

# Cannabis use before age 15 and subsequent executive functioning

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## Background

Many studies have suggested that adolescence is a period of particular vulnerability to neurocognitive effects associated with substance misuse. However, few large studies have measured differences in cognitive performance between chronic cannabis users who started in early adolescence (before age 15) with those who started later.

## Aims

To examine the executive functioning of individuals who started chronic cannabis use before age 15 compared with those who started chronic cannabis use after 15 and controls.

## Method

We evaluated the performance of 104 chronic cannabis users (49 early-onset users and 55 late-onset users) and 44 controls who undertook neuropsychological tasks, with a focus on executive functioning. Comparisons involving

neuropsychological measures were performed using generalised linear model analysis of variance (ANOVA).

## Results

The early-onset group showed significantly poorer performance compared with the controls and the late-onset group on tasks assessing sustained attention, impulse control and executive functioning.

## Conclusions

Early-onset chronic cannabis users exhibited poorer cognitive performance than controls and late-onset users in executive functioning. Chronic cannabis use, when started before age 15, may have more deleterious effects on neurocognitive functioning.

## Declaration of interest

None.

Studies have demonstrated neuropsychological deficits associated with acute exposure to cannabis.<sup>1,2</sup> However, results from studies examining persistent cognitive impairments associated with chronic cannabis use are contradictory, with some studies,<sup>3,4</sup> but not all,<sup>5,6</sup> showing significant neuropsychological deficits even after some weeks of abstinence. One possible explanation for these inconsistent findings is that cannabis is more neurotoxic for some populations than for others. Individuals who are exposed to potentially neurotoxic substances before age 15, while the brain is still developing,<sup>7</sup> may be at higher risk of developing persistent neuropsychological deficits compared with older individuals. One model of genetic control postulates that species with delayed brain development have a larger relative volume of later-developing structures (for example cortical areas, particularly the prefrontal cortex). Consequently, later-developing structures interact with environmental factors for prolonged postnatal periods, which can importantly contribute to the tuning and shaping of circuitry. Prefrontal cortex anatomical development continues after birth with full maturation being achieved only around the early 20s.<sup>8</sup> In addition, different areas within the prefrontal cortex mature at different times. This area of the brain encompasses a number of distinct cognitive processes with different developmental trajectories, including planning, verbal fluency, complex problem-solving and impulse control.<sup>9</sup>

Studies have suggested that adolescence is a period of particular vulnerability to development of neurocognitive effects associated with substance use.<sup>10–12</sup> Findings from animal studies have suggested that cannabinoid 1 (CB<sub>1</sub>) receptor levels peak in early adolescence<sup>13</sup> and animals exposed to cannabis in adolescence are more vulnerable to learning impairments compared with animals exposed in adult life. Medina *et al* demonstrated that after a month of abstinence, adolescent cannabis users showed slower psychomotor speed, poorer complex attention and memory skills, and degraded planning/sequencing abilities compared with

34 non-users.<sup>14</sup> Furthermore, there was an inverse correlation between lifetime marijuana exposure and cognitive performance in the same cognitive domains, suggesting a dose-dependent effect. The authors conclude that frequent marijuana use during adolescence may negatively influence neuromaturation and cognitive development. Wilson *et al* evaluated the possible role of age on first use of cannabis interfering with brain and body development.<sup>15</sup> Brain volume measurements (whole brain, grey matter, white matter and lateral ventricle volumes) and global cerebral blood flow were evaluated in 57 chronic cannabis users. Participants who started using cannabis before age 17 had smaller total brain and cortical grey matter volumes with larger white matter volumes. Both males and females who started regular early use were physically smaller in height and weight, with greater effects in males.

Executive functioning is a term that refers to complex mental control processes reflected in future-oriented behaviour that includes cognitive flexibility in problem-solving, focused attention, inhibition of impulsive responses, monitoring, evaluating and adjusting self-directed perception and working memory. From a neurophysiological point of view, executive functions mainly rely on circuits involving prefrontal areas.<sup>16</sup> According to DSM-IV,<sup>17</sup> compulsive use and intense, persistent desire to use a substance, despite the presence of physical and psychological consequences related to the substance use, is a core symptom of dependence syndrome. In this sense, executive deficits might play a central role in the development of addictive behaviours and, consequently, in substance use disorder treatment issues.<sup>18</sup>

Undoubtedly, adolescents are vulnerable to impaired cognitive effects associated with cannabis misuse.<sup>19</sup> The results suggest that chronic cannabis users process complex information more slowly and performance worsens in cognitive overload tasks as lifetime consumption increases.<sup>20</sup> With this in mind, we examined the

impact on executive functioning in 104 chronic cannabis users who were seeking treatment at the Drug and Alcohol Unit (UNIAD) of the University of São Paulo. Because of the unusually large sample size, we were able to divide the chronic cannabis users into two groups based on age of initial use. Our main aim was to examine executive functioning of individuals who started chronic cannabis use before age 15 (early-onset group) compared with individuals who started chronic cannabis use after age 15 (late-onset group) and controls (non-users). We hypothesised that the early-onset group would perform poorly on cognitive tests evaluating executive functioning compared with both the late-onset group and the healthy controls.

## Method

### Participants

We recruited chronic cannabis users who were seeking treatment at the Substance Use Disorder Program, Federal University of São Paulo. To assess study eligibility, telephone screening interviews were administered to all potential participants. After enrolment in the study, participants were interviewed to provide a complete medical and psychiatric history. Although abstinence was encouraged, it was not required. All participants participate in a day-long interview in order to start treatment at UNIAD. The neuropsychological assessment was performed on the first day of the treatment.

The following inclusion criteria were used for chronic cannabis users: males and females, aged 18 to 55 years, with DSM-IV cannabis misuse or dependence (cannabis as the misuse substance of choice) as determined by Composite International Diagnostic Interview (CIDI).<sup>21</sup> Exclusion criteria included current history of other DSM-IV Axis I disorders, with the exception of nicotine-related disorders as determined by CIDI; current use of psychoactive medications, history of head trauma with loss of consciousness for more than 5 min, intellectual disability or estimated IQ below 80, and non-correctable vision or hearing impairment.

Individuals in the control group qualified for this study if they were between the ages of 18 and 55, did not use any psychoactive substance, did not have a history of head trauma, and had no lifetime diagnosis of Axis I DSM-IV disorders. They had not used cannabis at all in the last 3 months and had been exposed no more than five times in their lifetime. The study protocol was approved by the local institutional review board. All participants were required to sign a written informed consent, in accordance with the Federal University of São Paulo review board.

### Instruments

A detailed assessment was administered at enrolment consisting of a semi-directed protocol measuring psychosocial functioning, medical history and history of substance use. We used the modified Time Line Follow Back calendar (TLFB)<sup>22</sup> to obtain detailed information regarding type, amount, and frequency of substance exposure. Composite International Diagnostic Interviews were used to assess DSM-IV Axis I diagnosis. Urine analyses for tetrahydrocannabinol detection were performed on all participants on the same day as the interview to evaluate the reliability of what they reported in the interview. Tests were not performed to detect other substances.

The neuropsychological battery consisted of the following.

(a) Stroop Test – Victoria Version, composed of three cards, each one containing six rows of four items.<sup>23</sup> The first card contains 24 rectangles filled with colours (green, pink, blue and

brown). The participant should name as quickly as possible the printed colours. The second card has nouns written in coloured words and the participant is required to name as quickly as possible the colour of the words, disregarding their verbal content (for example the participant is expected to respond green when the word 'each', written in green, is presented). On the third card, the coloured stimuli are colour names, so that the printed colour never corresponds to the colour name (for example 'Brown' is written in blue ink). This later task, thus, requires the individual to inhibit an automatic reading response and to produce a more effortful colour-naming response by exerting an inhibitory control.

(b) Wisconsin Card Sorting Test – version 64 (planning, executive functioning, conceptualisation, perseveration, and ability to form abstract concepts).<sup>24</sup>

(c) Frontal Assessment Battery – FAB, a short neuropsychological instrument aimed at assessing executive functions.<sup>25</sup> The FAB consists of six subtests, each exploring functions related to frontal functioning: conceptualisation (similarities task), mental flexibility (phonological fluency task), motor programming (by means of Luria's motor series), sensitivity to interference (conflicting instructions task), inhibitory control (go/no-go task) and environmental autonomy (evaluation of prehension behaviour).

(d) Vocabulary and block design (Wechsler Adult Intelligence Scale – Revised (WAIS-R)) for IQ estimation.<sup>26</sup> Vocabulary is a WAIS-R subtest that evaluates the degree to which one has learned, been able to comprehend and verbally express vocabulary; there are 35 words. Block design is a subtest that measures visuospatial and motor skills. In the test the participant has to take blocks that have all white sides, all red sides, and red and white sides and arrange them according to a pattern. They are timed on this task and compared to a normative sample. Estimates of full-scale IQ were made using vocabulary and block design.<sup>27</sup>

### Statistical analyses

For primary analysis, we divided the sample of chronic cannabis users into two groups: the early-onset group, who initiated use of cannabis before the age of 15; and the late-onset group, who initiated use of cannabis at the age of 15 or later. The mean age of first use was 16.6 (s.d. = 3.5) years. However, we chose 15 years as the cut-off in order to stress the impact of cannabis exposure in early adolescence as opposed to late adolescence. This was possible because of the large sample size (104 participants) and wide range of age of first use (8 to 30 years).

We compared the demographic characteristics of both the early- and late-onset groups with those of the controls using Student's *t*-test (for variables with normal distribution) or Mann–Whitney *U*-test. We used Student's *t*-test to compare age of first use, age starting daily use, pattern of use, years of daily use, estimation of life consumption, and days of abstinence in early-onset and late-onset groups.

Comparisons involving neuropsychological measures were performed using generalised linear model analysis of variance (ANOVA). In order to minimise the problem of multiple comparisons in neuropsychological analyses, we decided to select only the more relevant measures according to the literature for each test. For example, for the WCST, we limited analyses to two measures (number of correct categories and perseverative errors). The alpha level was set at  $P < 0.05$  (two-tailed) for all analyses.

**Results**

In total 148 (participants including 44 controls) were enrolled in the study. Of the 104 chronic cannabis users, 55 initiated use of cannabis before the age of 15. The three groups were matched for age, years of education, and IQ (Student's *t*-test,  $P > 0.05$ ), differing only in gender. There were more males in the early-onset group (72.7%) and the late-onset group (83.7%) than in the control group (45.5%) (Student's *t*-test,  $P < 0.001$ ). Sociodemographic data are summarised in Table 1.

Those in the early-onset group were abstinent for 4.1 (s.d. = 6.9) days at the time of assessment, whereas the late-onset group were abstinent for 3.8 (s.d. = 5.6) days ( $P > 0.05$ ). The early-onset group was first exposed to cannabis at the age of 13.9 (s.d. = 1.5) years and progressed to daily use at the age of 19.3 (s.d. = 6.3) years (5.4 years later). The late-onset group began cannabis use at the age of 18.4 (s.d. = 2.8) years and started daily use at the age of 21.2 (s.d. = 3.8) years (2.8 years later). The estimated average lifetime consumption for the early-onset group was 6790 joints; for the late-onset group it was 5160 joints, as calculated using the TLFB (Table 2).

There were no differences in IQ, vocabulary or block design results when comparing the early-onset, late-onset, and control groups (Table 3). The early-onset group had more perseverative errors (10 (s.d. = 6.63) *v.* 6.44 (s.d. = 3.52),  $F = 5.18$ ,  $P = 0.001$ ) and completed fewer categories (2.77 (s.d. = 1.32) *v.* 3.5

(s.d. = 1.28),  $F = 4.12$ ,  $P = 0.008$ ) on the WCST compared with controls (Figs 1 and 2). On the Stroop test, card (noun-colour), the early-onset group also performed poorly compared with controls (18.20 (s.d. = 5.82) *v.* 15.64 (s.d. = 2.96, Fig. 3),  $F = 3.50$ ,  $P = 0.006$ ). Performance on the FAB was poorer in the early-onset group (15.85 (s.d. = 2.41)) in comparison with both the late-onset (16.82 (s.d. = 1.25),  $F = 5.17$ ,  $P = 0.014$ ) and the control group (17.09 (s.d. = 1.11),  $F = 7.01$ ,  $P = 0.002$ , Fig. 4). Neuropsychological data are summarised in Tables 3 and 4. Comparisons involving late-onset and control groups were non-significant.

**Discussion**

**Main findings**

This study evaluated the neurocognitive functioning of early- and late-onset chronic cannabis users and controls. The early-onset, but not the late-onset, group performed poorly on selected executive tasks compared with controls. In addition, the early-onset group performed poorly on the FAB compared with both the late-onset and the control groups. Our findings indicate that early-onset chronic cannabis users are cognitively impaired compared with controls, suggesting that early exposure to cannabis is associated with more adverse effects on the brain. These results are in line with previous studies examining cognitive effects associated with early cannabis exposure.<sup>28–30</sup>

**Table 1** Demographic information

	Early-onset group ( <i>n</i> = 55)	Late-onset group ( <i>n</i> = 49)	Control group ( <i>n</i> = 44)	<i>P</i>
Age, years: mean (s.d.)	30.4 (8.3)	30.0 (4.1)	27.8 (8.0)	NS
Gender, males: %	72.7	83.7	45.5	<0.001
Estimated IQ, mean (s.d.)	99.1 (8.6)	98.1 (8.8)	100.0 (9.8)	NS
Years of education, mean (s.d.)	12.4 (3.0)	13.6 (3.5)	14.0 (2.6)	NS

NS, Not statistically significant ( $P \geq 0.05$ ).

**Table 2** Information about use of cannabis by group

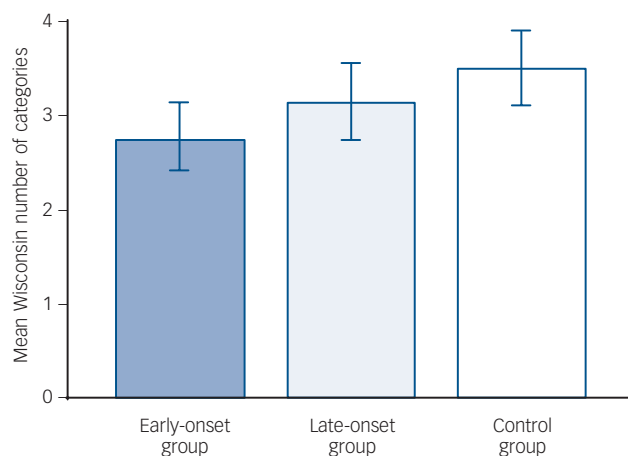
	Early-onset group ( <i>n</i> = 55)	Late-onset group ( <i>n</i> = 49)	<i>P</i>
Age of first use, years: mean (s.d.)	13.9 (1.5)	18.4 (2.8)	<0.001
Age of daily use, years: mean (s.d.)	19.3 (6.3)	21.2 (3.8)	NS
Pattern of use, joints/day: mean (s.d.)	1.7 (1.5)	1.5 (1.7)	NS
Years of daily use: mean (s.d.)	10.9 (8.0)	8.7 (5.0)	NS
Lifetime consumption	6790	5160	NS
Days of abstinence: mean (s.d.)	4.1 (6.9)	3.8 (5.6)	NS

NS, Not statistically significant ( $P \geq 0.05$ ).

**Table 3** Descriptive statistics of vocabulary, block design and IQ estimation by group

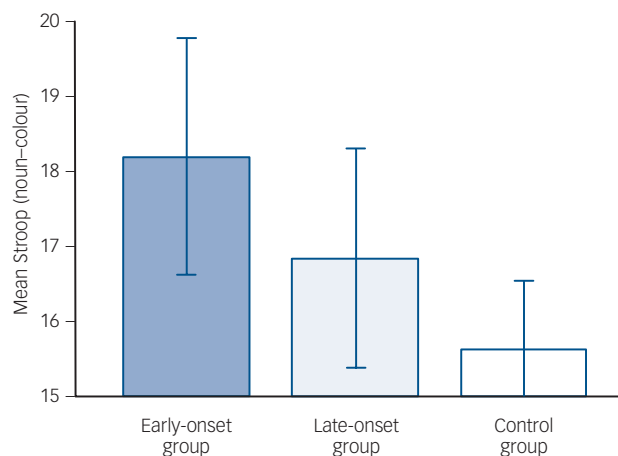
	Groups, mean (s.d.)			<i>t</i> -test, <i>P</i>			ANOVA, <i>P</i>
	Early-onset group ( <i>n</i> = 55)	Late-onset group ( <i>n</i> = 49)	Control group ( <i>n</i> = 44)	Early-onset <i>v.</i> control groups	Late-onset <i>v.</i> control groups	Early-onset <i>v.</i> late-onset groups	
WAIS-R							
Vocabulary	43.67 (8.22)	43.71 (8.21)	45.72 (7.08)	0.193	0.212	0.980	0.361
Block design	32.36 (9.53)	32.20 (9.50)	31.27 (10.63)	0.592	0.657	0.932	0.846
Estimated IQ	99.09 (8.64)	98.18 (8.82)	100.02 (9.82)	0.617	0.344	0.598	0.622

WAIS-R, Wechsler Adult Intelligence Scale – Revised



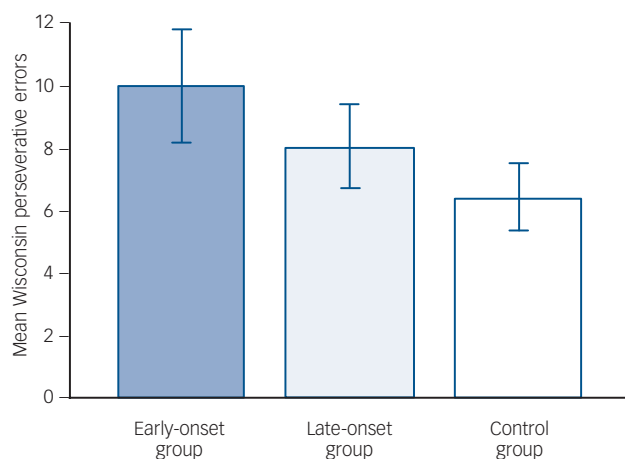
**Fig. 1** Wisconsin Card Sorting Test number of categories in early-onset, late-onset and control groups.

Error bars: 95% confidence intervals.



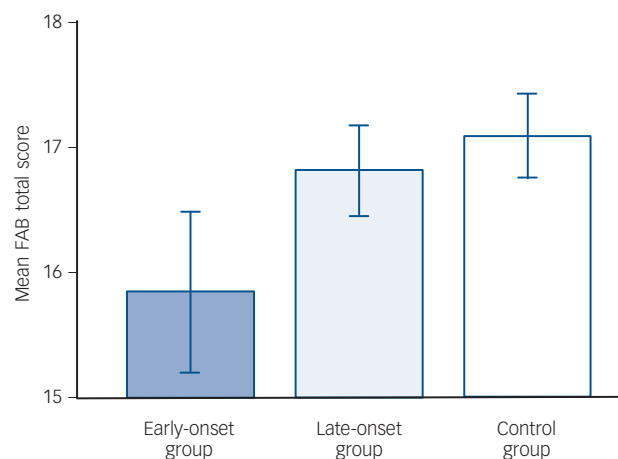
**Fig. 3** Stroop Test (noun-colour) time in seconds in early-onset, late-onset and control groups.

Error bars: 95% confidence intervals.



**Fig. 2** Wisconsin Card Sorting Test perseverative errors in early-onset, late-onset and control groups.

Error bars: 95% confidence intervals.



**Fig. 4** Frontal Assessment Battery (FAB) total score in early-onset, late-onset and control groups.

Error bars: 95% confidence intervals.

**Table 4** Descriptive statistics of neuropsychological results by group

	Groups, mean (s.d.)			t-test, P			ANOVA	
	Early-onset group (n = 55)	Late-onset group (n = 49)	Control group (n = 44)	Early-onset v. control groups	Late-onset v. control groups	Early-onset v. late-onset groups	F	P
Wisconsin Card Sorting Test								
Categories <sup>a</sup>	2.77 (1.32)	3.16 (1.34)	3.5 (1.28)	0.008	0.221	0.161	3.665	0.028
Perseverative errors <sup>b</sup>	10.00 (6.63)	8.09 (4.53)	6.44 (3.52)	0.001	0.061	0.095	5.644	0.004
Frontal Assessment Battery <sup>a</sup>	15.85 (2.41)	16.82 (1.25)	17.09 (1.11)	0.002	0.270	0.014	7.014	0.001
Stroop (noun-colour) <sup>c</sup>	18.20 (5.82)	16.85 (4.96)	15.64 (2.96)	0.006	0.164	0.215	3.464	0.034

a. Lower scores are worse performance.

b. Higher scores are worse performance.

c. Card 2 – Victoria Version, Card 2 has common words printed in different colours – time in seconds – higher scores are worse performance.

## Implications of early cannabis use

In the past few decades, a steady increase in people seeking treatment for cannabis-related problems has been registered in Western countries, with an associated decrease in the age of first cannabis use.<sup>31</sup> Adolescence is a period in which the brain appears to be particularly vulnerable to the neurotoxic effects of cannabis. Mounting evidence has associated cannabis use with psychiatric morbidity, such as depression and psychosis, and the strength of this association appears to be highly influenced by age at first exposure.<sup>32</sup>

Cannabis exposure during adolescence may potentially be associated with long-lasting neuronal consequences. Cross-sectional and longitudinal structural brain imaging studies have revealed that the brain before age 15 is under a complex process of biological maturation, especially in the prefrontal cortex, which has peak grey matter volumes at age 11, which is then followed by rapid grey matter loss in late adolescence.<sup>33</sup> During adolescence, rapid changes in neural organisation occur, including a reduction in the number of synapses in cortical and subcortical structures as well as changes in neurotransmitter and receptor levels.<sup>34</sup> It has been further suggested that these changes in central nervous system organisation may make the brain uniquely vulnerable to insults by substances of misuse.<sup>35</sup> Early cannabis use was found to be strongly associated with misuse and dependence during adolescence; thus, it may be both more 'addicting' and cause greater effects.<sup>36</sup> Ehrenreich *et al* evaluated a broad spectrum of attentional functions in 99 marijuana users, with a computerised battery.<sup>28</sup> They studied 48 participants exposed to cannabis before 16 years of age, 51 who first used cannabis after the age of 16, and 49 controls. Associations involving visual attention measures and age of first exposure to cannabis were found, suggesting that exposure to marijuana during adolescence may lead to persistent attentional deficits.

Taken together, those findings suggest that exposure to exogenous cannabinoids in critical periods of brain development, including early adolescence, may be more neurotoxic. In the postnatal brain, endocannabinoids act as retrograde messengers to regulate the function of many synapses. Furthermore, several maturational events appear to depend on the modulatory influence of the endocannabinoid system in these critical periods.<sup>37</sup> Dysregulation of these fine-tuned developmental processes may underlie both cognitive impairments and psychopathology associated with early exposure to cannabis use.<sup>19</sup> Alternatively, the present findings may be accounted for by previous cognitive impairments in the early-onset group, which would make individuals in this group more prone to exposure to substances at an early age. This hypothesis, however, appears not to be supported by the present findings since the three groups were matched for estimated IQ and a measure of premorbid functioning assessed by vocabulary (the WAIS-R).

The early-onset group showed a particularly poor performance in the FAB, and revealed deficits in comparison with both the late-onset and the control groups. The FAB is a short neuropsychological battery aimed at assessing conceptualisation, mental flexibility, programming, sensitivity to interference, inhibitory control and environmental autonomy. Its results have been shown to significantly correlate with medial and dorsolateral prefrontal activity as measured by neurofunctional brain imaging studies.<sup>38,39</sup> Performance on the six subtests of the FAB provides a composite global score that evaluates the severity of the dysexecutive syndrome affecting both cognition and motor function.<sup>25</sup> In addition, the poor performance of the early-onset group on the Stroop test and perseverative responding (as measured by the WCST) suggest that exposure to cannabis in early

adolescence may lead to lower mental flexibility. This could explain partially why chronic users find it difficult to maintain treatment and to discontinue substance use despite evident physical and psychological consequences.

Aharonovich *et al* suggest that mild cognitive impairments negatively affect retention in out-patient cognitive-behavioural therapy treatment for cocaine dependence.<sup>40</sup> Cognitive deficits, particularly in executive functioning, have been associated with poorer adherence to treatment in several studies.<sup>41,42</sup> In this sense, executive deficits appear to negatively affect treatment outcome and may represent a potentially important aspect for designing specific or target-orientated cognitive strategies for treatment of substance use disorders, especially for those who initiated use at an early age.<sup>43</sup>

We did not find differences in executive functioning performance when comparing the late-onset and control groups. Another important issue is whether starting cannabis use at a later age is inoffensive to cognition. It is possible that participants who start to use cannabis at a later age may use different neural networks and compensate for their deficits more than individuals who initiated the use of cannabis at an earlier stage of brain development. Chang *et al* showed that the brain network might be altered in some cannabis users but without an apparent change in cognition.<sup>44</sup> The long-term chronic effects of marijuana on the altered brain network may be reversible with prolonged abstinence. A plausible explanation for this is that the brain, in response to chronic cannabis use, appears to undergo neuro-adaptation by accessing compensatory processes in order to maintain usual cognitive performance.<sup>45</sup> Future studies should focus on neurocognitive tasks including decision-making; this is a core part of the executive dysfunction now understood to be one of the hallmark features of addiction that also includes impaired impulse dysregulation.

## Limitations

The findings from the present study should be interpreted with caution while considering the following limitations. First, the cross-sectional study design does not allow us to make any conclusions about causality. Some executive deficits are explicitly found, but it is not possible to establish whether they are the consequences of cannabis use or were present before first use. Second, the present study evaluated cannabis users in a period of early abstinence. At least in part, the results may be related to substance residues or withdrawal symptoms.<sup>46</sup> This effect was minimised because both the cannabis user groups (early and late onset) were matched for pattern of use, years of daily use, life consumption and days of abstinence. Third, these two groups were predominantly composed of males whereas the control group had equal numbers of males and females. However, the early- and late-onset groups were matched for gender and the early-onset group performed poorly on the FAB compared with both the late-onset and control groups. Yet, the results did not change when only males were analysed.

In conclusion, our findings suggest that early-onset, but not late-onset, chronic cannabis users exhibit executive deficits. Although the underlying mechanisms are not fully understood, cannabis exposure at an early age may have greater deleterious effects on neurocognitive functioning. Future longitudinal studies examining adolescents who initiated cannabis use recently may be especially informative

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