SOME NEUROPSYCHOLOGICAL PROFILES OF CANNABIS DEPENDENT USERS ON LONG-TERM ABSTINENCE IN A REHABILITATION CENTRE IN NIGERIA

Valentine A. Ucheagwu[1], Rita N. Ugwokwe-Ossai[2], Paul D. Okoli[2], & Jesse P. Ossai[2]

[1]Department of Psychology, Madonna University Okija Campus, Anambra,
Nigeria Laboratory of Human and Animal Psychology, Chukwuemeka
Odumegwu Ojukwu University Igbariam Campus, Anambra, Nigeria
[2]Department of Psychology, Nnamdi Azikiwe University, Awka, Nigeria

ABSTRACT

The present study examined some neuropsychological profiles of cannabis dependent users on long abstinence in Nigeria. Ninety participants were recruited for the study. Their ages ranged from 27 – 35 years with a mean age of 30.78. Five neuropsychological instruments were used for the study: Symbol Digit Modality Test (SDMT), Digit Symbol Modality Test (DSMT), Trail Making Tests A & B (TMT – A/B), Rey Auditory Verbal Learning Test (RAVLT) and Rivermead Post Concussion Syndrome questionnaire (RPC). The findings of the study showed significant differences on verbal learning; RAVLT Trial 5: $F(2,81) = 15.20$, RAVLT Total Trial: $F(2,81) = 11.06$, Delayed verbal memory, $F(2,81) = 10.94$ all at $P \leq 0.05$ level of testing with cannabis users performing worse than the psychiatric and healthy controls. Significant differences were also seen on processing speed: DSMT: $F(2,81) = 3.53$ with cannabis users performing worse than the healthy control but better than the psychiatric group. Drug users had significant less performance than the healthy control on TMT A; $F(2,81) = 8.04$ and TMT B; $F(2,81) = 7.41$ as measures of executive function. Also, drug users had significant worse complaints of somatic, cognitive and emotional symptoms following brain injury as measured by RPC; $F(2,81) = 7.11$ all at $P \leq 0.05$ level of testing. Discussions of the study was based upon long term effects of cannabis use on neuro-cognition even after prolonged abstinence and reasons for the mixed findings surrounding this area of study. Implications of the study were also examined.

Keywords: Neuro-cognition, Cannabis Users, Abstinence, Processing Speed, Memory

Corresponding Author: Valentine, A. Ucheagwu, Department of Psychology, Madonna University Okija Campus, Anambra, Nigeria. E-mail: afamval@yahoo.com; Phone: +234-8066640319

INTRODUCTION

Addiction is generally defined as compulsive and persistent use of drugs despite negative consequences (Pascoli, Terrier, Hiver & Cuscher, 2015). Ideally dependent drug users will continue drug consumption despite negative consequences typically related to social and psychological defects that are often delayed in time (Pascoli et al., 2015). Neurobiological explanations of addiction have shown various areas of the brain to be involved in compulsive drug seeking. Pascoli et al. (2015) using optogenetic self stimulation show that the Dopamine (DA) neurons of the ventral tegmental area (VTA) are implicated in drug addiction. Consequently their study implicated the D_1 receptor expressing neurons of the nucleus acubems (NAc) as involved in cue induced relapse after weeks of abstinence while resistant to punishment was associated with enhanced neural activity in the orbitofrontal context (OFC) of mice addicted to drugs. In humans similar neural areas have been identified as addictive brain areas. Everitt and Robbins (2016) described the transition from ventral to dorsal striatum involving the DA neurons as major pathways of drug use to drug compulsion. Taken together all the evidences on drug addiction based on neurobiology, it becomes clear that neural plasticity occurs during addiction and such plasticity accounts for drug addiction.

Aside the neural plasticity leading to addiction, drug users also show relative cognitive impairments (Cadet & Bisagno, 2016). Accumulating evidence suggests that dependent and recreational cocaine use is associated with broad neuropsychological impairments (Goldstein, Leskovjan, Hoff, Hitzeman, Bashen, Khalsa & Colleagues, 2004; Jovanovski, Erb & Zakzanis, 2005; Vonmoos, Hulka, Preller, Jenni, Baumgaitner, Stohler et al, 2013; Soar, Mason, Potton & Dawkins, 2012).

Vonmoos, Hulka, Preller, Mander, Baungartner and Quednow (2014) studied cognitive impairment in cocaine users and its possible reversibility. Their findings showed that increased cocaine use within 1 year was associated with reduced cognitive performance primarily in the working memory. By contrast, decreased cocaine use was linked to small cognitive improvements in all domains studied (attention, working memory, declarative memory and executive functions). Importantly, users who ceased taking cocaine seemed to recover completely, attaining a cognitive performance level similar to that of control group. In addition, recovery of working memory showed correlation with the age of onset with early onset users showing hampered recovery. Studies have shown deficits in attention, working memory and declarative memory in chronic cocaine users whereas the heterogeneous concept of executive functions have yielded mixed results (Javanovski, et al. 2005; Vonmoos et al. 2013). Other studies have equally demonstrated that cocaine users additionally display inferior social cognition including prosodic and cross modal emotion recognition, emotional empathy, mental perspective taking and social decision making (Hulker, Eisenegger, Preller, Vonmoos, Jenni, Bendrick and Colleagues, 2014; Hulker, Preller, Vonmoos, Broicher & Quednow, 2013; Preller, Hulka, Vonmoos, Jenni, Baungartner, Oziobek and Colleagues, 2014).

Becker, Collins, Schultz, Urosevic, Schmaling and Luciana (2018) studied longitudinal changes in cognition in young adult cannabis users. Their study

examined associations between chronic use (CU) and cognition over time in chronic daily adolescent onset chronic users (CUs) as compared to normal controls. Both groups completed a neuropsychological battery at study intake and again 2 years later. Their baseline group differences indicated deficits in verbal learning and memory, motivated decision making, planning and working memory in CUs. At the longitudinal follow-up, the majority of Cus continued to report regular and heavy cannabis use. Relative impairments in the domains of working memory, planning and verbal memory remained stable suggesting that these are enduring vulnerabilities associated with continued CU during young adulthood. However impairments in motivated decision making were evident in both groups. In addition, CUs demonstrated relatively better performance in short duration speeded tasks, while an earlier age of CU onset was associated with poorer verbal learning and memory and planning performance over time. Other studies have equally supported the effects of cannabis on neurocognitive functions both the acute (Grady, 1999; Morrison, 2015; Mckeown, Lee, Holt, Powell, Kapur & Murray, 2009) and residual effects of cannabis (Herman, Sartorius, Welzel, Walter, Skopp, Ende & Mani, 2007; Solowji, Stephens, Roffman, Bator, Kadden, Miller, Christiaonsen, McRee, Vendetts, 2002).

Crean, Crane and Mason (2011) reviewed some evidence of long term effects of cannabis use on executive cognitive functions. According to the authors this area of research has been fraught with inconsistencies in findings and is complicated by discrepant definition of what constitutes long term effects. Crean et al asserted that only a handful of researchers have examined the long term effects of cannabis use in executive functions. In seven studies reviewed by Crean et al. (2011), five found no attention or concentration impairments in participants who had remained abstinent from 28 days to one year (Lyons, Bar, Panizzon, Toomey, Eisen, Xian & Tsuang, 2004; Pope, Gniber, Hudson, Huestis, Yurgelun–Toos, 2001, 2002, 2003, Verdejo-Garcia, Lopez–Torrecillas, Aguillar de Arcos, Perez-Garcia, 2005). Other areas of neuropsychological abilities have equally been examined among abstinent cannabis users including working memory, verbal fluency, inhibition and impulsivity, decision making and risk taking (see Crean et al 2011 for exhaustive discussion). Overall cannabis appears to continue to exert impairing effects in executive functions even after 3 weeks of abstinence and beyond. While basic attentional and working memory abilities are largely restored, the most enduring and detectable deficits are seen in decision making, concept formation and planning (Crean et al 2011).

The present study was on examination of some neuropsychological abilities among cannabis users in a rehabilitation centre in Anambra State. The neurocognitive abilities examined were verbal learning/memory, processing speed and executive functions of the participants. To the researchers best of knowledge, no studies have been carried out in Nigeria on neuropsychological profiles of cannabis users particularly those on abstinence for over 3 months. The problems of paucity of literature on this area of long term cognitive effects of cannabis following abstinence may affect post detoxification management. Crean et al (2011) had earlier stated the benefits of neurocognitive assessment on rehabilitation of drug addicts. The gap in knowledge and treatment

created by such lack of studies on neuro-cognition of cannabis dependents is what the present study seeks to fill.

Thus the following hypotheses were proposed to guide the research:

i. Cannabis users on abstinence will differ significantly on verbal learning and memory from healthy controls and psychiatric patients.
ii. Cannabis users on abstinence will differ significantly from the healthy controls and psychiatric patients on test of processing speed.
iii. Cannabis drug users will differ significantly from health control and psychiatric patients on test of executive functioning as well as post concussive symptom reports.

METHOD

Participants

Ninety participants took part in the study. They were recruited from the population of psychiatric patients, drug users and healthy controls. The psychiatric samples were thirty (30) inpatients recruited from the government neuropsychiatric hospital in Anambra State Nigeria. They included 22 males and 8 females diagnosed with psychotic disorders by the attending psychiatrists. The psychiatric group was receiving treatment in the mental health facility during the study. All the participants were on newer forms of antipsychotic medications as at the time of the study and have stayed in the hospital for at least 3 months. On the other hand, the drug users were recruited from the inpatient rehabilitation facility owned by the Nigeria Drug Law Enforcement Agency in Anambra State. They included 30 participants identified to be cannabis users. Twenty five (25) of the participants reported that they also take codeine and alcohol and sparingly cocaine. However the predominant drug of usage was cannabis. All the cannabis participants reported that they had had used cannabis for over 5 years and had for the past one year been using cannabis on a near daily basis. The reason for choosing the Drug Rehabilitation centre was its strict rules on inpatient admission. Patients are not allowed to assess drugs neither were there rooms for drug smuggling into the patients' wards. This to a large extent assures abstinence as soon the drug user is still in admission. The normal controls were recruited from the population of undergraduate students and secondary school leavers who reported no use of drugs (cannabis, cocaine, codeine, tramadol, etc.) and no symptoms of psychotic disorder based on Symptom Checklist 90 R self report. They were matched on age and education with the addiction group.

Table 1 shows no significant differences among the groups on age and length of education respectively.

Table 1.   Summary Table of Education and Age of the Participants

Group	Mean Age	Mean Length of Education	F (age)	F (edu)
Drug users	30.52	7.65		
Psychiatric patients	31.68	7.08	0.85[a]	1.34[a]
Normal Controls	30.75	8.03		

a = No Significant difference at P ≤ 0.05.

Instrument

Five neuropsychological tests were used in the study. The Symbol Digits Modalities Test (SDMT, Smith, 1991) is a speeded task that has been used extensively with diverse clinical groups for the assessment of processing speed (Martin & Bush, 2008). This requires an examinee to look at a series of nine geometric figures that have each been paired with a number. The test items present the geometric figures that have each been paired with a number. Test items present the geometric figure only and the examinee must quickly write in the target number that goes with each figure (Martin & Bush, 2008). The score is the number of correct substitution completed within 90 seconds. However the present study allowed the participants to work as fast as they could and the score was the time it took the participants to complete the task. Similar to the SDMT was the Digit Symbol Modality Test (DSMT). The DSMT (WAIS III: Psychological Corporation, 1957) shares the same features with the SDMT other than the examinee looks at a series of nine numbers that have each been paired with a geometric figure. In DSMT, test items present the numbers only and the examinee must quickly write in the target figures that go with each number (Lezak, et al 2012). The Trial Making Test (TMT; Army Individual Test Battery, 1944) is a commonly used neuropsychological assessment instrument (Arbuthnott & France, 2000; Reitan & Wolfson, 1983) that consists of two subtests. TMT – A involves drawing a line that connects consecutive numbers from 1 to 25 while TMT – B involves drawing a line connecting alternating numbers and letters in sequence (1 – A – 2 – B etc). Traditional scoring is the time in seconds required to complete each part of the test. The present study included the number of errors made on the task. The TMT provides information regarding attention, visual scanning, speed of eye-hand coordination and information processing (Miltrushina, Boone & D'Etia, 1999). The Rey Auditory Verbal Learning Test (RAVLT) affords an analysis of learning and retention. It involves a five-trial presentation of a 15 – word list (List A), a single presentation of an interference list (List B), two post interference recall trials (one immediate, one delayed) and recognition of the target words presented with distracters (RWL) (Lezak, Howieson, Bigler & Tranel (2012). RAVLT has been shown to be reliable and valid in neuropsychological assessment of memory in various disorders including multiple sclerosis (Brown, Kinsella, Ong & Volvels, 2000) and Alzheimer type dementia (Bigger, Rosa, Schultz et al, 1989, Ferman, Smith, Boone et al, 2006). RAVLT has been shown to have adequate reliability and divergent validation using Nigeria samples (Ucheagwu, Ugokwe-Ossai, Okpaleke & Ugokwe, 2017). The Rivermead Post Concussion Symptoms questionnaire (King, Crawford, Wenden, Moss & Wade, 1995) is designed to assess the presence and severity of post concussion syndrome (PCS) which is a set of somatic, cognitive and emotional symptoms following traumatic brain injury. The authors show that RPQ had good reliability both for test – retest and inter-rater reliability.

Procedure

The psychiatric sample were tested in the psychiatric hospital where they were inpatients receiving treatment. All the psychiatric participants were taking newer forms of antipsychotic medication. Because of their medication, they were all tested in the afternoon. This was to allow

for sometime after taking the medication the previous night. Because of antipsychotic side effects, some patients eligible for the study did not participate. Only patients that reported no or fewer signs of motor retardation and dizziness were recruited for the study. They were tested individually after adequate rapport and written consent were obtained from the patients and care-givers respectively. Conversely the drug users were equally tested at the drug rehabilitation centre where they were admitted for rehabilitation. As at the time of the study, none of the participants were on antipsychotics. The only medication known to be administered was multivitamins. The drug addicts were tested individually after adequate consent was obtained from the participants and authorities of the rehabilitation centre. The normal controls were invited to the psychology laboratory of the university (Lead Author's University) where they were equally tested individually after obtaining written consent from the participants. The research ethical committee of the Madonna University Department of Psychology approved the study which follows the Helsinki declaration on involvement of human participants in research.

Design and Statistics

The between group design was used for the study while the multivariate analysis of variance was used for data analysis.

RESULTS

The statistical estimations were to establish neuropsychological differences among cannabis drug dependents, psychiatric patients and healthy controls. The analysis did not include the female participants because only eight participants were involved and they were from the psychiatric group only.

The findings of the study showed significant differences on the Rivermead Post Concussion Questionnaire (RPQ) $F_{(2, 81)}$ = 7.11 at $P ≤ 0.001$, RAVLT Trial 5: $F_{(2, 81)}$ = 15. 20 at $P ≤ 0.001$; RAVLT Total Trial: $F_{(2, 81)}$ = 11.06 at $P ≤ 0.001$; RAVLT Interference: $F_{(2, 81)}$ = 7.89 at $P ≤ 0.001$; RAVLT Delayed Trial: $F_{(2, 81)}$ =10.94 at $P ≤ 0.001$; TMT A (TIME) $F_{(2, 81)}$ = 8.04 at $P ≤ 0.001$; TMT B (TIME) $F_{(2,81)}$ = 7.41 at $P ≤ 0.001$; TMT A (ERROR) $F_{(2, 81)}$ = 25.21 at $P ≤ 0.001$; TMT B (ERROR) $F_{(2, 81)}$ = 7.46 at $P ≤ 0.01$; SDMT: $F_{(2, 81)}$ = 10.68; DSMT: $F_{(2, 81)}$ = 3.53 at $P ≤ 0.03$. However no significant differences were seen on RAVLT Trial 1 and RAVLT Recognition at $P ≤ 0.005$ respectively.

Table 2 shows the mean scores of the groups as they reflect the neuropsychological behaviours. Equally Table 3 shows the pair wise comparisons of the 3 groups on neuropsychological behaviours that show significant differences.

DISCUSSION

The findings of the study showed significant differences among the groups studied on verbal memory and learning using the Rey Auditory verbal learning test (RAVLT). Trial 5 of the RAVLT has been shown to identify the number of words learnt during the verbal learning tasks (Lezak et al, 2012). The analysis of the present data showed that cannabis users on abstinence had the least score on verbal learning and pair wise comparisons of the three groups showed significant learning differences between the cannabis addicts on one hand and health

Table 2. Mean Scores of Neuropsychological Profiles of the Participants

Dependent	Variable	Mean	Std Error
	Psychiatric patients	17.15	2.06
RPQ	Drug Users	26.04	1.96
	Normal	16.87	1.10
	Psychiatric patients	6.62	0.51
RAVLT Trial 1	Drug Users	5.77	0.49
	Normal	6.95	0.47
	Psychiatric Patients	9.08	0.54
RAVLT Trial 5	Drug Users	5.62	0.51
	Normal	9.07	0.50
	Psychiatric Patients	39.63	2.13
RAVLT Total Trial	Drug Users	28.07	2.02
	Normal	39.77	1.95
	Psychiatric Patients	7.75	0.59
RAVLT Interference	Drug Users	5.40	0.56
	Normal	8.35	0.54
	Psychiatric Patients	7.84	0.57
RAVLT Delayed Trial	Drug Users	4.83	0.54
	Normal	7.96	0.52
	Psychiatric Patients	14.08	0.66
RAVLT Recognition Trial	Drug Users	12.67	0.63
	Normal	12.62	0.61
	Psychiatric Patients	112.27	9.07
TMT A (TIME)	Drug Users	109.19	8.61
	Normal	68.87	8.33
	Psychiatric Patients	168.68	13.35
TMT B (TIME)	Drug Users	156.51	12.67
	Normal	103.91	12.26
	Psychiatric Patients	0.15	0.91
TMT A (ERROR)	Drug Users	0.82	0.08
	Normal	0.14	0.08
	Psychiatric Patients	3.34	0.66
TMT B (ERROR)	Drug Users	2.50	0.62
	Normal	0.06	0.60
	Psychiatric Patients	371.29	22.45
SDMT	Drug Users	255.35	21.31
	Normal	238.17	20.63
	Psychiatric Patients	326.37	51.55
DSMT	Drug Users	300.32	48.92
	Normal	156.43	47.35

controls and psychiatric patients on the other hand. Equally the RAVLT total trial score (ie: scores total scores of trials 1-5 of the RAVLT) showed that cannabis addicts performed significantly worse than the other 2 groups.

Table 3. Summary Table of Pair Wise Comparison

Defendant Variable	Group	Group	Diff	Sig.
RPQ	Normal	Psychiatric Patients	-0.28	0.92
		Drug Users	-9.17	0.001
RAVLT Trial 5	Normal	Psychiatric Patients	-.013	0.97
		Drug Users	3.45	0.001
RAVLT Total Trial	Normal	Psychiatric Patients	0.14	0.96
		Drug Users	11.70	0.001
RAVLT Interference	Normal	Psychiatric Patients	0.61	0.45
		Drug Users	2.96	0.001
RAVLT Delayed Trial	Normal	Psychiatric Patients	0.12	0.86
		Drug Users	3.13	0.001
TMT A (TIME)	Normal	Psychiatric Patients	-43.40	0.001
		Drug Users	-40.32	0.001
TMT B (TIME)	Normal	Psychiatric Patients	-64.77	0.001
		Drug Users	-52.64	0.004
TMT A (ERROR)	Normal	Psychiatric Patients	0.15	0.24
		Drug Users	-0.67	0.001
TMT B (ERROR)	Normal	Psychiatric Patients	-3.28	0.001
		Drug Users	-2.43	0.005
SDMT	Normal	Psychiatric Patients	-133.12	0.001
		Drug Users	-17.19	0.56
DSMT	Normal	Psychiatric Patients	-169.94	0.02
		Drug Users	-143.89	0.04

This finding show that cannabis users on abstinence for over 3 months still show impairments on verbal learning performance. Previous studies show verbal impairment in cannabis chronic users when compared with health control (Becker et al 2018) both at acute intoxication and long term chronic use. However studies relating to abstinence of heavy chronic users show that at 28 days, no difference is seen between chronic users on abstinence and control group (non heavy users) on verbal fluency and verbal information (Pope et al, 2001, Crean et al., 2011). These findings were in contrast with our present finding that chronic heavy users on abstinence for over 3 months still showed impairment on verbal learning. However differences may be as a result of diverse neuropsychological tests used by various researchers. The present study used the RAVLT while Pope et al study used measures dealing more on verbal fluency. Equally previous studies recruited cannabis users (light users) as control group while our control groups were persons that were cannabis naive. This may have contributed to differences in our findings. Thus our findings showed relative lasting residual effect of cannabis on verbal learning even after 3 months of abstinence. Conversely, the same significant difference was observed on delayed task of RAVLT which measures verbal memory. Cannabis users on abstinence still showed significant poor performance than other groups on delayed verbal memory task

of RAVLT. Our finding was in line with those of Solowji et al. (2002) and Solowji and Battisti, (2008), who showed that long term cannabis users performed significantly less well than the short term users and controls on tests of memory and attention using the RAVLT and time estimation tasks. According to them long term users show impairments in memory and attention with increasing years of regular cannabis use. However our study was little different from theirs because our cannabis participants were abstinent for over 3 months but still showed decreased verbal memory when compared with healthy controls.

On the other hand, significant differences were only seen on the processing speed performance using the digit symbol modality test (DSMT) between the healthy controls and cannabis participants. Importantly cannabis users performed better than the psychiatric participants on DSMT and also on another task of processing speed the symbol digit modality test (SDMT). Similarly cannabis users show significantly less performance than the healthy controls on measures of executive functions using the TMT A and B. Mixed findings have trailed the residual effects of cannabis on executive function following some days (maximum 20 days) of abstinence. Pope et al (2001, 2002) as well as Jager, Kahn, Ven Den Broken Van Reea and Ramsey (2006) on all five studies found no significant differences on executive functions of heavy cannabis users, former heavy cannabis users and control subjects on 28 days abstinence. Contrary to this, Solowy et al (2002) and Herman et al (2007) reported positive significant differences on abstinence between chronic users and healthy controls. These differences may

as well be attributed to the nature of neuropsychological tests used to assess executive functioning, the nature of participants recruited for the study as well the length of abstinence.

Implication for Treatment

Cognitive impairments have been generally associated with poorer drug abuse treatment outcome (Aharonovich, Brooks, Nunes & Hasin, 2008; Abboth & Gregson, 1981) and those impairments have been found to impede acquisition of new coping behaviours (McCrady & Smith 1986), learning and retention of new material (Alternman & Hall, 1989) and also increases the likelihood of treatment dropouts (Teichner, Horner, Routzch, Herron & Theros, 2002). This suggests that incorporating the standard cognitive remediation into the rehabilitation of cannabis users will optimize treatment outcome. It is therefore important to equally include standard neuropsychological assessment in the protocols for assessment and treatment of cannabis dependent users.

Since the present study suggests long term effects of cannabis use on neuro-cognition, intermediate neuropsychological assessment of cannabis users under rehabilitation will help determine cannabis users still affected with cannabis neuro-cognitive effects over long term rehabilitation and abstinence and possibly improve on their neuro remediation.

Our present study has certain limitations. We were not able to divide the cannabis users into months of abstinence like 3 months, 5 months, 1 year, although all our participants have had at least 3 months of abstinence and were still in the rehabilitation centre. Future studies including different abstinence time may

further tell us more about abstinence and neuro-cognition. Although our present study to the author's best of knowledge was the first to assess the neuro-cognitive status of cannabis users on 3 months of abstinence in a rehabilitation centre, we believe that neuro-plasticity following cannabis use may still improve based upon time. Equally our study failed to categorize the users under duration of exposure and quantity of cannabis abused. However, we reported that all participants had used cannabis for over 5 years prior to admission and based upon self report have been using cannabis on everyday basis at least 1 year before admission into rehabilitation. These description criteria have ideally covered bases for dependence and heavy use, but further categorization could have given more credence to the study. Equally we did not involve any biological test to ensure total abstinence among the drug addicts. We had simply relied on the nature and security of the centre for abstinence. Future studies involving such measures will give better credence to the results obtained.

Psychiatric patients were included into the study also as a form of control to the cannabis participants. Some cannabis users from clinical experience show some signs of psychotic features when first admitted in a rehabilitation centre. This was also reported in 25 participants from our study. Thus to cushion the effect of psychotic features on the findings, we decided to recruit the psychiatric participants with psychotic features under remission undergoing psychiatric rehabilitation. Overall, our study shows that cannabis users have impairments in verbal learning and memory when compared to healthy and psychiatric controls. Equally

they showed significant impairment in processing speed and executive functions when compared with the healthy control but performed better than the psychiatric participants.

REFERENCES

Abbott, M.W., & Gregson, R.A. (1981). Cognitive dysfuntion on the prediction of relapse in alcoholics. *Journal Studies of Alcohol, 42(3)*, 230-243.

Aharonorich, E., Brooks, A.C, Nunes, E.V & Hasin, D.S. (2008). Cognitive deficits in marijuana users: Effects on motivational enhancement therapy plus cognitive behavioural therapy treatment outcome. *Drug and Alcohol Dependence, 95 (3),* 279-283.

Alterman, A.I., & Hall, J.G (1989). Effects of social drinking and familial alcoholism risk on cognitive functioning: Null findings. *Alcohol Clinical Experimental Research, 1-3,* (6), 799-803.

Arbuthnott, K. & Frank, J. (2000). Trail Making Test, Part B as a measure of executive control: Validation using a set switching paradigm. *Journal of Clinical and Experimental Neuropsychology, 22,* 518-522.

Army Individual Test Battery (1994). *Manual of directions and scoring.* Washington, DC. War Department, Adjutant General's office.

Becker, M.P., Collins, P.F., Schultz, A., Nroseric, S., Schmahy, B. & Luciana, M. (2018). Longitudinal changes in cognition in young adult cannabis users. *Journal of Clinical and Experimental Neuropsychology, 40(6)*, 529-543.

Bigler, E.D., Rosa, L., Schultz, F. et al (1989). Rey auditory verbal learning and Rey-Osterriech complex figure design

performance in Alzheimer's disease and closed head injury. *Journal of Clinical Psychology, 45,* 277-280.

Cadet, J.C. & Bisagno, V. (2016). Neuropsychological consequences of chronic drug use: Relevance to treatment approaches. *Frontiers in Psychiatry, 6, 189. Doi: 10.3389/-/psyt.2015.00189.*

Crean, R.D., Crane, N.A., & Mason, B.J. (2011). An evidence based review of acute and long term effects of cannabis use in executive cognitive functions. *Journal of Addiction Medicine, 5, 1,* 1-8.

Ferman, T.J., Smith, G.T., Boone, B.F. et al (2006). Neuropsychological differentiation of dementia with lewy body from normal ageing and Alzheimer's disease. *The Clinical Neuropsychologist, 20,* 623-636.

Goldstein, R.Z., Leskorjan, A.C., Hoff, A.L., Hitzemann, R., Bashan, F., Khalsa, S.S. et al (2004). Neuropsychological impairment in cocaine and alcohol addiction: Association with metabolism in the prefrontal cortex. *Neuropsychologia, 42,* 1447-1458.

Grady, C.L. (1999). *Neuroimaging and activation of the frontal lobes*. In B.C. Mather, J.C. Cummings (eds.), the human frontal lobes: function and disorders. New York: Guilford Press.

Smith, A. (1991). *Symbol digit modalities Test*. Los Angeles: Western Psychological Services.

Hermann, D., Sartorius, A., Welzel, H., Waltor, S. Skoff, G., Ende, G & Mann. K. (2007). Dorsolateral Prefrontal Cortex N-acetyl aspartate/total Creatine (NAA/ter) loss in male recreational cannabis users. *Biological Psychiatry, 61 (11)*, 1281-1291.

Hulka, L.M., Eisenegger, C., Preller, K.H., Vonmoos, M., Jenni, D., Bendrick, K. et al (2014). Altered social and non social decision making in recreational and dependent cocaine users. *Psychological Medicine, 44,* 1015-1028.

Hulka, L.M., Preller, K.H., Vonmoos, M., Breicher, S.D, Queduaw, B.B. (2013). Cocaine users manifest impaired prosodic and cross modal emotion processing. *Frontiers of Psychiatry, 4,* 1-12.

Jager, G., Kahn, R.S. Van den Brink, W., Van Ree, J.M. & Ramsey, W.F. (2006). Long term effects of frequent cannabis use on working memory and attention: an FMRI study. *Psychopharmacology, 185 (3),* 358-368.

Jovanovski, O., Erb, S. & Zakzanij, K.K. (2005). Neuro-cognitive deficits in cocaine users: a quantitative review of the evidence. *Journal of Clinical Experimental Neuropsychology, 27,* 189-204.

King, N., Crawford, S., Wenden, F., Moss, N. & Wade, D. (1995). The Rivermead post concussion symptoms questionnaire. *Journal of Neurology, 242*, 587-592.

Lezak, M.O., Howieson, D.B., Bigler, E.D. & Tranel, D. (2012). *Neuropsychological Assessement (5ed).* Oxford: Oxford University press.

Lyons, M.J., Bar, J.C., Panizzon, M.S., Toomey, R., Esen, S., Xian, H. & Tsuang, M.T. (2004). Neuropsychological consequences of marijuana use: a twin study. *Psychological Medicine, 34 (7)*, 1239-1250.

Marton, T.A & Bush, S.S. (2008). *Assessment tools and research methods for human information processing speed.* In J. Deluca and J. H. Kalmar (eds.), information processing speed in clinical populations. New York: Routledge Taylor & Francis Group.

McCrady, B.S. & Smith, D. E. (1986). Implications of cognitive impairment for the treatment of alcoholism. *Alcohol Clinical Experimental Research, 10 (2),* 145-149.

Mitrushina, M. N., Boone, K.B., & O'Elita, L.F. (1999). *Handbook of normative data for neuropsychological assessment.* New York: Oxford University press.

Morrison, P.D., Zois, V., Mckeown, D.A., Lee, T.D., Holt, D.W., Powell, J.F., Kapur, S. & Murray, R. M. (2009). The acute effects of synthetic intravenous Delta-Tetrahydro cannabinol in psychosis, mood and cognitive functioning. *Psychological Medicine, 39 (10),* 1607-1616.

Pascoli, V., Terrier, J., Hiver, A & Luscher, C. (2015). Sufficiency of mesolimbic dopamine neuron stimulation for the progression to addiction. *Neuron, 88,* 1054-1066

Pope, H.G, Gruber, A.J, Hudson, J.I., Cohane, G; Heytis, M.A, & Yurferlun-Toud, D. (2003). Early onset cannabis use and cognitive deficits: what is the nature of association? *Drug Alcohol Dependence, 69 (3),* 303-310.

Pope, H.G., Gruber, A.J., Hudson, J.I., Hestis, M.A., Yurgelun Todd, D. (2007). Neuropsychological performance in long term cannabis users. *Archives of General Psychiatry, 58 (10),* 909-915.

Pope, H.G., Gruber, A.J., Hudson, J.I, Huestis, M.A., Yurgelun Todd, D. (2002). Cognitive measures in long term cannabis users. *Journal of Clinical Pharmacology, 42* (11) (suppl), 415-475.

Preller, K., Hulka, L., Vonmoos, M., Jenni, D., Baumgartner, M., Ozuebek, C.A. et al (2014). Impaired emotional empathy and related social network deficits in cocaine users. *Addiction Biology 19 (e-pub ahead of print).*

Psychological Corporation (1997). *WAIS – III WMS – III technical manual*. San Antonio, TX: Author.

Reitan, R. M. & Wolfson, D. (1993). *The Halstead- Reitan neuropsychological test battery (2nd ed)*. Tucson, A2: Neuropsychology Press.

Soar, K., Mason, C., Potton, A., Dawkins K. (2012). Neuropsychological effects associated with recreational cocaine use. *Psychopharmacology, 222*, 633-643.

Solowji, N., Stephens, R.S., Roffman, R.A., Babor, T., Kadden, R., Miller, M., Christiansen, K., McRee, B., Vendeth, J., Marynana, P. & Treatment Project Research Group (2002). Cognitive functioning of long term heavy cannabis users seeking treatment. *JAMA, 6 (287),* 1123-1131.

Solowy, W. & Battisti, R. (2008). The chronic effects of cannabis on memory in humans: a review. *Drug Abuse Review, 1 (1),* 81-98.

Teichner G, Horner M.D., Roltzeh, J., Herron, J. & Theros, A (2002). Substance abuse treatment outcome for cognitively impaired and intact outpatients. *Addictive Behaviours, 27 (5),* 751-763.

Ucheagwu, V.A., Ugokwe-Ossai, R.N., Okpaleke, U & Ugokwe J. (2017). Inter-trial reliability, cardio and demographic markers of Rey Auditory Verbal learning test performance in young adult sample from Nigeria. *American Journal of Psychiatry and Neuroscience, Vol. 5 (6),* 70-77.

Verdejo-Garcia, A.J., Lopes- Torrecillas, F., Agular decross, F., Perez-Garcia, M. (2005). Differential effects of MDMA, cocaine and cannabis use severity in distinctive components of the executive functions in Poly substance users: a multiple regression analysis. *Addictive Behaviour 30 (1)*, 89-101.

Vonmoos, M., Hulka, L.M., Preller, K.H., Jenni, D., Baumgartner, M.R., Stohler, R. et al (2013). Cognitive dysfunctions in recreational and dependent cocaine users: role of attention deficit hyperactivity disorder, craving and early age at onset. *British Journal of Psychiatry, 203,* 35-43.

Vonmos, M., Hulka, L. M., Preller, K.H., Minder, F., Baumgartner, M.R. & Quediow, B.B (2014). Cognitive impairment in cocaine users is drug induced but partially reversible: Evidence from a longitudinal study. *Neuropsychopharmacology, 39*, 2200-2210.