# Final Report to Beat Drugs Fund Association

## Project title

# Cognitive Rehabilitation for Vocational Training of Primarily Ketamine Users: A Randomized Control Trial (BDF120021)

Prepared & submitted

by

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## Introduction

During the rehabilitation journey in youngsters with drug abuse, employment can be one of the most indispensable and essential elements which may provide them with a positive identity and hope (The Society for the Rehabilitation Offender, 1998; Richardson, et al., 2010). Predicators to their employment and possible gender differences have been suggested (Diller, Copeland & Jansen, 2008; Hougue, 2010). Local statistics of drug use showed that ketamine was the top one psychotropic drug taken by secondary students (Li, Tam & Tam, 2010; Tsui et al., 2011). Apart from the physical (ulcerative cystitis, kidney dysfunction; Chu et al., 2008) and psychological effects of ketamine use (increased depression and psychosis; Krystal et al., 1994; Morgan, Muetzelfeldt & Curran, 2010), cognitive problems have also been documented. They include impairment in working and episodic memory (Amann, 2009; Morgan 2006; Stewart 2001), memory process in encoding (Rowland et al., 2005), as well as executive function (Krystal, et al., 2000; Morgan et al., 2004). Local studies also documented similar harmful cognitive effects of ketamine abuse among Hong Kong young people (Chen et al., 2005; Tang et al., 2010). Long term effect of ketamine use on brain structure abnormalities (frontal and prefrontal regions) and function have been reported in recent neuro-imaging studies (Liao, et al., 2010; 2011). It is anticipated that higher cortical functions such as executive function will be affected (Chen et al., 2005).

Cognitive impairment in people with drug abuse may be a barrier in work rehabilitation (Richardson et al., 2010). There is a paucity of research on direct relationship between ketamine-abuse cognitive problems and vocational outcomes, but indirect evidences from recent reviews of the schizophrenia literatures suggested that cognitive impairment can be the rate-limiting factor in work capacity (Liberman, 1996), and similar outcomes may be assumed in ketamine users. It is because regional frontal abnormalities has been found in schizophrenia (Crespon-Facorro et al., 2000), which is comparable to ketamine users who had reduced dorsal prefrontal gray matter and white matter abnormalities (Liao, et al., 2010; 2012). It was also reported that ketamine impaired dopamine system regulation (Kegeles et al., 2000; Smith et al., 1998) and induces psychiatric symptoms similar to positive and negative symptoms of schizophrenia (Krystal et al., 1994), as well as executive and memory functions (Jackson et al., 1992; Krystal et al., 1994). A local study indicated that cognitive functioning was a significant predictor in schizophrenia (Tsang et al., 2010). Thus, reducing the effect of this cognitive impairment was hypothesized to improve work rehabilitation outcomes and ultimately employability among ketamine users in the present study.

In rehabilitation and treatment of drug abusers, conventional community-based vocational rehabilitation (i.e. vocational assessment, counselling, training and supported employment services to drug abusers) has been practiced. In tackling the specific cognitive problems associated with ketamine abuse, cognitive rehabilitation (CR) has been proposed as an adjunct therapy to successful vocational outcomes in this population group. To date, few CR studies had been identified in drug abusers, but meta-analysis showed effectiveness of CR in schizophrenia (McGurk, et al., 2007). The effect sizes for overall cognition and six out of the seven domains of cognitive performance (attention/vigilance, speed of processing, verbal working memory, verbal learning and memory, reasoning/problem solving and social cognition) were significant. Most of the effects were in the medium or low-to-medium effect size range (ranging from 0.39-0.54). It was assumed that similar CR training effect might also occur in ketamine users. Moreover, there is a new trend of using the computer-assisted approach for drug use disorders (Moore, et al., 2011) and may incorporate into cognitive skill training (Grohman & Fals-steward, 2003). Bell and his associates (2001 & 2003) tried to combine computer-assisted cognitive exercises with a vocational programme to enhance the generalization to daily activities. McGurk's group (2005) showed that patients who underwent CR with supported employment found more jobs, more hours of work and greater wages than patients with supported employment alone. To date, virtual reality, a cutting-edge technology, has been widely used in neuro-cognitive rehabilitation (McGeorge et al., 2001; Rose et al., 1998) and in psychiatric conditions (North, North & Coble, 1998; Riva et al., 1998). Virtual reality has the advantage of providing a virtual work environment with the potential for infinite repetitions of the same work skills training tasks (Kahan, 2000; Hodges et al., 2001). The nature and pattern of feedback can be easily modified according to patients' impairments, before they enter a more demanding and complicated real work environment (Bell &Weinstein, 2011; Weiss & Jessel, 1998).

The present study thus used virtual reality (VR) as an intervention tool for cognitive training and possible enhancement in vocational outcomes. In fact, local studies using similar training programmes have already been developed by the investigator of this project and his team. Preliminary positive findings in cognitive rehabilitation for persons with schizophrenia were found (Man, Law & Chung, 2012; Tsang & Man, 2013). The effectiveness of this virtual reality-based vocational training system (VRVTS) had been readily available for going through this randomized control trial and positive results were anticipated in this study and the programme would be applicable to local treatment and rehabilitation services.

**b) Objectives of the study**

i. To improve the cognitive function and vocational outcomes of youngsters who were primarily ketamine users through vocational training systems (VTS).

ii. To investigate if there was any significant differences among two treatment groups (virtual reality-based group /VRG, tutor-administered group/TAG) and a wait-listing control group/CG) in terms of cognitive performance, vocational outcomes and work-related self-efficacy, during pre-test, post-test, 3-month and 6-month follow up.

- Tool for measuring improvement in cognitive function: Test of Non-Verbal Intelligence – version III (TONI-III); Digit Vigilance Test (DVT); Rivermead Behavioral Memory Test (RBMT), Wisconsin Card Sorting Test – Computer Version 4 (WCST-CV4)

- Tools for measuring improvement in vocational outcomes: Employment Status (5 categories); On-site test (testing on vocational knowledge and skills); Self-efficacy checklist in work (10-items).

**Methods**

i. Design

This study was a single-blinded, randomized controlled trial (RCT) in which the assessors were blinded to the group assignment, did not know the expected results of the training programmes. They were responsible for the outcome assessments during pre-test, post-test, and 3-month and 6-month follow up. Independent research personnel were responsible for training participants.

ii. Procedures

The study had got approval from the Research Ethics Committees of The Hong Kong Polytechnic University and all participants had signed written informed consent form to take part in the study. The participants were recruited from major organization providing drug treatment and rehabilitation services, as indicated in the website of Narcotics Division, Security Bureau of HKSAR. All of these participants were randomly assigned to the two treatment groups (VRG, TAG) using a computational random number generator. Age-, gender- and education-matched wait-listing control group (CG) was also recruited.

Before training implementation in both the VRG and TAG, the participants were briefed on the training procedures. They were required to attend 10 sessions of training over a period of five to six weeks. Each session lasted for about 60 minutes. For the sake of better adaptation and to observe any cases of cyber sickness, the participants would be allowed to browse the VR scenario for 5 to 10 minutes during the first session. For the TAG, a tutor administered the training according to the training manual by practicing routines and tutorials with specific instructions and similar contents to the VRG.

iii. Instrumentation

*Vocational training systems (VTS)*

Two training programmes using a boutique scenario as the training background were developed due to two reasons. First, being a salesperson was identified as one of the six most commonly held jobs by people with schizophrenia in Hong Kong and it might be considered suitable with people with drug abuse (Tsang, Ng & Chiu, 2002; Wong et al., 2001). Second, a salesperson required cognitive skills for interacting with customers and for handling conflicts and handling customers' requests (Cheung & Tsang, 2005). A boutique scenario had thus been adopted so as to allow total control and consistency in stimulus delivery with the presentation of hierarchical and repetitive stimulus challenges that could be varied from simple to complex. Immediate feedback on performance was also given, which helped to create self-awareness.

As mentioned earlier, one of the abovementioned programmes was a virtual boutique, using a 3D non-immersive type of VR training while the other was a tutor-administered training using a printout manual of the programme. These programmes had prior proven evidence of improving cognitive function and vocational outcome in a local study (Tsang & Man, 2013). They were similar in content and structure but used different delivery modes. A total of 10 training modules were divided into three levels: pre-trainee level, trainee level and sales level. The participants had to complete elementary training tasks (pre-trainee and trainee levels) under the supervision of a manager (computerized e-tutor in the case of VR training). After the participants had completed all training in each level, they had to pass a competence test before entering the sales level, which involved more advanced attention, memory and problem-solving tasks. In fulfilling the role of a salesperson, each subject had to complete some preparatory work (e.g. sorting clothes and checking clothes) before the problem-solving tasks. Some conversations were generated with the manager and customers to increase the real-life experience. For VR training, a desktop computer was required to run the programme in the VRG (see Figure $1_{a\text{-}d}$).

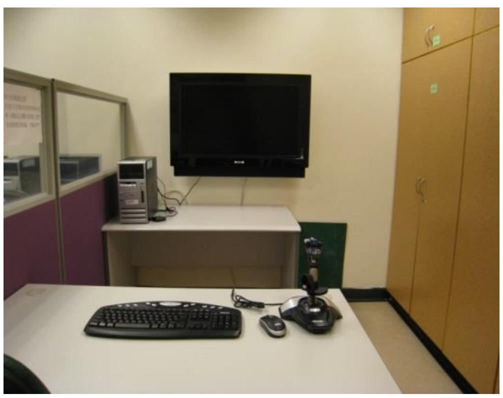

Figure 1a. Hardware of VRVTS

Figure 1b. Snapshot of the VR programme (inner shop)


Figure 1c. Screenshot of the VRVTS (entrance)

Figure 1d Screenshot of the VRVTS (store room)

vi. Primary outcome measures - Cognitive perspective

*General intellectual abilities*

The Test of Non-verbal Intelligence – Version III (TONI-III; Brown, Sherbenou & Johnsen, 1997) has been developed to be a non-verbal abstract/figural problem-solving test. The content, instructions and responses do not require verbal or written language. The test content includes only figural drawings and examinees can respond by gestures, such as pointing or even blinking eyes. According to the examiner's manual, a score of 70 or below would be classified as "very poor". Therefore, subjects who scored below 70 would be excluded from the present study.

*Attention test*

Digit Vigilance Test (DVT; Lewis, 1992) is a test that is sensitive to subtle changes in neuropsychological status but relatively insensitive to the effect of repeated administrations. The DVT is a simple task designed to measure sustained attention and psychomotor speed during rapid visual tracking and accurate selection of target stimuli. It appears to isolate alertness and vigilance while placing minimal demands on two other components of attention: selectivity and capacity.

*Memory Test*

Rivermead Behavioural Memory Test – Chinese version (RBMT-CV; Wilson et al., 1985; Man & Li, 2001) comprises a number of subtests, each attempting to provide an objective measure of one of a range of the everyday memory problems reported and observed in patients with memory difficulties. Two scores are given for each subtest: a simple pass/fail or screening score and a standardized profile score ranging from 0 to 24. The screening score offers a simple way of estimating whether or not a patient is likely to have everyday memory problems, while the profile score offers a more sensitive measure of change and is more suitable for measuring change resulting from, for example, deterioration in the patient or from improvements following treatment. This test is also widely used to measure memory impairment in schizophrenia (Tyson et al., 2005) and may be considered suitable for ketamine users.

*Executive function*

Wisconsin Card Sorting Test (Heaton et al., 1993) is mainly designed to test one's ability to shift or switch attention between sets stimuli. In this study, the Computer Version 4 (WCST-CV4, PAR) was used to measure executive functioning. Initially, a number of stimulus cards were presented to the participant. The participants were not told how to match the cards; however, they were told whether a particular match was right or wrong. The mistakes made during this learning process were analyzed to arrive at a score. The test took approximately 12-20 minutes to carry out and generated a number of psychometric scores, including numbers, percentages and percentiles of categories achieved, trials, errors and preservative errors. Clinically, the test is widely used in patients with acquired brain injury, neurodegenerative disease and mental illness such as schizophrenia (Chan et al., 2006).

v. Primary outcome measures -Work perspective

*Employment status*

It was categorized into five groups: 1) return to full-time employment; 2) return to part-time employment; 3) return to supported employment; 4) return to sheltered employment; and 5) being unemployed or unable to resume work during the three month and six month follow-up.

vi. Secondary outcome measures

*Self-designed checklist on participants' knowledge and skills in performing sales-related activities (on-site test).*

It was a self-designed on-site test that assessed a subject's performance in sales-related activities. For examples, sorting skills and selling techniques. An in-depth interview had been conducted with a boutique owner before designing the items on the checklist. Also, an expert panel had been formed to comment on the subject area to be tested. This test was given before and after training to assess the participants' knowledge and skills in performing sales-related activities.

*Participants' self-efficacy in performing sales-related activities (self-designed).* It consisted of 10 items to measure the participants' self-perceived ability in performing sales-related activities. It used a 10-point Likert scale ranging from (1) "Strongly disagree" to (10) "Strongly agree" so the participants could rate their own self-efficacy in performing sales-related activities before and after training. Also, an expert panel had been formed to comment on the subject area to be tested.

vii. St*atistical analysis*

The data analyses were conducted using IBM SPSS Statistics version 23. The demographic data such as age, gender, education level were computed by descriptive statistics. The Chi-square test or one-way analysis of variance (ANOVA) was proposed to examine whether any significant baseline differences were present before intervention.

Repeated-measures ANOVA had been originally proposed to be used to analyze differences in the dependent variables (outcome measures) among independent variable (the three groups and four different time points). However, according Shapiro-Wilk Test of normality, the criteria for normality was not met in most of the dependent variables. So a non-parametric alternative test, Friedman Test (a non-parametric statistics similar to parametric repeated measures ANOVA), Kruskall Wallist test (a non-parametric test to compare 2 or more sample data) were used instead to test the differences. Post-hoc analysis was thus conducted by Wilcoxin Signed Ranks Tests, instead of typical tests like the Tukey's test.

c) Number and nature of subjects involved

90 participants, who were ketamine users, receiving treatment and rehabilitation services of Substance Abuse Clinic (SAC) or voluntary residential and rehabilitation treatment programmes, were successfully recruited. They were randomly and equally assigned to one of the two vocational training systems (see instrumentations session) and a wait-listing control group. They were defined according to drug taking pattern commonly used in drug abuse studies (Dauman et al., 2001; Gouzoulis Mayfrank et al., 2000).

Inclusion criteria:

- Use of ketamine with frequency at least twice per month over 6 months within the last 2 years and no other illicit psychotropic drug used up to once per month within the last 2 year.
- Chinese ethnicity of both genders
- Age between 15 and 30
- Under treatment and rehabilitation following abstinence
- Negative results obtained from the rapid urinary test of ketamine
- Able and willing to provide informed consent to participate in the study

Exclusion criteria:

- Mental retardation
- Neurological disorder
- Physical handicaps, for example blindness
- Significant medical diseases requiring regular medication
- Poly-drug group (use ketamine with other illicit psychotropic drug such as Ectascy or methamphetamine, with frequency at least twice per month over 6 months withn the last 2 years)

The wait-listing control group were recruited and assessed in a similar way based on the inclusion and exclusion criteria. They would then receive a delayed intervention (either VR or TAG) but the training data would not be computed. The sample size of 90 (each group of 30) was estimated according to a) related literatures (Cohen, 1988) and b) using the software "Power Analysis and Sample Size for Windows" v. 11, PASS 14 (NCSS.com, 2015) accordingly.

## Results

i. Descriptive statistics

Table 1 shows that the participants in the three different groups did not differ in their demographic characteristics and baselines of outcome measures. Table 2 presents the post-intervention, 3-month follow-up and 6-month follow-up regarding the primary and secondary outcome measures.

ii. *Primary outcome measures*

In order to compare the cognitive functioning and work-related performance among the three groups at two time points (baseline and post-intervention) and four time points (baseline, post-intervention, 3-month follow-up and 6-month follow-up), Friedman test and Wilcoxon signed-ranks test were used respectively. The results are summarized in Table 3. There was a significant time effect in TONI III for all three 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)]. Kruskall Wallis test was used to find any significant differences in the change of TONI III post-intervention-baseline test scores among the three groups. No significant difference was found ($\chi^2$ = 0.75, p = 0.69). Moreover, there was a significant time effect in DVT-time [(Z (2,31) =3.07, p<0.01, effect size = 1.09)] for the VRG only.

An overall significant difference was found in RBMT ($\chi^2$=10.19, p = 0.02) for the VRG only (See Table 3). A post-hoc comparison of multiple Wilcoxon signed-ranks test was conducted to compare group differences across the four time points. It was revealed that RBMT post-intervention score (p <0.01) was significantly different from that of the baseline, and the benefit was maintained in 3-month follow-up (p=0.01, effect size = 0.80) (See Table 4).

There was a significant time effect in WCST-percentage-errors (VRG $\chi^2$= 8.57, p = 0.04; TAG $\chi^2$= 16.63, p < 0.01; CG $\chi^2$ = 10.86, p = 0.01) for all three groups (See Table 3). Multiple Wilcoxon signed-ranks test revealed that WCST-percentage-errors had significantly increased when comparing 3-month-follow-up-baseline (p< 0.01, effect size = 0.52) and 6-month-follow-up-baseline (p<0.01, effect size = 0.48) in the VRG, when comparing 3-month-follow-up-baseline (p= 0.01, effect size = 0.37) and 6-month-follow-up-baseline (p<0.01, effect size = 0.91) in the TAG, and when comparing post-intervention-baseline (p=0.01, effect size = 0.72) and 6-month-follow-up-baseline (p<0.01, effect size = 0.60) in the CG (See Table 4). Mann-Whitney U test showed no significant difference between VRG and TAG's change in 3-month-follow-up-baseline (Z= 0.13, p=0.89). Kruskall Wallis test indicated that the difference between the change in WCST-percentage-errors in 6-month-follow-up-baseline among the three groups was insignificant ($\chi^2$ = 0.04, p=0.98).

**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 response | 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 score 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 response | 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 response | 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 response | 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 score 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: $\chi 2=0.75$, $p=0.69$ |
| | 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 response | | | | |
| | 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 response | 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

There was a significant time effect in WCST-preservative errors (VRG $\chi^2$= 12.31, p <0.01; TAG $\chi^2$= 12.88, p < 0.01; CG $\chi^2$ = 13.23, p < 0.01) for all three groups (See Table 3). Multiple Wilcoxon signed-ranks test revealed that WCST-preservative errors had significantly changed when comparing 3-month-follow-up-baseline (p=0.01, effect size= 1.73) and 6-month-follow-up-baseline (p< 0.01, effect size = 0.46) in the VRG, when comparing 6-month-follow-up-baseline (p<0.01, effect size = 0.05) in the TAG, and when comparing post-intervention-baseline (p=0.01, effect size= 0.86) and 6-month-follow-up-baseline (p= 0.01, effect size = 0.89) in the CG (See Table 4). Kruskall Wallis test was used to test the difference among the three groups in the change of 6-month-follow-up-baseline and no significant difference was found (Z= 3.97, p=0.14) (See Table 4).

There was a significant time effect in WCST-percentage-conceptual level response (VRG $\chi^2$= 13.61, p <0.01; TAG $\chi^2$= 12.88, p = 0.01; CG $\chi^2$ = 10.01, p = 0.02) for all three groups (See Table 3). Multiple Wilcoxon signed-ranks test revealed that WCST- percentage conceptual level response had significantly increased when comparing 3-month-follow-up-baseline (p< 0.01, Effect size = 1.46) and 6-month-follow-up-baseline (p<0.01, effect size = 0.36) in the VRG, when comparing 3-month-follow-up-baseline (p = 0.01, effect size= 0.28) and 6-month-follow-up-baseline (p<0.01, effect size = 0.67) in the TAG, and when comparing 6-month-follow-up-baseline (p<0.01, effect size = 0.85) in the CG (See Table 4). Kruskall Wallis test indicated that the difference between the change in WCST- percentage conceptual level response in 6-month-follow-up-baseline among the three groups was insignificant ($\chi^2$ = 0.19, p=0.91). Mann-Whitney U test showed that there was no significant difference between the change in WCST- percentage-conceptual level response in 3-month-follow-up-baseline between the VRG and the TAG (Z=1.06, p=0.29).

iii. Secondary outcome measures

*a. On-site test*

There was a significant time effect in on-site test (VRG $\chi^2$= 24.08, p <0.001; TAG $\chi^2$= 20.04, p < 0.001; CG $\chi^2$ = 7.71, p = 0.05) for all three groups (See Table 3). After conducting a post-hoc comparison of Wilcoxon signed-ranks test, it was found that both the VRG (p<0.01, effect size= 1.24) and the TAG (p<0.01, Effect size= 0.89) showed significant improvement with large effect size in the on-site test than the CG, with the benefit maintained at 3-month follow-up (VRG p<0.01, effect size= 0.42; TAG p<0.01, effect size= 0.66), and 6-month follow-up (VRG p<0.01, effect size = 1.42; TAG p<0.01, effect size = 0.53) (See Table 4). Mann-Whitney U test indicated that there was no significant difference in the change of on-site post-intervention-baseline test score between the VRG and the TAG (Z= 1.85, p = 0.06).

*b. Self-efficacy score*

There was a significant time effect in self-efficacy score (VRG $\chi^2$= 13.61, p <0.01; TAG $\chi^2$= 13.59, p < 0.01) for the VRG and the TAG (See Table 3). After conducting a post-hoc comparison of Wilcoxon signed-ranks test, it was found that both the VRG (p<0.01, effect size=

0.90) and the TAG ($p<0.01$, effect size= 0.68) showed significant improvement with large effect size in the self-efficacy score, but no benefit was maintained at 3-month follow-up and 6-month follow-up (See Table 4). Mann-Whitney U test indicated that there was significant difference in the change of self-efficacy post-intervention-baseline test score between the VRG and the TAG ($Z= 2.53$, $p = 0.01$) (See Table 4), with the TAG showed better improvement in the self-efficacy score than the VRG (See Table 2).

Summary of results:

1. TONI3 (nonverbal intelligence)
    a. Result: No significant difference in change of TONI3 score among 3 groups, suggesting that all groups had similar improvement across time.
    b. Interpretation: The change in TONI3 score was accounted by main time effect only. No group effect was observed. Maturation effect may account for the change. The result may also suggest that VRG and TAG have no additional benefit in improving intelligence.
2. DVT (attention)
    a. Result: Only VRG had significant improvement in DVT score, with large effect size
    b. Interpretation: The improvement in DVT score indicated significant improvement in sustained attention. The result indicated that VRG had distinctive treatment effect in improving attention. The result may be accountable by the mode of training in VRG which more intensively required sustained attention.

3. RBMT (memory)
    a. Result: Only VRG showed significant improvement in RBMT score immediately after and 3 month after treatment, with large effect size.
    b. Interpretation: The improvement in DVT score indicated significant improvement in memory. The result indicated that VRG had distinctive treatment effect in improving memory and the effect can be maintained for 3 months.
4. WCST (executive functioning)
    a. Result: Significant improvement across all treatment groups, no significant difference in change observed among the groups
    b. Interpretation: The change in WCST score was accounted by main time effect only. No group effect is observed. Practice effect and maturation effect may explain the improvement in the score across the time as the WCST score continued to increase with the number of trial. The result may suggest that VRG and TAG had no additional benefit in improving executive functioning.
5. Onsite Test (sales-related activities)
    a. Result: Both VRG and TAG showed significant improvement in onsite test. The improvement was shown immediately after treatment, and at 3 months and 6 months

follow-ups. Post-hoc analysis showed that the improvement in TAG was significantly larger than that of VRG at 3 months and 6 months follow-ups.

   b. Interpretation: Both VRG and TAG showed significant effect in enhancing sales job skills. TAG was superior in sustaining the training effect when compared with VRG. The result may suggest that job skills learned in real environment or under real person instruction may be more sustainable than virtual reality.

6. Self-efficacy (sales-related activities)
   a. Result: Both VRG and TAG showed significant improvement in Self-efficacy immediately after treatment but the effect did not last for 3 months and 6 months follow-ups. Post hoc test showed that TAG had a larger improvement comparing with VRG.
   b. Interpretation: Both VRG and TAG enhanced self-efficacy but the effect did not sustain. TAG was more effective than VRG in improving participants' self-efficacy in sales-related activities. The result may suggest that human contact and real person instruction may be more effective in enhancing self-efficacy in vocational training.

7. All the subjects at 3-month follow up were unemployed. And there were no statistically significant difference in employment status at 6-month follow up across the three groups respectively ($\chi^2$= 5.875; p=0.209) though VRG had got more open employment (VRG=31.8%) than TAG (16.7%) and CG group (13.6%); part-time employment (VRG=18.2%; TAG= 0%; CG=0%), lower percentage in unemployment (VRG=50%; TAG=83.3%; CG=86.4%).

**Discussion**

The main goal of this study was to investigate the feasibility of virtual reality-based vocational training system (VRVTS) on enhancing cognitive performance and thus vocational outcomes of Ketamine users. It was found that participants in the VRG showed significant improvement in cognitive functions in respect of attention and memory across time, but not in the TAG and the CG. The reason of improvement in the domain of sustained attention as measured by DVT in the VRG might be due to its unique mode of training, though the VRG had the same training contents as the TAG. Participants in the VRG had to pay attention to the instructions and choices of answer that were shown on computer screens in order to give correct responses shortly. They had to concentrate on multi-modal (visual and auditory) stimulus in an extended period of time. If they gave a wrong answer, they had to move back to the last working step and continued practices. It was shown that the ability to concentrate may be consolidated through persistent repetition of interaction with VR experience (Optale et al., 2010) and endurance to stimuli was crucial in training of sustained attention (Cho et. al., 2002). Moreover, a pilot study using fMRI indicated that active spatial navigation in VR could generally boost the activity of cingulate cortex, which was responsible for attention (Baumann et. al., 2003).

Besides, improvement in overall memory performance in the VRG was statistically significant but not in other groups. This was demonstrated by RBMT, a specific test which measured spatial, retrospective and prospective memory (Aldrich & Wilson, 1991). The result could probably due to greater spatial processing demand with virtual environment that could induce activity in posterior hippocampus and parahippocampal cortex (Rose et al., 2005; Lee & Rudebeck, 2010). Hence, capacity of working memory may be enhanced because of the activation of the corresponding brain regions (Lee & Rudebeck, 2010; Baumann, et. al., 2003).

However, the three groups showed improvement in executive functions and non-verbal intelligence. As WCST and TONI-3 were tests that could be used for repeated measurements, there should not be any practice effects. The improvements among the three groups were attributed to the maturation or history effects as all participants engaged in other rehabilitation services that had been run by the organizations.

The secondary outcome measures focused on on-site test, self-efficacy score and also the employment outcome of the Ketamine users. Both the VRG and the TAG showed significant improvement in on-site vocational skills test compared to that of the CG, and the benefit was maintained at 3-month follow-up and 6-month follow-up. They had a similar effect on the difference of learning vocational skills in sales-related activities across time. Therefore, the generalization of learnt vocational specific skills was possible in participants of both the VRG and the TAG. On one hand, VR environment could enhance participants' motivation and evoke social interactions that imitated those happening in real conditions with a prolonged effect after intervention (Calafell et. al., 2014). On the other hand, a tutor could provide face-to-face prompt feedback and guidance to facilitate the building up of vocational skills and help participants to sustain the learnt skills effectively in the TAG.

Furthermore, the self-efficacy score of the TAG and the VRG increased significantly immediately after treatment compared to the CG, but no maintenance effect was noted at 3-month follow-up and 6-month follow-up. This may be due to the termination of training lowered the sense of the mastery of skills perceived by the participants. Improvement in self-efficacy in the TAG was greater than that of the VRG. The reasons could be related to greater skills competency and skill generalization perceived by participants in the TAG compared to that in the VRG. Since self-efficacy was one of the predictors of employment outcomes (Michon et. al., 2005), it was believed that the VR and TA training would benefit participants in a long-run.

Nevertheless, the number of participants being employed in the VRG was larger than TAG and CG. Caution had to be taken when concluding whether improving cognitive functioning could directly influence vocational outcome of Ketamine users. There were several determinants of work disability which made the Return-To-Work process complex and multidimensional (Haugli et. al., 2011). Other than biological factors (e.g. physical capacity, medical status; Waddell. & Burton, 2005) and psychological factors (e.g. self-efficacy, inappropriate fear and belief, anxiety, depression; Haugli et. al., 2003), social factors (e.g. work relationship, stress at work and social support; Franche & Krause, 2002) have to be considered in order to view a person holistically.

The present study faced several limitations. Firstly, the original sample size estimation suggested a group of size of 40 in the main study. Due to difficulties to recruit sufficient number for this longitudinal study, a sample size of 30 were successfully recruited for pre- and post-testing, and not 100% follow up rate at 3-month and 6-month were noted. The reasons for not joining the two training programmes were reported to be due to long-duration and heavy-commitment in training. It also explained partly why an application for an extension of the project duration to achieve the target number was not made. In addition, using a sample size of 30, some positive findings have already been found in key outcome measures in cognitive function and work perspective. The use of a larger sample size of 40 may not be absolutely necessary. This can be reflected and justified by the medium effect size and low p value (less than 0.05 or 0.01 significance level) of primary outcome measures. For examples, effect size and p-values of changes over time in DVT, RMBT, WCST % error and onsite test in VRG were 0.25/<0.01, 2.08/0.02, 0.37/0.04, 1.24/<0.001 respectively (see Table 3). Secondly, all of the subjects recruited in this study had been receiving conventional vocational training. The degree of cognitive challenges they each received may have been different, or with different durations. This non-specific effect on cognition was considered to be uncontrollable, not measured and could be a confounding factor. Thirdly, subjects in the present study were required to attend 10 sessions of training over five weeks, each lasting for 45-60 minutes. It was assumed that this length of training was adequate to improve different cognitive functioning.

## Conclusion

The present study examined that VRVTS was effective in improving some cognitive functions (i.e. attention and memory) and emotional aspect (i.e. self-efficacy) for Ketamine users, which may in turn enhance their employability. However, we did not address whether there was recovery in neuron conductivity and re-growth of neuron sprouts after drug abuse. Since the reversibility of brain damage was a key factor for the efficacy of VR training and that could be revealed by functional Magnetic Resonance Imaging (fMRI) (Cole et.al., 2010), we suggest that further research could investigate the brain activity of drug abusers who undergo treatment with VR cognitive training using fMRI. Moreover, the effectiveness of a mixed mode of training (i.e. virtual-reality based mixed with tutor-administered) should be explored in future studies.

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