage(8).

In order to assess the cognitive function of patients with schizophrenia, some evaluation tools has been developed like The MATRICS Consensus Cognitive Battery (MCCB) and the Brief Assessment of Cognition in Schizophrenia (BACS)(9). MCCB, which includes 10 different cognitive subtests, is an accepted standard for measuring cognitive change in schizophrenia and has been recommended by the United States Food and Drug Administration (FDA) to assess cognitive impairment in schizophrenia (10, 11). It demonstrates excellent reliability and practicality. Recently, studies have shown that the MCCB is both applicable for first-episode schizophrenia and chronic schizophrenia(12) and investigations using the MCCB have focused on different cognitive domains in patients with schizophrenia.

Regarding the therapy, antipsychotics are the mainstay of treatment for schizophrenia with a defined curative effect of positive, negative and cognitive symptoms(13). However, the neurological side effects of antipsychotics hinder the efficacy to schizophrenia(14). And patients' compliance to antipsychotics is often not satisfactory enough in clinical setting(15), especially after the improvement of positive symptoms. Furthermore, drugs always fails to alleviate cognitive deficits such as attention and working memory(8). Patients always remained cognitive symptoms after long-term use of antipsychotics(16) and excessive dose of antipsychotics may induce poorer cognitive function(17). Some studies also showed that long-term used of antipsychotics might impair the cognitive function(18).

Researches also showed psychological consulting may improve cognitive functioning in patients with schizophrenia, such as cognitive behavior therapy(19), cognitive remediation(20) and cognitive enhancement therapy(21) but these counseling therapies often require a practice therapist, a treatment plan reflective of each patient's. In addition, patients may have problems to understand and the therapeutic effect sometimes was delayed. All the limitation mentioned above might hinder the wide application of counseling therapies. Therefore, the remained impairment of cognitive function in patients with schizophrenia patients in remission stage needs a new adjunct treatment.

Virtual reality (VR) is a emerging technologies applied to treatment in psychiatric disorder. It creates interactive computer-generated worlds that produces a sensation of being in life-sized environments(22). Many studies have investigate the effect of virtual reality training(VRT) used in schizophrenia. A research about twelve patients with schizophrenia showed that VRT significantly improved negative symptoms, psychopathology, social anxiety and discomfort, avoidance and social function in patients with schizophrenia after they received VR treatment(23). In addition, a significant reduction was observed in paranoid ideation and momentary anxiety in patients with psychotic disorder and paranoid ideation after virtual-reality-based cognitive behavioral therapy (24). Furthermore, Freeman and colleagues reported that VR social environments and VR cognitive therapy led to large reductions in delusional conviction in patients with persecutory delusion(25). In regarding to cognitive function, many studies have

demonstrated virtual reality could help mitigate cognitive function impairment in many disease conditions. Faria and colleagues found that post 12 sessions of VRT, stroke patients improved in global cognitive functioning, attention, memory, visuo-spatial abilities, executive functions(26). Another research showed post-stroke patients gain improvement in sustained attention after 24 sessions of VR training(27). VRT also exerted an enhancement effect on memory, attention span and execution function in older adults after VR memory training(28).

However, there is still limited literature focusing on the effect of VRT to improve cognitive function in patients with schizophrenia in remission stage and studies about VRT applied to Han Chinese people is lacked. To resolve this issues, the present study designed a virtual reality supermarket training system (VRSTS) which is closed to Han Chinese people's daily life. And then explored the effect of VRSTS on cognitive function impairment administered in patients with schizophrenia in remission stage of Han Chinese descent. We hypothesized that VRSTS could recover the impairment of cognitive function in patients with schizophrenia in remission stage

Method

This is an interventional study conducted in Ningbo Psychiatric Hospital and First Affiliated Hospital of Zhejiang University School of Medicine from June 1,2019, to October 20 2019. The study was approved by the ethics committee of the First Affiliated Hospital of the Medical School of Zhejiang University in accordance with the Declaration of Helsinki and was registered in the China Clinical Trial Registry under registration number ChiVTR1800016121.

Participants

68 patients with schizophrenia were recruited form Ningbo Psychiatric Hospital. The inclusion criteria were as follows: between 18 and 55 years old; met the ICD-10 criteria for schizophrenia; on remission stage: PANSS item scores of ≤ 3 at least 6 months according to Andreasen's criteria(6); only received atypical antipsychotics and treatment dose has been stable for more than 1 month; normal vision and right-handedness. Exclusion criteria: a history of brain trauma, epilepsy and other neurological diseases or serious physical diseases; a diagnosis of a history of mental retardation and a history of substance abuse in the past 30 days (except smoking); received electroconvulsive therapy in the past year; a history of using typical antipsychotics; and pregnant women or those who planned to get pregnant; Wechsler adult intelligence scale-revised China (WAIS-RC) scores ≥ 80 . After description of the study to the subjects, written informed consent was obtained before the study was conducted. All patients received scale assessments and MCCB at baseline (T0) and post intervention (T1). The scales included the Positive and Negative Syndrome Scale (PANSS) and the Personal and Social Performance Scale (PSP).

Patients fulfilling inclusion criteria were randomly allocated to either VRT group or treatment-as-usual (TAU) group. The definition of TAU group refers to Olivier and colleagues(29). For VRT group, patients received VRT for two weeks and antipsychotic treatment as usual while TAU group only received antipsychotic treatment as usual.

Cognitive function assessment

Cognitive function was assessed by a trained psychiatrist using the MCCB at T0 and T1. The raters were blinded to the group of the participants. The MCCB includes 10 neurophysiologic tests clustered in 7 cognitive domains: speed of processing (SP), attention/vigilance (AV), working memory (WM), verbal learning (VeL), visual learning (ViL), reasoning and problem solving (RPS), and social cognition (SC)(30). Each domain score was standardized to a T score using the MCCB computer scoring program (Psychological Assessment Resources, Inc., version 2.1.1). Furthermore, the overall composite T score was calculated by averaging the standardized value of each test's T score.

VRT procedure

VRT was executed once a day, 5 times per week and last for two weeks. A supermarket situation based on VR technique was designed for patients with schizophrenia. The virtual supermarket simulates a supermarket with a variety of goods such as drinks, tea sets, kitchen ware, fruits and vegetables. There is also a shopping cart for catch the goods. Unity 5.3.5f1 (<https://unity3d.com>) and visual studio 2015 (Microsoft) were used to design and create the VR program.

Patients were asked to complete different shopping tasks with different lists. The shopping tasks include task A and task B and each task consisted of 4 different levels. At the beginning of each task, participants become familiar with the procedures as follows:

- 1)The patients learned to wear the helmet in a comfortable way to enter the virtual supermarket and use the joysticks to manipulate in the virtual supermarket;
- 2)While a list of goods occurred on the screen, the patients read the list and close it after remembering the list;
- 3)The patients caught the good presented in the list and put it in the shopping cart in the virtual supermarket by using joysticks;
- 4)If the patients forgot the content of the list, he could press the button in the joysticks and the list would occur again.

The situation of VRT is presented as figure 1. It included two kind of tasks. Task A asked patients to find goods of a certain category and put them into the shopping carts, such as fruits, vegetables and drinks, while task B instructed participants to catch specific goods such as apples, tomatoes and cola. The number of goods ranged from 3 to 6 as the levels of task increased. As the goods number is increased, the working memory span needed is increased.

Statistical analysis

The data are expressed as the mean \pm SD for continuous variables. Baseline data include age, gender, course of disease, education year was analyzed for the comparability of baseline data. Chi-square test

was used to compare gender of two groups. Normally distributed data were analyzed by independent t test, while non-normally distributed data were analyzed by mann-whitney U test. Changes in T scores of the MCCB results, PANSS scores and PSP scores at T0 and T1 both in two groups were analyzed by covariance analysis (covariates: course of disease, corresponding variables at T1). All statistical analyses were performed using SPSS version 19.0 (IBM, Chicago, IL, USA) for windows.

Results

Demographic characteristics and baseline data of two groups.

The total sample comprised of 68 patients with schizophrenia. One patient in TAU group was found he ever adjusted drug dosage in the past month so he did not receive allocated intervention. 4 out of the patients in VRT group were withdrawn because they could not finish the MCCB and another patient in TAU group was over 55 years old at the beginning of the trial so they discontinued intervention. The other 30 patients in VRT group and 32 patients in TAU group completed the study. The final sample included 62 patients.

There were no significant differences in age, gender, educational years, Age of onset, T scores of MCCB domains, PANSS scores and PSP scores at baseline between VRT group and TAU group (all $P > 0.05$). However, the course of disease of patients in TAU group (mean \pm SD, 249.94 \pm 97.55) was significantly more than VRT group (195.10 \pm 107.86). (Table 1) One patient in each group respectively once felt dizzy during the VRT but they finished the therapy because the dizziness was tolerable and disappeared after VRT. No other uncomfortable feeling was reported.

MCCB T scores of two groups

As shown in Figure 2, many improvements of MCCB T scores were observed during VRT from T0 to T1. Covariance analysis showed that after adjust the covariates (the corresponding variables at T0 and course of disease, similarly hereinafter), the MCCB composite T score at T1(37.15 \pm 7.54) in VRT group is significantly higher than in TAU group (32.94 \pm 8.28) ($F=13.885$ \times $P<0.001$)

In addition, covariance analysis suggested T scores of SP (30.53 \pm 12.69), WM (45.33 \pm 11.18), VIL (39.38 \pm 15.32) and RPS (36.33 \pm 7.22) at T1 in VRT group were significantly higher than that in TAU group after adjust the covariates. ($F=4.65$ \times $P=0.035$, $F=4.907$, $P=0.031$, $F=3.875$ \times $P=0.041$, $F=5.156$ \times $P=0.027$ separately). However, no significantly difference was found in T scores of AV, VERL, SC at T1 between two groups. (all $p > 0.05$)

Clinical symptoms assessment of two groups

PANSS scores of two groups

Covariance analysis showed after adjust the covariates, PANSS general psychopathology scores at T1 in VRT group is significantly less than in TAU group ($F=5.224$ \times $P<0.034$). However, no significantly difference

was found in PANSS total scores, neither in PANSS positive and PANSS negative scores at T1 between two groups. (all $p > 0.05$) (Table 2)

PSP scores of two groups

Covariance analysis showed after adjust the covariates, there is no significant difference in PSP scores at T1 between two groups ($P=0.492$) (Table 2)

Discussion

The dilemma that patients with schizophrenia in the remission stage always suffered the remained cognitive impairment. The VRT was a potential method for rehabilitation. Previous study showed VRT could improve cognitive functions but researches focus on schizophrenia is still limited. 10 session of VR program was described as a promising method for significant gains in cognitive function of patients with schizophrenia (31) but the patients in this study were all old patients and the VR program is related with navigation in the sea. The present study designs the VRSTS, which offers a virtual situation closed to daily life. It was an immersive virtual supermarket and participants easily generate a feeling of being in a real supermarket and pleasure so that they enjoyed the process of choosing goods in the supermarket. The present study found 10 sessions of VRSTS mitigate the impaired cognitive function in patients with schizophrenia in the remission stage. To our delight, the general psychopathology symptoms also gain improvement after VRSTS.

The present results showed MCCB composite scores and the cognitive domains include SP, WM, VIL and RPS are significantly improved after 10 sessions of VRSTS.

And it is consistent with the previous research which reported that 40 patients with schizophrenia got significantly improvement in MCCB domain of SP, AV, WM, VERL and RPS after 10 sessions of VR game program (32). The different MCCB domains improved in two studies might be related with different tasks in virtual situation. In the present study, in order to complete the task in virtual supermarket, participants need to receive the instruction from the screen, remember the information, find and recognize the good in the virtual supermarket and put them into shopping cart. This process involves many domains of cognitive function. In addition, while the VRT task level increased, the number of good is increased, the working memory span needed is increased. As a result, while patients efforted to finish tasks and repeat training in the virtual situation, their cognitive function improved at the same time.

Regarding the clinical symptoms of patients, VRT has been applied in rehabilitation of schizophrenia and showed effect on relieving the symptoms. A study showed patients with schizophrenia exhibited a significant reduction in overall clinical symptoms 10 sessions of VR training (33), and social function improved after a VR interview training (34). But in our study, we found VRT only improved the general psychopathology symptoms in patients rather than positive symptoms or negative symptoms. It may relate with the design of VR situation. Our task of VRSTS simulates a daily life situation, shopping in a supermarket; it may not help with positive and negative symptoms of schizophrenia but exerts positive

effect on general symptoms rehabilitation. We suggest VRSTS may be a better choice for residual general psychopathology symptoms as some antipsychotics for long-term use would induce some metabolic syndrome(35).

When it comes to social function, a study found that after rehabilitation training based on VR, patient with schizophrenia got improved on PSP score(36). However, the present study indicated the VRSTS could not help with the personal and social performance. It may relate with the therapy period. VRSTS in the study above lasted 8 weeks but our study treatment only lasted for two weeks. More researches were needed to investigate the effect of VRSTS to improve social function.

In addition, it is worth mentioning that the side effect of VRT seems slight, only 2 out of 62 participants felt uncomfortable during VRT and it is mild so they could finish VRT. And the feedback from patients to VRSTS is pretty satisfactory. The staffs asked each patient's evaluation about the VRSTS after they complete VRSTS training and no patients felt dissatisfied and some of them thought the task in virtual situation is pretty challenging and attractive. This may related to the interactive therapy environment created by VR technology(22).

Although cognitive remediation and rehabilitation is an essential component of care for people with schizophrenia(37), resources for rehabilitation services is still insufficient. As VRSTS could partly ameliorate cognitive function and the acceptability of patients in this study is pretty high, it may be a prospective treatment of schizophrenia in the remission stage for rehabilitation and if VRSTS was widely used, it may overcome the bottleneck of rehabilitation in China.

Limitation

Nevertheless, the current trial has a few limitations. Firstly, the sample size of participants is small. Secondly, the patients received different types of second-generation antipsychotics, which may interfere with the patients' cognitive function and clinical symptom. Furthermore, the two groups were not matched in course of disease; it may influence their performance in virtual supermarket. So we used covariance analysis (covariates: years of education) to compare the outcome between patients with schizophrenia and healthy controls. Another shortcoming is that our study lacks follow-up after the two groups finish the intervention so we could not identify the long-term effect of VRT. As a result, more researches involve larger sample size and longer follow-up time are needed in the future.

Conclusion

To conclude, we found therapeutic effects of VRSTS on patients with schizophrenia in the remission stage. It may improve cognitive function impairment and general psychopathology symptoms. The present study suggests VRSTS is a promising adjunct intervention for the rehabilitation of schizophrenia in the remission stage.

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Declarations

Conflicts of interest

All authors declare that they have no conflicts of interest. All authors wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Note

a independent t test, b Mann-Whitney U, c Chi-Square test (VRT N = 30; TAU N = 32)

Contributors

Yi Xu and Manli Huang contributed to the study design and concept and wrote the protocol. Shangda Li managed the literature searches, statistical analysis and manuscript writing. Bin Sun contributed to data acquisition. Ning Wei, Zhe Shen helped with the statistical analysis and manuscript writing. Kangyu Jin^a, Haoyang Zhao and Yaping Chen assisted with the experiment. All authors were involved in the preparation and review of the manuscript and approved the final version to be submitted.

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 38. Legend.

Tables

Table 1: Mean±SD Values on demographic characteristics and baseline data of two groups.

	VR group (n=30)	TAU group (n=32)	P
Age	42.53±7.75	44.91±8.60	0.178 ^b
Gender(male/female)	20/10	19/13	0.606 ^c
course of disease	195.10±107.86	249.94±97.55	0.040 ^{a*}
Educational years	11.5±4.35	10.75±2.27	0.673 ^b
Age of onset	24.60±5.97	23.38±6.26	0.389 ^b
MCCB			
SP	24.23±12.46	22.66±13.17	0.630 ^a
AV	33.33±9.18	28.72±11.52	0.088 ^a
WM	40.23±17.08	42.50±19.78	0.632 ^a
VERL	33.37±7.14	34.72±8.02	0.487 ^a
VIL	30.57±10.21	35.56±15.19	0.136 ^a
RPS	33.53±4.05	35.81±8.10	0.344 ^b
SC	24.00±9.51	21.28±8.38	0.236 ^a
Composite score	31.34±5.80	31.61±7.89	0.882 ^a
PANSS			
PANSS total	43.08±4.83	42.36±6.61	0.767 ^b
PANSS P	7.83±1.12	7.91±1.45	0.944 ^b
PANSS N	12.33±2.57	10.18±2.71	0.064 ^b
PANSS G	19.83±2.48	20.09±3.48	0.709 ^b
PSP	70.82±8.34	67.08±5.71	0.239 ^a

Note: a independent t test, b Mann-Whitney U, c Chi-Square test (VRT N=30; TAU N=32)

Abbreviation: VRT: virtual reality therapy; TAU: treatment-as-usual; MCCB: MATRICS Consensus Cognitive Battery; SP: speed of processing; AV: attention-vigilance; WM: working memory; VeL: verbal learning; ViL: visual learning; RPS: reasoning/problem solving; SC: social cognition; PNASS: Positive and Negative Syndrome Scale, PANSS G: PANSS general psychopathology, PANSS P: PANSS positive; PANSS N: PANSS negative; PSP: Personal and Social Performance Scale

Table 2: Clinical symptoms before and after intervention of two group [Mean±SD]

	VRT group		TAU group		F	P
	T0	T1	T0	T1		
PANSS						
PANSS total	38.18±6.00	36.45±5.34	40.00±4.71	39.50±4.32	1.843	0.191
PANSS P	7.91±1.45	7.36±0.67	7.83±1.12	7.75±1.14	4.158	0.056
PANSS N	10.18±2.71	10.72±3.64	12.33±2.57	12.25±2.42	0.07	0.794
PANSS G	20.09±3.48	18.36±2.42	19.83±2.48	19.50±2.58	5.224	0.034*
PSP	70.82±8.34	72.36±8.15	67.08±5.71	68.25±5.41	0.491	0.492

Note: (VRT N=30; TAU N=32) T0: baseline; T1: post intervention

Abbreviation: VRT: virtual reality training; TAU: treatment-as-usual; PANSS: Positive and Negative Syndrome Scale, PANSS G: PANSS general psychopathology, PANSS P: PANSS positive; PANSS N: PANSS negative; PSP: Personal and Social Performance Scale

Figures

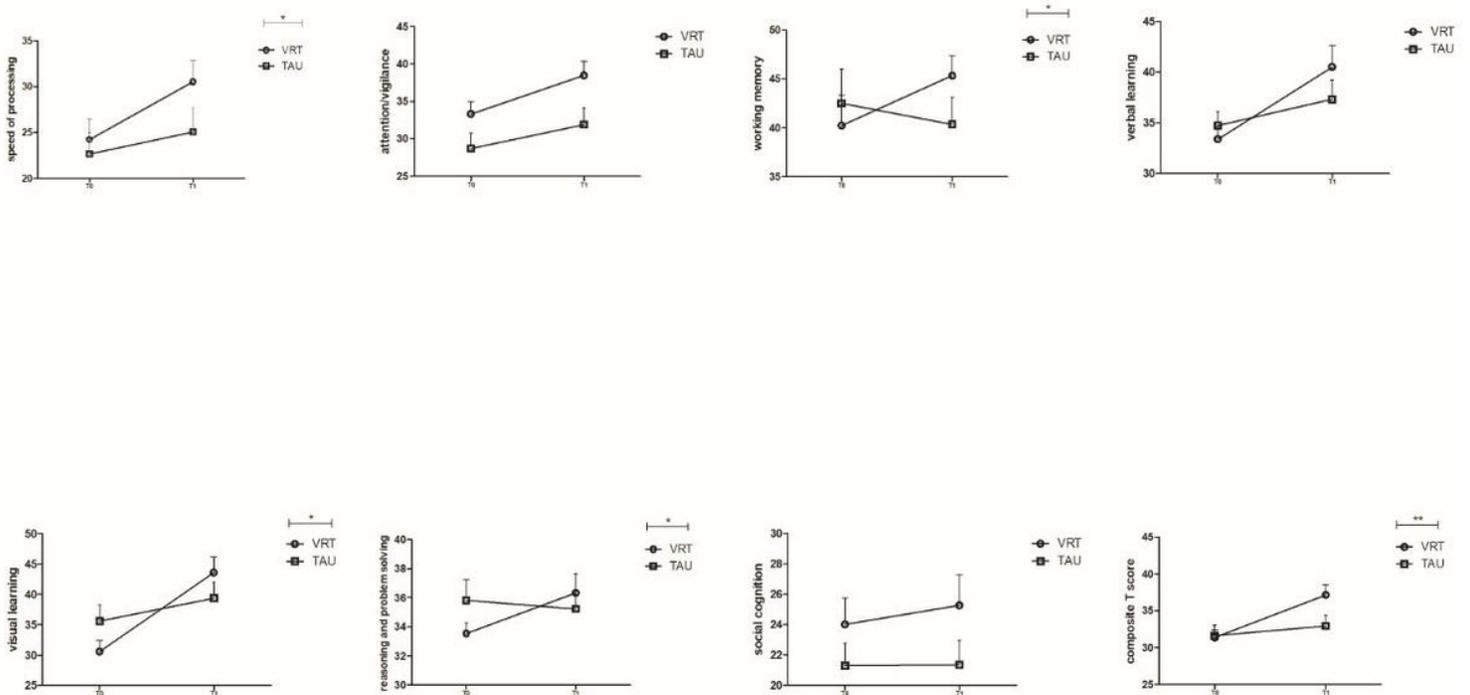


Figure 1

Participant perspective of the virtual reality supermarket.



Figure 2

Line chart showing the changes of MCCB T scores between T0 and T1 of VRT group and TAU group.