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Brain activation to negative stimuli mediates a relationship between adolescent marijuana use and later emotional functioning

Mary M. Heitzeg,[a,*] Lora M. Cope,[a] Meghan E. Martz,[a,b] Jillian E. Hardee,[a] Robert A. Zucker [a,b]

[a] *Department of Psychiatry, Addiction Research Center, University of Michigan, 4250 Plymouth Road, Ann Arbor, MI 48109, USA*
[b] *Department of Psychology, University of Michigan, 2044 East Hall, 530 Church Street, Ann Arbor, MI 48108, USA*

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ABSTRACT

This work investigated the impact of heavy marijuana use during adolescence on emotional functioning, as well as the brain functional mediators of this effect. Participants (n = 40) were recruited from the Michigan Longitudinal Study (MLS). Data on marijuana use were collected prospectively beginning in childhood as part of the MLS. Participants were classified as heavy marijuana users (n = 20) or controls with minimal marijuana use. Two facets of emotional functioning—negative emotionality and resiliency (a self-regulatory mechanism)—were assessed as part of the MLS at three time points: mean age 13.4, mean age 19.6, and mean age 23.1. Functional neuroimaging data during an emotion-arousal word task were collected at mean age 20.2. Negative emotionality decreased and resiliency increased across the three time points in controls but not heavy marijuana users. Compared with controls, heavy marijuana users had less activation to negative words in temporal, prefrontal, and occipital cortices, insula, and amygdala. Activation of dorsolateral prefrontal cortex to negative words mediated an association between marijuana group and later negative emotionality. Activation of the cuneus/lingual gyrus mediated an association between marijuana group and later resiliency. Results support growing evidence that heavy marijuana use during adolescence affects later emotional outcomes.

1. Introduction

Marijuana is the most commonly used illicit drug in the United States, with 36.4% of high school seniors reporting past-year use (Miech et al., 2015). Recent trends show an increase in marijuana use coupled with a substantial decrease in perceptions of harm (Johnston et al., 2014). This is concerning given the adverse outcomes associated with marijuana use, including cognitive impairment, lower lifetime achievement, and increased risk for addiction (Hall, 2014; Volkow et al., 2014). Adolescent marijuana users may be at particular risk for adverse outcomes. Compared to adult-onset users, adolescent-onset marijuana users are more likely to experience symptoms of dependence within two years of use onset (Chen et al., 2009), are at increased risk of developing other drug dependence (Lynskey et al., 2003), and show increased deficits in executive functioning (Fontes et al., 2011). Furthermore, studies of brain functioning during cognitive tasks have demonstrated differences in brain activation and connectivity in marijuana users compared with controls (Abdullaev et al., 2010; Harding et al., 2012; Padula et al., 2007; Schweinsburg et al., 2008; Smith et al., 2010; Tapert et al., 2007), some of which are more apparent in those with adolescent-onset use (Becker et al., 2010; Gruber et al., 2012; Jager et al., 2010; Lopez-Larson et al., 2015).

Of particular relevance to the present work is evidence that marijuana use during adolescence may have long-lasting effects on emotion (see review in Chadwick et al., 2013). Marijuana use is often comorbid with mood disorders (Stinson et al., 2006; Swadi and Bobier, 2003), and facets of negative affectivity (*e.g.*, neuroticism, symptoms of depression and anxiety) have been correlated with marijuana use among both adults (Degenhardt et al., 2001; Simons and Carey, 2002) and adolescents (Miller and Plant, 2002). Although it has been suggested that these associations may be explained by the use of marijuana as self-medication for depression and anxiety symptoms (Green and Ritter, 2000; Hooshmand et al., 2012), consistent support for this interpretation is lacking (Degenhardt et al., 2003; Kandel and Chen, 2000). Indeed, emerging evidence suggests that early marijuana use may contribute to the development of depression and anxiety later in life (Chen et al., 2002; Lev-Ran et al., 2014; Patton et al., 2002; van Laar et al., 2007). This is supported in animal models, which have demonstrated that early exposure to cannabinoids disrupts emotional processes and leads to later depressive phenotypes (Bambico et al., 2010; Rubino et al., 2008) and increased social anxiety (O'Shea et al., 2006; O'Shea et al., 2004; Quinn et al., 2008; Schneider et al., 2008).

Delta-9-tetrahydrocannabinol (THC), the main psychoactive component of marijuana, binds to CB1 cannabinoid receptors in the brain. Endogenous cannabinoids are involved in the regulation of emotional responses, including mood, anxiety, and aggression (Martin et al., 2002), and laboratory studies support an acute impact of THC on mood and emotion (McDonald et al., 2003). CB1 receptor expression is highest during adolescence, dropping thereafter into adulthood with the most pronounced decreases observed in limbic regions critically involved in emotion regulation (Heng et al., 2011). Thus, adolescent exposure to THC may have lasting consequences on the developing brain that specifically impact the regulation of emotion. Some sup-

* Corresponding author.
Email addresses: mheitzeg@umich.edu (M.M. Heitzeg); lcope@umich.edu (L.M. Cope); mmartz@umich.edu (M.E. Martz); jhardee@umich.edu (J.E. Hardee); zuckerra@umich.edu (R.A. Zucker)

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port for this comes from structural imaging studies showing volumetric differences in adolescent marijuana users compared with controls in limbic regions, including the amygdala, hippocampus, and insula (Ashtari et al., 2011; Lopez-Larson et al., 2011; McQueeny et al., 2011). For example, larger amygdala volumes were observed in female marijuana users compared with controls, which was further associated with depression and anxiety symptoms (McQueeny et al., 2011). Other work has observed that marijuana users have differences in cerebral blood flow and resting connectivity compared with controls in brain regions involved in emotion, including the insula and temporal cortex (Jacobus et al., 2012; Pujol et al., 2014).

Together, the evidence supports an association between marijuana use during adolescence and an alteration of the neural systems supporting emotion regulation. However, to date only one study has investigated the effects of marijuana use on brain functioning during an emotion task. This study of adult heavy marijuana smokers found decreases in anterior cingulate and amygdala activation during the viewing of masked affective faces, suggesting a difference in the way marijuana users process emotional information (Gruber et al., 2009). To date, no studies have investigated how the use of marijuana specifically during adolescence impacts these processes; thus, one goal of the current study was to address this gap by investigating brain functioning during emotion arousal in 17–22 year-old heavy marijuana smokers who began their use earlier in adolescence. Furthermore, although there is evidence for a prospective relationship between early marijuana smoking and later negative emotionality (Chen et al., 2002; Lev-Ran et al., 2014; Patton et al., 2002; van Laar et al., 2007), the literature regarding the intermediary brain processes in this relationship has been less clear. The work reviewed above has been cross-sectional, and consequently, inferences cannot be made regarding causal relationships among history of marijuana use, brain functioning, and negative affect. Therefore, this study uses a prospective design to better address the nature of the relationship and to investigate whether emotion-related brain function in late adolescence/emerging adulthood mediates a relationship between prior marijuana use and later emotional functioning.

We investigate two facets of emotional functioning, which are grounded in the temperament and personality literature—negative emotionality and resiliency (Eisenberg et al., 2000; Eisenberg et al., 1997a; Eisenberg et al., 1997b; Eisenberg and Spinrad, 2004; Eisenberg et al., 2003). Negative emotionality is the propensity to experience depressed mood, anxiety, and irritable anger. Resiliency is the ability to flexibly adapt one's level of control—in either direction—in response to the demands of the environment. It involves thoughtful, deliberate control of behavior in challenging or stressful circumstances and freer expression in circumstances where it is appropriate (Eisenberg et al., 2000; Eisenberg et al., 1997a; Eisenberg et al., 1997b; Eisenberg and Spinrad, 2004; Eisenberg et al., 2003). This type of self-regulation is a critical aspect of emotional regulation (Eisenberg et al., 2010; Eisenberg and Sulik, 2012). Note that the construct of resiliency is not directly related to the idea of resilience to adversity. Rather, resiliency has its conceptual roots in the temperament-based work of the Blocks (*e.g.*, Block and Block, 1980b), who identified the related construct of ego resiliency.

Using a prospective, longitudinal design, we investigate negative emotionality and resiliency measured at three time points: (1) at the approximate age when the heavy marijuana smokers initiated use (age 13, on average); (2) within one year prior to participation in the functional magnetic resonance imaging (fMRI) study of emotion arousal (age 20, on average); and (3) approximately three years after basis from age 11 up to the time of participation in the fMRI study. This design allows us to investigate the impact of marijuana use during adolescence on the development of negative emotionality and resiliency and on emotion-related brain function, and to investigate whether emotion-related brain function mediates a relationship between prior marijuana use and later emotional functioning.

2. Materials and methods

2.1. Participants

Forty participants were selected from an ongoing fMRI study of adolescents and young adults recruited from the Michigan Longitudinal Study (MLS). The MLS is an ongoing, prospective community-recruited study of families with parental alcohol use disorder (AUD) along with a contrast sample of families without AUD drawn from the same neighborhoods (Zucker et al., 1996; Zucker et al., 2000). All parent diagnoses were ascertained by a clinical psychologist based on Diagnostic Interview Schedule – Version 4 (Robins et al., 2000) and established at time of recruitment and *via* multiple face-to-face diagnostic assessments of the parents over the course of the youth's life. Families in which the target offspring exhibited signs of fetal alcohol syndrome (FAS) were excluded from the original ascertainment. Exclusionary FAS characteristics included prenatal or postnatal growth retardation or both, central nervous system involvement, and characteristic facial dysmorphology (Loukas et al., 2001; Sokol and Clarren, 1989). From the time of enrollment, all family members are assessed at 3-year intervals with an extensive psychosocial battery of measures assessing temperament, behavioral symptomatology, IQ, school performance, social interaction, *etc*. During the 11–26 year-old period, all offspring are also assessed annually on substance use and problems. Full details on the prospective assessment and data collection protocol in the MLS can be found elsewhere (Zucker et al., 1996).

One hundred and thirty 17–22 year old offspring from the MLS have completed an emotion arousal task during fMRI (described below). Exclusionary criteria for the fMRI study included neurological, acute, uncorrected, or chronic medical illness, current or recent (within 6 months) treatment with centrally active medications, or history of psychosis in first-degree relatives. The presence of most active primary Axis I disorders was also exclusionary; this did not include unmedicated mood and anxiety disorders, antisocial personality disorder, or substance use disorder. These were allowed because their exclusion would preferentially eliminate part of the phenomena of interest. Diagnosis was determined using the Diagnostic Interview Schedule-Child (Costello et al., 1984) for participants under the age of 18 and the Diagnostic Interview Schedule-Version IV for participants 18 and older (Robins et al., 2000). All participants were right-handed as determined with the Edinburgh Handedness Inventory (Oldfield, 1971).

Participants were told to abstain from alcohol and illicit substances/recreational drugs for 48 h prior to scanning. Participants were given a multi-drug 5-panel urine screen before scanning. Because THC metabolites are detectible in urine for a week or longer, if a participant tested positive for marijuana, we relied on self-report regarding abstinence in the 2 days prior to the study; in this case, report of marijuana use in the prior 48 h was exclusionary. Three participants included in this study tested positive for marijuana (see Table 1). All analyses were performed without the three participants who tested positive for marijuana and results were substantively the same.

Study materials and procedures were approved by the University of Michigan Medical School Institutional Review Board. All partici-

participation in the fMRI study (age 23, on average). Information on occasions of marijuana use was collected prospectively on an annual

pants over the age of 18 provided written informed consent after ex-

Table 1
Demographic, substance use, and emotional functioning variables.

	Controls (n = 20)	Heavy Users (n = 20)	All Subjects (n = 40)	Group Comparison Statistics
Females	n = 6	n = 8	n = 14	p = .741[a]
Age	20.51 (1.26)	19.84 (1.45)	20.17 (1.38)	$t(38)$ = 1.57 p = .124
Family History AUD – parent lifetime	n = 17	n = 15	n = 32	p = .695[a]
Family History AUD – child's lifetime	n = 14	n = 14	n = 28	p = 1.000[a]
Full Scale IQ[b]	109.69 (11.00)	104.78 (8.92)	107.17 (10.16)	$t(35)$ = 1.50 p = .144
Substance use measures				
Lifetime marijuana occasions	2.19 (2.85)	618.12 (430.41)	310.15 (433.05)	**Z = 5.45 p < .001**[c]
Age first marijuana	17.7 (2.5)[d]	13.4 (2.7)	15.0 (3.33)	**Z = 3.66 p < .001**[c]
Marijuana frequency/year	0.9 (1.4)[d]	112.1 (84.4)	56.5 (81.5)	**Z = 5.45 p < .001**[c]
Positive drug screen (marijuana)	n = 0	n = 3	n = 3	p = .231[a]
Age first drink	14.4 (3.4)	13.4 (2.0)	13.9 (2.78)	$t(38)$ = 1.16 p = .253
Drinks per year	357.4 (230.84)	466.0 (303.00)	411.7 (271.51)	$t(38)$ = 1.28 p = .210
Binge drink occasions/year	24.0 (30.80)	38.8 (45.94)	32.2 (39.51)	Z = 1.00 p = .327[c]
Lifetime smoker	n = 16	n = 15	n = 31	p = 1.000[a]
Current smoker	n = 6	n = 7	n = 13	p = 1.000[a]
DSM diagnosis				
Antisocial personality disorder	n = 4	n = 7	n = 11	p = .480[a]
Mood or anxiety disorders	n = 4	n = 6	n = 10	p = .716[a]
Alcohol use disorder	n = 3	n = 7	n = 10	p = .273[a]
Marijuana use disorder	n = 0	n = 4	n = 4	p = .106[a]
Nicotine dependence	n = 1	n = 3	n = 4	p = .605[a]
Other drug use disorder	n = 0	n = 1	n = 1	p = 1.000[a]
Any disorder	n = 8	n = 10	n = 18	p = .516[a]
Q-sort				
Initiation – Age 13.4 (1.3)				
Resiliency	5.63 (0.93)	5.84 (1.01)	5.63 (0.96)	$t(38)$ = 0.669 p = .507
Negative emotionality	4.01 (1.29)	4.42 (1.30)	4.01 (1.29)	$t(38)$ = 1.005 p = .321
Scan – Age 19.6 (2.3)				
Resiliency	6.32 (1.09)	5.39 (0.81)	6.33 (1.09)	**$t(38)$ = 3.09 p = .004**
Negative emotionality	3.88 (1.19)	4.83 (0.92)	3.88 (1.19)	**$t(38)$ = 2.84 p = .007**
Follow-up – Age 23.0 (1.5)				
Resiliency	7.14 (0.80)	5.96 (1.21)	6.62 (1.15)	**$t(30)$ = 3.31 p = .002**
Negative emotionality	3.12 (0.92)	4.24 (1.18)	3.61 (1.17)	**$t(30)$ = 3.00 p = .005**

Significant differences are denoted in bold.

[a] 2-sided Fisher's Exact Test.

[b] Wechsler Intelligence Scale (n = 37; data missing for 2 controls and 1 heavy user).

[c] Mann–Whitney U test.

[d] n = 12.

planation of the experimental protocol. Participants under the age of 18 signed their assent to participate in the study and at least one parent gave written informed consent.

marijuana use and emotional functioning were collected prospectively beginning in childhood as part of the MLS. Functional neuroimaging data were collected at one time point (between the ages of 17 and 22). Of the 130 MLS offspring in the fMRI study, 15% reported heavy marijuana use (>100 lifetime occasions) up until the age of participation in the fMRI study. These participants comprised the heavy marijuana user group (n = 20). We matched 20 controls with minimal (1–10 lifetime occasions) or no marijuana use to the heavy marijuana user group. Because marijuana use is highly comorbid with alcohol and other drug use (Degenhardt et al., 2001; Kandel et al., 2001; Martin et al., 1996), we took steps to reduce the potential confound of other substance use by identifying controls with similar alcohol and nicotine use profiles as the heavy marijuana users. No heavy marijuana users reported consuming fewer than 100 lifetime drinks; therefore, <100 lifetime drinks was exclusionary for the control group. From the remaining participants, 20 controls were individually matched to the heavy marijuana group based on age at the time of the fMRI scan (within 1 year) and parental AUD during the participant's lifetime. Binge drinking history, smoking status, and gender were matched across groups as closely as possible. See Table 1 for demographic, substance use, and diagnostic characteristics for the final control group (n = 20) compared with the heavy marijuana user group (n = 20).

2.2. Measures

2.2.1. Substance use

Between ages 6 and 10, alcohol and drug use was assessed at 3-year intervals with a health and daily living questionnaire as part of the MLS. Specifically, children were asked if they ever used marijuana, had more than a sip of alcohol, smoked cigarettes, or used other drugs. If yes, the age at which this occurred and quantity/frequency of use were recorded. Beginning at age 11, substance use was assessed annually using the self-report Drinking and Drug History Form for Children (Zucker and Fitzgerald, 1994). This form provides measures of quantity and frequency of alcohol and nicotine use and frequency of marijuana and other illicit drug use.

2.2.2. Emotional functioning

The California Q-Sort (Block and Block, 1980a) is an examiner-rated measure that permits the observer to systematically describe the subject's personality and functioning with a standardized language. It is collected at 3-year intervals as part of the MLS beginning at ages 6–8. It is completed by clinically-trained assessors following a 3–4 h session with the subject (Shedler and Block, 1990). Specifically, 100 statements that portray a variety of behavioral adaptations are placed in a forced-choice, nine-category normal distribution by assigning rankings to the statements, ranging from 1 (least descriptive of the subject) to 9 (most descriptive). Scores for negative emotionality and resiliency were derived from the Q-Sort based on Eisenberg et al. (2003). Negative emotionality is the propensity to experience depressed mood, anxiety, and irritable anger. The negative emotionality subscale is based on 11 items with sample statements including: "*fearful/anxious*," "*brood/worry*" and "*cries easily*." Resiliency is the ability to flexibly adapt one's level of control in response to the environment. The resiliency subscale is based on 23 items with sample statements including: "*responds to reason*," "*responds to humor*" and

The focus of the current work is to investigate the impact of a history of marijuana use during adolescence on emotional functioning and brain functional mediators of this effect. Information regarding

"*curious/exploring*." Consistent with prior work (Eisenberg et al., 1996), both negative emotionality and resiliency had adequate internal consistency (Cronbach's α = .88 and .70, respectively). Lower scores on negative emotionality and higher scores on resiliency indicate more adaptive traits.

Q-Sort scores from three time periods were of interest in the present study: (1) scores collected closest to the time of first marijuana use in the heavy user group ("initiation"—mean age 13.4 ± 1.3); (2) most recent scores before the time of fMRI scan ("scan"—mean age 19.6 ± 2.3); and (3) scores collected at least 1 year after the fMRI scan ("follow-up"—mean age 23.1 ± 1.6). Follow-up scores were available for 32 participants (heavy users n = 14; controls n = 18). A Fisher's exact test (2-sided) did not reveal a significant difference between groups on likelihood of available follow-up data (p = .235).

2.2.3. fMRI paradigm

Emotion processing was probed using an emotion-arousal word task (Glaser et al., 2014; Heitzeg et al., 2008; Hsu et al., 2010; Hsu et al., 2012; Mickey et al., 2011). Words were selected from the Affective Norms for English Words (Bradley and Lang, 1999), which provides norms for two dimensions (valence and arousal) on scales of 1–9. For valence, 1 indicates negative and 9 indicates positive; for arousal, 1 indicates low and 9 indicates high. Thirty-six words were selected based on published valence and arousal norms (Bradley and Lang, 1999) for three conditions: negative (valence < 3, arousal > 5; *e.g.*, *war, danger, gloom, ugly*), neutral (4.5 < valence < 5.5, arousal > 2; *e.g.*, *time, table, lawn, pencil*), and positive (valence > 7, arousal > 5; *e.g.*, *soft, hope, bright, love*).

Words were presented in a blocked design. Each block had 6 trials (single word presentations) lasting 4 s: 3 s of stimulus-on and 1 s of stimulus-off (during which a fixation mark appeared in the middle of the screen). For each trial, participants were instructed to press a button if they understood the word. After each block, participants were instructed to relax and continue looking at a blank screen for 18 s. There were 3 runs, each with 6 blocks—2 blocks of each condition (positive, negative, neutral)—counterbalanced using a Latin Squares design, for a total of 6 blocks (36 words) per condition across the entire experiment. The task lasted 12 min and 36 s.

After the scan, participants completed a questionnaire on 54 words, 36 of which had been presented in the scanner. Equal numbers of words were included across conditions (positive, negative, and neutral). For each word, participants were instructed to identify whether they recognized the word as being from the scanner task and also rate its emotional valence and arousal on 9-point scales identical to that of the Affective Norms for English Words (Bradley and Lang, 1999). Two memory metrics were calculated from this questionnaire: (1) Recognition performance for each word type was calculated by adjusting hit rate (p) with false alarm rate (fp) using the formula $(p - fp)/(1 - fp)$ (Epstein et al., 2006); and (2) Memory bias was calculated by subtracting recognition performance for neutral words from that for negative words and for positive words. One participant from the control group did not complete more than 80% of the valence ratings and two participants did not complete more than 80% of the arousal ratings; therefore, their data are not included in analyses.

2.2.4. fMRI data acquisition

Participants were scanned on a 3.0T GE Signa scanner (GE Healthcare) using a T2*-weighted single-shot combined spiral in/out

2.3. Data analysis

2.3.1. Group comparisons

Independent samples t-tests (controls *vs*. heavy marijuana users) were computed for normally-distributed demographic and substance use (drinks per year and age of first drink) variables. For data with skewed (age of first marijuana use and binge drink occasions per year) or bimodal (lifetime marijuana use occasions and marijuana frequency per year) distributions, independent-samples Mann–Whitney U tests were used to test for group differences. Fisher's exact tests were computed for the categorical variables. Mixed-effects ANOVAs were computed for recognition, memory bias, valence, and arousal measures with word type (positive, negative, neutral) as a within-subjects factor and group as a between-subjects factor.

To determine whether trajectories of emotional functioning differed between groups, mixed-effects ANOVAs were used, with time point (initiation, scan, follow-up) as a within-subjects factor and group as a between-subjects factor. Tests of within-subjects contrasts investigated linear and quadratic trends in the data across the time points. Post hoc t-tests investigated group differences at each time point, using Bonferroni correction for 6 comparisons (3 time points each for resiliency and negative emotionality; α = .008). Resiliency and negative emotionality data were normally distributed at each time point (kurtosis and skewness > −1.0 and < 1.0) and did not violate assumptions of homogeneity of variance (Levene's test p's > .07) or sphericity of the covariance matrix (Mauchley's test p's > .27).

2.3.2. fMRI data preprocessing

Functional images were reconstructed using an iterative algorithm (Fessler et al., 2005). Runs exceeding 2 mm translation or 2° rotation in any direction were removed. In the current sample, 4 runs (3.3%) were removed due to motion (heavy marijuana users: 2 runs; controls: 2 runs). For the remaining data, subject head motion was corrected using FSL 5.0.2.2 (Analysis Group, FMRIB, Oxford, United Kingdom) (Jenkinson et al., 2002). Slice timing corrections, normalization, and smoothing were conducted in SPM8 (Wellcome Department of Imaging Neuroscience, London, UK). Functional images were spatially normalized to the Montreal Neurological Institute (MNI) template and smoothed with a 6 mm full-width half-maximum Gaussian spatial smoothing kernel to improve signal-to-noise ratio and account for differences in anatomy. Low frequency noise was removed with a high-pass filter (128 s).

2.3.3. Individual subject statistical maps

Individual analyses were completed using a general linear model. Negative, neutral, and positive words were modeled separately with the canonical hemodynamic response function. Six motion parameters and white matter signal intensity were modeled as nuisance regressors to remove residual motion artifacts and capture non-task-related noise, respectively. Two contrasts of interest were modeled: negative words *vs*. neutral words (NEG) and positive words *vs*. neutral words (POS).

sequence (Glover and Law, 2001; repetition time [TR] = 2000 ms; echo time [TE] = 30 ms; flip angle = 90°; field of view [FOV] = 200 mm; 64 × 64 matrix; in plane resolution = 3.12 × 3.12 mm; slice thickness = 4 mm). In addition, a high-resolution anatomical T1-weighted scan was obtained (TR = 25 ms; minimum TE; FOV = 25 cm; 256 × 256 matrix; slice thickness = 1.4 mm). Motion was minimized with foam padding around the head and participants were instructed on the importance of remaining still before the session and between blocks.

2.3.4. fMRI group analyses

Independent samples *t*-tests were conducted in SPM8 to detect differences in brain activation to emotional stimuli between heavy marijuana users and controls. Type I error was controlled at $\alpha = .05$ by establishing the statistical significance threshold at $p < .005$, uncorrected for multiple comparisons, with a 77 voxel extent, based on simulation results generated by AlphaSim in AFNI (Cox, 1996). Average beta weights from eight clusters showing a significant difference between groups (see Section 3.3 and Table 3) were extracted using MarsBaR (Brett et al., 2002) and imported into IBM SPSS Statistics v22 (IBM Corporation, 2013) for further analysis.

In addition, amygdala activation was examined based on a prior study of marijuana use and emotional processing (Gruber et al., 2009). A mask of left and right amygdala was created using the automated anatomical labeling atlas (Tzourio-Mazoyer et al., 2002) in Wake Forest University Pickatlas (Maldjian et al., 2003, 2004). A threshold of $p < .05$ was used.

2.3.5. Regression and mediation

Partial correlations were conducted in SPSS between regions with significant group differences and: (1) emotional functioning (*i.e.*, resiliency and negative emotionality) at the time of scan (controlling for emotional functioning at age of initiation) and (2) emotional functioning at follow-up (controlling for emotional functioning at time of scan). Significance was established at $\alpha = .005$ (Bonferroni-corrected for multiple comparisons across 10 brain regions – see Table 3).

Regions with significant partial correlations with follow-up emotional functioning (controlling for emotional functioning at the time of the scan) were included in mediation analyses. To investigate the hypothesis that heavy marijuana use is related to less adaptive outcomes through effects on emotion arousal circuitry, a bias-corrected bootstrapped indirect effect analysis was conducted using an SPSS macro (Preacher et al., 2007). Group (heavy marijuana users or controls) was the independent variable, brain activation during emotion arousal was the mediator, and follow-up emotional functioning was the dependent variable. Emotional functioning at the time of the scan was included as a covariate. Bootstrapping (10,000 resamples) was performed to determine bias-corrected 95% confidence intervals (Preacher and Hayes, 2004).

3. Results

3.1. Group comparisons

Group comparison results for demographic, substance use, and emotional functioning variables are reported in Table 1. The groups did not differ on age at scan, full-scale IQ, family history of AUD, or substance use other than marijuana use.

Post-scanning questionnaire (*i.e.*, valence, arousal, recognition performance, and memory bias) scores (means and standard deviations) and statistics (2 [group] × 3 [word type] mixed-effects ANOVA) are reported in Table 2. For valence, there was a significant main effect of word type, no main effect of group, and no interaction. For arousal, there was a significant main effect of word type, no main effect of group, and no interaction. Similar to other studies, negative words were not rated differently in arousal than neutral words (Glaser et al., 2014; Heitzeg et al., 2008). For recognition performance, there was a significant main effect of word type, no main effect of group, and no interaction. Finally, for memory bias (2 [group] × 2 [word type] mixed-effects ANOVA), there were no significant main effects or interactions.

3.2. Trajectories of emotional functioning

Trajectories of emotional functioning are illustrated in Fig. 1a. For resiliency, there was a significant linear effect of time point ($F_{1,30} = 18.86$, $p < .001$), a main effect of group (controls > heavy marijuana users; $F_{1,30} = 8.86$, $p = .006$), and a group × time point interaction ($F_{1,30} = 8.44$, $p = .007$). Post hoc *t*-tests found that groups were not significantly different on resiliency at age of initiation but differed at scan time and at follow-up (see Table 1 and Fig. 1a). Exploratory one-way repeated-measures ANOVAs conducted in each group separately revealed that resiliency showed a linear increase across the time points in the control group ($F_{1,17} = 29.74$, $p < .001$),

Table 2
Post-scanning questionnaire scores.

	Controls	Heavy users	All subjects	Main effect of group	Main effect of word type	Interaction
Valence				$F(1,37) = 3.13$, $p = .085$	**$F(2,74) = 184.76$, $p < .001$**	$F(2,74) = 0.31$, $p = .734$
Positive	7.10 (1.08)	7.03 (1.13)	7.06 (1.09)		**Pos > Neu** $p < .001$	
Negative	2.82 (1.17)	2.38 (1.09)	2.59 (1.14)		**Pos > Neg** $p < .001$	
Neutral	5.17 (0.28)	4.87 (0.69)	5.02 (0.54)		**Neu > Neg** $p < .001$	
Arousal				$F(1,36) = 1.15$, $p = .290$	**$F(2,72) = 38.15$, $p < .001$**	$F(2,72) = 1.00$, $p = .371$
Positive	6.23 (1.35)	6.36 (1.23)	6.30 (1.27)		**Pos > Neu** $p < .001$	
Negative	4.33 (1.39)	3.74 (1.83)	4.02 (1.64)		**Pos > Neg** $p < .001$	
Neutral	4.59 (1.10)	4.05 (1.28)	4.30 (1.22)		Neu > Neg $p = 1.000$	
Recognition performance				$F(1,38) = 0.16$, $p = .689$	**$F(2,76) = 3.48$, $p = .036$**	$F(2,76) = 0.34$, $p = .711$

Positive	.55 (.21)	.61 (.27)	.58 (.24)		Pos > Neu p = .056	
Negative	.61 (.39)	.59 (.38)	.60 (.38)		Neg > Pos p = 1.000	
Neutral	.42 (.34)	.48 (.36)	.45 (.34)		Neg > Neu p = .098	
Memory bias				$F(1,38) = 0.15$, $p = .705$	$F(1,38) = 0.11$, $p = .740$	$F(1,38) = 0.51$, $p = .478$
Positive	.12 (.27)	.13 (.38)	.13 (.32)			
Negative	.19 (.48)	.11 (.35)	.15 (.42)			

Note: Numbers for *controls*, *heavy users*, and *all subjects* are means, with standard deviations in parentheses. Main effects and interactions were tested with separate 2 (group) × 3 (word type) mixed-effects ANOVA. Significant *F*-tests were followed with post hoc pairwise comparisons using Bonferroni correction. For all main effects and interactions, significant results are denoted in bold.

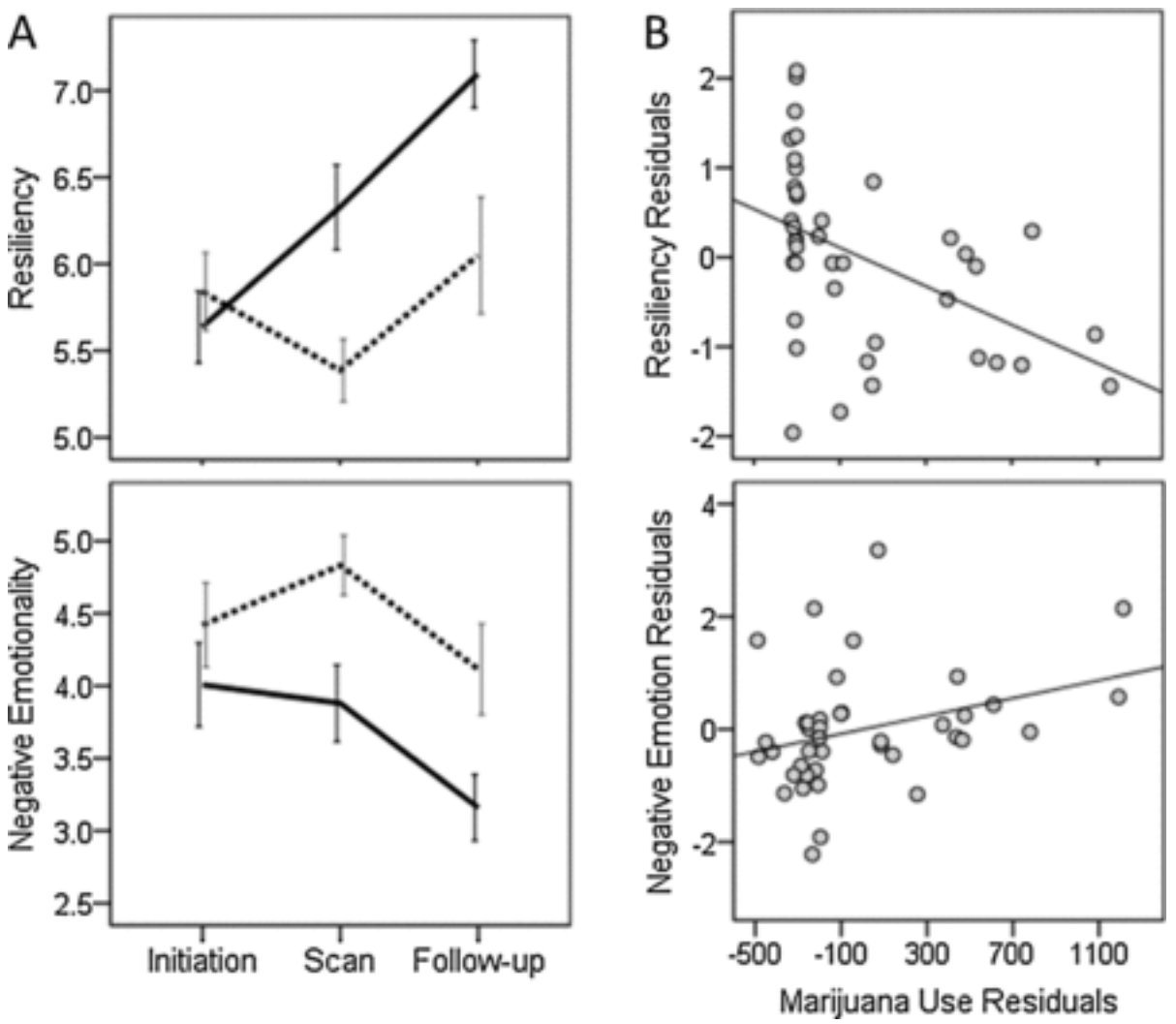


Fig. 1. (A) Trajectories of resiliency (top) and negative emotionality (bottom), from initiation to follow-up, in heavy users (dotted line) and controls (solid line). Resiliency increased across time points in the control group but not the heavy marijuana users. For negative emotionality there was a significant linear effect of time point (decreasing) in controls but not heavy marijuana users. (B) Partial regression plots showing association between lifetime occasions of marijuana use until time of scan and resiliency (top) and negative emotionality (bottom) at time of scan, controlling for measures at initiation.

but not in the heavy marijuana user group ($F_{1,13} = 0.93$, $p = .352$). No significant quadratic effects were observed (p's > .090).

For negative emotionality, there was a significant linear effect of time point ($F_{1,30} = 4.78$, $p = .037$), a main effect of group (heavy marijuana users > controls; $F_{1,30} = 12.36$, $p = .001$), but no group × time point interaction ($F_{1,30} = 0.62$, $p = .435$). Post hoc t-tests found that groups were not significantly different on negative emotionality at age of initiation but differed at scan time and at follow-up (see Table 1 and Fig. 1a). Although there was not a significant interaction, exploratory one-way repeated-measures ANOVAs conducted in each group separately revealed a significant linear effect of time for negative emotionality (decreasing) in controls ($F_{1,17} = 5.23$, $p = .035$), but not heavy marijuana users ($F_{1,13} = 0.83$, $p = .378$). No significant quadratic effects were observed (p's > .110).

3.3. Brain imaging

In the whole-brain two-sample t-test, the heavy marijuana users had less activation compared with controls during NEG in four clusters: (1) right middle frontal and dorsolateral superior frontal gyri (caudal dlPFC; Fig. 3a and b), (2) right middle and superior temporal gyri (MTG/STG), (3) right calcarine fissure and surrounding cortex, including cuneus and lingual gyri (cuneus/lingual; Fig. 3c), and (4) right superior temporal gyrus and insula (STG/insula; Fig. 2a). During POS, heavy users had less activation in the right inferior parietal lobe (IPL) and increased activation in the right dorsolateral superior frontal gyrus (dlPFC) relative to controls. In the amygdala region-of-interest analyses, heavy users had less activation in the right and left (Fig. 2b) amygdalae during NEG and in the right (Fig. 2c) and left amygdalae during POS compared with controls. See Table 3 for all

Further exploratory analyses were conducted to investigate the impact of lifetime occasions of marijuana use on emotional functioning over time. These analyses focused on the interval between initiation and the time of scan. Nonparametric partial correlations (Spearman's) were conducted between lifetime occasions of marijuana use until time of scan and each emotional functioning measure at scan age, controlling for emotional functioning at initiation age. A significant negative correlation was observed between marijuana use and resiliency (rho = −.51, df = 37, p = .001); a significant positive correlation was observed between marijuana use and negative emotionality (rho = .34, df = 37, p = .037). Partial regression plots are provided in Fig. 1b.

whole brain and region of interest results. To determine whether differences in activation to neutral words were impacting these group differences, we conducted an independent samples t-test in SPM8 using the contrast of neutral words *vs*. rest. There were no differences between heavy marijuana users and controls.

3.4. Regression

Partial correlations between brain activation and emotional functioning at scan time and at follow-up are reported in Table 4. There were negative correlations between negative emotionality measured at scan time and activation in right STG/insula (Fig. 2a) and left amygdala (Fig. 2b) during NEG. There was also a negative correla-

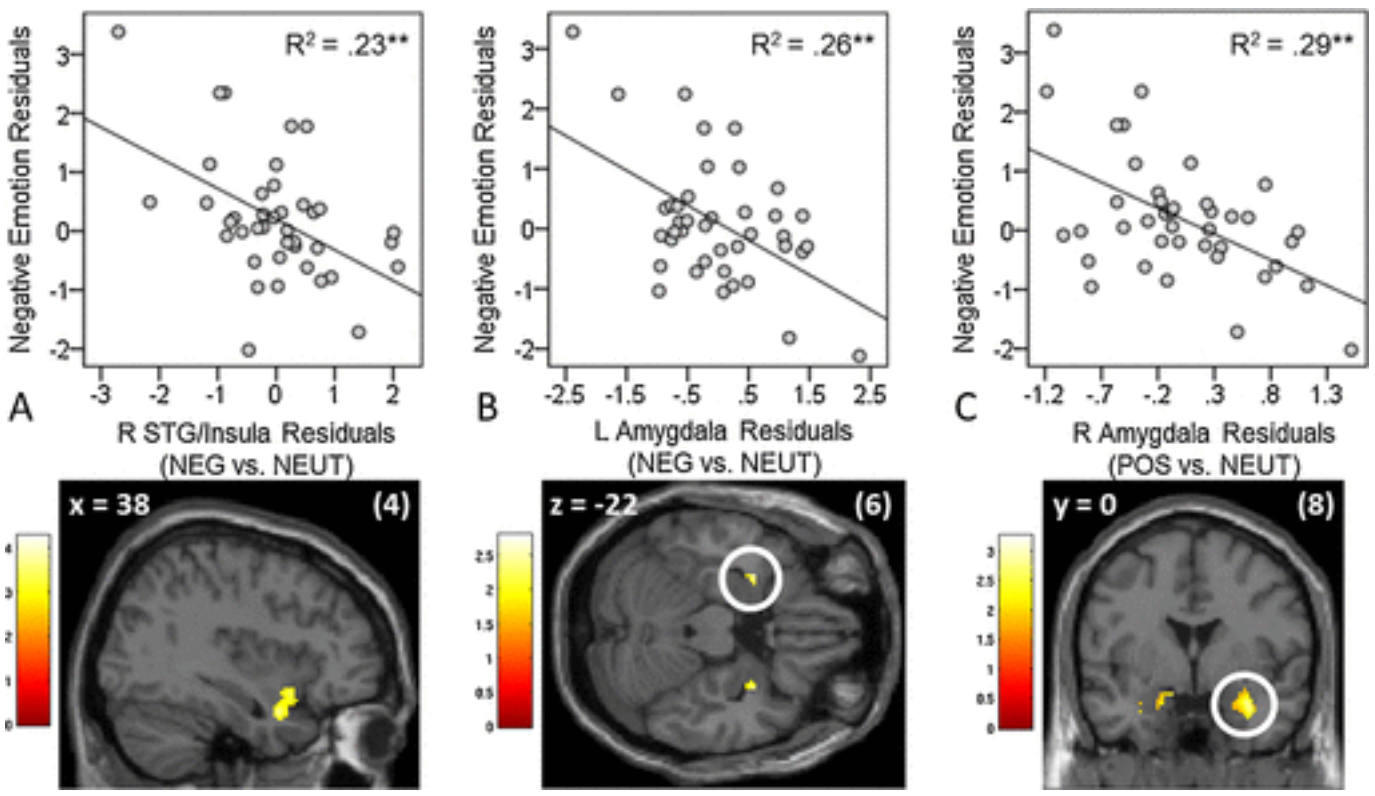


Fig. 2. (A) Partial correlation between negative emotionality measured at scan time and activation in right STG/insula during NEG (negative *vs*. neutral words), controlling for negative emotionality measured at initiation (top). BOLD activation in the right STG/insula (cluster 4 in Table 3), centered at x = 38, y = 6, z = −24 (bottom). (B) Partial correlation between negative emotionality measured at scan time and activation in left amygdala during NEG, controlling for negative emotionality measured at initiation (top). BOLD activation in the left amygdala (cluster 6 in Table 3), centered at x = −30, y = 2, z = −22 (bottom). (C) Partial correlation between negative emotionality at scan time and activation in right amygdala during POS (positive *vs*. neutral words), controlling for negative emotionality at measured at initiation (top). BOLD activation in the right amygdala (cluster 8 in Table 3), centered at x = 32, y = 0, z = −22 (bottom). Coordinates are in MNI space; color bar represents t-values. **p < .01.

Table 3
Brain imaging group comparison results.

Cluster	Label	Cluster size	BA	x	y	z	t-Value	Peak-level p-value (unc.)
NEG: Controls > Heavy Users								
1	R caudal dlPFC	243	8	30	10	40	4.29	<.001
			6	20	8	64	4.10	<.001
2	R MTG/STG	103	21	62	−4	−18	3.84	<.001
			38	46	0	−14	3.47	.001
3	R Cuneus/Lingual	102	17	16	−84	2	3.62	<.001
			18	8	−84	−2	3.18	.001
4	R STG/Insula	96	38	38	6	−24	3.60	<.001

Table 4
Emotional functioning correlations with brain clusters.

	Time of scan (age 19.6) n = 40				Follow-up (age 23.1) n = 32			
	Resiliency[a,c]		Negative Emotionality[a,c]		Resiliency[b,c]		Negative Emotionality[b,c]	
	r	p	r	p	r	p	r	p
Negative *vs*. Neutral (NEG)								
R caudal dlPFC	.05	.757	−.14	.385	**.54**	**.002**	**−.51**	**.004**
R MTG/STG	.22	.177	−.15	.356	.33	.071	−.22	.241
R Cuneus/Lingual	.22	.173	−.23	.157	**.60**	**<.001**	−.45	.011
R STG/Insula	.22	.181	**−.48**	**.002**	.24	.196	−.23	.213
R Amygdala	.08	.632	−.38	.018	.30	.099	−.23	.210
L Amygdala	.28	.087	**−.51**	**.001**	−.09	.642	.09	.640
Positive *vs*. Neutral (POS)								
R dlPFC	−.09	.580	.13	.426	−.33	.067	.30	.102
R IPL	.39	.015	−.25	.118	.12	.508	.01	.972
R Amygdala	.30	.065	**−.53**	**<.001**	.15	.417	−.16	.406

			13	38	12	−14	3.28	.001
5	R Amygdala[a]	67	–	36	2	−24	2.81	.004
6	L Amygdala[a]	17	–	−30	2	−22	2.48	.009
POS: Controls > Heavy Users								
7	R IPL	81	40	54	−30	52	3.54	.001
8	R Amygdala[a]	117	–	32	0	−22	2.79	.004
9	L Amygdala[a]	62	–	−16	−4	−18	3.26	.001
POS: Heavy Users > Controls								
10	R dlPFC	101	9	20	58	32	4.30	<.001

MFG, middle frontal gyrus; DLPFC, dorsolateral prefrontal cortex; MTG, middle temporal gyrus; STG, superior temporal gyrus; IPL, inferior parietal lobe; BA, Brodmann area; R, right hemisphere; n.s., not significant.

[a] *a priori* regions of interest.

tion between negative emotionality at scan time and activation in right amygdala during POS (Fig. 2c).

Positive correlations were observed between resiliency measured at follow-up and activation in caudal dlPFC and cuneus/lingual gyrus

L Amygdala	.37	.022	−.24	.149	−.20	.281	.24	.188

Significant correlations are denoted in bold.

[a] Partial regression controlling for measures at time of marijuana use initiation (average age 13.4).

[b] Partial regression controlling for measures at time of scan (average age 19.6).

[c] $\alpha = .005$ (two-tailed).

during NEG. A negative correlation was observed between negative emotionality at follow-up and activation in caudal dlPFC during NEG. No other correlations passed correction for multiple comparisons. Mediation analyses therefore focused on these two brain regions and resiliency and negative emotionality at follow-up.

3.5. Mediation

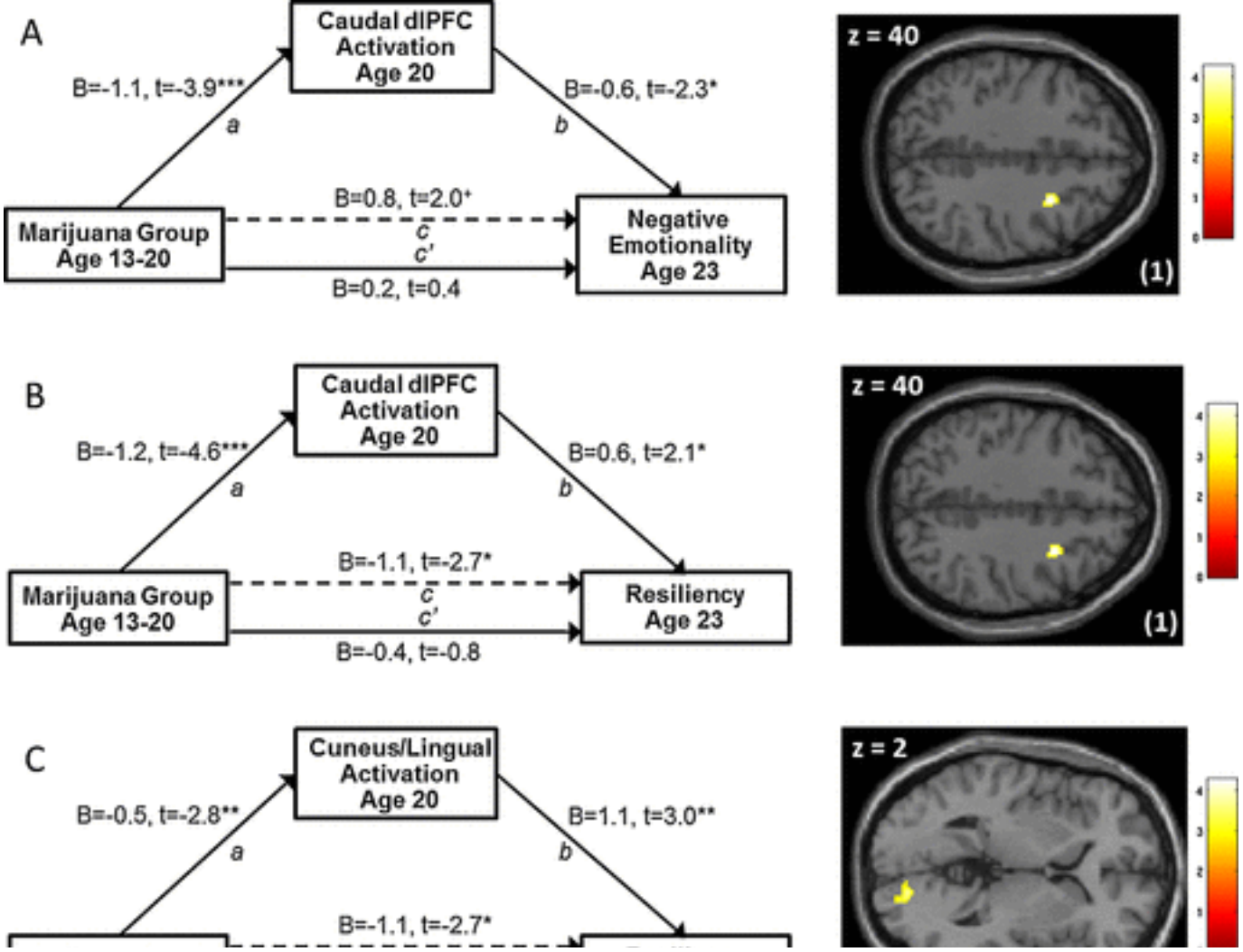
Activation of the caudal dlPFC during NEG mediated the relationship between marijuana group and later negative emotionality (95%

CIs: 0.095–1.631; Final model: adjusted $R^2 = .32$, $F = 5.94$, $p = .003$; Fig. 3a) as well as later resiliency (95% CIs: −1.814 to −0.030; Final model: adjusted $R^2 = .30$, $F = 5.49$, $p = .004$; Fig. 3b). Activation of cuneus/lingual gyrus mediated the relationship between marijuana group and later resiliency (95% CIs: −1.29 to −0.132; Final model: adjusted $R^2 = .39$, $F = 7.53$, $p < .001$; Fig. 3c).

4. Discussion

The goal of this work was to investigate the impact of heavy marijuana use during adolescence on later emotional functioning, as well as potential brain function mediators of this effect. Using a prospective design, we investigated two outcomes related to emotional functioning: negative emotionality and resiliency. We found that heavy marijuana users did not differ from controls in emotional functioning early in adolescence when marijuana use was initiated, whereas in late adolescence/early adulthood, heavy users had more negative emotionality and less resiliency than controls. To investigate the impact of adolescent marijuana use on emotion-related brain functioning, we compared neural responses to emotional words in heavy marijuana users and controls. Compared with controls, heavy users had less activation in emotion processing and integration regions, including the right insula, prefrontal cortex, and occipital cortex during the viewing of negative words, and in a region involved in attentional control (right inferior parietal lobe) during the viewing of positive words. Amygdala activation was lower to both negative and positive words in heavy users compared with controls. Further, we found heightened activation to positive words in the dorsolateral prefrontal cortex among heavy users. Activation in prefrontal cortex during the viewing of negative stimuli mediated an association between marijuana use and both negative emotionality and resiliency at follow-up. Activation in visual association regions of the occipital cortex mediated an association between marijuana use and later resiliency, but not negative emotionality.

A main finding of this prospective study is that marijuana use in adolescence may impact later emotional functioning. Heavy marijuana users scored higher on negative emotionality than controls at the approximate ages of 20 and 23, whereas groups did not differ at approximately age 13, when heavy users initiated use. Furthermore, exploratory analyses revealed that negative emotionality decreased from early adolescence to young adulthood in controls—consistent with normative changes (Roberts et al., 2006)—but not in heavy users. Importantly, we observed an association between greater lifetime marijuana use occasions and higher negative emotionality at age 20, after controlling for early levels (*i.e.*, at use initiation) of negative emotionality. These findings are in line with other longitudinal work showing that adolescent marijuana users had increased depression, anxiety, and suicidality in young adulthood, but marijuana use was not associated with premorbid differences in negative affect (Patton et al., 2002; Pedersen, 2008). Thus, the current results add to previous work supporting an association between early marijuana use and later



negative affectivity (Chadwick et al., 2013; Chen et al., 2002; Lev-Ran et al., 2014; Patton et al., 2002; van Laar et al., 2007).

We also investigated the impact of marijuana use on resiliency, as self-regulation plays a critical role in emotional functioning (*e.g.*, Eisenberg and Spinrad, 2004; Eisenberg et al., 2010; Eisenberg and Sulik, 2012). We found no difference between groups in resiliency at the age of marijuana initiation, whereas differences emerged in late adolescence/early adulthood, with lower resiliency in the heavy use group. Although conceptualized as a temperament/personality trait, evidence indicates that resiliency improves throughout adolescence and into adulthood in healthy individuals (Eisenberg et al., 2010; Eisenberg and Sulik, 2012). Here we found that resiliency increased over time in controls but not in heavy users. Furthermore, lifetime occasions of marijuana use was negatively correlated with resiliency, even after taking into account early level of resiliency.

Resiliency is inversely related to depression and internalizing problems in children (Block and Kremen, 1996) and emerging adults (Taylor et al., 2014), and positively related to effective social interaction (Block and Kremen, 1996) and social status (Eisenberg et al., 1997b). A reciprocal longitudinal relationship has been demonstrated between resiliency and positive emotionality from adolescence to early adulthood, as well as with the effective management of negative emotions (Milioni et al., 2014). It is possible, therefore, that adolescent marijuana use may impact emotional functioning partially through an influence on resiliency; however further work in a larger sample is required to determine these longitudinal relationships.

A central goal of this study was to characterize the neural mechanisms through which adolescent marijuana use exerts its effects on later emotional functioning. We found that activation in the right prefrontal cortex to negative words mediated the association between heavy marijuana use and both negative emotionality and resiliency at follow-up. Specifically, activation in the right middle frontal gyrus and dorsolateral superior frontal gyrus was lower in heavy users than controls, an effect that was associated with decreased resiliency and increased negative emotionality at follow-up. This area of the prefrontal cortex has been referred to as the caudal dorsolateral prefrontal region (caudal dlPFC) and is closely connected with motor and supplementary motor regions (Petrides, 2005). Prior work has high-arousal emotional words (Compton et al., 2003), and emotional film clips (Goldin et al., 2008), as well as the evaluation of one's own emotional state (Terasawa et al., 2013a). Cuneus activation has also been associated with the ability to attribute mental states to others, termed "theory of mind" (ToM) (Vollm et al., 2006). A recent study reported that adult marijuana users had differences in brain activation compared with controls during a ToM task, including lower activation in the right cuneus (Roser et al., 2012). Therefore, an impact of heavy marijuana use during adolescence on the functioning of occipital regions involved in the evaluation of emotional stimuli with respect to oneself and to others may impair self-regulation of emotional processes (as measured here with resiliency).

In addition to the regions found to mediate later outcome, heavy marijuana users had less activation than controls in the insula to negative words. These findings are consistent with previous work showing adolescent marijuana users had reduced cerebral blood flow in the insula compared with controls (Jacobus et al., 2012). Furthermore, studies of adult marijuana users found less activation in the insula to loss outcomes during a monetary incentive task (Nestor et al., 2010) and to errors in an inhibitory control task (Hester et al., 2009) compared with controls. The insula is critical to the integration of emotional and homeostatic information, and may be involved in translating interoceptive signals into conscious feelings (Critchley et al., 2005; Critchley et al., 2004; Naqvi and Bechara, 2009; Terasawa et al., 2013a). For example, the magnitude of insula activation while participants evaluated their own emotional and bodily states was found to be associated with social anxiety and neuroticism (Terasawa et al., 2013b). Insula activation has also been associated with self-report measures of anxiety (Stein et al., 2007) and anticipation of aversive exposure (Simmons et al., 2006) in anxiety-prone individuals. Here we found less insula activity to negative words in heavy marijuana users compared with controls, which was further associated with more negative emotionality at the time of scan. Together, this evidence suggests that heavy marijuana use may lead to impairment in the integration of emotional experience.

Activation of the amygdala was also reduced in heavy marijuana users compared to controls—an effect observed for both negative and

found activation of the caudal dlPFC and associated regions during the reading of high-arousal emotional words (Compton et al., 2003). The supplementary motor and premotor regions are important for emotion processing and empathy (Lamm et al., 2011) and may regulate approach-withdrawal tendencies to emotional stimuli by integrating limbic and motor responses (Oliveri et al., 2003; Rodigari and Oliveri, 2014). A recent meta-analysis found that activation in these regions decreased to negative stimuli in alexithymia, a trait characterized by difficulties with experiencing and processing emotions (van der Velde et al., 2013). The current findings suggest that heavy marijuana use during adolescence may impact caudal dlPFC functioning, impairing the processing and integration of emotional stimuli and lead to increased negative emotionality.

Additionally, we found that activation in the occipital cortex to negative emotional stimuli mediated the relationship between marijuana use and later resiliency. Specifically, activation in the cortical region surrounding the calcarine fissure, including portions of the right cuneus and lingual gyrus, was lower in heavy marijuana users than controls. This activation was further associated with decreased resiliency at follow-up, when controlling for resiliency at the time of scan. Although the cuneus and lingual gyrus are classically considered as visual processing and integration regions, there is a large literature associating both regions with aspects of emotion functioning, including the processing of emotional faces (Kitada et al., 2010), positive words. Along with the insula, the amygdala is part of a network involved in translating interoceptive responses to emotional stimuli into emotional experience (Critchley et al., 2005). Blunted amygdala response has been observed in individuals with difficulties experiencing and processing emotions (van der Velde et al., 2013). Acutely, cannabidiol, a psychoactive component of cannabis, has been shown to decrease amygdala activation to anxiety-inducing emotional stimuli; this effect was further associated with a reduction in electrodermal activity (Fusar-Poli et al., 2009), supporting links among marijuana, amygdala functioning, and interoceptive response to emotion. Furthermore, prior evidence indicates that the impact of marijuana use on amygdala-mediated emotional responding is not restricted to negative stimuli. Gruber et al. (2009) reported less amygdala activation in adult heavy marijuana smokers compared with controls to both happy and angry faces presented below the level of conscious processing. Here we found less amygdala activation to both positive and negative words in heavy marijuana users compared with controls, which further correlated with negative emotionality. Therefore, marijuana may have an impact on amygdala functioning that impairs general emotional arousal and integration.

The finding of an association between negative emotionality and reduced activation of the insula and amygdala is opposite to effects described in the depression and anxiety literature, which reports enhanced activation to negative stimuli (see reviews in Bruhl et al., 2014; Stuhrmann et al., 2011). However, a longitudinal study of individuals with comorbid major depression and marijuana dependence found that greater marijuana use was associated with reduced amygdala activation to emotional stimuli (Cornelius et al., 2010). This suggests that the mechanism through which marijuana impacts negative emotionality differs from the mechanism underlying depression and anxiety. For example, the associations between insula and amygdala functioning and negative emotionality in the current study may be more pertinent to differences in the experience and processing of emotions (van der Velde et al., 2013) rather than depression and anxiety.

Finally, heavy marijuana users showed reduced activity in the right inferior parietal lobule and greater activation in the right dlPFC during the viewing of positive words. The inferior parietal cortex is part of an attentional system involved in the automatic allocation of attention to task-relevant information (Ciaramelli et al., 2008), whereas the dlPFC is involved in more effortful attentional control (Blasi et al., 2007; MacDonald et al., 2000). Thus, the current results suggest a decrease in automatic attention to positive words in heavy users with a corresponding increase in effortful attentional control necessary to attend to the task. This is consistent with prior work demonstrating heightened activation of right-hemisphere prefrontal attentional control circuitry in adolescent marijuana users (Abdullaev et al., 2010; Tapert et al., 2007), which may reflect the need for increased effort in attending to task-related stimuli.

The results of this study should be considered with a few limitations in mind. First is the relatively small sample size, suggesting that results should be interpreted as somewhat preliminary, and further, that additional differences between groups may have been missed. Furthermore, although there is evidence of sex differences in the impact of marijuana on emotional functioning (McQueeny et al., 2011; Medina et al., 2009; Rubino et al., 2008; Zamberletti et al., 2012), this study was not adequately powered to investigate sex as a moderator. It will be important to address this issue in future work. Second, the control group included individuals who had occasional marijuana

Conflict of interest statement

All authors are free of any actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations within three years of beginning the submitted work that would inappropriately influence, or be perceived to influence, their work.

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use in adolescence (<10 lifetime uses). The impact of low levels of marijuana use on brain development is not known; therefore an ideal control group would have no marijuana use. However, given the high levels of comorbid alcohol and marijuana use in adolescence (Johnston et al., 2014), it was infeasible to create a marijuana-naïve control group while maintaining similar levels of alcohol use across groups. Third, the majority of participants in this study (80%) had a family history of AUD, which may limit the generalizability of results to those at heightened risk for behavioral and emotional problems.

Using a prospective design, we found that heavy marijuana users who began using in adolescence had higher negative emotionality and lower resiliency in their early twenties. Furthermore, differences in neural responses to emotionally-laden words mediated the associations between marijuana use and later negative emotionality and resiliency in these subjects. Because marijuana use is on the rise while perceptions of harm are decreasing, this is timely work. It adds to a growing body of evidence pointing to adverse effects of adolescent marijuana use on emotional functioning and is the first to characterize the functional neural correlates of these effects prospectively. As evidence for adverse consequences of marijuana use during adolescence on brain functioning accumulates, such research has the potential to improve prevention and intervention efforts through better education, thus reducing marijuana use and associated negative consequences.

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