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Contributions of childhood abuse and neglect to reward neural substrates in adolescence

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ABSTRACT

Background: Childhood adverse experiences may come to bear particularly during adolescence, when neural reward systems are developing rapidly and psychopathology spikes. Despite prior work differentiating threat- (abuse) vs. deprivation- (neglect) related adversity, no research has yet identified their relative nor interactive contributions to reward neural substrates during adolescence. In the present study, we leveraged a diverse sample of adolescents with different childhood adversity profiles to examine neural responses to reward in relation to varying degrees of abuse vs. neglect.

Methods: Adolescents (N = 45; 23 females; mean age = 14.9 years, SD = 1.9) completed a child-friendly monetary incentive delay task during fMRI acquisition. The self-report Childhood Trauma Questionnaire assessed childhood abuse and neglect. Whole brain ANCOVA analyses evaluated reward anticipation (reward vs. no reward expected) and feedback (hitting vs. missing the target with a reward vs. no reward) in relation to abuse and neglect dimensions.

Results: Whole-brain analyses revealed that abuse, adjusted for neglect, is associated with greater differences between task conditions (reward vs. no reward, hit vs. miss) in regions associated with threat/emotion regulation (prefrontal and temporal cortices, as well as posterior regions including fusiform and posterior cingulate/precuneus). Additionally, level of neglect modulated neural response associated with abuse in prefrontal and temporoparietal regions, such that youths with high levels of both abuse and neglect showed qualitatively different, more exaggerated neural patterns compared to youths with elevated adversity in only one dimension.

Conclusions: Our findings suggest that early experiences of abuse and neglect have a long developmental reach resulting in reward-related neural alterations in adolescence. Moreover, our results bolster theoretical conceptualizations of adversity along threat and deprivation dimensions and provide evidence that "adding up" adverse life events may not be sufficient to capture the qualitatively different neural profiles produced by differing combinations of types of adversity, which may in turn necessitate different treatment approaches.

1. Introduction

Adverse early life experiences have long-lasting effects on mental health and development (Ford, et al., 2010; Merrick et al., 2017). Such early influences may come to bear particularly during the seismic shifts of adolescence (Morelli et al., 2021, provisionally accepted), when neural systems undergo significant development and, concurrently, psychopathology symptoms spike (Casey et al., 2010; Somerville and Casey, 2010). Prior research has primarily focused on single adverse childhood experiences (e.g., parental death, physical abuse) and cumulative adverse childhood experiences, typically measured as counts of adverse events. This work has found that such early experiences increase the risk for a wide variety of psychopathology, often with adolescent onset (Evans et al., 2013). More recently, rather than conceptualizing varying adverse childhood experiences monolithically, theoretical work has divided adverse childhood experiences along two dimensions: deprivation (e.g., emotional neglect, material deprivation) vs. threat (e.g., physical abuse, traumatic events) (McLaughlin et al., 2014). Based primarily on animal model research, these dimensions of early experience are thought to have distinct effects on neural development, such that deprivation is characterized by hyposensitivity (Hanson et al., 2015; McLaughlin et al., 2017) and threat by hypersensitivity to salient

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environmental cues (McLaughlin et al., 2014; McLaughlin et al., 2019); Deprivation-related adverse experiences are more strongly associated with the frontoparietal networks whereas threat-related adverse experiences are more strongly associated with emotion-processing networks (McLaughlin et al., 2019; Rakesh et al., 2021).

One arena in which deprivation and threat may come to bear in distinct ways is in neural responses to reward, especially during adolescence. Normative maturation of reward-related neural systems (striatum, amygdala) dramatically accelerates during adolescence, outpacing the development of cognitive control abilities (mediated by prefrontal/frontal cortex) until early adulthood (Somerville and Casey, 2010). Such disjointed development of reward and cognitive control systems increases vulnerability to psychopathology during adolescence, as many of the same disorders associated with adverse childhood experiences (depressive, anxiety, substance use, and irritable behavior syndromes) onset or worsen during adolescence (Merikangas et al., 2010). Indeed, alterations in reward processing underlie psychopathology associated with adverse childhood experiences. Specifically, depressive symptomatology (anhedonia) is marked by blunted neural response to reward (Der-Avakian and Markou, 2012; Wiggins et al., 2017), whereas substance use (Tanabe et al., 2019), irritability (Dougherty et al., 2018), and, to a lesser extent, anxiety symptoms (Carlton et al., 2020) are associated with outsized neural sensitivity to reward and, in the case of irritability, outsized sensitivity to non-reward (i.e., loss, failing to receive a reward) as well (Deveney et al., 2013; Hodgdon et al., 2021, submitted).

Despite non-human animal work informing theory on adverse early life experiences (McLaughlin et al., 2014), there have been very few human neuroimaging studies testing the effects of adverse childhood experiences on neural reward processing. Of the few human functional MRI studies, almost all examined adverse childhood experiences by combining threat and deprivation factors (e.g., Baranger et al., 2016; Birn et al., 2017; Hanson et al., 2016), or by examining only one factor (e.g., deprivation operationalized as history of institutionalization (Goff et al., 2013; Mehta et al., 2010) or threat as abuse (Dillon et al., 2009)), but not both in the same study. Not surprisingly, findings from these studies are mixed, with some documenting increased (e.g., Casement et al., 2014; Morgan et al., 2014; Novick et al., 2018) and others decreased (e.g., Hanson et al., 2015; Holz et al., 2017) striatum, amygdala, and prefrontal cortex activation associated with adverse childhood experiences. Moreover, only a handful of these studies have focused on adolescence, using a wide variety of reward-type tasks, with similarly mixed findings (Casement et al., 2014; Dennison et al., 2016; Hanson et al., 2015; Mehta et al., 2010; Takiguchi et al., 2015). To our knowledge, only one study has examined the differential contributions of threat vs. deprivation to reward circuitry (Hein et al., 2020). Using an emotional face paradigm with happy and angry faces, stimuli theorized to be socially rewarding and threatening, respectively, this study found that childhood violence exposure (threat) was related to greater sustained amygdala activation to angry faces whereas childhood social deprivation was associated with decreased ventral striatum activation to happy faces in adolescents (Hein et al., 2020). However, no studies have examined threat vs. deprivation using an fMRI paradigm specifically designed to probe aspects of reward. Moreover, threat- and deprivation-related experiences often co-occur and yet, paradoxically, are theorized to involve neural hyper- and hypo-sensitivity, respectively, and to affect different brain regions (Busso et al., 2017; McLaughlin et al., 2014; McLaughlin et al., 2019); nevertheless, neural profiles of threat and deprivation combinations remain unknown.

To address these gaps in the literature, we here utilize a well-validated paradigm designed to probe reward anticipation and receipt to assess neural responses in adolescents with varying profiles of threat- and deprivation-related adverse childhood experiences. Leveraging our diverse sample for improved generalizability, we examine the relative contributions of threat (childhood abuse) and deprivation (childhood neglect) to reward-related neural alterations and, as a preliminary exploration, examine the interaction of threat and deprivation (abuse by neglect). We expected that, compared to low levels of threat-related childhood adverse experiences, high levels of threat-related childhood adverse experiences would be associated with greater and more exaggerated differences in neural responses to the task conditions in brain regions associated with reward processing, emotion regulation, and threat (e.g., precuneus, temporoparietal junction). Compared to low levels of deprivation-related childhood adverse experiences, high levels of deprivation-related childhood adverse experiences would be associated with more blunted, smaller differences in neural responses to the task conditions in brain regions associated with reward processing and cognitive functioning (e.g., ventromedial prefrontal cortex, dorsal prefrontal cortex). For our exploratory interaction analysis (threat-abuse × deprivation-neglect), we expected that a combination of high threat and high deprivation will result in a different neural profile in response to reward conditions than either high threat or high deprivation alone, in brain regions associated with reward processing, emotion regulation, threat, and cognitive functioning.

2. Methods

2.1. Participants

Forty-eight participants aged 11–19 years old (M = 14.92, SD = 1.88) were recruited to participate in one of the two research studies in the San Diego area. Participants were treatment-seeking (n = 31 for trauma-focused cognitive behavioral therapy and n = 17 for anxiety- and depression-focused cognitive behavioral therapy) and had varying profiles of childhood adversity. Prior to therapy, participants completed a child-friendly monetary incentive delay task to elicit neural activity in the reward processing circuits during the fMRI acquisition. Exclusion criteria included magnetic resonance imaging (MRI) contraindications (e.g., metal implants, orthodontic braces, claustrophobia, weight over 300 lbs.), major medical problems with clear impact on the central nervous system, participant being not able to understand procedures sufficiently to provide assent (based on the assessment from a qualified research team member). Of the 48 participants, n = 2 were excluded due to an incomplete MRI scan and n = 1 due to a corrupted dataset because of technical error. Thus, data from a N = 45 participants were included in the analysis. Demographic characteristics of the entire sample are presented in Table 1a; Demographic characteristics grouped by recruitment sources are presented in Table 1b. To summarize, samples were generally equivalent on clinical and sociodemographic characteristics, but the treatment-seeking-for-trauma sample was more likely to be Hispanic/Latino/a/x. Thus, we conducted additional analyses to evaluate the impact of recruitment source and race/ethnicity (see *Additional Analyses*).

Study procedures and consent forms were approved by the

Table 1a
Sample Characteristics of the Entire Sample (N = 45).

	Mean	Standard Deviation	Range
Age	14.92	1.88	11.92–19.44
CTQ Total	37.29	9.88	25.25–67
CTQ Abuse	6.66	1.88	5–13
CTQ Neglect	8.73	2.89	5–19
SCARED* – Anxiety symptoms	11.67	11.56	0–58
MFQ* – Depression symptoms	23.48	16.08	0–40
	N	**Percentage**	
Gender - Female	23	51.1%	
Race/Ethnicity			
African American/Black	4	8.9%	
Asian/Pacific Islander	2	4.4%	
White	7	15.6%	
Hispanic/Latino/a/x	23	51.1%	
Biracial	8	17.8%	
Other/Unknown	1	2.2%	

Table 1b
Sample Characteristics Grouped by Recruitment Sources.

N	Treatment-seeking for trauma			Treatment-seeking for anxiety/depression			Group Comparison	
	31			14				
	Mean	**Standard Deviation**	**Range**	**Mean**	**Standard Deviation**	**Range**	**t (df = 43)**	**Sig.**
Age	14.55	1.74	11.92–18.68	15.73	1.20	12.39–19.44	2.00	0.052
CTQ Total	37.13	10.69	25.25–67	37.64	8.15	26–52	0.16	0.875
CTQ Abuse	6.55	1.83	5–13	6.90	2.01	5–11.33	0.59	0.560
CTQ Neglect	8.84	3.20	5–19	8.46	2.11	5.5–11.5	0.40	0.689
	Mean	**Standard Deviation**	**Range**	**Mean**	**Standard Deviation**	**Range**	**t (df = 42)**	**Sig.**
SCARED – Anxiety Symptoms	25.59	16.67	4–58	18.46	13.91	0–49	1.35	0.183
MFQ** – Depression Symptoms	11.93	12.28	0–40	11.08	10.05	1–35	0.22	0.827
	N	**Percentage**		**N**	**Percentage**		**X^2 (df = 1)**	**Sig.**
Gender (Female)	15	51.6%		7	50.0%		0.10	0.920
Race/Ethnicity								
African American/Black	3	9.7%		1	7.1%		0.08	0.782
Asian/Pacific Islander	2	6.5%		0	0		0.95	0.331
White	0	0		7	50.0%		18.36	<0.001
Hispanic/Latino/a/x	22	71.0%		1	7.1%		15.72	<0.001
Biracial	4	12.9%		4	28.6%		0.62	0.203
Other/Unknown	0	0		1	7.1%		2.265	0.132

*See Supplement for information on these measures.
**Spanish-speaking parents and participants were provided a translator and Spanish-translated consent forms and questionnaires. N = 17 parents in the trauma sample used the Spanish form of MFQ.

University of California San Diego Institutional Review Board and accepted by joint agreement by the San Diego State University Institutional Review Board. Informed consent from participants more than 18 years of age and parents of minor participants were obtained after a complete description of the study.

2.2. Measures

2.2.1. Threat- and deprivation-related adverse childhood experiences

History of childhood abuse (threat) and neglect (deprivation) experiences were measured using the *Childhood Trauma Questionnaire* [CTQ] (Bernstein and Fink, 1998). CTQ is a 25-item self-report measurement assessing the frequency and severity of physical, sexual, and emotional abuse; and physical and emotional neglect. Items are on a 5-point Likert scale ranging from "1 = none to minimal" to "5 = severe to extreme." The CTQ demonstrates high convergent and discriminant validity when compared with therapist-rated maltreatment (Bernstein et al., 1997). The neglect composite score (Cronbach's $\alpha = 0.77$) was calculated as the mean of the items in the emotional neglect and physical neglect subscales; the abuse composite score (Cronbach's $\alpha = 0.82$) was calculated as the mean of the items in the physical, sexual, and emotional abuse subscales. The scale showed high reliability overall (Cronbach's $\alpha = 0.85$).

2.2.2. fMRI data acquisition

Using highly similar data acquisition parameters and identical participant procedures, adolescents were scanned on two scanners, depending on their recruitment source. Scanner/recruitment source was included as a covariate in post-hoc analyses to assess the impact on results (see *Additional Analyses*). Multiband procedures increased spatial and temporal resolution and thus, ability to infer threat- and deprivation-related neural correlates.

Subjects referred to us for trauma treatment (trauma sample) were scanned using a 3 T Siemens Magnetom Prisma with a 30-channel head coil, whereas participants referred to us seeking anxiety/depression treatment (anxiety/depression sample) were scanned on a 3 T General Electric scanner with 32-channel head coil. Where acquisition parameters differed, this is denoted with the value for the trauma sample first, and the anxiety/depression sample second. For both scanners, T2 blood oxygen level dependent (BOLD) images were acquired using a 3D multiband EPI pulse sequence across 3 runs. Each run consisted of 60 interleaved sagittal slices approximately parallel to the AC-PC line, with whole-brain coverage (voxel size = 2.4 × 2.4 × 2.4 mm/2 × 2 × 2 mm, 358/370 image volumes per run, matrix size = 104 × 104 × 60, acceleration factor = 6, TR = 800 ms, TE = 30.8/29 ms, flip angle = 52°, FOV = 216/208 mm). Anatomical images with prospective motion correction (T2-weighted MPRAGE PROMO) were obtained for anatomical localization and spatial normalization (429/256 sagittal slices, flip angle = 9°/8°, matrix size = 256 × 256 × 176, FOV = 256 mm, voxel size = 1 × 1 × 1 mm).

2.2.3. Reward processing task

During fMRI acquisition, brain activity associated with reward anticipation and feedback was assessed using the piñata task, a previously validated child-friendly monetary incentive delay task (Fig. S1) (Dougherty et al., 2018; Helfinstein et al., 2013; Knutson, Westdorp, Kaiser, & Hommer, 2000). In this task, participants were instructed to press a button to hit a target (the piñata) in order to receive stars, which would be exchanged for money at the end of the session (up to $15). First, participants saw a cue (2000 ms) as to whether or not they could earn a reward (50% reward condition, 50% no-reward condition), followed by a variable delay period (2500–5500 ms) during which participants waited to hit the target. The cue plus variable delay comprised the anticipation period. When the target appeared, participants pressed the button to try to hit it. In reward trials, if participants hit the pinata within the allotted time (500 ms, adjusted in real-time based on performance), the pinata broke (1500 ms) and stars fell into their basket (1500 ms); if they missed it, the pinata swung away (1500 ms) and an empty basket was shown (1500 ms). In non-reward trials, the pinata swung away and an empty basket was shown regardless of their performance. The task was projected onto a screen that participants viewed via a mirror attached to the head coil. Three task runs of 4 min 52 s were conducted for a total of 60 trials (30 reward trials, 30 no-reward trials).

2.2.4. fMRI data preprocessing

Preprocessing protocols were implemented using Analysis of Functional NeuroImages (AFNI; https://afni.nimh.nih.gov/afni). Preprocessing steps included functional image realignment, slice-time correction, spatial smoothing of 4 mm, and non-linear registration for spatial standardization to the Talairach template (Talairach, 1988). Image volume pairs with framewise displacement >1 mm were censored from individual level analysis. All participants evidenced mean framewise displacement (head motion) ≤ 0.30 mm. See Supplement for more details.

2.3. Statistical analysis

2.3.1. First level analysis

Individual-level general linear models were run to generate estimates of brain activation during the anticipation and feedback periods, separately. For the anticipation period, reward condition (reward vs. no reward) was convolved with AFNI's "dmBLOCK" basis function over the variable duration. For the feedback period, reward condition and performance (hit vs. miss) were convolved with the "BLOCK" function. Analyses generated beta coefficients at each voxel for reward and no reward trials during the anticipation period, as well as for reward/hit, reward/miss, no reward/hit, and no reward/miss trials during the feedback period. Nuisance regressors included head motion in x, y, z, roll, pitch, yaw directions and third-degree polynomials to model low-frequency drift.

2.3.2. Second level analysis

Separate models were run for the anticipation and feedback periods. During the anticipation period, whole-brain, group-level ANCOVAs via AFNI's 3dMVM program were conducted, with reward condition as the within-subjects factor and childhood abuse and neglect as quantitative between-subjects factors. This model allowed us to examine unique effects of abuse and neglect, and their interactions, in relation to task conditions. Thus, our contrasts of interest for the anticipation period were: effects of abuse adjusted for neglect (Abuse, Abuse × Condition), effects of neglect adjusted for abuse (Neglect, Neglect × Condition), and the interaction of abuse by neglect (Abuse × Neglect, Abuse × Neglect × Condition).

During the feedback period, within-subjects factors included reward condition (reward vs. no-reward) and performance (hit vs. miss), and quantitative between-subjects factors included childhood abuse and neglect. Here, our contrasts of interest were: effects of abuse adjusted for neglect (Abuse, Abuse × Condition, Abuse × Performance, Abuse × Performance × Condition), effects of neglect adjusted for abuse (Neglect, Neglect × Condition, Neglect × Performance, Neglect × Performance × Condition), and the interaction of abuse by neglect (Abuse × Neglect, Abuse × Neglect × Performance, Abuse × Neglect × Performance × Condition).

An additional line of analysis examining the neural correlates of reward processing as a function of CTQ total score was conducted. The same procedures applied, except that CTQ total score was entered as the quantitative between-subject factor. See Supplement for details.

Cluster threshold was estimated using 3dClustSim with mixed-model spatial autocorrelation function (-acf) and the NN1 bi-sided option, allowing for separate clusters of positive and negative voxels. 3dClustSim applied a group mask consisting of brain regions where 90% of participants had valid data. A whole-brain corrected threshold of $p < .05$ was estimated to be equal to height threshold of $p < .005$ uncorrected and extent threshold of $k \geq 58$.

2.3.3. Additional statistical analysis

Additional statistical analysis was performed using SPSS v.27. Post-hoc analysis examined a range of factors that could have impacted results: age, gender, recruitment source, parental Spanish-speaking status, race/ethnicity, average censored motion, depression, anxiety, and duration of time between scan and abuse/neglect scores (see Supplement). For these post-hoc analyses, values from each significant cluster were extracted and averaged, and exported to SPSS v. 27. In SPSS, for each cluster, analyses were recreated with each of these factors added as covariates to determine whether the clusters were still significant.

3. Results

3.1. Sample characteristics

Self-report scores for childhood abuse (physical, emotional, and sexual abuse) ranged from low to moderate (5 to 13 out of a possible 5 to 25 [M = 6.66, SD = 1.87]), whereas childhood neglect (physical and emotional neglect) ranged from low to moderately high (5 to 19 out of 5 to 25 [M = 8.73, SD = 2.89]). Abuse and neglect scores were significantly correlated ($r = 0.462$, $p = .001$), which is not uncommon given the high co-occurrence of abuse and neglect.

3.2. Abuse (adjusted for neglect)

3.2.1. Reward anticipation

During the reward anticipation period, the main effect of Abuse was significant in the right inferior frontal gyrus and the right dorsolateral prefrontal gyrus (Fig. 1A.1, Table 2), such that abuse is positively associated with the degree of activation, whether or not a reward is anticipated.

The interaction effect of Abuse × Condition was significant in the right dorsal prefrontal cortex, right inferior frontal gyrus, and right ventrolateral prefrontal cortex (Fig. 1A.2, Table 2). Across these clusters, patterns were similar: whereas adolescents with lower levels of abuse show little difference in activation between the reward vs. non-reward conditions, adolescents who experienced higher levels of abuse show greater activation in the non-reward compared to reward condition.

3.2.2. Performance feedback

During the performance feedback period, the main effect of abuse was significant in the right ventromedial prefrontal cortex (Fig. 1B.1, Table 2), such that abuse is positively associated with the degree of activation, regardless of condition and performance.

The interaction effect of Abuse × Performance was significant in two frontal regions (left insula and right post/precentral gyrus), as well as several posterior regions (left fusiform gyrus, left middle occipital gyrus, right inferior parietal lobule, and left cuneus) (Fig. 1B.2, Table 2). In these clusters, adolescents who experienced lower abuse levels show little difference in activation after hit vs. miss; by contrast, adolescents with higher levels of abuse show less activation to misses compared to hits.

The interaction of Abuse × Condition was significant in the left lingual gyrus (Fig. 1B.3, Table 2). Adolescents with higher levels of abuse show greater activation in response to trials where there was no potential reward vs. trials when there was a chance of reward, whereas adolescents with lower levels of abuse show the opposite pattern, greater activation to reward vs. no reward trials.

The interaction of Abuse × Performance × Condition was significant in multiple temporoparietal (left temporoparietal junction, right middle/superior temporal gyrus, right precuneus, right temporal pole, right parahippocampal gyrus, left middle/inferior temporal and fusiform gyri, right angular/inferior parietal lobule, left precuneus/angular gyrus), posterior (left precuneus/posterior cingulate gyrus), and prefrontal (left dorsolateral) cortical regions (Fig. 1B.4, Table 2). Across all of these clusters, the patterns were similar: individuals with lower levels of abuse show little difference in activation between reward vs. no reward conditions across both hits and misses, while individuals with higher abuse show much more exaggerated differences among conditions, especially during misses: greater activation when missing a potential reward vs. missing when there was no potential reward (reward/miss vs. no reward/miss), and the opposite pattern albeit somewhat attenuated when hitting the target, less activation when hitting and receiving the reward vs. when no reward was given (reward/hit vs. no reward/hit).

3.3. Neglect (adjusted for Abuse)

No clusters were significant for effects of neglect.

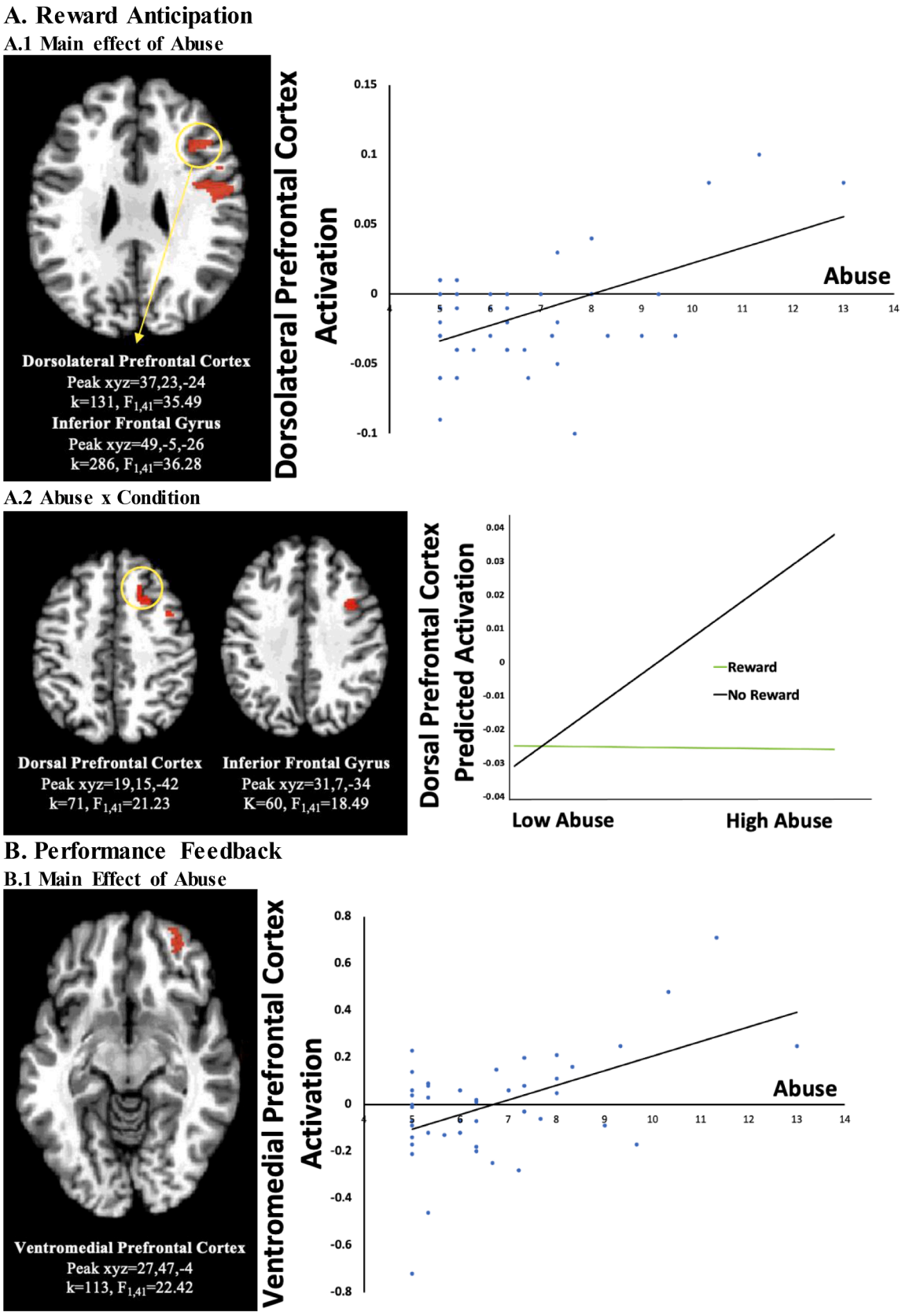

Fig. 1. Neural Effects of Abuse (adjusting for Neglect). Brain images depict selected significant clusters with threshold set at whole-brain corrected $p < .05$. (See Table 2 for a listing of all significant clusters in contrasts of interest.) For main effects, data points are depicted in scatter plots with trend lines overlaid. Illustrative graphs decomposing interaction effects were generated by calculating predicted brain activation values based on minimum and maximum abuse or neglect scores within our data, to cover the full range. Only one cluster is plotted as an example when a contrast contains multiple regions with similar patterns.

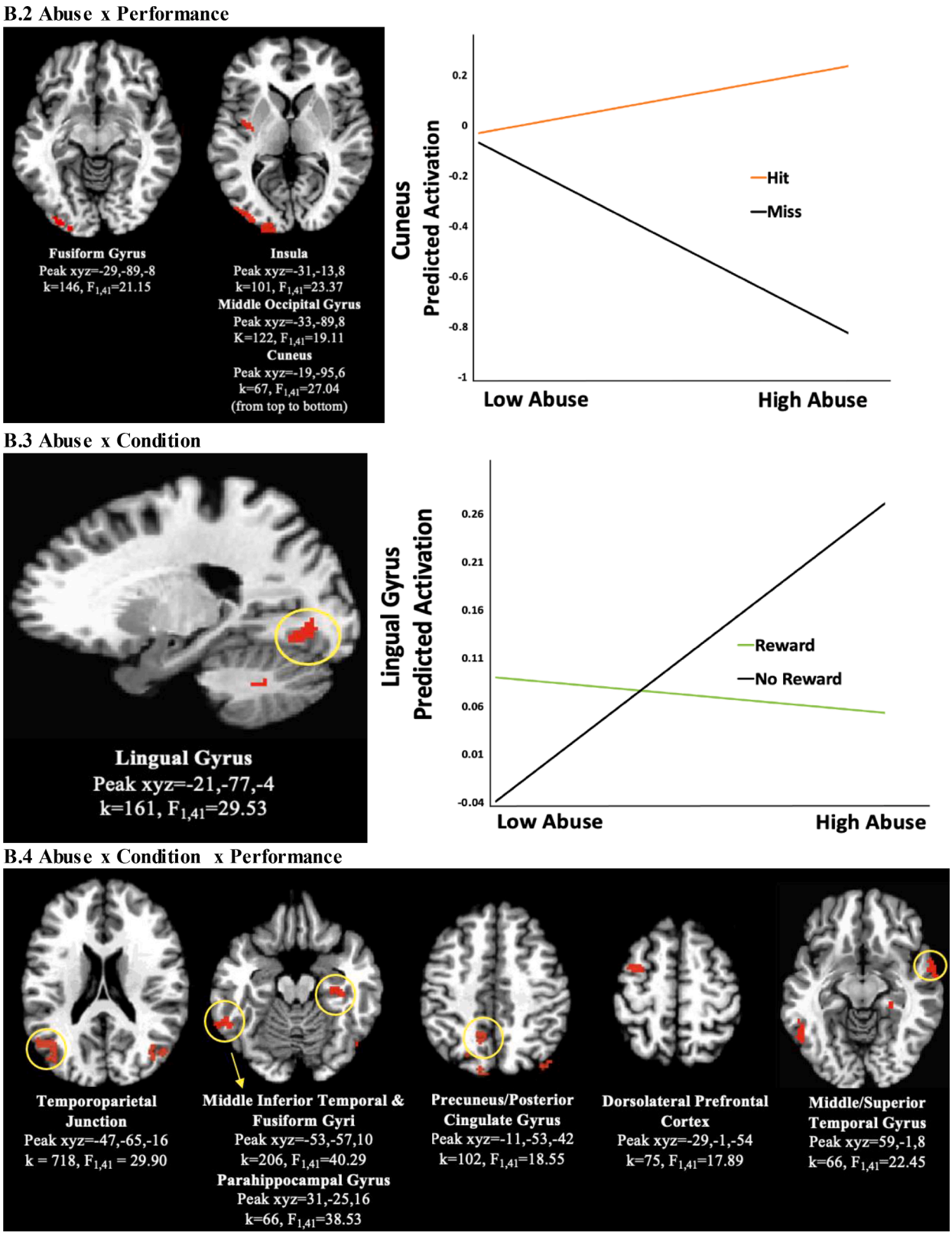

Fig. 1. (*continued*).

3.4. *Abuse × Neglect*

3.4.1. *Reward anticipation*

During the reward anticipation period, the interaction effect of Abuse × Neglect × Condition was significant in the left precuneus/parietal lobule (Fig. 2A, Table 2). This interaction was driven by adolescents with a combination of high abuse and high neglect: these youths show greater activation to the no reward vs. reward condition. By contrast, adolescents with high scores in only one dimension (i.e., high levels abuse with low levels of neglect, or high levels of neglect with low

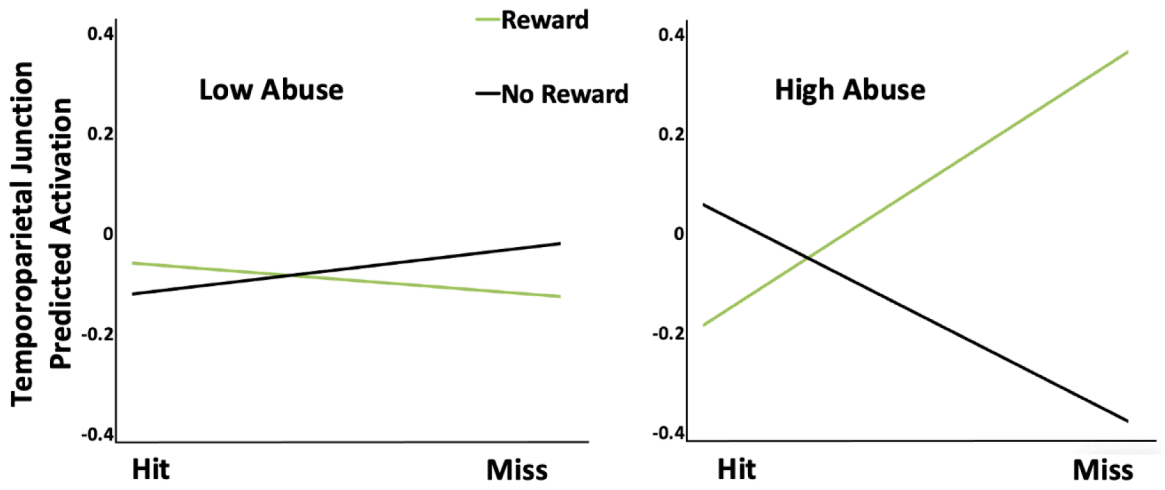

Fig. 1. (*continued*).

Table 2
Significant Clusters from Contrasts of Interest in Whole Brain Analysis.

k	F (df = 1,41)	Z Score	Effect Size (Cohen's d)	PRE	x	y	z	BA	Region
Abuse (adjusted for neglect)									
Reward Anticipation									
Abuse Main Effect									
286	36.28	5.07	0.90	0.47	49	−5	−26	6	Precentral Gyrus
131	35.49	5.03	0.89	0.46	37	23	−24	9	Middle Frontal Gyrus
Abuse × Condition									
71	21.23	4.11	0.69	0.34	19	15	−42	8	Superior Frontal Gyrus
60	18.49	3.88	0.64	0.31	31	7	−34	9	Middle Frontal Gyrus, Inferior Frontal Gyrus, Precentral Gyrus
59	26.64	4.5	0.77	0.39	37	57	6	10	Middle and Superior Frontal Gyri
Performance Feedback									
Abuse Main Effect									
126	28.939	4.65	0.80	0.41	25	33	12	32	Anterior Cingulate
113	22.42	4.2	0.71	0.35	27	47	−4	10	Middle and Superior Frontal Gyri
Abuse × Performance									
179	26.91	4.52	0.77	0.40	65	−15	−20	43	Post/Precentral Gyri
146	21.15	4.11	0.69	0.34	−29	−89	−8	18	Inferior Occipital Gyrus, Fusiform Gyrus
122	19.11	3.94	0.65	0.32	−33	−89	8	19	Middle Occipital Gyrus
101	23.37	4.28	0.72	0.36	−31	−13	8	13	Insula
88	29.37	4.68	0.81	0.42	39	−35	20	13	Inferior Parietal Lobule, Insula
67	27.04	4.53	0.78	0.40	−19	−95	6	18	Cuneus, Middle Occipital Gyrus
Abuse × Condition									
161	29.53	4.69	0.81	0.42	−21	−77	−4	18	Lingual Gyrus
Abuse × Performance × Condition									
718	29.9	4.71	0.82	0.42	−47	−65	−16	19	Middle Temporal Gyrus, Precuneus
285	27.51	4.56	0.78	0.40	−39	−79	−38	19	Precuneus, Middle Temporal Gyrus, Cuneus
230	26.76	4.51	0.77	0.39	43	9	38	38	Superior Temporal Gyrus
206	40.29	5.27	0.95	0.50	−53	−57	10	37	Inferior and Middle Temporal Gyri
102	18.55	3.89	0.64	0.31	−11	−53	−42	31	Precuneus, Cingulate Gyrus
75	17.89	3.83	0.63	0.30	−29	−1	−54	6	Middle Frontal Gyrus
66	38.53	5.18	0.93	0.48	31	−25	16	35	Parahippocampal Gyrus
66	22.45	4.21	0.71	0.35	59	−1	8	21	Middle and Superior Temporal Gyri
65	24.93	4.39	0.74	0.38	49	−67	−38	39	Angular Gyrus, Inferior Parietal Lobule
60	16.74	3.72	0.61	0.29	−29	−59	−36	39	Precuneus
Neglect (adjusted for abuse): no significant clusters									
Abuse × Neglect									
Reward Anticipation									
Abuse × Neglect × Condition									
70	23.47	4.28	0.72	0.36	−25	−69	−50	7	Superior Parietal Lobule, Precuneus
Performance Feedback									
Abuse × Neglect × Performance × Condition									
60	24.25	4.34	0.73	0.37	13	61	−18	10	Superior Frontal Gyrus
60	18.97	3.93	0.65	0.32	−33	−73	−26	39	Middle Temporal Gyrus, Angular Gyrus
60	21.1	4.1	0.68	0.34	43	−59	−32	39	Angular Gyrus

levels of abuse) show more attenuated differences in activation between the conditions, and in the opposite direction (i.e., less activation to the no reward vs. reward condition). Youths with low levels of both abuse and neglect show little difference in activation between the no reward vs. reward conditions.

3.4.2. Performance feedback

During the performance feedback period, the interaction effect of Abuse × Neglect × Performance × Condition was significant in the right ventromedial prefrontal cortex and the bilateral temporoparietal junction (Fig. 2, Table 2). Across all levels of abuse and neglect, activation to

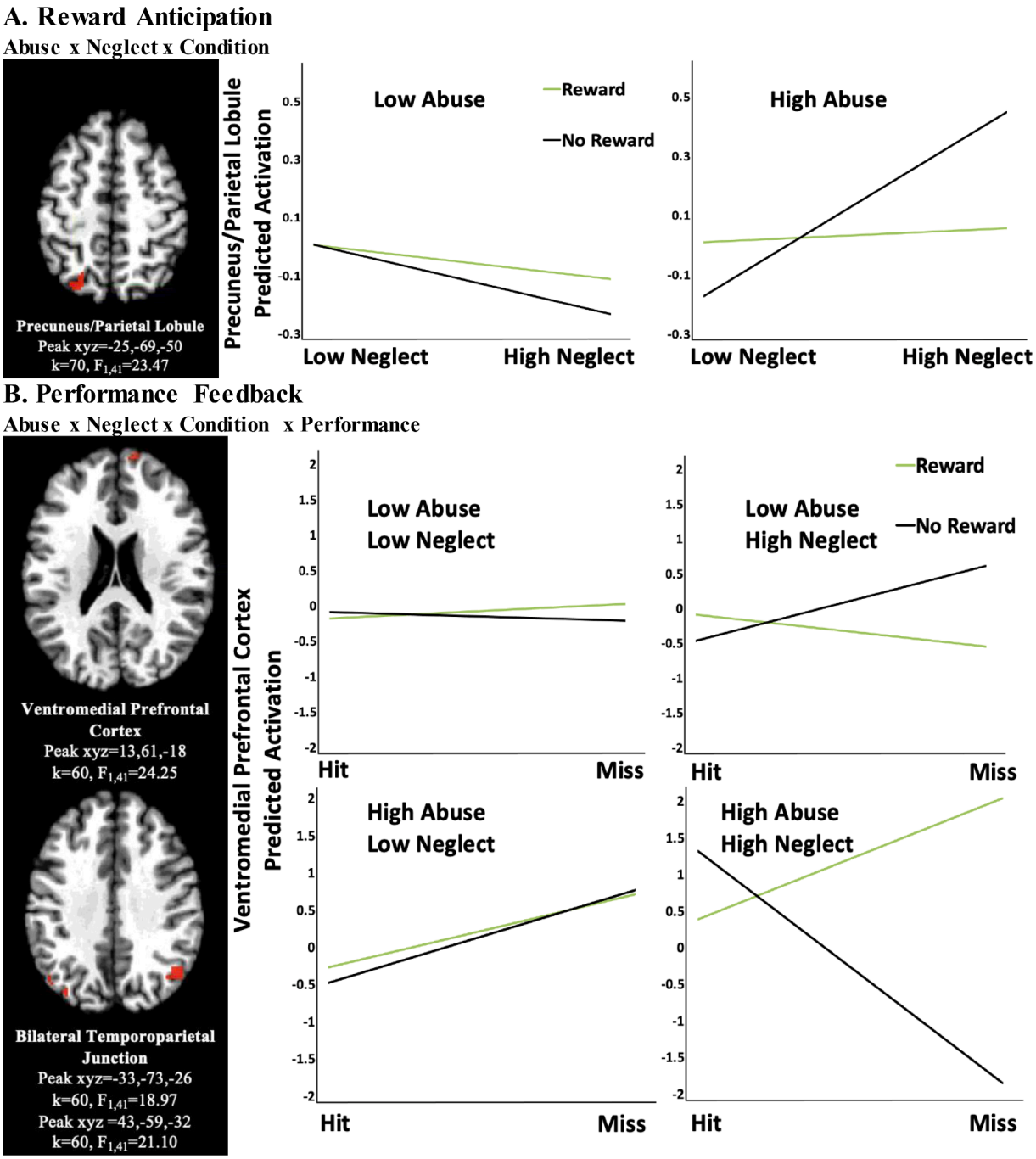

Fig. 2. Abuse by Neglect Interactions on Brain Activation. See Fig. 1 for details on images.

reward vs. no reward trials when adolescents hit the target differed little. However, patterns of activation when youths missed the target in reward vs. no reward conditions differed greatly across levels of abuse and neglect. Here, youths with low levels of both abuse and neglect showed little difference in activation by either performance or reward condition. Youths with elevated childhood adversity in just the abuse dimension also showed little difference between the reward vs. no reward conditions, although slightly more activation overall in the miss condition. Youths with high levels of neglect with low abuse showed greater activation after missing the target when there was no reward vs. a reward. However, youths with a combination of high abuse and high neglect show a strikingly different, more exaggerated pattern compared to youths with other abuse/neglect profiles: greater activation after missing a potential reward vs. after missing the target when there was no potential reward.

Full model results, including task effects, are provided in Table S1.

3.5. CTQ total score

See Supplement for details.

3.6. Additional analyses

Post-hoc analysis of age, gender, recruitment source, parental Spanish-speaking status, race/ethnicity, average censored motion, depression, anxiety, and duration of time between scan and abuse/neglect scores indicated that these factors were not primarily driving results. See Supplement for details.

4. Discussion

Developmental theory emphasizes that early influences unpack over time, as maturing brain systems come "online" and social and environmental changes (e.g., in school, peers, romantic relationships, life transitions) make neurodevelopmental vulnerabilities due to adverse early experiences more relevant or apparent (Cicchetti and Rogosch, 2002; Wiggins and Monk, 2013). In this vein, we demonstrated that histories of childhood adverse experiences are associated with alterations in reward-related brain activation in adolescence, a time when reward circuitry is shifting rapidly. Further, theorizing the current study in the DMAP model (Dimensional Model of Adversity and Psychopathology) (McLaughlin and Sheridan, 2016; Sheridan and McLaughlin, 2014), we demonstrated that threat and deprivation could have differential associations with neural alterations in reward processing. Developmental investigations such as the present study will be necessary to chart the unfolding consequences of dimensions of early adversity and develop developmentally-informed interventions based on neural substrates for individuals across the lifespan (Mittal and Wakschlag, 2017).

Our study was the first to examine the relative contributions of threat (childhood abuse) and deprivation (childhood neglect) to reward processing, as well as combinations of differing levels of threat- and deprivation-related adversity, within an fMRI paradigm designed to elicit reward-related neural responses. Overall, childhood abuse was associated with altered activation in multiple brain regions associated with threat/emotion and emotion regulation, including prefrontal and temporal cortices (e.g., dorsolateral prefrontal cortex, ventromedial prefrontal cortex, temporoparietal junction). These findings strengthen conceptualizations of abuse as threat-related adversity and are in line with prior work in animals and humans showing threat-related neural alterations as a long-lasting consequence of early experiences of abuse. In addition to regions typically associated with threat/emotion regulation in the face of threat (e.g., prefrontal cortex), other regions related to reading emotions in others (e.g., temporoparietal junction, fusiform gyrus, posterior cingulate) were also implicated in relation to abuse. This may reflect the hypersensitivity to potential threat in others (e.g., angry facial expressions or body language) developed as a result of childhood abuse.

Notably, ours was also the first study to show that level of childhood neglect modulates neural profiles of abuse, such that a combination of high levels of both abuse and neglect was associated with a qualitatively different, more exaggerated pattern – differences in activation between task conditions in the opposite direction – compared to either high abuse or high neglect alone. This finding is particularly intriguing because threat and deprivation have been theorized to exert opposing effects (hyper- and hypo-sensitivity, respectively, to environmental cues) (McLaughlin et al., 2014), yet threat and deprivation experiences often co-occur. Our work here suggests that combinations of adverse experiences are not necessarily additive – in contrast to a broad characterization of cumulative early life stress – but rather can result in a "special" profile, which may require correspondingly special, qualitatively different intervention.

Across multiple clusters, our results were driven by two prevailing patterns: alterations in brain activation associated with abuse/abuse modulated by neglect when participants missed the target and/or alterations when there was no potential reward. Overall, these nonreward situations appeared to probe the abuse/threat-related neural alterations most effectively, more so than when participants received the reward. This pattern echoes some theoretical work noting the overlap between threat and nonreward (Brotman et al., 2017; Burokas et al., 2012), even going so far as to theorize that blocked reward and threat are equivalent, as they activate the same neural circuitry and sympathetic nervous reactions (Gray, 1987). Thus, not receiving a reward in this task may have acted as a threat probe, eliciting activation in threat pathways which are altered as a consequence of childhood abuse. This further strengthens the conceptualization of abuse as threat and moreover provides evidence for the conceptual and neural overlap of threat and reward, domains which have been traditionally investigated separately.

Of note, beyond the modulating effect of neglect within the context of the abuse by neglect interaction analysis, there were no effects of neglect on reward-related brain function after adjusting for abuse. This is somewhat surprising, because neglect/deprivation is by definition lack of a rewarding environment and so hyposensitivity – or at least alterations – in reward would have been logical. For instance, other studies examining the differential associations of threat and deprivation with neural and developmental outcomes have mainly implicated cognitive deficits as a consequence of deprivation and deficits in emotion regulation and perception of salient stimuli as a consequence of threat (Hildyard and Wolfe, 2002; McLaughlin et al., 2014; McLaughlin et al., 2019; Rakesh et al., 2021). Yet no unique effects of neglect were identified in the present study. We hypothesized that there might be several reasons that we did not observe effects of neglect (after adjusting for abuse) in the current study. First, the present study is limited in its relatively small sample size ($N = 45$) and our aim of examining two different dimensions of childhood adversity could make such limitation more vulnerable. Future replications with larger sample size will be necessary. Second, the abuse and neglect scores were significantly correlated. We included abuse and neglect in the statistical model with the intention of observing both the relative and interactive effects of both dimensions. The correlation between abuse and neglect, which is not surprising given the high co-occurrence rate, could affect the estimates of the effects in the statistical models. Third, abuse scores ranged from low to moderate and neglect from low to moderately high in the present study. Despite the relatively wide range of scores, extremely high abuse and neglect scores were lacking. Thus, we may miss some non-linear effects occurring at the extreme end of abuse and neglect experiences. Fourth, it may be that neglect/deprivation is better conceptualized as lack of cognitive complexity in the environment rather than lack of reward. However, additional research will be necessary to fully parse the neural consequences of neglect across multiple domains.

The present study has several additional limitations. First, the measurement of childhood adversity is limited due to the retrospective nature of the CTQ and the lack of a specific time frame for the self-reported abuse and neglect experiences. Second, we examined the effects of childhood adversity in two separate dimensions: threat vs. deprivation and operationalized threat vs. deprivation as physical, emotional, and sexual abuse vs. physical and emotional neglect, respectively. Other aspects of childhood adversity, such as maternal depression, material deprivation (e.g., poverty, food insecurity), traumatic events, etc., were not included in the present investigation and could exert different effects on brain functioning. By operationalizing the threat vs. deprivation dimensions of childhood adversity as the two subsets of childhood trauma (abuse and neglect), we could miss other important aspects. A more inclusive list of threat- and deprivation-related childhood adverse experiences is needed for future research.

To conclude, our findings further our understanding of how neural development and pathways are affected when children experience adversity early in life, suggesting these early experiences have a long developmental reach that comes to bear "when the rubber meets the road" in adolescence as key neural systems and the social environment are rapidly changing. Thus, programs to reduce abuse and neglect in early childhood will have cascading effects throughout development. Also, assessments to understand adolescent behavior should consider an individual's history of adversity. Additionally, our findings bolster theoretical conceptualizations of adversity along threat and deprivation dimensions and provide evidence that "adding up" adverse life events may not be sufficient to capture the qualitatively different neural profiles produced by differing combinations of types of adversity. Our results pave the way for additional, more fine-grained research characterizing profiles of risk, which is the groundwork necessary for personalized medicine in mental health.

CRediT authorship contribution statement

Ruiyu Yang: Conceptualization, Methodology, Formal analysis, Visualization, Writing – original draft,**Qiongru Yu:**Conceptualization, Methodology, Resources, Writing – review & editing,**Cassidy Elizabeth Owen:**Visualization,**Gabriele Ibarra Aspe:**Visualization,**Jillian Lee Wiggins:**Supervision, Funding acquisition, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2021.102832.

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