Do Differences in Learning Performance Precede or Follow Initiation of Marijuana Use?

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ABSTRACT. Objective: Studies examining cross-sectional associations between age at marijuana initiation and memory deficits yield mixed results. Because longitudinal data are sparse, controversy continues regarding whether these deficits reflect premorbid risk factors or sequelae of early marijuana initiation; here, we examine this question in a community sample followed since birth. **Method:** Masked examiners administered four subtests of the Wide Range Assessment of Memory and Learning (WRAML/WRAML2) from childhood until young adulthood to 119 urban, predominantly African American participants. Multivariable generalized estimated equation models measured longitudinal trajectories of learning. Participants were grouped as never users ($n = 26$), later initiators (≥ 16 years old; $n = 31$), and earlier initiators of marijuana use ($n = 62$). **Results:** Marijuana onset groups did not significantly

differ on WRAML scaled scores or IQ in childhood, nor did they differ on WRAML scaled scores in adolescence. On most WRAML2 subtests, these groups did not significantly differ in young adulthood after taking into account sex and childhood IQ. However, on Story Memory, later initiators attained higher scaled scores in young adulthood, even after including additional covariates of anxiety, depression, postsecondary education, past-month marijuana use, and past-week high-risk drinking. They showed a significantly more positive trajectory than never users that was driven by within-group improvement after adolescence. Earlier initiators showed within-group decline in Story Memory after adolescence. **Conclusions:** Differences in learning following earlier initiation of marijuana use may not be solely attributable to premorbid deficits. (*J. Stud. Alcohol Drugs*, 80, 5–14, 2019)

CONTROVERSY CONTINUES OVER whether cognitive differences often associated with marijuana use stem from acute or persistent marijuana neurotoxicity, whether pre-existing cognitive vulnerabilities predispose adolescents to use marijuana, or whether other, confounding variables explain this association. As legal sale of marijuana expands in the United States, this question holds both policy and scientific importance. In adults and adolescents, learning and memory are the most consistently impaired domains of cognitive function among marijuana users (Broyd et al., 2016; Lisdahl et al., 2014). Following brief cessation of marijuana use, chronic use remains associated with encoding and retrieval difficulties; detrimental effects on storage are less likely (Crane et al., 2013; Dougherty et al., 2013).

Lingering cannabinoids in the body and cannabis withdrawal syndrome may contribute to these short-term deficits, in addition to possible persistent neurotoxic effects of marijuana. One review of research published between 2004 and 2015 (Broyd et al., 2016) reported that, after prolonged cessation (definitions range from 3–4 weeks to years), several studies found recovery of learning and memory or aspects thereof (Hanson et al., 2010; Lyons et al., 2004; Medina et al., 2007; Tait et al., 2011; Thames et al., 2014), but some studies found no recovery of some or all measured parameters (Lyons et al., 2004; Medina et al., 2007; Winward et al., 2014).

For adolescents and young adults, marijuana initiation comes at a sensitive time of educational attainment and psychosocial and neurological development, including neuronal pruning and white matter increases (Crane et al., 2013; Lisdahl et al., 2014). Some cross-sectional studies of adolescents and younger adults do not find detrimental effects of earlier onset of marijuana use on learning and memory (Hooper et al., 2014; Tamm et al., 2013); however, several do (Jacobus et al., 2015; Schuster et al., 2016; Wagner et al., 2010). Few longitudinal, prospective studies have examined the relationship between marijuana use and cognitive impairment while accounting for premorbid cognitive function.

Received: January 27, 2018. Revision: August 29, 2018.

This research was funded by Grant DA06532 from the National Institute on Drug Abuse to Deborah A. Frank, Ruth Rose-Jacobs, and Jane M. Liebschutz and by Grants MO1 RR00533 and RR025771 from the National Institutes of Health/National Center for Research Resources.

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Two studies found that adolescent-onset users are more likely to experience decreased intellectual ability than are non-users (Jackson et al., 2016; Meier et al., 2012). One study, examining adult outcomes, attributed this pattern to neurotoxicity (Meier et al., 2012); the other study, examining young-adult outcomes in twins, postulated familial psychosocial factors (Jackson et al., 2016). Still another study examined both intellectual ability and other neuropsychological domains, including learning, and found no impairments in young adults following 3-months' abstinence from marijuana (Fried et al., 2005). Moreover, prospective analysis of marijuana initiation and learning trajectories is lacking in low-income, African American youth and other disadvantaged groups, despite potentially worse life outcomes following substance use. Disproportionate rates of adverse outcomes between African American and other racial/ethnic groups have been shown empirically (Brown et al., 2004), consistent with the theory of cumulative adversity (Green et al., 2017).

On one hand, a number of neurobiological associations are potentially consistent with the neurotoxicity hypothesis. Adults who initiated marijuana use during adolescence have smaller cortical gray matter volumes, larger cortical white matter volumes, decreased prefrontal cortex (PFC) thickness and white matter integrity, abnormal PFC and parietal functional activation, and smaller striatal dopamine release than adults who initiated during adulthood (Lisdahl et al., 2014). In comparison to non-users, adolescent and young-adult marijuana users show several structural and functional abnormalities in the hippocampus, PFC, and other brain regions (Lisdahl et al., 2014). In addition, early-onset use and heavy use of marijuana are associated with deficits in attention/executive and memory function served by prefrontal, parietal, striatal, and hippocampal networks (Dahlgren et al., 2016; Gruber et al., 2012; Smith et al., 2014, 2015; van de Giessen et al., 2017). On the other hand, these neurobiological associations could reflect a pre-existing susceptibility to marijuana use (Cheetham et al., 2012; Smith et al., 2014).

In addition, in samples with known intrauterine substance exposures, it is possible that long-term neurobiological developmental mechanisms could play a role in any potential relationship between adolescent marijuana use and learning and memory problems or other forms of cognitive dysfunction. Intrauterine exposures have been associated with increased risk for adolescent substance use (Day et al., 2006; Frank et al., 2011) and with some subtle forms of executive dysfunction in childhood or adolescence (Fried & Smith, 2001; Leech et al., 1999; Rose-Jacobs et al., 2011).

Other confounding variables may also explain the relationship between adolescent initiation of marijuana use and cognitive dysfunction. Pre-existing cognitive vulnerabilities in childhood, particularly executive dysfunction (that can re-

sult from prefrontal network dysfunction and affect learning and memory), may contribute to later adolescent marijuana use (Edalati & Krank, 2016; Squeglia et al., 2014). Familial-cultural deficits (e.g., less parental monitoring, poor parent-to-child affect, less emphasis on scholarship) may explain lower intellectual ability in marijuana users (Jackson et al., 2016). Further, childhood maltreatment or exposure to violence as a witness or victim may explain both substance use and cognitive deficits (Edalati & Krank, 2016; Malarbi et al., 2017).

The present analyses examine learning of structured verbal information (stories), unstructured verbal information (word list), structured nonverbal information (pictures), and unstructured nonverbal information (abstract designs) using subscales from the Wide Range Assessment of Memory and Learning (WRAML/WRAML2) (Sheslow & Adams, 2003). Using data from a longitudinal, prospective study of intrauterine substance exposure in urban, predominantly African American participants, we examined associations of age at initiation of marijuana use with learning trajectories from childhood through young adulthood, accounting for pre- and post-initiation covariates, including intrauterine exposures. We hypothesized that, in temporal sequence, earlier onset users would have the least optimal learning trajectories, and those with no history of use would have the most optimal trajectories.

Method

Protection of human subjects

The study was approved at inception and annually thereafter by the Institutional Review Board at Boston City Hospital (now Boston Medical Center) and the Boston University School of Medicine. Mothers/caregivers provided written informed consent at intake and for each new protocol. Participants age 8 years and older (in this text, "participants" refers to offspring in the study) provided written assent at each protocol point, and they provided written informed consent after they turned 18 years old. A federal Certificate of Confidentiality protected all dyads' data from subpoena.

Recruitment

As we have previously reported, from 1990 to 1993, trained interviewers recruited postpartum infant-mother dyads at Boston City Hospital for a study examining the developmental effects of intrauterine cocaine exposure (IUCE). Dyads were screened 8–72 hours after delivery to include cocaine-using and non-using mothers age 18 years or older and fluent in English, and to exclude premature delivery (<36 weeks); neonatal intensive care; congenital malformations; fetal alcohol syndrome; maternal or infant HIV; and

prenatal opiate, amphetamine, phencyclidine, barbiturate, or hallucinogen exposures (Frank et al., 2014).

Our initial, postpartum sample of eligible, consenting mothers included 252 dyads. Consenting mothers and/or subsequent caregivers, and their eligible children, were followed at several protocol points, with the following points included in the present analyses: postpartum, and ages 6, 8.5, 9.5, 10.5, 12–14.4, 14.5–16.4, 16.5–17.9, 18–20, and 21–24 years old. We administered measures for the present study at a subset of these protocol points (see *Measures* section below).

Classification of exposures

Intrauterine substance exposures for cocaine and marijuana were classified based on biological assays (maternal urine, infant urine, and meconium) and on maternal interviews conducted postpartum to estimate the amount of prenatal exposure (heavier, lighter, or none) (Frank et al., 2014). Heavier exposures reflected the sample's top quartile of maternal self-reported use or the top quartile of metabolites in meconium assays for marijuana and cocaine, for which biomarkers were available and affordable at that time. Postpartum interviews were the sole method of ascertaining exposure to tobacco and alcohol (heavier, lighter, or none). Heavier alcohol exposures reflected a report of ≥ 0.5 drinks/day; lighter use reflected a report of < 0.5 drinks/day. Heavier tobacco exposures reflected a report of ≥ 10 cigarettes per day; lighter use reflected a report of < 10 cigarettes per day.

Measures

Trained research assistants masked to the participants' intrauterine exposure status and prior assessment scores conducted each assessment.

Self-report of marijuana use initiation. Participants reported whether they had ever used marijuana or any other recreational drugs (yes/no) at each protocol point starting at ages 12–14.4 years. We used the earliest concurrently or retrospectively self-reported age at initiation in determining group membership as never users, later initiators (≥ 16 years old), or earlier initiators of marijuana use. Ages at initiation for earlier initiators ranged from 9 to 15 years; the median age was 14 years. Ages at initiation for later initiators ranged from 16 to 20 years; the median was 17 years. We used 16 years as the age cutoff because, although some authors use alternative cutoffs (Fontes et al., 2011; Pope et al., 2003; Schuster et al., 2016; Wagner et al., 2010), the most frequent cutoff we found in the relevant literature for defining later versus earlier initiators was 16 years of age (Crane et al., 2015; Gruber et al., 2012, 2014; Jacobus et al., 2015; Sagar et al., 2015; Tamm et al., 2013).

Measures of recent substance use. At each assessment starting at ages 12–14.4 years, to enhance the accuracy of

self-reporting substance use, we used urine assays to test for metabolites of marijuana, tobacco, and illicit recreational substance use. No instructions regarding abstaining from substances were given to participants before each assessment.

During the assessment at ages 21–24 years, using a Timeline Followback protocol (Fals-Stewart et al., 2000), participants self-reported the number of days of marijuana use in the past month. Negative self-reports were confirmed or disconfirmed by urine assays; 16% of 57 past-month marijuana users denied recent use on self-report but were positive by urine assay and were considered to have used marijuana. Participants also reported the number of days of high-risk drinking in the past week, defined as days when females consumed ≥ 4 or males consumed ≥ 5 alcoholic drinks (U.S. Department of Health and Human Services and U.S. Department of Agriculture, 2015). Marijuana use with concomitant, heavy alcohol use is associated with worse neuropsychological trajectories than marijuana use alone (Jacobus et al., 2015). Both measures of recent substance use at ages 21–24 years were collapsed as yes/no variables.

Learning and memory. Neuropsychological evaluation, including the WRAML/WRAML2, was conducted at ages 6–8.5 years (childhood), 14.5–16.4 years (adolescence), and 21–24 years (young adulthood). We obtained age-appropriate scaled scores for the Story Memory, Verbal Learning, Picture Memory, and Design Memory subtests at these assessments.

In Story Memory, the examiner reads two stories to the participant. Immediately after each story, the examiner asks the participant to recall as many parts of the story as possible and awards points based on the number of standard items recalled.

In Verbal Learning, the examiner reads the participant a list of simple words, and the participant immediately attempts free recall of the words. The examiner conducts four total learning trials and awards 1 point for each correctly recalled word within each trial.

In Picture Memory, the examiner shows the participant a drawing depicting a scene (a zoo, classroom, garage, or living room) for 10 seconds. Then, the examiner immediately shows a similar drawing with items in the scene changed, moved, or added. After presentation of the altered scene, the participant marks the changes, and the examiner awards 1 point for each correctly identified item. This procedure is followed for each of the four scenes.

In Design Memory, the examiner presents a card with an array of geometric shapes and sequences for 5 seconds, followed by a 10-second delay. Then, the participant draws the shapes and sequences from memory. This procedure is followed for five total cards. The examiner awards 1 point for each shape or sequence that is correctly placed and accurately drawn based on standard criteria.

Premorbid IQ. We obtained the Wechsler Intelligence Scale for Children, Third Edition (WISC-III; Wechsler,

1991), prorated full-scale IQ at age 8.5 years using the Information, Vocabulary, and Block Design subtests. These values were missing for a few participants, for whom we used preadolescent WISC-III full-scale IQ ($n = 2$) or early adolescent Wechsler Abbreviated Scales of Intelligence IQ ($n = 1$) (Wechsler, 1999), when these measurements preceded any initiation of marijuana use for these individuals.

Self-report of depression and anxiety in young adulthood.

At age 21–24 years, we evaluated depression symptoms with the Beck Depression Inventory-II (Beck et al., 1996)—a self-report measure of affective, cognitive, and somatic symptoms in the past 2 weeks—because depression symptoms are associated with worse learning performance on neuropsychological testing (Hermens et al., 2010). We also evaluated current anxiety symptoms with the Beck Anxiety Inventory (Beck & Steer, 1993), a self-report measure of anxious feelings and physiological sensations in the past week; comorbid anxiety symptoms can also affect learning performance (Kizilbash, 2002).

Other self-report. Because childhood trauma, even in children without posttraumatic stress disorder, is associated with deficits in learning and memory (Malarbi et al., 2017), we included the Violence Exposure Scale for Children–Revised, a 21-item child self-report measure assessing lifetime exposure to violent interactions as a victim or a witness at home or in community settings (Fox & Leavitt, 1995). Participants completed the measure at each assessment from age 8.5 years through ages 14.5–16.4 years. Participants were classified as having higher exposure if they were ever in the top quartile for total score; other participants were rated as having lower exposure (Barthelemy et al., 2016).

During the young-adult evaluation, participants reported whether they had attained any postsecondary education (yes/no).

Statistical analysis

We analyzed longitudinal trajectories of learning performance (mean age-adjusted scaled scores) between childhood, adolescence, and young adulthood with multivariable linear generalized estimating equation (GEE) models. We also examined bivariate relationships between intrauterine exposures and WRAML scores from childhood to adulthood in exploratory analyses to determine whether to include intrauterine exposure level in the models. Based on the low and transient number of significant associations between intrauterine exposures and WRAML scores, we decided to exclude them from the models (see Results section).

We then used two models to examine mean learning differences and trajectories based on marijuana initiation group. Independent variables for our primary GEE model included marijuana initiation group, assessment protocol point (childhood, adolescence, young adulthood), and their interaction, along with the covariates sex and pre-initiation IQ. To

examine unexpected results found in the young adulthood data, we ran a secondary model predicting cross-sectional learning differences in young adulthood. The secondary model included the primary model's predictors, as well as young-adult anxiety symptoms, depressive symptoms, and yes/no dichotomous variables: attainment of any formal postsecondary education, past-month marijuana use, and past-week high-risk drinking. We included these variables in the secondary model to examine both significant variables and any variables relevant to cognitive function identified in this section.

Results

Sample characteristics and retention

Our analytic sample was 119 (62 females), comprising 86% of the 139 individuals assessed in young adulthood. Most individuals were excluded because of missing visits or measures. Two individuals who reported initiation of marijuana use before the earliest assessment in this analysis (ages 6–8.5 years) were removed from the analysis, as were four individuals for whom no pre-initiation IQ was available. There were no significant differences between our analysis sample and the entire young adulthood sample in terms of intrauterine exposures (IUCE, alcohol, tobacco, or marijuana), maternal ethnicity, maternal education, maternal parity, child's sex, pre-initiation IQ, earlier WRAML scores, or adolescent drug use.

The analytic sample was also 47% of the initial postpartum recruitment sample of 252 dyads (73% of families returned for the 6-month visit, and 59% returned for the 6-year visit). There were no significant differences between our analysis sample and the postpartum sample in terms of intrauterine exposures (IUCE, alcohol, tobacco, or marijuana), maternal ethnicity, maternal education, maternal parity, or child's sex. Therefore, attrition did not affect how representative the analysis sample was of the recruitment sample in terms of these variables. However, data on pre-initiation IQ, earlier WRAML scores, or adolescent drug use are not available for the entire postpartum sample because of this pattern of attrition.

Bivariate analyses of intrauterine substance exposure groups

Intrauterine substance exposure variables were not significantly associated with pre-initiation IQ or with most WRAML scores in childhood, adolescence, and young adulthood in bivariate analyses (see Supplemental Tables B–F). (Supplemental material appears as an online-only addendum to this article on the journal's website.) Significant results included an association between heavier IUCE and Picture Memory in childhood, and an association between lower but not heavier

IUCE and Story Memory in young adulthood (the latter result being inconsistent with a dose-response neuroteratologic pattern). Intrauterine marijuana exposure was marginally associated with Picture Memory in childhood. These results were not found at other ages or on other measures, suggesting a lack of consistent influence of the exposures on cognitive development from childhood to adulthood.

Marijuana initiation groups

In the primary model, there were no significant differences between earlier marijuana initiators, later initiators, and never users in childhood (or pre-initiation) IQ, or in WRAML subscale scaled scores (Table 1). Group mean performances were generally in the low-average to average range for all WRAML variables at all time points. There were no significant group differences over time on Verbal Learning or Picture Memory scaled score trajectories from childhood to young adulthood (Design Memory was not assessed in young adulthood). Initiation groups significantly differed in past-month marijuana use but not in self-reported past-week high-risk drinking in young adulthood.

On Story Memory, scaled score trajectories from childhood to young adulthood differed (Figure 1), as later initiators' slopes were significantly more positive ($z = 2.67$, $p = .008$; $\beta = 1.78$, 95% CI [0.47, 3.09]) than never users' slopes; earlier initiators' slopes were nonsignificantly more negative than never users' ($z = -1.30$, $p = .20$; $\beta = -0.88$, 95% CI [-2.22, 0.45]). Exploratory analyses showed that key patterns emerged after adolescence. Earlier initiators significantly declined in Story Memory scaled score from adolescence to young adulthood ($z = -2.21$, $p = .03$; $\beta = -0.88$, 95% CI [-1.65, -0.10]). Later initiators significantly improved ($z = 2.22$, $p = .03$; $\beta = 1.04$, 95% CI [0.12, 1.95]). Never users showed no statistically significant change ($z = -0.85$, $p = .40$; $\beta = -0.44$, 95% CI [-1.46, 0.58]).

In addition, in young adulthood, later initiators attained significantly better Story Memory scaled scores than earlier initiators ($z = 3.84$, $p < .0001$; $\beta = 2.13$, 95% CI [1.04, 3.22]), as well as significantly better scores than never users ($z = 2.84$, $p = .005$; $\beta = 1.94$, 95% CI [0.60, 3.28]). Even after including additional covariates of anxiety, depression, postsecondary education, past-month marijuana use, and past-week high-risk drinking in the secondary model (see Supplemental Table A), later initiators performed significantly better than earlier initiators, although their advantage over never users was no longer statistically significant.

We performed additional analyses to examine the potential influence of outliers and to adjust for childhood learning performance, maternal ethnicity, caregiver education (highest among all caregivers from birth to adolescence), and developmental violence exposure in a subsample of 89 participants without missing covariate data. These analyses yielded similar results to those shown above.

Discussion

Current findings in this cohort of primarily African American young adults followed from birth suggest that premorbid deficits may not solely explain differences in cognitive functioning observed in adolescent marijuana users, given that IQ and performance on measures of learning and memory in childhood did not significantly differ between marijuana initiation groups. Also of note, marijuana initiation groups did not significantly differ on most learning and memory measures and at most time points. In our other primary aim, we found that marijuana initiation group trajectories did not significantly differ on measures of unstructured verbal learning (learning a word list) or structured nonverbal learning (picture learning) between childhood and young adulthood.

Trajectories of learning performance for structured verbal narratives (story learning) were better in later initiators compared to individuals with no history of marijuana use. Although overall trajectories were not significantly worse in earlier initiators than in never users, earlier initiators showed a significant within-group decline between adolescence and young adulthood, unlike the other groups. Relatively inefficient learning for earlier initiators is consistent with much of the relevant literature (Broyd et al., 2016; Lisdahl et al., 2014). Earlier initiators may require preventative intervention for cognitive, academic, and social problems associated with marijuana use. The relatively better trajectory among later initiators was unexpected and contradicts the linear temporal-sequence relationship expected under the marijuana neurotoxicity hypothesis. Later initiators may have avoided use during a sensitive period (and thus a worse learning trajectory), but improved age-adjusted learning performance is less expected than stable or declined performance.

A direct, neurocognitive benefit of later marijuana initiation is unlikely, and findings from this and other studies suggest that adolescent marijuana initiation is most often associated with either adverse effects or no effects on cognitive function. Random chance is a possible explanation for this pattern, but relatively high group mean performance (roughly 2/3 of a standard deviation higher than the other groups in young adulthood) and significantly improved within-group mean performance over time seem unlikely to be due to chance.

Unmeasured, confounding psychosocial variables may help explain current findings. In support of this suggestion, control for measured variables (anxiety, depression, postsecondary education, past-month marijuana use, and past-week high-risk drinking) rendered nonsignificant the advantage for later initiators compared with never users on Story Memory in young adulthood. Other research has found that personality (particularly, openness to experience) may mediate positive associations between marijuana use and cognitive function (Daly, 2013); perhaps later initiators in our sample

TABLE 1. Sample characteristics by marijuana initiation group

Variable		Overall (<i>N</i> = 119)	Never marijuana user (<i>n</i> = 26)	Later marijuana initiator (<i>n</i> = 31)	Earlier marijuana initiator (<i>n</i> = 62)	Statistical test ^c	<i>p</i>
Postpartum							
Sex	Female	62 (52%)	16 (62%)	16 (52%)	30 (48%)	$\chi^2(2, N = 119) = 1.27$	.53
	Male	57 (48%)	10 (38%)	15 (48%)	32 (52%)		
Maternal ethnicity	Black (U.S. born)	94 (79%)	15 (58%)	25 (81%)	54 (87%)	FET < 0.0001	.02
	Black (other)	14 (12%)	6 (23%)	5 (16%)	3 (5%)		
	White (not Hispanic)	9 (8%)	4 (15%)	1 (3%)	4 (6%)		
	Hispanic	1 (1%)	1 (4%)	0 (0%)	0 (0%)		
	Other	1 (1%)	0 (0%)	0 (0%)	1 (2%)		
Maternal years of education	<i>M</i> (<i>SD</i>)	11.51 (1.33)	11.73 (1.59)	11.32 (1.17)	11.52 (1.30)	$H \chi^2(2, N = 119) = 0.37$	.83
Intrauterine marijuana exposure	0 = unexposed	91 (76%)	23 (88%)	23 (74%)	45 (73%)	FET = 0.0014	.61
	1 = lighter	14 (12%)	1 (4%)	4 (13%)	9 (15%)		
	2 = heavier	14 (12%)	2 (8%)	4 (13%)	8 (13%)		
Intrauterine alcohol exposure	0 = unexposed	85 (71%)	18 (69%)	23 (74%)	44 (71%)	FET = 0.0027	.88
	1 = lighter	25 (21%)	6 (23%)	7 (23%)	12 (19%)		
	2 = heavier	9 (8%)	2 (8%)	1 (3%)	6 (10%)		
Intrauterine tobacco exposure	0 = unexposed	56 (47%)	15 (58%)	14 (45%)	27 (44%)	FET = 0.0004	.57
	1 = lighter	29 (24%)	7 (27%)	7 (23%)	15 (24%)		
	2 = heavier	34 (29%)	4 (15%)	10 (32%)	20 (32%)		
Intrauterine cocaine exposure	0 = unexposed	55 (46%)	12 (46%)	16 (52%)	27 (44%)	$\chi^2(4, N = 119) = 0.68$	.95
	1 = lighter	41 (34%)	9 (35%)	9 (29%)	23 (37%)		
	2 = heavier	23 (19%)	5 (19%)	6 (19%)	12 (19%)		
Age 6.5–8.5 years							
Pre-initiation IQ ^a	<i>M</i> (<i>SD</i>)	86.87 (15.25)	89.96 (17.44)	86.74 (16.07)	86.21 (13.91)	$H \chi^2(2, N = 119) = 1.08$	.58
WRAML Story Memory Scaled Score	<i>M</i> (<i>SD</i>)	8.17 (2.40)	8.10 (2.50)	7.89 (2.16)	8.35 (2.49)	$H \chi^2(2, N = 119) = 0.60$	.74
WRAML Verbal Learning Scaled Score	<i>M</i> (<i>SD</i>)	9.50 (2.65)	9.19 (2.81)	9.71 (2.79)	9.53 (2.54)	$H \chi^2(2, N = 119) = 0.08$	.96
WRAML Design Memory Scaled Score	<i>M</i> (<i>SD</i>)	8.41 (2.47)	8.31 (3.02)	8.65 (2.52)	8.34 (2.22)	$H \chi^2(2, N = 119) = 0.36$	.83
WRAML Picture Memory Scaled Score	<i>M</i> (<i>SD</i>)	9.73 (2.47)	9.54 (3.03)	9.66 (2.04)	9.85 (2.58)	$H \chi^2(2, N = 119) = 0.26$	.88
Age 14.5–16.4 years							
WRAML2 Story Memory Scaled Score	<i>M</i> (<i>SD</i>)	9.18 (2.98)	9.17 (2.82)	9.31 (2.87)	9.11 (3.15)	$H \chi^2(2, n = 107) = 0.17$	.92
WRAML2 Verbal Learning Scaled Score	<i>M</i> (<i>SD</i>)	9.72 (2.60)	9.74 (2.72)	9.79 (2.78)	9.67 (2.50)	$H \chi^2(2, n = 107) = 0.17$	.92
WRAML2 Design Memory Scaled Score	<i>M</i> (<i>SD</i>)	6.91 (2.44)	7.17 (2.23)	7.10 (2.61)	6.69 (2.46)	$H \chi^2(2, n = 107) = 1.36$	.51
WRAML2 Picture Memory Scaled Score	<i>M</i> (<i>SD</i>)	7.75 (2.59)	8.22 (2.98)	8.28 (2.42)	7.27 (2.46)	$H \chi^2(2, n = 107) = 3.79$	.15
Age 21–24 years ^b							
Ever in sample's highest quartile of violence exposure	Yes	59/119 (50%)	11/26 (42%)	12/31 (39%)	37/62 (60%)	$F(2, 548) = 2.33$	.10
Beck Anxiety Inventory total score (<i>n</i> = 106)	<i>M</i> (<i>SD</i>)	9.15 (9.71)	5.26 (4.90)	10.32 (10.63)	9.81 (10.22)	$H \chi^2(2, n = 106) = 3.50$	.17
Beck Depression Inventory-II total score (<i>n</i> = 106)	<i>M</i> (<i>SD</i>)	8.78 (8.56)	4.91 (3.72)	9.68 (9.53)	9.60 (8.92)	$H \chi^2(2, n = 106) = 3.13$	.21
Marijuana use within 30 days of assessment (self-report and urine assay; <i>n</i> = 98)	Yes	57/98 (58%)	0/18 (0%)	18/29 (62%)	39/51 (76%)	FET < 0.0001	<.01
High-risk drinking within 7 days of assessment (<i>n</i> = 97)	Yes	13/97 (13%)	2/18 (11%)	5/29 (17%)	6/50 (12%)	FET = 0.0619	.73
Any postsecondary education (<i>n</i> = 111)	Yes	55/111 (50%)	17/23 (74%)	16/30 (53%)	22/58 (38%)	$\chi^2(2, n = 111) = 5.65$	.01
WRAML2 Story Memory Scaled Score	<i>M</i> (<i>SD</i>)	8.89 (3.11)	8.79 (2.99)	10.28 (2.81)	8.15 (3.10)	$H \chi^2(2, n = 100) = 8.13$	.02
WRAML2 Verbal Learning Scaled Score	<i>M</i> (<i>SD</i>)	8.91 (2.97)	9.79 (1.87)	9.55 (2.34)	8.23 (3.45)	$H \chi^2(2, n = 100) = 3.90$	.14
WRAML2 Picture Memory Scaled Score	<i>M</i> (<i>SD</i>)	10.38 (3.15)	10.39 (3.60)	11.03 (2.87)	10.02 (3.14)	$H \chi^2(2, n = 99) = 1.57$	.46

Notes: FET = Fisher's Exact Test, *H* = Kruskal–Wallis *H* Test; WRAML = Wide Range Assessment of Memory and Learning; *F* = analysis of variance test. ^aPre-initiation IQ was determined from the Wechsler Intelligence Scales for Children (WISC-III) pro-rated full-scale IQ at age 8.5 years where available (*n* = 116); otherwise, for never users and later initiators, preadolescent WISC-III full-scale IQ (*n* = 2) or early adolescent Wechsler Abbreviated Scales of Intelligence IQ (*n* = 1) was used, as these measurements preceded any initiation of use. ^bWRAML2 Design Memory was not evaluated at age 21–24 years.

FIGURE 1. Estimated means for Story Memory scaled score, adjusted for sex and pre-initiation IQ

reflect this pattern. Or, given how normative marijuana use was in our sample, perhaps later initiation was a proxy for individuals having unmeasured familial, social, and neurocognitive protective factors preventing earlier initiation and its associated detrimental outcomes.

Specificity of this result to Story Memory is also difficult to explain. Although the structure inherent in a story can make it easier to learn than a word list, we would not expect this structure to primarily benefit later initiators to the extent that they would outperform those who denied any history of marijuana use at every assessment (and whose urine tests were negative for marijuana use in young adulthood as well). Most neuropsychological studies use word lists or stories to evaluate learning and memory, and again, they usually find adverse or no effects of adolescent marijuana use. However, one cross-sectional study of a community-based sample found better word-list memory, executive control, and social cognition in occasional users, and worse executive control in frequent users, compared with never users (Scott et al., 2017). Therefore, it is not unheard of for lighter users in some samples to display relative strengths (in our sample, later initiators reported lower recent use than earlier initiators).

Conversely, earlier initiators' poor WRAML Story Memory trajectories might reflect both neurobiological and psychological factors. Their timing of marijuana initiation may be associated with unique effects on learning. Although they reported higher recent use, earlier initiators performed worse than later initiators on Story Memory in young

adulthood after controlling for recent use in our secondary model, reducing the potential explanatory role of acute intoxication. Further, earlier marijuana initiation has cognitive and neurobiological associations independent of lifetime amount or severity of marijuana use (Crane et al., 2015; Lisdahl et al., 2014). The less optimal learning trajectories may also reflect maladaptive psychological confounds, such as familial-cultural deficits (Jackson et al., 2016) or poorer effort during testing (Hirst et al., 2017), that could have an impact independent of depression and anxiety symptoms (which we controlled for in our secondary model of young adulthood cross-sectional outcomes).

In contrast to our earlier report (Frank et al., 2011), marijuana initiation groups did not differ in level of any of the intrauterine substance exposures, possibly because of differences in independent and dependent variables and in sample composition. For example, some individuals missed a childhood assessment, leaving them eligible for the 2011 report but not the current one ($n = 25$), or were missing adolescent or young adulthood assessments, which made them ineligible for this report ($n = 4$).

Study strengths

The longitudinal design of the present study allowed for examination of more premorbid factors than most studies of adolescent marijuana use, in addition to allowing long-term follow-up of participants with known intrauterine drug exposures. As a result, we were able to identify and control for

potentially confounding risk factors for memory/cognitive dysfunction not controlled for in most prior studies, particularly premorbid memory and cognitive function. In addition, potential biases that apply to samples recruited at later ages (e.g., selection bias for children with behavior problems, retrospective recall bias leading to distorted report of past behavioral and developmental problems) are less likely. In addition, given that the present study did not involve participants selected from treatment samples with a known history of maladaptive substance use, current findings are more likely to generalize to a wider range of community-based populations.

Study limitations

Although we were able to evaluate cognitive performance associations with timing of marijuana initiation (while controlling for recent use), we were unable to examine lifetime exposure factors—such as lifetime frequency, duration, and dosage of marijuana use, as well as periods of abstinence—which are important in investigating neurotoxicity (Wagner et al., 2010). Earlier initiators may or may not use marijuana more frequently, longer (months, years), at higher doses, or without periods of abstinence; one or more of these factors could have played a role in our findings. Because many of both marijuana user groups had used marijuana within the past month of assessment, we cannot fully disaggregate the potential causal impact of recent intoxication or withdrawal. Nevertheless, earlier initiators performed similarly to never users on most learning measures (consistent with their similar premorbid functioning), except for on Story Memory, suggesting that potentially negative impacts of recent intoxication or withdrawal were often minimal. In addition, we doubt recent intoxication or withdrawal caused improved performance in later initiators (to a level of performance similar to never users on most measures and better on Story Memory).

Caution must be shown in generalizing findings from this relatively small sample of community-dwelling, low-income youth of color to other populations. Our relatively disadvantaged sample, including many individuals with intrauterine exposures, might be a higher risk group than some populations of marijuana users. However, these analyses revealed scarce and transient learning and memory differences between exposure groups.

Further, these findings may not apply to other neurocognitive domains (e.g., aspects of attention and executive function) not included in the present analysis. Examining how premorbid levels of these domains and their trajectories may correlate with, cause, and/or result from associations between marijuana initiation timing and learning performance warrants future research. Researchers may also find structural or functional neurological alterations without behavioral impairment on testing that result from the effects

of marijuana, confounding variables, or compensation for one of those factors. In addition, performance in the quiet, controlled, one-to-one laboratory testing environment may not capture learning difficulties experienced in the face of everyday distraction or stressors.

Conclusions

In this community sample of predominantly African American young adults, we found that learning performance before initiation of marijuana use was not associated with earlier initiation. Therefore, learning deficits in this study and in the literature associated with marijuana use may not stem solely from pre-existing vulnerabilities but from marijuana neurotoxicity and/or other confounding variables.

Furthermore, earlier and later marijuana use initiators did not exhibit suboptimal learning trajectories on most measures compared with those who never used. The one exception was a decline in learning performance among earlier initiators between adolescence and young adulthood. We also observed an unexpected, relatively better verbal narrative learning trajectory among later initiators; further research may elucidate the nature of this association. However, given our finding that earlier initiators may suffer suboptimal developmental learning trajectories, earlier adolescent marijuana use and/or its correlates (e.g., family psychosocial problems) may impair later neurocognitive development. This risk, in addition to other risks associated with earlier marijuana initiation—such as problematic substance use, psychosis, and underachievement in school (Crane et al., 2013; Frank et al., 2014; Hooper et al., 2014; Lisdahl et al., 2014)—necessitates early clinical intervention and public policy initiatives to delay initiation.

Acknowledgments

The authors thank the families and children for their gracious participation in this work. We have no conflicts of interest to declare.

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