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ARTICLE

Adolescents are more sensitive than adults to acute behavioral and cognitive effects of THC

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Increased cannabis availability has contributed to increased use with concomitant incidence of adverse effects. One risk factor for adverse drug reactions may be age. There is preclinical evidence that acute effects of delta-9-tetrahydrocannabinol (THC), the primary active constituent of cannabis, are greater during adolescence, but this has not been fully studied in humans. The present study sought to determine whether adolescent men and women are more sensitive than adults to acute THC. Adolescents aged 18–20 ($N = 12$) and adults aged 30–40 ($N = 12$), with less than 20 total lifetime uses of THC-containing products, received capsules of THC (7.5, 15 mg) and placebo across three study sessions in randomized order under double blind conditions. During each session, subjective, cardiovascular, behavioral, and EEG measures were obtained. Behavioral measures included Simple Reaction Time, Stop Task, Time Production and N-back and EEG measures included P300 amplitudes during an auditory oddball task and eyes-closed resting state. THC affected subjective state and heart rate similarly in both age groups. However, adolescents were more sensitive to performance impairing effects, exhibiting dose-dependent impairments on reaction time, response accuracy, and time perception. On EEG measures, THC dose-dependently decreased P300 amplitude in adolescents but not adults. Adolescents were more sensitive to behavioral and cognitive effects of THC, but not to cardiovascular effects or subjective measures. Thus, at doses that produce comparable ratings of intoxication, adolescents may exhibit greater cognitive impairment and alterations in brain function.

INTRODUCTION

Changes in the legal status of cannabis have led to increased use. From 2002 to 2019, past year cannabis use in adults in the U.S. increased from 7.0 to 15.2 percent [1]. This increase is likely associated with greater incidence of adverse effects after acute administration, especially in vulnerable individuals. However, few controlled studies have identified specific risk factors for the intoxicating or adverse effects of cannabis or its primary psychoactive constituent, delta-9-tetrahydrocannabinol (THC).

Adolescence is one factor that may increase risk for adverse responses to cannabinoids. During adolescence, cannabinoid receptor (CB_1R) expression levels in the brain are greater than any other period of life [2–4]. In humans, peak CB_1R messenger RNA (mRNA) expression occurs at ages 15–17 followed by a decline to base levels near age 35 [5, 6]. There is some evidence that adolescents are more sensitive to the effects of THC than adults. In rodents, THC produces greater effects on locomotion in adolescents than adults [7, 8], and adolescents demonstrate greater impairments in spatial and non-spatial learning [9, 10]. However, age-related differences in responses to THC in rodents have been inconsistent, with some reports of greater effects of THC on locomotion and aversive responses in adults [7, 11, 12]. In humans, one placebo-controlled study with vaporized cannabis in adolescents (aged 16–17) and adults (aged 24–28) resulted in mixed findings [13]. Specifically, THC produced lesser effect in adolescents than adults on subjective, cardiovascular measures,

and some behavioral tasks (e.g., prose recall), but greater effects on other tasks (e.g., response inhibition accuracy). However, adolescents in that study also reported significantly more cannabis use per month than adults, raising questions about tolerance. Indeed, preclinical studies indicate that repeated THC dosing reduces physiological and behavioral responses to the drug to a greater extent in adolescents relative to adults [8, 14]. Thus, there is some evidence that younger age is related to more pronounced responses to THC, but this has not been fully tested in humans. The knowledge that youth are more sensitive to either the subjective or the performance impairing effects of THC would inform policy decisions about public health risks for adolescents. For example, younger individuals may exhibit greater psychomotor impairment (e.g., on roads and highways), an increased likelihood of acute psychotic-like symptoms, or stronger motivation to continue use. Added to these potentially higher risks from acute doses of THC, adolescents are also susceptible to adverse consequences from chronic THC use, related to brain development and long-term mental health problems [15–21].

EEG offers a potentially sensitive objective measure of the acute psychoactive effects of THC [22]. THC administered by several routes (oral, smoked, and intravenous) has been shown to reduce the amplitudes of event-related potentials (ERPs), including the P300 component, which is an index of attention and working memory [23–27]. In one study, high potency cannabis (up to 69 mg THC) reduced the magnitude of visually evoked ERPs in a

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visual attention task [28]. There is also evidence that THC alters the amplitudes of neural oscillations during resting state, also known as oscillatory power, although the findings are mixed. Smoked cannabis and THC by oral or intravenous routes has been shown to increase alpha [29–32] and gamma [33] power, and reduce beta [29, 33–35] and theta [34, 35] power. However, one study found no effects on oscillatory power after vaporized THC [36], and another found that THC produced variable effects on oscillatory power, corresponding to changes in subjective state (i.e., euphoria corresponded with increases in alpha power) [37]. These mixed findings on oscillatory power may be related to differences in participant characteristics, including age of the participants. To our knowledge, no studies assessed effects of age on response to THC using EEG. We reasoned that EEG would offer a sensitive and objective measure of THC effects, and expected that THC would produce greater effects on both P300 amplitude and resting state EEG in adolescents.

We compared subjective, cognitive, and EEG measures in response to acute oral doses of THC (7.5 and 15 mg) and placebo in healthy male and female adolescents (aged 18–20) and adults (aged 30–40) who reported less than 20 total lifetime uses of cannabis and no cannabis use in the last 30 days. We recruited light users to minimize the confounding effects of tolerance, and to approximate responses to THC or cannabis in adolescents during their initial drug exposures. We hypothesized that adolescents would be more sensitive to THC effects across all measures. Subjective measures were assessed with standardized drug effects questionnaires, cognitive measures included attention, inhibitory control and time perception tasks, and EEG included ERP responses and resting state EEG measures.

METHODS AND MATERIALS
Study design
This study used a combined within and between subject design. Adolescents (18–20 yrs) and adults (30–40 yrs) participated in three 5 h sessions in which they received capsules containing THC (7.5 or 15 mg) or placebo. The age groups were matched on sex and we attempted to minimize group differences in body weight and cannabis use. THC was administered under double blind and randomized conditions. Dependent measures included subjective mood states, psychomotor performance tasks, cardiovascular measures, and EEG. EEG recordings included event-related potentials during an auditory oddball task and oscillatory power during resting state.

Subjects
Participants were adolescents (aged 18–20; 6 male, 6 female) and adults (aged 30–40; 6 male, 6 female) who had used THC-containing products 1–20 times in their lifetime and 0 uses in the last 30 days. Individuals aged 18–20 meet the World Health Organization definition of adolescent [38], and regulatory concerns precluded testing those under 18. We selected the range of 30–40 years for adults to separate the groups by at least 10 years. Individuals reporting recent use were excluded due to age-related CB_1R desensitization [8, 14]. A negative urine test for THC was required at each session. Screening consisted of physical examination, electrocardiogram, modified Structural Clinical Interview for DSM-5, and self-reported health and drug use history. Inclusion criteria were English fluency, right-handedness, at least a high school education, and body mass index of 19 to 26 kg/m^2. Exclusion criteria included a history of psychosis, severe posttraumatic stress disorder or panic disorder, past year substance use disorder (except nicotine), pregnant or nursing, working night shifts, and current medication aside from birth control. Subjects provided informed consent prior to beginning the study procedures, which were approved by the University of Chicago Institutional Review Board.

Drug
THC (Marinol® [dronabinol]; Solvay Pharmaceuticals; 7.5 mg and 15 mg) was placed in opaque capsules with dextrose filler. Placebo capsules contained only dextrose. These doses of THC produce performance impairments and subjective intoxication [39–41]. The 15 mg and 7.5 mg

doses reflect the amount of THC in one-half and one-quarter of a cannabis cigarette containing 0.2 g of 15% THC, respectively. Equivalent doses of THC, whether oral or smoked, have been shown to produce similar peak levels of intoxication, although the duration of effects is longer with oral administration [42].

Self-report measures
Mood states and subjective drug effects were assessed during sessions before and at regular intervals after drug administration using the Drug Effects Questionnaire (DEQ) [43, 44], the Addiction Research Center Inventory (ARCI) [45, 46], and Profile of Mood States (POMS) [47]. The DEQ consists of five questions assessing subjective drug effects using 100 mm visual analog scales: Do you feel a drug effect?, Like the drug effect?, Dislike the drug effect? Feel high?, or Want more of what you received? The ARCI consists of 53 true/false questions measuring typical drug effects including a 12-item Marijuana (ARCI-M) subscale specific to cannabis. The POMS consists of 72 mood adjectives rated on a Likert scale from 0 (not at all) to 4 (extremely), divided into 8 subscales: Friendliness, Anxiety, Elation, Anger, Fatigue, Depression, Confusion and Vigor, and two composite scales: Positive Mood (Elation minus Depression) and Arousal (Vigor plus Anxiety minus Confusion plus Fatigue). At the end of each session, subjects also completed an end-of-session drug identification questionnaire and the 5 Dimensions of Altered States of Consciousness (5D-ASC) questionnaire [48].

Cardiovascular measures
Blood pressure and heart rate were monitored at regular intervals using portable blood pressure cuffs (Critikon Dinamap Plus; GE Healthcare Technologies, Waukesha, WI).

Behavioral measures
From 100 to 150 min. post-administration, participants performed four behavioral tasks in randomized task order: the Simple Reaction Time Task [49], Stop Task [50], Time Production Task [51], and N-back Task [52]. The Simple Reaction Time Task was used as a measure of attention. Subjects executed a key press as quickly as possible to a target presented on the computer screen at variable intervals. The difference between a participant's mean and modal reaction time (RT) was calculated to assess momentary lapses in attention [53, 54]. The Stop Task assessed subjects' ability to inhibit prepotent motor response. The primary measure of interest was response accuracy, or the proportion of correct responses on trials without stop signals, as this measure has shown age-related effects after acute THC [13]. Stop reaction time (Stop RT) was a secondary measure. The Time Production Task assesses the ability to assess time. Participants held a key for 20, 30, 40, and 50 s in a randomized order while attending to distractor stimuli. Produced time was the outcome measure of interest. The N-back task assesses executive attention and working memory. Participants responded when the current visual and audio stimulus (a letter) was the same as the one presented 1, 2, or 3 trials earlier. The outcome measure of interest was the discriminability between targets and non-targets (d prime; [55]) on 3-back trials.

EEG measures
Auditory oddball P300 task. An auditory oddball task was used to assess the P300. The task included a three stimuli oddball design in which frequent sounds were jittered with infrequent (oddball) sounds and rare distractor sounds in a 7:2:1 ratio, each projected for 1500 ms. The task consisted of 15 blocks of 10 stimuli. Subjects pressed one key when they heard an oddball sound and another when they did not. EEG data from incorrectly recognized trials were discarded. The Pz electrode was selected a priori to measure the P300 wave and transient event-related spectral perturbation (ERSP) during oddball trials. Data were epoched from −500 to 1000 ms around the stimulus triggers and P300 peaks were measured within a 450 to 800 ms time window. Event-related spectral perturbations (ERSPs) were assessed for changes in event-related oscillatory power during oddball epochs, specifically alpha suppression associated with attending to target stimuli [56]. Data files were analyzed using the EEGLAB.

Resting state. EEG data were continuously recorded while participants rested comfortably with eyes closed for 5 min. Subjects were instructed to minimize excessive blinking and head movements and remain awake. The primary outcome measure was oscillatory power across five frequency bands (delta, 1–4 Hz; theta, 4–8 Hz; alpha 8–13 Hz; beta 13–30 Hz; gamma 30–80 Hz) assessed using a custom script. Scalp electrodes chosen for the

analysis (Supplementary Fig. S1) were selected to reflect default mode network hubs (medial prefrontal cortex, posterior cingulate cortex, left temporoparietal cortex, and right temporoparietal cortex) observed in simultaneous fMRI-EEG studies [57]. Reductions in oscillatory power across frequency bands are associated with reduced connectivity within the default mode network and altered states of consciousness [58–61].

Statistical analysis. Subjective and cardiovascular measures: Peak change scores were calculated for each subject using the pre-capsule baseline and the highest or lowest value during the session. These scores were analyzed using two-way repeated-measures analysis of variance (RM-ANOVA) with dose as within-subjects factor and age as between-subjects factor. For one subjective measure, DEQ "Feel Drug", and one cardiovascular measure, heart rate, we examined the time course of the drug effect using a three-way RM-ANOVA (age, dose, time).

Behavioral measures: Scores on Simple Reaction Time, Stop Task, and N-back were analyzed using two-way RM-ANOVA (dose, age). For Time Reproduction, a three-way RM-ANOVA (age, dose, time) was used.

EEG measures: RM-ANOVA were performed on P300 amplitude and latency from each subject, with dose as within-subjects factor and age as between-subjects factor. ERSPs were analyzed with statistical *p*-value maps. For resting state, RM-ANOVA were performed for all electrodes over default mode network regions (Supplementary Fig. S1) across the five frequency bands with dose as within-subjects factor.

Across measures, outliers, identified as three standard deviations from the mean, were deleted from analyses. One outlier was detected and removed from analysis of the Simple Reaction Time task. For RM-ANOVA, if significant interactions were found, simple main effects one-way ANOVA compared dose effects in each age group separately. Linear effects of dose were used to indicate dose-dependent effects. If significant linear effects of dose were found, follow-up planned contrasts compared each THC dose to placebo with Tukey's HSD test to correct for multiple comparisons. All data distributions were evaluated for deviations from normality with the Shapiro–Wilk Test. All data were normally distributed except for response accuracy in the Stop Task, in which responses across all drug conditions and age groups were skewed negatively due to frequent cases of 100% response accuracy. All analyses were conducted with SPSS (version 25; SPSS Inc, Chicago, IL).

RESULTS
Demographic characteristics
The mean age of the adolescent group was 19 and the adult group 31 (Table 1). Both groups consisted of six men and six women, and the groups did not differ significantly in body weight, recent drug use (including cannabis use), or lifetime use of drugs.

Self-report and cardiovascular measures
On subjective ratings, THC (7.5 and 15 mg) dose-dependently increased ratings on several measures (peak change; Supplementary Fig. S2). Specifically, on the DEQ, THC increased ratings for Feel Drug, Feel High, Like Drug, and Dislike Drug. These effects were more pronounced at the higher dose, and the adolescent and adult groups did not differ significantly on either peak change scores or, on the measure of Feel Drug, across time (Feel Drug; Fig. 1A) (dose x time, $F_{1,22} = 84.26$, $p < 0.001$, $\eta_p^2 = 0.793$). On the ARCI, THC increased measures of marijuana-like effects (ARCI-M), LSD-like effects (ARCI-LSD), and amphetamine-like effects (ARCI-A). On the POMS, THC increased Anxiety, Fatigue, Confusion, and Depression, and reduced Positive Mood. ARCI and POMS effects were dose-related and similar across the two groups (peak change; Supplementary Fig. S2).

On cardiovascular measures, THC dose-dependently increased heart rate in both age groups (Supplementary Fig. S3) (dose x time, $F_{1,22} = 21.48$, $p < 0.001$, $\eta_p^2 = 0.494$) and the groups did not differ significantly. THC did not significantly affect blood pressure for either age group (data not shown).

Behavioral measures
Across behavioral measures, adolescents and adults did not differ in the absence of the drug (i.e., after placebo). THC dose-dependently increased lapses in attention during the Simple RT task in adolescents but not adults (mean RT minus mode RT) (Fig. 1B) (age x dose, $F_{1,21} = 6.13$, $p = 0.041$, $\eta_p^2 = 0.184$; dose [adolescents], $F_{1,10} = 6.59$, $p = 0.026$, $\eta_p^2 = 0.375$). One adolescent was removed from analysis as an outlier due to intoxication beyond appropriate performance in the task after the 7.5 mg dose. In the Stop Task, there was a trending difference in the effects of THC in Stop Task response accuracy in the age groups: the drug impaired response accuracy in adolescents, but not adults (Fig. 1C) (age x dose, $F_{1,22} = 3.745$, $p = 0.065$, $\eta_p^2 = 0.140$). Despite the absence of an interaction, we conducted exploratory separate ANOVA within each age group, and found that the drug decreased accuracy in the adolescents but not the adults (dose, $F_{1,11} = 7.74$, $p = 0.017$, $\eta_p^2 = 0.392$). Adolescents also demonstrated poorer accuracy than the adults regardless of drug (age, $F_{1,22} = 5.42$, $p = 0.029$, $\eta_p^2 = 0.191$). No drug or age effects were found on stop signal reaction time. On the Time Production task, THC dose-dependently increased time dilation in adolescents but not adults (Fig. 1D) (age x dose x time, $F_{1,22} = 5.96$, $p = 0.023$ $\eta_p^2 = 0.213$; dose x time, $F_{1,22} = 12.45$, $p = 0.002$ $\eta_p^2 = 0.361$). That is, for adolescents but not adults, the drug decreased reproduced time, an effect specific to the 40 s time trial (age x dose, $F_{1,22} = 6.57$, $p = 0.018$ $\eta_p^2 = 0.23$). However, dose-dependent effects of THC occurred at 30, 40, and 50 s trials in adolescents (dose [30 s], $F_{1,11} = 5.96$, $p = 0.033$ $\eta_p^2 = 0.351$; dose [40 s], $F_{1,11} = 15.49$, $p = 0.002$ $\eta_p^2 = 0.585$; dose [50 s], $F_{1,11} = 26.69$, $p < 0.001$ $\eta_p^2 = 0.708$). THC dose-dependently impaired working memory during N-back,
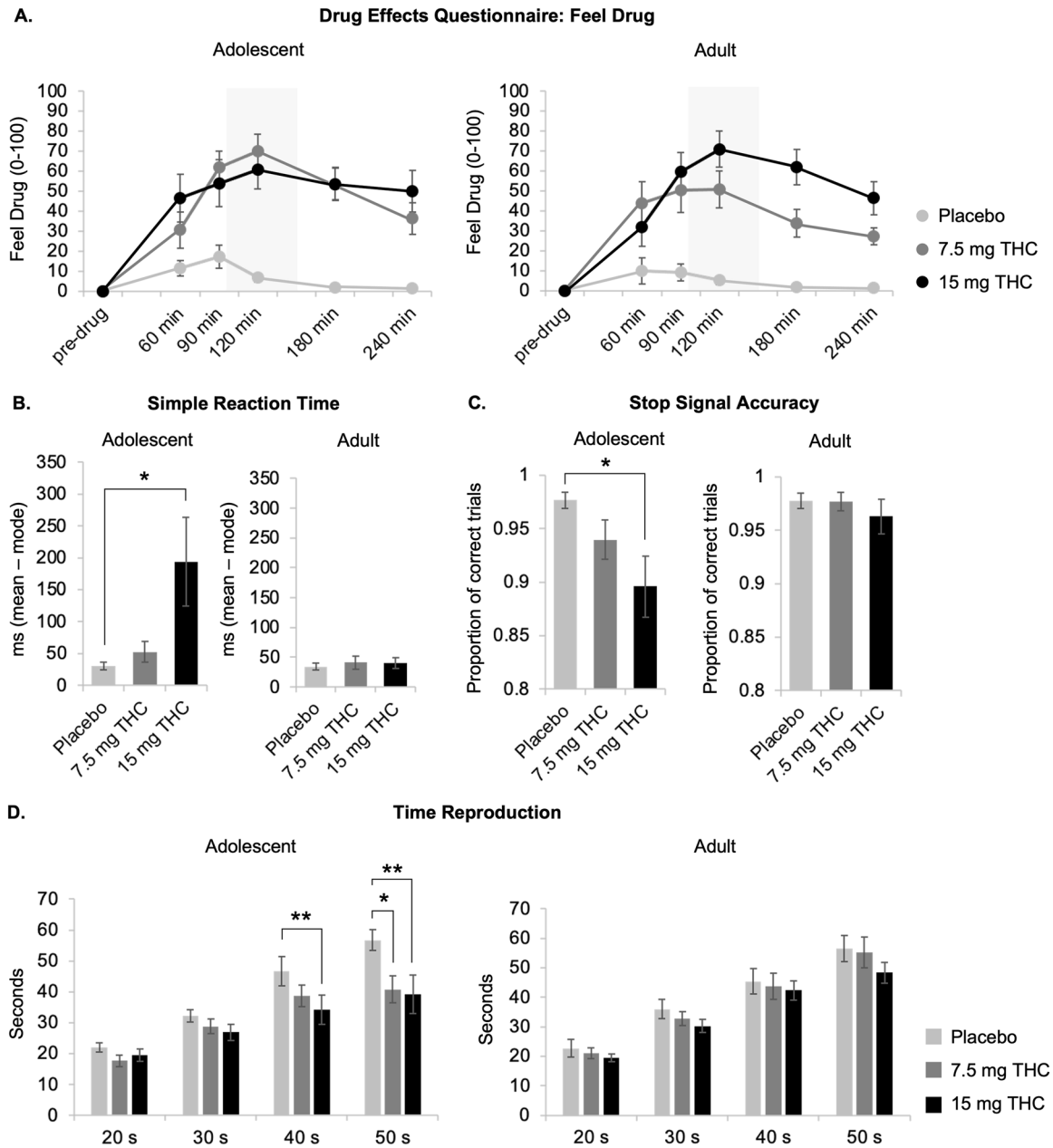
Table 1. Demographics and drug use characteristics.

Category	Adolescent	Adult
	n or Mean ± SD (Range)	*n* or Mean ± SD (Range)
Subjects (male/female)	12 (6/6)	12 (6/6)
Age, years	19 ± 0.7 (18–20)	31 ± 1.7 (30–34)
Body mass index, kg/m²	22.6 ± 2.3 (19.5–26.5)	23.4 ± 2.7 (19.5–26.6)
Weight, kg	67.5 ± 11.6 (46–84)	70.3 ± 9.6 (56–86)
Race		
Caucasian	6	7
African American	0	1
Asian	1	0
Other/>1 Race	5	4
Current drug use (*n* = Adolescent, Adult)		
Cannabis, months since last use	4.4 ± 6.9 (1–24)	6.3 ± 8.2 (1–24)
Alcohol, drinks/week (*n* = 6, 10)	2.4 ± 3.5 (0–11)	3.7 ± 3.2 (0–9)
Alcohol, drinking days/week	0.8 ± 1.0 (0–2.5)	2.0 ± 1.9 (0–6)
Tobacco, times/week (*n* = 1, 2)	0.02 ± 0.7 (0–0.2)	0.5 ± 1.4 (0–5)
Caffeine, servings/day (*n* = 11, 11)	0.8 ± 0.7 (0–2)	1.2 ± 1.1 (0–4)
Total lifetime drug use, nonmedical		
Cannabis (*n* = 12, 12)	8.5 ± 5.9 (1–20)	16.0 ± 5.4 (3–20)
Classical psychedelic (*n* = 3, 5)	0.4 ± 0.9 (0–3)	1.2 ± 2.1 (0–6)
MDMA (*n* = 0, 2)	0	0.3 ± 0.8 (0–2)
Stimulant (*n* = 2, 2)	0.6 ± 1.5 (0–5)	0.2 ± 0.4 (0–1)
Opiate (*n* = 0, 0)	0	0

Fig. 1 Mean (± SEM) behavioral measures after placebo (0 mg), 7.5 and 15 mg THC across adolescent and adult participants. Time course of subjective drug effects; gray shaded region indicates period of behavioral assessments (**A**). Simple Reaction Time (ms milliseconds) (**B**). Stop Signal accuracy; proportion of no-signal trials with correct response (**C**). Time Reproduction; 20, 30, 40, and 50 s indicate time trials (**D**). Repeated-measures ANOVA resulted in significant main effects of dose ($p < 0.05$) for all tasks. Age x dose interactions were found for the Simple Reaction Time and Time Reproduction tasks. Follow-up paired t-tests compared each THC dose to placebo (*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$).

but the adolescent and adult groups did not differ significantly (Supplementary Fig. S4) (dose, $F_{1,22} = 8.09$, $p = 0.009$, $\eta_p^2 = 0.280$).

EEG measures
In the auditory oddball task, incorrect responses were removed from analysis. The mean (± SD) percentage of discarded trials during the task across placebo, 7.5 mg and 15 mg THC conditions was 2.72% (± 1.4%), 3.72% (± 2.6%), and 4.06% (± 2.4%) for adults and 5.67% (± 3.8%), 11.89% (± 25.8%) and 15.27% (± 25.8%) for adolescents, with no significant effects of drug or age. During oddball trials, THC dose-dependently reduced P300 amplitudes for adolescents, but not adults (Fig. 2) (age x dose, $F_{1,22} = 7.710$, $p = 0.011$, $\eta_p^2 = 0.252$; dose [adolescents], $F_{1,11} = 12.94$, $p = 0.004$,

$\eta_p^2 = 0.541$). We also assessed time frequency analyses to detect transient event-related spectral perturbations (ERSPs) during oddball trials when the P300 was evoked. Significant group by drug interactions on spectral power were observed (Supplementary Fig. S5). Adolescents demonstrated an absence of alpha power reductions (alpha desynchronization) during the task after 15 mg THC (Fig. 3) relative to placebo.

During resting state, THC did not alter oscillatory power over default mode network regions in either age group, in any of the five frequency bands (Fig. 4). However, regardless of drug condition, the adolescent group showed significantly lower oscillatory power relative to adults across electrodes and frequency bands (age, $F_{1,469} = 47.93$, $p < 0.001$, $\eta_p^2 = 0.093$).
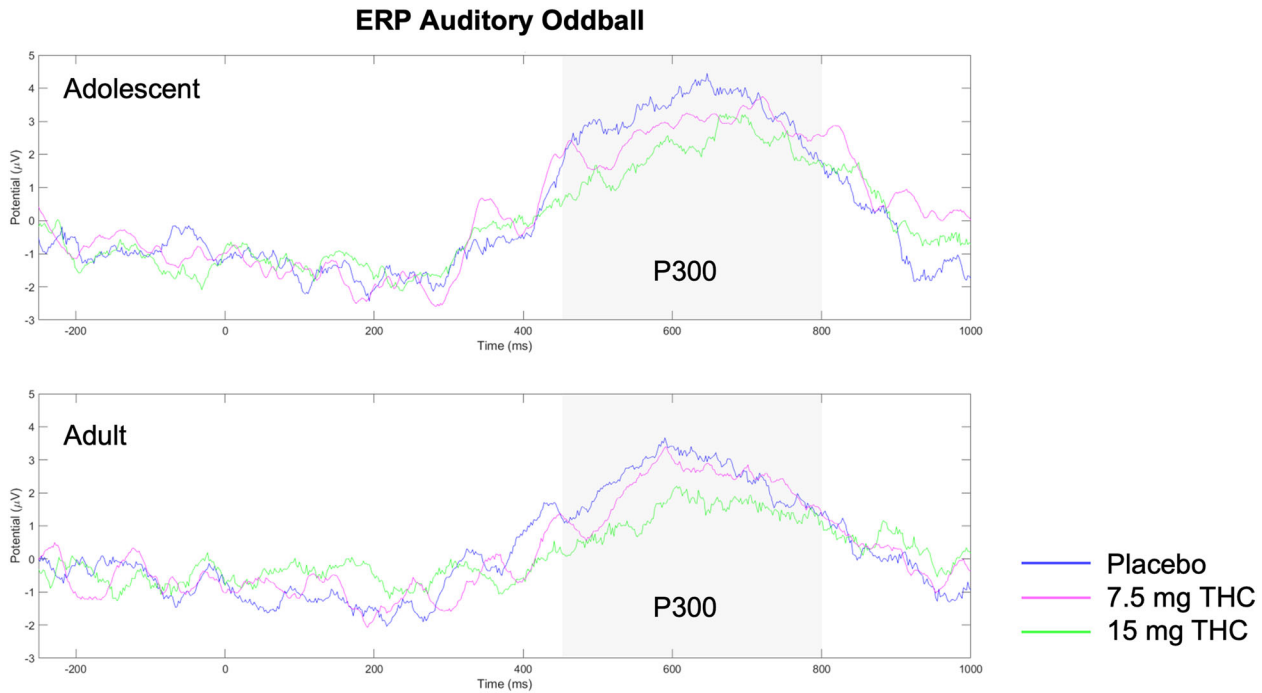
ERP Auditory Oddball

Fig. 2 P300 event-related potentials (ERPs) under the Pz electrode in responses to rare (oddball) auditory stimuli in the auditory oddball task. Stimuli presentation occurred at time zero. Repeated-measures ANOVA resulted in significant age x dose interaction in P300 amplitudes ($p < 0.05$). Shaded area indicates latency window for peak detection of P300 waveforms in analysis.
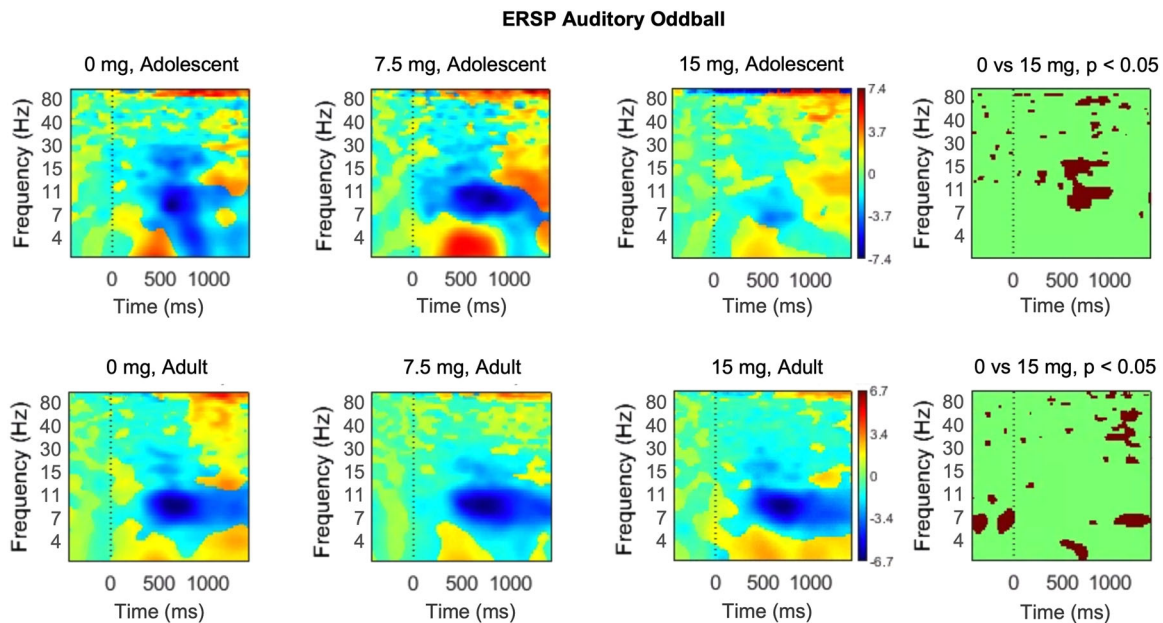
ERSP Auditory Oddball

Fig. 3 Time frequency analysis of event-related spectral perturbation (ERSPs) under the Pz electrode in responses to rare (oddball) auditory stimuli in the auditory oddball task. Stimuli presentation occurred at time zero. Heat map shows event-related changes in spectral power (from pre-stimulus baseline) in decibels; blue indicates event-related reductions in power. Power reductions were localized in the alpha range (8–13 Hz). At right, green panels show differences between placebo and 15 mg THC conditions for each age group, including a region of significant difference in alpha reduction (desynchronization) in adolescents ($p < 0.05$).

Similarly, in a secondary analysis examining oscillatory power over each of the four default mode network regions, adolescents showed lower power relative to adults but THC did not affect these in either group (medial prefrontal cortex: age, $F_{1,113} = 12.49$, $p = 0.001$, $\eta_p^2 = 0.100$; posterior cingulate cortex: age, $F_{1,118} = 22.80$, $p < 0.001$, $\eta_p^2 = 0.162$; left temporoparietal cortex age, $F_{1,115} = 10.28$, $p = 0.002$, $\eta_p^2 = 0.082$; right temporoparietal cortex: age, $F_{1,117} = 8.34$, $p = 0.005$, $\eta_p^2 = 0.067$).

End of session questionnaires
On the end of session questionnaire (Supplementary Table S1), most participants correctly guessed that they had received "placebo" on placebo sessions. After 7.5 mg THC, 75% of adolescents correctly guessed cannabis compared to 25% of adults. After 15 mg THC, 67% of the adolescents correctly identified cannabis compared to 50% of adults. At both doses and in both groups, the most frequent incorrect guess was
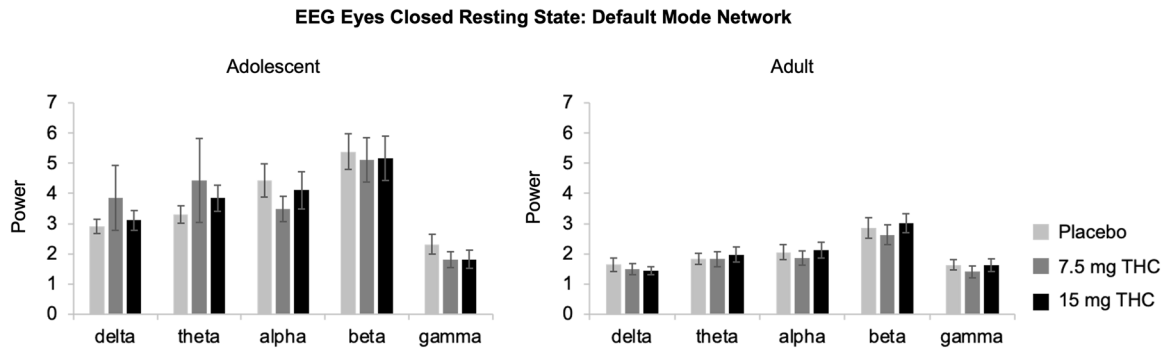
EEG Eyes Closed Resting State: Default Mode Network

Fig. 4 Effects of THC (7.5 and 15 mg) and placebo on oscillatory power during eyes-closed resting-state over the default mode network. Data are expressed as mean ± SEM. Adolescents showed decreased power across all doses, regions, and frequency bands (repeated-measures ANOVA; main effect of age, $p < 0.05$; no interactions).

"sedative" drug. THC dose-dependently increased scores on all five subscales of the 5D-ASC, including Oceanic Boundlessness ($F_{1,22} = 12.83$, $p = 0.002$, $\eta_p^2 = 0.368$), Dread of Ego Dissolution ($F_{1,22} = 23.24$, $p < 0.001$, $\eta_p^2 = 0.514$), Visionary Restructuralization ($F_{1,22} = 21.28$, $p < 0.001$, $\eta_p^2 = 0.492$), Auditory Alterations ($F_{1,22} = 10.59$, $p = 0.04$, $\eta_p^2 = 0.325$) and Vigilance Reduction ($F_{1,22} = 71.47$, $p < 0.001$, $\eta_p^2 = 0.765$) (Supplementary Fig. S6). The adolescent and adult groups did not differ in subjective report of altered states of consciousness.

DISCUSSION
Our goal was to determine whether healthy adolescents aged 18–20 were more sensitive to oral THC than adults aged 30–40. Compared to adults, adolescents exhibited stronger effects of the drug on measures of psychomotor impairment and EEG, while the groups did not differ on cardiovascular or subjective measures. This suggests that age differentially affects different outcome measures, in a way that could affect risk. That is, doses that produce comparable feelings of intoxication may produce greater behavioral impairment and greater disruptions in neural function in adolescents.

Our finding that adolescents were more sensitive to cognitive effects of THC is consistent with both preclinical and human studies. In rodents, THC produced greater impairment in spatial and non-spatial learning [9, 10] and greater residual cognitive deficits in adolescents compared to adults [7]. In a previous study with humans, THC also produced greater cognitive impairment in adolescents than adults, but in that study, adolescents were *less* sensitive to the subjective and cardiovascular effects of the drug [13]. The difference in findings could be related to methodological differences. For example, in the previous study, participants reported using cannabis as recently as 3 days prior to sessions, and the adolescents reported heavier habitual use than adults. In the present study, we sought to match the age groups on prior cannabis use and minimize recent use to improve the ability to detect age-related effects.

Our findings during EEG can also be related to previous research. The finding that THC reduced P300 amplitudes is consistent with previous reports with THC and cannabis [23–27], but in our study, this occurred only in adolescents, and not adults. Additionally, 15 mg THC blocked reductions of alpha power in adolescents and not adults during the oddball task. Event-related reductions of alpha power (alpha desynchronization) are associated with task engagement [56]. Increased alpha power is observed during the absence of cortical activity, including over occipital cortex during eyes-closed resting state [62, 63]. During our eyes-closed resting state, the lack of THC effects on neural oscillations was surprising, yet consistent with one prior report [36]. Our finding that adults exhibited lower oscillatory power,

regardless of drug, is also consistent with previous reports, and may be related to cortical maturation from adolescence into adulthood [64, 65].

It is interesting to note that age affected responses to the drug on cognitive measures more than subjective measures. This is consistent with the fact that the decline in CB_1R expression and function from adolescence to adulthood is most prominent in the prefrontal cortex, a brain region involved in cognition [3]. Other neurotransmitter receptor systems also vary with age. Unlike CB_1R mRNA, the mRNA of dopamine 1 receptors and most serotonin (5-HT) receptors increases from adolescence into adulthood [66, 67], while 5-HT2A mRNA expression peaks in prefrontal cortex during adolescence similar to CB_1R [66]. Heterodimeric receptor complexes of 5-HT2A and CB_1Rs [68, 69] mediate THC-induced memory impairments in mice [69] and are associated with cognitive processing in humans [68]. These receptor complexes may contribute to age differences in cognitive effects of THC.

One important consideration in studying age-related responses to drugs is the possibility of pharmacokinetic differences. There is some evidence that pharmacokinetic properties of THC differ in adolescent and adult male mice [12]. 5 mg/kg THC resulted in greater peak plasma levels, but lower brain concentrations of THC in adolescents. Adolescents also exhibited faster THC conversion into 11-COOH-THC, and higher peak levels of the psychoactive metabolite 11-OH-THC in plasma and brain. Age can affect drug metabolism in humans via the hepatic cytochrome P_{450} system [70], which is known to metabolize THC. However, it is unlikely that pharmacokinetic factors affected the present findings as age-related differences were detected only on some outcome measures. Pharmacokinetic factors such as differences in absorption or clearance would be expected to affect all measures to a similar extent. Moreover, the time course of drug effects was not significantly different in the groups (see Fig. 1A).

The present study had several limitations. First, the sample size was modest, and insufficient to examine sex differences in age-related responses to THC. Related to this, female subjects were tested at any phase of the menstrual cycle, and variations across the cycle may have obscured age-related differences. A second limitation is that the groups differed in their ability to identify the drug they received: That is, adolescents were somewhat more accurate than adults in identifying THC as "cannabis" at the end of the session. Whether subjects identified the drug early in the sessions, and whether this affected their responses later in the session (through expectancy effects) is not known. Other limitations include the small range of doses of drug tested, the restricted demographic characteristics of the participants (e.g., education, body weight, race), and the selection and timing of the outcome measures. The findings raise other interesting questions beyond the scope of this study, such as whether the age at which participants first use cannabis (see [71]) affects later responses to acute THC.

Together, our findings indicate that adolescents are more sensitive than adults to the effects of THC on cognitive performance and on measures of neural function, but not to cardiovascular effects or subjective measures. These observations raise questions about the relative risk for adolescents. That is, compared to adults, adolescents may exhibit greater behavioral or neural impairment at doses that produce similar feelings of intoxication. It remains to be determined how these differences might be affected by or contribute to repeated use or compared to other age groups across the lifespan.

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AUTHOR CONTRIBUTIONS

CHM for conception and design of the work; the acquisition, analysis, of data; and drafting of the manuscript. ZH for acquisition and analysis of data. RL for the interpretation of data; critical revision of manuscript for intellectual content. HdW for conception and design of the work; interpretation of data; critical revision of manuscript for intellectual content. All authors approved final manuscript for submission.

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