Virtual reality-based cognitive training for drug abusers: a randomised controlled trial

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ABSTRACT

Non-pharmacological means are being developed to enhance cognitive abilities in drug abusers. This study evaluated virtual reality (VR) as an intervention tool for enhancing cognitive and vocational outcomes in 90 young ketamine users (KU) randomly assigned to a treatment group (virtual reality group, VRG; tutor-administered group, TAG) or wait-listed control group (CG). Two training programmes with similar content but different delivery modes (VR-based and manual-based) were applied using a virtual boutique as a training scenario. Outcome assessments comprised the Digit Vigilance Test, Rivermead Behavioural Memory Test, Wisconsin Cart Sorting Test, work-site test and self-efficacy pre- and post-test and during 3- and 6-month follow-ups. The VRG exhibited significant improvements in attention and improvements in memory that were maintained after 3 months. Both the VRG and TAG exhibited significantly improved vocational skills after training which were maintained during follow-up, and improved self-efficacy. VR-based cognitive training might target cognitive problems in KU.

(149 words)

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When rehabilitating young drug abusers, employment may be among the most indispensable and essential elements because it can provide a positive identity and hope (Richardson, Wood, Li, & Kerr, 2010). Predicators to employment have been suggested for this population (Diller, Copeland, & Jansen, 2008; Hogue, Dauber, Dasaro, & Morgenstern, 2010). According to previous studies, ketamine is the psychotropic drug most frequently used by secondary students Li, Tam, & Tam, 2010; Tsui et al., 2011). In addition to the physical (e.g., ulcerative cystitis, kidney dysfunction) and psychological effects (e.g., increased depression and psychosis) of ketamine use (Chu, et al., 2008; Krystal et al., 2000; Morgan, Mofeez, Bradner, Bromley, & Curran, 2004), the associated cognitive problems have also been well documented, including impairments in working and episodic memory (Amann et al., 2009; Morgan & Curran, 2006; Stewart, 2001), the process of memory encoding (Rowland, Astur, Jung, Bustillo, Lauriello, & Yao, 2005) and executive function (Krystal, 2000; Morgan & Curran, 2006). Other studies have identified long-term adverse effects of ketamine use on brain structure abnormalities (frontal and prefrontal regions) and function (Laio, et al., 2010 & 2011), as well as effects on higher cortical functions such as executive function (Chen, Lee, Chan, Chen, & Tang, 2005).

To date, few studies have addressed the direct relationship between cognitive problems associated with ketamine abuse and rehabilitation or vocational outcomes. However, indirect evidence from recent reviews of the schizophrenia literature suggests that cognitive impairment may be the rate-limiting factor affecting work capacity (Liberman, 1996). Similar outcomes may be assumed in ketamine users because similar regional frontal abnormalities have been identified in patients with schizophrenia (Crespon-Facorro, Kim, Andreasen, & Daniel, 2000) and in ketamine users, who had reduced dorsal prefrontal grey matter and white matter abnormalities (Liao et al., 2011 & 2011). Furthermore, ketamine impairs dopamine system regulation (Kegeles et al., 2000; Smith et al., 1988), induces psychiatric symptoms similar to both the positive and negative symptoms of schizophrenia (Krystal et al., 2000), and has been reported to affect executive and memory functions (Jackson, Loek, & Colpaert, 1992). Therefore, the present study proposed that reducing the effect of this cognitive impairment in ketamine users might improve cognitive function and thus might also serve as a pre-requisite for improving functional outcomes such as employability.

A new field of research uses computer-assisted approaches for drug use disorders (Jackson, Loek, & Colpaert, 1992), particularly for cognitive skill training (Grohman & Fals-steward, 2003). To date, virtual reality (VR), a cutting-edge technology, has been widely used in neuro-cognitive rehabilitation (McGeorge et al., 2001). VR has the advantage of providing a virtual environment with the potential for repeated practice of skills (Kahan, 2000; Hodges, Anderson, Burdea, Hoffman, & Rothbaum, 2001), and the nature and pattern of feedback can easily be modified according to the patient's impairments before placing them in a more demanding and complicated real-life environment, such as a workplace (Weiss & Jessel, 1988). Accordingly, the present study used VR as an intervention tool for cognitive enhancement to test the hypothesis that ketamine users assigned to 2 treatment groups (virtual reality-based group, VRG; tutor-administered group, TAG) would improve to a greater extent when compared with their counterparts in a wait-listed control group (CG) in terms of cognitive performance, vocational outcomes and work-related self-efficacy both before the test and during the 3- and 6-month follow-up evaluations.

Methods

Design and participants

This study was a single-blinded, randomised controlled trial (RCT) in which the assessors were blinded to both the group assignments and the expected results of the training programmes. The assessors were responsible for the pre- and post-test and 3- and 6-month follow-up outcome assessments. Participants were trained by independent research personnel. F One hundred and forty-five ketamine users who abstained from drug use before and during the study period were recruited from the treatment and rehabilitation services of the Substance Abuse Clinic (SAC) or voluntary residential and rehabilitation treatment programmes. Ultimately, 90 participants were successfully recruited for the study (Figure 1).

Figure 1 about here

The participants were randomly and equally assigned to 1 of 2 vocational training systems (VRG or TAG) or a wait-listed CG, which were defined according to the drug-taking pattern commonly used in drug abuse studies (Daumann, Pelz, Becker, Tuchtenhagen, & Gouzoulis-Mayfrank, 2001; Gouzoulis et al., 2000).

Inclusion criteria:

- Use of ketamine at a frequency of least twice per month for 6 months within the last 2 years and no use of other illicit psychotropic drugs once or more per month within the last 2 years.
- Both sexes eligible
- Age between 15 and 30 years
- Abstinent and under treatment and rehabilitation
- Negative rapid urinary ketamine test
- Able and willing to provide informed consent to participate in the study

Exclusion criteria:

- Mental retardation [score ≤70 on the Test of Intelligence–version III or Test of Non-verbal Intelligence (TONI)-III]
- Neurological disorder
- Physical handicap (e.g., blindness)
- Significant medical diseases requiring regular medication
- Poly-drug group (use ketamine with other illicit psychotropic drug such as ecstasy or methamphetamine, with frequency at least twice per month over 6 months within the last 2 years)

The wait-listed CG was recruited and assessed according to the same inclusion and exclusion criteria. The CG members received a delayed intervention (either VR or TAG) but the training data were not computed.

Procedures

This study was approved by the Ethics Committee of Hong Kong Polytechnic University. All participants provided written consent prior to their random assignment to a study group (VRG, TAG or CG), which was achieved using a computational random number generator.

Prior to training implementation, participants in both the VRG and TAG were briefed regarding the training procedures and were required to attend 15 training sessions during a period of 5–6 weeks. Each session lasted for approximately 60 minutes. VRG participants were required to watch a non-immersive 3-D display in front of a computer screen within a quiet room but were not required to wear VR glasses. To ensure better adaptation and avoid 'cyber sickness' while navigating the virtual environment, the participants were allowed to browse the VR scenario for 5–10 minutes before the first session. The TAG participants received training from a tutor according to a training manual. The tutor used verbal instructions to guide each participant through the routines and tutorial, the contents of which were similar to those experienced by the VRG.

Interventions

Vocational training systems (VTS)

Two training programmes which used a boutique scenario as the training background were developed. These programmes were similar in content and structure but used different delivery modes. One programme used a 3D non-immersive type of VR training (virtual reality-based vocational training system or VRVTS) to create a virtual boutique and was developed by Unity (a VR game developing platform). The other programme involved tutor-administered training using a printout of the programme manual.

The 15-session training programme was divided into 3 levels with 5 sessions each: pre-trainee level, trainee level and sales level (see Figure 2). During the first 2 levels, the participants were required to complete elementary training tasks under the supervision of a manager (computerised e-tutor in the case of VR training). After completing all the elementary, the participants were required to pass a competence test before entering the sales level, which involved more advanced attention, memory and problem-solving tasks. To fulfil the role of a salesperson, each subject had to complete preparatory work (e.g., sorting and checking clothes) before the problem-solving tasks. Some conversations with the manager and customers were generated to increase the real-life experience.

A desktop computer with a Pentium IV 2.40 GHz CPU and a Windows 2000 operating system or higher was required to run the VR programme (see Figure $3_{a\text{-}d}$). Additionally, a joystick, keyboard, mouse, 38″-wide LCD monitor and set of stereo speakers were required as input and output devices.

Figure 2 about here

Figure 3 about here

Measures

Primary outcome measures: cognitive assessment

i. General intellectual abilities

The TONI-III was developed as a test of non-verbal abstract/figural problem-solving (Brown, Sherbenou, & Johnsen, 1997). A score of ≤70 is considered 'very poor'. Subjects who received scores of <70 were excluded from the present study.

ii. Attention test

The Digit Vigilance Test (DVT) is a simple task designed to measure sustained attention and psychomotor speed during the rapid visual tracking and accurate selection of target stimuli. It isolates alertness and vigilance while placing minimal demands on 2 other components of attention (selectivity and capacity) (Lewis, 1992).

iii. Memory test

The Rivermead Behavioural Memory Test (RBMT) comprises several subtests, each of which is intended to provide an objective measure of a range of everyday memory problems reported and observed in patients with memory difficulties (Man & Li, 2001).

iv. Executive function

The Wisconsin Card Sorting Test (WCST) is mainly designed to test a subject's ability to shift or switch attention between sets of stimuli (Heaton, Cheluen, Talley, Kay, & Curtiss, 1933). In this study, the Computer Version 4 (WCST-CV4, PAR) was used to measure executive functioning.

Primary outcome measures-work assessment

Employment status

This parameter was stratified into 5 categories: 1) return to full-time employment; 2) return to part-time employment; 3) return to supported employment; 4) return to sheltered employment and 5) unemployed or unable to resume work at the 3- and 6-month follow-up points.

Secondary outcome measures

Self-designed checklist of participants' knowledge and skills regarding the performance of sales-related activities (on-site test)

This self-designed on-site test assessed the participants' subjective self-evaluation of their performance of sales-related activities. This test comprised 10 questions covering 6 areas (identification, sorting, social skills and customer service, handling request and overall performance), which were scored using a 10-point Likert Scale. Examples of the areas include the abilities to identify different items (e.g., woman's shirt or man's pants in the shop), approach customers appropriately and direct customers to the changing room if necessary.

An in-depth interview with a boutique owner was conducted before designing the items on the checklist. Subsequently, an expert panel was formed to comment on the validity of the tested subject area.

Participants' self-efficacy when performing sales-related activities (self-designed)

This tool comprised 10 items intended to measure the participants' self-perceived ability to perform sales-related activities. The items were scored using a 10-point Likert scale ranging from (1) 'Strongly disagree' to (10) 'Strongly agree'. The participants were asked to rate their own self-efficacy regarding the performance of sales-related activities before and after training. An expert panel was formed to comment on the tested subject area before usage.

Statistical analysis

The data analyses were conducted using IBM SPSS Statistics, version 23. Demographic data, such as age, sex and education level, were assessed using descriptive statistics. The chi-square test and one-way analysis of variance (ANOVA) were used to determine the significance of differences in baseline (i.e., pre-test) values. Although a repeated-measures ANOVA was originally proposed for the analysis of differences in dependent variables (outcome measures) among the independent variables (3 groups and 4 time points), most of the dependent variables failed to meet the criteria for normality according the Shapiro–Wilk test. Therefore, the Friedman test (an alternative non-parametric test similar to the parametric repeated measures ANOVA) and Kruskal–Wallis test (a non-parametric test used to compare 2 or more groups of sample data) were used to test the differences. The post-hoc analysis was conducted using the Wilcoxon signed-rank tests, rather than more typical tests such as Tukey's test.

RESULTS

Sample Description

Table 1 demonstrates the lack of statistical differences among the VRG, TAG and CG in terms of demographic characteristics (e.g., age, sex, education) and baseline (pre-test) values of the primary (e.g., TONI-III, DVT, RBMT and WCST) and secondary outcome measures (e.g., on-site test and self-efficacy). Table 2 presents the mean values (standard deviations) of the primary and secondary outcome measures for the 3 groups and the respective changes in values at the post-intervention and 3- and 6-month follow-up time points. However, the TONI-III and DVT-time were only measured during the pre- and post-intervention time points.

Table 1 about here

Table 2 about here

Primary outcome measures

The Friedman test and Wilcoxon signed-rank test were used respectively to compare cognitive functioning and work-related performance among the 3 groups at 2 time points (baseline and post-intervention) and 4 time points (baseline, post-intervention and 3- and 6-month follow-ups). The results of the TONI-III exhibited a significant time effect in all 3 groups [VRG Z = 2.81, p <0.01, effect size = 0.04; TAG Z = 2.50, p = 0.01, effect size = 0.16; CG Z= 2.59, p = 0.01, effect size = 0.04)]. The Kruskal–Wallis test revealed no significant differences (χ^2 = 0.75, p = 0.69) in the changes in TONI III scores from baseline to post-intervention among the 3 groups. Moreover, the results of the DVT-time exhibited a significant time effect only in the VRG [(Z (2,31) = 3.07, p <0.01, effect size = 1.09)].

Table 3 about here

An overall significant difference in the RBMT (χ^2=10.19, p = 0.02) was observed only in the VRG (see Table 3). In a post-hoc comparison of group differences across the 4 time points (multiple Wilcoxon signed-rank test analysis), the RBMT post-intervention score (p <0.01) was found to differ significantly from the baseline score, and this benefit was maintained at the 3-month follow-up (p = 0.01, effect size = 0.80) (see Table 4).

The WCST percentage errors exhibited a significant time effect in all 3 groups (VRG χ^2= 8.57, p = 0.04; TAG χ^2 = 16.63, p <0.01; CG χ^2 = 10.86, p = 0.01) (see Table 3). Figure 4 shows the WCST percentage error change before and after training, and during 3-month and 6-month follow up. A multiple Wilcoxon signed-rank test revealed that the WCST percentage errors increased significantly in both the VRG and TAG when the 3-month (p <0.01, effect size = 0.52 and p = 0.01, effect size = 0.37, respectively) and 6-month follow-up were compared with the baseline (p <0.01, effect size = 0.48 and p <0.01, effect size = 0.91, respectively), and in the CG when comparing the post-intervention (p = 0.01, effect size = 0.72) and 6-month follow-up with the baseline (p <0.01, effect size = 0.60) (see Table 4). The Mann–Whitney U test revealed no significant difference between the VRG and TAG in terms of the change from baseline to the 3-month follow-up (Z = 0.13, p = 0.89). The Kruskal–Wallis test indicated that the difference among the 3 groups in the changes in WCST percentage errors from baseline to the 6-month follow-up was insignificant (χ^2 = 0.04, p = 0.98).

Figure 4 about here

Table 4 about here

A significant time effect was also observed in the WCST preservative errors in all 3 groups (VRG χ^2 = 12.31, p <0.01; TAG χ^2 = 12.88, p <0.01; CG χ^2 = 13.23, p <0.01) (Table 3). A multiple Wilcoxon signed-rank test revealed significant changes in the WCST preservative errors when comparing the baseline to the 3-month (p = 0.01, effect size = 1.73) and 6-month follow-up in the VRG (p <0.01, effect size = 0.46), in the TAG when comparing the baseline to the 6-month follow-up (p <0.01, effect size = 0.05), and when comparing the baseline to the post-intervention (p = 0.01, effect size = 0.86) and 6-month follow-up in the CG (p = 0.01, effect size = 0.89) (Table 4).

Again, a significant time effect was observed in the WCST percentage conceptual level responses of all 3 groups (VRG χ^2 = 13.61, p <0.01; TAG χ^2 = 12.88, p = 0.01; CG χ^2 = 10.01, p = 0.02). A multiple Wilcoxon signed-rank test revealed that in the VRG, the WCST percentage conceptual level response had increased significantly from the baseline to the 3-month (p <0.01, effect size = 1.46) and 6-month follow-up time points (p <0.01, effect size = 0.36). The Kruskal–Wallis test indicated that the difference among the 3 groups in terms of changes in the WCST percentage conceptual level responses from the baseline to the 6-month-follow-up was insignificant (χ^2 = 0.19, p = 0.91). Furthermore, the Mann–Whitney U test indicated the lack of a significant difference between the VRG and TAG in terms of the change in the WCST percentage conceptual level response from baseline to the 3-month follow-up (Z = 1.06, p = 0.29).

Secondary outcome measures

a. On-site test

A significant time effect was observed in the on-site test results of all 3 groups (VRG χ^2 = 24.08, p <0.001; TAG χ^2 = 20.04, p <0.001; CG χ^2 = 7.71, p = 0.05) (Table 3). A post-hoc comparison (Wilcoxon signed-rank test) revealed significant improvements in the on-site test, with a large effect size, in both the VRG (p <0.01, effect size = 1.24) and TAG (p <0.01, effect size = 0.89), compared to the CG. This carry-over effect was maintained at the 3-month (VRG p <0.01, effect size = 0.42; TAG p <0.01, effect size = 0.66) and 6-month follow-up time points (VRG p <0.01, effect size = 1.42; TAG p <0.01, effect size = 0.53) (see Table 4). A Mann–Whitney U test indicated no significant difference between the VRG and TAG in terms of the change in the on-site test score from the post-intervention to the baseline (Z = 1.85, p = 0.06).

b. Self-efficacy score

A significant time effect was observed in the self-efficacy scores of the VRG and TAG (VRG χ^2 = 13.61, p <0.01; TAG χ^2 = 13.59, p <0.01) (Table 3). A post-hoc comparison revealed significant improvements in the self-efficacy scores of both the VRG (p <0.01, effect size = 0.90) and TAG (p <0.01, effect size = 0.68), which were maintained at the 3- and 6-month follow-up points. However, these 2 groups differed significantly in terms of the change in self-efficacy scores from the baseline to the post-intervention (Z = 2.53, p = 0.01) (Table 4). Specifically, the TAG exhibited a greater improvement in the self-efficacy score, compared to the VRG.

c. Employment status

No statistically significant difference in employment status was observed among the 3 groups at the 6-month follow-up (χ^2 = 5.875; p = 0.209). However, the VRG had a higher employment rate (31.8%), compared to the TAG (16.7%) and CG (13.6%), as well as a higher part-time employment rate (VRG = 18.2%; TAG = 0%; CG = 0%) and lower unemployment rate (VRG = 50%; TAG = 83.3%; CG = 86.4%).

DISCUSSION

This study evaluated the ability of the VRVTS to enhance the cognitive performance of ketamine users and, as a result, their vocational outcomes. Unlike the TAG and CG, the VRG exhibited significant improvements in attention and memory over time, which might be attributed to the unique mode of VR training applied in this group. Participants in the VRG were required to attend to the instructions and response options shown on the computer screens and provide correct responses quickly, and to concentrate on multi-modal (visual and auditory) stimuli over an extended period. Participants who gave a wrong answer were required to move back to the last working step and resume practice. Previous studies have shown that the ability to concentrate may be consolidated through the persistent repetition of interactions with VR experience (Optale et al., 2010) and have demonstrated the crucial nature of endurance to stimuli during sustained attention training (Cho et al., 2002). Moreover, a functional magnetic resonance imaging (fMRI) study indicated that active spatial navigation during VR could generally boost activity in the cingulate cortex, which is responsible for attention (Baumann, Neff, Fetzick, Stangl, Basler, Vereneck, & Schneider, 2003).

Overall, ketamine users in the VRG, but not in other groups, exhibited a statistically significant improvement in memory performance as demonstrated by the RBMT, a specific test of spatial, retrospective and prospective memory (Aldrich & Wilson, 1991). This outcome might be attributable to the greater spatial processing demands made by a virtual environment, which might induce activity in the posterior hippocampus and parahippocampal cortex (Lee & Rudebeck, 2010; Rose, Brooks, & Rizzo, 2005). Hence, ketamine users exposed to VR might exhibit enhanced memory functioning because of activation of the corresponding brain regions (Lee & Rudebeck, 2010).

However, all 3 groups exhibited improvements in executive functions and non-verbal intelligence. The WCST and TONI-III have been validated for use in repeated measurements, and should not be confounded by practice effects. Therefore, these improvements across all groups might be attributed to other training programmes administered to ketamine participants by the rehabilitation organisations.

Compared to the CG, both the VRG and TAG exhibited significant improvements on the on-site vocational skills test, and these benefits were maintained at both the 3- and 6-month follow-up time points. Ketamine users in both the VRG and TAG were able to generalise the specific vocational specific skills learned during training. On one hand, the VR environment may enhance motivation and evoke social interactions imitative of those occurring in real settings, with a prolonged post-intervention effect (Calafell, Maldonado & Sabate, 2014). On the other hand, a tutor could provide prompt face-to-face feedback and guidance to facilitate the accumulation of vocational skills and help participants to sustain the skills learned effectively during participation in the TAG.

Furthermore, the self-efficacy scores increased significantly in both the TAG and VRG immediately after treatment, compared to the CG. However, these effects were not maintained at the 3- and 6-month follow-up time points. The termination of training might have reduced the participants' sense of skill mastery as perceived immediately after training. Furthermore, the TAG exhibited a greater improvement in self-efficacy, compared to the VRG. As self-efficacy is a predictor of employment outcomes (Michon, Weeghel, Kroon, & Schene, 2005), this result suggests that the training provided to both the VRG and TAG would yield long-term benefits to ketamine users.

During the study period, a larger number of ketamine users in the VRG were employed, compared with the TAG and CG. However, this outcome is considered inconclusive, and conclusions regarding the ability of improved cognitive functioning to directly influence the vocational outcomes of ketamine users should be made cautiously. Several determinants of work disability contribute to the complex and multidimensional employment process (Haugli, Maeland, & Magnussen, 2011). Accordingly, biological (e.g., physical capacity, medical status) (Waddell & Burton, 2005), psychological (e.g., self-efficacy, inappropriate fear and belief, anxiety, depression) (Haugli, Steen, Laerum, Nygard,

& Finset, 2003) and social factors (e.g., work relationship, stress at work and social support) (Franche & Krause, 2002) must be considered holistically.

The present study had some limitations of note. c However, the participants might have faced different degrees of cognitive challenges or been exposed to training periods of different durations, which may have imposed a dosage effect. These non-specific effects on cognition were considered uncontrollable and not fully measurable and were thus considered possible confounders when interpreting the results. Furthermore, ketamine users who participated in this study were required to attend 15 training sessions. The programme duration might have been too short to yield improvements in various aspects of cognitive functioning, such as executive function. Moreover, this study did not clearly address the potential recovery of neuron conductivity and re-growth of neuron sprouts after ketamine abuse. The reversibility of brain damage is a key factor affecting the efficacy of VR training, and can be evaluated using fMRI (Cole, Smith, & Beckmann, 2010). Therefore, further research could use fMRI to investigate the brain activity of drug abusers participating in treatment programmes that include VR-based cognitive training.

In summary, VRVTS may be an innovative alternative tool for the neuropsychological rehabilitation and enhancement of the cognitive functions of ketamine users. Moreover, the effectiveness of a mixed or combined training mode (e.g., combination of VR-based and tutor-administered modes) should be evaluated to determine whether better cognitive and vocational outcomes could be achieved.

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Declaration of Interest

The author reports no conflicts of interest. The author alone is responsible for the content and writing of the paper.

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TABLE 1. Demographic characteristics and baseline outcome measures

Demographic data and outcome measures	VRG (n=30)	TAG (n=30)	CG (n=30)	F/χ2	p-Value
	Mean (SD)				
Age (years)	22.80 (5.41)	24.7 7(4.14)	24.60 (3.91)	0.46	0.63
Gender	male	male	male		
Education					
Form 3 or below	18	16	15	4.82	0.08
Form 4 to Form 7	12	14	15		
Age started taking ketamine	15.85 (2.13)	17.61 (1.79)	16.80 (3.56)	1.31	0.29
Frequency of taking ketamine (times/month)^	30.11 (16.35)	52.75 (30.29)	49.60 (10.40)	2.18	0.14
Duration of taking ketamine (months)	69.90 (38.54)	73.11 (46.29)	82.90 (32.36)	0.17	0.84
Duration of abstinence (days)	134.80 (33.60)	138.56 (40.76)	144.20 (32.88)	0.11	0.89
TONI III	98.83 (8.79)	97.80 (6.13)	97.20 (4.02)	0.33	0.85
DVT-time# (sec)	369.50 (41.7)	321.00 (42.63)	342.00 (91.13)	3.36	0.19
RBMT (0-24)	21.17 (1.12)	19.80 (2.04)	18.90 (1.663)	4.30	0.12
WCST-% errors#	110.67 (14.99)	116.60 (11.52)	119.90 (12.00)	2.29	0.32
WCST- % preservative errors#	103.17 (15.41)	108.00 (19.51)	106.50 (22.66)	1.66	0.44
WCST-% conceptual level responses	90.67 (16.59)	96.00 (11.91)	99.60 (11.61)	1.79	0.41
On-site test (10-100)	67.25 (8.75)	70.60 (13.11)	62.30 (9.24)	1.46	0.48
Self-efficacy score (10-100)	71.33 (11.02)	74.80 (9.62)	63.70 (17.47)	4.62	0.10

N.B.: TONI III = The Test of Nonverbal Intelligence; DVT = Digit Vigilance Test; RBMT = Rivermead Behavioural Memory Test; WCST = Wisconsin Card Sorting Test.

#The smaller the standard scores the better the performance and vice versa.

^ The frequency of taking ketamine was self-reported by the participants in response to the question "How many time per day you took ketamine?" and the monthly frequency was calculated by multiplying the reply by 30 days (a month)

TABLE 2. Post-intervention, 3 months follow-up, and 6 months follow-up outcome measures

Outcome measures	VRG	TAG	CG
	Mean (SD)		
Post-intervention outcome measures			
	(n=30)	(n=30)	(n=30)
TONI III	99.33 (13.60)	99.30 (12.02)	94.40 (7.40)
DVT-time# (sec)	360.33 (29.34)	327.80 (30.48)	338.90 (74.71)
RBMT (0-24)	18.83 (1.12)	20.80 (1.68)	18.90 (1.69)
WCST-% errors#	104.67 (17.17)	110.60 (9.16)	113.90 (7.16)
WCST- % preservative errors#	103.00 (20.57)	118.40 (16.02)	123.00 (14.84)
WCST-% conceptual level responses	106.00 (15.82)	109.40 (10.04)	112.00 (5.91)
On-site test (10-100)	79.33 (10.61)	90.00 (6.23)	71.00 (12.91)
Self-efficacy score (10-100)	80.17 (8.47)	88.00 (5.50)	76.40 (14.32)
Employment status			
Unemployment	30 (100%)	30 (100%)	30 (100%)
3 months follow-up outcome measures			
	(n=26)	(n=22)	(n=25)
RBMT (0-24)	20.50 (2.36)	20.80 (1.81)	20.60 (2.01)
WCST-% errors#	108.42 (7.04)	111.00 (9.48)	111.90 (3.381)
WCST- %preservative errors#	115.70 (10.10)	115.20 (19.40)	116.70 (3.68)
WCST-% conceptual level responses	109.70 (7.91)	110.20 (10.25)	110.10 (5.17)
On-site test (10-100)	79.58 (8.58)	88.90 (8.462)	72.35 (13.55)
Self-efficacy score (10-100)	77.08 (14.80)	83.00 (6.83)	76.10 (13.54)
Employment status			
Unemployment	26 (100%)	22 (100%)	25 (100%)
6 months follow-up outcome measures			
	(n=22)	(n=18)	(n=22)
RBMT (0-24)	18.92 (4.01)	20.40 (.84)	20.30 (2.63)
WCST-% errors#	108.67 (8.54)	116.60 (9.32)	115.10 (6.03)
WCST- % preservative errors#	113.17 (11.73)	133.80 (15.19)	122.70 (12.28)
WCST-% conceptual level responses	108.50 (8.29)	114.80 (10.63)	114.60 (6.70)
On-site test (10-100)	78.75 (7.37)	88.80 (10.58)	70.40 (14.01)
Self-efficacy score (10-100)	77.67 (17.19)	85.00 (6.57)	73.60 (17.90)
Employment status			
Full-time employment	7 (31.8%)	3 (16.7%)	3 (13.6%)
Part-time employment	4 (18.2%)	0 (0%)	0 (0%)
Unemployment	11 (50%)	15 (83.3%)	19(86.4%)

TONI III = The Test of Nonverbal Intelligence; DVT = Digit Vigilance Test; RBMT = Rivermead Behavioural Memory Test; WCST = Wisconsin Card Sorting Test.
#The smaller the standard scores the better the performance and vice versa.

Table 3. Comparison of outcome measures among 3 groups

Domain	Primary outcome measures	Time effect in each group			Remarks
		VRG	TAG	CG	
Nonverbal intelligence	TONI III				
	Z	2.81	2.50	2.59	Kruskal-Wallis Test: Comparison of change in TONI III score among 3 groups: $\chi2=0.75$, $p=0.69$
	p-Value	<0.01**	0.01**	0.01**	
	effect size	0.04	0.16	0.04	
Attention	DVT-time#				
	Z	3.07	0.97	1.08	Only VRG showed significant improvement
	p-Value	<0.01**	0.33	0.28	
	effect size	0.25	0.18	0.04	
Memory	RBMT				
	Chi-Square	10.19	5.44	7.48	Only VRG showed significant improvement
	p-Value	0.02*	0.14	0.06	
	effect size	2.08	0.53	0.05	
Executive functioning	WCST- % errors				
	Chi-Square	8.57	16.63	10.86	See Post-hoc analysis (Table 4)
	p-Value	0.04*	<0.01**	0.01**	
	effect size	0.37	0.58	0.62	
	WCST- % preservative errors				
	Chi-Square	12.31	12.88	13.23	See Post-hoc analysis (Table 4)
	p-Value	<0.01**	<0.01**	<0.01**	
	effect size	0.43	0.13	0.88	
	WCST- % conceptual level responses				
	Chi-Square	13.61	12.88	10.01	See Post-hoc analysis (Table 4)
	p-Value	<0.01**	0.01**	0.02*	
	effect size	0.94	1.22	1.41	
Domain	Secondary outcome measures				
Work performance	On-site test				

Chi-Square	24.08	20.04	7.71	See Post-hoc analysis
p-Value	<0.001***	<0.001***	0.05*	
effect size		1.24	2.00	0.78
Self-efficacy score				
Chi-Square	13.61	13.59	6.03	See Post-hoc analysis
p-Value	<0.01**	<0.01**	0.11	
effect size	0.90	1.74	0.79	

TONI III = The Test of Nonverbal Intelligence; DVT = Digit Vigilance Test; RBMT = Rivermead Behavioural Memory Test; WCST = Wisconsin Card Sorting Test.
*<0.05; **<0.01; ***<0.001.

Table 4. Post-hoc analysis of change in outcome measures across 4 time points

Primary outcome measures	Groups	Post-intervention - baseline			3-month-follow-up - baseline			6-month-follow-up - baseline		
		Z	p-Value	Effect size	Z	p-Value	effect size	Z	p-Value	Effect size
RBMT	VRG	3.11	<0.01**	2.10	2.55	0.01**	0.80	0.64	0.52	
WCST-% errors	VRG	2.28	0.02		2.83	<0.01**	0.52	2.80	<0.01**	0.48
	TAG	1.69	0.09	1.72	2.52	0.01**	0.37	2.81	<0.01**	0.91
	CG	2.54	0.01**		2.20	0.03		2.71	<0.01**	0.60
	Group difference 1	VRG-TAG		3-month-follow-up-baseline				0.13	0.89	
	Group difference 2	VRG-TAG-CG		6-month-follow-up- baseline				χ2=0.04	0.98	
WCST-% preservative errors	VRG	1.97	0.05	0.86	2.52	0.01**	0.73	2.76	<0.01**	0.46
	TAG	1.79	0.07		1.79	0.07		2.81	<0.01**	0.05
	CG	2.54	0.01**		1.49	0.14		2.54	0.01**	0.89
	Group difference	VRG-TAG-CG		6-month-follow-up-baseline				3.97	0.14	
WCST-% conceptual level responses	VRG	2.28	0.02		2.81	<0.01**	0.46	2.94	<0.01**	0.36
	TAG	1.69	0.09		2.52	0.01**	0.28	2.87	<0.01**	0.67
	CG	2.30	0.02		2.22	0.03		2.71	<0.01**	0.85
	Group difference 1	VRG-TAG		3-month-follow-up-baseline				1.06	0.29	
	Group difference 2	VRG-TAG-CG		6-month-follow-up-baseline				χ2=0.19	0.91	
Secondary outcome measures										
On-site test	VRG	3.07	<0.01**	0.24	3.07	<0.01**	1.42	3.07	<0.01**	1.42
	TAG	2.81	<0.01**	0.89	2.81	<0.01**	1.66	2.81	<0.01**	1.53
	CG	1.85	0.07		1.69	0.09		1.69	0.09	
	Group difference	1.85	0.06							
Self-efficacy score	VRG	3.08	<0.01**	0.90	1.42	0.16		0.95	0.34	
	TAG	2.81	<0.01**	0.68	1.18	0.24		2.10	0.04	
	CG									
	Group difference	2.53	0.01							

TONI III = The Test of Nonverbal Intelligence; DVT = Digit Vigilance Test; RBMT = Rivermead Behavioural Memory Test; WCST = Wisconsin Card Sorting Test.
<0.01; *<0.001

Figure 1
Flow diagram of the randomization procedures

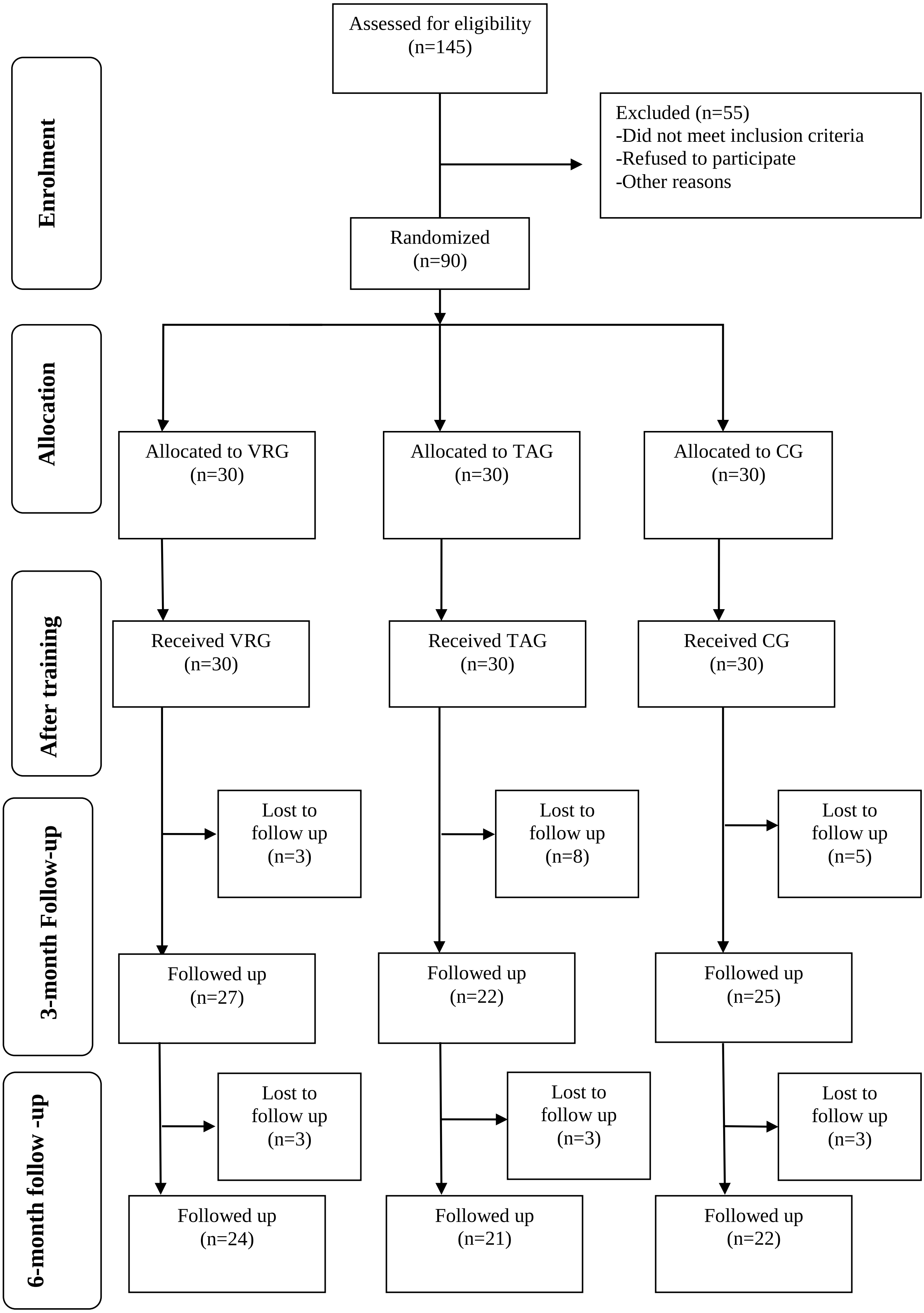

Figure 2

Training content of VRST

Pre-trainee level	
Session 1	
Training modules	**Tasks**
Orientation	-Identify areas of female, male and children's clothes, changing room, store room and cashier -Identify what is placed on each shelf
Problem-solving task: Trainee was asked to get a male T-shirt	
Session 2	
Identify clothes	-Identify male, female and children's clothing from different baskets -Identify clothes based on categories -Identify sizes of the clothes based on the labels
Problem-solving task: Trainee was asked to identify clothes based on two criteria at the same time, e.g. female jeans	
Session 3	
Stock finding	-Orientation of the store room -Locating clothes in the store room
Problem-solving task: Trainee was asked to locate a T-shirt in the store room or count the stock	
Session 4	
Sorting	-Sorting of clothes according to their category -Hanging up clothes based on the rules, i.e. light colors to dark colors -Hanging up clothes in different areas based on the category
Problem-solving task: Trainee was asked to hang up one basket of clothes based on the categories and rules	
Session 5	
Checking clothes	-Checking of hangers to make sure all were facing the same direction. If a different direction was found, the trainee had to place it back in the correct direction -Checking of clothes to see whether or not they were wrinkled Removal if wrinkles were found

Problem-solving task: Trainee was asked to check all of the shelves in the shop	
Trainee level **(Before starting the trainee level, the trainee had to revise all of the skills learned in sessions 1-5 for 10 min)**	
Session 6	
Greeting customers	-Greeting of customers whenever they came into the shop -Saying goodbye and thank you to the customers when they left
Session 7	
Directing customers	-Directing customers to different areas -Directing customers to find the clothes she/he requested
Session 8-9	
Handling requests	-Bringing customers to the fitting room -After customers tried on the clothes the trainee was to handle any customer requests: 1. Too big/too small 2. Too long/too short 3. Customer wanted to buy an item that could not be found in the shop
Sales level	
Session 10-12	
Handling requests	Handling of customer requests after items were sold: 1. Customer disliked the clothes 2. Customer wanted to change an item
Session 13-15	
Problem solving	Handling of three scenarios randomly selected from the following: 1. No such size 2. No such color 3. No such clothes, e.g. green pants 4. Clothes missing buttons 5. Customer complained the size of clothing was too small after he/she tried it on at home 6. Customer came back to change an item but there is no stock 7. Customer insisted on getting back money instead of changing one item for another 8. Finding a suitable item for the customer

	9. Customer requested a price deduction 10. Customer asked whether the color of the cloth would fade after washing 11. Trousers were still too long after shortening 12. The customer disliked all clothes after trying a few on

Figure 3a Hardware of the VRVTS

Figure 3b Inner shop

Figure 3c Screenshot of the VRVTS (entrance)

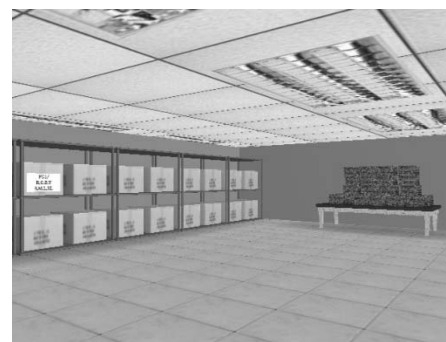

Figure 3d Screenshot of the VRVTS (store room)