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Cognitive Functioning as a Trait Marker in Patients with *Cannabis* Use Disorders-A Pilot Study

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ABSTRACT

Introduction: *Cannabis* use disorders are global emerging problem nowadays, with high prevalence and morbidity. Though cognitive impairments are one of the most replicated findings in individuals with cannabis dependence, but there are very few studies assessed cognitive functioning as a risk factor for cannabis use disorder. In this study, we assessed cognitive functioning as an end phenotype in *Cannabis* use disorders.

Methodology: In this study comparison of cognitive functioning was done among three groups-patients with *Cannabis* dependence syndrome, their First Degree Relative (FDR) and normal Healthy Controls (HC). Each group included 30 participants. Individuals of all three groups were assessed in domains of complex attention, executive functions, language, learning and memory and perceptual motor.

Results: Performance of patients with *Cannabis* dependence was impaired in attention, verbal memory, executive functions compared to both other groups. Attention, semantic verbal fluency and memory were found to be an end phenotype as both patient and FDR group performed poorly than HC group. Verbal memory was impaired in patients' group compared to group of first degree relatives, whose performance in-turn impaired than normal healthy controls. Performances of verbal and visual memory were correlated positively with age of onset and negatively with frequency of *Cannabis* intake. Age of first degree relatives was inversely correlated with verbal memory.

Conclusion: Performance of individuals with *Cannabis* dependence was impaired than normal healthy controls in all domains of cognitive functioning. As per definition, verbal memory could be considered as an end phenotype marker in *Cannabis* use disorders.

Keywords: *Cannabis;* Morbidity; First Degree Relative (FDR); Phenotype; Patients

INTRODUCTION

Cannabis is a widely used psychoactive substance all over the world. According to a global epidemiological study by Degenhardt et al., point prevalence of *Cannabis* use disorders was 0.2% and it contributed to 0.08% of total DALY loss. A recent epidemiological survey revealed 2.8% of Indian population was currently using *Cannabis* whereas 0.25% met diagnosis of *Cannabis* dependence syndrome.

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Cannabis use modulates certain neurophysiological changes; through activation of cannabinoid (mainly type 1, CB1) receptors. These CB1 receptors were widely distributed in central nervous system and implicated in second messenger systems, protein signaling pathways, reward pathways, regulation of some neurotransmitters like GABA and dopamine. Widespread action might be responsible for dependence or psychological effect. Among many risk factors, genetics play an important role in precipitating dependence and other psychological effect of *Cannabis*. There are certain genetic polymorphisms which (The Catechol-O-Methyl Transferase gene: *COMT*, the AKT serine/threonine kinase 1 gene: *AKT1*, The dopamine ß-hydroxylase gene: *DBH*, The serotonin transporter gene: *5-HTT/SLC6A4*) predispose individual with *Cannabis* use to dependence or psychosis or cognitive impairment. So, there may be chance of familial predisposition of *Cannabis* use. Use of psychoactive substances could impair brain circuits responsible for executive control, specifically response inhibition, mental planning, working memory, and attention control. There are a number of studies regarding effect of *Cannabis* on cognitive functioning. *Cannabis* use was found to be associated with impairment in cognitive domains such as sustained attention, response monitoring, decision making and memory. Most of the studies emphasized heavy and long term use of *Cannabis* for such impairments. Heavy use of *Cannabis* and related neuroanatomical and neurophysiological changes were reported as predictors of cognitive impairments in some studies. Specially, learning and memory deficits were impaired in heavy and long term *Cannabis* users, which were in tandem with hippocampal attrition. Pope, et al., reported residual cognitive effect in patients with *Cannabis* dependence even in abstinence, though it was negligible after 28 days of abstinence. Fontes, et al., reported cognitive impairments were inversely correlated with age of onset of *Cannabis* use. In spite of advance neurobiological findings, biological underpinning of *Cannabis* use disorders is still obscure. Emerging data suggested that biological relatives of patients with substance use have higher risk of developing drug dependence in future.

So, the possibility of pre-morbid risk of drug dependence cannot be ruled out. Identification of biological vulnerability markers provides a scientific basis for development of effective preventive and therapeutic strategies for individuals at risk.

Studies are lacking in the field of preexisting vulnerability in addiction especially in *Cannabis* use disorders.

The concept of endophenotype offers a useful strategy for evaluating the underlying factors that makes an individual vulnerable to any psychiatric disorder as well as substance use. Endophenotype have been defined as quantitative traits that are intermediate between the predisposing genes (genotype) and the clinical symptoms (phenotype) of a complex disorder. According to the criteria outlined by Gottesman and Gould, endo phenotypes are quantifiable traits which:

- Associated with the disorder.
- Genetically determined.
- Largely state independent (*i.e.*, they should manifest in periods of health and during acute illness).
- Segregate with the disorder within families.
- Overrepresented in unaffected family members relative to the general population.

Based on proximity of deficit, endophenotypes are divided further into two levels 'level 1' degree of deficit in FDR group is almost similar to patient probands; and 'level 2' degree of deficit in patient group is impaired significantly than FDR group.

In our study, cognitive functions were assessed as a putative endophenotype for *Cannabis* dependence. Relation of cognitive functioning and cannabis exposure could be bidirectional; such as, impaired cognitive functioning could be result of chronic or early cannabis exposure, or impaired cognitive functioning makes an individual vulnerable for *Cannabis* use.

So, in this study the mentioned domains of cognition were assessed and comparison was done among three groups- patients with cannabis dependence, their unaffected first degree relatives and normal healthy controls [1-6].

MATERIALS AND METHODS

The study was done in a tertiary care hospital in central India. Patients were recruited from outpatient and in-patient in department of psychiatry attending in the hospital. The study was done among three groups, patients with cannabis dependence syndrome, their First Degree Relatives (FDR) and normal Healthy Controls (HC) 30 participants were included in each group (95% CI and 65% power). For participants of all three groups' age range remained restricted to 18 years to 45 years and 8 years of formal education. Patients were included as per ICD 10 diagnostic criteria for *Cannabis* dependence. In our study patients with *Cannabis* dependence were included who had positive urine screening for *Cannabis* as well as on the basis of self-reporting. All participants in FDR and HC groups were screened by GHQ 5 to rule out any mental disorder. Moreover, any participant of all three groups was excluded to take part in the study if dependence criteria of any substance were fulfilled except tobacco and caffeine. Participants from HC groups were excluded if they had any family history of Alzheimer's disease, mental retardation and organic brain disease, substance use disorder (except for tobacco and caffeine). Informed consent was taken from each participant (**Figure 1**).

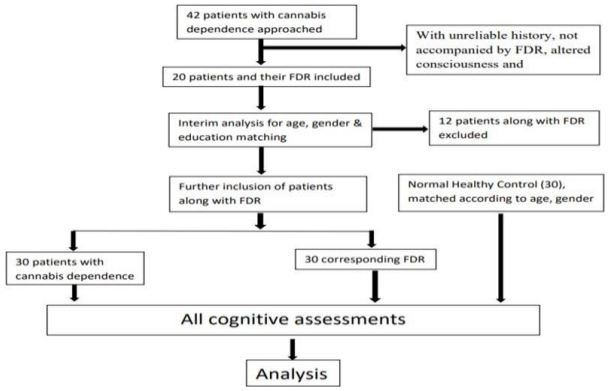

Figure 1: All cognitive assessments.

Primary objective of this study was to assess and compare cognitive functioning among patients with *Cannabis* dependence syndrome, first degree relatives and normal healthy controls. Secondary objective was to look for association and correlation between the degree of cognitive functioning in three groups (patients with *Cannabis* dependence syndrome, first degree relatives and normal healthy controls) and their sociodemographic and clinical variables.

Attention and concentration, language, memory and executive functions were tested across three groups (**Table 1**).

Table 1: Cognitive assessments done in each domain.

Attention and concentration	Digit forward and digit backward
Language	**Verbal fluency**-F-A-S test, animal naming test
	Verbal memory-Rey Auditory verbal learning test
Memory	**Recent**-Orientation
	Remote-Personal history-verified from attendant.
	Visual-Rey Osteirreth complex figure test.
Executive function	Stroop test, Trail making test

Data Analysis

42 patients with *Cannabis* dependence were approached. The patients with unreliable history, not accompanied by FDR, with altered consciousness were excluded. After 20 subjects are included, along with their FDR; an interim analysis was done. 12 patients were excluded after interim analysis as their mean age was not in sync with mean age of FDR group. As per plan, all participants were group matched with respect to age, education and gender. In this study SPSS version 15.0 software was used. Shapiro-Wilk test was done to check whether continuous variables were in normal distribution. Most of our continuous variables including age, income and scores of cognitive functioning followed a skewed distribution, and so non-parametric tests were used. Kruskal-Wallis tests were used to delineate significant difference across three groups. For post-hoc test serial Mann-Whitney tests were used [7-12].

RESULTS

Sociodemographic Data

Three groups were matched in terms of gender, marital status, religion, residence but there is significant difference in education (p=0.011) and occupation (0.000) (**Table 2**). Mean age of patients' group with cannabis dependence was 30.57 ± 12.90, and there was no significant difference with groups of FDR and HC (**Table 3**).

Table 2: Age and income across three groups.

Variables	Group-*Cannabis* patients (n=30)	Group-FDR (n=30)	Group-HC (n=30)	p
		Mean ± SD		
Age (years)	30.57 ± 2.90	30.27 ± 13.20	27.50 ± 5.34	0.953
Income	15050 ± 9142.88	15050 ± 9142.88	21170 ± 23726.27	0.977

Table 3: Sociodemographic parameters across three groups.

		Group-*Cannabis* patients n=30 (%)	Group-FDR n=30 (%)	Group HC n=30 (%)	p
Gender	Male	30 (100%)	27 (90%)	30 (100%)	0.104

	Female	0 (0%)	3 (10%)	0 (100%)	
Marital status	Married	15 (50%)	16 (53.3%)	21 (70%)	0.24
	Single	15 (50%)	14 (46.7%)	9 (30%)	
Education	Uneducated	1 (3.3%)	1 (3.3%)	0 (0%)	0.011
	Primary	7 (23.3%)	3 (10%)	0 (0%)	
	High school	16 (53.3%)	16 (53.3%)	15 (50%)	
	Intermediate	2 (6.7%)	1 (3.3%)	9 (30.0%)	
	Graduation	4 (13.3%)	8 (26.7%)	5 (16.7%)	
	PG	0 (0%)	1 (3.3%)	1 (3.3%)	
Occupation	Professional	0 (0%)	1 (3.3%)	0 (0%)	0
	Skilled	2 (6.7%)	8 (26.7%)	17 (56.7%)	
	Semiskilled	7 (23.3%)	5 (16.7%)	7 (23.3%)	
	Unskilled	6 (20.0%)	8 (26.7%)	3 (10.0%)	
	Unemployed	15 (50.0%)	7 (23.3%)	3 (10.0%)	
	Housewife	0 (0%)	1 (3.3%)	0 (0%)	
Religion	Hindu	27 (90%)	27 (90%)	29 (96.7%)	0.692
	Muslim	3 (10%)	3 (10%)	1 (3.3%)	
Residence	Rural	14 (46.7%)	14 (46.7%)	20 (66.7%)	0.2
	Urban	16 (53.3%)	16 (53.3%)	10 (33.3%)	
Tobacco	Yes	27 (90%)	17 (56.7%)	16 (53.3%)	0.004
	No	3 (10%)	13 (43.3%)	14 (46.7%)	

Cognitive Functions

Performance of attention task (digit forward and digit backward) was significantly varied across three groups ($p<0.05$ for both the test). Post-hoc test revealed performance of digit forward in patients with *Cannabis* use was significantly impaired from normal healthy control group, though there was no significant difference between group of FDR and HC.

In digit backward test, performance of patients with *Cannabis* use was significantly lower from normal healthy control. Performance of FDR group was reduced from HC group but no significant difference between performance of patients and FDR group (**Table 4**).

Table 4: Comparison of cognitive performances across three groups.

Variables	Group-*Cannabis* patients n=30 (%)	Group-FDR n=30 (%)	Group HC n=30 (%)	P	Post-hoc
Digit forward	4.87 ± 0.97	5.43 ± 0.77	5.63 ± 0.56	0.003	C<H, F-H, C<F
Digit backward	3.07 ± 0.64	3.27 ± 1.05	3.80 ± 0.66	0.001	C<H, F<H, C-F1
Verbal-fluency F	3.70 ± 1.47	4.10 ± 1.16	6.43 ± 1.22	0	C<H, F<H, C-F
Verbal-fluency A	3.20 ± 1.10	3.47 ± 1.11	6.20 ± 1.16	0	C<H, F-H, C<F
Verbal-fluency S	3.40 ± 1.45	3.78 ± 1.14	6.37 ± 1.00	0	C<H, F-H, C<F

Categorical fluency	8.60 ± 2.55	10.43 ± 2.22	11.27 ± 2.68	0.001	C<H, F-H, C<F
Visual memory copy	26.42 ± 10.76	29.15 ± 7.95	32.67 ± 5.23	0.078	
Visual memory time	2.48 ± .85	2.35 ± .87	2.04 ± .96	0.094	
RAVLT hits	9.17 ± 1.97	10.67 ± 1.90	13.13 ± 1.36	0	C<H, F-H, C<F
RAVLT commission	3.33 ± 1.24	2.50 ± 1.22	1.33 ± .99	0	C<H, F-H, C<F
RAVLT omission	5.10 ± 1.95	4.33 ± 1.90	1.93 ± 1.36	0	C<H, F-H, C<F
Stroop test score	163.50 ± 100.42	172.07 ± 94.73	133.00 ± 76.21	0.288	
Stroop mistake	4.03 ± 2.34	2.52 ± 1.25	2.25 ± .70	0	C<H, F-H, C<F
Trail time A	58.75 ± 32.59	38.62 ± 10.08	42.00 ± 28.79	0.004	C<H, F-H, C<F
Trail time B	99.17 ± 50.64	95.93 ± 46.51	79.64 ± 52.71	0.123	

In verbal memory test especially phonemic test, performance of patients with *Cannabis* use was impaired than FDR group, whose performance in turn impaired from HC group. Though in categorical verbal memory, patients with *Cannabis* use performed worse than FDR and HC group, but no significant difference was found between later two groups.

In our study visual memory was not differed significantly across three groups.

In tests for executive functioning, performance of patients with *Cannabis* dependence was impaired compared to normal control as well as their FDR. Significant difference ($p<.05$) was found in mistakes of Stroop test and time for trail-A test. But there was no significant difference between FD R an d HC group [13-18].

Correlation of Sociodemographic and Clinical Variables with Cognitive Functioning

In our study visual copy score was correlated with *Cannabis* frequency and verbal memory deficit was correlated with frequency of *Cannabis*. Verbal memory deficit was negatively correlated with age of onset of *Cannabis* use (**Table 5**).

Table 5: Cannabis patient: Spearman's correlation of socio demographic parameters with cognitive functioning.

Cannabis patient-Spearman's Correlation of socio demographic parameters with cognitive functioning		
	Cognitive variables	**P**
Cannabis onset	RAVLT, T1-5	<.05
Cannabis frequency	Visual memory copy score RAVLT, T1-5	0.047 <.05
FDR-Spearman's correlation of sociodemographic parameters with cognitive functioning		
Age	RAVLT, T2	0.038

Endophenotype

Patients with *Cannabis* users have impairment in attention, verbal fluency, verbal and visual memory, executive function compared to HC group suggesting that these domains are 'disease markers. Subsequently, we found that FDR group performed poorly than HC group in attention (digit backward), semantic verbal fluency and verbal memory; therefore, qualifying for the definition of endophenotype (**Figure 2**). Among these parameters, attention and verbal fluency was found close to illness, where performance of FDR was comparable to patients with cannabis use, therefore, qualifying for being a 'level-1' endophenotype while verbal memory were considered 'level-2 endophenotype.

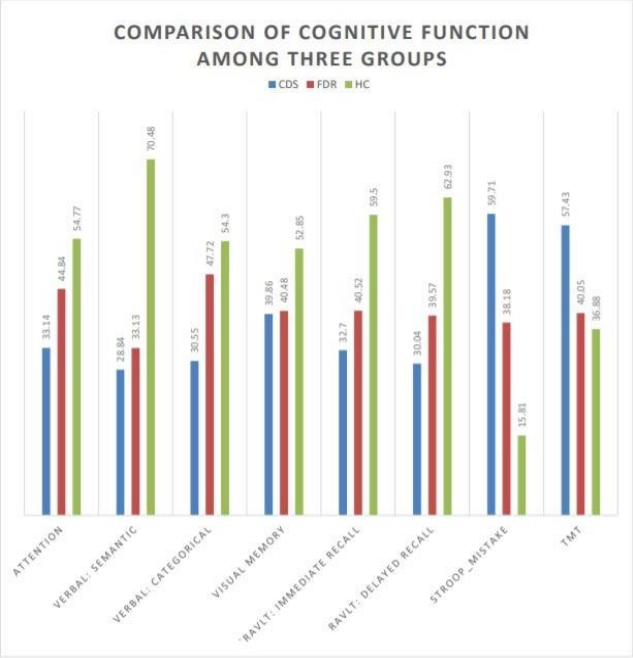

Figure 2: Comparision of Gognitive Function among three groups.

DISCUSSION

We intended to identify candidate cognitive endophenotype for *Cannabis* dependence. Significant impairment was found in all domains of cognition (attention, verbal fluency, verbal and visual memory, executive function) in patients with *Cannabis* dependence compared to normal healthy controls. Our findings were in sync with previous studies. In our study, group of patients with *Cannabis* dependence included all 30 male participants. It would be better if we include female subjects too, but availability was the main limiting factor. To overcome gender as a confounding factor, we have tried not to include any female as a participant in other 2 groups. Across some studies it was found that males are better in visuo-spatial ability whereas females outperform in memory and language. A study by Bloomfield, et al., assessing cerebral glucose metabolism in *Cannabis* users found that there were significant group differences at baseline frontal metabolism between male and female. Female group showed significant attenuation of regional brain metabolic responses to methylphenidate (dopamine enhancing agent). The gender differences suggested that females might be more sensitive to the adverse effects of cannabis in brain. Though in another study, sex differences in cognitive performance were not significant.

Attention was assessed across a number of studies and found impaired in patients with *Cannabis* use. Assessment tools were varied across studies, for e.g. Digit Symbol Substitution Task (DSST), immediate and delayed Digit Recall Task (DRT), Useful Field of View (UFOV) task, trail making task. A study by found impaired attention in *Cannabis* users even in frequency of 1-10 times/month. In verbal fluency tests, our results replicated findings of study by Pope et al., though in later study there was no significant difference between late onset users (<17 years) and control groups. A study by revealed impaired verbal memory even after 28 days of abstinence from *Cannabis*, compared to non-users. Themes, et al., reported more impairment of verbal memory in recent users compared to past users, performance of whom in turn reduced than non-users. In our study we found verbal memory deficit was negatively correlated with age of onset of *Cannabis* use, which is in sync with results of previous studies. Bolla, et al., found impairment using Rey complex figure copy test, which is similar to our study and found dose related impairment in patients with cannabis use. There were studies which replicated these finding. Thames, et al., used similar tools of our study (trail making test and stroop test) to assess executive function and found impairment in *Cannabis* users, especially in recent users. Though assessment tools for executive functions varied like Wisconsin card sorting test and continuous performance test but the finding were consistent across studies. Besides, cognitive impairment was found more impaired in lower cognitive reserve subjects though this is not a much replicated finding across studies.

Endophenotype refers to certain phenotype (such as here cognitive functioning), which corresponds to certain genes. Here, the functional consequences of risk alleles have been assessed (cognitive functioning) rather than risk gene itself. So, susceptibility gene as well as its associated neurocognitive variables may act as predisposing factor for cannabis use disorders. Patients with cannabis use performed poorly than HC group, which makes it a disease marker; suggesting the possibility of cannabis related impairment in verbal memory. Performance of FDR group in attention, semantic verbal fluency and memory was found inferior to HC group, which fulfills definition of endophenotype. Attention and verbal fluency fulfilled the definition of level 1 endophenotype which is symptom related and may be co-segregated in families. Verbal memory of FDR group lied between patients and HC group, which defined it as a level 2 endophenotype. So, verbal memory impairment was found as symptom which has a segregated genetic pool and independent of disease (state) condition.

Some studies previously found impairment of cognitive domains in unaffected biological siblings of substance use disorders assessing executive functioning in stimulant use disorders found significant impairment in siblings of patient compared to normal healthy control. This findings suggested premorbid cognitive impairment might be there to precipitate drug dependence; along with-it impairment of patient group more than siblings group suggested drug induced impairment in cognitive functions. Similar findings were reported by Ersche, et al., in patients with stimulant use disorder. Besides, it replicated in patients with alcohol use disorders. A longitudinal study found that children of patients with alcohol use disorder had poor inhibitory control, which might predict substance use in them. An original study explored error related negativity in offspring of individuals with *Cannabis* use disorders and found impairment in them compared to offspring of healthy control group. This could be explanatory in view of deficits in the ability to self-monitor, ongoing

behavior for errors or unsuitable actions, arguments; probably because of reduced error salience. So, our study findings were consistent with this study and explored possibility of cognitive endophenotype in *Cannabis* use disorders [19, 20].

CONCLUSION

Our study has certain limitations. Power is significantly less because of small sample size. We have included patients with cannabis dependence and assessed their cognitive functions, while other co-morbidities (both physical and psychiatric) were not ruled out in this study. It is a major limitation of this study as in psychiatric disorders, cognitive functioning may be hampered irrespective of substance use. It would be better if various forms (like edible, smoked, intravenous) of *Cannabis* were included, as this could confound the findings. Analysis according to age of onset of cannabis use is lacking in our results because of small sample size. As it is a cross-sectional study so longitudinal relationship between cannabis use and cognitive functioning could not be explored.

As this was a pilot study, which pointed towards possible endophenotype in *Cannabis* use disorders, it can be performed in large sample size. In case of any established cognitive endophenotype, primary prevention of *Cannabis* use disorders may be done for defined population. Unaffected biological relatives should have cognitive screening and further rehabilitation according to their status. Further, psycho-education should be given to unaffected first degree relatives of patients with *Cannabis* dependence about harmful effects of cannabis and risk of precipitating *Cannabis* use disorders; monitoring for early signs should be explained to them.

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