Neuropsychological deficits in long-term frequent cannabis users

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Abstract—The authors examined neuropsychological functioning in 20 long-term (LT), 20 shorter term (ST) heavy frequent cannabis users, and 24 controls after abstinence for ≥24 hours prior to testing. LT users performed significantly worse on verbal memory and psychomotor speed. LT and ST users had a higher proportion of deficits on verbal fluency, verbal memory, attention, and psychomotor speed. Specific cognitive domains appear to deteriorate with increasing years of heavy frequent cannabis use.

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The number of cannabis users in Greece has doubled in the past decade.[1] Due to the possible therapeutic use of cannabinoids, it is important to replicate and extend previous findings of cannabis use on cognitive functions. Although the intoxication effects of cannabis use are well documented,[1,2] the effects on cognition after frequent, long-term use remain inconclusive.[2] A recent well-controlled study failed to demonstrate consistent neuropsychological deficits in frequent long-term cannabis users after an abstinence period of 28 days.[3] Others have found neuropsychological deficits in long-term cannabis users after an abstinence period of between 12 and 24 hours[4] and persistent neurocognitive deficits in heavy cannabis users after 28 days of abstinence.[5] In this study, we examined whether cognitive functions differ in groups of heavy, frequent cannabis users with longer and shorter term use after an abstinence period of ≥24 hours prior to neuropsychological testing.

Methods. We recruited participants aged 17 to 49 years from the drug abuse treatment program offered at the Saint Nicholas Clinic in Athens, Greece, in three groups: 1) 20 current heavy long-term frequent cannabis users, 2) 20 current heavy shorter term frequent cannabis users, and 3) 24 control subjects reporting that they had used cannabis at least once, but no more than 20 times in their lives, and had not used cannabis in the past 2 years. All participants underwent a detailed interview before entry into the study. Participants included reported regular cannabis use for at least 5 years, were currently smoking cannabis at least 4 days per week, and provided written consent for participation in the study. Our threshold for heavy frequent long-term cannabis use was four or more joints per week for at least 10 years (table 1). We excluded participants who reported 1) use or abuse of any other class of drugs (e.g., opiates, cocaine, stimulants) for more than 3 months throughout their lives and had used any of these drugs in the past year prior to participation in the study or 2) met a current *Diagnostic and Statistical Manual, 4th Edition* (DSM-IV) diagnosis of dependence on any other drug or alcohol (except cannabis); 3) met a current DSM-IV Axis I disorder; 4) current use of any psychoactive medication that may affect cognitive performance; 5) any other medical condition that might affect neuropsychological performance; 6) non-native speakers of the Greek language. Participants provided urine samples after at least 24 hours (range 36 to 240) of abstinence from cannabis use and another during the testing session. A urinary toxicology screen further confirmed that no other illicit substances were being used by the participants. We than administered a brief battery of neuropsychological tests to assess a range of cognitive abilities found in previous studies[3-5] to be affected by chronic and heavy cannabis use. All neuropsychological tests were administered using standard procedures in single sessions (table 2). Test results were analyzed with a series of analyses of variance, controlling for confounding variables that might affect neuropsychological performance (age, education level, estimated premorbid IQ, sex, severity of depression) through analyses of covariance.

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Results. Initial analyses revealed differences between the groups for the confounding variables age ($F_{2,61}$ = 7.315; p = 0.001) and estimated premorbid IQ ($F_{2,61}$ = 6.052; p = 0.004). However, there were no differences between the groups as regards years of education ($F_{2,61}$ = 0.448; p = 0.641), severity of depression ($F_{2,61}$ = 0.141, p = 0.869), sex (proportion males/females) (χ^2_2 = 1.365; p = 0.505) and length of abstinence (t = 0.143; p = 0.887) (table 1).

Further analyses showed a group effect on all the trials of the Rey Auditory Verbal Learning Test (RAVLT) except trial 1 ($F_{2,59}$ = 0.115, p = 0.891) and trial 3 ($F_{2,59}$ = 0.115, p = 0.891). The learning curves of long-term (LT) and shorter term (ST) users were similar with post hoc multiple comparisons showing a difference between LT and ST users only on learning trial 2 of the RAVLT (p = 0.043). However, the LT group recalled fewer words on total trials 1 to 5 and delayed recall and recognition trials of the RAVLT. Post hoc multiple comparisons indicated differences between LT group and controls on trial 2 (p = 0.023), trial 4 (p = 0.016), trial 5 (p = 0.002), trial 6 (p = 0.000), delayed recall (p = 0.000), recognition (p = 0.015), and total trials 1 to 5 (p = 0.006) of the RAVLT. Differences were also found between ST and control groups on trial 5 (p = 0.008), trial 6 (p = 0.000), and delayed recall (p = 0.005) and recognition (p = 0.012) trial of the RAVLT. Analysis of covariance controlling for age and IQ showed a

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Table 1 *Demographic variables and cannabis use features of the sample (means, SD, and ranges)*

Variable	Total no. of cannabis users	Shorter term cannabis users (ST)	Long-term cannabis users (LT)	Control group
No.	40	20	20	24
Sex, M (%)	25 (62.5)	14 (70.0)	11 (55.0)	13 (54.2)
Age, y				
Mean (SD)*	28.45 (6.74)	24.25 (2.83)	32.65 (6.93)	28.42 (9.04)
Range	21–49	21–33	24–49	17–48
Years of education				
Mean (SD)	10.58 (2.59)	10.80 (2.21)	10.35 (2.96)	11.17 (3.20)
Range	6–16	6–16	6–16	6–20
Estimated IQ, mean (SD)	101.30 (5.72)	101.10 (5.90)	101.70 (5.40)	104.80 (4.30)
Duration of cannabis use				
Mean (SD)	11.28 (5.62)	6.95 (1.50)	15.60 (4.81)	—
Range	5–25	5–9	10–25	
Frequency of cannabis use				
Mean (SD)	20.43 (3.15)	20.70 (3.40)	20.15 (2.92)	—
Range, d/mo	16–28	16–28	16–28	
Length of abstinence				
Mean (SD)	124.55 (76.36)	122.80 (76.32)	126.30 (78.33)	—
Range, h	36–240	36–240	36–240	

Premorbid intelligence (IQ) was estimated by administering the vocabulary and matrix reasoning subscales of the Wechsler Abbreviated Scale of Intelligence, Gr- adapted version.[1] The vocabulary subscale is a good measure of crystallized intelligence, correlates well with general intellectual ability, and is relatively insensitive to cortical insults (i.e., a good measure of premorbid intellectual ability). The matrix reasoning subscale is a measure of nonverbal fluid reasoning and correlates well with general intellectual ability. These two subscales yield an estimated full-scale IQ.

* Significant at the $p < 0.05$ level; all other comparisons were not significantly different.

group effect for the Trail Making Test (TMT) Part A (TMT-A) ($F_{2,55} = 9.031$; $p < 0.001$) and Part B (TMT-B) ($F_{2,58} = 7.915$; $p = 0.001$). Post hoc multiple comparisons indicated differences between the LT group and controls on the TMT-A ($p = 0.036$) and TMT-B ($p = 0.011$). Differences were also found between ST group and controls on the TMT-A ($p < 0.001$) and TMT-B ($p < 0.001$). Analyses of covariance further indicated a group effect for phonemic fluency ($F_{2,59} = 13.100$; $p = 0.000$) and semantic fluency ($F_{2,59} = 16.908$; $p = 0.000$). Post hoc multiple comparisons showed that the LT group had worse performance on phonemic fluency ($p = 0.002$) and semantic fluency ($p = 0.000$) than the controls. Differences were also found between ST group and controls on phonemic fluency ($p < 0.001$) and semantic fluency ($p = 0.004$). A group effect was also found for the Boston Naming Test (BNT) ($F_{2,59} = 5.018$; $p = 0.01$). Post hoc multiple comparisons showed that only the LT group had a worse performance on the BNT than the controls ($p = 0.008$). (table 3).

Table 2 *Neuropsychological test battery arranged by cognitive function assessed*

Cognitive function(s) assessed	Test used
Verbal fluency/language	Boston Naming Test[8]
	Verbal fluency test: phonemic and semantic fluency[7]
Verbal memory/learning	Rey Auditory Verbal learning Test[9]
Psychomotor speed/ attention	Trail Making Test Part A[6]
Executive functioning	Trail Making Test Part B[6]
Severity of depression	Beck Depression Inventory–Fast Screen[10]

Normative data were taken from the sources indicated.

We also recorded the proportion of impairment on individual neuropsychological measures using two different criteria for impairment (1 and 1.5 SD below the control group mean). There were several different patterns in the proportion of impairments seen across the groups (see tables E-1 and E-2 on the *Neurology* Web site at www.neurology.org). We found a steady increase in the proportion of subjects classified as impaired, with the lowest rates in the control group and the highest in the LT group. The correlation of duration of cannabis use and neuropsychological measures for collapsed cannabis users (n = 40) revealed significant negative correlations between trials 2, 6, delayed recall, total trials 1 to 5 of the RAVLT, semantic fluency, BNT, and years of cannabis use (see table E-3). Duration of cannabis use therefore appears to be related to neuropsychological performance in certain cognitive domains.

Discussion. We investigated the chronic effects of frequent heavy cannabis use on cognitive functions, with duration of use as our main variable.

Table 3 *Neuropsychological test performance of long- and shorter term cannabis users and normal controls: Mean (SD)*

				p Value for comparisons		
	Shorter term cannabis users	Long-term cannabis users	Control group	Shorter term vs long term	Long term vs control	Shorter term vs control
RAVLT						
Trial 1	7.45 (2.46)	6.85 (1.53)	7.92 (1.74)	>0.99	>0.99	>0.99
Trial 2	9.95 (1.96)	7.70 (1.45)	10.04 (1.78)	0.043*	0.023*	>0.99
Trial 3	10.35 (1.48)	9.45 (1.10)	11.88 (2.01)	>0.99	0.057	0.065
Trial 4	11.30 (2.30)	10.20 (3.01)	12.71 (2.12)	>0.99	0.016*	0.073
Trial 5	11.50 (1.93)	10.25 (1.97)	13.17 (1.58)	>0.99	0.002*	0.008*
Trial 6	8.30 (2.54)	7.25 (1.86)	11.38 (2.06)	>0.99	<0.001*	0.000*
Delayed recall	9.30 (3.59)	6.60 (2.52)	12.17 (2.35)	0.401	<0.001*	0.005*
Recognition	11.30 (3.11)	11.20 (1.99)	13.75 (1.70)	>0.99	0.015*	0.012*
Total on trials (1-5)	50.50 (9.67)	42.65 (7.92)	55.29 (7.54)	0.404	0.006*	0.273
Semantic fluency	48.35 (7.95)	38.40 (6.85)	57.17 (9.74)	0.063	<0.001*	0.004*
Phonemic fluency	27.35 (9.25)	28.20 (4.60)	40.67 (9.18)	>0.99	0.002*	<0.001*
TMT-A (s)	53.15 (16.52)	52.79 (13.89)	34.67 (9.31)	0.104	0.036*	<0.001*
TMT-B (s)	100.42 (39.87)	107.55 (37.60)	65.25 (14.40)	0.332	0.011*	<0.001*
BNT	14.35 (0.75)	13.45 (1.00)	14.67 (0.64)	0.102	0.008*	>0.99
BDI–Fast Screen	7.85 (3.87)	7.84 (4.22)	7.33 (3.27)	>0.99	>0.99	>0.99

* Significant at the $p < 0.05$ level; all other comparisons were not significantly different.

For the TMT-A, the analysis was performed on 60 subjects due to the removal of one outlier case from the long-term users and three outlier cases from the controls. For the TMT-B, the analysis was performed on 63 subjects due to the removal of one extreme outlier case from the long-term users.RAVLT = Rey Auditory Verbal Learning Test; TMT-A = Trail Making Test Part A; TMT-B = Trail Making Test Part B; BNT = Boston Naming Test; BDI = Beck Depression Inventory.

By requiring an abstinence period of ≥24 hours prior to neuropsychological testing, we simulated an unintoxicated cognitive state in which LT users typically operate for substantial periods in their life. LT users performed significantly poorer on verbal memory vs ST users and controls. LT and ST users generated fewer words and demonstrated higher impairment rates than controls on both phonemic and semantic fluency. LT and ST users showed inferior performance vs the control subjects on psychomotor speed, attention, and executive functions. The greatest deficits regarding the LT users were seen on almost every trial of the RAVLT, indicating a generalized verbal memory deficit with impaired verbal learning, retention, and retrieval. LT users' performance was significantly poorer than the published norms (table 2) on most measures of the RAVLT. Our findings are in accordance with certain studies[4,5] showing that heavy long-term frequent cannabis use leads to subtle deficits in specific neuropsychological domains.

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