Childhood Adversity Is Associated with Left Basal Ganglia Dysfunction During Reward Anticipation in Adulthood

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Background: Childhood adversity increases the risk of psychopathology, but the neurobiological mechanisms underlying this vulnerability are not well-understood. In animal models, early adversity is associated with dysfunction in basal ganglia regions involved in reward processing, but this relationship has not been established in humans.

Methods: Functional magnetic resonance imaging was used to examine basal ganglia responses to: 1) cues signaling possible monetary rewards and losses; and 2) delivery of monetary gains and penalties, in 13 young adults who experienced maltreatment before age 14 years and 31 nonmaltreated control subjects.

Results: Relative to control subjects, individuals exposed to childhood adversity reported elevated symptoms of anhedonia and depression, rated reward cues less positively, and displayed a weaker response to reward cues in the left globus pallidus. There were no group differences in right hemisphere basal ganglia response to reward cues or in basal ganglia response to loss cues, no-incentive cues, gains, or penalties.

Conclusions: Results indicate that childhood adversity in humans is associated with blunted subjective responses to reward-predicting cues as well as dysfunction in left basal ganglia regions implicated in reward-related learning and motivation. This dysfunction might serve as a diathesis that contributes to the multiple negative outcomes and psychopathologies associated with childhood adversity. The findings suggest that interventions that target motivation and goal-directed action might be useful for reducing the negative consequences of childhood adversity.

C hildhood adversity, including abuse, neglect, and exposure to dysfunctional household environments (e.g., witnessing parental violence, living with substance-abusing individuals), increases the risk for psychopathology and substance abuse (1–6) and can lead to dysregulated hypothalamic-pituitary-adrenal stress responses (7), neuropsychological impairments (8), and dysfunction in brain regions implicated in learning and memory (9). However, potential effects on brain reward circuitry in adulthood have gone unexplored, although there is evidence of altered reward processing in maltreated children (10). This is important because reward system dysfunction might underlie anhedonia (11), a core component of stress-related psychopathology (12). Although maltreatment is associated with anhedonia (13) and melancholia (14), neural mechanisms underlying these relationships remain unknown.

In experimental animals, chronic stressors can weaken preferences for sucrose solutions and conditioning for rewarded locations, delay approach to palatable foods, and increase thresholds for brain stimulation reward (15–19). These effects are hypothesized to reflect dysfunction in dopaminergic (DA) circuits that project to the basal ganglia (19), which are sensitive to

early adversity (20). Importantly, in experiments using cue-outcome designs these DA circuits are more strongly associated with incentive motivational processes elicited by reward-predicting cues than with hedonic processes triggered by rewarding outcomes (21–23), suggesting that early adversity might preferentially affect responses to reward-predicting cues. Consistent with this assumption, early adversity in marmosets decreased motivation to obtain rewards without affecting consummatory behavior (17). Thus, we hypothesized that childhood adversity in humans could weaken basal ganglia responses to reward-predicting cues while leaving responses to actual rewards intact.

To test this hypothesis, we used functional magnetic resonance imaging (fMRI) and a monetary incentive delay (MID) task (22,23) to investigate reward-processing in young adults exposed to maltreatment (24). This task was selected because it recruits basal ganglia activity across a variety of samples, including adolescents (25), young adults (22,23), and older adults (26). Trials began with cues signaling potential rewards, losses, or no-incentive. Next, participants pressed a button in response to a briefly presented target; they were instructed that rapid reaction times (RTs) increased their chances of receiving gains and avoiding penalties. Finally, feedback indicated whether money was gained or lost. Analyses focused on basal ganglia regions of interest (ROIs). Participants also rated cues and outcomes for arousal and valence.

We predicted that, relative to control subjects, maltreated participants would show slower RT on reward trials, rate reward cues as less positive, and show weaker basal ganglia responses to reward cues. Group differences in response to gains were not predicted, on the basis of recent animal findings (17) and evidence that early adversity affects DA transmission (19) that is most strongly associated with reward anticipation (22,23,27).

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Methods and Materials

Participants

Maltreated Group. Maltreated participants were recruited from a study exploring relations between social risk factors and psychopathology in young adulthood (24). Recruitment was directed at 63 individuals: 18 could not be relocated, 21 were excluded (Supplement 1), 3 could not be scheduled, and 2 declined. The remaining 19 underwent fMRI scanning; data from 6 individuals were excluded due to excessive head movement. The final sample consisted of 13 young adults (4 men) (Table 1). Eight have been studied since infancy (mean $\pm$ SD age at enrollment = 8.88 months $\pm$ 5.36 months), and five have been studied since young adulthood (20.60 years $\pm$ 1.34 years).

Participants were recruited on the basis of evidence of emotional, physical, and/or sexual abuse during childhood that met state guidelines for maltreatment. Evidence of abuse was rated in the original study from multimodal assessments including the Adult Attachment Interview (28,29), the revised Conflict Tactics Scale (30), the Traumatic Stress Schedule (31), whether a report of concern for safety was substantiated by protective services before age 7 years, and whether major disruption of placement with the primary caretaker had occurred. Reliability of abuse ratings was high (intraclass correlation coefficient = .99, $n = 37$). Among the 13 participants, 12 reported abuse before age 12 years (emotional abuse $n = 1$; physical or sexual abuse $n = 6$; multiple types of abuse $n = 5$), with 1 participant reporting abuse beginning at age 13 years (sexual abuse) (see Supplement 1 for details).

Maltreated participants were right-handed (32), reported no history of medical or neurological conditions, and met fMRI safety criteria. Two maltreated participants reported using psychotropic medications in the weeks before scanning (citalopram, $n = 1$; hydrocodone, $n = 1$).

Control Subjects. Maltreated participants were compared with community control subjects ($n = 31$) who performed the same task for another study (33). Data from two control subjects were discarded due to excessive head movement. The final sample included 16 men (Table 1). Control subjects were right-handed (32); reported no history of neurological or medical conditions, no current or past psychopathology, no psychotropic

medication use; and met fMRI safety criteria. Control subjects were older and more educated than maltreated participants, but gender and racial composition were similar (Table 1). Community control subjects were used because the study from which maltreated individuals were recruited did not yield an adequate number of nonmaltreated individuals for comparison.

Procedure

Informed Consent. Participants consented to an institutional review board-approved protocol and were debriefed after the study. Maltreated and control participants were compensated $100 and $80, respectively, for the fMRI session and were given $20–$22 as "earnings" from the task.

Psychopathology Assessments. Structured clinical interviews for DSM disorders (SCID-I [34]) were administered once to control subjects to rule out psychopathology. Two SCIDs were administered to maltreated participants. The first covered lifetime through young adulthood (age at first SCID: 20.10 $\pm$ 1.43 years). The second was administered shortly before the experimental session (1.17 $\pm$ 1.58 months before) and focused on the interval between young adulthood and the experimental session (interval between SCIDs: 4.48 $\pm$ 1.47 years). Both groups completed the Mood and Anxiety Symptoms Questionnaire (MASQ: 35), which assesses anxious arousal (AA), anhedonic depression (AD), and general distress due to anxiety (GDA) or depression (GDD). Maltreated participants completed the Center for Epidemiological Studies Depression Scale (CES-D: 36); control subjects completed the Beck Depression Inventory (BDI-II: 37).

MID Task. The MID task was based on previous studies (22) and identical to a prior version (23). There were five blocks of 24 trials. Trials began with one of three visual cues (1.5 sec) signaling potential outcomes (reward: +$; loss: −$; no-incentive: $0) (8 trials/cue/block). After a jittered interstimulus interval (ISI: 3–7.5 sec), a red square was presented for a variable duration. Participants responded to the square with a button press. After a second ISI (4.4–8.9 sec), visual feedback (1.5 sec) indicated delivery of a gain (range: $1.96 to $2.34; mean: $2.15), penalty (range: $1.81 to −$2.19; mean: −$2.00), or "no change". Reward trials ended with gains or no change, loss trials ended with penalties or no change, and no-incentive trials ended in no change. An intertrial-interval separated the trials (3–12 sec).

To achieve a balanced design, one-half the reward and loss trials ended in gains and penalties, respectively. However, participants were told that rapid RTs increased their chances of receiving gains and avoiding penalties, so that RT could be used to probe incentive motivation. After blocks two and four, participants rated cues and outcomes for arousal (1 = low, 5 = high) and valence (1 = negative, 5 = positive). Ratings data were not collected for two maltreated participants due to time constraints, and reward cue valence ratings were not collected from one control subject due to error.

Table 1. Sociodemographic and Self-Reported Mood Data

	Maltreated Group		Control Group			
	Mean	SD	Mean	SD	Statistic	p
% Female	69%	NA	45%	NA	$\chi^2(1) = 2.14$	> .13
Age	24.58	.88	37.08	13.77	$t(40) = 4.87$	< .001
Education	12.92	2.22	15.28	1.65	$t(40) = 3.84$	< .001
% Caucasian	77%	NA	76%	NA	$\chi^2(1) = .006$	> .94
MASQ-GDD[a]	22.77	12.90	14.89	2.97	$t(39) = 3.10$	< .005
MASQ-GDA[a]	17.15	7.10	14.00	2.46	$t(39) = 1.56$	> .13
MASQ-AD[a]	55.69	20.84	42.57	7.81	$t(39) = 2.20$	< .047
MASQ-AA[a]	20.62	3.93	18.54	1.95	$t(39) = 1.81$	> .09
CES-D	12.15	12.93	NA	NA	NA	NA
BDI-II[a]	NA	NA	2.25	2.46	NA	NA

MASQ, Mood and Anxiety Symptom Questionnaire (35); GDD, General Distress Depressive symptoms; GDA, General Distress Anxious symptoms; AD, anhedonic depressive symptoms; AA, anxious arousal symptoms; CES-D, Center for Epidemiological Studies Depression Scale (36); BDI-II, Beck Depression Inventory (37).

[a]One control participant had missing values for the MASQ and BDI.

MRI Acquisition

The MRI data were acquired on a 1.5-T Symphony/Sonata scanner (Siemens Medical Systems; Iselin, New Jersey), with tilted slice acquisition and z-shimming to minimize susceptibility artifacts (38). During structural imaging, a T1-weighted magnetization prepared rapid gradient echo volume was acquired (repetition time [TR]/echo time [TE]: 2730/3.39 msec; field-of-view [FOV]: 256 mm, 1 $\times$ 1 $\times$ 1.33 mm voxels; 128 slices). During functional imaging, gradient echo T2*-weighted echo planar images were acquired (TR/TE: 2500/35 msec; FOV: 200 mm, 3.125 $\times$ 3.125 $\times$ 3 mm voxels; 35 slices; 222 volumes).

Table 2. Current and Lifetime Axis I Diagnoses for Maltreated Participants

Subject	Period	Diagnoses
1	Current	Generalized anxiety disorder
	Lifetime	Major depressive disorder; alcohol abuse; cannabis abuse
2	Current	None
	Lifetime	Major depressive disorder; specific phobia
3	Current	None
	Lifetime	Alcohol abuse
4	Current	None
	Lifetime	Anxiety disorder, not otherwise specified
5	Current	Major depressive disorder; agoraphobia without panic disorder; generalized anxiety disorder; post-traumatic stress disorder
	Lifetime	Major depressive disorder; alcohol dependence; hallucinogen dependence; eating disorders
6	Current	None
	Lifetime	None
7	Current	None
	Lifetime	Major depressive disorder
8	Current	None
	Lifetime	None
9	Current	None
	Lifetime	Alcohol dependence; bipolar I disorder
10	Current	None
	Lifetime	Alcohol dependence; cannabis dependence; opioid dependence
11	Current	None
	Lifetime	Panic disorder without agoraphobia; cannabis abuse
12	Current	None
	Lifetime	Generalized anxiety disorder; social phobia; alcohol abuse; cannabis abuse
13	Current	None
	Lifetime	None

Data Analysis

Mood. Between-groups *t* tests tested for differences on the MASQ.

RT and Affective Ratings. After removing outliers (RTs exceeding mean ± 3 SD), RTs were entered into a Group × Cue × Block analysis of variance (ANOVA). Ratings were entered into Group × Cue or Group × Outcome ANOVAs. Significant differences were followed-up with *t* tests. The Greenhouse-Geisser correction was used when sphericity was violated.

fMRI. Neuroimaging data were analyzed with FS-FAST (http://surfer.nmr.mgh.harvard.edu) and FreeSurfer (39). Preprocessing included motion and slice-time correction, removal of slow trends with a second order polynomial, intensity normalization, and spatial smoothing (6 mm full-width-at-half-maximal Gaussian filter). Hemodynamic responses were modeled as a γ function convolved with stimulus onsets. A temporal whitening filter estimated and corrected for autocorrelation in the noise. Participants with head movement >3.75 mm or degrees were excluded (approximately the size of 1 functional voxel; control: *n* = 2; maltreated: *n* = 6). For remaining participants, motion parameters were included as nuisance regressors.

Four basal ganglia ROIs were defined by FreeSurfer's subcortical segmentation algorithm: nucleus accumbens (NAcc), caudate, putamen, and globus pallidus (39,40) (Supplement 1). Average β weights measuring the fit of the data to the model were extracted from each ROI for the cues and three outcomes (gains, penalties, no change feedback on no-incentive trials) and entered into Group × Cue (or Outcome) × Hemisphere ×

Structure (NAcc, caudate, putamen, pallidus) ANOVAs. Significant effects were followed-up with ANOVAs and *t* tests. Analysis of covariance (ANCOVA) was not used, because groups differed on the potential covariates, age, and education, violating a key assumption of ANCOVA (41) (Supplement 1).

Basal Ganglia Volumetry. Basal ganglia volumes were extracted from FreeSurfer, divided by intracerebral volume, multiplied by 100 to yield percent intracerebral volume scores, and entered into a Group × Hemisphere × Structure ANOVA.

Regression Analyses Including Age and Education. Group differences were followed-up with hierarchical regressions to determine whether they remained after removing variance associated with age and education. Possible effects of age on findings were also investigated by comparing maltreated participants to a subsample of 13 age-matched control subjects (Supplement 1); it was not possible to select a subsample of education-matched control subjects.

Results

Clinical Data

Seventy-seven percent of maltreated participants met DSM-IV criteria for an Axis I disorder at some time (Table 2). On the SCID proximal to scanning, one participant met criteria for MDD, agoraphobia, Generalized Anxiety Disorder (GAD), and post-traumatic stress disorder; another met criteria for GAD (see Supplement 1 for results excluding these participants). No other participants displayed current axis I disorder.

The mean CES-D score for the maltreated group was low (Table 1). The CES-D scores of 16–26 indicate mild depression, whereas scores above 26 indicate increasingly severe depression (42); by these criteria, the maltreated group was not depressed. Ten maltreated participants indicated no depression (CES-D < 16), two indicated mild depression (CES-D = 17, 23), and one indicated more severe depression (CES-D = 49) (see Supplement 1 for results excluding these participants). However, despite absence of clinical depression, maltreated and control groups differed on MASQ GDD and AD scores (Table 1).

RT

There was a significant Cue effect [$F(2,80) = 23.40$, $p < .001$]. The RT was fastest on reward trials (335.16 ± 68.15 msec), intermediate on loss trials (354.54 ± 69.50 msec), and slowest on no-incentive trials (397.90 ± 88.82 msec) (all *p* values < .001) (Figure 1), indicating that participants were motivated to obtain gains and avoid penalties. There was a trend for Group [$F(1,40) = 2.89$, $p = .097$], because maltreated participants responded more slowly (389.07 ± 68.69 msec) than control subjects (350.63 ± 67.42
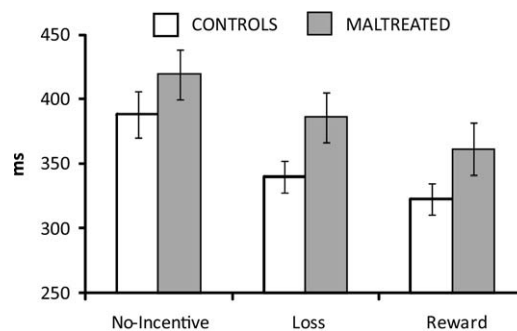

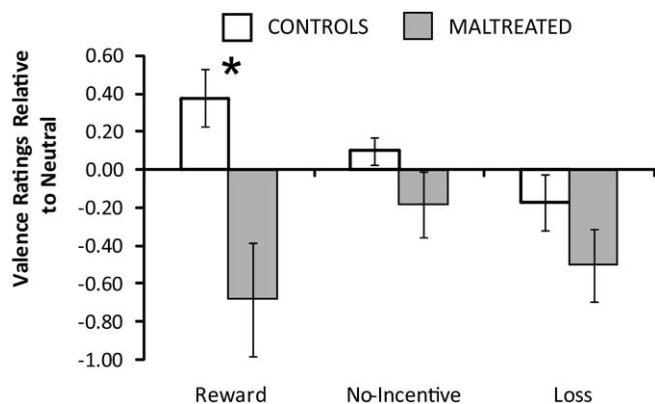**Figure 1.** Reaction time to the target by Group and Cue. Error bars reflect the SEM.

Figure 2. Valence ratings in response to cues. Data are plotted as change scores relative to neutral valence, which was 3 on the 5-point scale (1 = most negative, 3 = neutral, 5 = most positive). Maltreated participants rated reward cues significantly less positively than control subjects. Bars indicate the SEM. *$p < .05$.

msec). However, contrary to predictions, group differences were not specific to reward trials, Group × Cue [$F(2,80) < 1$].

Affective Ratings

As predicted, analysis of cue-elicited valence revealed a Group effect [$F(1,37) = 10.33$, $p = .003$], and a Group × Cue interaction [$F(2,74) = 4.14$, $p = .02$]. Reward cues were rated less positively by maltreated participants (2.32 ± .98) relative to control subjects (3.38 ± .78) [$t(37) = 3.55$, $p = .001$, Hedges' $G = 1.24$ (SE = .38; 95% CI: .49–1.99)] (Figure 2). Group differences for no-incentive and loss cues were nonsignificant (p values > .13).

No further evidence for group differences emerged, although there was a trend ($p < .09$) for maltreated participants to rate all outcomes as less positive than control subjects. Additional analyses revealed that cues and outcomes elicited intended affective responses (Supplement 1).

Basal Ganglia Responses

Cues. There were two effects involving Group: a Group × Structure interaction [$F(3,120) = 3.26$, $p < .05$] and a Group × Cue × Hemisphere interaction [$F(2,80) = 3.77$, $p = .03$]. To evaluate the triple interaction, Group × Cue ANOVAs were performed in each hemisphere. The interaction was significant in the left hemisphere [$F(2,80) = 3.84$, $p < .04$] [right hemisphere, $F(2,80) < 1$]. Two steps were taken to decompose this interaction. First, within-group tests examined whether cues elicited differential activity in each group. In control subjects, a one-way ANOVA on data averaged across left hemisphere ROIs confirmed the predicted Cue effect [$F(2,56) = 7.54$, $p = .005$]: responses to reward cues (.048 ± .06) were stronger (p values < .006) than responses to no-incentive (.006 ± .05) or loss cues (.021 ± .05), which did not differ ($p = .17$). By contrast, a similar ANOVA in maltreated participants was nonsignificant [$F(2,24) = 1.18$, $p = .32$]: follow-up t tests revealed no differences among responses to no-incentive (.021 ± .04), loss (.039 ± .04), or reward cues (.019 ± .05) (p values > .10). Second, a between-groups t test investigated the predicted difference in reward cue responses averaged across left hemisphere ROIs; the test was nonsignificant [$t(40) = 1.42$, $p = .16$].

In light of the Group × Structure interaction, additional Group × Cue ANOVAs were conducted for each left hemisphere structure to investigate whether group differences were stronger in

particular ROIs. The Group × Cue interaction was not significant in the left NAcc or caudate [all $F(2,80) < 2.74$, p values > .08] but was significant in the left putamen [$F(2,80) = 3.60$, $p < .05$] and left pallidus [$F(2,80) = 3.73$, $p = .03$]. Accordingly, between-groups t tests were conducted in these regions (Figure 3).

For the left putamen, control subjects generated a marginally stronger response to reward cues (.052 ± .07) than maltreated participants (.018 ± .04) [$t(40) = 1.73$, $p = .09$, Hedges' $G = .57$ (SE = .34; 95% CI: −.10–1.23), but responses to no-incentive and loss cues were similar (p values > .36). For the left pallidus, control subjects generated a stronger response to reward cues (.052 ± .05) than maltreated participants (.001 ± .05) [$t(40) = 2.55$, $p = .02$, Hedges' $G = .83$ (SE = .35; 95% CI: .16–1.51], but responses to no-incentive and loss cues were again similar, p values > .53. Finally, within-group one-way ANOVAs confirmed that the Cue effect was significant in both regions for control subjects [all $F > 12.18$, p values < .001] but in neither
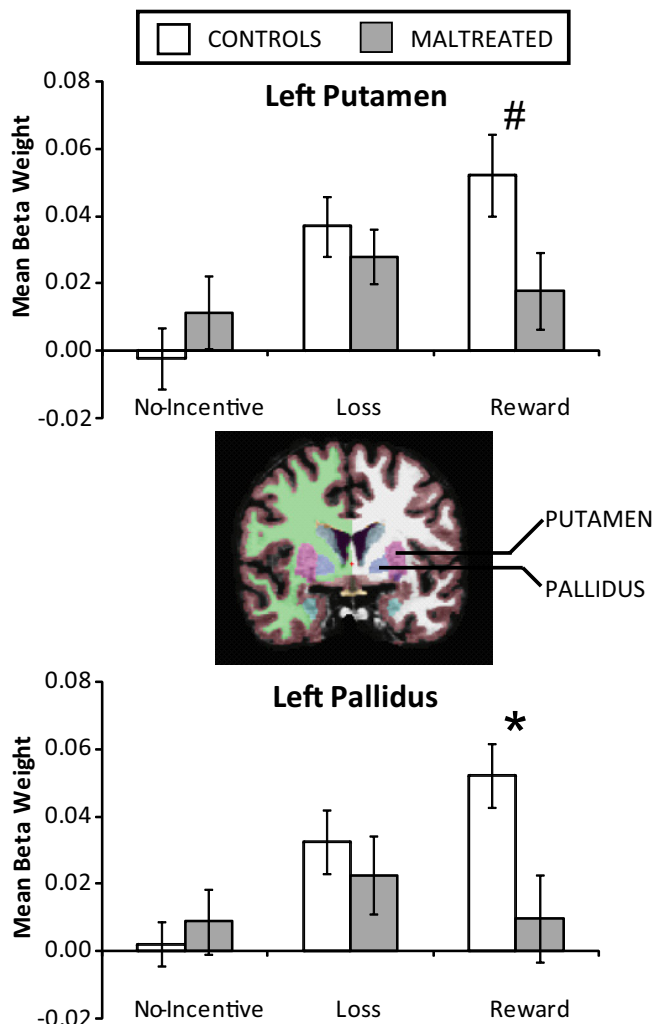

Figure 3. Left hemisphere reward anticipation deficit in the maltreated group. Mean β weights in the left putamen (top) and left globus pallidus (bottom) by Group and Cue. The coronal image in the center depicts the FreeSurfer subcortical segmentation for a representative participant, with the putamen in pink and the globus pallidus in blue. The maltreated group showed a blunted response to reward cues in both structures. Furthermore, whereas control subjects showed significant modulation of activity as a function of Cue in both regions, the maltreated group did not. *$p < .05$; #$p < .10$.

region for maltreated participants [all $F < 1.03$, $p > .36$]. Thus, the predicted group difference in reward cue response emerged for the left pallidus, with a similar trend in the left putamen.

Outcomes. The ANOVA revealed no evidence for between-group differences in outcome responses (all effects involving Group, p values $> .18$).

Basal Ganglia Volumes

There was a Group effect [$F(1,40) = 18.60$, $p < .001$] and several interactions involving Group: Group × Hemisphere [$F(1,40) = 4.43$, $p = .04$], Group × Structure [$F(3,120) = 5.86$, $p = .003$], and Group × Hemisphere × Structure [$F(3,120) = 3.24$, $p = .04$]. Group × Hemisphere ANOVAs were conducted at each structure, to decompose the highest-order interaction. The interaction was only significant for the putamen [$F(1,40) = 5.77$, $p = .02$] [all $F(1,40) < 1.24$, p values $> .26$ for other structures]. The t tests revealed larger putamen volumes for maltreated participants in the left hemisphere (maltreated: .406 ± .03; control subjects: .356 ± .04) [$t(40) = -3.80$, $p < .001$, Hedges' $G = -1.24$ (SE = .36; 95% CI: -1.95 to $-.54$)] and right hemisphere (maltreated: .385 ± .03; control subjects: .348 ± .04), [$t(40) = -2.98$, $p = .005$, Hedges' $G = -.95$ (SE = .35; 95% CI: -1.66 to $-.29$)].

These results likely reflect the group difference in age. Indeed, among control subjects, age was significantly negatively correlated with putamen volume in the left (control subjects: $r = -.70$, $p < .001$; maltreated: $r = -.47$, $p = .11$) and right (control subjects: $r = -.60$, $p = .001$; maltreated: $r = -.33$, $p = .27$) hemispheres. Accordingly, hierarchical regressions predicting putamen volume by age (entered first) and group (entered second) revealed strong effects for age (left putamen: $\beta = -.61$, $p < .001$; right putamen: $\beta = -.56$, $p < .001$), whereas Group was not a significant predictor of volume (left putamen: $\beta = .24$, $p = .06$; right putamen: $\beta = .17$, $p = .22$).

Regression Analyses

Additional regressions tested for effects of Group (entered second: 0 = control, 1 = maltreated) on reward cue valence ratings, MASQ AD, and MASQ GDD after accounting for age and education (entered first). For each variable, Group emerged as a significant predictor after accounting for age and education (MASQ AD: $\beta = .39$, $p < .05$; MASQ GDD: $\beta = .37$, $p = .05$; reward cue valence ratings: $\beta = -.47$, $p = .01$). Furthermore, Group improved each model ($\Delta R\text{s}^2 > .08$, $\Delta F\text{s} > 4.02$, p values $< .053$).

Next, two sets of regressions evaluated whether group differences in left putamen and left pallidus reward cue responses remained after accounting for other variables. In the first models, variables not hypothesized to relate specifically to reward processing (volumetric data, age, education, MASQ GDA, MASQ AA) were entered first, and Group was entered second. Group predicted left putamen and left pallidus reward cue responses in these models (Table 3), although the putamen results narrowly missed significance (left putamen: Group $\beta = -.39$, $p = .06$; left pallidus: Group $\beta = -.52$, $p = .04$). Furthermore, Group improved the models (left putamen: $\Delta R^2 = .08$, $\Delta F = 3.80$, $p = .06$; left pallidus: $\Delta R^2 = .10$, $\Delta F = 4.66$, $p = .04$).

In the second models, reward cue valence ratings and MASQ AD scores were added in step one. The MASQ AD was used rather than MASQ GDD, because the scales were correlated ($r = .85$, $p < .001$), and anhedonia is directly related to reward responsiveness (43). Not surprisingly, the Group effect was weakened (Table 3). Group no longer predicted reward cue

Table 3. Hierarchical Regression Results for Left Putamen and Left Pallidus Reward Cue Response

Predictor	Step	β	t	p
Left Putamen				
First model				
Volume	1	.01	.05	.96
Age	1	−.39	−1.78	.08
Education	1	−.04	−.20	.85
MASQ-GDA	1	.24	.99	.33
MASQ-AA	1	−.43	−1.74	.09
Group	2	−.39	−1.95	.06
Second model				
Volume	1	−.07	−.28	.78
Age	1	−.38	−1.65	.11
Education	1	−.10	−.55	.59
MASQ-GDA	1	.31	1.14	.26
MASQ-AA	1	−.27	−1.05	.30
MASQ-AD	1	−.27	−1.08	.29
Reward Cue valence ratings	1	.26	1.37	.18
Group	2	−.18	−.79	.44
Left Pallidus				
First model				
Volume	1	.13	.52	.61
Age	1	−.21	−1.01	.32
Education	1	−.06	−.31	.76
MASQ-GDA	1	.24	1.01	.32
MASQ-AA	1	−.42	−1.75	.09
Group	2	−.52	−2.16	.04
Second model				
Volume	1	.12	.43	.67
Age	1	−.19	−.79	.44
Education	1	−.11	−.55	.58
MASQ-GDA	1	.18	.62	.54
MASQ-AA	1	−.31	−1.20	.24
MASQ-AD	1	.00	.00	.99
Reward Cue valence ratings	1	.28	1.43	.16
Group	2	−.34	−1.21	.24

Group was coded 0 = control subjects, 1 = maltreated. See Table 1 for additional details. Abbreviations as in Table 1.

response in left putamen ($\beta = -.18$, $p = .44$) or left pallidus ($\beta = -.34$, $p = .24$) and no longer improved the models (left putamen: $\Delta R^2 = .02$, $\Delta F < 1$, $p = .44$; left pallidus: $\Delta R^2 = .04$, $\Delta F = 1.45$, $p = .24$). These results indicate that group differences in reward cue valence ratings, MASQ AD, and left putamen/left pallidus reward cue responses share common variance. Indeed, left hemisphere basal ganglia reward responses were negatively correlated with MASQ AD across groups (putamen: $r = -.31$, $p = .05$; pallidus: $r = -.26$, $p = .097$) and positively correlated with reward cue valence ratings (putamen: $r = .36$, $p = .02$; pallidus: $r = .29$, $p = .07$).

Discussion

Consistent with findings in nonhuman animals (15–19), maltreated participants reported elevated depressive and anhedonic symptoms, rated reward-predicting cues less positively, and showed decreased anticipatory reward activity in the left pallidus relative to control subjects. Results indicate that childhood adversity that includes maltreatment is associated with impaired reward processing (13,14). Furthermore, the findings highlight a neural mechanism that could contribute to relationships between childhood adversity and psychopathology: decreased anticipatory reward activity in the left basal ganglia. The pallidus

integrates reward information and conveys it to motor cortex via the thalamus (44). Thus, pallidus dysfunction might weaken the ability of reward-predicting cues to elicit goal-directed actions.

The relationship between childhood adversity and decreased subjective and neural responses to reward-predicting cues rather than rewards themselves was predicted on the basis of findings in nonhuman animals. For example, early maternal deprivation in marmosets impaired motivation to work for liquid reinforcement but did not affect consummatory behavior (17). We expected similar results, because DA neurons that project to the basal ganglia are susceptible to stress-related dysfunction (18,19) and critical for incentive motivation (21,27). However, it should be noted that early adversity can also weaken the hedonic impact of obtained rewards (16,19), possibly via effects on opioid systems (45). Accordingly, group differences in consummatory responses might emerge in larger samples or different paradigms.

The findings are consistent with the hypothesis that childhood adversity might have affected the development of DA systems. However, any strong causal interpretation of the data would be premature. In this small sample, we cannot disentangle effects of maltreatment per se from many potential correlates of maltreatment, such as inherited dysfunction in neural activity, parental depression or substance abuse, or the contribution of previous psychiatric issues (Table 2). Prospective studies using larger samples are needed to distinguish among such correlated factors.

Although the SCID and CES-D revealed little evidence of current clinical depression in maltreated participants, the groups differed on self-reported symptoms of depression and anhedonia. Moreover, when MASQ-AD scores and reward cue valence ratings were controlled, the Group effect on left pallidus reward cue responses became nonsignificant. One possibility is that the anhedonic symptoms and basal ganglia dysfunction are two manifestations of the same dysfunction. Indeed, MASQ-AD scores and reward cue responses in the left pallidus and left putamen were negatively correlated. In addition, the attenuated response to reward-predicting cues in the left pallidus is consistent with evidence of basal ganglia dysfunction in clinical depression. For example, relative to control subjects, depressed individuals showed weaker basal ganglia responses to reward-predicting cues and gains in the MID task (33), reduced ventral striatal responses to positive words (46), decreased caudate glucose metabolism (47) and blood flow (48), and reduced extracellular caudate and putamen DA (49).

The restriction of deficits to the left hemisphere was not predicted but echoes reports that poststroke depression more often follows damage to the left versus right hemisphere (50), with globus pallidus lesions highly predictive of depression (51). Moreover, a study in healthy participants reported a positive correlation between D2-receptor availability in the left putamen and incentive motivation (52), consistent with the fact that left hemisphere group differences were specific to reward anticipation. Findings are also consistent with reported relationships between childhood maltreatment and electrophysiological abnormalities over the left hemisphere (53). The reason for this hemispheric asymmetry is unclear, but asymmetrical projections of DA neurons might play a role (54).

Critically, results do not reflect a global deficit in maltreated participants. There were no significant group differences in affective ratings to any stimulus except reward cues and no differences in basal ganglia response to: 1) loss or no-incentive cues in the left hemisphere, 2) any cue in the right hemisphere, or 3) any outcome. Furthermore, group differences in left pallidus reward cue responses remained after controlling for anxiety and general distress (Table 3).

The study possesses several limitations. First, several maltreated individuals were excluded due to active substance abuse, and the striatum is tonically hypoactive in substance abusers (55). Thus, we might have excluded individuals with severe reward processing dysfunction, yielding a conservative estimate of effects of maltreatment on reward processing. Second, the lack of group differences in response to loss cues and penalties might reflect a weakness of the MID task: because participants knew they would be paid for participation, the loss cues and penalties might not have been sufficiently aversive to elicit group differences. Notably, other studies report relationships between childhood adversity and sensitivity to emotionally negative stimuli (e.g., [56]). Third, the current sample was too small to determine whether a dose–response relationship exists between extent or age of onset of maltreatment and responses to reward cues or to examine whether specific types of maltreatment have different effects on reward processing. Larger studies are needed to address these issues and to investigate whether particular genetic backgrounds or social supports can protect reward systems from adversity-induced dysfunction (57,58).

Fourth, because control subjects and maltreated participants were from different cohorts, variables besides maltreatment might have affected the results. Three considerations mitigate this concern. First, the loss and no-incentive conditions and cue/outcome design served as internal controls that allowed us to pinpoint the predicted differences in reward anticipation; the lack of differences in other conditions argues against a general deficit in maltreated participants. Second, the strong basal ganglia response to reward cues demonstrated by the control subjects is the norm in the MID task and has been demonstrated in samples differing in age, education, and sociodemographic data (22,23,25,26). Thus, the findings reflect a deficit in maltreated participants rather than atypical results in the control subjects. Third, Group predicted left pallidus reward cue responses after adjusting for age, education, anxiety, and basal ganglia volumes. Nonetheless, groups might have differed on other variables not measured, especially because maltreated individuals tend to be exposed to multiple forms of childhood adversity (59). Consequently, results should be interpreted in terms of childhood adversity rather than maltreatment per se.

Supplementary material cited in this article is available online.

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Supplementary Material

Methods and Materials

Maltreatment Assessments

For all maltreated participants, a 6-point rating for severity of overall abuse from birth to age 18 was assigned by reviewing scores from three separate study measures that assessed abusive experiences: the Conflict Tactics Scale-2nd version (CTS-2: S1), the Traumatic Stress Schedule (TSS: S2), and the Childhood Traumatic Experiences Scales-Revised (CTES-R: S3) coded from the Adult Attachment Interview (S4). State protective services involvement was also assessed from interviews, beginning in infancy for the longitudinal cohort, as was information on whether the participant had ever been placed in foster care between 0-18 years. Each individual's overall severity of abuse was classified into one of 6 levels as follows: 1-no occurrence of violence; 2-harsh punishment only; 3-witnessed violence only; 4-emotional/verbal abuse only; 5-physical abuse (using state guidelines for abuse), sexual abuse (using state guidelines for abuse), or protective services/foster care involvement; 6-two or more under level 5. Reliability of the overall severity of abuse scale was ICC = .99, with 37 participants from the larger longitudinal study coded for reliability. The final sample had scores of 4 ($n = 1$), 5 ($n = 7$), or 6 ($n = 5$), reflecting significant emotional, physical, and/or sexual maltreatment during childhood. The component measures contributing to the final rating are described below.

Severity of Abusive Experiences: Conflict Tactics Scale (2nd version). The CTS-2 is a widely used 78-item measure of the type and frequency of strategies used to resolve conflict between family members. Each item rates on an 8-point scale the frequency with which a

particular conflict tactic occurred during the past year or during another rating period of interest. The rating period specified in the present study was "the year that things were worst between you and your parent." Tactics include physically abusive behavior and emotionally abusive behavior, e.g., "My parent hit or kicked me; my parent insulted or swore at me." The overall scale has a stable factor structure, moderate test-retest reliability, and demonstrated validity (S5).

Severity of Abusive Experiences: Traumatic Stress Schedule-Short Version. The TSS is an eight-question survey about traumatic experiences, including exposure to hazards, natural disasters, accidents, and assaults. In assigning the rating for overall abuse, only the first three questions of the TSS were relevant because they focus on experiences of sexual or physical assault. In case of a positive answer to any of the items, participants were asked to indicate who the assailant was, provide a brief description of the event, and described why they (the participant) believed this had happened to them.

Severity of Abusive Experiences: Childhood Traumatic Experiences Scales-Revised. The CTES-R rates the severity of abuse revealed during the AAI, which is a semi-structured, one hour interview that investigates attachment-related experiences with primary caretakers. For this study, additional questions probing sexual and physical abuse experiences were added to the standard AAI protocol in order to gain added information on traumatic childhood experiences. The AAI was administered to participants in young adulthood. Interviews were transcribed and coded for severity of physical abuse, sexual abuse, verbal abuse and witnessing interpersonal violence, on four 5-point scales. Inter-rater reliabilities ranged from $r_i = .89$ (verbal abuse) to $r_i = .98$ (sexual abuse). Convergent validity with other measures of childhood abuse has been demonstrated with the CTES-R (S4).

Exclusion Criteria for Maltreated Participants

Exclusion criteria included: use of dopaminergic-acting drugs (including antipsychotics or stimulants) or substance abuse or dependence in the last six months; current use of medications affecting blood flow; electro-convulsive treatment in the last six months; current primary diagnosis of panic disorder, psychotic disorder, PTSD, or organic mental disorder; any head injury involving loss of consciousness for two minutes or longer. Note that one participant met criteria for current PTSD (Table 2), but this diagnosis was secondary to the primary diagnosis of MDD.

MID Task: Additional Details

Reward and loss trials were designed to be either "successful" or "unsuccessful". In the reward condition, successful trials were associated with monetary gains (range: $1.96 to $2.34; mean: $2.15) whereas unsuccessful trials led to no change. In the loss condition, successful trials were associated with no change whereas unsuccessful trials were associated with monetary penalties (range:-$1.81 to -$2.19; mean:-$2.00). Gains were slightly larger than penalties to compensate for the fact that individuals typically assign greater weight to a loss than a gain of equal magnitude (S6). No feedback about cumulative earnings was provided.

The task featured five blocks of 24 trials (8 reward, 8 loss, 8 no-incentive). To permit a balanced design, delivery of gains and penalties was fixed: in each block, half of the reward and loss trials led to success or failure, respectively. However, participants were told that trial outcomes were influenced by their RT to the target, such that faster responding would improve the chances of receiving gains on reward trials and avoiding penalties on loss trials. To increase the believability of this instruction, target presentation duration was varied across successful and

unsuccessful trials. Participants completed a practice block of 40 trials immediately prior to

scanning, and RTs collected during practice were used to titrate target duration during the

experiment. Specifically, for successful and unsuccessful trials the target was presented for

durations corresponding to the 85th and 15th percentiles, respectively, of the individual's RT

distribution during practice (i.e., long duration on successful trials, short duration on

unsuccessful trials). This manipulation was used to make it plausible that participants had not

responded quickly enough to the (short duration) target on unsuccessful trials, but had responded

quickly enough to the (long duration) target on successful trials, thus legitimating the delivery of

the outcomes. By titrating target durations based on each participant's practice RTs, we aimed to

equilibrate the task across participants. Nonetheless, between-groups *t*-tests were used to confirm

that mean target durations did not differ between groups. The test for the short target duration

was not significant, $t(40) = -1.42$, $p = .16$, as durations were similar for controls (270.82±27.52

ms) and maltreated participants (287.69±49.52 ms). The test for long duration targets was also

non-significant, $t(40) = -1.15$, $p = .26$, as durations were again similar for controls (383.83±86.35

ms) and maltreated participants (416.92±86.64 ms). Thus, there was no difference in task

difficulty across groups.

A single pseudo-randomized stimulus presentation order was developed using optseq2

(S7), a tool for maximizing the efficiency of event-related fMRI designs, and ISI/ITI durations

were generated using a genetic algorithm that maximizes statistical orthogonality, which is

critical for estimating hemodynamic responses to closely spaced stimuli (S8). To maximize task

engagement, participants were further told that good performance would yield an opportunity to

play a bonus block associated with larger gains ($3.63-$5.18) and few penalties. All participants

"qualified" for the bonus block. Data from this block were collected using standard acquisition

parameters to permit confirmation of signal recovery in the other blocks and were not included in the analyses. Previous behavioral and fMRI findings in independent samples demonstrate that this combination of instructions and task parameters elicit motivated behavior and recruit reward-related brain activity (S9).

FreeSurfer Segmentations: Quality Control and Correspondence with Manual Tracing

The basal ganglia ROIs were defined using FreeSurfer's subcortical segmentation procedure (S10), which was run along with the accompanying cortical parcellation algorithms (S11). The segmentation works by using information about the image intensity of different tissue classes and probabilistic information regarding the relative location of different brain regions to assign a neuroanatomical label to each voxel in a participant's structural image (S10). The probabilistic information was generated from a training data set that was manually labeled using validated techniques developed by the Center for Morphometric Analysis at Massachusetts General Hospital (e.g., S12). FreeSurfer's segmentation and cortical parcellation streams are designed to be run in fully automated mode and permit segmentation and parcellation of very large numbers of brains daily (S10). However, in the current study these procedures were run in stages and quality control was implemented at three separate points.

The first quality control point involved confirming that: (a) each participant's T1 image was correctly cross-registered to the MNI305 atlas in Talairach space; (b) a skull stripping procedure had correctly removed the skull and dura from each participant's brain image; and (c) intensity normalization of the images was correct so that intensity-based segmentation steps would proceed accurately. Few problems were detected at any quality control points, but they were most frequent at this point and often consisted of an inaccurate cross-registration and/or

incomplete removal of dura or eyes from around the orbitofrontal cortex. These problems were manually corrected and the first stage was re-run and re-checked. The second quality control point involved confirming that: (a) outlines of the pial and white matter surfaces of the brain were correctly drawn; (b) white matter segmentation was accurate; and (c) the subcortical segmentation, including the segmentation of the four basal ganglia ROIs, was complete. Problems at this stage were usually minor, typically involving small errors in the pial and white matter surfaces (e.g., dura included in the pial surface, incomplete coverage of white matter in the superior temporal lobes). Any problems were manually corrected and the stage was re-run and re-checked. The final quality control point involved inspecting inflated cortical surfaces and accompanying cortical parcellations (S11). Errors were rarely detected at this stage, most likely due to the careful checks implemented at points one and two.

Multiple studies indicate that FreeSurfer's automated approach provides segmentation accuracy comparable to expert manual labeling (e.g., S10, S13). Of particular interest, researchers at the Center for Morphometrical Analysis recently compared the size of basal ganglia structures as determined via FreeSurfer versus their validated manual tracing methods for a sample of 20 adults. For the left putamen and left pallidus (the main regions of interest emerging from the current study), the correlation between these methods was 0.80 and 0.75, respectively (courtesy of Dr. Nikos Makris, Center for Morphometric Analysis, Massachusetts General Hospital, Boston, MA).

Statistical Tests

In light of the group differences in age and education, the possibility of analyzing the data using ANCOVAs with age and education as covariates was considered. However, there is a clear

consensus in the technical literature that using ANCOVA to attempt to control for group differences in this fashion is inappropriate (S14, S15). This literature indicates that when there are significant group differences on a covariate, the resulting ANCOVA will be mis-specified (S15). Conceptually, the difficulty stems from the potential removal of meaningful variance from the dependent variable. With respect to the present study, it seemed probable that educational attainment could be related to maltreatment, and both basal ganglia structure and function appear to decline with age (S16, S17). Thus, data were initially analyzed using ANOVAs so that unadjusted group differences could be inspected. Following identification of significant group differences, follow-up regressions tested whether effects of *Group* remained after removing variance associated with age and education. For the technical and conceptual reasons cited above, these regression analyses may be overly conservative; however, they seemed appropriate as follow-up analyses. An important goal for future work will be to address this issue directly by comparing maltreated individuals with a group of age and education-matched controls.

Results

Motion Parameters

T-tests on six motion parameters (cumulative translation in the *x*, *y*, and *z* directions and cumulative *pitch*, *roll*, and *yaw*) were conducted to investigate the possibility of group differences. Descriptive statistics are listed in Table S1 and reveal that for each dimension, the mean cumulative movement was less than 1.5 mm or degrees. Accordingly, the *t*-tests were non-significant for pitch, yaw, and translation in the *x*, *y*, and *z* directions (all *t*-values < 1, all *p*-values > .32). The *t*-test for cumulative roll was significant, $t(40) = 2.34$, $p < .03$, reflecting greater average roll in the controls (.855±.85 mm) than in the maltreated participants (.286±.31

mm). Importantly, however, motion parameters were included in the GLM as nuisance regressors, thereby controlling for this small between-group difference.

Affective Ratings

Cues. An ANOVA on arousal ratings revealed an effect of *Cue*, $F(2,76) = 4.41$, $p = .015$, but neither the effect of *Group* nor the *Group* x *Cue* interaction was significant, *F*s < 1. Follow-up *t*-tests revealed that the *Cue* effect was due to greater arousal in response to both reward (2.98±.77) and loss (3.03±.74) cues relative to no-incentive cues (2.63±.81) (reward vs. no-incentive, $p = .03$; loss vs. no-incentive, $p = .02$). There was no difference in arousal ratings elicited by reward versus loss cues, $p = .85$.

Outcomes. A *Group* x *Outcome* ANOVA on valence ratings revealed an effect of *Outcome*, $F(2,76) = 82.63$, $p < .001$, a trend for a *Group* effect, $F(1,38) = 3.10$, $p = .086$, and a non-significant interaction, $F(2,76) = 1.30$, $p = .28$. The *Outcome* effect reflected the fact that gains were rated more positively (4.26±.85) than no change feedback (3.08±.43), which was rated more positively than penalties (1.80±.77); all follow-up pairwise *t*-tests between outcomes were significant, $p < .001$. The trend for *Group* reflected more positive ratings across outcomes in the controls (3.11±.34) versus the maltreated group (2.88±.44).

An ANOVA on arousal ratings yielded an effect of *Outcome*, $F(2,76) = 7.31$, $p = .003$, but no effect of *Group* ($F < 1$) and no *Group* x *Outcome* interaction, $F(2,76) = 1.52$, $p = .23$. Follow-up *t*-tests indicated that the main effect of *Outcome* was due to the fact that gains (3.49±.93) were rated as more arousing than either penalties (2.94±1.17) or no change feedback (2.70±.76) (gains vs. penalties, $p = .02$; gains vs. no change feedback, $p < .001$). Arousal ratings elicited by penalties and no change feedback did not differ, $p = .20$.

Key Results After Dropping Maltreated Participants with Recent Use of Psychotropic Medications, Elevated CES-D Scores, or Current Axis I Diagnoses

Two maltreated participants reported psychotropic medication use in the weeks immediately prior to scanning, three reported elevated depressive symptoms on the CES-D, and two met diagnostic criteria for an Axis-I disorder on the SCID proximal to fMRI. There was overlap in these sub-groups: one participant was represented in all three, one had elevated CES-D scores and met diagnostic criteria for multiple Axis I disorders, and the other two participants were using medication and reported elevated symptoms on the CES-D, respectively. Thus, it was possible to assess the influence of all these participants on the findings by repeating the key analyses after excluding participants (a) using psychotropic medication use, and (b) reporting elevated CES-D scores; because of the overlap, these analyses also excluded the participants who met diagnostic criteria for Axis-I disorders.

To this end, between-groups *t*-tests were first run on MASQ AD, MASQ GDD, reward cue valence ratings, and left pallidus and putamen reward cue responses after excluding the two participants reporting psychotropic medication use. The two main findings were confirmed: the difference in reward cue valence rating was still significant, $t(36) = 3.28$, $p = .002$ (controls: 3.38±.78; maltreated: 2.35±1.03), as was the difference in left pallidus response to reward cues, $t(38) = 2.04$, $p = .048$ (controls: .052±.05; maltreated: .016±.05). However, the differences in left putamen reward cue response, MASQ AD, and MASQ GDD were no longer significant, *p*s > .11. The same pattern of results was again observed when the three maltreated participants with elevated CES-D scores were excluded: the difference in reward cue valence rating was still significant, $t(35) = 3.36$, $p = .002$ (controls: 3.38±.78; maltreated: 2.28±1.06), as was the

difference in left pallidus response to reward cues, $t(37) = 2.04$, $p = .049$ (controls: .052±.05; maltreated: .014±.05). However, the differences in left putamen reward cue response, MASQ AD, and MASQ GDD were not significant, ps > .16.

Key Results Using Controls Matched on Age

Following the suggestion of an anonymous reviewer, the key analyses were repeated using a group of 13 age-matched controls who were also more closely matched with respect to gender distribution. Specifically, the maltreated group (mean age = 24.58±.88 years; 9 females, 4 males) was compared to the 13 youngest controls (mean age = 24.26±3.99 years; 7 females, 6 males). There were no significant differences between these groups in age, $t(24) = -.29$, $p = .78$, or gender distribution, $\chi^2(1)=.65$, $p = .42$, although the difference in education remained significant (controls: mean = 15.54±1.51 years; maltreated: mean = 12.92±2.22 years; $p = .002$). Next, between-groups *t*-tests on MASQ GDD, MASQ AD, reward cue valence ratings, and responses to reward cues in the left putamen and left pallidus were conducted. Results are presented in Table S2. Notably, every group difference found using the entire control sample was replicated, and numerical differences in left putamen and left pallidus were larger using this control sub-sample. These results indicate that the group differences found using the entire control sample are unlikely to reflect differences in age or imperfect gender-matching.

Table S1. Descriptive Statistics and Between-Group *T*-test Results for Motion Parameters

Dimension	Group	Mean	SD	*t*-value	*p*-value
Roll	Control	.855	.846	2.344	.024
	Maltreated	.286	.310		
Pitch	Control	1.216	1.013	-.449	.656
	Maltreated	1.366	.980		
Yaw	Control	.665	.663	.396	.695
	Maltreated	.586	.422		
X	Control	.502	.433	.986	.330
	Maltreated	.370	.327		
Y	Control	1.038	.793	-.059	.953
	Maltreated	1.054	.766		
Z	Control	1.465	.881	.695	.491
	Maltreated	1.246	1.079		

Table S2. Comparison of Maltreated Group with Age-Matched Controls

	Maltreated Group		Control Group			
	Mean	*SD*	Mean	*SD*	Statistic	*p*-value
% Female	69%	N/A	54%	N/A	$\chi^2(1)=.650$	$> .419$
Age	24.58	.88	24.26	3.99	$t(24)=.29$	$> .779$
Education	12.92	2.22	15.54	1.51	$t(24)=3.52$	$< .003$
% Caucasian	77%	N/A	69%	N/A	$\chi^2(1)=.195$	$> .657$
MASQ-GDD	22.77	12.90	14.23	1.92	$t(24)=2.36$	$< .036$
MASQ-AD	55.69	20.84	40.62	7.86	$t(24)=2.44$	$< .028$
Reward Cue Valence	2.32	0.98	3.46	0.72	$t(22)=3.29$	$< .004$
Left Putamen Reward Cue	0.02	0.04	0.07	0.07	$t(24)=2.62$	$<.016$
Left Pallidus Reward Cue	0.01	0.05	0.07	0.05	$t(24)=2.86$	$<.010$

Supplementary References

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