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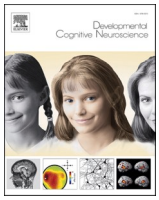

Different forms of childhood maltreatment have different impacts on the neural systems involved in the representation of reinforcement value

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ABSTRACT

Background: The current study aimed to address two gaps in the literature on child maltreatment, reinforcement processing and psychopathology. First, the extent to which compromised reinforcement processing might be particularly associated with either neglect or abuse. Second, the extent to which maltreatment-related compromised reinforcement processing might be associated with particular symptom sets (depression, conduct problems, anxiety) or symptomatology more generally.

Methods: A sample of adolescents (N = 142) aged between 14 and 18 years with varying levels of prior maltreatment participated in this fMRI study. They were scanned while performing a passive avoidance learning task, where the participant learns to respond to stimuli that engender reward and avoid responding to stimuli that engender punishment. Maltreatment (abuse and neglect) levels were assessed with the Childhood Trauma Questionnaire (CTQ).

Results: We found that: (i) level of neglect, but not abuse, was negatively associated with differential BOLD responses to reward-punishment within the striatum and medial frontal cortex; and (ii) differential reward-punishment responses within these neglect-associated regions were particularly negatively associated with level of conduct problems.

Conclusion: Our findings demonstrate the adverse neurodevelopmental impact of childhood maltreatment, particularly neglect, on reinforcement processing. Moreover, they suggest a neurodevelopmental route by which neglect might increase the risk for conduct problems.

1. Introduction

The incidence of exposure to early life stressors (ELS) in childhood is extremely high with 1 in 8 children in the United States experiencing some form of maltreatment by 18 years of age (Wildeman et al., 2014). ELS exposure significantly increases the risk for both externalizing and externalizing psychiatric psychopathology (Green et al., 2010; McLaughlin et al., 2010; Shonkoff and Garner, 2012). This likely reflects the impact of this exposure on neurodevelopment (Bremner and Vermetten, 2001; McLaughlin et al., 2019a).

Core functional impacts seen following exposure to ELS are: (i) heightened threat sensitivity (McCrory et al., 2013; McLaughlin et al., 2015; Pine et al., 2005; Pollak, 2005; Pollak and Sinha, 2002; Toth and Cicchetti, 2011; Tottenham et al., 2011); (ii) executive dysfunction (Blair et al., 2019; Harms et al., 2018; Mackiewicz Seghete et al., 2017; Mueller et al., 2010); and, the focus here, (iii) reduced reward responsiveness (Birn et al., 2017; Gerin et al., 2017; Harms et al., 2016). This is seen in animal pre-clinical work where exposure to early-life adversity disrupts reward processing (Hollon et al., 2015; Matthews and Robbins, 2003; Sasagawa et al., 2017). In humans it manifests, for example, as disrupted reinforcement-based probabilistic learning (Guyer et al., 2006; Hanson et al., 2017; Pechtel and Pizzagalli, 2013), reduced volume in core reward-related regions such as the striatum and orbital functional cortex (Dannlowski et al., 2012; De Brito et al., 2013),

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disruption of the white matter tract linking nucleus accumbens with orbitofrontal cortex (DeRosse et al., 2020) and reduced responses during anticipation and/or receipt of reward within striatum, anterior cingulate cortex (ACC) and middle frontal gyrus (MFG) (Birn et al., 2017; Boecker et al., 2014; Boecker-Schlier et al., 2016; Gerin et al., 2017; Hanson et al., 2015; Mehta et al., 2010).

Two issues have received relatively little attention. First, the extent to which *different forms* of ELS might have differential impacts on reward sensitivity. Much of the previous literature has either grouped together participants who have experienced different forms of ELS (Birn et al., 2017; Boecker et al., 2014; Gerin et al., 2017) or only considered one form of ELS; e.g., emotional neglect (Hanson et al., 2015) or deprivation (Mehta et al., 2010). Yet, different forms of childhood ELS may have distinct consequences for development, even if many individuals who experience ELS experience multiple forms of stressor (Dennison et al., 2017; Lambert et al., 2017; McLaughlin and Sheridan, 2016; Pollak et al., 2000; Sheridan et al., 2017; van Schie et al., 2017). In particular, it has been suggested that *threatening* contexts (as might occur during physical/sexual abuse) increase threat responsiveness while *deprivation* (as might be engendered through physical/emotional neglect) disrupt aspects of memory, learning (including learning from reward) and executive function (Lambert et al., 2017; McLaughlin and Sheridan, 2016; Novick et al., 2018; Sheridan et al., 2017) – though it should be noted that there has been a disrupted reinforcement learning in patients with MDD with a history of childhood sexual abuse relative to patients with MDD without a history of childhood sexual abuse (Pechtel and Pizzagalli, 2013). However, very little empirical work has systematically evaluated this issue, particularly in the context of an instrumental learning task.

Second, reduced reward responsiveness has been seen in a variety of psychiatric conditions. It is commonly associated with depressive symptomatology (Admon and Pizzagalli, 2015; Stringaris et al., 2015). However, reduced sensitivity to reward has also been associated with increased impulsiveness in ADHD (Plichta and Scheres, 2014), Generalized Anxiety Disorder (Benson et al., 2015; White et al., 2017) and conduct problems/aggression (Crowley et al., 2010; Finger et al., 2008; White et al., 2013). A series of studies have reported that the decreased reward responsiveness seen in individuals exposed to ELS relates to either the depressive symptomatology or the conduct problems of the participants assessed (Birn et al., 2017; Goff et al., 2013; Goff and Tottenham, 2015; Hanson et al., 2015, 2018, 2017; Holz et al., 2017). However, these studies have typically examined the association between reward responsivity and a single disorder, so it is difficult to determine the extent to which ELS-induced reductions in reward responsiveness might be particularly related to a specific form of symptomatology.

The current study aimed to address these two issues: First, to determine the association between level of neglect and abuse with differential reward versus punishment responsiveness in the context of an instrumental learning task. Notably, most of the previous work has examined the association between ELS exposure and reward receipt in non-learning contexts (i.e., during performance of the Monetary Incentive Delay task; (Birn et al., 2017; Boecker et al., 2014; Boecker-Schlier et al., 2016; Mehta et al., 2010). It has been considered important to examine reward-based *learning* because the information may provide insight into mechanisms by which the environment changes brain function and because it may inform intervention strategies (McLaughlin et al., 2019a). This task investigates a prerequisite to learning – appropriate differential responsiveness to reward-punishment during an instrumental learning task. Second, to determine the association between BOLD responses to reward-punishment in regions sensitive to neglect or abuse and different groups of symptoms previously related to reduced reward responsiveness (depression, anxiety, ADHD and conduct problems). On the basis of previous work (Birn et al., 2017; Boecker et al., 2014; Boecker-Schlier et al., 2016; Gerin et al., 2017; Hanson et al., 2015; Mehta et al., 2010), we predicted that differential reward-punishment responsiveness within the striatum and medial frontal cortex would be negatively associated with exposure to ELS (potentially, particularly neglect; cf. (Goff et al., 2013; Novick et al., 2018); i.e., increasing ELS exposure would be associated with a reduction in the BOLD responses to reward-punishment. We predicted that differential reward-punishment responsiveness within identified regions would be negatively associated with symptomatology. However, in the absence of prior literature, we made no predictions regarding which symptom groups might be more/less related to this responsiveness.

2. Methods

2.1. Participants

142 youths aged 14–18 years ($M = 16.4$ years, $SD = 1.20$; average IQ = 98.6, $SD = 10.01$; 91 male) participated in the study (see Table 1). Participants were recruited either shortly after their arrival at a residential care facility or from the surrounding community. Youth recruited from the care facility had been referred for behavioral and mental health problems. Participants from the community were recruited through flyers or social media. Clinical characterization was done through psychiatric interviews by licensed and board-certified child and adolescent psychiatrists with the participants and their parents to adhere closely to common clinical practice.

2.2. Childhood trauma questionnaire (CTQ)

Child ELS was assessed using the CTQ, a 28-item self-report measure containing five sub-scales indexing Emotional Abuse (EA), Sexual Abuse (SA), Physical Abuse (PA), Emotional Neglect (EN) and Physical Neglect (PN). It has excellent psychometric properties including internal consistency, test-retest reliability, and convergent and discriminant validity with interviews and clinician reports of maltreatment (Bernstein et al., 1997). Individuals responded to each item using a 5-point Likert scale; scores range from 25 (no history of abuse/neglect) to 125 (extreme abuse/neglect).

2.3. Self-report measures of psychopathology

Psychopathology was indexed via the: (i) Screen for Child Anxiety and Related Emotional Disorders (SARED; (Birmaher et al., 1999); (ii) Mood and Feelings Questionnaire (MFQ; (Angold et al., 1995); (iii) Conners ADHD scale (parents rated) (Conners, 2008); and (iv) Strengths and Difficulties Questionnaire (Conduct Problems and Hyperactivity subscales) (Goodman, 1997).

2.4. fMRI task

2.4.1. The passive avoidance (PA) fMRI task

In the PA task (Finger et al., 2011; Newman and Kosson, 1986; White et al., 2013) participants are presented with 1 of 4 shapes on each trial and are required to decide whether or not to respond to (choose) the shape. Each trial involves the presentation of a shape (1500 ms), then a jittered fixation point interval (1000–4000 ms), followed by a reward/punishment feedback (15,000 ms) and, finally, a second jittered fixation point interval (1000–4000 ms). Two of the 4 shapes used in the paradigm yield a virtual reward (80% probability of winning $1 or $5) if responded to. Two of the shapes yield a virtual punishment (80% probability of losing $1 or $5) if responded to. Shapes are presented in a randomized order and participants respond via a button press with their right index finger. There are 27 trials for each shape, totaling 108 trials. See Fig. 1 for more details.

2.5. MRI parameters

MRI data were collected using a 3T Siemens Skyra scanner. A total of 313 functional images were taken with a T2 * weighted gradient echo

Table 1
Demographic and clinical variables.

	Mean	Std. Deviation	Range	Correlation with Neglect	Correlation with Abuse	Steiger's Z	p
CTQ Total Score (Max=125)	41.36	16.05	25–93	**0.831** * *	**0.907** * *	**-3.531**	0.000
Neglect (EN+PN) (Max=50)	17.41	7.58	10–48	–	**0.565** * *	–	–
EN (Max=25)	9.91	4.62	5–24	**0.931** * *	**0.530** * *	–	–
PN (Max=25)	7.50	3.54	5–24	**0.815** * *	**0.515** * *	–	–
Abuse (EA+PA+SA) (Max=75)	23.95	10.64	15–64	0.565 * *	–	–	–
EA (Max=25)	9.75	4.90	5–25	**0.618** * *	**0.870** * *	–	–
PA (Max=25)	7.34	3.56	5–23	**0.481** * *	**0.706** * *	–	–
SA (Max=25)	6.86	4.87	5–25	0.136	**0.628**	–	–
Age	16.43	1.20	14.13–18.75	-0.01	0.063	-0.924	0.355
IQ	98.64	10.01	77–133	0.14	0.06	1.019	0.308
MFQ	13.36	12.66	0–56	**0.418** * *	**0.489** * *	-1.038	0.299
SCARED	20.78	16.15	0–73	**0.289** * *	**0.512** * *	**-3.191**	0.001
Conners (ADHD)	4.92	6.12	0–20	0.142	**0.193** *	-0.656	0.512
SDQ Conduct Problems	4.08	3.15	0–10	**0.390** * *	**0.340** * *	0.691	0.490
	N	**Percent**					
Male	91	64.08	–	-0.023	**-0.262** * *	**3.093**	0.002
MDD	29	20.42	–	**0.356** * *	**0.358** * *	-0.028	0.978
GAD	42	29.58	–	**0.215** *	**0.424** * *	**-2.855**	0.004
PTSD	23	16.20	–	**0.335** * *	**0.504** * *	**-2.433**	0.015
ADHD	84	59.15	–	**0.299** * *	**0.169** *	1.707	0.088
CD	74	52.11	–	**0.295** * *	**0.262** * *	0.438	0.661
Antipsychotic	15	10.56	–	-0.065	-0.117	0.661	0.509
Simulant	28	19.72	–	-0.016	-0.146	1.655	0.098
SSRI	27	19.01	–	-0.001	0.101	1.268	0.205

Note: MDD: Major Depressive Disorder, GAD: Generalized Anxiety Disorder; PTSD: Post Traumatic Stress Disorder; ADHD: Attention Deficit Hyperactivity Disorder; CD: Conduct Disorder; p = significance level of the Steiger's Z calculation (i.e., whether there were significant differences in correlation strength between the variable and neglect versus abuse).

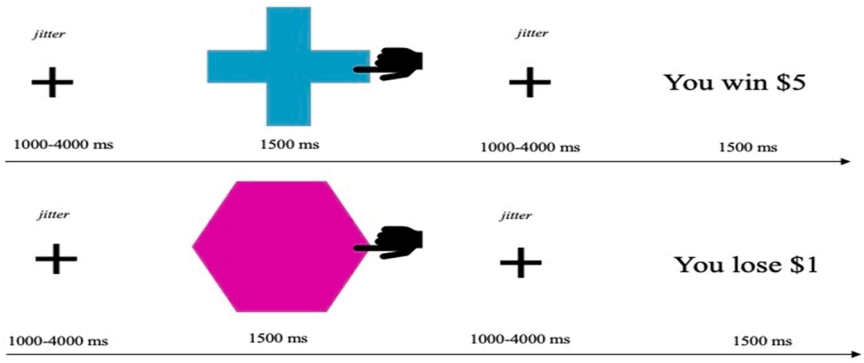

Fig. 1. Schematic representation of the PA task (Finger et al., 2011; Newman and Kosson, 1986). Participants are presented with one of four objects to which they decide to respond or not to respond. Reinforcement is provided in a probabilistic manner and the selection of two of the four objects results in a net profit over the course of the task while selection of the other two objects results in a net loss. The schematic depicts a participant choosing to respond to two different trials; one engendering reward, the other punishment. If the participant avoids responding, they can gain neither reward nor punishment.

planar imaging (EPI) sequence (repetition time = 2500 ms; echo time = 27 ms; 240 mm field of view; 94 × 94 matrix; 90° flip angle). Whole-brain coverage was obtained with 43 axial slices (thickness 2.5 mm, voxel size 2.6 × 2.6 × 2.5 mm^3). A high-resolution T1 anatomical scan (MP-RAGE, repetition time = 2200 ms; echo time=2.48 ms; 230 mm field of view; 8° flip angle; 256 × 208 matrix; thickness 1 mm; voxel size .9 × .9 × 1 mm^3) in register with the EPI data set was obtained covering the whole brain with 176 axial slices.

2.6. Functional MRI analysis: data preprocessing and individual level analysis

Functional MRI data were preprocessed and analyzed using Analysis of Functional NeuroImages (AFNI) software (Cox, 1996). The first four volumes, collected before equilibrium magnetization was reached, were discarded. The anatomical scan for each participant was registered to the Talairach and Tournoux atlas (Talairach and Tournoux, 1988) using the TT_N27 template and each participant's functional EPI data were registered to their Talairach anatomical scan in AFNI. Functional images were motion corrected to a reference volume close to the acquisition of the high-resolution anatomical dataset and spatially smoothed with a 6-mm full width half maximum Gaussian kernel to reduce the influence of anatomical variability among the individual maps in generating group maps. For subsequent analyses, images were resized to 3 mm voxels using the volreg command. Next, the data then underwent time series normalization to a T1 image, and these results were multiplied by 100 for each voxel. Therefore, the resultant regression coefficients are representative of a percentage of signal change from the mean.

Afterward, four indicator regressors were generated: one for approached stimuli, one for avoided stimuli, one for reward feedback, and one for punishment feedback. Every volume and its predecessor on which motion exceeded 0.5 mm (Euclidean Norm) was censored. Conditions were modeled with a gamma variate hemodynamic response function to account for the slow hemodynamic response. GLM fitting was performed with the four regressors listed, six motion regressors, and a regressor modeling baseline drift (-polort 4). This produced a β-coefficient and an associated *t*-statistic for each voxel and regressor. No other confound regressors were used.

2.7. Statistical analyses

To reduce skewness and kurtosis, Rankit-transformation was applied to participants' abuse (EA+PA+SA), neglect (EN+PN) and total CTQ scores. Post-transformation skewness and kurtosis scores were 0.31 &

−0.49, 0.25 & −0.45, 0.13 & −0.336 respectively (Pre-transformation-Abuse: 1.63 & 2.42; Neglect: 1.36 & 1.78; Total CTQ: 1.26 & 1.01).

2.7.1. Clinical correlations

Correlation analyses were conducted to determine the associations between Rankit-transformed and normalized abuse, neglect and total CTQ scores, age, IQ, sex and whether the individual received a particular diagnosis or not (scored 1 or 0 respectively). Steiger's Z calculations were performed to determine whether there were significant differences in correlation strengths between amount of abuse/neglect and any of the psychiatric diagnoses. For all these analyses significance was considered at $p < 0.05$.

2.7.2. Behavioral and movement data

A 2 (Sex: Male, Female) x 2 (Error type: Omission, Commission) ANCOVA with Rankit-transformed and z-score normalized abuse and neglect scores as covariates was performed on the error data. Univariate ANCOVAs [2 (Sex: Male, Female) with Rankit-transformed and z-score normalized abuse and neglect scores as covariates] were conducted on three participant motion variables: censored volumes, average motion per volume, and maximum displacement during scanning.

2.7.3. BOLD response data

A full 2 (Sex: Male, Female) x 2 (Feedback: Reward, Punishment) ANCOVA with Rankit-transformed and z-score normalized abuse and neglect scores as covariates was performed on the BOLD response data for the feedback phase. This ANCOVA reveals regions showing neglect/abuse interactions with Feedback directly related to our study goals and predictions. In addition, it will identify any regions showing neglect-by-abuse-by-Feedback interactions which, while not predicted a priori, have potential theoretical significance. The procedures used to unpack these interactions and the results from the unpacking are presented in the Supplemental material. Correction for multiple comparisons was performed using a spatial clustering operation in AFNI's *3dClustSim* utilizing the autocorrelation function (-acf) with 10,000 Monte Carlo simulations for the whole-brain analysis. The initial threshold was set at $p = 0.001$. This process yielded an extant threshold of $k = 19$ voxels for the whole brain (multiple comparison corrected $p < 0.05$). To facilitate future meta-analytic work, effect sizes (partial eta square [ηp^2]) are reported in the Tables.

Interactions of covariates with variables identified via the ANCOVAs were interpreted via correlational analyses using SPSS 22.0 ($p < 0.05$).

2.7.4. Multiple regression analyses

Two stepwise multiple regression analyses were conducted to predict BOLD responses to reward-punishment within regions showing significant Neglect-by-Feedback interactions on the basis of clinical variables (SCARED, MFQ, Conners ADHD scale, SDQ-CP and SDQ-hyperactivity). Cases with missing values were excluded listwise.

2.7.5. Standard mediation analyses

(Bootstrap samples = 10,000) were conducted using the Hayes PROCESS program (version 3.5) (https://www.processmacro.org/download.html) in SPSS (version 25) to determine the extent to which BOLD responses to reward-punishment within regions showing significant Neglect-by-Feedback interactions mediated the relationship between neglect/abuse and clinical variables (SCARED, MFQ, Conners ADHD scale, SDQ-CP and SDQ-hyperactivity).

2.7.6. Follow-up analyses

Examining potential confounds of diagnosis: We examined potential confounds of diagnostic status via a series of ANCOVAs involving an additional covariate coding Conduct Disorder (present vs. not present), ADHD (present vs. not present), Major Depressive Disorder (present vs. not present), Generalized Anxiety Disorder (GAD) and PTSD (present vs. not present).

2.7.7. The confound of potential suppressor effects

To ensure that the absence of Abuse-by-Feedback feedback interaction could not be attributed to suppressor effects of the neglect covariate, we re-ran our main analysis twice: once with only Rankit-transformed neglect score as a covariate and a second time with only Rankit-transformed abuse score as a covariate.

3. Results

3.1. Levels of ELS and clinical correlations

Of the 142 participants, 11 endorsed no prior ELS (total score on the CTQ=25). The other 131 youths had CTQ scores> 25 with 91 reporting significant amounts of ELS; i.e., their CTQ subscale scores were above validated thresholds (EA≥10/SA≥8/PA≥8/EN≥15/PN≥8; (McLaughlin et al., 2015; Walker et al., 1999). Of the 79 adolescents exposed to significant abuse (i.e., EA≥10/SA≥8/PA≥8), 41 did not meet criteria for significant neglect exposure (i.e., EN≥15/PN≥8). Of the 50 exposed to significant neglect, 12 did not meet criteria for significant abuse exposure. All youth reporting significant sexual/physical abuse were discussed with their consultants to confirm that this had been previously identified/was followed up.

There were no significant associations between abuse, neglect or CTQ total score and either age, IQ or medication status (see Table 1). However, CTQ total and abuse subscores were all significantly greater in female than male participants ($t(140) = 2.645$ & 3.887; $p = 0.009$ & < 0.001 respectively). Abuse and neglect scores were significantly correlated ($r = 0.56$) but the variance inflation factor was < 3 (VIF=1.16). In addition, there were significant positive correlations between both amount of abuse and amount of neglect (and total CTQ score) and *all* five psychiatric diagnoses assessed and the self-report measures (see Table 1). Importantly, there were no significant differences in correlation strengths between amount of abuse/neglect and any of the psychiatric diagnoses or self-report measures [Steiger's Z's = −0.028 to 1.71; *ns*] except GAD and PTSD. With respect to GAD and PTSD, amount of abuse showed a significantly greater association with diagnosis than amount of neglect (see Table 1).

3.2. Behavioral and movement data

The ANCOVA performed on the error data revealed a significant main effect of error type ($F(1, 138) = 26.71$; $p < 0.001$; participants made more omission (failing to respond to stimuli more often associated with reward than punishment) than commission errors (responding to stimuli more often associated with punishment than reward); M[Omission] = 12.08; M[Commission] = 18.79). However, there were no significant interactions with, or main effects of, either level of neglect or abuse.

Participants were excluded due to excessive motion (> 20% censored volumes; mean = 0.7%, SD = 1.7%) or low response rate (< 65% responses; mean = 73/80, SD = 5.37) on the task ($N = 11$). The three univariate ANCOVAs revealed no relationships between Neglect or Abuse scores and censored volumes, average motion per volume, and maximum displacement during scanning within the final sample ($F(1, 138) = 0.001–0.755$; $p = 0.387–0.978$).

3.3. BOLD response data

The analysis of the BOLD response data revealed regions showing both Neglect-by-Feedback and Neglect-by-Abuse-by-Feedback. *No* regions showed Abuse-by-Feedback interactions. The data from the Neglect-by-Feedback interactions are presented in Table 2. Because we did not make any a priori predictions about Neglect-by-Abuse interactions, that data is presented in the Supplemental material (Supplemental Table 1 and Supplemental Fig. 1). All other significant results are listed in Supplemental Table 2.

Table 2
Brain regions displaying significant Neglect-by-Feedback interactions.

	Coordinates of peak activation[b]							
Region[a]	Left/Right	BA	x	y	z	F	Voxels	η^2
Neglect-by-Feedback								
Rostromedial Frontal Cortex	Left	32/9	-10	44	26	21.603	43	0.139
Caudate	Right	–	11	-10	26	39.131	138	0.226

Note: [a] According to the Talairach Daemon Atlas (http://www.nitrc.org/projects/tal-daemon/), [b] Based on the Tournoux & Talairach standard brain template, BA = Brodmann's Area.

3.3.1. Neglect-by-feedback interaction

This was observed within bilateral caudate and rostromedial frontal cortex ($F(1134) = 38.69$ & 20.97; $p < 0.001$; $\eta p^2 = 0.224$ & 0.135, see Table 2 and Fig. 2). Within both regions, prior neglect was negatively associated with response to the differential response to reward versus punishment ($\rho = -0.437$ & -0.333 respectively, both $p < 0.001$ – within both regions this particularly reflected a reduction in the typically suppressed response to punishment; i.e., a positive association between neglect and punishment; $\rho = 0.325$ & 0.238). Moreover, within both regions the correlation of prior neglect and differential reward-punishment responses was significantly stronger than that between prior abuse and differential reward-punishment responses (bilateral caudate: $r_{neglect} = -0.46$, $r_{abuse} = -0.18$; Steiger's $z = -3.83$; $p = 0.0001$; rostromedial frontal cortex: $r_{neglect} = -0.26$, $r_{abuse} = 0.05$; Steiger's $z = -4.01$; $p = 0.00006$).

3.3.2. Multiple regression analyses

Both multiple regressions conducted for the regions showing significant Neglect-by-Condition interactions revealed significant regression equations [$F(4,98) = 4.54$ & 3.04; $p = 0.002$ & 0.021] with R^2 of 0.154 and 0.11 (for striatum and rmFC respectively). In both cases, significant predictors for differential reward vs punishment response were SDQ-CP ($B = -0.018$ & -0.02; $p < 0.001$ and $p = 0.002$) and Conners ADHD scores ($B = 0.005$ & 0.008; $p = 0.035$ & 0.012). In both cases, SCARED ($B = -0.002$ & -0.002; $p = 0.116$ & 0.178) and MFQ ($B = 0.000$ & 0.003; $p = 0.824$ & 0.061) scores were not significant predictors.

3.3.3. Mediation analyses

None of our mediation analyses revealed significant mediation by BOLD responses to reward-punishment within regions showing significant Neglect-by-Feedback interactions of the association between neglect/abuse and any of the clinical variables (SCARED, MFQ, Conners ADHD scale, SDQ-CP and SDQ-hyperactivity) – all bootstrap confidence intervals included zero.

3.3.4. Follow-up BOLD response analyses

Examining potential confounds of diagnosis and suppressor effects:

3.3.5. Diagnostic status

Our ANCOVAs involving covariate coding diagnostic status were only associated with minor changes to the results reported in Table 2 (for a full overview, see eTables 3–7).

3.3.6. Potential suppressor effects

The ANCOVA with the neglect covariate largely replicated the neglect by feedback interactions (see eTable 8). The ANCOVA with the abuse covariate again failed to identify regions showing significant abuse-by-feedback interactions.

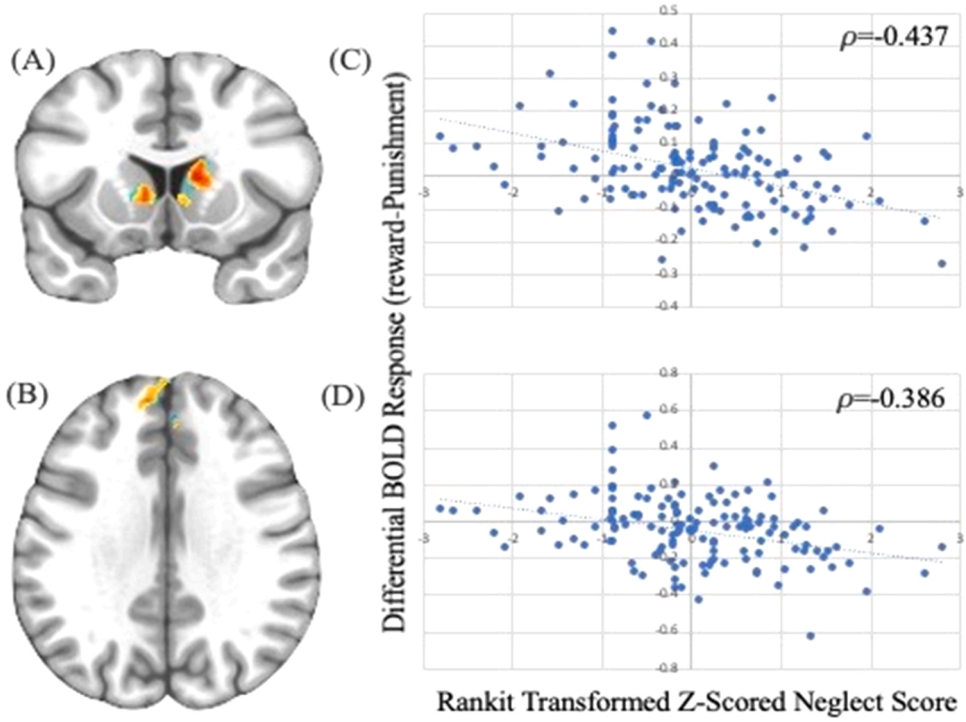

Fig. 2. Regions displaying significant Neglect-by-Feedback interaction. (A) Striatum; (B) Rostromedial frontal cortex. (C) and (D) Differential BOLD responses (Reward-Punishment) were significantly negatively correlated with Neglect scores. Plots depict partial correlations and adjusted residuals for each region, with dotted lines depicting the corresponding partial correlation coefficients (ρ); both significant at $p < 0.001$.

4. Discussion

The two aims of the current study were: (i) to determine the association of level of neglect and abuse with differential reward versus punishment responsiveness; and (ii) to determine the association between BOLD responses to reward-punishment in regions sensitive to neglect or abuse and different groups of symptoms previously related to reduced reward responsiveness. Our main results were that: (i) neglect was particularly associated with reduced differential reward versus punishment responsiveness within striatum and mFC; and (ii) reward versus punishment responsiveness within these regions of striatum and mFC was significantly negatively associated with conduct problems.

Previous work has indicated that prior exposure to ELS is associated with reduced reward responsiveness within striatum and mFC (Birn et al., 2017; Boecker et al., 2014; Boecker-Schlier et al., 2016; Gerin et al., 2017; Hanson et al., 2015; Mehta et al., 2010) and either increased response to punishment or a failure to suppress responding to punishment within striatum and lateral frontal cortex (Birn et al., 2017). The current study replicates and extends this work by revealing that reduced differential reward-punishment responsiveness within striatum and mFC in the context of an instrumental learning task was particularly associated with level of *neglect*. This particularly reflected either increased response to punishment or a failure to suppress responding to punishment within these regions. There have been previous suggestions that different forms of childhood ELS have distinct consequences for neurodevelopment (Dennison et al., 2017; Lambert et al., 2017; McLaughlin and Sheridan, 2016; McLaughlin et al., 2019b; Pollak et al., 2000; Sheridan et al., 2017; van Schie et al., 2017) and that neglect, in particular, might be associated with compromised reinforcement processing (Goff et al., 2013); (see Novick et al., 2018). The current findings are clearly in line with these suggestions.

The current study observed no direct association between level of abuse and differential reward-punishment responsiveness. However, it should be noted there were indications that abuse tempered the association between neglect and differential reward-punishment responsiveness in portions of mFC. Specifically, within these regions, the negative association between level of neglect and differential reward-punishment responsiveness was no longer significant for individuals who had been exposed to higher levels of abuse (see Supplemental Materials and Supplemental Table 1/Fig. 1 for details). This may indicate that higher levels of abuse are associated with disrupted reinforcement processing, as might be expected from pre-clinical animal work (see Novick et al., 2018), to an extent that the association of reward-punishment responsiveness and neglect is disrupted. However, we made no predictions about abuse-by-neglect interactions prior to this study and future work will be necessary to explore this issue.

Previous work has related reduced reward responsiveness to depression (Admon and Pizzagalli, 2015; Stringaris et al., 2015), ADHD (Plichta and Scheres, 2014), GAD (Benson et al., 2015; White et al., 2017) and conduct disorder (Crowley et al., 2010; Finger et al., 2008; White et al., 2013). Moreover, ELS-associated reductions in reward responsiveness has been related to depressive and CD symptomatology (Birn et al., 2017; Goff et al., 2013; Goff and Tottenham, 2015; Hanson et al., 2015, 2018, 2017; Holz et al., 2017). Previous work, however, has not typically examined the association between reward-related dysfunction and different forms of symptom simultaneously. The current data indicate that neglect-associated differential reward-punishment responsiveness was particularly inversely related to levels of conduct problems rather the depression. This is consistent with suggestions that compromised differential reward-punishment responsiveness leads to reduced learning and impaired decision-making increasing the probability that poor behavioral choices, including aggression and antisocial behavior, will be made (Blair et al., 2018). However, it should be noted that our mediation analyses indicated that the dysfunctional neural response did not mediate the association between neglect and conduct problems.

Moreover, there is an important caveat that should be noted here though. As can be seen in Table 1, disruptive behavior disorders (ADHD and CD) were more prevalent in the current participants (59% and 52% respectively) than either depression or anxiety (MDD: 20%; GAD: 30%). It is possible that the relatively high prevalence of CD increased the probability that an association with differential reward-punishment BOLD responsiveness would be found with conduct problems (though note the most significant association was with conduct problems rather than severity of the marginally more prevalent diagnosis, ADHD severity). Of course, it is also possible that the association was particularly associated with conduct problems because of the choice of the instrumental passive avoidance learning task. Impairment on this task has been repeatedly demonstrated in patients with antisocial behavior (Blair et al., 2004; Finger et al., 2011; Newman and Kosson, 1986) but not seen in patients with ADHD (at least if the association with conduct problems is partialed out; (Hartung et al., 2002). Previous work related to depression has typically been with the Monetary Incentive Delay task where instrumental learning is not required (cf. (Admon and Pizzagalli, 2015; Ng et al., 2019; Stringaris et al., 2015). Again, future work will be needed to disentangle these possibilities.

Three other caveats to the current results should also be considered. First, consistent with considerable previous work (Briggs-Gowan et al., 2010; Green et al., 2010; Jaffee et al., 2004; Lansford et al., 2007; McLaughlin et al., 2010; Norman et al., 2012; Shonkoff and Garner, 2012), increasing exposure to both neglect and abuse was associated with increasing severity of psychopathology (see Table 1). Accordingly, the current results might reflect psychopathology rather than exposure to neglect. Ameliorating this concern is the fact that there were no significant differences in correlation strengths between amount of neglect and amount of abuse and any of the psychiatric diagnoses except GAD and PTSD. Further, the follow-up analyses that we conducted with psychiatric diagnoses as separate covariates for our main ANCOVA did not significantly change our results (see eTables 3–7) suggesting that psychiatric diagnostic status did not significantly confound the current results. Second, many adolescents who had experienced abuse had also experienced neglect potentially making the association of these different forms of ELS difficult to untangle. Importantly, though, with respect to the current results, the regions showing significant neglect-by-task interactions showed these interactions whether the abuse covariate was present in the ANCOVA (see Table 2) or not (see eTable 8) while there was no association with activation in these regions if only the abuse covariate was present. Third, there was no association between level of neglect (or abuse) and behavioral impairment in instrumental learning on the task. Given the clinical relevance of instrumental learning particularly with respect to conduct problems (e.g., Blair et al., 2018), it will be important to determine if/under what circumstances dysfunctional differential reinforcement processing at the neural level is accompanied by behavioral impairments in learning. Relatedly, it will be important in future work to examine the association between neglect and abuse and neural computations of functions related to reinforcement-based learning (e.g., prediction error signaling). The current study revealed dysfunction in the differential response to received rewards and punishments. It did not investigate responses to rewards and punishment as a function of expectations based on previous reinforcement history (i.e., prediction error signaling). However, pilot analyses of BOLD response data on the current PA task revealed this task implementation was not optimized to reveal a strong prediction error signal. Future computational modeling-based work with other tasks will investigate this issue.

In conclusion, the current study supports previous work suggesting that childhood ELS negatively impacts reinforcement processing. It extends this work by suggesting that level of neglect, rather than level of abuse, might be particularly associated with compromised reinforcement processing. Moreover, the current study suggested that this impact of neglect on reinforcement processing might be particularly associated with an increased risk for conduct problems.

Author contributions

Study PI Karina S. Blair conducted and is responsible for the data analysis. She had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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 material

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.dcn.2021.101051.

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