



## Differential neural sensitivity to social inclusion and exclusion in adolescents in foster care

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### ABSTRACT

**Objectives:** Adolescents in foster care may exhibit differential patterns of brain functioning that contribute to their pervasive socioemotional challenges. However, there has been limited investigation of implicated neural processes, particularly in the social domain. Thus, the current study investigated neural responses to exclusionary and inclusionary peer interactions in adolescents in foster-care.

**Methods:** Participants comprised adolescents aged 11–18 years in foster care (N = 69) and a community sample (N = 69). They completed an fMRI adaptation of Cyberball, a virtual ball-throwing paradigm, that included periods of exclusion and over-inclusion. To investigate neural sensitivity to peer social experiences, we quantified neural responses that scaled with consecutive inclusionary and exclusionary interactions (using parametric modulators).

**Results:** Relative to the community sample, adolescents in foster care exhibited increasing response to consecutive exclusionary events in lateral prefrontal regions and decreasing response to consecutive inclusionary events in the intraparietal sulcus and temporo-occipital cortex. Further, exploratory analyses revealed that dorsolateral prefrontal activation to exclusion was related to externalizing problems, particularly in the foster care sample.

**Conclusions:** Findings highlight greater neural sensitivity to exclusionary, and lesser sensitivity to inclusionary, peer interactions in adolescents in foster care. Engagement of prefrontal clusters may reflect greater salience and emotion regulatory processes during exclusion, while parietal and temporal clusters may reflect reduced attention and behavioural engagement during inclusion. Thus foster care involvement is associated with broad changes in neural responses during peer interactions, and further these potentially relate to externalizing problems that have been identified in this vulnerable population.

### 1. Introduction

Being separated from primary caregivers and placed into foster care is a stressful experience that frequently co-occurs with other childhood adversities, such as abuse and neglect (Brown et al., 2019; Kessler et al., 2010). These experiences increase the likelihood of individuals being assessed as having poorer emotional understanding, higher emotional reactivity, lower social competencies, and a lack of adaptive coping strategies (Kim and Cicchetti, 2010; McLaughlin et al., 2015; Repetti et al., 2002; Shields and Cicchetti, 2001). There is a growing interest in

identifying the mechanisms that underlie these pervasive socioemotional consequences, including the potential role of the brain. Investigation of neural functioning related to peer processes is particularly relevant during adolescence – a developmental period marked by significant social changes, including increased time spent with peers (Hartup and Stevens, 1997) and greater affective salience of social events (Steinberg and Morris, 2001).

As minimal research has focused on neural processes in foster care youth, we turn to the larger neuroimaging literature on childhood adversity to contextualize this study. Alterations have been consistently

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noted in the neurocognitive domains of threat processing, reward processing and emotion regulation. The most commonly reported finding has been amygdala hyperactivation in response to emotional stimuli in those exposed to early life adversity, suggestive of heightened awareness of social threats or generalized emotional sensitivity (Hein and Monk, 2017; McLaughlin et al., 2015). Others have identified altered activation of the prefrontal cortex (PFC) and anterior cingulate cortex (ACC) during emotion regulation and inhibitory control processes (Lim et al., 2015; Marusak et al., 2015; McLaughlin et al., 2015). A smaller set of studies have noted ventral striatum and orbitofrontal cortex (OFC) hypoactivation during reward-related processes in youth exposed to adversity (Goff and Tottenham, 2015; Hanson et al., 2015; Hanson et al., 2016). However, meta-analyses have also implicated regions involved in social cognitive processes, such as the posterior superior temporal gyrus (Hein and Monk, 2017) and precuneus (Kraaijenvanger et al., 2020), suggesting that investigation of social processes may yield further insight into potential neural differences in foster care youth.

Of particular importance is a small set of studies that have investigated neural responses to social rejection in adolescents that have experienced adversity. Neuroimaging research on social exclusion is most frequently investigated using Cyberball, a virtual ball-tossing paradigm, and meta-analyses of community samples have identified consistent responses to exclusion in the medial prefrontal cortex (mPFC); particularly ventromedial [vm]PFC and ventral anterior cingulate cortex [vACC]), posterior cingulate, precuneus, ventrolateral (vl)PFC, and to a lesser extent, the dorsal anterior cingulate cortex (dACC) and insula (Cacioppo et al., 2013; Mwilambwe-Tshilobo and Spreng, 2021; Vijayakumar et al., 2017). Many of these regions also appear to be differentially recruited during social exclusion in adolescents exposed to adversity. This includes dorsomedial (dm)PFC hyperactivation during social exclusion in adolescents with greater levels of childhood emotional maltreatment (van Harmelen et al., 2014) and hyperactivation of the dACC, amygdala, and vlPFC in adolescents who have been chronically rejected by peers (Rudolph et al., 2016; Will et al., 2016). However, the only study to directly examine social rejection in a foster care sample interestingly found reduced activity in the dACC, insula, precuneus, and dorsolateral (dl)PFC (Puetz et al., 2014). We speculate these contradictory results may arise from the Cyberball design employed by Puetz et al. (2014), which contrasted social exclusion to a non-social form of exclusion (specifically technical difficulties that resulted in participants being excluded from the game), although differences may also relate to varied operationalizations of adversity across the literature.

Although inconsistencies remain with regards to the direction and location of effects, these preliminary findings highlight altered neural processing of negative social experiences in adolescents exposed to adversity. However, adolescents who have experienced adversity, and those in foster care, may also exhibit altered neural processing of positive social experiences, such as inclusion and peer acceptance. While this hypothesis is yet to be investigated, there is prior evidence that childhood adversity is associated with reduced neural sensitivity to different forms of rewards (i.e., monetary incentives and positive affective stimuli) (Guyer et al., 2006; Hanson et al., 2015; Mehta et al., 2010). Examining both negative and positive social interactions may thus provide a novel perspective and more complete understanding of the neural processes influencing these aspects of socioemotional functioning in adolescents in foster care.

Crucially, life experiences may alter neural functions in a manner that confers latent vulnerabilities to psychopathologies in foster care youth. Indeed, the impact of adversity more broadly on psychopathology is known to be established through alterations of neurocognitive systems, particularly through the domains of threat processing, reward processing and emotion regulation discussed above (McCrory et al., 2017). In foster care youth, these alterations may result from specific features of their childhood experiences such as high levels of chronic stress exposure (Liming et al., 2021; Sprang et al., 2009), threat and/or

deprivation (Carrera et al., 2020), and harshness and/or unpredictability (Perry et al., 2019; Roos et al., 2016). While some neurocognitive changes may be immediately functional or adaptive, they may also confer less optimized responses to normative social interactions later in development (McCrory et al., 2017). Some studies also highlight the potential for high quality foster care placement following severe early adversity (i.e., institutionalization) to normalize these neurocognitive changes, with positive effects noted for reward processing (Sheridan et al., 2018), cognitive outcomes (McDermott et al., 2013; Nelson et al., 2007) and resting brain function (Debnath et al., 2020). However, the broader foster care population may have varied life experiences prior to entering the foster care system, and may additionally experience varied quality, duration and stability of placements that are predictors of subsequent mental health problems (Fisher et al., 2013; Horwitz et al., 2001; Leathers et al., 2019). Crucially, associations between neural functions and psychopathology are yet to be interrogated in a representative foster care sample, which has a nearly 4-fold greater prevalence of mental illness than the general population (Bronard et al., 2016).

Altered neural functions related to social exclusion and inclusion may also have implications for real-world interpersonal processes in foster care youth, who are more likely to report problems in their peer relationships (Minnis et al., 2006), including being rejected by peers (Anthonyamy and Zimmer-Gembeck, 2007), and being targets and/or perpetrators of bullying (Banny et al., 2013; Duke et al., 2010; Shields and Cicchetti, 2001). These social problems occur in the context of normatively heightened sensitivity to peer influences (Steinberg and Monahan, 2007) and fear of negative evaluations (van den Bos et al., 2014) during adolescence, which are likely shared by foster care youth.

Therefore, the current study investigated the neural correlates of peer exclusion and inclusion in adolescents in foster care, using an adaptation of Cyberball. Prior research on a community sample (of non-separated controls) has found that activation in the insula and dmPFC scaled with consecutive exclusionary and inclusionary events, respectively, while activation in the rostromedial PFC was similarly elicited by both conditions (Cheng et al., 2020). We aim to extend this literature by comparing neural responses of adolescents in foster care to those who are not separated from their primary caregivers. Based on findings of increased neural responses to social exclusion and reduced activation to rewarding stimuli in the context of adversity, it was hypothesized that the *Foster Care* group, compared to *Controls*, would exhibit increasing dACC, dmPFC and vlPFC response to consecutive exclusionary events and decreasing response to consecutive inclusionary events. As exploratory analyses, we investigated whether activation in regions exhibiting group differences during Cyberball was related to mental health problems. We hypothesized that greater activation of identified clusters to social exclusion and reduced activation of clusters to social inclusion (particularly PFC and limbic regions) would be related to greater mental health problems.

## 2. Methods and materials

### 2.1. Participants

175 adolescents (aged 11–18 years) were recruited from Lane County, Oregon, USA. The *Foster Care* group (N = 78) was recruited from the child welfare system (specifically, those currently in foster care) and the *Control* group (N = 97) were non-separated adolescents recruited from the community<sup>2</sup>. Of the 97 *Control* adolescents, nine dropped out of the study, seven elected not to participate in the MRI, eight completed an alternate (pilot) version of Cyberball, one failed to complete the task

<sup>2</sup> An additional sample of 11 adolescents from the juvenile justice system were recruited into the larger project, but were not incorporated into the current analyses.

and one had technical errors in collecting task data. In addition, two participants were excluded when visual quality inspection of the imaging data revealed extreme motion and/or orbitofrontal signal dropout. Of the 78 *Foster Care* adolescents, three dropped out of the study, three elected not to participate in the MRI, one failed to complete the Cyberball task, and two participants were excluded due to technical errors in collecting task data. Current analyses were conducted on the remaining 138 participants (69 *Foster Care* and 69 *Control*). There were no group differences in age, sex, race, ethnicity or socioeconomic status, but the *Foster Care* group had lower IQ (as measured by Wechsler's Abbreviated Scale of Intelligence; Wechsler, 1999) and higher levels of internalizing and externalizing problems (as measured by the Child Behavior Checklist; Achenbach, 1999). See Table 1 for demographics, Table S1 for clinical characteristics of the sample, and Table S2 for ethnicity and race of the sample. Ethics approval was granted by the Institutional Review Board of the University of Oregon (#10312013).

Mean (SD), unless otherwise noted. IQ: Intelligence Quotient measured using the Wechsler's Abbreviated Scale of Intelligence. CBCL: Child Behavior Checklist (t-scores). ACE: Adverse Childhood Experiences (Felitti et al., 1998) Cumulative = total score. Income-to-Needs Ratio was calculated based on household income relative to the federal poverty guidelines based on household size (U.S. Department of Health and Human Services, 2017).

## 2.2. Materials

### 2.2.1. Cyberball

Is an animated interactive ball-tossing computer game used to simulate the experience of social exclusion (Williams et al., 2000). Adolescents were informed they were playing Cyberball with two adolescent peers at partner sites in real time via the Internet (although throws were computer-automated). To lend credibility to this cover story, participants made video profiles to introduce themselves and viewed other players' video profiles.

Our adaptation of Cyberball comprised an inclusion run followed by an exclusion run, each consisting of 44 ball throws. In the inclusion run, participants experienced periods when computer players repeatedly (consecutively) threw the ball to the participant rather than one another. These periods of "over-inclusion" were interspersed with fair play such that, overall, 17 of 27 throws by the computer players were to the participant (63%). In the exclusion run, participants experienced periods of exclusion in which computer players only threw the ball to one another. These were interspersed with periods of fair play such that, overall, 6 of the 38 throws by computer players were to the participant (16%). Upon receiving the ball, participants used a button box to indicate which of the other players they wanted to throw to, and if they did not make a decision within 5 s, the ball was automatically thrown to a player at random. Time elapsed between each computer player catching and throwing the ball was a random number between 0 and 3 s ( $M = 1.5$ ,  $SD = 0.9$ ), and the ball took approximately 1.4 s to travel through the

**Table 1**  
Demographic characteristics of the sample.

	Foster Care	Control	Foster Care vs Control
Sex N (M:F)	41:28	32:37	$\chi^2 = 1.86$ , $p = 0.173$
Age	14.02 (1.69)	14.17 (1.53)	$t(135) = -0.56$ , $p = 0.580$
IQ	99.29 (12.37)	107.01 (11.89)	$t(134) = -3.72$ , $p < 0.001$
CBCL Internalizing	59.20 (10.67)	53.74 (9.57)	$t(133) = -3.16$ , $p = 0.002$
CBCL Externalizing	58.45 (11.43)	48.94 (9.15)	$t(130) = -5.38$ , $p < 0.001$
ACE (Cumulative)	3.54 (0.66)	1.41 (0.73)	$t(111) = -6.16$ , $p < 0.001$
Income-to-Needs Ratio	1.57 (1.01)	1.87 (1.04)	$t(116) = 1.58$ , $p = 0.117$

air. Thus, the timing of events, including participant button presses, varied from trial to trial and did not systematically align with the MRI repetition time.

### 2.2.2. Behavioral measures.

**2.2.2.1. Adversity.** Adolescents completed the Adverse Childhood Experiences (ACE) questionnaire (Felitti et al., 1998) adapted for use with adolescents. Ten items prompted participants to indicate (yes/no) as to whether they had ever experienced abuse, neglect, household dysfunction, and parental divorce, with total scores reflecting cumulative exposure to adverse experiences.

**2.2.2.2. Mental health problems.** Caregivers completed the Child Behavior Checklist for Ages 6–18 (CBCL/6–18). An internalizing score was obtained by summing the anxious/depressed, withdrawn/depressed and somatic complaints subscales, while an externalizing score was obtained by summing the rule-breaking and aggressive behavior subscales. T-scores were used in analyses.

### 2.2.3. fMRI acquisition and processing

Data were acquired on a 3T Siemens Skyra MRI scanner at the Lewis Center for Neuroimaging in Eugene, Oregon. High-resolution T1-weighted structural images were collected with the MP-RAGE sequence (TE = 3.41 ms, TR = 2500 ms, flip angle = 7°, 1.0 mm slice thickness, matrix size = 256 × 256, FOV = 256 mm, 176 slices, bandwidth = 190 Hz/pixel). Two functional runs of T2\*-weighted BOLD-EPI images were acquired with a gradient echo sequence (TE = 27 ms, TR = 2000 ms, flip angle = 90°, 2.0 mm slice thickness, matrix size = 100 × 100, FOV = 200 mm, 72 slices, bandwidth = 1786 Hz/pixel). There were 60 to 87 images per run, as run length varied with participants' response times during Cyberball. To correct for local magnetic field inhomogeneities, a field map was also collected (TE = 4.37 ms, TR = 639.0 ms, flip angle = 60°, 2.0 mm slice thickness, matrix size = 100 × 100, FOV = 200 mm, 72 slices, bandwidth = 1515 Hz/pixel).

Raw images were converted from DICOM to NifTI format with MRIConvert (<https://lcn.uoregon.edu/downloads/mriconvert/>), and preprocessed using Statistical Parametric Mapping software (SPM12, Wellcome Department of Cognitive Neurology, London, UK). Anatomical images were coregistered to the 152 Montreal Neurological Institute (MNI) stereotaxic template, segmented into six tissue types, and used to create a group anatomical template using DARTEL. Functional images were unwarped using field maps and corrected for head motion via image realignment. A group averaged field map was created and used for two participants; one that did not have a field map and another whose fieldmap did not align with their functional volumes. Unwarped and realigned mean functional images were coregistered to the anatomical image (that was coregistered to the MNI template). Transformations were applied to warp the functional data to the DARTEL group template, and these normalized images were smoothed using a 6-mm FWHM Gaussian kernel. Preprocessing, and all other analysis, scripts are available at [https://github.com/dsnlab/TDS\\_cyberball\\_fostercare](https://github.com/dsnlab/TDS_cyberball_fostercare).

Motion artifacts were identified as changes in image intensity relative to the mean across all subjects, as well as volume-to-volume changes in Euclidean distance. Specifically, a regressor of no interest was constructed by marking the following volumes: (a) > 0.3 mm movement in Euclidean distance relative to previous volume, (b) *mean intensity across voxels* was extreme (3SDs above or 1.5SDs below) relative to mean across subjects and runs, and (c) *SD intensity across voxels* was extreme (3SDs above or below) relative to mean SD across subjects and runs. Volumes immediately preceding and following marked volumes were also flagged. Head motion was identified in 91 of 276 total Cyberball runs (across participants), and of volumes marked for motion, an average of 6.93% of volumes were flagged per run ( $SD = 6.54%$ , range

= 1–26, or up to 31.7%) and this did not significantly differ by group ( $t(75) = -2.0$ ,  $p = 0.09$ ; Foster Care: 8.01%,  $SD = 7.46\%$ ; Controls: 5.60%,  $SD = 4.98\%$ ). Additionally, models included four motion parameters (absolute distance, absolute rotation, and first derivatives of each of these values) as regressors of no interest. Two (*Control*) participants were excluded on the basis of head motion: one based on initial visual inspection of the data suggesting extreme head motion, and the other after pre-processing due to excessive dropout in functional images.

#### 2.2.4. fMRI design and analysis

Cyberball was modeled as an event-related design in SPM12. Fixed-effects analysis comprised a general linear model with two regressors for computer generated throws, modeled as zero-duration events: throws to participants (Inclusion Throw) and throws to computer players (Exclusion Throw). Throws occurred within the Inclusion Run or Exclusion Run. Parametric modulators tracked consecutive Inclusion Throws within the Inclusion Run (referred to as Increasing Inclusion) and consecutive Exclusion Throws within the Exclusion Run (referred to as Increasing Exclusion). Although Exclusion throws were modelled in the Inclusion Run (and vice versa), parametric modulators were not created for these events due to an insufficient number of such events. Each parametric modulator was mean-centered relative to the average number of continuous throws of that type (Increasing Inclusion:  $M = 2.76$ ,  $SD = 1.86$ ; Increasing Exclusion:  $M = 6.23$ ,  $SD = 3.98$ ). An additional zero-duration regressor of no interest marked when participants' avatar "caught" the ball, signaling the participant's turn to throw the ball. This regressor controlled for neural responses related to participants' decision-making (and subsequent button-press) as used in previous studies with event related designs (Bolling et al., 2011). A final regressor modelled a "wait" period at the start of each run, where the screen displayed the words "Connecting to other players..." and a progress bar (lasting approximately 8 s).

This fixed effects model was convolved with the canonical hemodynamic response function, and parameter estimates created six linear contrast images: one for each of four event types (Inclusion Throw in Inclusion Run, Exclusion Throw in Inclusion Run, Inclusion Throw in Exclusion Run, and Exclusion Throw in Exclusion Run) relative to wait periods, and one for each of two parametric modulators (Increasing Inclusion and Increasing Exclusion). Current analyses focus on these parametric modulators.

**2.2.4.1. Group differences in BOLD response.** Random-effects analyses used the fixed-effects contrast images in an ANOVA (specifically "flexible factorial" model in SPM12). It analyzed BOLD response using a 2x2 design that examined the interaction between group (*Foster Care*, *Control*) and parametric modulator condition (Increasing Inclusion, Increasing Exclusion), while controlling for demographics (age, sex, IQ). We also interrogated simple (main) effects of this model, focusing on group differences within each parametric modulator. Results focus on significant group interactions, but results for the *Foster Care* group are presented in Table S3 (while the *Control* group has been presented in Cheng et al., 2020).

Reported results exceed the minimum cluster size threshold needed to control for false positives at a 0.05 family-wise error (FWE) rate given a voxel-wise threshold of  $p = 0.001$  (bi-sided, nearest neighbour = 3,  $k = 68$ ). Cluster extent thresholds were identified with AFNI 3dClustSim, version AFNI\_17.3 (Oct 12, 2017), using smoothness estimates based on the spatial autocorrelation function (acf) parameters averaged from each individual's first level model residuals (calculated by 3dFWHMx, acf parameters: 0.70516, 4.6613, 8.9944). For visualization of interactions and exploratory analyses, regions of interest (ROIs) were created as 6 mm spheres around peak voxels within significant clusters. Mean parameter estimates of activity were extracted for each fixed effect contrast relevant for the significant cluster by averaging across voxels in the ROI using MarsBaR (v0.21). For uncorrected statistical maps, see

<https://neurovault.org/collections/8473/>.

**2.2.4.2. Exploratory brain-behavior correlations.** ROI estimates (extracted from significant clusters) were used in all exploratory analyses. To limit the number of clusters examined, we did not conduct analyses within occipital and cerebellar clusters. ROI estimates were based on the nature of group differences for each significant cluster; if a cluster was identified from a group-by-parametric modulator interaction, then estimates were derived from the difference in ROI response to the two parametric modulators. Two sets of exploratory analyses were conducted: i) We examined whether neural responses were related to adversity across the full sample (i.e.,  $ROI \sim adversity$ ), and whether group differences in neural response were driven by adversity (i.e.,  $ROI \sim group + adversity$ ). We used Bonferroni correction to account for multiple comparisons across 8 ROIs ( $p < 0.006$ ). ii) We examined whether neural responses were related to mental health problems (CBCL internalizing and externalizing scores) across the full sample (i.e.,  $CBCL scores \sim ROI$ ). To correct for multiple comparisons, we first determined alpha 0.05 across the two highly correlated CBCL scales ( $R = 0.59$ ) using Sidak's adjustment (lowered to 0.038), and then conducted Bonferroni correction across the eight ROIs ( $p < 0.0048$ ).

**2.2.4.3. Supplemental analyses.** i) We conducted whole brain analyses to examine group and age interactions in predicting BOLD response to Increasing Inclusion and Increasing Exclusion (see Table S4 and Fig. S1). ii) We also examined whether ROI estimates were correlated with behavioral measures of social functioning (see Tables S5 and S6, and Fig. S2).

### 3. Results

#### 3.1. Group differences in BOLD response

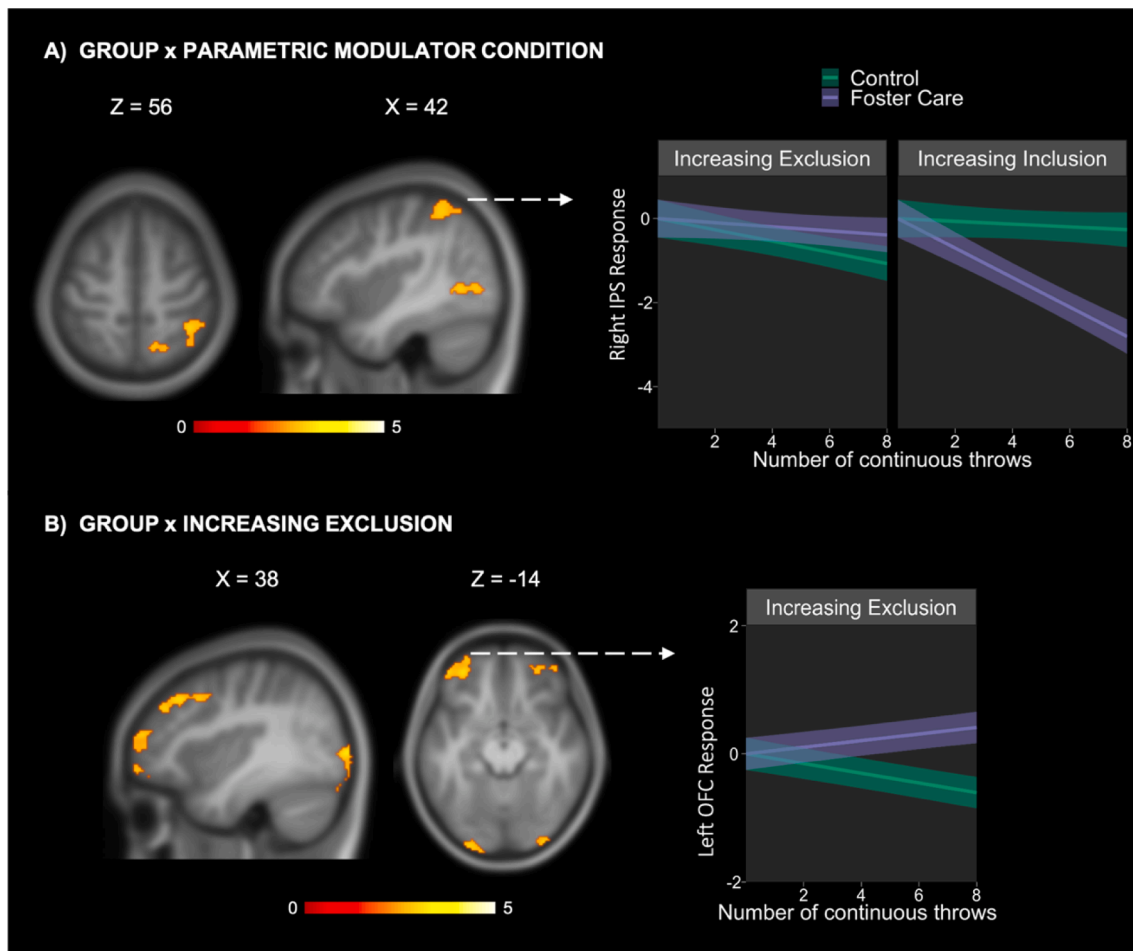
There was a significant interaction between group and parametric modulator condition (Increasing Inclusion vs Increasing Exclusion) that predicted activation in the right intraparietal sulcus, temporo-occipital cortex and precuneus, and bilateral cerebellum; groups exhibited minimal differences in responses to Increasing Exclusion, but the *Foster Care* group exhibited decreased activation to Increasing Inclusion compared to *Controls* (Fig. 1a).

When examining simple (main) effects, there was a significant group difference for Increasing Exclusion in the right rostralateral PFC and bilateral lateral OFC, dlPFC, and inferior occipital cortices; the *Foster Care* group exhibited increased activation with consecutive exclusionary throws relative to *Controls* (Table 2, Fig. 1b). Group differences for Increasing Inclusion were present in the left premotor cortex and right cerebellum, with the *Foster Care* group exhibiting decreased activation with consecutive inclusionary throws relative to *Controls*.

Hemi = hemisphere, K = cluster size, T = peak T statistic, BA = peak Brodmann area.

#### 3.2. The role of adversity

The *Foster Care* group reported higher levels of childhood adversity than *Controls* (see Table 1). Across the full sample, adolescents with higher levels of adversity exhibited greater scaling of ROI responses to cumulative interactions, including significantly greater increases in left dlPFC response to Increasing Exclusion ( $p = 0.004$ ) and right intraparietal sulcus response to Increasing Exclusion vs Increasing Inclusion ( $p = 0.0057$ ). Correlation coefficients for all ROIs are presented in Fig. 2. Group differences in BOLD response for most ROIs remained when controlling for adversity, although associations in the left dlPFC, right intraparietal sulcus and right temporo-occipital cortex no longer survived correction for multiple comparison (see Table S7 for model summaries).



**Fig. 1.** Group differences in BOLD response to a) parametric modulator conditions and b) simple effects for Increasing Exclusion, with selected interaction patterns illustrated. Results are FWE cluster-corrected at  $p < 0.05$  (voxel-wise  $p < 0.001$ ,  $k = 68$ ). IPS: intraparietal sulcus; OFC: orbitofrontal cortex.

**Table 2**  
Group differences predicting modulated BOLD response.

Region	Hemi	K	T	Coordinates	BA
<u>Increasing Exclusion: Foster Care &gt; Control</u>					
Inferior occipital cortex	R	371	4.66	36-90 2	18
Rostrrolateral PFC	R	332	4.56	30 64 12	10
Lateral OFC	R	165	4.45	28 48-16	10
dIPFC	R	429	4.38	36 28 40	8
Lateral OFC	L	205	4.34	-34 46-16	11
Inferior occipital cortex	L	472	4.14	-28-96 -12	18
dIPFC	L	76	3.93	-50 26 38	9
<u>Increasing Inclusion: Control &gt; Foster Care</u>					
Premotor	L	74	4.74	-18 4 46	6
Cerebellum	R	72	4.23	10-62 -54	
Cerebellum	R	80	4.16	10-56 -28	
<u>Condition x Group</u>					
Cerebellum	R	71	4.36	12-60 -54	
Intraparietal sulcus	R	200	4.28	38-46 52	40
Cerebellum	L	77	4.00	-10-76 -24	
Temporooccipital cortex	R	344	3.90	42-60 0	37
Precuneus	R	77	3.72	12-62 54	

**3.3. Associations with mental health problems.**

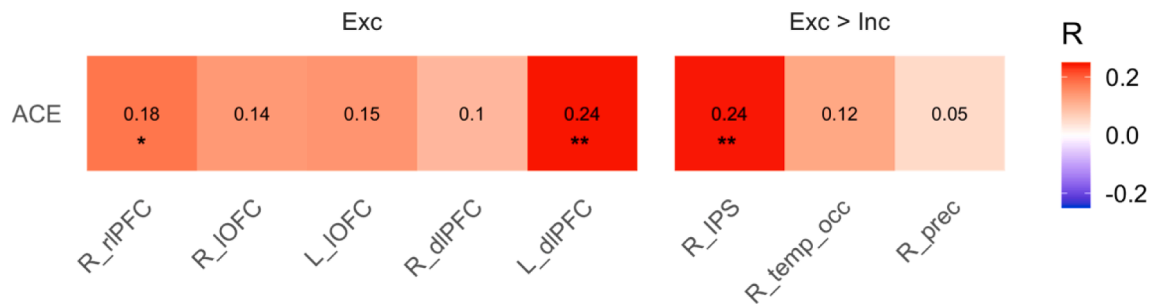
A second set of exploratory analyses examined associations between ROI response and mental health problems across the full sample (correlation coefficients illustrated in Fig. 3a). A significant positive

correlation was identified between left dIPFC response to Increasing Exclusion and externalizing problems ( $p = 0.003$ ), and post-hoc analyses revealed this was present within the *Foster Care* group ( $p = 0.005$ ) and not the *Control* group ( $p = 0.321$ ; see Fig. 3b). There were no significant associations with internalizing problems.

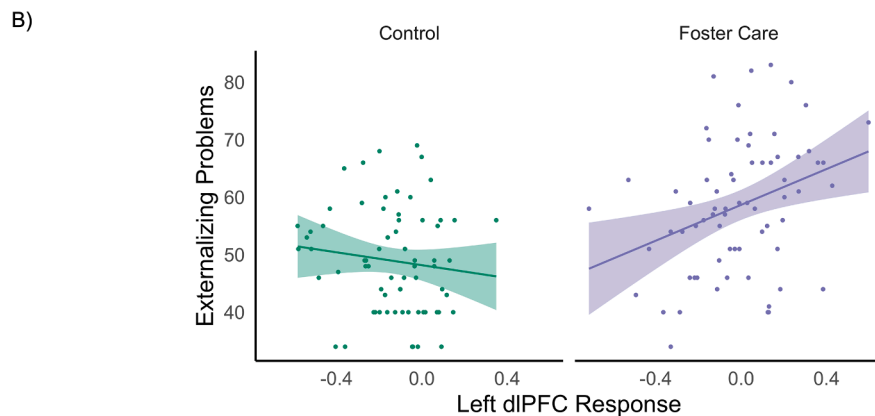
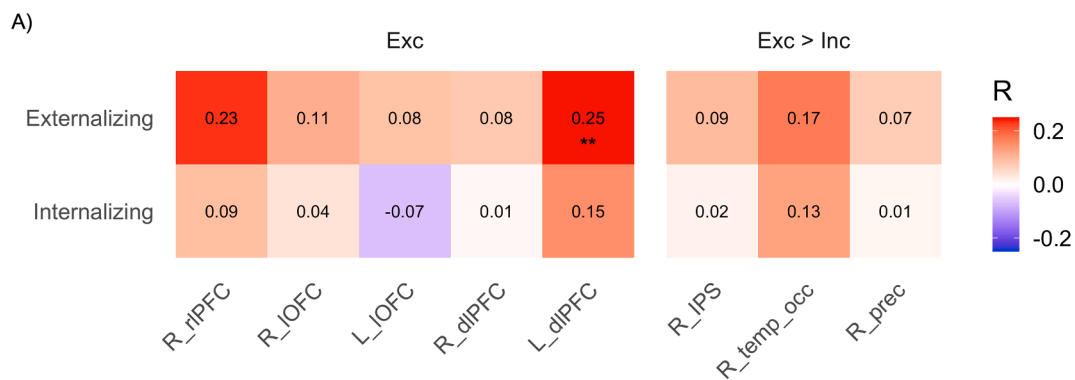
**4. Discussion**

The current study investigated neural responses to social interactions in adolescents in foster care who had been separated from their primary caregivers and reported, on average, more adverse experiences. Compared to the community sample, those in foster care exhibited an overall pattern of greater activation to cumulative exclusionary, and reduced activation to cumulative inclusionary, peer interactions in regions across the brain. Group differences were predominantly located in the lateral prefrontal cortices with additional clusters in the precuneus, intraparietal sulcus and temporo-occipital cortex. Further, exploratory analyses indicated that these neural patterns were related to externalizing problems, which were more prevalent in foster care youth.

Relative to the community sample, adolescents in foster care exhibited increasing response to cumulative exclusionary interactions within multiple prefrontal clusters (right rostrrolateral PFC, bilateral OFC, and dIPFC) and bilateral inferior occipital cortices. Although the specific locations within the PFC did not match our hypotheses, the pattern of PFC hyperactivation is consistent with our predictions and with prior findings for social exclusion in adolescents that have experienced childhood maltreatment (van Harmelen et al., 2014) and chronic peer rejection (Will et al., 2016). Our results were not consistent



**Fig. 2.** Associations between ROI response and adversity highlight the rostrolateral (rIFFC) and left dorsolateral (dlPFC) prefrontal cortices, as well as the right intraparietal sulcus (IPS). \*  $p < 0.05$ , \*\*  $p < 0.006$  (significant following Bonferroni correction for 8 ROIs). ACE: Adverse Childhood Experiences, total score; Exc: Increasing Exclusion; Exc > Inc: Increasing Exclusion > Increasing Inclusion; R: correlation coefficient; lOFC: lateral orbitofrontal cortex; temp\_occ: temporooccipital cortex; prec: precuneus.



**Fig. 3.** a) Associations between ROI response and mental health problems. \*  $p < 0.05$ , \*\*  $p < 0.004$  (significant following Sidak adjustment for two correlated CBCL scales and Bonferroni correction for 8 ROIs). Exc: Increasing Exclusion; Exc > Inc: Increasing Exclusion > Increasing Inclusion; R: correlation coefficient; rIFFC: rostrolateral prefrontal cortex; lOFC: lateral orbitofrontal cortex; dlPFC: dorsolateral prefrontal cortex; IPS: intraparietal sulcus; temp\_occ: temporooccipital cortex; prec: precuneus. b) Correlations between externalizing problems and left dlPFC response to Increasing Exclusion within each group reveal stronger brain-behavior correlations in foster care youth.

with the only prior study of social rejection in a foster care sample, which identified prefrontal deactivation to social exclusion (Puetz et al., 2014). However, the authors of that study compared social exclusion to non-social forms of exclusion, which may account for differences. Rostral PFC response during exclusion has been positively related to rejection sensitivity (Masten et al., 2009), a dispositional tendency posited to develop from childhood experiences of rejection by caregivers (Feldman and Downey, 1994). The lateral PFC is broadly implicated in regulatory processes (Nee and D’Esposito, 2016), which are altered in children exposed to parental maltreatment (Shields and Cicchetti, 2001). Taken together with greater signal in the lateral OFC, a region implicated in learning and updating stimulus-reward associations

(Noonan et al., 2012), a possible interpretation of our findings is that adolescents in foster care may be engaging in greater affective decision-making and regulatory processes during exclusion compared to the controls. Further research is needed to interrogate this hypothesis and determine whether such heightened lateral PFC activation corresponds to altered behavioral responses to exclusion.

Adolescents in foster care also exhibited greater reductions in neural response to cumulative inclusionary interactions relative to the community sample. These reductions were present in the premotor cortex during cumulative inclusion, and also appeared to drive interactions between group differences in cumulative inclusion relative to exclusion in the dorsal precuneus, right temporo-occipital cortex, and intra-

parietal sulcus. The dorsal precuneus mediates behavioral engagement through mental imagery and spatially guided behavior (Zhang and Li, 2012). It has extensive connections with the premotor cortex, and together they support visuospatial cognitive processes, including attention shifting between targets (Cavanna and Trimble, 2006). The right intraparietal sulcus, which forms part of the dorsal attention network, is implicated in the representation of others' actions, and is also strongly connected to the dorsal precuneus (de Hamilton and Grafton, 2006). Reduced activity in these regions, along with the temporo-occipital cortex (a region that plays an important role in motion perception; Zeki, 2015), may reflect decreased engagement to inclusionary interactions over time in the foster care sample compared to controls. These results are broadly aligned with prior findings of blunted processing of social rewards in the context of childhood adversity (Goff and Tottenham, 2015), and it is hypothesized that such alterations may influence decisions and behaviors in normative social environments in a manner that impairs the ability to develop and maintain healthy relationships (McCrary et al., 2017).

These findings raise the issue of factors responsible for neural sensitivity to social interactions in foster care youth. Exploratory analyses revealed that responsivity of the dlPFC and intraparietal sulcus was correlated with self-reported adversity. Furthermore, controlling for adversity decreased the strength of group differences in BOLD response, suggesting that adverse childhood experiences – which were reported at a greater frequency in our foster care sample – are a contributing factor. However, we do not know when or where these adversities occurred; children are often removed from families due to issues such as child abuse and/or neglect, domestic violence and parental mental illness, but certain adversities are equally prevalent in foster care homes (Bruskas and Tessin, 2013). Further, there may be a number of other factors related to foster care (e.g., age at placement, number and duration of placements, characteristics of the foster parents; Orme and Buehler, 2001) that also contribute to results. We were unable to obtain such details due to confidentiality issues, and thus cannot investigate the role of these factors. Future research with more extensive characterization of foster care youth is needed to interrogate the underpinnings of these neural differences and to understand them in the context of the broader literature on adversity.

Our findings also suggest that the identified pattern of neural differences has implications for mental health outcomes in foster care youth. Specifically, greater responsivity of the dlPFC to exclusion was related to higher levels of externalizing problems in the foster care sample only. Meta-analyses have previously implicated altered dlPFC activation in aggressive (Raschle et al., 2015) and disruptive behaviors (Alegria et al., 2016), reflecting altered cognitive regulatory processes in youth with externalizing problems. Interestingly, supplemental analyses indicated that adolescents with greater activation in the same dlPFC cluster to exclusion also reported less resistance to peer influence, although this finding did not survive correction for multiple comparisons. Lateral PFC activation has been related to peer sensitivity in a number of studies (e.g., Morningstar et al., 2019; Pei et al., 2020). Further, there is a broader literature highlighting the role of peer influence in deviant behaviors (Dishion and Tipsord, 2011), which tend to be more prevalent in foster care youth (Bronsard et al., 2016). Overall, these findings suggest that altered dlPFC function may potentially be a vulnerability marker for social and emotional problems in foster care youth. However, it is also important to note that – contrary to prior literature (Banny et al., 2013; Duke et al., 2010; Shields and Cicchetti, 2001) – the foster care and community samples exhibited similar levels of peer problems (such as victimization by and aggression toward peers). Thus, more comprehensive characterization of social functioning (such as the quality of close friendships and engagement in prosocial behaviors) is required to better understand the implications of identified neural patterns. Taken together, further research is needed to corroborate these exploratory associations with social and emotional functions, and determine whether and how such altered regulatory processes may

account for well-established peer problems and mental health outcomes in the foster care population (Benbenishty et al., 2018; Bronsard et al., 2016; DeLuca et al., 2019).

Findings need to be considered in light of limitations. First, in order to mitigate the potential for carryover of negative affect, the Inclusion Run always preceded the Exclusion Run. Thus our design did not account for order effects. Second, there were approximately half the number of average throws contributing to cumulative inclusionary throws as there were to cumulative exclusionary throws. Third, participants only responded with a button press to Inclusion Throws (i.e., to throw to another player). Importantly, these limitations were not confounded by group (*Foster Care* and *Control* groups completed the same protocol), and are thus unlikely to contribute to group differences in neural responses. Fourth, we were unable to correlate neural responses to inclusion/exclusion with altered behavioral responses to these conditions. Future research should administer behavioral measures (such as the Need Threat Scale) following each run to better understand the implications of the identified neural patterns. Finally, it is important to note limitations with retrospective assessments of adversity, which may identify different mechanisms underlying disease risk compared to prospective assessments (Baldwin et al., 2019), as well as caregiver-reports of mental health problems as concordance across youth, caregiver and teacher reports varies by problem type (internalizing vs externalizing) and contexts (e.g., home vs school; Makol et al., 2021).

In conclusion, this study provides novel insight into neural processing of positive and negative peer interactions in adolescents in foster care. Relative to the community sample, adolescents in foster care exhibited greater scaling of neural responses to ongoing or cumulative exclusionary events in a number of prefrontal regions, which may be interpreted as increased engagement of emotion regulatory processes in this group. This was accompanied by signal reductions in response to cumulative inclusionary events in more posterior regions that support attention and behavioral engagement. Findings highlight a broad pattern of greater neural sensitivity to exclusionary, and less sensitivity to inclusionary, peer interactions in this vulnerable population of adolescents, with potential implications for mental health outcomes.

#### CRediT authorship contribution statement

**Nandita Vijayakumar:** Conceptualization, Methodology, Formal analysis, Visualization, Writing – original draft. **Theresa W. Cheng:** Conceptualization, Methodology, Formal analysis, Visualization, Writing – original draft. **Jessica E. Flannery:** Investigation, Writing – review & editing. **John C. Flournoy:** Investigation, Writing – review & editing. **Garrett Ross:** Project administration, Data curation, Writing – review & editing. **Arian Mobasser:** Investigation, Writing – review & editing. **Zdena Op de Macks:** Project administration, Data curation, Writing – review & editing. **Philip A. Fisher:** Funding acquisition, Writing – review & editing. **Jennifer H. Pfeifer:** Conceptualization, Methodology, Funding acquisition, Supervision, 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.2022.102986>.

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