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Life stress in adolescence predicts early adult reward-related brain function and alcohol dependence

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Stressful life events increase vulnerability to problematic alcohol use, and they may do this by disrupting reward-related neural circuitry. This is particularly relevant for adolescents because alcohol use rises sharply after mid-adolescence and alcohol abuse peaks at age 20. Adolescents also report more stressors compared with children, and neural reward circuitry may be especially vulnerable to stressors during adolescence because of prefrontal cortex remodeling. Using a large sample of male participants in a longitudinal functional magnetic resonance imaging study ($N = 157$), we evaluated whether cumulative stressful life events between the ages of 15 and 18 were associated with reward-related brain function and problematic alcohol use at age 20 years. Higher cumulative stressful life events during adolescence were associated with decreased response in the medial prefrontal cortex (mPFC) during monetary reward anticipation and following the receipt of monetary rewards. Stress-related decreases in mPFC response during reward anticipation and following rewarding outcomes were associated with the severity of alcohol dependence. Furthermore, mPFC response mediated the association between stressful life events and later symptoms of alcohol dependence. These data are consistent with neurobiological models of addiction that propose that stressors during adolescence increase risk for problematic alcohol use by disrupting reward circuit function.

Keywords: stressful life events; reward; fMRI; adolescence; alcohol dependence

Alcohol use disorders are a leading cause of global disease burden, with 1.9% of individuals worldwide experiencing alcohol use-related disability at any given time (World Health Organization, 2008). Problematic alcohol use is especially common in men, who are more than twice as likely as women to experience substance abuse or dependence (Kessler *et al.*, 2005; Hasin *et al.*, 2007). Furthermore, of the individuals who meet criteria for alcohol use disorders during their lifetime, half experience their first episode of alcohol abuse or dependence between mid-adolescence and the mid-twenties (Kessler *et al.*, 2005). The hazard rate for alcohol abuse or dependence peaks at age 20 (Hasin *et al.*, 2007). This makes late adolescence a key developmental phase to examine risk factors and mechanisms of problematic drinking.

Stress is a consistent predictor of increased alcohol use and alcohol use disorders, and stressors during adolescence may be particularly detrimental. Prospective data in adolescents and young adults demonstrate that stressful life events predict increased alcohol use (Newcomb and Harlow, 1986; Wills, 1986; Wills *et al.*, 1996). Epidemiological data indicate that exposure to adversity before the age of 18 is associated with the incidence and persistence of alcohol use disorders (Lloyd and Turner, 2008; Green *et al.*, 2010; McLaughlin *et al.*, 2010). Complementing these data, studies in animals indicate that early-life stressors, such as maternal separation or foot shock, result in increased alcohol consumption (Sinha, 2001). Furthermore, research in both humans (Larson and Ham, 1993; Ge *et al.*, 1994) and rodents (Spear, 2000; Lupien *et al.*, 2009) indicates that adolescents are more susceptible to the effects of stressors than children or adults. Notably, common adolescent stressors, such as trouble at school or with parents, may have a greater impact on emotional functioning than more distal major events (Rowlison and Felner, 1988; Compas *et al.*, 1989). Although these studies demonstrate that stressful life events during adolescence, especially the accumulation of common stressors, may increase risk for alcohol use and alcohol use disorders, the neural mechanisms linking stress to problematic substance use are not adequately understood.

One mechanism by which stress may confer vulnerability to problematic alcohol use is by disrupting neural response to rewards. In their prominent neurobiological model of addiction, Koob and Le Moul (1997, 2005) propose that stressful life events decrease neural response to normally rewarding cues, such as monetary or social rewards, and thereby sensitize individuals to the reinforcing properties of drugs. Complimenting this model, neurodevelopmental theories of psychopathology posit that reward systems are especially vulnerable to the effects of stressors during childhood and adolescence as the brain continues to mature (Forbes and Dahl, 2005; Nelson *et al.*, 2005; Andersen and Teicher, 2008; Davey *et al.*, 2008; Arnsten and Rubia, 2012; Spear, 2013). During adolescence, stressors may differentially impact reward function in late-developing regions of the prefrontal cortex (PFC), particularly the dorsomedial and orbitofrontal PFC, which go through a period of rapid neurodevelopment between the early teens and the mid-twenties (Gogtay *et al.*, 2004; Tamnes *et al.*, 2010; Mills *et al.*, 2012). These regions of the PFC are involved in higher-order executive functions (e.g. incentive appraisal, goal representation, emotion regulation, evaluation of social cues, self-reflection; Frith and Frith, 2001; Mitchell *et al.*, 2005; Etkin *et al.*, 2011).

Because of inhibitory projections from the PFC to subcortical regions, stress-related disruption of medial and orbitofrontal PFC function may result in disinhibition of stimulus–reward associations—a core function of the amygdala (Baxter and Murray, 2002)—and incentive salience or reward 'wanting'—a core function of the ventral striatum (Berridge and Robinson, 1998). In the context of alcohol use, heightened stimulus–reward associations and motivation to pursue

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rewards may promote stronger associations between alcohol-related cues and hedonia, as well as increased alcohol-directed behavior (Koob and Le Moal, 1997; 2005). Consistent with this model, research in adolescent male rats found that repeated social defeat—a potent stressor—decreases dopamine activity in the medial PFC (mPFC) and heightens drug-seeking behavior (Burke *et al.*, 2012). The increase in stressors and stress reactivity coupled with PFC plasticity during adolescence may help explain the coincident uptick in substance use disorders during this period.

Research linking psychosocial stress to disruptions in brain reward circuitry and problematic alcohol use is limited. However, neuroimaging studies have explored the relationship between stress and brain reward function. For example, response to monetary rewards in the mPFC, orbitofrontal cortex (OFC) and ventral striatum is disrupted by acute laboratory stressors such as watching aversive films or submerging one's hand in ice water (Ossewaarde *et al.*, 2011; Porcelli *et al.*, 2012). There are also two neuroimaging studies that report a link between early-life stressors and brain reward function: Dillon *et al.* (2009) found that adults with a history of childhood maltreatment had decreased responses to monetary rewards in the globus pallidus compared with control participants; Mehta *et al.* (2010) found that adolescent adoptees who experienced global deprivation in Romanian institutions during early childhood had decreased striatal response during anticipation of monetary rewards compared with non-institutionalized non-adopted adolescents. There is also evidence that alcohol use disorders are associated with disrupted reward circuit function: Wrase *et al.* (2007) demonstrated that alcoholics relative to healthy individuals had decreased neural response during anticipation of monetary rewards in the ventral striatum, but increased striatal response to alcohol-related cues. These studies provide preliminary evidence for the relationship between stressful life events, reward circuit function and addiction. However, additional research is needed to evaluate whether reward circuit disruption is a mechanism by which adolescent life stress increases risk for problematic alcohol use.

The present study examines the association between cumulative stressful life events during late adolescence and brain reward function and problematic alcohol use at age 20 in a large community sample of young men. Common adolescent stressors (e.g. arguments with a family member, academic or social problems) were assessed annually from ages 15 through 18. At age 20, participants completed an assessment of problematic alcohol use and underwent functional magnetic resonance imaging (fMRI) during a monetary reward task to assess neural response during reward anticipation and following rewarding outcomes. We anticipated that (i) higher levels of cumulative life stress during adolescence would be associated with decreased mPFC, OFC, ventral striatum and amygdala response during reward anticipation at age 20, (ii) stress-related decreases in neural response during reward anticipation would also be associated with higher levels of problematic alcohol use at age 20 and (iii) neural response to reward would mediate the association between stressful life events and problematic alcohol use. We expected stressful life events and alcohol dependence to be more strongly associated with neural response during reward anticipation than following rewarding outcomes because neurobiological models of problematic substance use (e.g. Koob and Le Moal, 1997) and previous studies linking stress to reward circuit function (e.g. Mehta *et al.* 2010) have focused on reward anticipation, or 'wanting', rather than response to rewarding outcomes, or 'liking'.

METHOD

Participants

Participants were 186 boys from the Pittsburgh Mother and Child Project (PMCP), an ongoing study of child risk and resilience for psychopathology (Shaw *et al.*, 2003). The original PMCP sample included 310 low-income families with infant boys. Families were recruited from a government nutrition program in the Pittsburgh metropolitan area. Child and family assessments were initially completed when the boys were 12 or 18 months old and follow-up assessments were conducted at ages 2, 3.5, 5, 5.5, 6, 8, 10, 11, 12, 15, 16, 17, 18 and 20 years. Mean per capita family income at the initial assessment was $12 565 per year (s.d. = $7690) with a mean Hollingshead (1975) socioeconomic status of 23.32 (s.d. = 9.29), indicating that the sample was predominantly working class. The informed consent process conformed with the Declaration of Helsinki and university research review committee approval and oversight.

At age 20, the sample retention rate was 83% ($N = 258$), and 186 participants were eligible and able to complete the fMRI scan. Of these young men, 29 were excluded from fMRI analyses for this study. Reasons for exclusion included failure to complete any adolescent life stress assessments ($n = 8$), <80% response rate on the reward task ($n = 6$), not understanding the reward task (e.g. consistently responding at inappropriate times; $n = 4$), <80% ventral striatum coverage ($n = 5$), poor-quality scan ($n = 1$), psychosis ($n = 1$), severe autism ($n = 1$) and marijuana use immediately before the scan ($n = 2$). This left data from 157 participants with stressful life events available for analyses. Of these 157 participants, five did not complete the problematic alcohol use assessment. Therefore, analyses relating neural response to reward to problematic alcohol use were based on 152 participants.

Questionnaires

Adolescent stressful life events were assessed when participants were 15, 16, 17 and 18 years of age. Participants rated the 1 year incidence (0 or 1) and distress (0, 1 or 2) associated with 30 common negative events from two life event inventories: the Life Event Questionnaire for Adolescents (LEQ; Masten *et al.*, 1994) and the Interpersonal Problem Situations Inventory for Urban Adolescents (IPSI; Farrell *et al.*,1998). The LEQ assesses common adolescent stressors such as injury or death in the family, poor performance in school, difficult financial circumstances and arguments with family members. The IPSI measures perceived injustice from adults and bullying from peers. Items from the LEQ and IPSI are non-overlapping. A cumulative stressful life event score was calculated by summing the LEQ and IPSI incidence and distress ratings across ages 15 through 18 years. Cumulative scores could range from 0 to 468, with higher scores indicating more stressful life events.

Alcohol dependence was assessed when participants were 20 years of age using the Alcohol Dependence Scale (ADS; Skinner and Allen, 1982). The ADS includes 25 items that assess alcohol-related problems (e.g. withdrawal, tolerance, compulsive drinking) over the past 6 months. Each item is scored '0' for 'no' and '1' for 'yes'. Total scores range from 0 to 25, with higher scores indicating more severe symptoms.

Tobacco use, childhood neighborhood disadvantage and caregiver education were also assessed and included as covariates in all regression analyses. Tobacco use was included as a covariate because it is associated with decreased reward-circuit function (Rose *et al.*, 2013). It was assessed at age 20 using a single item from the Alcohol and Drug Consumption Questionnaire (Cahalan *et al.*,1969). Neighborhood disadvantage was included as a covariate to determine whether life stress would predict reward-related blood-oxygen-level-dependent (BOLD) response after controlling for childhood demographic factors that can increase exposure to adversity (Vanderbilt-Adriance and Shaw, 2008). Childhood neighborhood disadvantage was ascertained using PMCP demographic data collected at ages 17 months through 15 years, as

described by Vanderbilt-Adriance and Shaw (2008), and mean neighborhood disadvantage across all assessment points was used for analysis. Maternal education in years when the participants were 17 was included as a covariate to control for socioeconomic status. In addition, past-year stressful life events were assessed at age 20 using the Life Event Survey (LES; Sarason *et al.*, 1978). Scores on the LES were used as a covariate in secondary analyses to determine whether the effects of adolescent life stress on neural response to reward were sustained when accounting for life stress at the time of the scan.

Scores on LEQ-IPSI, ADS and LES were square-root transformed before analysis to approximate a normal distribution. Additional description of the measures, including methods for imputation of missing data and alpha coefficients for each measure, is provided as Supplementary Material.

Reward task

Participants performed a reward-guessing task during fMRI acquisition. This task was designed to index brain activation during anticipation of monetary incentives and following feedback about monetary gain and loss. Previous studies show that this task reliably elicits activation in neural reward circuitry (Forbes *et al.*, 2009, 2010). Participants were instructed to guess whether the value of a visually presented card, with possible value from 1 to 9, would be greater than or less than 5. Each trial began with the presentation of a blank card. Participants had 4 s to guess the value of the card via button press. The type of trial (gain or loss) was then displayed for 6 s using an image with hands shuffling cards with an upward facing yellow arrow to indicate potential reward trials and a downward facing yellow arrow to indicate potential loss trials. This incentive anticipation interval was followed by an outcome interval, in which the 'actual' value of the card was displayed for 500 ms, feedback on the trial outcome was displayed for 500 ms (a green upward-facing arrow for win or a yellow circle for a no-change outcome on win trials, a red downward-facing arrow for loss or a yellow circle for a no-change outcome on loss trials), and then a crosshair was displayed for 9 s. The final 3 s of the crosshair served as a baseline condition. There were 24 trials, 20 s each administered over a single 8 min run. Trials were presented in pseudorandom order, and outcomes were predetermined with a balanced number of trial types (12 possible win, 12 possible loss; 6 win, 6 loss and 12 no-change outcomes). Analyses focused on the 12 possible win trials and the 6 win outcomes. Based on the effect sizes in a previous study (Casement *et al.*, 2014), this number of trials had >95% power to elicit a significant BOLD response in each of our regions of interest. Participants were told that they would receive their winnings after the scan ($1 per win outcome and 50 cents per loss); in fact, all participants received $10.

Magnetic resonance imaging acquisition, processing and analysis

Neuroimaging was conducted on a Siemens 3.0 Tesla TIM Trio scanner. BOLD functional images were acquired using a gradient echo planar imaging (EPI) sequence that included 39 axial slices (3.1 mm wide) beginning at the cerebral vertex and extending across the entire cerebrum and most of the cerebellum (repetition time (TR)/echo time (TE) = 2000/28 ms, field of view (FOV) = 20 cm, matrix = 64 × 64). A reference EPI scan was acquired before fMRI data collection to visually inspect for artifacts (e.g. ghosting) and ensure adequate signal across the entire volume. In addition, a 160-slice high-resolution sagittally acquired T1-weighted anatomical image was collected for coregistration and normalization of functional images (TR/TE = 2300/2.98 ms, FOV = 20 cm, matrix 256 × 240). Preprocessing and analysis of imaging data were conducted using Statistical Parametric Mapping software (SPM8; http://www.fil.ion.ucl.ac.uk/spm). Preprocessing included segmentation of the anatomical scan and functional image realignment, coregistration, normalization and smoothing (details in Supplementary Material).

Second-level random effects models were used to estimate reward responsivity while accounting for scan-to-scan and between-participant variability. For each participant, condition effects were calculated at each voxel using *t*-tests for two contrasts: reward anticipation > baseline and reward outcome > baseline. Reward anticipation was defined as the 12 potential-win intervals after the guessing condition (6 s each). Reward outcome was defined as the intervals that included number presentation, arrow feedback and the first 6 s of the crosshair during the six win-outcome trials (7 s each). The last 3 s of all 24 trials served as the baseline condition. Analysis of imaging data focused on four pre-specified regions of interest (ROIs): the mPFC, striatum, OFC and amygdala. AlphaSim (http://afni.nimh.nih.gov/afni/) cluster extent thresholds were calculated a priori to determine the minimum cluster size necessary to maintain a corrected $P < 0.05$ across all four ROIs. Further description of each ROI and the AlphaSim thresholds is provided as Supplementary Material.

Regression analyses were performed in SPM to determine whether cumulative negative life events were associated with neural response during reward anticipation and reward outcome across participants. All regression analyses included a dichotomous index of tobacco use (daily, <daily), mean neighborhood disadvantage and caregiver education level (in years) as covariates. Additional regression analyses were conducted in SPM with LES scores included as a fourth covariate. Unstandardized regression coefficients, standard errors (SE), and confidence intervals (CI) were computed in SPSS. To accomplish this, functional masks from SPM regressions of reward response on cumulative life stress were saved and used as functional ROIs for *t*-tests of BOLD response during reward anticipation and reward outcome. Beta values for the average BOLD response within each functional mask were extracted using the 'eigenvariate' tool in SPM, and regressions were performed in SPSS using the covariates described above.

To link disruptions in neural response to reward to problematic alcohol use, conjunction analysis (Nichols *et al.*, 2005; see Supplementary Material) was used to determine whether ADS scores were associated with reward anticipation and reward outcome in regions that were also associated with adolescent life stress. ADS scores were individually entered as predictors of reward anticipation response and reward outcome response. Results were masked for regions in which there was a significant relationship between cumulative stressful life events and reward-related BOLD response. Conjunction analyses used the same covariates as regressions of reward response on cumulative negative life events.

Finally, for each region that was significantly associated with both stressful life events and problematic alcohol use, mediation analyses were used to examine whether neural response during reward anticipation or reward outcome accounted for a significant portion of the association between stressful life events and ADS scores. To accomplish this, a second set of functional masks was created, based on significant clusters yielded by regressions of BOLD response on problematic alcohol use. These functional masks were saved and used as functional ROIs for *t*-tests of BOLD response during reward anticipation and reward outcome. Average BOLD response beta values across each significant cluster were extracted from these results and tested as a mediator of the relationship between stressful life events and problematic alcohol use in SPSS using the same covariates that were applied in SPM. Mediation analyses were implemented using the bootstrap method with the SPSS PROCESS macro (Hayes, 2013; see Supplementary Material for further description).

Table 1 Participant characteristics at time of scan ($N = 157$)

Characteristic	Percentage
Race	
Black	37
White	54
Other or mixed race	9
Highest level of school completed	
Below grade 12	11
Grade 12 or GED	50
Some college	36
Associate's degree or trade school	3
Primary caregiver's highest level of school completed	
Below grade 12	4
Grade 12 or GED	34
Some college or trade school	50
Completed 4 years of college	9
Completed graduate or professional school	3
ADS score > 8	17
	Mean (s.d.)
Age	19.52 (0.51)
Age of first significant alcohol use (≥10×/year)	16.84 (1.56)
Stressful life events score, ages 15-18	43.69 (26.44)
Age 15	11.16 (7.79)
Age 16	9.93 (7.65)
Age 17	13.93 (10.59)
Age 18	8.67 (6.40)
LES score, age 20	8.82 (9.51)
ADS score	4.91 (4.39)
Mean neighborhood disadvantage	0.20 (0.67)

Note: Scores above 8 on the ADS indicate likely alcohol dependence. Scores above 0 for mean neighborhood disadvantage indicate moderate to high risk. GED, General Educational Development test of high-school level academic skills.

RESULTS

Participant characteristics

Table 1 describes the characteristics of the sample when they underwent neuroimaging at age 20. Two-tailed Pearson's correlation indicated that higher levels of cumulative stressful life events during adolescence were associated with more problematic alcohol use at age 20 ($r = 0.18$, $P = 0.03$). The association between cumulative stressful life events and problematic alcohol use was not significant when adjusting for stressful life events at age 20 ($r = 0.09$, $P = 0.26$). Two-tailed Pearson's correlation indicated that higher levels of stressful life events at age 20 were associated with more problematic alcohol use ($r = 0.25$, $P = 0.002$).

Reward-related BOLD response

Whole-brain and ROI results for within-subject *t*-tests of BOLD response during reward anticipation (reward anticipation > baseline) and reward outcome (reward outcome > baseline) are available as Supplementary Data (Supplementary Tables S1 and S2). These results confirm that all four regions of interest (i.e. mPFC, ventral striatum, OFC and amygdala; see Supplementary Material) had increased response during reward anticipation and reward outcome compared with baseline. Whole-brain results are presented to describe regions that were responsive to reward outside of our pre-defined ROIs (e.g. occipital and parietal cortex).

Association between stressful life events and reward-related BOLD response

During reward anticipation, higher cumulative life stress during adolescence was associated with reduced response in the mPFC at age 20 ($b = -0.04$, SE $b = 0.02$, 95% CI: -0.08, -0.01, $P = 0.01$; Table 2; Figure 1). This association was maintained when stressful life events at age 20 were accounted for ($b = -0.04$, SE $b = 0.02$, 95% CI: -0.07, -0.01, $P = 0.01$). Following rewarding outcomes, higher cumulative life stress was associated with reduced response in the mPFC ($b = -0.05$, SE $b = 0.01$, 95% CI: -0.08, -0.03, $P < 0.001$; Table 2; Figure 1). This association was not statistically significant when stressful life events at age 20 were accounted for.

Table 2 Cumulative stressful life events as a predictor of reward-related BOLD response

Condition	MNI coordinates			Cluster size	*t* ($df = 152$)
	x	*y*	*z*		
Reward anticipation					
mPFC (BA 10)	6	64	14	369	3.53
mPFC (BAs 24, 32)	−14	34	38	1117	3.17
Reward outcome					
mPFC (BAs 24, 32)	20	34	10	261	3.67
With past-year negative life events included as a covariate ($df = 151$)					
Reward anticipation					
mPFC (BAs 10, 32)	−14	32	38	671	3.38

Note: 'Tobacco use', 'neighborhood disadvantage' and 'caregiver education' were included in these analyses as covariates. Alpha Sim corrected $P < 0.05$ for all contrasts. BA, Brodmann Area; BOLD, blood-oxygen-level-dependent; MNI, Montreal Neurological Institute.

Association between reward-related BOLD response and severity of problematic alcohol use in regions that were associated with stressful life events

During reward anticipation, higher levels of problematic alcohol use were associated with reduced response in the mPFC ($b = -0.07$, SE $b = 0.03$, 95% CI: -0.12, -0.02, $P = 0.009$; Table 3; Figure 2). This association was maintained after adjusting for cumulative stressful life events ($b = -0.55$, SE $b = 0.25$, 95% CI: -1.06, -0.06, $P = 0.03$), stressful life events at age 20 ($b = -0.07$, SE $b = 0.03$, 95% CI: -0.12, -0.01, $P = 0.02$) and both cumulative stressors and stressful life events at age 20 ($b = -0.54$, SE $b = 0.24$, 95% CI: -1.01, -0.07, $P = 0.03$). Following rewarding outcomes, higher levels of alcohol dependence were also associated with reduced response in the mPFC ($b = -0.09$, SE $b = 0.02$, 95% CI: -0.14, -0.05, $P < 0.001$; Table 3; Figure 2). This association was maintained after adjusting for cumulative stressful life events ($b = -0.83$, SE $b = 0.29$, 95% CI: -1.40, -0.26, $P = 0.005$).

Bootstrap tests of mediation indicated that BOLD response in the mPFC during reward anticipation ($b = 0.02$, SE $b = 0.01$, 95% CI: 0.002, 0.06, $P < 0.05$) and following rewarding outcomes ($b = 0.04$, SE $b = 0.02$, 95% CI: 0.009, 0.08, $P < 0.05$) significantly mediated the association between cumulative stressful life events and problematic alcohol use. The direct effect of cumulative stressful life events on problematic alcohol use was no longer significant when the model included mPFC response during reward anticipation ($b = 0.07$, SE $b = 0.05$, 95% CI: -0.02, 0.16, $P = 0.15$) or following rewarding outcomes ($b = 0.05$, SE $b = 0.05$, 95% CI: -0.04, 0.15, $P = 0.25$).

Neural response during reward anticipation remained a significant mediator of the relationship between cumulative adolescent stressful life events and problematic alcohol use when past-year stressful life events were accounted for ($b = 0.03$, SE $b = 0.01$, 95% CI: 0.004, 0.063, $P < 0.05$). The direct effect of cumulative stressful life events on problematic alcohol use was no longer significant when mPFC response during reward anticipation was included in the model and past-year stress was included as a covariate ($b = 0.02$, SE $b = 0.05$, 95% CI: -0.08, 0.12, $P = 0.65$).

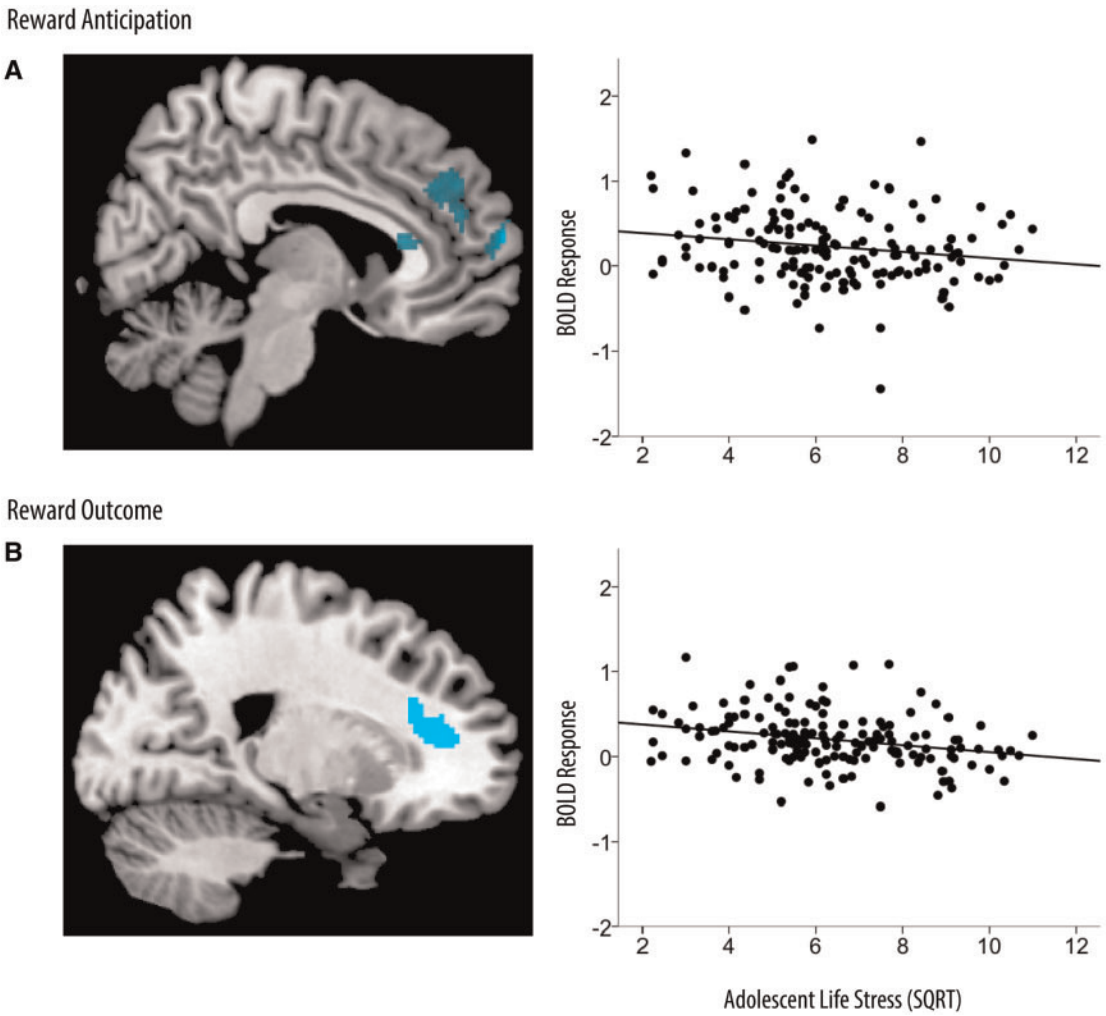

Fig. 1 Cumulative stressful life events as a predictor of reward-related BOLD response. Brain images and scatterplots depict significant associations between stressful life events and BOLD response in the mPFC during reward anticipation **(A)** and reward outcome **(B)**. Scatterplots depict average BOLD response across clusters in the mPFC during reward anticipation (MNI coordinates: 6, 64, 14; $R^2 = -0.21$) and reward outcome (MNI coordinates: 20, 34, 10; $R^2 = -0.34$). SQRT, square-root transformation.

DISCUSSION

This study provides the first evidence that cumulative life stress during late adolescence is associated with blunted mPFC response to reward in early adult men. Previous neuroimaging research showed that acute laboratory stressors were associated with decreased neural response in the mPFC (Ossewaarde *et al.*, 2011), and early childhood maltreatment and deprivation were associated with decreased neural response in the striatum (Dillon *et al.*, 2009; Mehta *et al.*, 2010), during anticipation of monetary rewards. The current study indicates that very common adolescent stressors, such as arguments with family or social and academic problems in school, are also associated with decreased neural response to reward in the mPFC during reward anticipation and following rewarding outcomes. This was true even when neighborhood disadvantage and caregiver education were accounted for, suggesting that life stress during late adolescence independently contributes to reward-related brain function and cannot be simply attributed to neighborhood demographics or family socioeconomic status in childhood. The association between cumulative stressful life events and mPFC response during reward anticipation was also maintained after adjusting for concurrent life stress at the time of the scan. Previous studies have found significant associations between stressful life events and neural response during reward anticipation but not following rewarding outcomes (i.e. Dillon *et al.*, 2009; Mehta *et al.*, 2010; Ossewaarde *et al.*, 2011). In combination, these results suggest that stressors may have a larger effect on circuits that support reward anticipation than circuits that support evaluation of received reward.

Our data are consistent with the hypothesis that stress-related alterations in brain reward function may be causally related to problematic alcohol use. Blunted mPFC function during reward anticipation and following rewarding outcomes was associated with more symptoms of alcohol dependence. Furthermore, mPFC response to rewards statistically mediated the relationship between stressful life events and problematic alcohol use. One interpretation of these results is that cumulative life stress during adolescence may dampen neural control mechanisms that help regulate alcohol-motivated behavior. Another possibility is that cumulative stress during adolescence diminishes mPFC response to normally rewarding events and thereby enhances the perceived benefits of alcohol use. Either interpretation is consistent with Koob and Le Moul's (1997) proposal that stressors progressively result in a dysregulated reward response system and sensitize individuals to the hedonic properties of addictive drugs. In fact, Koob and Le Moul (2005) specifically implicated hypoactivation of the PFC in response to persistent aversive states (such as stressors or drug withdrawal) as a vulnerability for negative reinforcement from drug use.

Adolescent stressful life events were not associated with neural response to reward in the striatum, OFC or amygdala. In contrast, Dillon *et al.* (2009) found associations between childhood maltreatment and decreased reward responsiveness in the putamen and globus pallidus in young adults, and Mehta *et al.* (2010) found associations between global deprivation during early childhood and decreased striatal response to monetary rewards in mid-adolescence. Neither Dillon *et al.* or Mehta *et al.* found associations between early life stress and reward-related mPFC function. Neurodevelopmental models of psychopathology posit that the PFC, particularly the dorsomedial PFC, is especially vulnerable to the effects of stressors during adolescence relative to childhood or later adulthood because early adolescence through the mid-twenties is a period of dramatic PFC maturation (Forbes and Dahl, 2005; Nelson *et al.*, 2005; Andersen and Teicher, 2008; Davey *et al.*, 2008; Arnsten and Rubia, 2012; Spear, 2013). Furthermore, structural neuroimaging studies in humans (Andersen *et al.*, 2008) and experimental studies in animals (Leussis *et al.*, 2008) indicate that adolescent stressors affect PFC volume but not the volume of earlier-maturing regions (e.g. hippocampus, caudate). Collectively, these studies suggest that the developmental timing of stressors may be an important moderator of reward circuit function. However, between-study differences in stress–reward associations could also reflect the influence of different types of stressors (e.g. maltreatment *vs* common stressful life events), samples (samples of mixed-gender and socioeconomic status *vs* men from predominantly low-income families) or reward tasks (monetary incentive delay task *vs* monetary guessing task). Comparisons of different types of stressors or reward tasks within a sample, or of the same types of stressors and reward tasks at

Table 3 Alcohol dependence at age 20 as a predictor of reward-related BOLD response

Condition	MNI Coordinates			Cluster size	*t* (*df* = 147)
	x	*y*	*z*		
Reward Anticipation					
mPFC (BA 32)	16	48	20	142	3.71
mPFC (BA 10)	−14	46	20	236	3.13
mPFC (BA 24)	0	28	16	86	3.08
mPFC (BA 32)	−6	46	20	84	2.79
Reward outcome					
mPFC (BA 32)	20	28	22	129	4.62
With past-year negative life events included as a covariate (*df* = 146)					
Reward anticipation					
mPFC (BA 32)	12	48	22	66	3.12
mPFC (BAs 10, 32)	−8	48	22	85	3.06

Note: Alpha Sim corrected $P < 0.05$ for all contrasts. Results were masked for regions in which there was a significant relationship between cumulative stressful life events and reward-related BOLD response. 'Tobacco use', 'neighborhood disadvantage' and 'caregiver education' were included in these analyses as covariates. BA, Brodmann Area; BOLD, blood-oxygen-level-dependent; MNI, Montreal Neurological Institute.

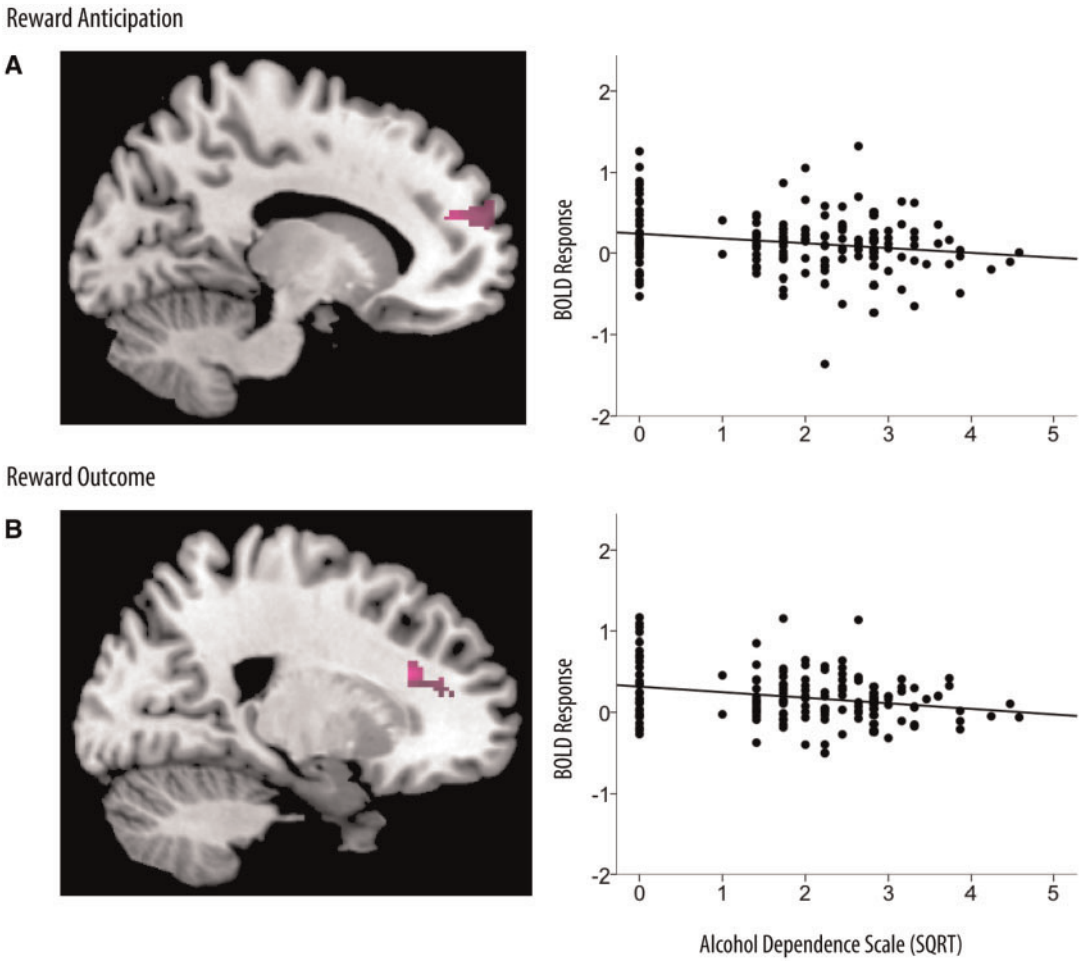

Fig. 2 Alcohol dependence as a predictor of reward-related BOLD response. Results were masked for regions in which there was a significant relationship between stressful life events and reward-related BOLD response. Brain images and scatterplots depict significant associations between alcohol dependence and BOLD response in the mPFC during reward anticipation **(A)** and reward outcome **(B)**. Scatterplots depict average BOLD response across clusters in the mPFC during reward anticipation (MNI coordinates: 16, 48, 20; $R^2 = -0.23$) and reward outcome (MNI coordinates: 20, 28, 22; $R^2 = -0.33$). SQRT, square-root transformation.

different developmental periods, could further delineate the neural circuitry and stages of neurodevelopment involved in stress-related brain reward function.

Further research in adolescent samples could clarify the relationship between stress-related reward circuit function and problematic use of alcohol and other drugs (e.g. tobacco, marijuana). For example, because a mediational model assumes that stressful life events precede and predict reward circuit dysfunction, and reward circuit dysfunction precedes and predicts alcohol dependence, additional longitudinal data are needed to conduct a true test of mediation and to elucidate the roles of these factors in the development of alcohol use problems over time. We cannot rule out the possibility that blunted reward circuit function predated our assessment of stressful life events from ages 15 through 18. However, given that the average age of first significant alcohol use (>10×/year) was 16.84, almost 3 years into the four annual assessments of stressful life events, stressful life events likely preceded the onset of alcohol dependence for the majority of our sample. Moreover, experimental studies in humans (Ossewaarde *et al.*, 2011; Porcelli *et al.*, 2012) and animals (Sinha, 2001; Pryce *et al.*, 2005) indicate that stressful life events can play a causal role in brain reward function. We would hypothesize, given our pattern of findings, that the influence of stressful life events on neural reward circuitry at sensitive points in brain development leads to a cascade of events involving the neural response to alcohol and other drugs, initiating the process of addiction in those who are vulnerable.

Another limitation of the present study is the relatively brief interval between conditions in the Reward Guessing Task. BOLD response to visual stimuli peaks roughly 5 s after stimulus onset and takes a similar length of time to return to baseline (Huettel and McCarthy, 2000). Furthermore, a 6 s interval between conditions only allows for 90% of expected signal to the second condition (e.g. the reward outcome condition in our experiment; Huettel and McCarthy, 2000). Given that the reward outcome stimulus occurred 6 s after the reward anticipation stimulus in this task design, BOLD response during the reward outcome interval likely reflects some degree of signal recovery from reward anticipation and may be slightly attenuated. Notably, the main conclusion of this study—that neural reward processing mediates the association between life stress and problematic alcohol use—was true for both reward anticipation and reward outcome. We report the reward outcome results despite the short interval between conditions because previous research indicates that these processes are neurally distinct (e.g. wanting *vs* liking; Berridge and Robinson, 1998), and neural response to reward anticipation and rewarding outcomes has been assessed separately in other literature on psychosocial stress and disruptions in reward circuit function (e.g. Dillon *et al.*, 2009; Mehta *et al.*, 2010).

It is particularly important to understand the role of stressors on reward circuit function during adolescence and young adulthood because the onset of alcohol use disorders peaks during this developmental phase (Kessler *et al.*, 2005; Hasin *et al.*, 2007). This study provides the strongest neuroimaging evidence to date of the putative links between adolescent stressors, brain reward function and problematic alcohol use. It is also the first study to report a relationship between common adolescent stressors, such as arguments with family or problems in school, and reward circuit function and problematic alcohol use in early adulthood. If common life stressors during late adolescence increase risk for mental illness by disrupting brain response to rewards, then interventions for adolescents that boost stress regulation and reward responsiveness (e.g. mindfulness training, behavioral activation, sleep extension) may counteract the detrimental impact of these stressors. Applying these interventions in adolescents, particularly stressed adolescents, could help preserve reward function in the mPFC and other reward circuitry, and decrease the prevalence of alcohol use disorders. This application of our current findings would be an exciting area for further research.

SUPPLEMENTARY DATA

Supplementary data are available at *SCAN* online.

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