The impact of trauma: a focus on the neural correlates of intergenerational transmission of child maltreatment

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Chapter 5

Pass it on? The neural responses to rejection in the context of a family study on maltreatment

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ABSTRACT

Background. Rejection by parents is an important aspect of child maltreatment. Altered neural responses to social rejection have been observed in maltreated individuals.

Methods. The current study is the first to examine the impact of experienced and perpetrated abuse and neglect on neural responses to social exclusion by strangers versus family using a multigenerational family design, including 144 participants. The role of neural reactivity to social exclusion in the intergenerational transmission of maltreatment was also examined.

Results. Exclusion by strangers was especially associated with increased activation in the left insula, while exclusion by a family member was mainly associated with increased activation in the ACC. Neural reactivity to social exclusion by strangers in the insula, ACC and dmPFC, was associated with experienced maltreatment but not with perpetrated maltreatment. In abusive parents, altered neural reactivity during exclusion was found in other brain areas, indicating different neural correlates of experienced and perpetrated maltreatment.

Conclusion. Hence, no mechanisms could be identified that are involved in the transmission of maltreatment. Hypersensitivity to social rejection by strangers in neglected individuals underscores the importance to distinguish between effects of abuse and neglect and suggests that the impact of experiencing rejection and maltreatment by your own parents extends beyond the family context.

Keywords: social rejection, child maltreatment, insula, ACC, dmPFC

INTRODUCTION

Child physical and emotional abuse and neglect are associated with increased risk for long-lasting behavioral, physical and mental health problems (e.g. Heim *et al.*, 2010; Spinhoven *et al.*, 2010; Twardosz and Lutzker, 2010; McCrory *et al.*, 2011a; Norman *et al.*, 2012; Spinhoven *et al.*, 2014). Among the adverse consequences is the increased risk for maltreated individuals to maltreat their own children (e.g. Kaufman and Zigler, 1987; Egeland *et al.*, 1988; Pears and Capaldi, 2001; Dixon *et al.*, 2005; Berlin *et al.*, 2011). To better identify risk factors for perpetrating abuse and neglect, it is crucial to examine factors that might play a role in the transmission of maltreatment. In this multigenerational family study, we aim to investigate the impact of experienced and perpetrated abuse and neglect on neural reactivity to social exclusion in 144 family members (90 parents and 54 offspring). The possible role of sensitivity to social rejection in the intergenerational transmission of maltreatment is also examined.

One of the core aspects of both child abuse and neglect is parental rejection of needs for attention and nurturance (Bolger and Patterson, 2001; Glaser, 2002), which can occur through parental aggression and hostility or via parental neglect and indifference (Loue, 2005). Chronic exposure to rejection during childhood is associated with emotional, cognitive, behavioral and social deficits, for instance, decreased self-esteem and hypersensitivity to signs of threat and rejection (Van Beest and Williams, 2006; DeWall and Bushman, 2011; Eisenberger, 2012; Sreekrishnan *et al.*, 2014). Rejection sensitivity is associated with increased feelings of aggression and aggressive behavior (Downey and Feldman, 1996; Downey *et al.*, 1998; Jacobs and Harper, 2013). Being rejected by your own parents can enhance sensitivity for social rejection in all sorts of situations, including next-generation parent-child interactions.

Multiple studies show that the network of brain areas associated with social rejection and exclusion includes the insula, anterior cingulate cortex (ACC) and medial prefrontal cortex (mPFC; e.g. Eisenberger *et al.*, 2003; DeWall *et al.*, 2010; Bolling *et al.*, 2011; Sebastian *et al.*, 2011; Cacioppo *et al.*, 2013; Eisenberger, 2015; Rotge *et al.*, 2015;). The insula and ACC are key brain regions involved in social functioning (Wager and Barrett, 2004; Shackman *et al.*, 2011; Cacioppo *et al.*, 2012, 2013), including empathic abilities (Carr *et al.*, 2003; Lamm *et al.*, 2007; Shirtcliff *et al.*, 2009; Rameson *et al.*, 2012). The mPFC is implicated in self-processing, cognitive control, social evaluation and regulation of stress and negative emotions (Ochsner and Gross, 2005; Güroğlu *et al.*, 2010; Etkin *et al.*, 2011; Sebastian *et al.*, 2011; Van den Bos *et al.*, 2011; Denny *et al.*, 2012).

Altered neural responses to social exclusion (compared to social inclusion) have been observed in maltreated individuals. For instance, children with early separation experiences showed reduced activation in the dorsal ACC (dACC) and dorsolateral PFC (dlPFC) and reduced dlPFC–dACC connectivity (Puetz *et al.*, 2014). Maltreated children

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also showed a hypoactivation to rejection-related words, including the left anterior insula and ventrolateral PFC (vlPFC; Puetz *et al.*, 2016). In young adults, in contrast, childhood emotional maltreatment (CEM) severity was found to be associated with increased dorsal mPFC (dmPFC) responsivity to social exclusion, suggesting they show increased levels of self- and other referential processing after social exclusion (Van Harmelen *et al.*, 2014).

A history of maltreatment appears to affect neural networks (i.e. insula, ACC and mPFC) that are also implicated in parenting behavior (Swain and Ho, 2017). These networks enable parents to respond to infant pain and emotions, understand non-verbal signals and infer intentions through empathy and mentalizing (Feldman, 2015; Rilling and Mascaro, 2017). Neural alterations in these areas implicated in social exclusion might mediate the association between experienced and perpetrated abuse and neglect. The current study is the first to examine the role of the neural correlates of social exclusion in the transmission of maltreatment.

Individual differences in response to social exclusion may depend on the relationship with the person who is excluding (Krill and Platek, 2009; Bernstein *et al.*, 2010; Sacco *et al.*, 2014; Scanlon, 2015). Since child maltreatment takes place within the family context, an important question is whether maltreated individuals display a general rejection sensitivity or a more specific hypervigilance for exclusion in their own parent–child context. No functional magnetic resonance imaging (fMRI) studies have been conducted comparing responsivity to exclusion by family members versus strangers. An electroencephalogram (EEG) study suggested however increased sensitivity to exclusion by family members as reflected by increased frontal P2 peaks and left frontal positive slow waves in mothers and children when excluded by one another versus by a stranger (Sreekrishnan *et al.*, 2014). The current study is the first that aims to unravel the neural activity following exclusion by one's own mother or child versus strangers and how this is specifically affected in maltreated and maltreating individuals.

In sum, this study examined the impact of experienced and perpetrated abuse and neglect on neural reactivity to social exclusion by strangers and family members. We used a multi-informant, multigenerational family design, including 144 participants from 8 to 69 years. We differentiated between effects of (experienced and perpetrated) abuse and neglect, as abuse and neglect may be differentially related to the affective and neural correlates of social rejection (e.g. Compier-de Block *et al.*, 2016; Nemeroff, 2016; Van den Berg *et al.*, 2017). We predicted that experienced and perpetrated child abuse and neglect are associated with altered sensitivity to social signals and rejection as reflected by decreased ACC, insular and/or increased dmPFC responsivity to social exclusion. As a second aim, we examined whether the effects represent a general sensitivity to exclusion or a specific sensitivity to one's own family members.

MATERIALS AND METHODS

Participants

The current sample was part of a larger sample from the 3G parenting study, a three-generation family study on the intergenerational transmission of parenting styles, stress and emotion regulation (see also Compier-de Block, 2017; Van den Berg *et al.*, 2017). Participants were recruited via three other studies that included the assessment of caregiving experiences (Penninx *et al.*, 2008; Scherpenzeel, 2011; Joosen *et al.*, 2013). We oversampled participants with an increased risk of maltreatment and included participants who had at least one child of 8 years or older. After consent for participation in the 3G study, their family members (parents, partners, offspring, adult siblings, nephews, nieces and in-laws) were invited to participate. For the current study, all participants from the 3G study who participated in the fMRI part of the study were included. In total, we included 144 participants from two generations (parents and their offspring) of 54 families.

Participants played one round of the Cyberball task with strangers and one with family. We included only the first round of Cyberball in our analyses (using a between-subject design) because affective and neural effects of exclusion were only observed in the first round of the task, irrespective of the familiarity of the other players. This was possibly due to habituation to the task. Participants played their first round of Cyberball with strangers (unfamiliar condition; 28 men and 44 women) or with family (familiar condition; n = 72; see Figure 1). In the familiar condition, 41 participants played with their child (18 men and 23 women) and 31 with their mother (11 men and 20 women). Separate analyses were run to link experienced maltreatment (all participants; n = 144) and perpetrated maltreatment (parents only; n = 90) to neural responses. See Supplementary data for more information.

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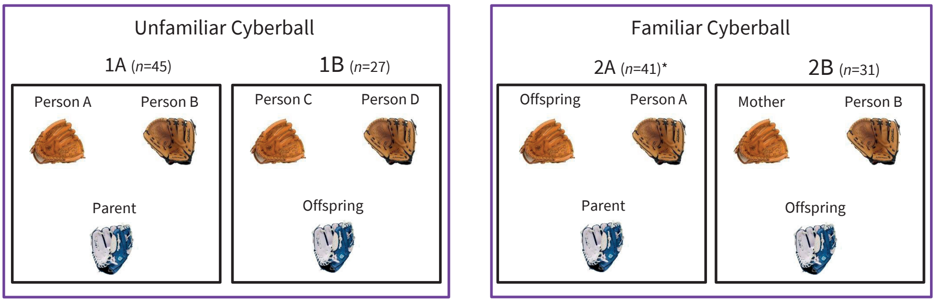

Figure 1. Unfamiliar (1A and 1B) and familiar (2A and 2B) Cyberball for parents (1A and 2A) and offspring (1B and 2B). *Four parents played with their mother because their offspring were too young to participate.

Procedure

Informed consent was obtained after describing the study to the participants. If eligible, offspring and their parents were asked to participate in the fMRI session, performing three tasks in the scanner, with the Cyberball task always second. Results on the other tasks are reported elsewhere (Van den Berg *et al.*, 2017). All participants younger than 18 years old were first familiarized with the scanner environment using a mock scanner. The full protocol was conducted according to the principles expressed in the Declaration of Helsinki and approved by the Medical Ethics Committee of the Leiden University Medical Center (LUMC).

Measures

Childhood maltreatment

Adapted versions of the Conflict Tactics Scales (CTS; Straus *et al.*, 1998) were administered in combination with the emotional neglect scale from the Childhood Trauma Questionnaire (CTQ-SF; Bernstein *et al.*, 2003; see also Compier-de Block, 2017) to measure experienced childhood abuse and neglect by mother and/or father. Parents also completed a CTS version to assess their own abusive or neglectful behaviors towards their child(ren). An overall *Neglect* score was calculated by averaging Emotional and Physical Neglect and an overall *Abuse*-score by averaging Emotional and Physical Abuse. For our analyses, we combined information from two informants (parents and offspring) whenever possible (see Supplementary data), resulting in a total of 237 informants on experienced childhood maltreatment and 163 informants on perpetrated maltreatment. Because the distributions of CTS scores were skewed, scores were logarithmically transformed (log10). Outliers, meaning values more extreme than a standardized value of ±3.29, were winsorized to the most extreme value within the normal range ± the difference between the two most extreme values within the normal range ($n = 1$ for experienced abuse and $n = 1$ for neglect).

Cyberball task

The Cyberball task is a commonly used paradigm to study the neural correlates of social exclusion (Williams *et al.*, 2000). For the current study, an adapted version of the task was used in which participants played two rounds of this virtual ball-tossing game with two other players (computer controlled confederates; see Supplementary data). All participants played one round with two strangers (unfamiliar round) and another round with a family member and a stranger (familiar round). For offspring, this family member was their own mother, and parents played with their oldest child (participating in the 3G study). The order of the rounds was counterbalanced across participants within the two generations. As described above, only the first round of Cyberball was included in our analyses. During the game, each player was represented by a picture of a different baseball glove (see Figure 1).

Each round consisted of an inclusion and exclusion block of 36 trials each. During the inclusion block, the ball was thrown to the participant in 33% of the total number of tosses (hence, achieving fair play in which the participant got an equal number of tosses as compared to the other players). After receiving the ball, participants could throw back the ball to one of the other players using a button press. The inclusion block was followed by a social exclusion block with the same players, during which participants received the ball only once at the start of the game (the unfair play in which participants were excluded from the game). Participants' tosses were self-paced, and ball tosses of the other players were preceded by a random jitter interval (100–4000 ms). It took 2 s before each toss reached the designated player, and ball tosses varied in trajectory. The task was projected on a screen at the end of the scanner and was visible via a mirror positioned on the head coil.

Mood and need satisfaction

Right before the Cyberball game (inside the scanner) and immediately after each round of the game, participants completed four items from a mood questionnaire (Sebastian *et al.*, 2010). The items measured feeling sad, happy, angry and insecure. After each Cyberball round, additional items from the Need Threat Scale (Van Beest and Williams, 2006) were completed to measure levels of need satisfaction. The five items from the Need Threat Scale measured belonging, control, self-esteem and meaningful existence. All questions were presented on the screen. Each item was rated on a scale from 1 ('not at all') to 10 ('very much'). Items were recoded and averaged to create an overall index of mood and need satisfaction at each time point with higher scores reflecting a better mood (see Table 1) and higher levels of need satisfaction.

Table 1. Mood (SD) before the Cyberball, after round 1 for parents and offspring.

	Parents	Offspring
Baseline	8.39 (1.04)	8.80 (0.86)
After round 1 of Cyberball	8.16 (1.23)**	8.55 (1.15)*

* $p < .05$; ** $p < .01$ compared to baseline

Covariates

Questionnaires were used to assess demographic information (age, gender, handedness and household social economic status [SES]). Three versions of Achenbach's behavior problems assessment were used to control for psychopathology symptoms. Parents completed the Child Behavioral Checklist (CBCL; Achenbach, 1991a) when their child was younger than 12 years old. For 12- to 17-year-old participants, the Youth Self Report (YSR; Achenbach, 1991b; Achenbach and Rescorla, 2001) was used, and older participants completed the Adult Self Report (ASR; Achenbach and Rescorla, 2003). A total psychopathology symptom score was calculated for all three questionnaires. Cronbach's α's were good to excellent (.76–.93).

fMRI acquisition

Imaging data were acquired using a whole-head coil on a 3.0-Tesla Philips Achieva scanner (Philips Medical Systems, Best, the Netherlands) located at the LUMC. To restrict head motion, foam cushions were used around the head. T2*-weighted echo-planar images (EPI) were obtained for all participants [repetition time (TR) = 2200 ms, echo time (TE) = 30 ms, matrix size: 80 × 79, 38 transverse slices of 2.75 mm, slice gap = 0.28 mm, field of view (FOV) = 220]. In accordance with the LUMC policy, all anatomical MRI scans were reviewed and cleared by a radiologist from the radiology department. No anomalous findings were reported.

fMRI data analysis

Functional imaging data were preprocessed and analyzed using Statistical Parametric Mapping version 8 (SPM8; Wellcome Department of Cognitive Neurology, London) software implemented in Matlab 5.0.7 (Mathworks, Sherborn, MA). Preprocessing, after extensive quality control of the data, included manually reorienting the functional images to the anterior commissure, slice time correction, image realignment, registration of the T1-scan to the mean echo-planar image, warping to Montreal Neurological Institute (MNI)-space as defined by the SPM8 T1-template, reslicing to 3 × 3 × 3 mm voxels and spatial smoothing with a Gaussian kernel (8 mm, full width at half-maximum). Subject movement (>3 mm) resulted in exclusion of the data from further analysis (n = 16).

MRI data were analyzed with the General Linear Model in SPM8. The fMRI time series were modeled as a series of events convolved with the hemodynamic response function (HRF). BOLD responses were distinguished for events on which participants received or did not receive the ball by a stranger or a family member (see Supplementary data). The first trials of the exclusion blocks during which participants received and played the ball once were not analyzed. The onset of the ball movement was modeled as a zero-duration event. Low-frequency noise was removed by applying a high-pass filter (cut-off 120 s) to the fMRI time series at each voxel. Statistical parametric maps for each comparison of interest were calculated on a voxel-by-voxel basis.

To examine the effect of social exclusion, the following contrasts were computed for all participants for the familiar and unfamiliar round: no-ball exclusion block > no-ball inclusion block. To test neural correlates of social exclusion, key region of interests (ROIs) were identified using the MARSBAR toolbox (Brett *et al.*, 2002) in SPM: namely, the insula, dACC and dmPFC (see Figure 2). We defined anatomical ROIs of the insula using the TD label atlas within the Wakeforest-pickatlas toolbox (Maldjian *et al.*, 2003). Because the boundaries of ACC subdivisions are to date not well defined (Lieberman and Eisenberger, 2015; Rotge *et al.*, 2015), and the whole brain peak voxels of the ACC were located in different areas of the ACC dependent on whether participants were playing with strangers or family members (see Figure 2), we extracted two distinct areas of the dACC as functional ROIs (Poldrack, 2007) using the MARSBAR toolbox (Brett *et al.*, 2002). We generated the dACC functional ROIs using whole-brain activation of the unfamiliar round to analyze the no-ball exclusion block versus no-ball inclusion block contrast for the unfamiliar condition and whole brain activation of the familiar round for the familiar condition (see Figure 2, Tables 2 and 3). Additionally, because CEM was found to be specifically associated with enhanced dmPFC activity to social exclusion (Van Harmelen *et al.*, 2014), this area was defined by a 10-mm sphere around the peak activation described by Van Harmelen *et al.* (2014; centered on MNI-coordinates x = −3, y = 48, z = 33). All results are reported in MNI space.

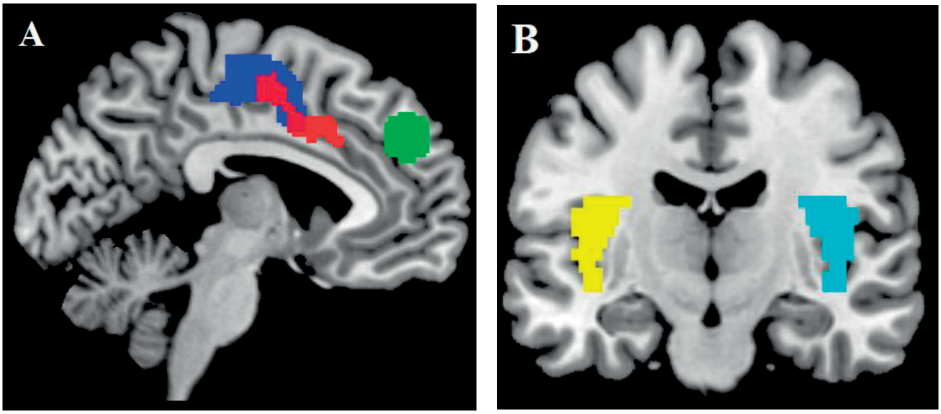

Figure 2. Region of interest (ROI) masks.
A = Red: functional ACC ROI mask for the unfamiliar condition based on whole brain activation for the contrast no-ball exclusion>no-ball inclusion at $p < 0.005$ (uncorrected); Dark blue: functional ACC ROI mask for the familiar condition based on whole brain activation for the contrast no-ball exclusion>no-ball inclusion at $p < 0.005$ (uncorrected); Green: dmPFC ROI mask based on the peak activation described by Van Harmelen et al. (2014; centered on MNI-coordinates x=-3, y=48, z=33).
B = Yellow: anatomical left insula ROI mask; Cyan: anatomical right insula ROI mask.

SPSS data analysis

Activity in the ROIs was examined using three-level multilevel regression analyses in SPSS 23, in which participants were nested within households and households were nested within families, to take the family structure of the data into account. This way, level 1 models variation at the participant level, level 2 captures variation among participants within the same households and level 3 estimates variation among families. Random intercept models were built sequentially, starting with an empty (null) model without explanatory variables in which the total variance in brain reactivity in response to social exclusion was divided into a component at each level. This empty model was used to test for random variation in the outcome variables at the different levels (see Supplementary data). We consistently used multilevel analyses for all ROIs to control for the nested structure of data.

As a next step, age, gender, handedness, SES and psychopathology were added to the model as possible covariates. Variables were only kept in the final covariates model when they were significant ($p < 0.05$). To explore fixed effects of abuse and neglect, main effects of abuse and neglect were added to Model 1.

Multilevel regression analyses were run for each ROI for the familiar and the unfamiliar contrast separately. Separate models were run for experienced and perpetrated maltreatment. For multilevel analyses in the context of the familiar Cyberball, participants playing with their own child (41 parents) or mother (31 offspring) were analyzed separately (see Figure 1). All (continuous) predictor variables and covariates were centered. All independent and dependent variables were measured at the individual level (except SES; see Supplementary data) and considered in the fixed part of the model. Unstandardized regression coefficients are reported. If similar significant ROIs were found for experienced and perpetrated abuse and/or neglect, mediation analyses were planned to assess their role in the intergenerational transmission of maltreatment. However, this was not relevant for the current findings.

Table 2. Significant clusters for the contrast no-ball exclusion block > no-ball inclusion block for the unfamiliar Cyberball round.

Clusters	Cluster level	Peak level		Coordinates		
	number of voxels	T	*p*-value	x	y	z
Left insula	832	5.74	<0.001	-33	8	7
		5.44	<0.001	-24	-4	1
		5.35	<0.001	-45	-7	13
Precentral gyrus		3.69	<0.001	-57	5	10
Postcentral gyrus	169	4.99	<0.001	48	-22	25
ACC	269	4.90	<0.001	-6	11	37
		3.85	<0.001	0	-7	55
		3.51	<0.001	9	5	43
Right insula	450	4.21	<0.001	45	2	4
		4.04	<0.001	36	-1	13
		3.91	<0.001	54	5	4

$p < 0.005$ uncorrected, > 25 voxels

Table 3. Significant clusters for the contrast no-ball exclusion block>no-ball inclusion block for the familiar Cyberball round for parents (A) and offspring (B).

A. Parents (*n* = 90)						
Clusters	Cluster level	Peak level		Coordinates		
	number of voxels	T	*p*-value	x	y	z
Postcentral gyrus	62	4.68	<0.001	-54	-25	43
		4.47	<0.001	-45	-28	49
Precentral gyrus		4.16	<0.001	-33	-25	55
ACC	152	4.57	<0.001	6	-7	52
		3.91	<0.001	-9	-7	52
		3.77	<0.001	-12	-31	49
Precentral gyrus	34	3.68	<0.001	33	-25	52

p < 0.005 uncorrected, > 25 voxels

B. Offspring (*n* = 54)						
Clusters	Cluster level	Peak level		Coordinates		
	number of voxels	T	*p*-value	x	y	z
ACC	567	6.34	<0.001	-6	-4	55
		6.00	<0.001	6	2	52
		5.44	<0.001	-6	5	43
Left insula	165	5.35	<0.001	-42	-4	10
Precentral gyrus	185	5.00	<0.001	36	-22	55
		4.11	<0.001	42	-19	67
		3.71	<0.001	42	-28	67
Postcentral gyrus	230	4.93	<0.001	-54	-19	49
		4.46	<0.001	-45	-22	55
		3.86	<0.001	-36	-28	52
Right insula	65	3.85	<0.001	42	-25	22
Postcentral gyrus		3.46	0.001	54	-19	22
		3.43	0.001	60	-25	25
Left insula	72	3.77	<0.001	-45	-22	19
Postcentral gyrus		3.77	<0.001	-63	-22	31
		3.29	0.001	-57	-22	22

p < 0.005 uncorrected, > 25 voxels

RESULTS

Transmission of maltreatment

Demographics and mean (SD) maltreatment scores are presented in Table 4. The correlation between experienced abuse and neglect was $r = .51$ ($p < 0.001$) and between perpetrated abuse and neglect $r = .34$ ($p = 0.001$). To examine intergenerational transmission of maltreatment in our sample, regression analyses were conducted with experienced childhood abuse and neglect as predictors and with perpetrated abuse and neglect as outcome measures separately for participants with offspring ($n = 88$ parents). Results indicated that, controlling for age, gender, household SES and psychopathology in the first block, experienced abuse ($\beta = .53$, $t(81) = 4.66$, $p < 0.001$) was the only significant predictor of perpetrated abuse. Experienced neglect did not predict perpetrated abuse ($p = 0.113$). None of the covariates were significant. Perpetrated neglect was not predicted by experienced neglect ($p = 0.306$) nor by experienced abuse ($p = 0.945$). Age ($\beta = 0.29$, $t = 2.54$, $p = .013$) and psychopathology ($\beta = 0.30$, $t = 2.68$, $p = .009$) were significant covariates for perpetrated neglect.

Table 4. Demographics, psychopathology, and maltreatment scores.

Variables	Mean (SD)	Range
Age	36.85 (16.38)	8.75 - 69.67
Gender (*n:* men/women)	57/87	-
Handedness (*n*: left/right)	18/126	-
CBCL	14.00 (7.64)	3.20 - 28.80
YSR	9.68 (8.27)	0.00 - 30.00
ASR	24.22 (15.69)	1.00 - 83.00
Abused[a]	1.65 (0.50)	1.02 - 4.50
Neglected[a]	1.89 (0.61)	1.00 - 5.00
Maltreated[a] (total)	1.77 (0.49)	1.02 - 4.75
Abusive[b] ($n = 90$)	1.49 (0.31)	1.00 - 2.53
Neglectful[b] ($n = 90$)	1.55 (0.32)	1.00 - 2.48
Maltreating[b] (total; $n = 90$)	1.52 (0.25)	1.00 - 2.11

Values of all included participants are presented ($n = 144$) unless otherwise specified.
Raw scores are presented.
[a]Combined experienced maltreatment scores by averaging parent and child reports as measured with the CTS. [b]Combined perpetrated maltreatment scores by averaging parent and child reports as measured with the CTS.
CBCL = Child Behavioral Checklist; YSR = Youth Self Report; ASR = Adult Self Report.

Mood and need satisfaction

A time (mood before versus after the first round of Cyberball) × type (playing with family or strangers) repeated measures ANOVA with mood as a dependent variable showed a significant main effect of time on mood for parents ($F(1, 80) = 8.76$, $p = 0.004$) and offspring ($F(1, 60) = 6.10$, $p = 0.016$), with mood scores significantly decreasing after the first Cyberball round compared to baseline for both parents and offspring. There were no significant interaction effects between time and type for parents ($p = 0.097$) or offspring ($p = 0.260$).

Correlation analyses revealed that levels of experienced or perpetrated abuse or neglect were not related to mood after exclusion during the Cyberball task for parents ($p > 0.05$). However, a lower mood after exclusion was significantly related with higher levels of experienced abuse ($r = -.37$, $p = 0.003$) and neglect ($r = -.38$, $p = 0.003$) for children. No relationships were found between experienced or perpetrated abuse or neglect and need satisfaction after the Cyberball task for parents or children ($p > 0.05$).

Unfamiliar Cyberball

Whole brain analyses

For the unfamiliar Cyberball ($n = 72$; see Figure 1), whole brain analyses for the contrast no-ball exclusion block versus no-ball inclusion block revealed a significant cluster of activation in the left insula at $p < 0.01$ family-wise error (FWE) corrected for multiple comparisons. For exploratory purposes, brain activation was also examined at the whole brain level with a threshold of $p < 0.005$ (uncorrected). To reduce the risk of false positives, only clusters larger than 25 significantly activated voxels were considered (Lieberman and Cunningham, 2009). At this threshold, the contrast no-ball exclusion block versus no-ball inclusion block showed activation in clusters including the insula and ACC (see Table 2).

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Multilevel ROI analyses: experienced abuse and neglect

Multilevel analyses were first performed for the contrast no-ball exclusion by strangers versus no-ball inclusion by strangers for all participants in the unfamiliar Cyberball condition ($n = 72$; see Figure 1). Analyses were run with experienced abuse and neglect as predictors and BOLD responses in the ROIs as outcome measures (see Tables 5A-8A and Supplementary data). In none of these multilevel analyses age, gender, handedness, SES nor psychopathology were significant covariates.

Adding abuse and neglect experience as predictors significantly improved the models for activation in the left (χ^2 (2) = 8.75, $p = 0.013$) and right insula (χ^2 (2) = 6.07, $p = 0.048$), dACC (χ^2 (2) = 8.70, $p = 0.013$) and dmPFC (χ^2 (2) = 11.09, $p = 0.004$). Higher levels of experienced maltreatment were associated with higher BOLD responses in the left and right insula and the dmPFC, and with lower BOLD responses in the dACC during social exclusion by strangers. Analyses on experienced abuse versus neglect revealed that the increased

Table 5A. Multilevel model of brain reactivity in the left insula in response to social exclusion as related to experienced and perpetrated abuse and neglect: unfamiliar Cyberball

Left insula: Unfamiliar round							
	Experienced maltreatment				Maltreating behavior		
	Parents and offspring (n = 72)				*Parents (n = 45)*		
	b	SE	*p*		*b*	SE	*p*
abused	0.28	1.68	.869	abusive	3.01	2.12	.162
neglected	2.31	1.65	.167	neglectful	-2.86	2.38	.236
	χ^2 (2) = 8.75*		.013		χ^2 (2) = 2.34		.311

* *p* < .05; ** *p* < .01
Significant covariates are included in the model (see Supplement)
SE = standard deviation

Table 5B. Multilevel model of brain reactivity in the left insula in response to social exclusion as related to experienced and perpetrated abuse and neglect: familiar Cyberball

Left insula: Familiar round										
	Experienced maltreatment							Maltreating behavior		
	Parents (n = 41)			*Offspring (n = 31)*				*Parents (n = 41)*		
	b	SE	*p*	*b*	SE	*p*		*b*	SE	*p*
abused	0.70	1.12	.538	3.42	2.65	.207	abusive	0.62	1.75	.724
neglected	-0.34	1.02	.740	-0.56	2.67	.836	neglectful	-0.22	1.27	.861
	χ^2 (2) = 0.40		.817	χ^2 (2) = 1.65		.437		χ^2 (2) = 0.12		.941

* *p* < .05; ** *p* < .01
Significant covariates are included in the model (see Supplement)
SE = standard deviation

reactivity in the left insula (β = 2.49, t = 2.03, p = 0.046) and dmPFC (β = 3.27, t = 2.07, p = 0.042) were mainly due to neglect.

Multilevel ROI analyses: perpetrated abuse and neglect

Similar multilevel analyses were run for parents in the unfamiliar Cyberball condition (n = 45; see Figure 1) with perpetrated abuse and neglect as predictors for the contrast no-ball exclusion by strangers versus no-ball inclusion by strangers (see Tables 5A-8A and Supplementary data). Age, gender, handedness, SES and psychopathology were not significant as covariates in any of those analyses.

Adding perpetrated abuse and neglect as predictors did not significantly improve the models for activation in the left (χ^2 (2) = 2.34, p = 0.311) or right insula (χ^2 (2) = 4.27, p = 0.119), dACC (χ^2 (2) = 2.80, p = 0.247) or dmPFC (χ^2 (2) = 2.39, p = 0.302) regarding exclusion by strangers.

Table 6A. Multilevel model of brain reactivity in the right insula in response to social exclusion as related to experienced and perpetrated abuse and neglect: unfamiliar Cyberball

Right insula: Unfamiliar round							
	Experienced maltreatment				Maltreating behavior		
	Parents and offspring (n = 72)				*Parents (n = 45)*		
	b	SE	*p*		*b*	SE	*p*
abused	-0.17	1.77	.922	abusive	0.78	2.20	.725
neglected	1.13	1.73	.516	neglectful	-5.17*	2.46	.041
	χ^2 (2) = 6.07*		.048		χ^2 (2) = 4.27		.119

* $p < .05$; ** $p < .01$
Significant covariates are included in the model (see Supplement)
SE = standard deviation

Table 6B. Multilevel model of brain reactivity in the right insula in response to social exclusion as related to experienced and perpetrated abuse and neglect: familiar Cyberball

Right insula: Familiar round										
	Experienced maltreatment							Maltreating behavior		
	Parents (n = 41)			*Offspring (n = 31)*				*Parents (n = 41)*		
	b	SE	*p*	*b*	SE	*p*		*b*	SE	*p*
abused	0.58	.74	.454	3.51	2.91	.237	abusive	0.71	1.57	.656
neglected	-0.16	1.02	.877	0.87	2.96	.770	neglectful	-0.41	1.03	.699
	χ^2 (2) = 0.59		.746	χ^2 (2) = 1.68		.432		χ^2 (2) = 0.20		.904

* $p < .05$; ** $p < .01$
Significant covariates are included in the model (see Supplement)
SE = standard deviation

Familiar Cyberball

Whole brain analyses

For the familiar Cyberball ($n = 72$; see Figure 1), whole brain analyses for the contrast no-ball exclusion block versus no-ball inclusion block showed a significant cluster of activation in the ACC at $p < 0.01$ FWE corrected for multiple comparisons. At $p < 0.005$ (uncorrected, 25 voxels) both parents and offspring showed activation in clusters including the ACC during exclusion (see Table 3 for an overview of all activated clusters). Moreover, offspring also showed activation in the left and right insula during exclusion by their parents, whereas this was not found for parents playing with their offspring.

Multilevel ROI analyses: experienced abuse and neglect

Multilevel analyses were repeated for the contrast no-ball exclusion by family versus no-ball inclusion by family for participants in the familiar Cyberball condition for parents (n = 41) and offspring (n = 31) separately (see Figure 1, Tables 5B–8B and Supplementary data).

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Table 7A. Multilevel model of brain reactivity in the dACC in response to social exclusion as related to experienced and perpetrated abuse and neglect: unfamiliar Cyberball

dACC: Unfamiliar round							
	Experienced maltreatment				Maltreating behavior		
	Parents and offspring (n = 72)				*Parents (n = 45)*		
	b	SE	*p*		*b*	SE	*p*
abused	-2.72	2.12	.206	abusive	-4.59	2.70	.096
neglected	2.61	2.05	.207	neglectful	1.34	3.03	.660
	χ^2 (2) = 8.70*		.013		χ^2 (2) = 2.80		.247

* *p* < .05; ** *p* < .01
Significant covariates are included in the model (see Supplement)
SE = standard deviation

Table 7B. Multilevel model of brain reactivity in the dACC in response to social exclusion as related to experienced and perpetrated abuse and neglect: familiar Cyberball

dACC: Familiar round										
	Experienced maltreatment							Maltreating behavior		
	Parents (n = 41)			*Offspring (n = 31)*				*Parents (n = 41)*		
	b	SE	*p*	*b*	SE	*p*		*b*	SE	*p*
abused	1.04	1.52	.497	1.36	2.47	.586	abusive	-0.84	2.03	.683
neglected	-0.28	1.34	.836	-0.80	2.43	.745	neglectful	0.73	2.05	.725
	χ^2 (2) = 0.47		.792	χ^2 (2) = 0.32		.851		χ^2 (2) = 0.20		.903

* *p* < .05; ** *p* < .01
Significant covariates are included in the model (see Supplement)
SE = standard deviation

Parents

For parents, a higher SES was associated with higher activity in the left (β = 0.37, t = 2.09, p = 0.043) and right insula (β = 0.43, t = 2.41, p = 0.021). Higher levels of psychopathology were associated with higher right insula activation (β = 1.71, t = 3.41, p = 0.006). Age, gender and handedness were not significant covariates in those analyses.

Adding experiences of abuse and neglect as predictors did not significantly improve the models for activation in the left (χ^2 (2) = 0.40, p = 0.817) or right insula (χ^2 (2) = 0.59, p = 0.746), dACC (χ^2 (2) = 0.47, p = 0.792) or dmPFC (χ^2 (2) = 3.91, p = 0.142) regarding exclusion by offspring.

Offspring

For offspring, higher levels of psychopathology were associated with higher activity in the right insula (β = 3.10, t = 2.60, p = 0.013). Right-handed participants exhibited higher dACC activation (β = −1.68, t = −2.61, p = 0.014). Age, gender and SES were not significant covariates in any of those analyses.

Table 8A. Multilevel model of brain reactivity in the dmPFC in response to social exclusion as related to experienced and perpetrated abuse and neglect: unfamiliar Cyberball

dmPFC: Unfamiliar round							
	Experienced maltreatment				Maltreating behavior		
	Parents and offspring (n = 72)				*Parents (n = 45)*		
	b	SE	*p*		*b*	SE	*p*
abused	1.17	2.16	.591	abusive	4.12	2.82	.151
neglected	2.50	2.12	.242	neglectful	-3.03	3.16	.343
	χ^2 (2) = 11.09**		.004		χ^2 (2) = 2.39		.302

* *p* < .05; ** *p* < .01
Significant covariates are included in the model (see Supplement)
SE = standard deviation

Table 8B. Multilevel model of brain reactivity in the dmPFC in response to social exclusion as related to experienced and perpetrated abuse and neglect: familiar Cyberball

dmPFC: Familiar round										
	Experienced maltreatment							Maltreating behavior		
	Parents (n = 41)			*Offspring (n = 31)*				*Parents (n = 41)*		
	b	SE	*p*	*b*	SE	*p*		*b*	SE	*p*
abused	0.82	1.75	.640	-2.19	2.71	.426	abusive	-2.08	2.43	.396
neglected	-3.26*	1.52	.038	1.36	2.68	.616	neglectful	1.83	2.13	.396
	χ^2 (2) = 3.91		.142	χ^2 (2) = 0.69		.707		χ^2 (2) = 0.997		.607

* *p* < .05; ** *p* < .01
Significant covariates are included in the model (see Supplement)
SE = standard deviation

Adding experiences of abuse and neglect as predictors did not significantly improve the models for activation in the left (χ^2 (2) = 1.65, *p* = 0.437) or right insula (χ^2 (2) = 1.68, *p* = 0.432), dACC (χ^2 (2) = 0.32, *p* = 0.851) or dmPFC (χ^2 (2) = 0.69, *p* = 0.707) regarding exclusion by parents for offspring.

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Multilevel ROI analyses: perpetrated abuse and neglect

Multilevel analyses were repeated for the contrast no-ball exclusion by family versus no-ball inclusion by family for all parents in the familiar Cyberball condition (*n* = 41; see Figure 1, Tables 5B–8B and Supplementary data). Younger participants (β = −0.03, *t* = −3.54, *p* = 0.003) and participants with higher levels of psychopathology (β = 1.50, *t* = 3.42, *p* = 0.004) exhibited higher activity in the right insula. Gender was a significant covariate for the dACC (β = 0.64, *t* = 2.09, *p* = 0.044; higher activation in men). Handedness and SES were not significant.

Adding perpetrated abuse and neglect as predictors did not significantly improve the models for activation in the left (χ^2 (2) = 0.12, *p* = 0.941) or right insula (χ^2 (2) = 0.20, *p* =

0.904), dACC (χ^2 (2) = 0.20, p = 0.903) or dmPFC (χ^2 (2) = 0.997, p = 0.607) in the context of exclusion by family.

DISCUSSION

This is the first multigenerational family study that examined the impact of experienced and perpetrated abuse and neglect on neural reactivity to social exclusion. Moreover, we examined whether the effects represented a general sensitivity to exclusion or a sensitivity in the family context. Previous neuroimaging studies showed that being excluded during the Cyberball task in the general population is typically associated with activation in the insula, ACC and mPFC (e.g. Eisenberger *et al.*, 2003; DeWall *et al.*, 2010; Sebastian *et al.*, 2011; Bolling *et al.*, 2011; Cacioppo *et al.*, 2013; Eisenberger, 2015; Rotge *et al.*, 2015). We also found that social exclusion was associated with insular and ACC activation. However, our whole brain analyses revealed differential reactivity to social exclusion by strangers versus family (one's own mother or child). That is, exclusion by strangers was significantly associated with increased BOLD responses in the left insula, while exclusion by a family member was mainly associated with increased activation in the ACC, especially in offspring.

There are no previous fMRI studies comparing neural responsivity to exclusion by family members versus strangers. However, an EEG study found increased responses in mothers and their offspring while they were excluded by one another compared to a stranger (Sreekrishnan *et al.*, 2014). The insula and ACC are both involved in social functioning (Wager and Barrett, 2004; Shackman *et al.*, 2011; Cacioppo *et al.*, 2012, 2013), including empathic abilities (Carr *et al.*, 2003; Lamm *et al.*, 2007; Shirtcliff *et al.*, 2009; Rameson *et al.*, 2012). However, the insula is found to be involved in automatic affective–empathic processing, whereas the ACC is associated with more general cognitive functions, for instance, task control and response selection (Gu *et al.*, 2010) but also with the motivational component of emotions (Craig, 2009). ACC activity is also found in response to viewing a loved one, for example a child (Bartels and Zeki, 2004).

Experienced abuse and neglect

Exclusion by strangers

As expected, maltreated individuals showed altered neural responses to social exclusion by strangers. Maltreated offspring and parents showed higher activity in the left and right insula and the dmPFC and lower reactivity in the dACC during social exclusion by strangers. Higher activity in the left insula and dmPFC during social exclusion by strangers was especially associated with experienced neglect. Increased dmPFC responsivity to social exclusion by strangers in neglected individuals is in line with previous findings for individuals who experienced CEM (Van Harmelen *et al.*, 2014), strengthening the hypothesis that neglected individuals show increased levels of self- and other-referential processing after social exclusion (e.g., Gusnard *et al.*, 2001; Kelley *et al.*, 2002; Mitchell *et al.*, 2005). Lower dACC reactivity in maltreated individuals is also in line with reduced dACC activation during social exclusion in children with early separation experiences (Puetz *et al.*, 2014) and might reflect avoidant or dissociative responses (Krause-Utz *et al.*, 2012; Herringa *et al.*, 2013; Puetz *et al.*, 2016).

Higher insula activity during social exclusion by strangers in maltreated individuals is consistent with increased insular activity in response to angry faces and trauma-related words in maltreated children (McCrory *et al.*, 2011b; Thomaes *et al.*, 2012) but is not in line with a blunted insula response to rejection-related words in maltreated children (Puetz *et al.*, 2016). Since the insula is associated with various functions including self-awareness and emotion processing (Phan *et al.*, 2002), altered insula activation seems to be linked to functional deficits in emotion processing in maltreated subjects (Hart and Rubia, 2012). Hypersensitivity to social rejection by strangers might help explain why maltreated (and especially neglected) individuals may exhibit specific difficulties with social relationships, including the parent-child relationships (DeGregorio, 2013).

Exclusion by family

Whole brain analyses showed differential reactivity to social exclusion by strangers versus family. In contrast to our expectations, higher levels of experienced abuse or neglect were not associated with altered BOLD responses in the insula, dACC or dmPFC during exclusion by family for both offspring and parents. It has been reported that mentalizing about strangers activates more dorsal parts of the MPFC, whereas more ventral regions of the MPFC may be activated during mentalization related to close significant others (for example family members) with whom individuals experience self-other overlap (Mitchell *et al.*, 2005; Krienen *et al.*, 2010). We might have missed important brain areas with our selected ROIs, and future research might also include other regions, for instance ventral parts of the PFC.

Generally, rejection by a member of an established in-group is associated with enhanced pain of rejection (Bernstein *et al.*, 2010). Little is known about the neural correlates of family-related entitativity (Rüsch *et al.*, 2014), but lower levels of perceived family-related entitativity in maltreated individuals might explain why they do not show altered neural activity after social exclusion by a family member compared to non-mal-treated individuals. Maltreated individuals may have become relatively insensitive for exclusion by their own family, while showing increased sensitivity for rejection in other situations (e.g., rejection by strangers). Another explanation might be that the presentation of the first name of a family member during the Cyberball game was not strong enough to elicit a clear (attachment) representation. For future research, it is therefore recommended to also use (neutral) pictures of family members to examine this in more detail.

Perpetrated abuse and neglect

Perpetrated abuse and neglect were not associated with activation in the insula, dACC or dmPFC during exclusion by strangers or family, even though it is suggested that these areas might play a role in parenting behavior (Feldman, 2015). Exploratory analyses (see Supplementary data) did suggest that abusive parents show lower reactivity in the precentral and postcentral gyrus during exclusion by strangers. While the precentral gyrus is mainly thought to control motor function, the postcentral gyrus is mostly known for processing sensory information. However, postcentral gyrus reactivity has also been identified in imaging studies of emotion and has been associated with the recognition of both positive and negative emotions and perspective taking (George *et al.*, 1996; Canli *et al.*, 2002; Hooker *et al.*, 2012; Meyer *et al.*, 2015). The precentral gyrus has also been associated with emotional memory, empathic concern and processing rewarding and aversive stimuli (Canli *et al.*, 2002; Montoya *et al.*, 2012; Meyer *et al.*, 2015). Moreover, the precentral gyrus is thought to be involved in the social monitoring system (SMS), an outer monitoring system enhancing perceptive and cognitive responses to social cues and information including social exclusion (Kawamoto *et al.*, 2015). Altered functioning of the SMS might induce antisocial behavior, including rejection and maltreating behavior. Although specific roles of the pre- and postcentral gyrus in affective processes remain to be examined, reduced activation in these areas might implicate that abusive parents are less sensitive to negative emotional and social stimuli.

Intergenerational transmission of maltreatment

While in our sample intergenerational transmission of abuse was observed, neglect did not appear to be transmitted from one generation to the next. This is likely due to the smaller sample size of this fMRI subsample, since transmission of neglect was found in the complete sample of the 3G study.

Altered neural reactivity to social exclusion by strangers in the insula, ACC and dmPFC was associated with experienced maltreatment, whereas abusive parents showed decreased reactivity in the precentral and postcentral gyrus during exclusion by strangers. Hence, we found different neural correlates of experienced and perpetrated maltreatment and therefore no neural mechanisms playing a role in the transmission of maltreatment were found.

Strengths and limitations

This is the first multigenerational family study in which differential neural effects of (experienced and perpetrated) abuse and neglect are examined, and the role of neural reactivity to social exclusion by strangers versus family is investigated. Research about the neural correlates of child maltreatment and maltreating parenting behavior in particular is scarce, and our family study design enabled the investigation of intergenerational transmission of maltreatment directly. Another strength is that parent (both fathers and mothers) and child reports of maltreatment were combined to minimize the influence of individual reporter bias. Moreover, our study allowed to differentiate between a general sensitivity for exclusion versus rejection sensitivity in the family context.

A limitation of the current study is the use of retrospective reports to measure maltreatment, which can be subject to recall bias. However, we combined parent and child reports in the maltreatment scores. Moreover, in our paradigm names of family members were used. For future research, pictures of own offspring and parents might be used, although this would decrease standardization of the task. Furthermore, our sample to examine the effects of perpetrated maltreatment was smaller than our sample to assess the effects of experienced maltreatment since only part of the sample were parents.

Conclusion

In sum, we found that exclusion by strangers was especially associated with increased activity in the left insula, while exclusion by a family member was mainly associated with higher activation in the ACC. Furthermore, altered neural reactivity to social exclusion by strangers in the insula, ACC and dmPFC was associated with experienced maltreatment but not with parents' own maltreating behavior, indicating different neural correlates of experienced and perpetrated maltreatment. More specifically, hypersensitivity to social rejection in maltreated individuals was mainly driven by experienced neglect. Furthermore, exploratory analyses showed that abusive parents exhibited lower activation in the pre- and post-central gyrus during exclusion by strangers, possibly reflecting lower levels of perspective taking and empathic abilities. Our study underscores the importance to distinguish between effects of abuse and neglect and suggests that the impact of experiencing rejection and maltreatment by your own parents goes beyond the family context.

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CONFLICT OF INTEREST.

None declared.

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SUPPLEMENT

METHOD

Participants

This sample included 1 parent-child pair with two parents and two offspring (*n* = 4), 12 pairs with two parents and one offspring (*n* = 36), 7 pairs with one parent and two offspring (*n* = 21), 13 pairs with one parent and one offspring (*n* = 26) and 1 pair with two offspring and three parents (two biological parents and a stepfather; *n* = 5). Additionally, 38 parents participated without their offspring and 14 offspring participated without their parents participating. The vast majority of all participants (96.5%) were Caucasian, three participants were of Latin-American descent and two of mixed descent. Elementary school or a short track of secondary school was completed by 30.6% of all participants, 37.5% held an advanced secondary school or vocational school diploma, 17.4% held a college or university degree and 7.6% a postgraduate diploma. 6.9% of all participants were still in elementary school.

Unfamiliar condition: *n* = 72, mean age = 36.2 years, SD = 16.17, age range: 8.8-67.6 years. Parents in the familiar condition: *n* = 41, mean age = 49.3 years; SD = 10.44, age range: 33.9-69.7 years. Children in the familiar condition: *n* = 31, mean age = 22.0 years; SD = 8.63, age range: 9.3-40.1 years.

Childhood maltreatment

For 95 out of 144 participants two informants (participants and their parents) reported on maltreatment history and for 47 participants we only had self-report information on experienced maltreatment, resulting in a total of 237 informants on experienced childhood maltreatment. For 2 participants, information on experienced childhood maltreatment was missing, hence they were only included in the analyses regarding maltreating behavior. Of all 144 participants, 90 had at least one child. For 74 of these 90 participants two informants (participants and their offspring) reported on maltreating behavior, while for the remaining 16 only one informant reported on perpetrated maltreatment (87.5% self-report, 12.5% child report). For one participant, it was not clear whether offspring had reported about their biological parents or their stepparents, hence in these cases child-report information was not included. This resulted in a total of 163 informants on perpetrated maltreatment.

Internal consistencies of the scales were as follows: α_{mother} = .94, α_{father} = .94 for physical abuse, α_{mother} = .82 and α_{father} = .76 for emotional abuse, α_{mother} = .77 and α_{father} = .67 for physical neglect, and α_{mother} = .92, α_{father} = .92 for emotional neglect.

Cyberball task

Prior to the task, participants received the following instruction: “During the game it is really important that you try to imagine yourself actually playing the ball-tossing game as vividly as possible. Try to imagine that you are in a park throwing a ball with two other people.” Prior to the start of the game in the scanner, a false Google™ page with a ‘Cyberball’ listing that was linked to a ‘loading screen’ was presented to enhance credibility of the game. Each participant got to select their own glove before the start of the game.

fMRI data analysis

The inclusion and exclusion block of the familiar round were both divided in four conditions: ‘receiving the ball by a family member’, ‘not receiving the ball by a family member’, ‘receiving the ball by a stranger’, ‘not receiving the ball by a stranger’. The inclusion and exclusion block of the unfamiliar round were divided into the following conditions: ‘receiving the ball by a stranger’, ‘not receiving the ball by a stranger’.

With a more exploratory aim, we included anatomical ROIs of two other regions based on activation at the whole brain level, namely the pre- and postcentral gyrus, using the TD label atlas (Maldjia et al., 2003; see Figure S1). Both areas are also associated with social exclusion (Bolling et al., 2011), perspective-taking and empathy (Meyer et al., 2015).

SPSS data analysis

Composite household SES scores were calculated by averaging standardized household income and standardized completed educational level of both parents living in the same household. Children living with their parents shared the household SES score of their parents.

5

RESULTS

Leaving out all left-handed participants in our sample (n = 18) did not change the main effects of abuse and neglect.

Exploratory multilevel analyses

Exclusion by strangers

With a more exploratory aim, multilevel regression analyses were repeated with BOLD responses in the pre- and postcentral gyrus as outcome measure and with (experienced and perpetrated) abuse and neglect as predictors (see Supplement Tables S1A and S2A). Adding experiences of abuse and neglect as predictors significantly improved the models for activation in the precentral (χ^2 (2) = 8.42, p = .015) and postcentral gyrus (χ^2 (2) = 9.96,

p = .007) regarding exclusion by strangers. Results showed no unique contribution of experienced abuse or neglect regarding exclusion by strangers.

Adding perpetrated abuse and neglect as predictors significantly improved the model for activation in the postcentral gyrus (χ^2 (2) = 11.07, p = .004), with a negative main effect for perpetrated abuse (p = .001). Additionally, a trend was found for the precentral gyrus model (χ^2 (2) = 5.99, p = .050), with a negative main effect for perpetrated abuse (p = .016).

Exclusion by family

Similar exploratory analyses were run for the familiar contrast (see Supplement Tables S1B and S2B). Adding experienced or perpetrated abuse and neglect as predictors did not improve the models for activation in the pre- and postcentral gyrus regarding exclusion by family. Furthermore, no main effects were found for experienced or perpetrated abuse and neglect regarding activation in the pre- or postcentral gyrus during exclusion by one's own offspring.

Table S1A. Multilevel model of brain reactivity in the precentral gyrus in response to social exclusion as related to experienced and perpetrated abuse and neglect: unfamiliar Cyberball.

Precentral gyrus: Unfamiliar round							
	Experienced maltreatment				Maltreating behavior		
	Parents and offspring (n = 72)				*Parents (n = 45)*		
	b	SE	*p*		*b*	SE	*p*
abused	-3.03	2.09	.152	abusive	-6.80*	2.70	.016
neglected	1.39	2.25	.539	neglectful	3.10	3.09	.321
	χ^2 (2) = 8.42*		.015		χ^2 (2) = 5.99		.050

* *p* < .05; ** *p* < .01
Significant covariates are included in the model (see Supplement)

Table S1B. Multilevel model of brain reactivity in the precentral gyrus in response to social exclusion as related to experienced and perpetrated abuse and neglect: familiar Cyberball.

Precentral gyrus: Familiar round										
	Experienced maltreatment							Maltreating behavior		
	Parents (n = 41)			*Offspring (n = 31)*				*Parents (n = 41)*		
	b	SE	*p*	*b*	SE	*p*		*b*	SE	*p*
abused	0.59	1.25	.641	0.78	2.05	.706	abusive	-0.70	1.75	.691
neglected	-0.14	1.07	.894	-1.04	2.03	.613	neglectful	-0.01	1.50	.997
	χ^2 (2) = 0.22		.896	χ^2 (2) = 0.31		.859		χ^2 (2) = 0.21		.901

* *p* < .05; ** *p* < .01
Significant covariates are included in the model (see Supplement)

Table S2A. Multilevel model of brain reactivity in the postcentral gyrus in response to social exclusion as related to experienced and perpetrated abuse and neglect: unfamiliar Cyberball.

Postcentral gyrus: Unfamiliar round							
	Experienced maltreatment				Maltreating behavior		
	Parents and offspring (n = 72)				*Parents (n = 45)*		
	b	SE	*p*		*b*	SE	*p*
abused	-4.36	2.79	.123	abusive	-11.70**	3.42	.001
neglected	1.68	3.00	.578	neglectful	7.49	3.91	.062
	χ^2 (2)= 9.96**		.007		χ^2 (2) = 11.07**		.004

* *p* < .05; ** *p* < .01
Significant covariates are included in the model (see Supplement)

Table S2B. Multilevel model of brain reactivity in the postcentral gyrus in response to social exclusion as related to experienced and perpetrated abuse and neglect: familiar Cyberball.

Postcentral gyrus: Familiar round										
	Experienced maltreatment							Maltreating behavior		
	Parents (n = 41)			*Offspring (n = 31)*				*Parents (n = 41)*		
	b	SE	*p*	*b*	SE	*p*		*b*	SE	*p*
abused	0.49	1.56	.758	1.37	2.31	.558	abusive	-2.51	2.05	.228
neglected	0.49	1.35	.721	-1.35	2.37	.573	neglectful	-0.13	1.67	.940
	χ^2 (2) = 0.34		.846	χ^2 (2) = 0.48		.785		χ^2 (2) = 2.04		.360

p < .05; ** *p* < .01
Significant covariates are included in the model (see Supplement)

Table S3. Multilevel model of brain reactivity in the left insula in response to social exclusion as related to experienced childhood abuse and neglect.

Left insula									
	Unfamiliar round			Familiar round			Familiar round		
	b	SE	*p*	*b*	SE	*p*	*b*	SE	*p*
Covariates	Parents and offspring (*n* = 72)			Parents (*n* = 41)			Offspring (*n* = 31)		
age	0.00	.01	.639	-0.02	.01	.187	0.01	.02	.584
gender	0.23	.30	.452	0.13	.24	.582	0.22	.42	.609
handedness	0.46	.40	.254	0.62	.62	.320	0.48	.71	.504
SES	-0.15	.22	.502	0.37*	.18	.043	0.53	.32	.110
PP	-0.60	.68	.386	0.60	.67	.375	1.44	1.08	.192
Model 1	Parents and offspring (*n* = 72)			Parents (*n* = 41)			Offspring (*n* =3 1)		
abused	0.28	1.68	.869	0.70	1.12	.538	3.42	2.65	.207
neglected	2.31	1.65	.167	-0.34	1.02	.740	-0.56	2.67	.836

* $p < .05$; ** $p < .01$
SES = social economic status; PP = psychopathology

Table S4. Multilevel model of brain reactivity in the right insula in response to social exclusion as related to experienced childhood abuse and neglect.

Right insula									
	Unfamiliar round			Familiar round			Familiar round		
	b	SE	*p*	*b*	SE	*p*	*b*	SE	*p*
Covariates	Parents and offspring (*n* = 72)			Parents (*n* = 41)			Offspring (*n* = 31)		
age	-0.01	.01	.578	-0.02	.01	.111	0.01	.03	.658
gender	0.20	.31	.518	0.18	.13	.244	0.15	.44	.727
handedness	0.29	.41	.488	0.34	.63	.594	0.33	.75	.660
SES	-0.12	.23	.606	0.43*	.18	.021	0.28	.41	.498
PP	-0.67	.71	.347	1.71**	.50	.006	3.10*	1.19	.013
Model 1	Parents and offspring (*n* = 72)			Parents (*n* = 41)			Offspring (*n* = 31)		
abused	-0.17	1.77	.922	0.58	.74	.454	0.57	.78	.485
neglected	1.13	1.73	.516	-0.16	1.02	.877	0.04	1.07	.974

* $p < .05$; ** $p < .01$
SES = social economic status; PP = psychopathology

Table S5. Multilevel model of brain reactivity in the dACC in response to social exclusion as related to experienced childhood abuse and neglect.

dACC									
	Unfamiliar round			Familiar round			Familiar round		
	b	SE	*p*	*b*	SE	*p*	*b*	SE	*p*
Covariates	Parents and offspring (*n* = 72)			Parents (*n* = 41)			Offspring (*n* = 31)		
age	-0.01	.011	.236	-0.03	.02	.124	-0.02	.02	.317
gender	0.256	.37	.497	0.59	.32	.070	-0.09	.39	.827
handedness	-0.56	.50	.265	0.64	.75	.400	-1.68*	.64	.014
SES	0.07	.28	.803	0.19	.22	.395	-0.60	.30	.051
PP	0.17	.85	.842	0.67	.84	.427	0.30	.97	.763
Model 1	Parents and offspring (*n* = 72)			Parents (*n* = 41)			Offspring (*n* = 31)		
abused	-2.72	2.12	.206	1.04	1.52	.497	1.36	2.47	.586
neglected	2.61	2.05	.207	-0.28	1.34	.836	-0.80	2.43	.745

* $p < .05$; ** $p < .01$
SES = social economic status; PP = psychopathology

Table S6. Multilevel model of brain reactivity in the dmPFC in response to social exclusion as related to experienced childhood abuse and neglect.

dmPFC									
	Unfamiliar round			Familiar round			Familiar round		
	b	SE	*p*	*b*	SE	*p*	*b*	SE	*p*
Covariates	Parents and offspring (*n* = 72)			Parents (*n* = 41)			Offspring (*n* = 31)		
age	0.02	.01	.078	-0.01	.02	.570	-0.02	.02	.419
gender	0.28	.38	.475	-0.26	.34	.453	0.37	.45	.417
handedness	0.36	.50	.481	1.37	.86	.123	0.36	.74	.627
SES	-0.30	.28	.290	0.17	.26	.526	0.32	.34	.347
PP	-1.25	.86	.154	0.79	.97	.424	0.69	1.11	.539
Model 1	Parents and offspring (*n* = 72)			Parents (*n* = 41)			Offspring (*n* = 31)		
abused	1.17	2.16	.591	0.82	1.75	.640	-2.19	2.71	.426
neglected	2.50	2.12	.242	-3.26*	1.52	.038	1.36	2.68	.616

* $p < .05$; ** $p < .01$
SES = social economic status; PP = psychopathology

Table S7. Multilevel model of brain reactivity in the left insula in response to social exclusion as related to perpetrated childhood abuse and neglect.

Left insula						
	Unfamiliar round			Familiar round		
	b	SE	*p*	*b*	SE	*p*
Covariates	Parents (*n* = 41)			Parents (*n* = 41)		
age	0.02	.02	.335	-0.02	.01	.183
gender	0.23	.36	.518	0.03	.21	.873
handedness	0.81	.58	.169	0.43	.42	.315
SES	-0.07	.32	.825	0.29	.18	.107
PP	0.11	.87	.897	0.14	.63	.824
Model 1	Parents (*n* = 45)			Parents (*n* = 41)		
abusive	3.01	2.12	.162	0.62	1.75	.724
neglectful	-2.86	2.38	.236	-0.22	1.27	.861

* $p < .05$; ** $p < .01$
SES = social economic status; PP = psychopathology

Table S8. Multilevel model of brain reactivity in the right insula in response to social exclusion as related to perpetrated childhood abuse and neglect.

Right insula						
	Unfamiliar round			Familiar round		
	b	SE	*p*	*b*	SE	*p*
Covariates	Parents (*n* = 41)			Parents (*n* = 41)		
age	0.00	.02	.909	-0.03**	.01	.003
gender	0.18	.40	.655	0.16	.12	.224
handedness	0.64	.64	.322	0.24	.24	.323
SES	-0.06	.34	.860	0.35	.18	.060
PP	-0.29	.96	.765	1.50**	.44	.004
Model 1	Parents (*n* = 45)			Parents (*n* = 41)		
abusive	0.78	2.20	.725	0.71	1.57	.656
neglectful	-5.17*	2.46	.041	-0.41	1.03	.699

* $p < .05$; ** $p < .01$
SES = social economic status; PP = psychopathology

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Table S9. Multilevel model of brain reactivity in the dACC in response to social exclusion as related to perpetrated childhood abuse and neglect.

dACC						
	Unfamiliar round			Familiar round		
	b	SE	*p*	*b*	SE	*p*
Covariates	Parents (*n* = 41)			Parents (*n* = 41)		
age	-0.02	.02	.484	-0.03	.02	.062
gender	0.83	.46	.082	0.64*	.31	.044
handedness	-0.59	.74	.429	0.05	.63	.941
SES	-0.13	.40	.745	0.09	.20	.676
PP	1.33	1.11	.240	0.43	.82	.602
Model 1	Parents (*n* = 45)			Parents (*n* = 41)		
abusive	-4.59	2.70	.096	-0.84	2.03	.683
neglectful	1.34	3.03	.660	0.73	2.05	.725

* $p < .05$; ** $p < .01$
SES = social economic status; PP = psychopathology

Table S10. Multilevel model of brain reactivity in the dmPFC in response to social exclusion as related to perpetrated childhood abuse and neglect.

dmPFC						
	Unfamiliar round			Familiar round		
	b	SE	*p*	*b*	SE	*p*
Covariates	Parents (*n* = 41)			Parents (*n* = 41)		
age	0.01	.02	.609	-0.00	.02	.944
gender	0.56	.49	.262	-0.20	.32	.539
handedness	0.71	.78	.367	0.65	.64	.328
SES	-0.27	.42	.519	0.26	.26	.321
PP	-0.35	1.17	.770	1.16	.92	.217
Model 1	Parents (*n* = 45)			Parents (*n* = 41)		
abusive	4.12	2.82	.151	-2.08	2.43	.396
neglectful	-3.03	3.16	.343	1.83	2.13	.396

* $p < .05$; ** $p < .01$
SES = social economic status; PP = psychopathology

Table S11. Multilevel model of brain reactivity in the precentral gyrus in response to social exclusion as related to experienced childhood abuse and neglect.

Precentral gyrus									
	Unfamiliar round			Familiar round			Familiar round		
	b	SE	*p*	*b*	SE	*p*	*b*	SE	*p*
Covariates	Parents and offspring (*n* = 72)			Parents (*n* = 41)			Offspring (*n* = 31)		
age	-0.02	.01	.091	-0.02	.01	.174	-0.01	.02	.646
gender	0.40	.35	.263	0.28	.28	.315	0.24	.35	.490
handedness	-1.03*	.48	.035	0.64	.65	.328	-0.18	.57	.755
SES	0.25	.27	.362	0.11	.18	.552	-0.62	.26	.025
PP	0.80	.81	.327	0.61	.72	.404	-0.22	.86	.797
Model 1	Parents and offspring (*n* = 72)			Parents (*n* = 41)			Offspring (*n* = 31)		
abused	-3.03	2.09	.152	0.59	1.25	.641	0.78	2.05	.706
neglected	1.39	2.25	.539	-0.14	1.07	.894	-1.04	2.03	.613

* $p < .05$; ** $p < .01$
SES = social economic status; PP = psychopathology

Table S12. Multilevel model of brain reactivity in the postcentral gyrus in response to social exclusion as related to experienced childhood abuse and neglect.

Postcentral gyrus									
	Unfamiliar round			Familiar round			Familiar round		
	b	SE	*p*	*b*	SE	*p*	*b*	SE	*p*
Covariates	Parents and offspring (*n* = 72)			Parents (*n* = 41)			Offspring (*n* = 31)		
age	-0.02	.01	.130	-0.01	.02	.684	-0.03	.02	.190
gender	0.63	.48	.195	0.66	.33	.058	0.23	.33	.482
handedness	-1.52*	.63	.019	0.36	.82	.664	-0.16	.52	.752
SES	0.25	.36	.480	0.06	.23	.800	-0.81*	.31	.013
PP	0.38	1.08	.725	0.27	.91	.771	-0.46	.92	.618
Model 1	Parents and offspring (*n* = 72)			Parents (*n* = 41)			Offspring (*n* = 31)		
abused	-4.36	2.79	.123	0.49	1.56	.758	1.37	2.31	.558
neglected	1.68	3.00	.578	0.49	1.35	.721	-1.35	2.37	.573

* $p < .05$; ** $p < .01$
SES = social economic status; PP = psychopathology

Table S13. Multilevel model of brain reactivity in the precentral gyrus in response to social exclusion as related to perpetrated childhood abuse and neglect

Precentral gyrus						
	Unfamiliar round			Familiar round		
	b	SE	*p*	*b*	SE	*p*
Covariates	Parents ($n = 41$)			Parents ($n = 41$)		
age	-0.04	.02	.121	-0.02	.01	.127
gender	1.14*	.47	.021	0.31	.26	.241
handedness	-1.03	.77	.189	0.15	.52	.772
SES	0.20	.43	.645	0.05	.17	.785
PP	1.08	1.14	.350	0.41	.70	.562
Model 1	Parents ($n = 45$)			Parents ($n = 41$)		
abusive	-6.80*	2.70	.016	-0.70	1.75	.691
neglectful	3.10	3.09	.321	-0.01	1.50	.997

* $p < .05$; ** $p < .01$
SES = social economic status; PP = psychopathology

Table S14. Multilevel model of brain reactivity in the postcentral gyrus in response to social exclusion as related to perpetrated childhood abuse and neglect

Postcentral gyrus						
	Unfamiliar round			Familiar round		
	b	SE	*p*	*b*	SE	*p*
Covariates	Parents ($n = 41$)			Parents ($n = 41$)		
age	-0.06	.03	.058	-0.01	.02	.618
gender	1.65*	.62	.011	0.71*	.29	.025
handedness	-1.68	1.01	.104	-0.05	.57	.934
SES	0.30	.57	.599	0.017	.22	.941
PP	1.07	1.49	.479	-0.12	.84	.890
Model 1	Parents ($n = 45$)			Parents ($n = 41$)		
abusive	-11.70**	3.42	.001	-2.51	2.05	.228
neglectful	7.49	3.91	.062	-0.13	1.67	.940

* $p < .05$; ** $p < .01$
SES = social economic status; PP = psychopathology

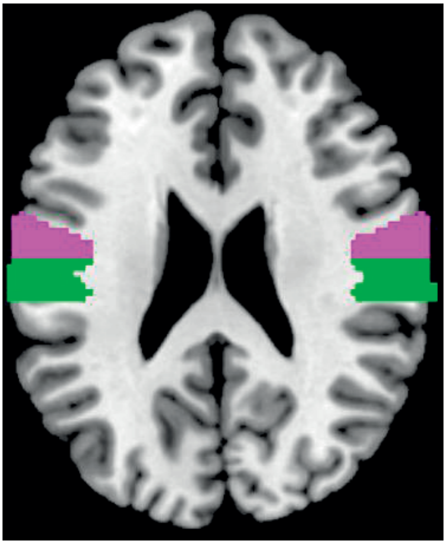

Figure S1. ROI masks of exploratory ROIs.
Purple: anatomical precentral gyrus ROI mask; Green: anatomical postcentral gyrus ROI mask.