

SUPPLEMENTAL INFORMATION

Heightened neural reactivity to threat in child victims of family violence

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Supplemental Experimental Procedures

Participants

Two groups of children were recruited from the London area (see Supplemental Table S1 for characteristics of the two groups). Children with documented exposure to physical abuse and/or intimate-partner violence [Family Violence group, n=20] were recruited via Islington Social Services (SS) in London following a two-phase strategy. First, the research team met with each SS team who identified potential families in their caseload. Prior to contacting a family (or a foster family for those children not living with their biological parents), a research assistant met individually with the social worker to discuss the suitability of the case for inclusion in the study. SS only put forward cases who: i. did not have a diagnosis of learning disability; ii. were judged as competent to consent; iii were in a stable foster or care placement (a minimum of 6 months) for those children not living with their biological parents.

In a second phase, the allocated social worker contacted the family or foster family to introduce them to the research. Interested families and foster families were then contacted by a research assistant and a home visit was arranged to describe to the child and the parents the study in more details, answer any outstanding questions, and to seek consent. For children living with their biological parents assent was obtained from the child and consent was obtained from at least one parent. Where there was shared parental responsibility, consent was obtained from both parties (i.e. from the child's biological parent if still contactable and from SS).

Comparison children (n=23) matched on age, self-reported Tanner stage, gender, handedness, IQ and ethnicity (Supplemental Table S1) were recruited from

secondary/primary schools and via advertisement in local newspapers and on the Internet. Inclusion criteria for the Comparison group included: i. no history of abuse, neglect, and/or exposure to domestic violence as reported by the main carer on the Child Bad Experience Questionnaire [S1] and the Dunedin Abuse Scales [S2], ii. no previous or ongoing contact with SS in respect of the child's quality of care or maltreatment. Consent was obtained from the child and their parent(s).

All participants completed a comprehensive battery of psychological measures (see Measures section below and Supplementary Table S1); the groups did not differ statistically on any measure. There was a non-significant trend for increased post-traumatic stress disorder symptomatology in the Family Violence group, but this was well below the clinical cut off (i.e., 65). None of the participants reported a history of head trauma, neurological disease, or contraindications for MRI. The study was approved by University College London Ethics Committee (0895/002).

Measures

Maltreatment history: SS case files for the Family Violence group were independently rated by the child's social worker in relation to neglect ($n = 14$; mean score = 2.20, s.d. = 1.40), sexual ($n = 5$; mean score = 0.55, s.d. = 1.23), physical ($n = 9$; mean score = 0.65, s.d. = 0.81) and emotional abuse ($n = 18$; mean score = 2.83, s.d. = 1.04) on Kaufman's four-point scale [S3]. Of those emotionally abused, 16 had witnessed intimate-partner violence. Eight cases were double-rated by a senior social work professional (intra-class coefficient correlations ranged from .67 [good] to 1 [complete agreement]). Using the same files, the child's social worker rated the presence or absence of harsh physical parental discipline, defined as the use of harsh corporal punishment to discipline the child for at least 3 years on a monthly basis with occasional use of an object; 11 children had been routinely disciplined in this way.

Violence exposure composite score: A 4-point dimensional violence composite score was created to index each child's possible exposure to different forms of family violence (harsh physical discipline, intimate partner violence and physical abuse). One point was awarded for exposure to each of: i. intimate partner violence; ii. harsh physical parental discipline; iii. physical abuse. An additional point was added if file

evidence indicated physical abuse occurred throughout the child's life. The Family Violence group had a mean composite score of 1.95 (s.d. =1.02, range = 1-4).

Child Bad Experience Questionnaire: Main carers for the Family Violence and the Comparison groups were administered the standardized clinical interview protocol from the Multi-Site Development Project [S1, S4] and recently used in large scale study investigating the impact of childhood trauma among British children [S5]. The interview included standardized probe questions on bullying, accidents, harsh discipline, physical, and sexual abuse.

Domestic violence: To screen for exposure to domestic violence in the Comparison group, the Physical Abuse scale from the Dunedin Abuse Scales [S2] was used to assess specific abusive behaviors from one intimate partner to the other. Respondents answered questions first about their behavior toward their current or most recent partner and second about the partner's behavior toward them. The measure yields separate scores for perpetration and victimization, for both male and female study members. The Physical Abuse scale contains all nine items of Straus's Conflict Tactics Scales [S6] (e.g., slap, choke, beat up), plus four items describing other physically abusive acts (e.g., twisting arm, bodily throw).

Cognitive ability: The Vocabulary and Matrix Reasoning subscales of the Wechsler Abbreviated Scales of Intelligence [S7] were used to provide an estimate of performance and verbal IQ as well as of Full Scale Intelligence Quotient.

Anxiety: The self-report State-Trait Anxiety Inventory for Children [S8] was used to assess state and trait anxiety. This measure consists of two separate 20-item scales, each rated on a 3-point scale (0=hardly ever, 1=sometimes, 2=often).

Depression: The Mood and Feelings Questionnaire [S9] is a 33-item self-report measure that assesses core depressive symptoms in children, with each item rated on a 3-point scale (0=not true, 1=sometimes, 2=true).

Post-traumatic stress symptomatology: The Trauma Symptom Checklist for Children – A [S10], a 44-item self-report measure, was used to assess acute and chronic

posttraumatic symptomatology and other symptom clusters. It includes two validity scales (Underresponse and Hyperresponse), four clinical scales (Anger, Anxiety, Depression, and Post-traumatic stress), and two dissociations scales (Fantasy and Overt Dissociation). Each item is rated on 4-point scale (0=never, 1=sometimes, 2=lots of times, 3=almost all of the time).

Experimental paradigm

Participants viewed blocks including angry, sad and neutral faces in pseudorandom order and, to ensure that they were attending to the stimuli, were required to indicate the gender of the target using a button-box response. The faces were derived from the *Pictures of Facial Affect* [S11], but cropped to remove hair (Figure 1A). Angry and sad faces were displayed at 100% emotional intensity, while neutral faces were morphed to a 25% “happy” intensity in order to avoid appearing threatening [S12]. Each face was presented sequentially for 2250 ms, remaining on-screen for the full 2250 ms even if a response was made before the end of the period. Interstimulus intervals were 750 ms, resulting in a stimulus onset asynchrony of 3000 ms. In each block, responses to six angry, six sad, and six neutral faces were acquired. The epoch length for each block (comprising 2000 ms instructions and eighteen face presentations) was 56 seconds plus a 2000 ms fixation cross presentation at the beginning of each block. Blocks of faces were separated by rest blocks in which no faces were presented but a fixation cross remained in the centre of the screen for 18 seconds. Performance was measured as reaction time and accuracy on the gender discrimination task (percent correct responses). Before entering the scanner room, all participants were trained on the imaging paradigm, but with a different set of identities all displaying neutral faces.

While our focus here is on functional differences between children who have or have not experienced family violence, a related literature has investigated structural differences in maltreated samples, including those who have experienced institutional neglect (Tottenham et al., 2010 [S13]; Mehta et al., 2009 [S14]) and maltreatment related PTSD (see Woon and Hedges, 2008 [S15] for a review).

Image acquisition and analysis

Participants were scanned at the Birkbeck-UCL Neuroimaging Centre using a 1.5 Tesla Siemens (Siemens Medical Systems) Avanto MRI scanner with a 32-channel head coil. Two hundred and five multislice T2*-weighted echo-planar imaging (EPI) volumes with blood oxygen level-dependent contrast were acquired in one run of approximately 7 minutes 30 seconds. The EPI sequence was optimized to reduce BOLD sensitivity losses in the amygdala due to susceptibility artifacts [S16] and the following parameters were used: 27 slices per volume; slice thickness = 2 mm; gap between slices=1 mm, TE=50 ms; TR=85.2 s; slice tilt= -30° (T>C); flip angle= 90° ; field of view=192 mmx192mm²; matrix size=64x64; voxel size=3x3x3 mm. Stimuli were projected centrally onto a screen at the front of the magnet, which participants viewed using a mirror mounted on the head coil ($21 \times 13^{\circ}$ of visual angle of the whole screen).

At the end of the session, a T1 structural scan was acquired (magnetization prepared rapid gradient echo; 176 slices; slice thickness=1 mm; gap between slices=0.5 mm; TR=2730 ms; TE=3.57 ms; field of view=256 mm x 256mm²; matrix size=256 x 256; voxel size=1x1x1 mm resolution). Additionally, field maps were collected in order to remove distortion caused by magnetic field inhomogeneity.

The images were pre-processed and subsequently analyzed using SPM8 (<http://www.fil.ion.ucl.ac.uk/spm/software/spm8/>, Wellcome Department of Imaging Neuroscience, London, UK), implemented in MATLAB 7.5. After discarding the first six functional volumes of each session to allow for T1 equilibrium, EPI images were spatially realigned to the first volume of the session to correct for motion artifacts. These images were also corrected for geometric distortions caused by susceptibility-induced field inhomogeneities. The field maps were processed for each participant using the FieldMap toolbox implemented in SPM8 to produce a voxel displacement map indicating the field distortions. EPI images were then unwarped using the voxel displacement map, normalized into standard anatomical space defined by the Montreal Neurological Institute (MNI) with a resampled voxel size of 3x3x3 mm, and smoothed with an 6 mm full-width at half-maximum Gaussian kernel filter.

After pre-processing, the smoothed, normalized functional imaging data were entered into a voxel-wise subject-specific general linear model (GLM) with four regressors of interest: angry, sad, neutral, and fixation. These four regressors were modelled as boxcar functions convolved with a canonical haemodynamic response function. In addition, to correct for residual effects of head motion, six subject-specific movement parameters (derived from the realignment phase of pre-processing) were included as regressors of no interest in each model. To remove low-frequency drifts, data were high-pass filtered using a set of discrete cosine basis functions with a cutoff period of 128 seconds. The parameter estimates were calculated for all brain voxels using the GLM, and contrast images for 'angry > neutral', 'sad > neutral', and 'angry > sad' were computed in subject-specific fashion. Next, the subject-specific contrast images were entered into separate second-level analyses for each contrast of interest, where group (Family Violence group, Comparison group) served as a between-subjects variable in independent sample t-tests with age and gender as covariates of no interest. The interaction between group and emotion for each contrast were then explored. *A priori* regions of interest (ROIs: amygdala and anterior insula) were anatomically defined using the WFU PickAtlas [S17]. Within each ROI we report results reaching significance at $p < .05$, Family-Wise Error (FWE) corrected. Mean contrast estimates within our ROIs were extracted using the MarsBaR Toolbox [S18] and correlated with the violence exposure composite score in the Family Violence group only using Pearson correlation in SPSS.

Behavioral data analyses

Response times (RTs) and accuracy were recorded and analyzed using 2x3 mixed model ANOVAs to investigate the effects of group (Family Violence vs. Comparison), emotion (angry vs. sad vs. neutral), and the interactions between these two factors. Effect sizes are reported as partial eta-squared (η_p^2 ; small $\geq .01$, medium $\geq .06$, large $\geq .14$) [S19]. Significance was set at $p < 0.05$ (two-tailed).

Supplemental Results

Behavioral data

In terms of errors on the task, a 2 (group: Family Violence versus Comparison) x 4 (emotion: angry, sad, neutral) mixed model ANOVA indicated a main effect of emotion [$F(2,82) = 7.50, p = .001, \eta_p^2 = .16$], a main effect of group [$F(1, 41) = 5.51, p = .02, \eta_p^2 = .12$], but crucially the group by emotion interaction was not significant [$F(2, 82) = 2.25, p = .11, \eta_p^2 = .05$]. Thus, as can be seen in Supplemental Table S2, while the overall accuracy was very high, participants made more errors for sad faces as compared to the angry ($p < .001$) and neutral ($p = .01$) faces and, overall, the maltreated group made more errors, relative to the Comparison group. For RTs, a 2 (group: Family Violence versus Comparison) x 4 (emotion: angry sad, neutral) mixed model ANOVA revealed no main effect of emotion [$F(2,82)=2.22, p = .12, \eta_p^2 = .05$], group [$F(1,41) = .96, p = .33, \eta_p^2 = .02$], or group by emotion interaction [$F(2,82) = .52, p = .60, \eta_p^2 = .01$].

fMRI data with group difference on errors as covariate of no interest

Given the significant group difference on errors on the task (see Behavioral data section above), we ran an additional analysis for the contrast ‘angry > neutral’ with age, gender, and behavioral accuracy on the task as covariates of no interest. This analysis yielded the same results as those reported in the main manuscript:

Compared to our Comparison group, the Family Violence group exhibited greater activation in the right amygdala (36, 2, -23, $z = 2.98, p = .035$, FWE corrected) and in the anterior insula bilaterally (left anterior insula: -39, 8, -2, $z = 3.55, p = .030$, FWE corrected; right anterior insula: 33, 14, 4, $z = 3.84, p = .011$, FWE corrected) when angry faces were contrasted with neutral faces.

fMRI data for the contrast ‘Angry > Sad’

In order to further assess the specificity of the heightened response to angry faces in the Family Violence group within our ROIs, we ran an independent sample t-test on the contrast ‘angry > sad’ where group (Family Violence group, Comparison group) served as a between-subjects variable and age and gender as covariates of no interest. This analysis revealed that, compared to our Comparison group, the Family Violence group exhibited greater activation in the left amygdala (-30, -4, -23, $z = 2.91, p = .041$, FWE corrected) and in the left anterior insula (-39, 5, -14, $z = 3.43, p = .046$, FWE corrected) when angry faces were contrasted with sad faces. These

regions in the right hemisphere showed the same pattern of activity, but did not reach a FWE corrected threshold.

Supplemental References

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Supplemental Table S1. Background characteristics and questionnaire data for comparison children and children exposed to family violence

<i>Background and questionnaire data</i>	<i>Comparison (N = 23)</i>		<i>Family Violence (N = 20)</i>		<i>p-value</i>
	<i>M</i>	<i>s.d.</i>	<i>M</i>	<i>s.d.</i>	
Demographic variables					
Gender, n. of males (%)	11.00 (47.83)		14.00 (70.00)		0.22
Age (in months)	150.83	14.12	144.65	16.89	0.20
Ethnicity, n. of Caucasian (%)	10.00 (43.48)		7.00 (35.00)		0.76
Parental Education ^a	2.70	1.26	1.85	1.21	0.06
Handedness	1 Left, 21 Right, 1 Ambidextrous		1 Left, 16 Right, 3 Unknown		0.21
Wechsler Abbreviated Scale of Intelligence					
Verbal IQ	53.87	7.90	50.80	8.08	0.23
Performance IQ	50.65	8.04	54.05	5.42	0.12
Full IQ	106.13	10.84	104.25	10.33	0.57
Tanner Stage					
n. of pre/early pubertal (%)	8 (34.78)		7 (35.00)		0.99
n. of mid/late pubertal (%)	15 (65.22)		13 (65.00)		0.99
Mood and Feelings Questionnaire ^b					
Total Score	11.74	7.86	11.11	8.92	0.81
Trauma Symptom Checklist for Children ^b					
Underscoring	56.91	14.72	57.74	18.40	0.87
Hyperscoring	47.68	3.88	53.68	14.61	0.07
Anxiety	46.36	11.62	46.79	13.39	0.91
Depression	44.27	9.45	44.95	11.96	0.84
Anger	43.27	7.57	45.84	10.52	0.37
Post-traumatic Stress	43.95	6.18	49.00	11.59	0.08
Dissociation	46.45	6.72	50.84	11.05	0.13
Dissociation (Overt)	47.32	7.45	51.16	11.81	0.21
Dissociation (Fantasy)	46.00	5.63	50.11	8.38	0.07
State/Trait Anxiety Inventory for Children ^b					
Trait	32.39	7.38	32.74	8.25	0.89
State	27.61	4.54	26.12	2.85	0.22
Total	60.00	10.05	59.50	9.51	0.87

^a Highest level of parental education was derived from the mean of the child's biological parent's highest level of education on a scale of 1 to 5 (1=No formal qualifications; 5=Postgraduate Level). These data were available for 13 of the children in the Family Violence group.

^b Child rated

All p-values derived from t-tests with the exception of the gender, ethnicity and Tanner stage comparisons, which used the Fisher's exact test and the handedness comparison, which employed a Chi-square test.

Supplemental Table S2. Performance on the gender recognition task for comparison children and children exposed to family violence

Performance on Gender Recognition Task	<i>Comparison (n = 23)</i>		<i>Family Violence (n = 20)</i>	
	M	s.d.	M	s.d.
Accuracy (% correct)				
Angry condition	98.42	2.76	95.97	6.00
Sad condition	95.03	5.62	94.02	5.20
Neutral condition	98.66	1.86	94.58	3.97
Reaction Time (ms)				
Angry condition	827	152	857	152
Sad condition	793	149	845	150
Neutral condition	814	146	864	166

Supplemental Table S3. Group differences (Family Violence > Comparison) for the contrasts Angry > Neutral and Sad > Neutral, $p < .001$ uncorrected with an extent threshold of 5 voxels

Brain Region	BA	L/R	MNI coordinates			k	Z value	p-value
			x	y	z			
<i>Angry > Neutral</i>								
Middle Frontal Gyrus	9	R	30	20	34	16	3.78	<0.001
Parahippocampal Gyrus	19	R	30	-46	-8	5	3.48	<0.001
Inferior Frontal Gyrus	44	L	-48	-1	19	10	3.46	<0.001
Superior Temporal Gyrus	22	L	-51	5	4	18	3.27	0.001
<i>Sad > Neutral</i>								
Inferior Frontal Gyrus	9	R	48	2	28	10	3.92	<0.001

Note: BA – Brodmann Area; L/R – left/right; MNI – Montreal Neurological Institute; k – cluster size

Group difference (Family Violence < Comparison) for the contrasts Angry > Neutral and Sad > Neutral did not produce any significant differences at $p < .001$ uncorrected with an extent threshold of 5 voxels.