

Recreational Marijuana Use, Adolescent Cognitive Development, and Schizophrenia Susceptibility

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ABSTRACT

BACKGROUND: We investigated how low marijuana (MJ) use levels, the typical use pattern in most adolescent users, affect cognitive maturation and schizophrenia risk.

METHODS: In two complementary adolescent samples where the majority reported minimal MJ use, we compared cognitive performances before and after MJ use initiation. The Iowa sample (40 first-degree relatives and 54 second-degree relatives of patients with schizophrenia and 117 control subjects with no schizophrenia family history) underwent a battery of standardized neuropsychological tests at 0, 18, and 36 months. Based on self-administered Timeline Followback interviews, 26.5% of adolescents had emergent MJ use (eMJ) during follow-up. The second sample ($n = 3463$), derived from a birth cohort, received substance use and sustained attention assessments between ages 10 and 15 years. Mixed linear models and regression analyses tested the effects of eMJ on longitudinal changes in cognitive performance.

RESULTS: In the Iowa sample, longitudinal changes in 5 of 8 cognitive domains were significantly associated with eMJ. On sustained attention, visuospatial working memory, and executive sequencing, adolescents with eMJ showed less age-expected improved performance. In addition, first-degree relatives with eMJ were less improved on processing speed and executive reasoning than first-degree relatives without eMJ. In the birth cohort, greater intraindividual variability in reaction times (indicative of poorer sustained attention) was significantly associated with more frequent MJ use and with recreational use levels.

CONCLUSIONS: Nonheavy MJ use disrupts normal adolescent maturation and compounds aberrant adolescent maturation associated with familial schizophrenia risk. These findings underscore the importance of reducing adolescent MJ access in the context of increased availability to high-potency MJ.

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Marijuana (MJ) poses a major public health problem worldwide (1). It is the most frequently used illicit drug and consistently the preferred illicit drug among youths (2). Most users first tried MJ during adolescence (3). Heavy adolescent MJ use has been associated with poor educational attainment and school dropout, diminished life satisfaction, cognitive impairment, disrupted brain maturation, and increased risk for drug addiction and psychotic disorders in adulthood (4). However, the most common adolescent usage pattern is low, sporadic use, with low MJ use levels generally regarded as not harmful (5,6). Greater understanding of the long-term effects of adolescent recreational MJ use has become especially pressing because MJ with high concentrations of Δ^9 -tetrahydrocannabinol (THC), the psychoactive component of MJ, is now widely available to the average user (7,8). Furthermore, liberalization of state laws governing MJ use has enabled greater MJ access among adults (9) and consequently increased accessibility in children of these adults.

A substantial body of evidence from animal studies indicates that adolescence is a sensitive period during which the brain is particularly vulnerable to the adverse effects of MJ. Exposure to THC in adolescent rhesus monkeys leads to less age-expected improvements in spatial working memory, indicative of developmental disruptions in actively maturing neural circuits (10). Chronic THC administration in adolescent rats, but not adult or prepubescent THC exposure, results in enduring cognitive deficits in adulthood (11). Such THC-related cognitive impairments are associated with altered fos protein expression in cannabinoid CB₁ receptor-rich brain regions, impaired endocannabinoid-mediated synaptic plasticity, disrupted dendritic spine pruning, and reduced numbers of prefrontal pyramidal neuronal spines (12–14). Adolescent THC exposure also activates microglia and induces neuroinflammation, leading to persistent cognitive deficits (15).

Despite clear evidence from animal studies that MJ is most deleterious during adolescent exposure and that THC impairs cognitive development, research involving humans has been

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less clear about MJ's harmfulness. Human studies found that MJ use is associated with impaired cognition involving multiple domains, including processing speed, attention, visuospatial abilities, and executive functions (16). Although an emerging body of longitudinal studies suggests that MJ exposure leads to progressive cognitive deterioration (17,18), studies involving twins discordant on MJ use do not support MJ exposure having a direct role in IQ decrement (19,20). Regardless, most human studies have been limited by cross-sectional study design; involve mostly adults, small samples, or challenges in parsing acute intoxication effects from long-term impairment; or have no pre-MJ use cognitive baseline for comparison (21). These limitations have led to both conflicting findings and uncertainty over the enduring deleterious impact of MJ. Therefore, we avoid these limitations in our report where we comprehensively assessed adolescent cognition before and after MJ use initiation. A second goal of our study is to better understand the association between adolescent MJ exposure and heightened schizophrenia (SZ) susceptibility (22).

Adolescent heavy users of MJ are four times more likely to be diagnosed with SZ at follow-up even despite careful adjustments for confounding factors (23–25). The reasons underlying this association remain a topic of intense debate with differing explanations for how adolescent MJ use might lead to SZ (26). One theory, the two-hit hypothesis (27), posits that an environmental factor (adolescent MJ) interacts with SZ neurobiological vulnerability to result in SZ illness. In this study, we therefore included biological relatives of patients with SZ to investigate the differential impact adolescent MJ use may have on cognitive maturation. We hypothesized that biological relatives with increased familial SZ risk will show greater disrupted cognitive maturation in association with emergent MJ use (eMJ) compared with adolescents with no SZ family history (NSFH).

We studied two distinct yet complementary longitudinal samples of adolescents who had no MJ use at their initial cognitive assessments. The first sample was ascertained through the University of Iowa, while the second was derived from the Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort. A subgroup within each sample began using MJ during the 3- to 5-year follow-up period.

METHODS AND MATERIALS: SAMPLE 1 (UNIVERSITY OF IOWA)

Adolescents ages 12 to 17 years at intake ($N = 211$; 40 first-degree relatives [FDRs] and 54 second-degree relatives [SDRs] of patients with SZ and 117 participants with NSFH) (Table 1) were recruited via advertisements. Following telephone screening, participants were assessed in person to confirm inclusion and exclusion criteria (see the Supplement). Adolescents and their parents gave written informed consent approved by the University of Iowa Institutional Review Board. They were administered the Child and Adolescent Psychiatric Assessment, Child Interview (28), a semistructured interview, to determine absence of prior MJ use and lifetime history of psychiatric disorders. SZ family history was verified using the Family History–Research Diagnostic Criteria, which has well-established reliability and validity (29). After intake, participants were reassessed every 6 months for up to 3 years.

Cognitive Assessments

At 0, 18, and 36 months, participants received the MATRICS Consensus Cognitive Battery (30), which was specifically developed to assess cognition in SZ (component tests and corresponding cognitive domains in Table 2). The MATRICS Consensus Cognitive Battery has solid psychometric properties (31), well suited for detecting longitudinal changes in adolescents and sensitive to substance use outcomes (32). Cognitive assessments were administered by trained raters using CMINDS (NeuroComp Systems, Inc.), a computerized test administration system with comparable validity and greater reliability than paper-based testing (33). Raw test scores were converted to z scores based on the sample's test performance at intake (mean = 0; SD = 1). z Scores were reversed where necessary. Larger negative z scores indicate poorer performance below intake sample mean.

Substance Use Assessments

After intake, participants completed an online version of the Timeline Followback interview (TLFB) (34) every 6 months to determine frequency and amount of MJ, alcohol, and tobacco use during the preceding 6 months. TLFB is a widely used self-report calendar method for assessing drug use in adolescents (35,36). It has good test-retest reliability and excellent concordance with collateral drug use reports in the preceding 6 months. Self-administered online TLFB assessments have comparable validity and reliability as in-person or telephone interviews. Based on these TLFB interviews plus urine drug screens and Child and Adolescent Psychiatric Assessment interviews (0, 18, and 36 months) (see the Supplement), initially MJ-naïve adolescents who began any MJ use during the follow-up period were categorized as emergent MJ users (eMJ+). Adolescents who reported no MJ use during follow-up were classified as eMJ–.

Iowa Sample Characteristics and eMJ Use

The 211 adolescents (mean intake age = 14.9 years [SD = 1.6]; 49.8% males) were predominantly right-handed (82.5%) and Caucasian (90.1%). Mean parental education was 14.8 years (SD = 2.3). Mean Wide-Range Achievement Test-3 reading score was 102.5 (SD = 11.3). Participants were followed for approximately 3 years (mean = 1034.5 days, SD = 157.7; spanning years 2013–2019) with high retention (95.7% and 91.9% at 18 and 36 months, respectively).

Of these 211 initially MJ-naïve adolescents, there were 56 (26.5%) adolescents who reported MJ use during follow-up (eMJ+; 28.2% of FDRs, 25.9% of SDRs, and 26.5% of participants with NSFH) (Table 1). As a group, eMJ+ had low lifetime levels of MJ use (median = 9.0 use days/lifetime [25th–75th interquartile range (IQR) = 59.0] or 0.25 use days/month [IQR = 1.7]). None met DSM-IV cannabis use disorder criteria. To further characterize MJ exposure, we calculated the total number of times of MJ use during consecutive 30-day epochs spanning the entire 3-year follow-up period (using TLFB interview data) and then grouped eMJ+ with similar use trajectories (Figure 1). Most eMJ+ (67.9% [$n = 38$]) had low, infrequent MJ use trajectory (median = 0.14 times/month; none with daily use or >50 times lifetime) (Figure 1C). Neither group, sex, handedness, parental education, Wide-Range Achievement Test-3 score, presence of psychiatric disorders at intake, nor

duration of follow-up differed significantly between eMJ+ and eMJ- ($p \geq .10$) (Table 1). Because eMJ+ were older and had a greater proportion with alcohol/tobacco use and FDRs were more likely to have psychiatric disorders, these variables were included as covariates in all analyses (see Statistical Analysis).

Statistical Analysis

Analyses were performed using SAS (version 9.4; SAS Institute). For the Iowa sample, we used linear mixed models to assess the relationships between longitudinal changes in cognitive performance and eMJ among adolescents grouped by SZ family history (FDR, SDR, or NSFH). For each

cognitive test, z scores at 0, 18, and 36 months were the dependent variable. Time (duration between intake and cognitive assessment) and an intercept term were specified as random effects modeling within-subject correlations in cognitive performance across time. Two predictor variables of interest (i.e., eMJ [eMJ+/eMJ-] and group [FDR/SDR/NSFH]), interaction terms (eMJ \times time, group \times time, eMJ \times group, and eMJ \times time \times group), and potential confounders (i.e., sex, age at study enrollment, psychiatric diagnoses, alcohol use during follow-up period, and tobacco use during follow-up period) were entered simultaneously as fixed effects.

Table 1. Iowa Sample: Comparisons of Sociodemographic and Clinical Characteristics of 211 Initially Marijuana-Naïve Adolescents Who Subsequently Began Using Marijuana During the Follow-up Period (eMJ+) (n = 56) vs. Those Without Emergent MJ Use (eMJ-) (n = 155) Divided According to Presence (FDR or SDR) or Absence (NSFH) of SZ Family History

Sociodemographic and Clinical Characteristics	FDR		SDR		NSFH		eMJ		Group	
	eMJ-	eMJ+	eMJ-	eMJ+	eMJ-	eMJ+	χ^2/F^a	p Value	χ^2/F^a	p Value
Intake, n (%)	29 (72.5%)	11 (27.5%)	40 (74.1%)	14 (25.9%)	86 (73.5%)	31 (26.5%)	-	-	-	-
18-Month Follow-up, n (%)	27 (93.1%)	11 (100.0%)	35 (87.5%)	14 (100.0%)	84 (97.7%)	31 (100.0%)	-	-	-	-
36-Month Follow-up, n (%)	24 (82.8%)	11 (100.0%)	33 (82.5%)	14 (100.0%)	81 (94.2%)	31 (100.0%)	-	-	-	-
Handedness ^b , L/M/R (% R)	2/8/19 (65.5%)	0/0/11 (100.0%)	3/3/34 (85.0%)	3/2/9 (64.3%)	4/7/75 (87.2%)	1/4/26 (83.9%)	0.01	.94	3.05	.22
Sex, Male, n (%)	19 (65.5%)	4 (36.4%)	16 (40.0%)	9 (64.3%)	47 (54.7%)	17 (54.8%)	2.30	.13	2.22	.33
Race, White, n (%)	26 (89.7%)	8 (72.7%)	36 (90.0%)	13 (92.9%)	80 (93.0%)	27 (87.1%)	1.60	.21	1.42	.49
Any Psychiatric Disorders at Intake ^c , n (%)	13 (44.8%)	3 (27.3%)	9 (22.5%)	2 (14.3%)	17 (19.8%)	5 (16.1%)	1.23	.27	7.84	.01
MDD ^c	10 (34.5%)	1 (9.1%)	6 (15.0%)	1 (7.1%)	10 (11.6%)	2 (6.5%)	-	-	-	-
ADHD ^c	6 (20.7%)	2 (18.2%)	8 (20.0%)	1 (7.1%)	9 (10.5%)	3 (9.7%)	-	-	-	-
Current/Past Drug Use at Intake ^c , n (%)	5 (17.2%)	2 (18.2%)	7 (17.5%)	5 (35.7%)	9 (10.5%)	7 (22.6%)	3.90	.048	1.98	.37
Tobacco use	2 (6.9%)	0 (0.0%)	1 (2.5%)	2 (14.3%)	3 (3.5%)	0 (0.0%)	-	-	-	-
Alcohol use	4 (13.8%)	1 (9.1%)	7 (17.5%)	4 (28.6%)	9 (10.5%)	7 (22.6%)	-	-	-	-
Age at Intake, Years, Mean (SD)	14.9 (1.7)	14.7 (1.3)	14.4 (1.8)	15.1 (1.3)	14.7 (1.6)	15.8 (1.4)	3.71	.06	1.85	.16
Parental Education, Years, Mean (SD)	13.5 (1.9)	14.8 (3.1)	14.7 (2.5)	15.1 (2.0)	15.1 (2.0)	15.1 (2.5)	1.93	.17	1.93	.15
WRAT3 Score, Mean (SD)	98.7 (16.0)	101.4 (8.5)	102.2 (12.4)	100.8 (8.0)	104.3 (10.5)	102.7 (8.2)	0.00	.96	1.28	.28
Follow-up Duration, Days, Mean (SD)	993.7 (204.6)	1079.5 (36.0)	996.6 (221.0)	1082.4 (28.8)	1057.6 (102.1)	1019.8 (185.0)	2.76	.10	0.00	.99
Substance Use During Follow-up ^d , Median (IQR)										
Marijuana	0.0 (0.0)	8.0 (108.0)	0.0 (0.0)	13.0 (128.0)	0.0 (0.0)	6.0 (59.0)	55.99	<.0001	2.51	.08
Alcohol	0.0 (2.0)	6.0 (46.0)	0.0 (1.5)	19.5 (36.0)	0.0 (5.0)	20.0 (41.0)	68.73	<.0001	2.48	.09
Tobacco	0.0 (0.0)	0.0 (10.0)	0.0 (0.0)	4.0 (22.0)	0.0 (0.0)	0.0 (1.0)	47.21	<.0001	7.65	.0006

ADHD, attention-deficit/hyperactivity disorder; eMJ, emergent marijuana use; eMJ+, emergent marijuana use during the follow-up period; eMJ-, no emergent marijuana use during the follow-up period; FDR, first-degree relative; IQR, interquartile range; L, left; M, mixed; MDD, major depressive disorder; MJ, marijuana; NSFH, no schizophrenia family history; R, right; SDR, second-degree relative; SZ, schizophrenia; WRAT3, Wide-Range Achievement Test, Reading subtest.

^a χ^2 Tests for categorical measures; F tests for continuous measures (non-rank-transformed and rank-transformed shown against mean and median rows, respectively).

^bAnnett Scale of Hand Preference.

^cChild and Adolescent Psychiatric Assessment interview.

^dTotal days of use.

RESULTS: SAMPLE 1

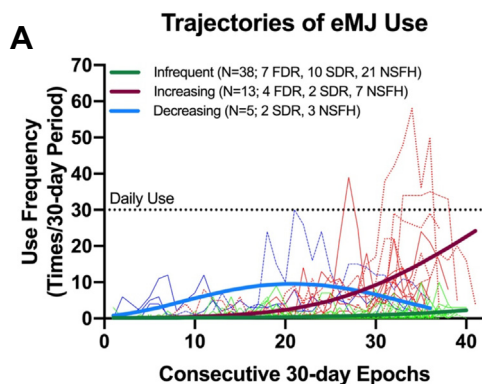
Longitudinal Changes in Cognition Associated With eMJ Use

For the continuous performance test, visuospatial sequencing test (VST), and Trail Making Test, there were significant eMJ × time interaction effects ($F_s \geq 5.80$, $p_s \leq .017$; β coefficients = 0.18, 0.14, and 0.08, respectively) (Table 2). Other interaction terms (including eMJ × time × group) were not statistically significant ($p \geq .28$). This indicates that the cognitive performance trajectories differed significantly across eMJ groups. eMJ+ had less within-subject improvements at follow-up compared with eMJ- (median within-subject z score changes at 18 and 36 months [from baseline] = 0.27 [IQR = 0.26] vs. 0.48 [IQR = 0.11], respectively) (Figure 2A–C). On the visual figure learning test, eMJ × time interaction approached but did not achieve significance ($p = .057$) (Table 2). On the continuous performance test, VST, visual figure learning test, and Trail Making Test, main effects of eMJ, group, or time were not statistically significant ($p_s \geq .09$), except for time effects on the continuous performance test and VST ($p < .001$).

For the symbol digit and maze solving tests, there were significant eMJ × time × group interaction effects ($F_s \geq 3.51$,

$p_s \leq .032$; β coefficients = 0.50 and 0.64, respectively) (Table 2). This indicates that the rate of cognitive change over time for these two tests depends on the combination of eMJ and group. Post hoc two-group contrasts found that changes in symbol digit and maze solving associated with eMJ among FDRs differed significantly from those in participants with NSFH ($t = 2.56$ and 2.43 , respectively; $p_s \leq .02$). In contrast, SDRs did not differ significantly from participants with NSFH ($t = 0.23$ and 1.17 , respectively; $p_s \geq .24$). To further illustrate these three-way interaction effects, we also examined mean within-subject changes between eMJ+ and eMJ- within FDR, SDR, and NSFH groupings (Figure 2D, E). For symbol digit, FDR/eMJ+ were less improved than FDR/eMJ- while NSFH/eMJ+ and NSFH/eMJ- had comparable improvements. On maze solving, FDR/eMJ- were unchanged at follow-up and FDR/eMJ+ performed worse (specifically at 18 months), while NSFH/eMJ- improved at follow-up and NSFH/eMJ+ showed mild worsening.

On letter number and category fluency, there were no statistically significant main effects of eMJ grouping, time, group, or any interaction terms on cognitive performance ($p \leq .14$), except for significant main effects of time on category fluency ($p < .001$). For MJ use dose relationships, there



B

Alternative Model	Null Model ^a	BIC	Entropy ^b	BLRT	Smallest Class (%)	N (per class)
1	-	2322	-	n/a	-	-
2	1	2146	351.4	<.01	100.0	56
3	2	2105	83.06	0.02	25.0	42/14
4	3	2100	8.9	0.04	8.9	38/13/5
5	4	2099	3.12	0.99	3.6	38/13/3/2

^ak number of classes; BIC: Bayesian information criteria (lower values preferred); ^bBIC log Bayes factor approximation ($2\log_e(B_{10})$; values closest to 1 preferred) = $2(\Delta BIC)$ where $\Delta BIC = BIC_{Alternative Model}(k-1 \text{ classes}) - BIC_{Null Model}$; BLRT: bootstrap likelihood ratio test (compares the p-value for null model to alternative model); Significant p-value indicates improved model fit).

C

Comparison of Emergent Marijuana (eMJ) Use Between Adolescents With Infrequent, Increasing and Decreasing Use Trajectories

eMJ Use Frequency	Infrequent (N=38)	Increasing (N=13)	Decreasing (N=5)
Median ^a (IQR)	0.14 (0.26)	4.25 (3.66)	3.85 (5.19)
Mean ^a (SD)	0.26 (0.31)	4.96 (4.66)	5.04 (3.18)
>50x Lifetime, N (%)	0 (0)	11 (91.7)	4 (80.0)
Daily ^b , N (%)	0 (0)	4 (33.3)	2 (40.0)

^aTimes/30 days; ^bat least one occurrence of ≥ 30 times during 30-day consecutive epoch period during follow-up period

cognition between the three use-trajectory groupings were not conducted because of small sample size in the decreasing use group. IQR, interquartile range.

Figure 1. Emergent marijuana use (eMJ) trajectories in the Iowa sample. Of the 211 initially MJ-naïve adolescents, 56 adolescents (11 first-degree relatives [FDRs] of patients with schizophrenia [SZ], 14 second-degree relatives [SDRs] of patients with SZ, and 31 participants with no SZ family history [NSFH]) began MJ use during the 3-year follow-up period. (A) For each eMJ participant, we first calculated the total number of times of MJ use during consecutive 30-day epochs through the longitudinal follow-up period. (B) We then used a mixture modeling approach (implemented in SAS PROC TRAJ) to separate these adolescents into similar MJ use trajectories (55). Based on the recommendations of Nylund *et al.* (56,57), we used the Bayesian information criterion (BIC), entropy, bootstrap likelihood-ratio test (BLRT), and percentage of the sample that is in the smallest group to determine the number of classes of MJ use trajectory. Lower values of BIC are desirable while entropy values closest to 1 are preferred. The BLRT compares the p value for each model with k groups to the model with k-1 groups. A significant value indicates that there is significant improvement in the model fit (56). The three-group model was therefore selected as the best fit: infrequent, increasing, or decreasing use. (C) The majority (67.9%) of eMJ adolescents were infrequent users (median = 0.14 ×/month; daily use: none). Six adolescents had daily MJ use (i.e., defined as having at least one occurrence of ≥ 30 times MJ use in any of the 30-day consecutive epoch periods during the follow-up period; 1 FDR, 3 SDRs, and 2 participants with NSFH; 4 adolescents with increasing and 2 with decreasing MJ use trajectories). A total of 15 eMJ adolescents reported >50 times/lifetime MJ use (11 increasing and 4 decreasing MJ use trajectories). Of note, MJ use trajectories illustrate how these 56 eMJ users are representative of adolescent MJ users in the general population, and differences in

Table 2. Iowa Sample: Linear Mixed Model Analyses^a Comprising Between-Subject Fixed Effects (*F* [*p*]) of eMJ and Group (FDR vs. SDR vs. NSFH), Within-Subject Random Effects of Time (Repeated Assessments at Intake, 18, and 36 Months), and Interaction Terms on Changes in Cognition Among 211 Adolescents Who Were MJ Naïve at Study Intake

Domain	Tests	eMJ		Group		Time		eMJ × Time		Group × Time		eMJ × Group		eMJ × Time × Group	
		<i>F</i>	<i>p</i>	<i>F</i>	<i>p</i>	<i>F</i>	<i>p</i>	<i>F</i>	<i>p</i>	<i>F</i>	<i>p</i>	<i>F</i>	<i>p</i>	<i>F</i>	<i>p</i>
Processing Speed	Symbol digit	1.33	.25	1.21	.30	27.95 ^b	<.001 ^b	0.95	.33	2.45	.09	4.17 ^b	.017 ^b	3.51 ^b	.032 ^b
Language	Category fluency	1.67	.20	0.05	.95	16.18 ^b	<.001 ^b	0.01	.91	0.44	.65	1.11	.33	0.89	.41
Sustained Attention	CPT	0.19	.66	0.63	.54	23.12 ^b	<.001 ^b	8.34 ^b	.004 ^b	0.68	.51	0.40	.67	0.71	.49
WM	Letter number	0.20	.66	0.15	.86	2.18	.14	0.01	.91	0.30	.74	0.65	.52	0.62	.54
Visuospatial WM	VST	1.16	.28	1.99	.14	18.92 ^b	<.001 ^b	7.11 ^b	.008 ^b	0.96	.38	1.28	.28	0.67	.51
Executive Reasoning	Maze solving	0.05	.82	3.17 ^b	.04 ^b	0.94	.33	0.10	.76	2.33	.10	6.09 ^b	.003 ^b	5.12 ^b	.007 ^b
Executive Sequencing	VFLT	2.81	.09	0.12	.89	2.73	.10	3.65	.057	0.88	.42	1.08	.34	1.60	.20
Visual Memory	Trail B	2.88	.09	2.77	.07	3.23	.07	5.80 ^b	.017 ^b	0.48	.62	0.69	.50	0.11	.89

eMJ (any MJ use during follow-up): yes, *n* = 56; no, *n* = 155. FDR, *n* = 40; SDR, *n* = 54; NSFH, *n* = 117. Tests: symbol digit association test—correct responses; category fluency—total correct responses (“animals,” “vegetables,” and “fruits”); CPT identical pairs—d-prime; letter number ordering—total correct responses; VST—total number of correct responses for forward condition; mazes solving test—total score; VFLT—total score; Trail Making Test—part b (time).

CPT, continuous performance test; eMJ, emergent marijuana use; FDR, first-degree relative; NSFH, no schizophrenia family history; SDR, second-degree relative; VFLT, visual figure learning test; VST, visuospatial sequencing test; WM, working memory.

^aIncluded in statistical models were additional fixed effects (covariates): sex, age at study enrollment, psychiatric diagnoses, alcohol use during the follow-up period, and tobacco use during the follow-up period (not shown; see Table S2), and an intercept term as random effects.

^bStatistically significant at *p* < .05.

were no statistically significant correlations between number of MJ use days and changes in cognitive performance (Spearman $|r| = 0.24$, *p* ≥ .09; median $|r| = 0.11$).

Secondary Analyses

In these linear mixed models analyses, we kept the significance level of .05 (see the Supplement for rationale). False discovery rate corrections (Table S1) did not substantively alter Table 2 findings (only symbol digit eMJ × time × group interaction effects become nonsignificant). Main effects of other covariates (including concurrent non-MJ substance use) in the linear mixed models are summarized in Table S2. Other than alcohol use on VST (*F* = 5.07, *p* = .03), there were no significant main effects of psychiatric diagnoses or alcohol/tobacco use on cognitive performance (*p* ≥ .07). Multicollinearity analysis found no evidence that the predictor variables were highly collinear (tolerance values ≥ 0.63). Inclusion of urine drug toxicology data and recency of MJ use did not reveal marked differences from Table 2 results (Tables S3–S5).

METHODS AND MATERIALS: SAMPLE 2 (ALSPAC BIRTH COHORT)

ALSPAC is an ongoing birth cohort study (37,38). Pregnant women resident in Avon, United Kingdom, with expected dates of delivery April 1, 1991, to December 31, 1992, were invited to participate in the study. The original sample (14,541 pregnancies/14,676 fetuses) was enrolled prenatally with additional eligible children who did not enroll prenatally joining the study from age 7 years. The total sample (15,454 pregnancies/15,589 fetuses) has undergone a wide variety of evaluations, including cognitive and substance use assessments during adolescence (Figure 3). Informed consent for the use of data collected via questionnaires and clinics was obtained from participants

following the recommendations of the ALSPAC Ethics and Law Committee at the time. The study website contains details of all data that are available through a fully searchable data dictionary and variable search tool (<http://www.bristol.ac.uk/alspac/researchers/our-data/>). Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and University of Iowa Institutional Review Board.

Assessment of Variability in Reaction Time

Intraindividual variability of reaction time (RT), an index of sustained attention (39), was derived from performance on a stop signal task that participants completed at ages 10 and 15 years. Although ALSPAC participants received cognitive testing at various time points, we restricted to only RT variability/sustained attention data because these longitudinal assessments provided the best match for the Iowa sample developmental time window (see the Supplement). To obtain valid RTs, we used only the primary trials in the stop signal task (i.e., experimental blocks 3 and 4; 32 trials/block) in which participants had 1) responded correctly, 2) >50% overall accuracy, and 3) mean RT within ±3 SDs of the ALSPAC sample mean. There were 6634 participants at age 10 years and 4367 at 15 years with valid RT data, yielding 3574 participants with valid trials at both time points (Figure 3). We derived two measures of intraindividual variability: 1) individual standard deviation (ISD) (standard deviation of RT) and 2) individual coefficient of variation (ICV) (ISD divided by the participant’s mean RT). Raw ISD and ICV were transformed to *z* scores based on the sample’s mean performance at age 10. Each participant’s within-subject changes (Δ ISD and Δ ICV) were computed by subtracting age 10 from age 15 *z* scores.

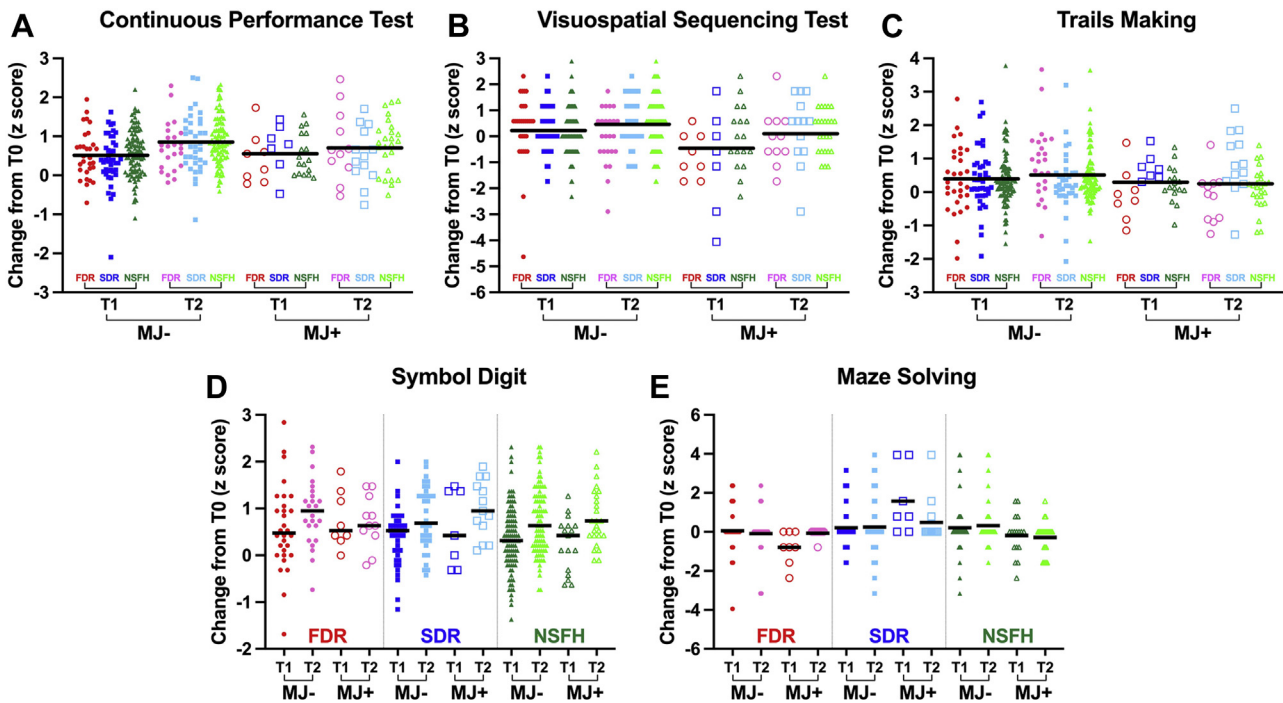


Figure 2. Iowa sample: scatterplots of within-subject changes in cognitive performance at 18-month (T1) and 36-month (T2) assessments (follow-up z score minus intake z score; horizontal bar denotes group mean) among adolescents with (marijuana [MJ+]; $n = 56$) vs. without (MJ-; $n = 155$) emergent MJ use (eMJ) subdivided by schizophrenia (SZ) family history (first-degree relatives [FDRs] of patients with SZ, second-degree relatives [SDRs] of patients with SZ, or participants with no SZ family history [NSFH]). **(A–C)** Significant eMJ \times time interaction effects ($F \geq 5.80, p \leq .017$) but nonsignificant eMJ \times time \times group, group \times time, or eMJ \times group effects. On the continuous performance test, visual spatial sequencing test, and Trail Making Test, MJ+ showed less within-subject improvements at follow-up than MJ-. **(D, E)** Significant eMJ \times time \times group interaction effects ($F \geq 3.51, p \leq .032$) wherein the impact of eMJ on longitudinal changes in symbol digit and maze solving test performance differed between FDRs, SDRs, and participants with NSFH. Differential patterns in longitudinal changes between FDR/MJ- and FDR/MJ+ differed significantly from those among participants with NSFH. For the symbol digit test, FDR/MJ+ were less improved than FDR/MJ-, while MJ+ and MJ- participants with NSFH had comparable improvements. For the maze solving test, FDR/MJ+ had worsened performance (specifically at 18 months) and FDR/MJ- were unchanged at follow-up, while NSFH/MJ- improved at follow-up and NSFH/MJ+ showed mild worsening.

Assessment of Substance Use

Data on lifetime MJ use at age 10 and at age 15 years were gathered by computer-administered self-report questionnaires. Participants selected one of six groups based on their lifetime MJ use frequency (Figure 3). Participants also reported problems associated with MJ use via the Cannabis Abuse Screening Test (CAST). CAST score ≥ 3 has been shown to discriminate DSM-IV cannabis use diagnoses (40). At age 10, all but 1 participant reported no lifetime MJ use; this participant was excluded from this study. After excluding participants with missing MJ use data at age 15 (Figure 3), the resultant sample used in statistical analyses ($n = 3463$) was categorized into six groups with increasing MJ use severity based on both lifetime MJ use frequency and CAST score. The majority (75.7%) had no lifetime MJ use at age 15. The second largest group reported 1–4 times lifetime MJ use (group 2; $n = 395$). In addition, we defined recreational MJ use as 1–49 times lifetime use and CAST < 3 (i.e., groups 2–4; $n = 621$) and combined participants who reported 1–49 times MJ use and CAST ≥ 3 (i.e., with probable DSM-IV cannabis use disorders) with participants reporting 50–99 times MJ use in group 5 (Figure 3).

Statistical Analysis

In the ALSPAC sample, we assessed the impact of adolescent lifetime MJ use on sustained attention maturation. First, we used linear regression models to test the ordinal effects of six groupings of increasing MJ use on Δ ISD and Δ ICV. We investigated three statistical analytic models: 1) model 1: complete-case analysis ($n = 3463$; covariate: age 10 z score; adjusting for baseline performance), 2) model 2: adjusted for baseline performance plus potential confounding maternal (educational level; perinatal depression; and first-trimester alcohol, tobacco, and MJ use) and participant (sex, hyperactivity score, depressive symptoms, and alcohol, tobacco, and other illicit drug use) factors known to mediate poor cognition and substance use ($n = 2353$ due to missing confounder data), and 3) model 3: multiple imputation analyses similar to model 2 to determine effects of subject attrition ($n = 6634$ with valid RT data at age 10 years; see the Supplement). If model 3 results were comparable as in models 1 and 2, it would suggest that missing data had not resulted in biased samples unrepresentative of the sample at age 10 with valid RT data. Second, we used logistic regression (models 1–3 repeated) to test how Δ ISD and Δ ICV predicted group membership in recreational MJ users versus nonusers.

RESULTS: SAMPLE 2

Effects of Adolescent MJ Use on Sustained Attention Maturation

Changes in ISD and ICV both showed significant linear associations with increased adolescent MJ use (models 1–3: $p < .05$) (Table 3). Adolescents who reported heavier MJ use had significantly greater within-individual increases in both measures of RT variability (Figure 4). Compared with nonusers, adolescents with recreational MJ use levels (i.e., 1–49 times lifetime MJ use and without moderate or severe impairment [CAST scores < 3]) also showed greater increases in ISD and ICV (models 2 and 3: $p \leq .04$), but this association was not significant in the complete-case analysis ($p \geq .11$). Such disrupted sustained attention maturation associated with low MJ use levels is consistent with the Iowa study findings.

DISCUSSION

We investigated cognitive development in adolescents who had no prior MJ use at baseline. Adolescents who subsequently began using MJ showed less improved performances in multiple cognitive domains than those without eMJ. This is consistent with previous research in both animals and humans demonstrating the adverse effects of MJ on disrupting adolescent cognitive maturation. With generally low use levels typical of most adolescent MJ users in the general population, MJ users in the Iowa sample had less age-expected improvements on tests assessing sustained attention, visuo-spatial working memory, and executive functioning. Among unaffected first-degree biological relatives who are at heightened risk for developing SZ, eMJ further disrupted maturation of processing speed and executive reasoning. These disruptions in cognitive maturation were evident even after factoring in potential confounds of age, sex, psychiatric diagnoses, concurrent alcohol and tobacco use, and recency of MJ use. Together with animal studies, our findings in FDRs further suggest that adolescent MJ exposure may serve as an important contributory factor in increasing SZ susceptibility via disrupted cognitive maturation.

Disrupted sustained attention maturation associated with relatively low adolescent MJ use levels was replicated in a complementary sample derived from a large birth cohort. The confluence of results from these two independent samples therefore underscores the importance of raising public awareness regarding the consequences of recreational MJ use among adolescents. This is particularly crucial when perceived harmfulness of MJ is declining. In addition, with less restrictive state laws governing MJ use in the United States and the predominance of high-THC forms of available MJ, drug use prevention programs that limit adolescent access to MJ and promote the deferment of MJ use until past the most vulnerable maturational period would be vitally important.

Unlike various limitations in previous studies (16,21), our research participants were initially MJ naïve, allowing us to factor cognitive performance prior to MJ use onset into our data analyses. Another strength is the examination of potential confounding factors (i.e., acute MJ intoxication, sociodemographic and clinical characteristics, concurrent substance use) that reduced but did not eliminate the

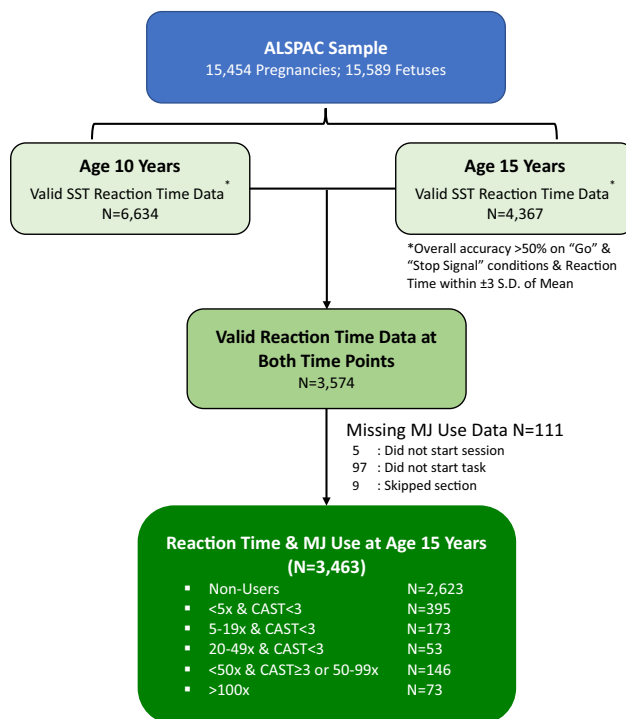


Figure 3. Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort: sample ($n = 3463$) was derived based on having valid reaction time (RT) data at both ages 10 and 15 years and lifetime marijuana (MJ) use data at age 15 years. From participants with valid RT data at age 10 ($n = 6634$) and age 15 ($n = 4367$), there were 3574 participants with valid RT data at both time points. On computer-administered self-report questionnaires, participants selected one of six groups based on their lifetime MJ use frequency: 1) no lifetime MJ use, 2) 1–4 times lifetime use, 3) between 5 and 19 times lifetime use, 4) between 20 and 49 times lifetime use, 5) between 50 and 99 times lifetime use, or 6) more than 100 times lifetime use. Participants also reported problems associated with MJ use via the Cannabis Abuse Screening Test (CAST). After excluding participants with missing MJ use data ($n = 111$), 3463 participants were available for statistical analyses, including $n = 2623$ MJ nonusers and $n = 621$ recreational MJ users (defined as 1–49 times lifetime MJ use and CAST score < 3 ; groups 2, 3, or 4). SST, stop signal task.

effects of eMJ in disrupting cognitive maturation. Therefore, our findings are less likely to have arisen solely from pre-existing differences in cognitive abilities or other factors that contribute to poor cognitive performance at follow-up. However, drug use in our study was principally based on self-report. This is almost inevitable in longitudinal studies covering several years in duration. Even though we augmented self-reports in the Iowa study with additional measures to enhance the validity and reliability of MJ use data, under-reporting of actual MJ use remains a possibility. Nevertheless, the prevalence and frequency of MJ use in both longitudinal samples are comparable with previous large-scale studies (5), suggesting that our results are representative of the general population. Another limitation is that the Iowa sample was relatively small, which we mitigated with the large ALSPAC study.

We found a linear dose relationship in the ALSPAC sample where heavier MJ use correlated with greater

Table 3. ALSPAC Birth Cohort: Linear and Logistic Regression Analyses for Adolescent Marijuana Use in Predicting Changes in Mean Reaction Time Variability

Model Type	Measures ^a	Model 1			Model 2			Model 3		
		b (SE)	F	p Value	b (SE)	F	p Value	b (95% CI)	t	p Value
Linear ^b	ΔISD	0.039 (0.012)	10.30	.001	0.045 (0.018)	6.46	.01	0.036 (0.002–0.069)	2.12	.03
	ΔICV	0.028 (0.012)	6.03	.01	0.033 (0.017)	3.76	.05	0.058 (0.023–0.092)	3.32	.001
	Measures ^a	OR (95% CI)	χ ²	p Value	OR (95% CI)	χ ²	p Value	OR (95% CI)	χ ²	p Value
Logistic ^c	ΔISD	0.90 (0.78–1.05)	1.81	.18	0.80 (0.65–0.98)	4.45	.04	0.37 (0.16–0.55)	8.04	<.0001
	ΔICV	0.89 (0.76–1.03)	2.50	.11	0.75 (0.61–0.93)	7.22	.007	0.69 (0.52–0.84)	4.45	<.0001

Model 1: Complete-case analysis involving participants with valid RT data at both ages 10 and 15 years adjusting for baseline performance at age 10 years (*n* = 3463 and 3244 for linear and logistic regression, respectively). Model 2: model 1 plus potential confounding maternal (educational level; perinatal depression; and first-trimester alcohol, tobacco, and marijuana use) and participant (sex, hyperactivity score, depressive symptoms, and alcohol, tobacco and other illicit drug use) factors known to mediate poor cognition and substance use (*n* = 2353 and 2212 for linear and logistic regression, respectively, due to missing data in maternal and/or participant covariates). Model 3: multiple imputation analyses similar to model 2 on *n* = 6634 participants with valid RT data at age 10 years. ISD: standard deviation of RT; ICV: ISD divided by RT; within-subject Δ: age 15 minus age 10 z score (positive values indicate an increase over time).

ALSPAC, Avon Longitudinal Study of Parents and Children; CAST, Cannabis Abuse Screening Test; ICV, individual coefficient of variation; ISD, individual standard deviation; MJ, marijuana; OR, odds ratio; RT, reaction time.

^aRestricted to only primary trials from the stop signal task (i.e., experimental blocks 3 and 4; stop signal trials excluded).

^bBased on lifetime MJ use frequency and CAST rating (38) at age 15 years, participants were classified as belonging to one of six groups of increasing MJ use: no use (*n* = 2623), 1–4× lifetime MJ use and CAST score < 3 (*n* = 395), 5–19× lifetime MJ use and CAST score < 3 (*n* = 173), 20–49× lifetime MJ use and CAST score < 3 (*n* = 53), <50× lifetime MJ use and CAST score ≥ 3 or 50–99× lifetime MJ use regardless of CAST score (*n* = 146), and ≥100× lifetime MJ use regardless of CAST score (*n* = 73).

^cChanges in reaction time variability for predicting group membership: recreational MJ users (i.e., 1–49× lifetime MJ use and CAST < 3 or groups 2, 3, and 4 in^a; *n* = 621) vs. nonusers (*n* = 2623).

variability in RTs. Recreational MJ use (defined here as having 1–49 times lifetime MJ exposure without use-related impairment) was also associated with increased RT variability. Although the nature of RT variability is still not fully understood, intraindividual RT variability has been shown to be an index of inattention (41) and a sensitive indicator of attentional control in normal aging (42) and in attention-deficit/hyperactivity disorder (39). Structural and functional prefrontal brain abnormalities have been correlated with increased RT variability (43–45). More importantly, previous

research has also found that individual variability in RT decreases during early-mid adolescence corresponding with normal maturational changes of enhanced attentional abilities (46). Therefore, there was consistency in linking disrupted sustained attention maturation with adolescent MJ use in both the Iowa and ALSPAC studies even though the two samples used different attention tasks and covered different, albeit overlapping, developmental time windows during the second decade of life (i.e., mid-late vs. early-mid teens). However, unlike the ALSPAC sample, we found no significant MJ dose-cognition relationships in the Iowa sample. This may in part be related to the skewed MJ use distribution (toward low use levels) and modest sample size.

Results from our regression analyses of the ALSPAC data are consistent with previous work finding that higher THC dose and heavier MJ use correlated with greater cognitive impairment (18,47). Such MJ dose effects together with our findings that low adolescent MJ use levels may be sufficient to disrupt cognitive maturation raise concerns regarding the impact of high-potency MJ on adolescents. MJ from up until the early 1990s is approximately one fourth in potency compared with MJ available during the past 25 years (48). Mean THC concentrations in confiscated MJ samples have risen to 15% to 20% (7,8). Oils, edibles, and other newer forms of MJ for vaping and wax dabbing have even higher THC concentrations of up to 80%. Compounding this escalation in MJ potency, the United States has also experienced liberalization of state laws governing medical and recreational MJ use in adults. Greater availability of increasingly more potent MJ presents a major public health problem worldwide (4,9). While adolescent MJ use rates have not seen appreciable increases following legislative changes in the United States (49), we need to remain vigilant in monitoring adolescent use patterns. Revisions of

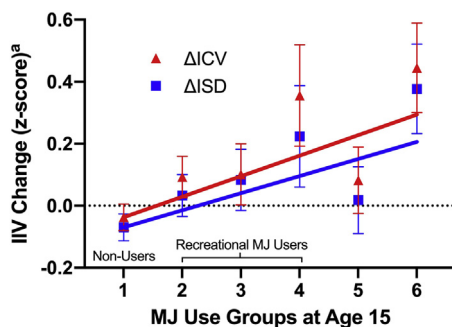


Figure 4. Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort: linear regression analysis for adolescent marijuana (MJ) use in predicting changes in mean reaction time variability (model 2; see text for details). MJ use groups: 1) no lifetime MJ use (*n* = 2623), 2) 1–5× lifetime MJ use and Cannabis Abuse Screening Test (CAST) score < 3 (*n* = 395), 3) 5–19× lifetime MJ use and CAST score < 3 (*n* = 173), 4) 20–49× lifetime MJ use and CAST score < 3 (*n* = 53), 5) <50× lifetime MJ use and CAST score ≥ 3 or 50–99× lifetime MJ use regardless of CAST score (*n* = 146), and 6) ≥100× regardless of CAST score (*n* = 73). Mean z score changes (error bars: SEM). ΔICV, change in individual coefficient of variation (ISD divided by reaction time); ΔISD, change in individual standard deviation (standard deviation of reaction time); IIV, intraindividual variability.

current counseling guidelines for adolescents and parents [e.g., (50)] may also be needed given the potential deleterious effects of recreational MJ use.

Much of the evidence linking heavy adolescent MJ use and SZ have been based on less potent forms of MJ (23,24). Therefore, we do not know if recreational use of high-potency MJ during adolescence is sufficient to increase SZ susceptibility. Future studies will need to examine adolescent MJ use in pre-SZ to determine if there are safe adolescent MJ use levels as it relates to SZ risk. In conjunction with animal studies (11–15), our findings in FDRs suggest that adolescent MJ exposure may play an important contributory role in SZ via disrupting normal cognitive maturation. Although individuals at risk for developing SZ may also be at risk for adolescent MJ use (51), other studies found no evidence in support of reverse causality (52). Sophisticated study designs are likely needed to definitively resolve the directionality of adolescent MJ use effects (53). Focusing on the impact of adolescent MJ use on brain maturational changes during the third decade of life coinciding with the typical ages of SZ illness onset may also likely yield new insights. Because adolescent THC exposure has been shown to activate neuroinflammatory response resulting in long-term cognitive impairment (15), future studies should investigate the role MJ-induced brain inflammation (54) may play in disrupting normal adolescent/early adulthood brain maturation and in mediating cognitive deficits and SZ susceptibility. Finally, given the differences (age range/adolescent developmental stages) and similarities (attention construct) between the Iowa and ALSPAC samples, future studies should also examine how adolescent MJ use may affect later-maturing cognitive domains (e.g., working memory).

Conclusions

Nonheavy MJ use, the typical use pattern for most adolescent users, disrupts normal adolescent cognitive maturation. Such deleterious effects from adolescent MJ exposure add to the aberrant adolescent maturation associated with familial SZ risk. With increased availability of high-potency forms of MJ in adults, ongoing efforts in restriction and deferment of adolescent MJ access are especially needed.

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ARTICLE INFORMATION

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