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Neurobehavioral markers of resilience to depression amongst adolescents exposed to child abuse

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Abstract

Childhood maltreatment is strongly associated with depression, which is characterized by reduced reactivity to reward. Identifying factors that mitigate risk for depression in maltreated children is important for understanding etiological links between maltreatment and depression as well as improving early intervention and prevention. We examine whether high reward reactivity at behavioral and neurobiological levels is a marker of resilience to depressive symptomology in adolescence following childhood maltreatment. A sample of 59 adolescents (21 with a history of maltreatment; Mean Age=16.95 years, SD =1.44) completed an fMRI task involving passive viewing of emotional stimuli. BOLD signal changes to positive relative to neutral images were extracted in basal ganglia regions of interest. Participants also completed a behavioral reward-processing task outside the scanner. Depression symptoms were assessed at the time of the MRI and again two years later. Greater reward reactivity across behavioral and neurobiological measures moderated the association of maltreatment with baseline depression. Specifically, faster reaction time to cues paired with monetary reward relative to those unpaired with reward and greater BOLD signal in the left pallidum was associated with lower depression symptoms in maltreated youth. Longitudinally, greater BOLD signal in the left putamen moderated change in depression scores over time, such that higher levels of reward response were associated with lower increases in depression over time among maltreated youths. Reactivity to monetary reward and positive social images, at both behavioral and neurobiological levels, is a potential marker of resilience to depression among adolescents exposed to maltreatment. These findings add to a growing body of work highlighting individual differences in reactivity to reward as a core neurodevelopmental mechanism in the etiology of depression.

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Keywords

Reward reactivity; maltreatment; basal ganglia; adolescent; depression

Childhood maltreatment is associated with elevated risk for numerous types of psychopathology across the lifespan (Green et al., 2010; McLaughlin et al., 2012), including major depression (Norman et al., 2012). Maltreatment has been associated with early onset of depression (Wilson, Vaidyanathan, Miller, McGue, & Iacono, 2014), greater depression comorbidity and associated disability (Widom, DuMont, & Czaja, 2007), and resistance to evidence-based treatments (Nanni, Uher, & Danese, 2012). Identifying factors that protect against the development of depression in youths exposed to maltreatment is critical for identifying early intervention and treatment strategies.

Disruptions in reward processing are thought to be a central neurodevelopmental mechanism underlying risk for major depression (Pizzagalli, 2014; Russo & Nestler, 2013). Reward processing involves a complex interplay of affective, motivational and learning components (Berridge, Robinson, & Aldridge, 2009), which modify behavioral responses to rewards. Reward reactivity—the degree to which reactions to stimuli are modulated based on their rewarding properties, is low among adolescents and adults with depression, as illustrated by reduced behavioral responses to reward and blunted neural activation in the basal ganglia in response to both anticipation and consumption of rewards (Forbes et al., 2009; Pizzagalli et al., 2009). Childhood maltreatment is associated with behavioral alterations of reward system function in children (Guyer, Kaufman, et al., 2006), and altered neural response to reward and positive social cues in the basal ganglia (Boecker et al., 2014; Dillon et al., 2009; Goff et al., 2013; Hanson, Hariri, & Williamson, 2015; Pizzagalli, 2014). Adults who have experienced childhood maltreatment show less reactivity to reward cues in the left pallidum and rate reward cues less positively than adults without maltreatment histories (Dillon, et al., 2009). fMRI studies examining basal ganglia regions of interest have reported associations between emotional neglect (Hanson, Hariri, et al., 2015) and early life institutionalization (Goff, et al., 2013) with blunted ventral striatum reactivity to reward and positive social stimuli across adolescence. In healthy young adults, family adversity was negatively associated with reactivity in the ventral striatum and putamen during anticipation of reward; during reward delivery, activation of the right pallidum and bilateral putamen increased with early family adversity (Boecker, et al., 2014). These findings suggest development of regions within the basal ganglia may be susceptible to stressful experiences in early life, potentially creating a diathesis for disorders involving disruptions in reward processing.

A recent study found that decreased behavioral and neural responses to reward across adolescence mediated the association of maltreatment with depression, suggesting it might be a mechanism underlying maltreatment-related depression (Hanson, Hariri, et al., 2015). Although previous studies (Goff, et al., 2013; Hanson, Hariri, et al., 2015) have conceptualized reactivity to rewards and positive social cues as mediators of the relationship between maltreatment and depression, evidence for this mechanism is inconsistent across studies (Goff, et al., 2013). Given that many children exposed to maltreatment do not subsequently develop depression (Collishaw et al., 2007), an alternative possibility is that variation in reward reactivity moderates the association of maltreatment with depression. Specifically, stable individual differences in reward reactivity indexed by temperamental factors such as positive affect emerge early in development (Compas, Connor-Smith, & Jaser, 2004) and might produce individual differences in risk for depression following maltreatment. In support of this hypothesis, positive affect—an affective state centrally involved in reward processing (Kringelbach & Berridge, 2009) that is positively associated with neural reactivity to reward in adolescents (Forbes et al., 2010)—buffers against the onset of mental health problems following stressful life events in adults (Southwick, Vythilingam, & Charney, 2005). Higher levels of trait positive affect buffer risk for depression amongst children with high negative emotion (Joiner & Lonigan, 2000), and protect against adjustment problems following parental divorce (Lengua, Wolchik, Sandler, & West, 2000). In two related studies involving samples of young adult university students, increased reactivity of the ventral striatum to reward buffered against anhedonia symptoms following stressful life events (Nikolova, Bogdan, Brigidi, & Hariri, 2012), and early-life stress (Corral-Frias et al., 2015), suggesting that higher reward reactivity might buffer against the development of depression following both early-life and recent stressful experiences.

The one prior study examining the interactive effects of early life stress and reward-reactivity on depression focused solely on reactivity within the ventral striatum (Corral-Frias, et al., 2015), whereas extensive evidence suggests that depression and maltreatment are associated with alterations across a number of regions within the basal ganglia (Bramen et al., 2010; Dillon, et al., 2009; Forbes et al., 2006; Forbes, et al., 2009). Given that different regions within the basal ganglia underlie discrete aspects of reward-related processing (Berridge, et al., 2009), broader consideration of these regions may shed light upon more specific neurobiological processes that underlie associations between maltreatment and depression. Although the findings reported by Corral-Frias et al. (2015) provide initial support for the role of reward-reactivity in resilience to depression following early-life stress, the sample is comprised of a population of comparatively high-functioning adults (i.e., university students) with low exposure to early-life stress and rates of depression well below population levels (Kessler et al., 2005; Merikangas et al., 2010). It is unknown whether reward reactivity is associated with resilience to depression among youths exposed to more severe and chronic forms of maltreatment. Finally, prior work examining reward reactivity as a protective factor following early-life stress has focused exclusively on neural measures. Determining whether behavioral markers of reward processing exhibit a similar pattern is important, given that such markers are easier to measure and could be more easily incorporated into screening and clinical practice.

In the current study, we investigate the degree to which reactivity to rewards and positive social cues, examined at neural, behavioral, and subjective levels, is associated with resilience to depression in maltreated adolescents. We examine this question in a longitudinal sample of adolescents recruited based on exposure to severe child maltreatment encompassing physical and/or sexual abuse, assessed both using self-report and interview methods. We define reward reactivity as the degree to which response to a stimulus changes based on its rewarding properties and operationalized this in three ways: i) behavioral reactivity measured as variation in reaction time to cues associated with differing levels of reward on a monetary incentive delay (MID) task; ii) neural reactivity measured as BOLD response in the basal ganglia to positive vs. neutral stimuli; and iii) affective reactivity measured as changes in subjective ratings of emotional intensity in response to positive versus neutral images. We examined whether these measures of reward reactivity moderated the association of maltreatment with depression cross-sectionally and over a two-year follow-up period. We expected that greater reward reactivity would be associated with resilience to depression symptoms among maltreated adolescents.

Methods and Materials

Procedure

Adolescents completed baseline (T1) and follow-up (T2) assessments approximately two years apart. At T1, participants were assessed for maltreatment history, completed a reward task (monetary incentive delay task; MID) and an fMRI emotional processing task, described below. Depression symptoms were assessed at T1 and T2 with a clinical interview.

Sample

A sample of 59 adolescents aged 13 to 20 years (mean=16.95 years, SD=1.44 years; 61.0% female) participated. Participants were recruited from a large community-based study of adolescents with and without childhood maltreatment exposure (McLaughlin, Peverill, Gold, Alves, & Sheridan, 2015). From this sample, we recruited 21 adolescents (61.9% female) with exposure to physical and/or sexual abuse and a sample of 38 adolescents with no maltreatment exposure (60.5% female). Maltreated adolescents were matched to control participants on age, sex, parental education, race/ethnicity, and IQ.

Exclusion criteria included psychiatric medication use (with the exception of stimulant medications for attention-deficit/hyperactivity disorder, which were discontinued 24 hours before the scan for 1 participant), braces, claustrophobia, active substance dependence, pervasive developmental disorder, non-English speaking, and presence of active safety concerns. All females were post-menarchal. A total of 51 adolescents (18 maltreated) completed the follow-up assessment. The average length of delay between baseline (T1) and follow-up (T2) was 23.08 months (SD=3.24), and this was approximately 2 months longer in the maltreated group; see Table 1 for sample socio-demographic characteristics. Written informed consent was provided by legal guardians and written assent was provided by adolescents in accordance with the IRBs of Harvard University and Boston Children’s Hospital.

Childhood Maltreatment

Childhood maltreatment was assessed at T1 using two validated measures: the Childhood Trauma Questionnaire (CTQ) (Bernstein, Ahluvalia, Pogge, & Handelsman, 1997), and the Childhood Experiences of Care and Abuse (CECA), an interview administered by trained research assistants (Bifulco, Brown, Lillie, & Jarvis, 1997). The CTQ assesses frequency of physical, sexual, and emotional abuse during childhood. The CECA assesses multiple aspects of caregiving experiences, including physical and sexual abuse. Participants who reported physical or sexual abuse during the CECA interview or who had a score on the physical or sexual abuse subscales of the CTQ above a validated threshold (Walker et al., 1999) were classified as maltreated. A maltreatment severity score was computed by summing items from the CTQ physical and sexual abuse subscales. Children in the maltreated group reported significantly greater levels of abuse and neglect than control subjects (see Table 1). Cases of current and past maltreatment not previously reported to child protective services were reported in line with mandated state reporting and IRB requirements.

Psychopathology

Participants completed the Diagnostic Interview Schedule for Children Version IV (DISC-IV) (Shaffer, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000) to assess lifetime (T1) and past-year mental disorders (T1 and T2). These interviews assessed the presence of internalizing disorders, including major depression, and externalizing disorders. We derived a symptom count measure for major depression (range 0–21) from the DISC-IV. Table 1 provides information on depression symptoms according to maltreatment. For lifetime history of internalizing and externalizing disorders see Supplement S1. The incidence of major depression at T1 in the sample was low: four participants (3 maltreated) had lifetime major depression, $\chi^2(1)=2.59$, $p=.108$. One control participant did not complete either T1 or T2 psychopathology assessments and was excluded from analyses involving this measure.

Reward Task

At T1 participants completed a monetary incentive delay (MID) task (Knutson, Fong, Bennett, Adams, & Hommer, 2003) outside the scanner to assess reward-related behavior. The MID included four trial types: loss trials (loss values of $1 or $5); neutral trials ($0); low-reward trials, (reward values of $0.10 or $0.20, equally presented); and, high-reward trials (reward values of $1 or $5, equally presented) (Figure 1). Cues for each trial type were presented for 500 ms, followed by a delay (2000–2375 ms). Finally, the target, which was identical to the cue, appeared on the screen, and participants were instructed to press a button as quickly as possible to win (low and high-reward trials) or avoid losing money (loss trials). Prior to the MID, participants completed a practice task (20 trials) to determine the initial presentation time of the target based on the participant’s reaction time (RT). During the task, participants saw each cue 52 times presented an equal number of times during four blocks for a total of 208 trials. Trial types were randomly distributed across blocks. An algorithm was embedded into the task to adjust target presentation time to maintain accuracy of approximately 60% across all trials. Because of this, we focus on RT rather than accuracy as our behavioral measure of reward reactivity. Reaction time on similar tasks has been associated with depression (Pizzagalli, et al., 2009). On average, participants won $38.49 during the MID (range: $18.30 to $57.70). No maltreatment-related differences emerged for total earnings on the MID task, $t(54)=.03$, $p=0.97$. Participants were told that they would win the amount of money they acquired during the task and were paid immediately upon task completion to increasing the rewarding properties of the task. Average RTs for each cue type were calculated for trials all where a response was made after the target was presented. Three control participants did not complete the MID task and were excluded from analyses involving this measure.

Functional Magnetic Resonance Image (fMRI) task

At T1 participants engaged in a widely-used event-related task to assess neural markers of emotional reactivity and regulation (Buhle et al., 2014) that has previously been used with children (McRae et al., 2012) and has been described previously (McLaughlin, et al., 2015). A similar task has been used to assess reward system reactivity in children who have experienced early-life adversity (Goff, et al., 2013). Task design and contrasts for analysis were based on substantial prior literature (Buhle, et al., 2014). Participants viewed neutral, negative, and positive images from the International Affective Picture System (IAPS) (Lang, Bradley, & Cuthbert, 2008). Given our focus on processing of positive/rewarding information, we analyze only trials involving passive viewing of positive and neutral stimuli in the present study. Before each positive image, all of which were social in nature, participants saw an instructional cue to "look" or "increase" (Supplement S2). We focus here only on trial involving passive viewing of positive and neutral images (i.e., the "look" cue). During look trials, participants were instructed to allow their emotions to unfold naturally and not to engage in active strategies to modify their emotional response. Participants rated subjective emotional intensity (subjective affect) in the scanner after each trial on a 5-point Likert scale.

Stimuli were presented in 4 runs lasting 9 minutes each. The task included 26 trials of each type. The emotional stimulus and intertrial interval (ITI) were jittered.

Image Acquisition

Scanning was performed on a 3T Siemens Trio scanner at the Harvard Center for Brain Science using a 32-channel head coil. See Supplement S3 for image acquisition parameters.

Image Processing

Pre-processing and statistical analysis of fMRI data was performed in Nipype (Gorgolewski et al., 2011). fMRI pre-processing included spatial realignment, slice-time correction, and spatial smoothing (6mm FWHM), implemented in FSL. Data were inspected for artifacts using a Python implementation of Artifact Detection Tools (http://www.nitrc.org/projects/artifact_detect) available in Nipype. Volumes with motion >1.5mm or >3SD change in signal intensity were excluded from analysis, and 6 rigid-body motion regressors were included in person-level models. Person- and group-level models were estimated in FSL. A component-based anatomical noise correction method (Behzadi, Restom, Liau, & Liu, 2007) was used to reduce noise associated with physiological fluctuations. Following estimation of person-level models, the resulting contrast images were normalized into standard space, and anatomical co-registration of the functional data with each participant's T1-weighted image was performed using surface-based registration in FreeSurfer (Fischl et al., 2002), which provides better alignment than other methods in children (Ghosh et al., 2010). Normalization was implemented in Advanced Normalization Tools (ANTs) software. Data for one participant in the maltreatment group was excluded from MRI analysis due to excessive motion.

Behavioral and Subjective Affect Data Analysis

Two mixed-model analysis of variance (ANOVA) for i) RT from the MID task and ii) subjective affect ratings from the fMRI task were estimated with reward condition (low, high, none, loss) and image type (positive, neutral) as within-subjects factors, respectively, and maltreatment as a between-subjects factor.

fMRI Analysis

Regressors were created by convolving a boxcar function of phase duration and amplitude one with the standard hemodynamic response function for each phase of the task (instructional cue, stimulus, and rating) separately by emotion and trial type. A general linear model was constructed for each subject. Individual-level estimates of BOLD activity were submitted to group-level random effects models. We extracted parameter estimates for BOLD signal in four basal ganglia regions of interest (ROIs; caudate, putamen, pallidum, and nucleus accumbens) for the passive viewing of positive (look positive > neutral) stimuli. We constructed structural ROIs in each participant's native space using FreeSurfer. We extracted the average estimate of BOLD signal within the entire ROI for each participant.

Moderation analyses

To determine whether reward-related reactivity was associated with lower levels of depression following child maltreatment, we constructed interaction terms between maltreatment and each of our reward processing measures. Linear regression was used to investigate whether the association of maltreatment with depression symptoms was moderated by three measures of reward reactivity, separately at T1 and T2. These measures included: i) change in RT based on reward value during the MID task; ii) BOLD response in basal ganglia ROIs to positive relative to neutral stimuli (separately by hemisphere); and iii) change in self-reported affect to positive relative to neutral stimuli. Changes in RT and subjective affect ratings were calculated as arithmetic difference scores such that a positive change score indicated greater reactivity to reward (i.e., faster RT on high-reward compared to low-reward or neutral trials on the MID, and higher ratings of positive relative to neutral images). Difference in RT between neutral and reward conditions has been used previously to measure reward-related behavior on the MID (Pizzagalli, et al., 2009).

Age, sex and IQ were used as covariates in all moderation models, as well as length of time between assessments for longitudinal analyses. In longitudinal models predicting depression symptoms, symptom-level at T2 was the dependent variable, and T1 depression symptoms were included as a covariate. Cross sectional models were also re-run with lifetime major depression diagnosis assessed at T1 a covariate to observe if this changed the pattern of findings. Higher-order interaction terms were removed if non-significant. To facilitate interpretation of significant interaction terms, tests of simple slope at high (+1SD) and low (−1SD) levels of the continuous predictor were conducted (Aiken & West, 1991).

Missing data analysis showed data were missing at random (Little's MCAR test p>0.05). Missing data were imputed for IQ, depression symptoms, length of delay and brain activation where there was less than 15% of data missing using the multiple imputation function in SPSS 22. Pooled analysis results are reported for all analyses involving imputed data.

Results

Childhood Maltreatment and Depression Symptoms

Controlling for age, IQ and sex and length of delay between T1 and T2, childhood maltreatment was associated with greater depression symptoms at T1 (B=3.24, p=.014) and T2 (B=2.29, p=.049), but not residual change in symptoms from T1 to T2 (B=0.285, p=.80).

Correlations between Reward Reactivity Measures

Table 2 describes the correlations between reward reactivity measures. Moderate to high positive correlations between measures of changes in BOLD signal to positive relative to neutral images was observed across basal ganglia regions ($.31<r<.90$, all p's<.05). Changes in RT were moderately positively correlated with measures of brain activation in the accumbens and the caudate regions ($.28<r<.45$, all p's<.05). Changes in ratings of subjective affect were not significantly correlated with any other measure ($-.09<r<.26$, all p's>.05).

Childhood Maltreatment and Reward Reactivity

For the repeated measures ANOVA examining effects of reward level and maltreatment on RTs, Mauchly's test indicated that the assumption of sphericity was violated ($\chi^2(5)=11.60$, p=.041) and the Huynh-Feldt correction was applied. Behavioral reactivity to reward on the MID in the entire sample followed expectations, with a main effect of reward level, $F(2.6,150.5)=11.71$, $p<.001$, reflecting faster RT in high reward trials than the other conditions, and faster RT to loss trials as compared to low and no-reward trials (all p's<0.05). RT differences based on reward value did not vary by maltreatment, $F(2.6,150.5) = 0.44$, $p=0.71$. Average RTs across trials were faster among maltreated youth, however this was only observed at the trend level, $F(1,54) = 3.07$, p=0.086, (Figure 2).

Childhood maltreatment was associated with greater BOLD response to positive relative to neutral stimuli in the left nucleus accumbens (B=7.46, p=.020) and left putamen (B=4.82, p =.033), which both remained significant after controlling for age, sex and IQ (B=7.65, p=.021; B=4.51, p =.047, respectively).

With regard to self-report ratings of affect, participants rated positive images as more emotionally intense than neutral images ($F(1,57)=396.92$, $p<.001$), and, independent of image type, maltreated youth rated images as more emotionally intense than controls ($F(1,56)=5.64$, p=.021). Maltreatment was not associated with affect ratings of positive relative to neutral images ($t(57)= .371$, p=.71).

We also explored correlations between reward reactivity measures and continuous measures of abuse and neglect from the CTQ subscales; neither neglect nor abuse was associated with any of the reward reactivity measures (See Supplement S4).

Reward Reactivity and Depression Symptoms

No associations were observed between BOLD response to positive relative to neutral images in any basal ganglia ROI and depression symptoms at T1 or residual change at T2, with the exception of the left putamen, where activation was positively associated with depression symptoms at T1 (B=0.18, p=.016), which remained significant after controlling for age, sex and IQ (B=0.18, p=.029). Neither RT differences based on reward value nor ratings of positive images relative to neutral images were related to depression symptoms at T1 or residual change at T2.

Moderating Effects of Reward Reactivity

Covariates—Age, sex and intelligence were not associated with depressive symptoms at T1 or change in depressive symptoms at T2 (all p's<.05) (Supplement S5).

Behavioral Response to Reward—Behavioral reactivity to reward cues moderated the association of maltreatment with T1 depression symptoms. This was true both when we examined differences in RT on the MID task between low-reward and neutral trials (B=−0.27, p=.010), and high-reward and neutral trials (B=−0.31, p<.001). Tests of simple slopes revealed that maltreatment was associated with higher depression only among adolescents who had low reward reactivity (i.e., small changes in RT based on reward, p<.001) and not among adolescents who had high reward reactivity (p=.43–.76) (Figure 3). Reward reactivity did not interact with maltreatment to predict residual change in depression symptoms between T1 and T2.

BOLD activation to positive stimuli—In line with expectations, our paradigm elicited significant BOLD response in the basal ganglia for the contrast of positive > neutral images, including the caudate, nucleus accumbens and pallidum (Figure 4).

Next, we determined whether neural response to positive stimuli relative to neutral stimuli moderated the association of childhood maltreatment with depression symptoms. Left pallidum activation to positive images moderated the association between maltreatment and T1 depression symptoms (B=−0.45, p=.026). Maltreatment was associated with greater depression symptoms only among adolescents with low activation in left pallidum (p<.001) but not high activation (p=.89), (Figure 4). A similar pattern, at the trend-level, was observed in the left caudate (B=−0.31, p=.093) and right putamen (B=− 0.29, p=.083) (Supplement S6).

Childhood maltreatment interacted with activation in left putamen to predict residual change in depression symptoms between T1 and T2, (B=−0.28, p=.023), (Figure 5). Maltreatment was associated with increases in depression symptoms for adolescents with low (p=.046), but not high (p =.337) activation in the left putamen to positive relative to neutral images.

Subjective affect—At the trend-level, the interaction of maltreatment and subjective ratings of positive relative to neutral images predicted T1 depression symptoms (B=−4.06, p=.075) (Supplement S7), but not residual change between T1 and T2 (B=−1.58, p=.420).

The trend level finding remained when lifetime diagnosis of major depression was included in the model (B=−3.45, p=.095).

Discussion

Childhood maltreatment is a potent risk factor for depression. Identifying factors associated with resilience to depression in maltreated children is critical for informing intervention efforts to prevent depression following maltreatment. We provide evidence indicating that individual differences in reactivity to positive and rewarding stimuli across behavioral and neurobiological levels moderate the degree to which childhood maltreatment is associated with depression in adolescence. Specifically, maltreatment was associated with depression only among youth with low reactivity to reward. This pattern was observed with regard to changes in reaction time to cues paired with reward compared to cues unassociated with reward and activation in the left pallidum when viewing positive images. Prospectively, maltreatment predicted increases in depression symptoms over time only for adolescents with low, but not high, activation of the left putamen to positive images. Together, these finding suggest that greater reactivity to positive and rewarding environmental cues is associated with resilience to depression among children who have experienced maltreatment.

Two prior studies have considered the role of neural reward reactivity as protective against the mental health consequences of stress, showing that ventral striatum reactivity to reward moderated the association of both past-year stressful life events with self-reported positive affect (Nikolova, et al., 2012) and early-life stress with anhedonia symptoms (Corral-Frias, et al., 2015) in a cross-sectional sample of university students. We extend these findings in four important ways. First, we demonstrate that reactivity to reward is associated with resilience to depression symptoms in adolescence following child maltreatment, a potent and severe form of early-life stress, within a community-based sample of adolescents exposed to maltreatment who were compared to socio-demographically matched adolescents with no history of maltreatment exposure. Second, we find a protective effect of reward reactivity at both behavioral and neural levels. Demonstrating that behavioral markers of reward processing exhibit a similar pattern to neural markers is important, given that such markers are easier to measure and could be more easily incorporated into screening and clinical practice. Third, we find this effect prospectively, demonstrating a protective role of reward reactivity against future onset of depression symptoms. Finally, we observe a protective effect for clinically meaningful depression symptoms assessed using a structured clinical interview. These findings suggest that greater reactivity to reward is associated with resilience to depression following childhood maltreatment, providing novel evidence for a psychological and neurobiological mechanism explaining differential susceptibility for depression among maltreated youths.

Why might reactivity to positive environmental cues and rewarding events be associated with resilience to depressive symptomology following maltreatment? Dopamine release is observed in both the ventral and dorsal striatum upon receipt of rewards (Breiter et al., 1997; Koepp et al., 1998), and the dorsal striatum plays a specific role in learning stimulus-response contingencies necessary for appetitive behavior (Mannella, Gurney, & Baldassarre, 2013; O'Doherty et al., 2004). Animal studies indicate putamen inactivation causes an inability to maintain or learn habitual responses to rewards (Yin, Knowlton, & Balleine, 2004). Among adults, depression is associated with reduced dopamine transmission in the mesolimbic pathway, including the putamen (Bowden et al., 1997), and reduced activation in the left putamen during reward anticipation (Pizzagalli, et al., 2009). The acquisition of an appetitive behavior prior to stress exposure in rodents protects against stress-induced changes to dopamine transmission in the mesolimbic pathway (Nanni et al., 2003), consistent with our finding that greater putamen activation buffered risk for future depression among maltreated adolescents. Moreover, stress-induced anhedonia was greater, appeared earlier, and was of longer duration among rats with pre-stress pessimistic rather than optimistic traits (Rygula, Papciak, & Popik, 2013). Our findings suggest that treatments that promote instrumental learning about rewards, such as behavioral activation (Dimidjian et al., 2006), might be particularly effective in treating or preventing depression among maltreated youths. We are unaware of intervention studies examining this possibility, despite the fact that maltreated children respond poorly to standard treatments for depression (Nanni, et al., 2012).

Given the passive nature of our fMRI task we may have expected that greater reactivity in regions associated with hedonic experience (nucleus accumbens and pallidum) rather than behavioral responding (dorsal striatum) to be more strongly implicated in resilience to depression (Berridge, et al., 2009). However, in addition to the cross-sectional findings involving the pallidum, we found that greater activation in the left putamen prospectively protects against the onset of future depression symptoms. As mentioned above, the putamen plays a crucial role in instrumental learning, particularly habit learning (Yin, et al., 2004). Given the positive images presented in the task were social in nature, it may be the case that behavioral reactivity to positive images in the form of facial mimicry—a learned but largely habitual social response (Dykas, Ehrlich, & Cassidy, 2011)—may explain the involvement of the putamen in the passive viewing task. Interestingly, early life adversity has been associated with reduced facial mimicry to positive emotions (Ardizzi et al., 2013), and the development of facial mimicry is fostered by positive reinforcement (Sims, Van Reekum, Johnstone, & Chakrabarti, 2012). It may be that maltreated children who learn and preserve the capacity to both react to and reciprocate positive social cues experience greater protection against depression.

Prior studies have shown that adults exposed to more stressful life events as children and adolescents who were institutionally raised for the first few years of life exhibit reduced ventral striatum reactivity to rewards (Goff, et al., 2013; Hanson et al., 2015). Further, early-life institutional rearing and emotional neglect have been associated with developmentally blunted responses in the ventral striatum during the transition from childhood to adolescence (Goff, et al., 2013; Hanson, Hariri, et al., 2015). In contrast, we observed *greater* reactivity to positive images in the left nucleus accumbens and left putamen among maltreated children compared to controls. These discrepant findings could reflect differences in the task used to elicit neural reward reactivity and divergent patterns based on the specific type of adversity being examined. Our task measured passive reactivity to positive stimuli, which is more aligned with the consummatory stage of reward processing and aligns with the task used by Goff and colleagues (2013), whereas the instrumental reward tasks used by Hanson and colleagues (Hanson, Albert, et al., 2015; Hanson, Hariri, et al., 2015) are likely to have captured activation related to reward expectancy and anticipation (Berridge, et al., 2009). Ventral striatal response during anticipation of reward is contingent upon both the need to make an instrumental response and the degree of uncertainty of reinforcement (Berns, McClure, Pagnoni, & Montague, 2001; Bjork & Hommer, 2007). Neurobiological evidence supports the divergence of these reward-processing phases, with "liking" stages being more strongly associated with the pallidum, and "wanting" with the ventral striatum (Berridge, et al., 2009). Childhood adversity appears to differentially influence neural response during these discrete reward processes, as one study reported early exposure to adversity (indexed by poverty and social disadvantage) was associated with reduced neural reactivity in the ventral and dorsal striatum during anticipation of reward and heightened reactivity during reward delivery in the putamen, right pallidum and insula (Boecker, et al., 2014). This suggests that childhood adversity might be associated with lower expectations of positive outcomes and greater surprise or pleasure when positive events occur (Mannella, et al., 2013).

A second, divergent possibility is that different types of adversity have different associations with reward processing. Studies that report associations of childhood adversity with reduced ventral striatum response to reward have focused on emotional neglect (Hanson, Hariri, et al., 2015), and institutional rearing (Goff, et al., 2013) which are forms of psychosocial deprivation. In contrast, our study focused on youths exposed to physical and sexual abuse a form of threatening early environment. Prior research suggests that negative emotional stimuli are more salient to children exposed to high levels of environmental threat (McCrory et al., 2013; McCrory et al., 2011; McLaughlin, et al., 2015) Our findings could indicate that while maltreated adolescents do not exhibit heightened response when anticipating rewards, the receipt of these rewards is more salient for them than youths without maltreatment histories. This pattern might be explained by the fact that children who have been abused typically live in environments characterized by low levels of positive affect and warmth (Bugental, Blue, & Lewis, 1990; Burgess & Conger, 1978; Kavanagh, Youngblade, Reid, & Fagot, 1988); thus, the receipt of rewards may be more unexpected or surprising to them. Indeed, nucleus accumbens response to reward receipt is magnified when rewards are unexpected or surprising (Berns, et al., 2001). Different types of adversity, as well as duration, timing (for an example, see Hanson, Albert, et al., 2015), or degree of exposure to other stressors, may influence reward processing in distinct ways and future research is needed to examine this possibility empirically.

We observed a trend for faster overall reaction times on the reward task among maltreated youth compared to non-maltreated youth. Previous findings have been mixed, with slower overall reaction times reported amongst maltreated adults (Dillon, et al., 2009) and, in maltreated children a consistently fast pattern of response has been observed, regardless of reward condition (Guyer, Nelson, et al., 2006). Although we did not replicate the finding of reduced sensitivity to reward value (Guyer, Nelson, et al., 2006), we did observe a similar pattern of faster reaction times overall amongst maltreated youth, which may reflect elevated arousal or impulsivity among maltreated youth when reward receipt or loss is contingent upon a behavioral response. Failure to fully replicate specific effects may be due to differences in the task, age and psychopathology between studies, but also because of the comparatively high monetary rewards we offered for good performance on the task, which may have resulted in high levels of motivated responding, and greater discrimination between reward cues. Nevertheless, the finding that individual change in reaction time, as a function of reward outcome, was associated with resilience to depression following maltreatment highlights the importance of considering idiographic approaches for understanding relationships between biobehavioral risk factors and psychopathology outcomes.

These findings build on existing mechanistic models describing the pathways linking childhood adversity with vulnerability for depression through reward processing by documenting that reward reactivity is associated with resilience to depression among maltreated youths. Future studies are needed to identify factors that lead children who have experienced maltreatment to diverge on their capacity to react and engage with rewarding experiences. As noted earlier, stable temperamental characteristics, such as trait positive affect, may promote reward reactivity and persist across time despite exposure to adversity, playing an enduring role in buffering risk for depression. Models and longitudinal studies exploring developmental interactions between trait and environmental factors are needed to better understand these associations.

The role heightened reward reactivity plays in protecting maltreated youth from depression needs to be distinguished from previous literature linking heightened reward sensitivity to vulnerability for engaging in risky behaviors during adolescence (Galvan, Hare, Voss, Glover, & Casey, 2007; Steinberg, 2008). On the other hand, greater reactivity to prosocial rewards has been associated with decreases in future risk taking behavior (Telzer, Fuligni, Lieberman, & Galván, 2013), suggesting that the nature of the rewarding stimulus and the context of reward may be important factors in determining risk or resilience. The findings in the current study are inconclusive regarding the importance of specific types of rewards; however, despite moderate correlations between the neural and behavioral measures of reward reactivity, the pattern of resilience was consistent across measures. This could suggest that although the same child may not respond similarly to different types of positive or rewarding cues (i.e., social or monetary), that being reactive to either may be protective against depression. Future studies would benefit from considering the context and nature of rewards/positive experiences with greater precision than in the current investigation.

The current findings must be considered in light of some limitations. We did not assess trait positive affect. Nor did we explore the role of reward reactivity in the prediction of anhedonia due to the measure of depression we used and our relatively small sample. Future studies should examine whether differences in neural reward-system reactivity are associated with anhedonia specifically, as has been suggested in both adolescent (Forbes, et al., 2009) and adult studies (Wacker, Dillon, & Pizzagalli, 2009) of depression. We also did not have a large enough sample size to consider sex as an additional moderator of these associations, although there is some evidence to suggest that as the degree of childhood adversity increases, the effects of sex on risk for depression diminishes (Dunn et al., 2011). Although we only extracted neural activation on passive viewing trials, it is possible that the regulation task could have inadvertently interfered with activation during subsequent passive viewing trials. We did not examine BOLD signal relating to regulation trials given the focus of previous literature on emotional reactivity to positive cues as a biological marker of resilience to depression following maltreatment (Corral-Frias, et al., 2015). Indeed, future studies could consider whether neural markers associated with effortful increases in positive emotion are associated with decreased risk for depression amongst maltreated youth, identifying this as a targeted intervention for this population. Our measure of affective reactivity may have been improved by using standardized measures of state positive affect. Finally, we focused our MRI analyses only on basal ganglia regions of interest shown in prior work to be associated with reward processing—including social reward (Baez-Mendoza & Schultz, 2013), childhood adversity, and depression. The degree to which reactivity in other regions implicated in social and emotional processing, such as the amygdala and ventromedial prefrontal cortex, are involved in resilience to depression following maltreatment remains to be examined in future research. Given our relatively small sample size to detect moderation both type 1 and type 2 error are possible.

Modulation of behavior to monetary rewards and activation in the basal ganglia to positive stimuli moderated the association of childhood maltreatment with depression symptoms, revealing that greater reactivity to positive environmental cues is associated with resilience to adolescent depression following childhood maltreatment. These findings warrant further exploration of an underlying neurodevelopmental factor related the capacity to react to positive environmental cues that confers resilience to depression following exposure to maltreatment. Greater knowledge of developmental mechanisms that are associated with altered reward processing following maltreatment and the specific impacts of different forms of adversity on subcomponents of reward processes is critical for developing targeted interventions aimed at reducing distress and preventing psychopathology in this highly vulnerable population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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General Scientific Summary

Childhood maltreatment is associated with elevated risk for depression during adolescence, and little is known about factors associated with resilience to depression among this vulnerable group. This study suggests that greater reactivity to positive and rewarding experiences are potential markers of resilience to depression amongst maltreated youth.

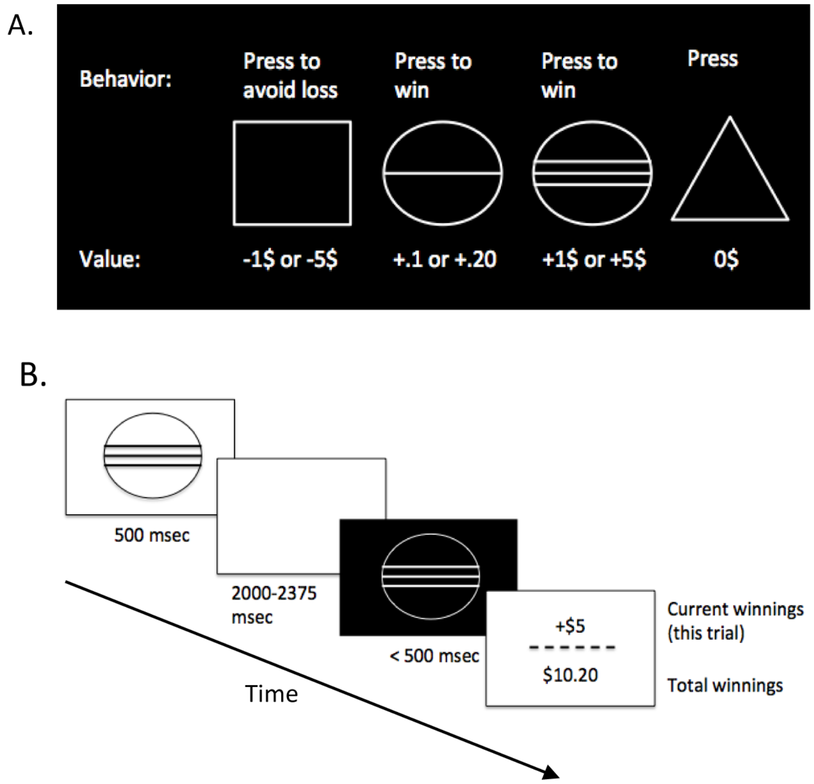

Figure 1.

(A) Potential values for each stimulus cue in the monetary incentive delay (MID) task. Cues were simple line drawings of geometric shapes. (B) Trial timing and example of a high reward stimulus during the MID.

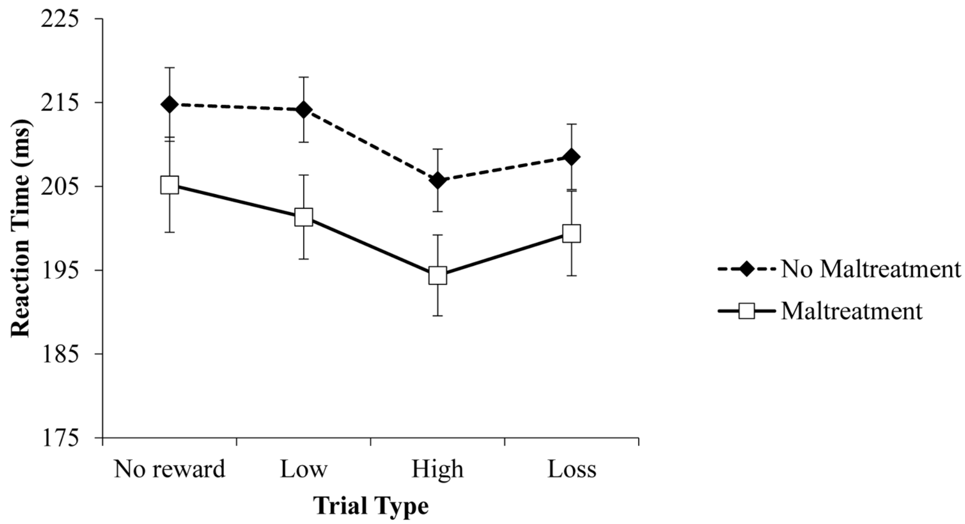

Figure 2.

Average reaction times by reward condition and group. Error bars represent standard error of the mean

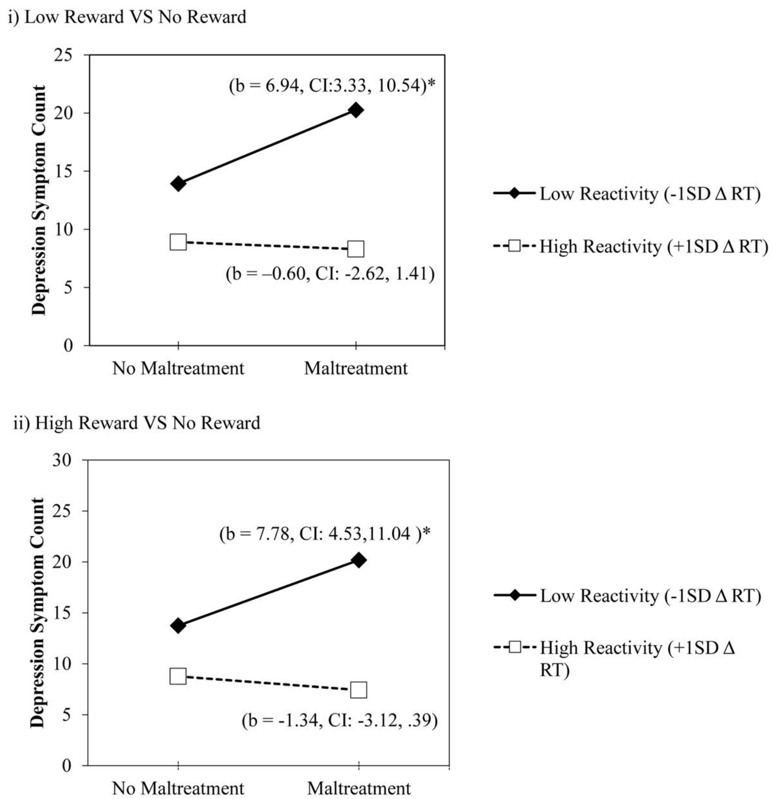

Figure 3.

Regression lines for association of maltreatment with depression symptoms at T1 as a function of ΔRT in i) low-reward, and ii) high-reward trials of the MID relative to neutral trials (2-way interactions). b =unstandardized regression co-efficient (i.e., simple slope); * = $p < 0.05$. CI refers to 95% confidence interval for unstandardized regression co-efficient. Dotted lines depict children with relative greater change in RT (+1SD), solid line depicts children relatively smaller change in RT (−1SD), relative to neutral trials. Δ = Change in reaction time.

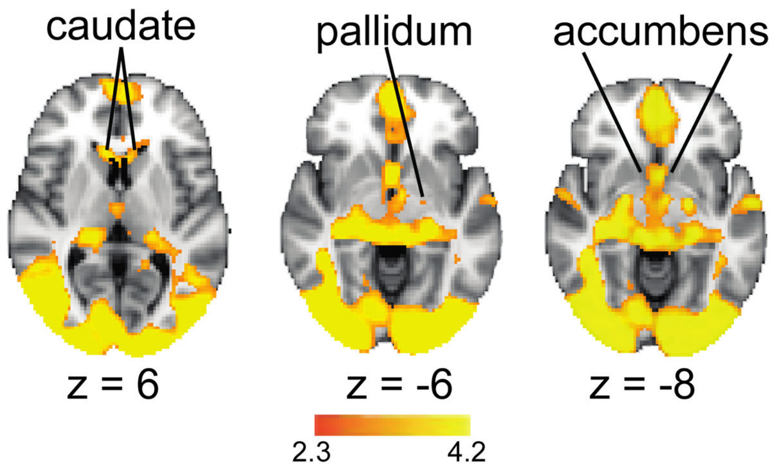

Figure 4.

Whole brain activity for positive stimuli in transaxial slices. Statistical map reflects regions of significant areas of activation (cluster-level corrected in FSL z >2.3, p < 0.05) in response to Look Positive > Look Neutral. Within the basal ganglia, significant clusters were found bilaterally in the caudate (Left: x = 6, y =18, z = 6; Right: x = 8, y = 22, z = 6), and nucleus accumbens (Left: x = −6, y = 10, =z = 8; Right: x = 6, y = 12, z = −8), and left pallidum (x = −18, y = −10, z = −6). Coordinates reflect MNI space.

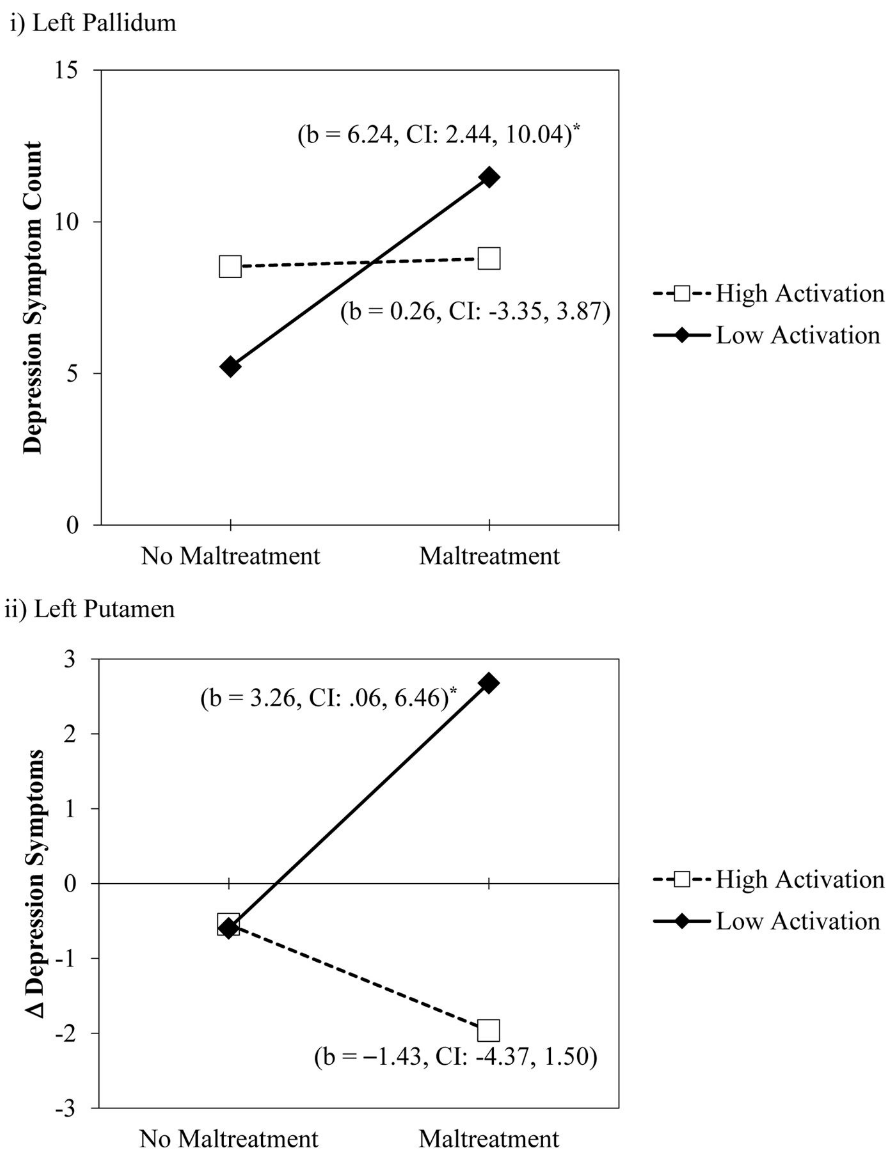

Figure 5.

Regression lines for association of maltreatment with i) depression symptoms at T1, and ii) residual change in depression symptoms as a function of BOLD activation to positive relative to neutral images in i) left pallidum and ii) left putamen (2-way interactions). b =unstandardized regression co-efficient (i.e., simple slope); * = p <0.05). CI refers to 95% confidence interval for unstandardized regression co-efficient. Dotted lines depict children with higher levels of activation (+1 SD), solid line depicts children with lower levels of activation (−1SD) to positive images (relative to neutral images), Δ = residual change score.

Table 1

Sample characteristics for participants with and without maltreatment histories.

	Control		Maltreatment			
	%	**N**	**%**	**N**	χ^2	***p-value***
Female	60.5	23	61.9	13	0.011	0.917
Non-white	44.7	17	23.8	5	2.53	0.111
Parent educational attainment[a]					3.79	0.286
High school or less	13.5	5	19.0	4		
Some college	18.9	7	33.3	7		
College degree	43.2	16	19.0	4		
Graduate school	24.3	9	28.6	6		
Right handed[b]	83.3	30	85.7	18	0.057	0.812
	Mean	SD	Mean	SD	*t*	*p-value*
Age (years)	17.1	1.41	16.7	1.52	0.90	0.373
WASI Percentile[c]	51.9	28.6	50.1	27.9	0.22	0.829
Time between T1 and T2 (months)[d]	22.2	2.68	24.7	3.63	2.75	0.008*
Depression Symptom Count T1[e]	6.7	4.60	10.0	5.08	2.51	0.015*
Depression Symptom Count T2[d]	6.0	4.53	8.6	4.02	2.02	0.049*
Maltreatment Severity (CTQ)						
Total CTQ[f]	22.7	2.79	42.0	11.15	10.17	<0.001*
Physical Neglect	5.7	1.09	8.0	3.07	4.08	<0.001*
Emotional Abuse	6.7	1.97	13.1	4.70	7.40	<0.001*
Physical Abuse	5.2	0.71	10.6	4.65	6.97	<0.001*
Sexual Abuse	5.1	0.49	10.3	6.18	5.25	0.01*

[a]Data missing for one parent in the control group

[b]Handedness data missing for two participants

[c]6 participants in the control group had missing values on the WASI

[d]8 adolescents (5 controls) did not complete T2 assessment

[e]3 participants in the control group had missing values for the DISC measures at T1

[f]Calculated as the sum of physical, sexual, and emotional abuse, and physical neglect subs-scales of the CTQ.

* *p*<.05, 2-tailed.

Table 2

Pearson correlations between measures of reward reactivity.

Measure		1	2	3	4	5	6	7	8	9	10	11
ΔBOLD	1. L-Accumbens	-										
	2. L-Caudate	0.309*	-									
	3. L-Pallidum	0.114	0.618**	-								
	4. L-Putamen	0.139	.360**	0.633**	-							
	5. R-Accumbens	0.730**	.325*	0.14	0.159	-						
	6. R-Caudate	.361**	.895**	.528**	.347**	.356**	-					
	7. R-Pallidum	0.112	.426**	.692**	.576**	0.114	.424**	-				
	8. R-Putamen	0.061	.487**	.815**	.707**	0.138	.523**	.761**	-			
ΔRT	9. High vs Low	0.19	.449**	0.075	0.008	.290*	.421**	−0.01	0.101	-		
	10. High vs None	−0.027	.279*	0.039	0.003	0.121	0.194	−0.038	−0.029	.466**	-	
	11. Low vs None	−0.19	−0.087	−0.023	−0.003	−0.118	−0.167	−0.033	−0.117	−.357**	.660**	-
ΔAffect	12. Positive vs Neutral	−0.09	0.174	0.247	0.177	0.105	0.208	0.258	0.184	0.036	0.198	0.179

* $p<0.05$,

** $p<0.01$ (2-tailed).

L=left, R=Right. ΔBOLD=change in BOLD signal for positive relative to neutral images. ΔRT=change in reaction times relative to high, low and non-rewarded trials. ΔAffect=change in affect rating of positive relative to neutral images.