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Research Article

Executive Functions and Cannabis Use in Adolescents

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Abstract

Adolescence is a development stage characterized by multiple neuro-cognitive and psychosocial changes and therefore considered a critical phase of human development. At this stage, is when young adults start consuming substances, consequently the addiction process begins. Several studies show that chronic cannabis abuse can cause neurofunctional and neuro-cognitive changes. Particularly it would negatively impact on divided attention, short-term verbal memory and working memory performance. In this study we investigate how abuse of cannabis can affect global cognitive functioning, also through the evaluation of executive functions. Sample population that took part in this study was grouped by the frequency of use of cannabinoid substances (chronic, occasional, and absent consumption). Statistical analysis showed a significant decrease in performance in working memory tasks by subjects who used chronic cannabis (group 1) compared to subjects who did not use it at all (group 3). Future studies could verify the extent of the neuro cognitive alterations through re-evaluations with controlled follow-ups.

Keywords: Working Memory; Executive Functions; Adolescents; Cannabis; Cognition

Introduction

Adolescence is a development stage characterized by multiple neurocognitive and psychosocial changes and it is therefore considered a critical phase of human development [1]. From the age of 12, a new brain maturation process, consisting of proliferation, migration and differentiation, synaptogenesis and pruning, begins, also involving a global remodelling of the brain [2-5]. During adolescence, full maturity is reached specifically by the higher cognitive functions, mainly functions and cognitive processes that involve the frontal and prefrontal cortex mature [6]. At this stage a key feature of the brain is represented by the immaturity of self - seeking processes (self - regulation): this process leads to an increase in impulse decontrol and astrong attraction to what is forbidden [7-9]. In this phase, individuals (especially adolescents) can be attracted to drugs, and these substances can greatly interfere with the development and subsequent functioning of cognitive processes. The substances consumption often starts in adolescence, as well as the addictive process [10]. According to some statistics, more than 90% of the addicted people started using various substances before the age of 18 years [11]. Cannabis is the most widely abused drug, with approximately 147 million people (2.5% of the world population) consume it (WHO, 2019), particularly adolescents [12,13]. Several studies show that the chronic use of cannabis is the cause of alterations of neurofunctional and neurocognitive functions, particularly it negatively impact divided attention, short-term verbal memory and working memory performance [14-19]. Especially, the working memory suffers the abuse of substances and its impairment can affect the correct functioning of the others cognitive functions. Other studies show that cognitive impairment is the cause of lower academic performance [20], of declarative memory deficit [21] and of a persistent decline in global cognitive functioning [22]. Previous studies have also shown that individuals who start consuming cannabis at an early age may be more vulnerable to long-lasting neuropsychological deficits than individuals who started using it later [23]. Studies showing that impairment persists into adulthood [24,25], with greater severity in chronic cannabis users, are particularly concerning, [26,27]. Most studies, identify temporal extent of use and not its frequency to define "chronic use". Pope and Yurgelun's paper [28] represents one of the few studies documenting the comparison between adolescents who use cannabis frequently and those who use it occasionally. The study was later continued by Pope., *et al*. [29], to evaluate consequences of with drawal rather than outcomes based on frequency. In our study we investigate how cannabis use (chronic, occasional and absence use) can influence global cognitive functioning, and executive functions, considering the weekly use frequency parameter and not just the temporal extension of use. For this purpose, we decided to administer WISC-IV [30] to two groups of occasional and chronic cannabis adolescents users. Working memory indices (WMI), processing speed (PSI) and intelligence quotient (IQ) were investigated by comparing the scores with a control group that did not use substances, and to understand to what extent this abuse could impair cognitive functions. We also performed a neuropsychological test with the administration of the BVN 12-18 Battery to investigate whether planning skills and memory skills (visuo-spatial) were also impaired following the abuse of cannabinoids.

Materials and Methods

Participants

For this study we recruited subjects between the ages of 15 and 16 in ten secondary schools in the province of Naples. The study originates from a collaboration between The Centre of Child Neuropsychiatry FINDS (Italian Foundation for Neuroscience and Developmental Disorders) and the University of Salerno alongside with the USR (Regional School Office) of Campania. The sample selection involved the preliminary administration of a questionnaire to identify the subjects habits of cannabinoids consumption. The questionnaire was used to determine the usage of cannabinoids and comprised of 5-item Likert scale response and a semi-open question, accounting for a total of 6 questions. The semi open question, represented the key response used as main criteria to subdivide the students in 3 different groups: group 1 comprising of 46 subjects identified as chronic users of cannabis (at least 4 times a week for at least a year), group 2 of 46 occasional cannabis users, (about once every two weeks for at least one year) and a group 3 (control) of comprising of 46 subjects identified as non-consumers od the substance. Therefore, the inclusion criterion saw chronic use as ≥ at 4 weekly intakes for at least one year, while occasional use ≤ once every 2 weeks for at least one year. The control group did not use any substance. All groups took part to the administration of WISC IV anonymously, in the school environment by qualified psychologists belonging to the two reference clinics (FINDS and University of Salerno). Later they were given the subtest Corsi and Tol from BVN 12 - 18 [31] (Table 1).

Group 1			Group 2			Group 3		
M_{age}	SD	Gender	M_{age}	SD	Gender	M_{age}	SD	Gender
15,3	0,23	M/F 32/14	15,3	0,11	M/F 30/16	15,4	0,11	M/F 33/13

Table 1: Subdivision of the sample.

Procedures and tools

The protocol used in this study is composed of a specifically constructed questionnaire, which investigates the frequency of cannabinoid consumption, the WISC IV [30], the BVN 12 - 18 [31], and the MT Trials - Advanced 3 [32].

Questionnaire: The questionnaire included 5 closed questions focusing on: possible use of cannabinoids (regular or occasional), possible consumption of other substances (regular or occasional), possible use of alcohol (regular or occasional), tendency to use cannabinoids (individual and group) and tendency to use other substances or alcohol (individual and group). Responses were given on a 5-point Likert scale ranging from one (strongly agree) to five (strongly disagree). For the affirmative answers on the use of cannabinoids, the weekly frequency was also investigated through an open question.

WISC-IV: Clinical and diagnostic tool to assess the intellectual abilities of children aged 6 to 16. It consists of 15 tests (10 main and 5 supplementary) divided into 4 indices. The 10 main tests are represented by: block design (BD), similarities (SI), digit span (DS), picture concepts (PCN), coding (CD), vocabulary (VC), letter-number sequencing (LN), matrix reasoning (MR), comprehension (CO), symbols search (SS). They are divided into 4 indices: perceptual reasoning index (PRI), which includes BD, PCN and MR, verbal comprehension index (VCI), which includes SI, VC and CO, working memory index (WMI) which includes DS and LN, and processing speed index (PSI) which includes CD and SS.

BVN 12-18: Test battery for neuropsychological evaluation to identify single disorders in specific areas and to define a general profile of mnemonic, praxic, visuospatial, perceptive, attentive, linguistic, executive skills, etc., useful for a deeper study after an initial diagnostic assessment. In particular, the ToL (Tower of London) subtest evaluates high executive functions such as planning and problem solving skills. The Corsi subtest, on the other hand, allows us to evaluate the span of visuospatial memory, that is, the amount of visuospatial information that can be retained in short-term memory (MBT).

Advanced MT Tests - 3: Tests to thoroughly assess reading, reading comprehension skills and math skills in adolescents. They include word and non-word reading tests, text comprehension tests, writing tests by dictation and tests of arithmetic skills and facts.

Procedures

All subjects included in the sample were given the questionnaire to investigate the frequency of use of the substances. Following the analysis of the responses to the questionnaire, we divided the sample into 3 groups: group 1, chronic cannabinoids users, group 2 occasional users, and group 3 of non consumers. The third group was obtained by a random selection among those who did not use substances, regular and frequent consumers of other substances (e.g., tobacco or alcohol) were excluded from the sample in order to avoid bias from the effects of the other substances that are not cannabinoids, thus, the sample included only subjects who did not make regular and frequent use of different drugs. All groups then undertook the WISC-IV, with Italian standardization. The scores of 4 indices were calculated, namely: the perceptual reasoning index (PRI), which includes BD, PCN and MR, the verbal comprehension index (VCI), which includes SI, VC and CO, the working memory (WMI) which includes DS and LN, and the processing speed index (PSI) which includes CD and SS. Individual tasks scores were analysed; in particular the main indices (VCI, PRI, WMI, PSI and IQ). Our hypothesis suggests that the group that uses chronic cannabis (group 1) has a significant drop (difficulty) in the tasks of working memory (WMI) and processing speed (PSI) with consequent impact on the intelligence quotient (IQ), consistent with what highlighted by the literature [33]. We then administered the subtests of BVN 12-18 for an in-depth study of visuospatial memory skills (Corsi test) and planning (London Towers subtest). We assume that the group of individuals who make chronic use of cannabis (Group 1) had a significant drop in the tasks and planning (TOL) memory and visual-spatial (Corsi test) compared with the control group (group 3). Furthermore, to estimate the percentage of specific learning disabilities, we administered the Advanced MT tests - 3 to the entire population.

Results and Discussion

Data analysis was performed using SPSS 25.0 statistical survey software [34]. Significance was accepted at the 5% level ($\alpha < 0.05$). We compared the weighted scores of the groups and the indices (VCI, PRI, WMI, PSI, IQ) emerged from WISC-IV using the Student 's T test, a parametric statistical test that can be used when the two groups in comparison are independent. Specifically, we used the T Test for paired samples, to make comparisons between groups, with two-tailed significance. The comparison between group 1 and group 3 revealed significant differences in the WMI indices ($t = -13.38$; $p < 0.05$), PSI ($t = -4.89$; $p < 0.05$) and IQ ($t = -8,24$; $p < 0.05$). When compared to those who do not make any use of cannabinoids, these results demonstrate that chronic use of cannabinoids has a remarkable effect on the operation of the working memory, on the speed of information processing, and also impacts on the IQ. The impact on the PRI is slightly significant ($t = -3.02$; $p < 0.05$), while the impact on the VCI is not significant (Table 2).

The comparison between group 1 and group 2 revealed significant differences in the WMI indices ($t = -11.37$; $p < 0.05$), PSI ($t = -4.75$; $p < 0.05$) and IQ ($t = -7,31$; $p < 0.05$). These results show that chronic use of cannabinoids, compared to those who use them less frequently, can affect the skills of working memory, information processing speed, consequently impacting global cognitive functioning, represented by the IQ index. We then compared the scores that emerged at the ToL subtest between group 1 and group 2 and significant differences emerged (t = -3.56; p < 0.05). These results demonstrate that chronic use of cannabinoids has a significant impact on planning skills compared to those who use them less frequently (Table 3).

Significant differences also emerged in the comparison between group 1 and group 3 (t = -4.52; p < 0.05), showing that those who use chronic cannabinoids have considerable difficulties in planning skills compared to those who do not makes no use (Table 2). On the other hand, no significant differences emerged between group 2 and group 3 (Table 4).

	Group 1				Group 3			
	Means	SD	t	p	Means	SD	t	p
VCI	98,83	4,33			101,65	5,77	-2,294	.026
PRI	99	6,78	-3,026	.004*	102,89	4,85		
WMI	83,17	6,11	-13,384	.000*	97,85	4,8		
PSI	92,24	5,78	-4,896	.000*	98,3	5,39		
IQ	89,17	6,51	-8,245	.000*	101,83	7,4		
ToL	7,3	0,94	-4,528	.000*	8,35	1,21		
CORSI	3,87	0,71	-9,388	.000*	5,46	1		
*p < 0.05								

Table 2: Comparison of indices between group 1 and 3.

	Group 1				Group 2			
	Means	SD	t	p	Means	SD	t	p
VCI	98,83	4,33			101,26	5,51	-2,028	.048
PRI	99	6,78			101,93	5,17	-2,238	.030
WMI	83,17	6,11	-11,375	.000*	96,22	4,58		
PSI	92,24	5,78	-4,757	.000*	98,37	5,82		
IQ	89,17	6,51	-7,319	.000*	99,91	6,39		
ToL	7,3	0,94	-3,564	.001*	8,07	1,06		
CORSI	3,87	0,71	-7,646	.000*	5,11	0,84		
*p < 0.05								

Table 3: Comparison of indices between groups 1 and 2

	Group 2		Group 3			
	Means	SD	Means	SD	t	p
VCI	101,26	5,51	101,65	5,77	-0,364	.718
PRI	101,93	5,17	102,89	4,85	-0,959	.343
WMI	96,22	4,58	97,85	4,8	-1,778	.082
PSI	98,37	5,82	98,3	5,39	.058	.954
IQ	99,91	6,39	101,83	7,4	-1,387	.172
ToL	8,07	1,06	8,35	1,21	-2,163	.036
CORSI	5,11	0,84	5,46	1	-2,697	.010
*p < 0.05						

Table 4: Comparison of indices between groups 2 and 3.

Finally we compared the performance at the Corsi subtest between group 1 and group 2 and significant differences emerged ($t = -7.64$; $p < 0.05$). These results indicate that chronic cannabinoid users experience significant difficulties in visuospatial memory skills (Table 3). There were also significant differences between group 1 and group 3 ($t = -9.38$; $p < 0.05$). These results show that chronic use of cannabinoids can impair visuospatial memory skills compared to those who do not use them. However, no significant differences emerged between group 2 and group 3 (Table 2).

To understand the main differences between groups, we performed the ANOVA test (Analysis of variance) with post hoc tests (Bonferroni). From these analysis it was possible to observe that the scores of group 1 differ significantly from those of group 3 at the following indices: WMI (-14.67; $p < 0.05$), PSI (-6.06; $p < 0.05$) and IQ (-12.65; $p < 0.05$), demonstrating that a chronic use of cannabinoid substances has a significant impact on the functioning of the working memory, the speed of information processing, also impacting on IQ. The comparison between the scores of group 2 and group 3 did not reveal significant differences, while the comparison between group 1 and group 2 showed differences in the WMI indices (-13.04; $p < 0.05$), PSI (-6.13; $p < 0.05$) and IQ (-10.73; $p < 0.05$), showing that the effects of chronic cannabis use on cognitive functioning are greater, while occasional use of this substance does not has a significant impact (Figure 1-3).

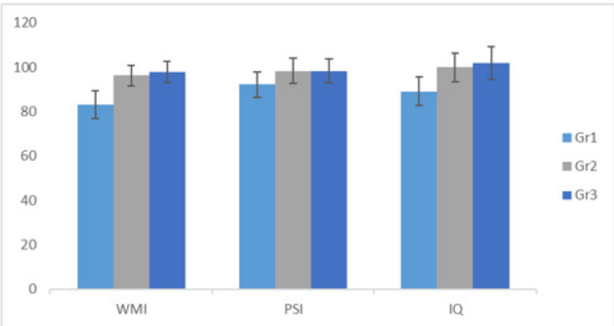

Figure 1: Comparison of indices WISC between the three groups.

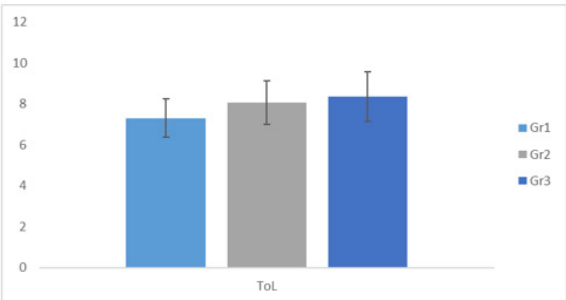

Figure 2: Comparison of ToL between the three groups.

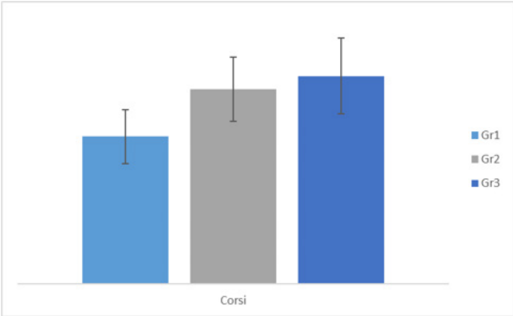

Figure 3: Comparison of Corsi between the three groups.

Furthermore, from the analysis of the tests administered for the evaluation of the reading and calculation skills of the cases examined, the following values emerged for the diagnosis of dyslexia and dyscalculia: with regard to group 1, 13,04% (6 subjects) diagnosed with dyslexia and 17,39% (8 subjects) diagnosed with dyscalculia; of these, 28,26% (13 subjects) were diagnosed with both dyscalculia and dyslexia. With regard to group 3, the following values emerged: 2,17% diagnosed with dyslexia and 2,17% diagnosed with dyscalculia; of these, 4,34% were diagnosed with both dyslexia and dyscalculia. With regard to group 2, the following values emerged: 4,34% (2 subjects) diagnosed with dyslexia and 2,17% diagnosed with dyscalculia; of these, 6,52% (3 subjects) who had received diagnoses of both dyslexia and dyscalculia (Figure 4-6).

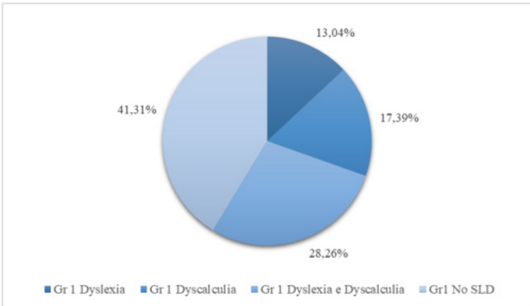

Figure 4: Percentages of SDL in group 1.

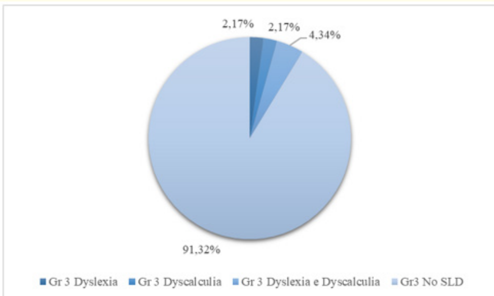

Figure 5: Percentages of SDL in group 3.

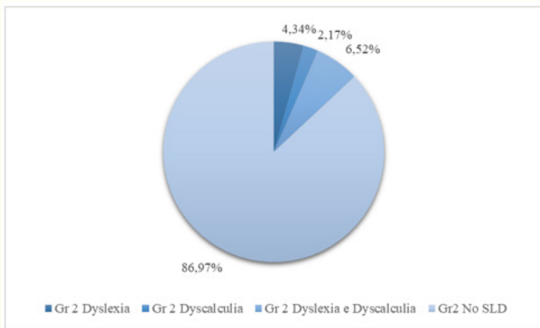

Figure 6: Percentages of SDL in group 2.

Conclusion

A persistent use of cannabis during adolescence (especially before 18 years of age) can cause neuropsychological deficits causing cognitive neuro alterations, particularly impacting the global intellectual functioning. Before the age of 18, the brain is still in the process of organizing and restructuring (the pruning phase is still in progress) and therefore more vulnerable to damage resulting from taking drugs and drugs. Some studies have shown that the use of cannabis has also influences on cognitive functions mainly have found lower than normal performance in tasks of attention, learning, working memory and information processing speed [17,28-35]. In particular, the impairment of working memory is widely used and documented, especially in studies that investigated a population of adolescents who make chronic use of cannabinoids ; in fact, from these studies, the obtained scores indicated a performance lower than the working memory by comparing them with non-consumers subjects [36]. Other studies that also considered sample including chronic cannabis users that undergo to a reasonably long abstinence, suggest that the deficit of working memory may persist for some time after the acute poisoning [27]. The novelty of our study is therefore the consideration of weekly attendance as a fundamental parameter to discriminate the results. The statistical analysis of our study showed that the group of subjects who use chronic cannabis (group 1 - use of cannabinoids 4 times a week for at least a year) show a significant fall in working memory tasks compared to the group who does not use it (group 3). In addition, there was also a decrease in the tasks of information processing speed and IQ, highlighting a significant difference with the control group (group 3). Analysis of the scores obtained by the group identified as occasional users of cannabis (group 2 - use of cannabinoids once every two weeks for at least a year), there is no decrease in working memory, processing speed, and IQ compared to the control group (group 3). Finally, if we compare group 1 with group 2, significant drops in working memory, processing speed and IQ of group 1 compared to group 2 are highlighted. The results of this study highlight the fact that the use of substances in early age causes neurocognitive alterations, particularly on cognitive processes such as working memory and processing speed, only if the use is chronic, where chronic must be understood as a highly frequent use of the substance. Therefore, the impact on cognitive functioning, highlighted by previous studies [37,38] must be considered not only in terms of time extension but also of frequency. Furthermore, as regards the neuropsychological investigation carried out on our sample, the statistical analysis showed that the group that used cannabis chronically (group 1) presented a notable impairment of planning skills compared to the control group (group 3), thus noting an impact of the substance also on executive functions, in particular on planning ones. The impairment of the afore mentioned functions as regards the group that used them occasionally (group 2) compared to group 3 was found to be present, albeit to a lesser extent, thus making it evident that the use of cannabinoids in adolescence, even if less frequently, causes an alteration of cognitive processes such as executive functions, specifically planning skills, with a significant impact on global intellectual functioning. Furthermore, the chronic use of cannabis is found to have an significant impact on the functioning of higher cognitive processes such as executive functions precisely, to an extent more significant compared to the group which was not any use (group 3). In addition, our analysis reveals that the chronical cannabis users (group 1) also performed poorly in higher visual-spatial material processing skills than the non- cannabinoid-using group (group 3). This figure indicates that the chronic use of cannabis is the cause of difficulties in amnesic ability significantly, and to a considerable extent those that enable the processing of material visuo-spatial. A more recent study, conducted by Morin., *et al.* [39] also found that cannabis use in adolescence was associated with generally lower performance in working memory (WMI), perceptual reasoning (PRI) and processing speed (PSI), although it does not make a good frequency discriminant. In fact, in our study we proposed weekly attendance as a fundamental parameter for discriminating outcomes as a novelty. The result of this study make it clear that people who start a chronic consumption of cannabis in early age (especially in adolescence) , are more vulnerable to cognitive deficits, detected in our studio as working memory and processing speed, and more specifically of global cognitive functioning. Several clinical studies agree in fact that the earlier the adolescent starts to consume cannabis, the greater the risk of subsequently developing psychiatric disorders or addiction to other substances abused [13,40-42]. Research has also found learning deficits [43,44]; in fact, our analysis highlighted the presence of Specific Learning Disorders in the sample examined, specifically as regards group 1 13.04% (6 subjects) diagnosed with dyslexia and 17.39% (8 subjects) diagnosed with dyscalculia; of these, 28.26% (13 subjects) were diagnosed with both dyscalculia and dyslexia. These data are consistent with what emerged in previous studies on the presence of ASD in adolescents who use cannabinoids chronically [43,44] however, in our sample, subjects with a diagnosis of dyslexia and dyscalculia specifically emerged. Differently, with regards to group 3, the following values emerged: 2.17% diagnosed with dyslexia and 2.17% diagnosed with dyscalculia; of these, 4.34% were diagnosed with both dyslexia and dyscalculia. Finally, with regards to group 2, the following values emerged: 4.34% (2 subjects) with a diagnosis of dyslexia and 2.17% with a diagnosis of dyscalculia; of these, 6.52% (3 subjects) who had received diagnoses of both dyslexia and dyscalculia.

A cross-sectional study does not allow us to discriminate between association and causal link. However, the association is significant if we take our parameters into consideration. Future studies could forecast an enlargement of the sample to further reinforce the significance and a follow up to monitor the persistence of the existences over time.

Author Contributions

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Conflicts of Interest

The authors declare that they have no conflict of interest.

Compliance with Ethical Standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Bibliography

1. Giedd JN. "Adolescent neuroscience of addiction: a new era". *Developmental Cognitive Neuroscience* 16 (2015): 192-193.
2. Giedd JN. "Structural magnetic resonance imaging of the adolescent brain". *Annals of the New York Academy of Sciences* 1021 (2004): 77-85.
3. Shaw P., *et al*. "Intellectual ability and cortical development in children and adolescents". *Nature* 440.7084 (2006): 676-679.
4. Winters KC and Lee S. "Likelihood of developing an alcohol and cannabis use disorder during youth: Association with recent use and age". *Drug and Alcohol Dependence* 92 (2008): 239-247.
5. Giedd N. "Adolescent brain maturation". In: Tremblay RE, Barr RG, Peters RDeV, Boivin M, eds. Encyclopedia on Early Childhood Development. Montreal, Quebec: Centre of Excellence for Early Childhood Development (2010): 1-5.
6. Gogtay N., *et al*. "Dynamic map-ping of human cortical development during childhood through early adulthood". *Proceedings of the National Academy of Sciences of the United States of America* 101 (2004): 8174-8179.
7. Reyna V F and Farley F. "Risk and rationality in adolescent decision making implications for theory, practice, and public policy". *Psychological Science in the Public Interest* 7.1 (2006): 1-44.
8. Romer D and Hennessy M. "A biosocial-affect model of adolescent sensation seeking: The role of affect evaluation and peer-group influence in adolescent drug use". *Prevention Science* 8.2 (2007): 89-101.
9. Martins S S., *et al*. "Adolescent ecstasy andother drug use in the National Survey of Parents and Youth: The role of sensation-seeking, parentalmonitoring and peer's drug use". *Addictive Behaviors* 33.7 (2008): 919-933.

10. Volkow N D., *et al*. "Effects of cannabis use on human behavior, including cognition, motivation, and psychosis: a review". *JAMA Psychiatry* 73 (2016): 292-297.

11. Public Health Agency of Canada (2018). Preventing Problematic Substance Use in Youth (2018).

12. Gardner M and Steinberg L. "Peer influence on risk taking, risk preference, and risky decision making in adolescence and adulthood: An experimental study". *Developmental Psychology* 41 (2005): 625-635.

13. Rubino T., *et al*. "Uso di cannabis in adolescenza come fattore di rischio per le malattie psichiatriche e la dipendenza da altre droghe". In "Cannabis e danni alla salute". (2011).

14. Broyd SJ., *et al*. "Acute and Chronic Effects of Cannabinoids on Human Cognition-A Systematic Review". *Biological Psychiatry* 79.7 (2016): 557-567.

15. Hindocha C., *et al*. "Acute memory and psychotomimetic effects of cannabis and tobacco both 'joint' and individually: a placebo-controlled trial". *Psychology Medicine* 47.15 (2017): 2708-2719.

16. Lundqvist T. "Cognitive consequences of cannabis use: comparison with abuse of stimulants and heroin with regard to attention, memory and executive functions". P*harmacology Biochemistry and Behavior* 81.2 (2005): 319-330.

17. Solowij N., *et al*. "Cognitive functioning of long-term heavy cannabis users seeking treatment". *JAMA* 287.9 (2002): 1123-1131.

18. Bolla KI., *et al*. "Dose-related neurocognitive effects of marijuana use". *Neurology* 59.9 (2002): 1337-1343.

19. Ilan AB., *et al*. "Effects of marijuana on neurophysiological signals of working and episodic memory". *Psychopharmacology (Berl)* 176.2 (2004): 214-222.

20. Grant I., *et al*. "Non-acute (residual) neurocognitive effects of cannabis use: a meta-analytic study". *Journal of the International Neuropsychological Society* 9 (2003): 679-689.

21. Grant I., *et al*. "Medical marijuana: clearing away the smoke". *Open Neurology Journal* 6 (2012): 18-25.

22. Meier RH., *et al*. "Persistent cannabis users show neuropsychological decline from childhood to midlife". *Proceedings of the National Academy of Sciences of the United States of America* 109 (2012): ES657-ES664.

23. Porath-Waller AJ. "Clearing the Smoke on Cannabis. Chronic Use and Cognitive Functioning and Mental Health". Canadian Centre on Substance Abuse (2009).

24. Alloway TP and Alloway RG. "Investigating the predictive roles of working memory and IQ in academic attainment". *Journal of Experimental Child Psychology* 106 (2010): 20-29.

25. Ullman H., *et al*. "Structure maturation and brain activity predict future working memory capacity during childhood development". *Journal of Neuroscience* 29.34 (2014): 1592-1599.

26. Cousijn J., *et al*. "Effect of baseline cannabis use and working- memory network function on changes in cannabis use in heavy cannabis users: a prospective fMRI study". *Human Brain Mapping* 35 (2014): 2470-2482.

27. Solowij N and Battisti R. "The chronic effects of cannabis on memory in humans: a review". *Current Drug Abuse Reviews* 1 (2008): 81-98.

28. Pope H G J and Yurgelun-Todd D. "The residual cognitive effects of heavy marijuana use in college students". *JAMA* 275.7 (1996): 521-527.

29. Pope HG Jr., *et al*. "Residual neuropsychologic effects of cannabis". *Current Psychiatry Reports* 3 (2001): 507-512.

30. Orsini A., *et al*. WISC-IV: Contributo alla taratura Italiana (WISC-IV Italian) ed. Florence, Italy: Giunti O. S. (2012).

31. Gugliotta M., *et al*. "BVN 12-18-Batteria per la Valutazione Neuropsicologica per l'adolescenza". Edizioni Erickson, Gardolo (2009).

32. Cornoldi C., *et al*. "Prove MT Avanzate-3-Clinica". Giunti OS: Organizzazioni Speciali (2017).

33. Fried P A., *et al*. "Neurocognitive consequences of marihuana - A comparison with pre-drug performance". *Neurotoxicology and Teratology* 27.2 (2005): 231-239.

34. IBM. to Acquire SPSS Inc. to Provide Clients Predictive Analytics Capabilities, in ibm.com, 8 agosto (2017).

35. Fletcher JM., *et al*. "Cognitive correlates of long-term cannabis use in Costa Rican men". *Archives of General Psychiatry* 53 (1996): 1051-1057.

36. Hoa TVo., *et al*. "Working Memory Impairment in Cannabis- and Opioid-Dependent Adolescents". *Substance Abuse* 35.4 (2014): 387-390.

37. Rubino T., *et al*. "Chronic delta (9) -tetrahydrocannabinol during adolescence provokes sex-dependent changes in the emotional profile in adult rats: behavioral and biochemical correlates". *Neuropsychopharmacology* 33.11 (2008): 2760-2771.

38. Lisdahl K M and Price J S. "Increased marijuana use and gender predict poorer cognitive functioning in adolescents and emerging adults". *Journal of the International Neuropsychological Society* 18.4 (2012): 678-688.

39. Morin JG., *et al*. "A Population-Based Analysis of the Relationship Between Substance Use and Adolescent Cognitive Development". *American Journal of Psychiatry* (2018).

40. O'Shea M., *et al*. "Chronic cannabinoid exposure produces lasting memory impairment and increased anxiety in adolescent but not adult rats". *Journal of Psychopharmacology* 18 (2004): 502-508.

41. O'Shea M., *et al*. "Repeated cannabinoid exposure during perinatal, adolescent or early adult ages produces similar longlasting deficits in object recognition and reduced social interaction in rats". *Journal of Psychopharmacology* 20 (2006): 611-621.

42. Casey BJ., *et al*. "The adolescent brain". *Development Review* 28.1 (2008): 62-77.

43. Schweinsburg AD., *et al*. "Abstinent adolescent marijuana users show altered fMRI response during spatial working memory". *Psychiatry Research: Neuroimaging* 163 (2008): 40-51.

44. Harvey MA., *et al*. "The relationship between non-acute adolescent cannabis use and cognition". *Drug Alcohol Review* 26 (2007): 309-319.