

Supplementary Online Content

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eMethods 1. Participant Recruitment

eMethods 2. Maltreatment and Abuse Chronology of Exposure scale (MACE)

eMethods 3. Scan Parameters and Image Preprocessing

eMethods 4. Emotional Face Matching Paradigm

eMethods 5. Sensitive Period Analysis – Random Forest Regression

eMethods 6. Statistical Analysis of pi-fMRI Representational Similarity Results

eResults 1. Sensitive Period Analysis of Amygdala Activation to Emotional > Neutral Faces and Neutral Faces > Shapes

eResults 2. Sensitive Period Analysis of Maltreatment on Representational Geometry

eDiscussion 1. Types of Maltreatment and Amygdala Response

eDiscussion 2. Prepubertal versus Postpubertal Exposure and d' Prime Distance.

eDiscussion 3. Retrospective Assessment of Timing of Exposure to Maltreatment

eTable 1. Main Effects of Amygdala Activation in Emotional Face Matching Task

eTable 2. Important Predictors of Differential Amygdala Activation to Emotional Faces, Neutral Faces, and Shapes

eTable 3. Identification of Important Predictor Variables

eFigure 1. Sensitive Periods

eFigure 2. Prepubertal Exposure and BOLD fMRI

eFigure 3. Graphs for Combined Prepubertal and Postpubertal Exposure

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods 1. Participant Recruitment

Our goal was to recruit a sample of subjects who were medically healthy, right handed, unmedicated and between ages 20-25 years. Exclusion criteria in this study were as follows: current or prior history of neurologic disease, experience of concussion or head trauma resulting in loss of consciousness for more than 5 minutes, exposure to more than 3 unrelated forms of adversity (e.g., natural disaster, motor vehicle accidents, animal attack, near drowning, house fire, mugging, witnessing or experiencing war, gang violence or murder, riot, or assault with a weapon). Subjects were selected according to exposure history and not psychopathology, except that substance abuse or high levels of drugs or alcohol use (more than 15 days per month) were grounds for exclusion. Urine and breathalyzer tests were conducted prior to imaging and assessment to exclude current use. Each subject received \$25 for the completion of online assessments, \$100 per interview and assessment session (typically one 4-hour sessions) and \$100 for a one-hour MRI protocol.

We collected data on race, ethnicity, education, parental education, family income, and perceived financial sufficiency during childhood (1= much less than enough money to meet our needs; 5 = much more than enough money to meet our needs). Perceived financial sufficiency was included as an alternative to family income, given that it is difficult for subjects to be sure of their parents' income, and family income could vary depending on locale, family size, and parental spending habits.

eMethods 2. Maltreatment and Abuse Chronology of Exposure scale (MACE)

The MACE consists of 52 items selected using Item Response Theory. Subjects were required to indicate whether they experienced a given event and check off each year of occurrence. The MACE scale provides ratings on 10 types of maltreatment (i.e., sexual abuse, parental verbal abuse, parental non-verbal emotional abuse, parental physical abuse, witnessing interparental violence, witnessing violence towards siblings, peer emotional bullying, peer physical bullying, emotional neglect and physical neglect) across 18 years of development. Overall MACE scores showed excellent test-retest reliability, and good-to-excellent reliability for measures of exposure from ages 3-18¹. The MACE showed good convergent validity as it correlated 0.738 and 0.698 with childhood trauma questionnaire (CTQ) and Adverse Childhood Experiences scores (ACE). However, based on variance decomposition analysis, MACE accounted for 2.00- and 2.07-fold more of the variance in psychiatric symptom ratings than ACE or CTQ¹, respectively. Moreover, each MACE category fits a Rasch Model meaning that each category provides a 'fundamental measurement' of exposure in which items are measured on at least an interval scale with a common unit^{2,3}. Scales used in psychiatry rarely attained this remarkable property, although we usually treat them as interval or ratio measurements.

eMethods 3. Scan Parameters and Image Preprocessing

During the task, functional data were acquired using T2-weighted echo planar imaging (TR = 3,000 ms, TE = 30 ms, flip angle = 76.1°, 42 slices, 3.5 × 3.5 × 3.5 mm voxel size, 3D matrix 64 × 64 × 141.24 field of view, 208 repetitions). A high-resolution three-dimensional T1-weighted image (TR time = 2,100 ms, TE = 2.25 ms, flip angle = 12°, 1.0 × 1.0 × 1.3 mm voxel size, 3D matrix 256 x 256 x 170 mm field of view, 128 repetitions) was also collected for anatomical reference.

Functional imaging data were preprocessed using FEAT (fMRI Expert Analysis Tool) version 4.1.6, part of FSL (Oxford Centre for Functional MRI of the Brain (FMRIB) Software Library, <http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/>). Pre-processing steps included removing nonbrain structure, slice-time correction, motion correction, registration of the structural images to the mean echo-planar image, transforming to MNI standard space (Montreal Neurological Institute), spatial smoothing using a 5 mm full-width-at-half-maximum Gaussian kernel and mean-based intensity normalization. Subject movement (>3 mm) resulted in exclusion of the data from further analysis.

FreeSurfer version 6^{4,5} was used to calculate left and right amygdala volume from the MPRAGE image.

eMethods 4. Emotional Face Matching Paradigm

The paradigm consisted of three blocks of negative face processing and three blocks of neutral face processing interleaved with seven blocks of sensorimotor control (geometric shapes). Each block contains six trios of perceptual faces or geometric shapes following a brief (2s) instruction statement: "Match Faces", "Match Shapes.". Subjects viewed each trio of faces or shape and were asked to match one of two simultaneously presented images (bottom) with an identical target image (top). In each block lasting 36s, each of the six face or shape trios was presented for 4s with a 2s interstimulus interval. During negative face block, three images of each gender and target affect (angry and fearful) were presented.

eMethods 5. Sensitive Period Analysis – Random Forest Regression

Random forest regression (RFR) predicts outcome by creating a forest of decision trees with each tree generated from a different subset of the data and constrained in the number of predictor it can consider at each decision point⁶. This "wisdom of the crowd" strategy is well suited to the analysis of highly collinear data sets and provides superior predictions than

conventional regression techniques⁷. The tree structure can also model interactions and does not assume a linear relationship between exposure and response. Selection of this analytical approach was based on a large series of Monte-Carlo simulations using actual exposure data and simulated outcomes (predicting 5-10% of the total variance) which showed that RFR with conditional trees most accurately identified the type and timing of maltreatment used to generate the outcomes, and we have used this approach in multiple studies^{8,9}.

Variable importance is assessed by permuting each variable, and determining how much this degrades model fit⁶. Permuting important predictors decreases fit to a large degree whereas permuting unimportant predictors has little impact. We use a variant of Brieman's approach with conditional inference trees¹⁰ that rectifies a problem in the estimation of importance of predictors with many versus few levels or categories¹⁰. To assess the significance of these mean \pm sd importance measures, the same analyses were re-run 2000 times using reshuffled outcome measures to obtain the random chance mean \pm sd importance of each predictor. Probability values comparing random chance versus actual importance measures were determined by Z-test with Bonferroni correction for the number of predictors in the model. We also included covariates for measure of multiplicity, severity and duration of maltreatment across childhood, as well as gender, age, parental education and perceived financial sufficiency during childhood to control for the confounding influence of sociodemographic variables.

Although RFR-CIT provides an excellent means of identifying important predictors in highly collinear data sets it does not provide a direct indication of the nature of the relationship between the predictor and outcome. Hence, we used the saved random forest to predict the outcome by adjusting degree of exposure to the predictor of interest from zero to maximum while holding all other predictors constant at their modal value to ascertain direction of effect as we have done in previous studies^{9,11}. For the representational similarities analyses we used group-wise t-tests to assess the directionality between severity of exposure to the significant predictors and magnitude of amygdala response. These measures were not corrected for multiple comparisons and were only used to indicate the directionality of the effect. The significance of the predictor was determined through permutation testing with Bonferroni correction.

eMethod 6. Statistical Analysis of pi-fMRI Representational Similarity Results.

At the individual subject level, we calculated the minimum spanning ellipses area for each stimulus category as well as the d' value reflecting the discriminability between clusters as defined by the mean Euclidean distance between ellipse centroids divided by the standard deviation derived from the Euclidean distances of each stimulus in a cluster from the category cluster centroid. Sensitive exposure periods were then determined using RFR with conditional inference trees. We assessed the directional effect of exposure by dividing subjects into separate groups who reported positive or negative histories of exposure during each sensitive period and used group values to visualize the effects.

eResults 1. Sensitive Period Analysis of Amygdala Activation to Neutral Faces > Shapes

The only important predictor of response to neutral faces > shapes was peer emotional bullying at age 13. Random forest prediction indicated that exposure to peer emotional bullying at age was associated with increased activation (eTable 2).

eResults 2. Sensitive Period Analysis of Maltreatment on Representational Geometry

The important predictors of ellipse area for neutral faces were parental physical abuse at age 4, parental non-verbal emotional abuse at 12-15 and emotional neglect at 15 (eFigure. 1). The most important predictor of d' Euclidean distance between emotional faces and shapes was parental non-verbal emotional abuse at age 12; other important predictors were parental non-verbal emotional abuse at 13, witnessing violence towards siblings at 14, peer physical bullying at 17 and sexual abuse at 17 (eFigure. 1). The important predictors of d' Euclidean distance between neutral faces and shapes were physical neglect at age 5, peer emotional bullying at 5, peer physical bullying at 9 and 11, parental non-verbal emotional abuse at 12, parental verbal abuse at 14-15, and parental physical abuse at 16-17 (eFigure. 1).

As seen in eTable 3, subjects with exposure to parental non-verbal emotional abuse (ages 12-15) and emotional neglect at age 15 had smaller ellipse area of neutral faces are relative to participants reporting no exposure at these ages. In contrast, subjects reporting high exposure to parental physical abuse at age 4 had larger emotional ellipse area than subjects reporting no exposure.

The effects of maltreatment on d' Euclidean distance for neutral faces and shapes also varied with age. The d' Euclidean distance between neutral faces and shapes was increased in participants with exposure to parental verbal abuse (ages 14-15), parental physical abuse at age 16 and peer physical abuse at 11. In contrast, high exposure to physical neglect (age 5), peer emotional bullying (age 5), peer physical abuse at age 9, and parental non-verbal emotional abuse (age 12) was associated with decreased d' between neutral faces and shapes. Further details are included in eTable 3.

In addition, high exposure to parental non-verbal emotional abuse (ages 12-13) and peer physical abuse (age 17) decreased the d' Euclidean distance between emotional faces and shapes.

eDiscussion 1. Types of maltreatment and amygdala response.

The present study is unique in that we were able to assess the contribution of exposure to ten types of maltreatment using a sophisticated analytical approach that effectively takes into account the collinearity between exposure types. We found that parental physical maltreatment and peer emotional abuse were the most important predictors of amygdala response to emotional faces versus shapes in this study. However, non-verbal emotional abuse, peer physical abuse and parental verbal abuse were also significant predictors of amygdala activation, and physical neglect and emotional neglect were significant predictors of d' prime discriminability between voxel-wise response to emotional faces versus neutral faces. Hence, amygdala response in early adulthood appears to be affected by a wide range of adverse experiences during childhood. A key contribution of this paper is the novel identification of peer emotional and physical bullying as important predictors.

A few earlier studies have looked at the relative importance of different types of exposure. For example, Dannowski et al¹² reported that the strongest predictor of amygdala response to threat was emotional abuse followed in order by emotional neglect, physical abuse, physical neglect and sexual abuse. Grant et al¹³, in contrast, reported that physical abuse was the strongest predictor, with other types of maltreatment falling to meet criteria for statistical significance. Unfortunately, the Childhood Trauma Questionnaire (CTQ) does not provide any information on exposure to peer victimization, which was the most important predictor in the present study. It's interesting in this context that Banny and Chicchetti¹⁴ reported that peer victimization was the most important determinant of risk for depression in a prospective study of youths and that earlier exposure to maltreatment emerged as a risk factor for depression only because it increased the likelihood of experiencing peer victimization. We need to keep in mind the possibility that certain forms of maltreatment may appear to be predictors of amygdala response using the CTQ, but this may be an indirect consequence of abuse and neglect increasing risk for peer victimization at a later date.

A number of papers have focused on the relationship between emotional neglect and amygdala response to threat. However, this may warrant further investigation. Maheu et al¹⁵ and Tottenham et al¹⁶ published important studies showing increased amygdala response to threat in primarily internationally adopted youths who experienced caregiver deprivation and emotional neglect. Subsequent studies have, perhaps too hastily, chosen to focus specifically on emotional neglect in non-adopted samples based on these initial reports^{17,18}. However, emotional neglect is almost certainly not the only factor that distinguishes internationally adopted youth from neglectful orphanages from typically developing controls (TDCs). Adopted youths may well have experienced more corporal punishment or physical maltreatment than TDCs¹⁹⁻²¹ and they are also likely to experience, post adoption, higher rates of peer victimization^{22,23}. Hence, without more detailed exposure data it is difficult to not know whether emotional neglect was actually the key determinant in these studies. Future studies should provide a more comprehensive assessment of childhood and adolescent experiences including peer victimization.

eDiscussion 2. Prepubertal versus postpubertal exposure and d' prime distance.

Interestingly, early exposure to peer emotional bullying and physical neglect were associated with greater d' prime distance between emotional and neutral faces, indicative of better discrimination. Conversely, peer emotional bullying at age 13 and NVEA at age 14 were associated with decreased distance indicating more overlapping patterns of response to emotional and neutral faces. We found in a separate analysis that there was an inverse correlation between emotional-neutral d' prime in the right amygdala and symptoms of anger-hostility. Hence, neurobiological effects of prepubertal versus postpubertal exposure on the relationship between amygdala function and anger-hostility may also serve adaptive purposes by diminishing potentially problematic symptoms of anger-hostility in early childhood but enhancing these symptoms in individuals with postpubertal or combined prepubertal and postpubertal exposure.

eDiscussion 3. Retrospective assessment of timing of exposure to maltreatment.

Concerns about the veracity of self-report of maltreatment stem largely from the recovered memory debate²⁴⁻²⁶, which does not deny that abuse occurs but disputes the capacity of individuals to fully repress then recover seminal memories as they should be profound and enduring. Unfortunately, many have misinterpreted this debate to conclude that retrospective recall of these critically important events is unreliable. The opposite is true as self-report rating of maltreatment have some of the highest test-retest reliability ratings in psychiatry / clinical psychology (e.g., Childhood Trauma Questionnaire, $r = 0.88$ ²⁷; Childhood Abuse and Trauma Scale, $r = 0.89$ ²⁸; MACE, $r = 0.91$ ¹), which makes sense given the potential indelibility of these memories. Further, the MACE meets Bland-Altman criteria for reproducibility^{29,30} meaning that not only are retest scores highly correlated with test scores but are essentially indistinguishable. Moreover, they do not show a significant negative attribution bias⁸.

The MACE, however, also provides information on timing of exposure that other scales do not, and a key concern is whether the MACE can disentangle timing of exposure. In the original article on the scale's development we addressed this first by showing that subjects were nuanced in their temporal ratings and that with few exceptions (e.g., witnessing of

intraparental violence and witnessing of violence toward siblings) that each type of adversity had its own unique time course that differed significantly from time course of exposure to any other type of maltreatment¹.

Second, participants were not only very consistent in reporting their overall degree of exposure but were also very consistent in reporting their time course of exposure to each type of maltreatment (average within subject test-retest reliability range .722–.994). Interestingly, the highest test-retest reliabilities for time course are for types of maltreatment that are usually episodic and perhaps most ingrained as specific events (e.g., sexual abuse $r=.994$; peer physical abuse $r=.954$; peer verbal abuse $r=.884$; parental physical abuse $r=.803$), they were also quite high for physical neglect ($r=.859$), but lowest for parental verbal abuse ($r=.722$). Hence, participants are clearly disentangling type of exposure as reflected in their unique time courses and are also reliable in reiterating these time frames.

This then leads to the question of validity. First, these retrospective chronology patterns obtained using the MACE correspond to temporal patterns observed during development for physical³¹ and sexual³² abuse as well as peer physical and emotional bullying³³, and match reported gender differences. The biggest concern however, is how accurate can self-report be for events taking place in early childhood. We have previously reported that rating of abuse, in the aggregate, had acceptable test-retest reliability from age 3 on³⁴. More specifically, ratings of sexual abuse had high test-retest reliability from age 2 on. The remaining forms of abuse were reliable from age 3 on, whereas peer emotional and peer physical bullying were reliable from age 5 on (which was the earliest age that these events were reported to occur in our test-retest sample). This fits with the observation that age of onset for adult memories of childhood typically occurs between 2 and 4 years of age and are earlier for salient events so that hospitalizations and birth of a sibling can be accurately recalled if they took place at age 2 and moving homes at age 3³⁵.

Ratings of neglect were reliable from age 1 on⁹. Severity of exposure to physical neglect was determined by response to questions regarding availability of family members to take care of you and protect you, to take you to the doctor when needed, if there was enough to eat, whether you had to wear dirty clothes, and whether people in the family looked out for each other¹. Emotional neglect was indicated by parental unavailability and absence of family members who made you feel loved, special or important¹. Hence, subjects made inferences about what they believed their family was like for ages they were too young to remember.

We have one data set available that we were able to use to provide some gauge of the accuracy of these early impressions. MACE data were collected on 18 adult subjects (29.3 ± 0.5 years) who were assessed at 18 months of age using the Strange Intruder Paradigm by Karlen Lyons-Ruth, scored with the AMBIENCE system, which provides some of the most definitive data obtainable on quality of early attachment. We used this data to study the association between attachment and amygdala volume 27 years later³⁶. We found in this data set that there was a significant predicted positive association between maternal-infant communication errors at 18 months and ratings of emotional neglect (but not physical neglect, or other forms of maltreatment) at ages 1-5, with peak correlations at ages 1-3 (see Figure 2 below). These data provide support that early neglect ratings are not only reliable but correlate with objective assessments obtained at that early age.

In using this scale to identify sensitive periods we have also found additional sources of validation. For example, we recently found that hair cortisol levels were most importantly predicted by degree of exposure to neglect at 2-3 years of age in a transdiagnostic sample ($N=258$), peaking at age 3. This fits with the longitudinal observation that neglected Romania orphans developed a blunted cortisol response unless they were placed in high quality foster care before 24-months of age³⁷. Both studies are indicative of a very early sensitive period. Similarly, we reported that fractional anisotropy in the inferior longitudinal fasciculus was predicted by witnessing domestic violence between ages 7 – 13, which corresponds to peak period of myelination of this fiber tract³⁸.

Finally, the Avon Longitudinal Study, in which a birth cohort ($N=494$) was prospectively assessed for exposure to childhood adversity at 8, 21, 33, 47, 61 and 73 months of age and then neuroimaging at 18-21 years of age³⁹, provided another opportunity to evaluate the ability of retrospective recall of early maltreatment on the MACE to identify early sensitive periods. Briefly, they found in the Avon Longitudinal Study that out of 30 *a priori* regions measured that the right caudal anterior cingulate and the right precuneus were the only regions that show a significant relationship with degree of exposure to early adversity during the first 6 years (sum of all ratings)³⁹. We found using random forest regression with conditional inference trees that that the most important predictor of right caudal anterior cingulate volume was physical maltreatment at age 5 while the most important predictor of right precuneus volume was witnessing interparental violence at age 5, physical maltreatment at ages 6 and 7 and peer physical bullying at age 13. In contrast, left caudal anterior cingulate was not significantly predicted by type and timing of maltreatment and left precuneus was most importantly predicted by peer emotional abuse at age 12. Hence, this fits with their finding of right sided sensitivity of these structures to adversity between 8 and 73 months but not left sides. We also confirmed lack of sensitivity to early adversity in the next four regions reported in the Avon Longitudinal Study list. In our data set these regions either had sensitive periods after age 6 (i.e., left frontopolar cortex, right ventromedial prefrontal cortex) or were not significantly predicted by type and timing (right and left mid-

dorsolateral prefrontal cortex). In short, these MACE measures are highly reliable and multiple lines of evidence suggest they are valid.

eTable 1. Main Effects of Amygdala Activation in Emotional Face Matching Task

Contrast	Side	Coordinates(M NI)	Number of voxels (k)	Peak voxel (t)
Emotional faces > Shapes	Right	20, -2, -10	135	25.94
	Left	-20, -6, -14	121	26.32
Neutral faces > Shapes	Right	20, -2, -16	122	8.98
	Left	-20, -8, -12	87	8.29
Emotional faces > Neutral faces	Right	20, -2, -16	135	16.92
	Left	-18, -4, -14	121	16.18

N=202; Estimates were extracted from activated clusters within bilateral amygdala ROI, anatomically defined using AAL Atlas. These activated clusters survive Family-Wise Error procedures for multiple correction ($p < .05$ across the entire brain)

eTable 2. Important Predictors of Differential Amygdala Activation to Emotional Faces, Neutral Faces and Shapes

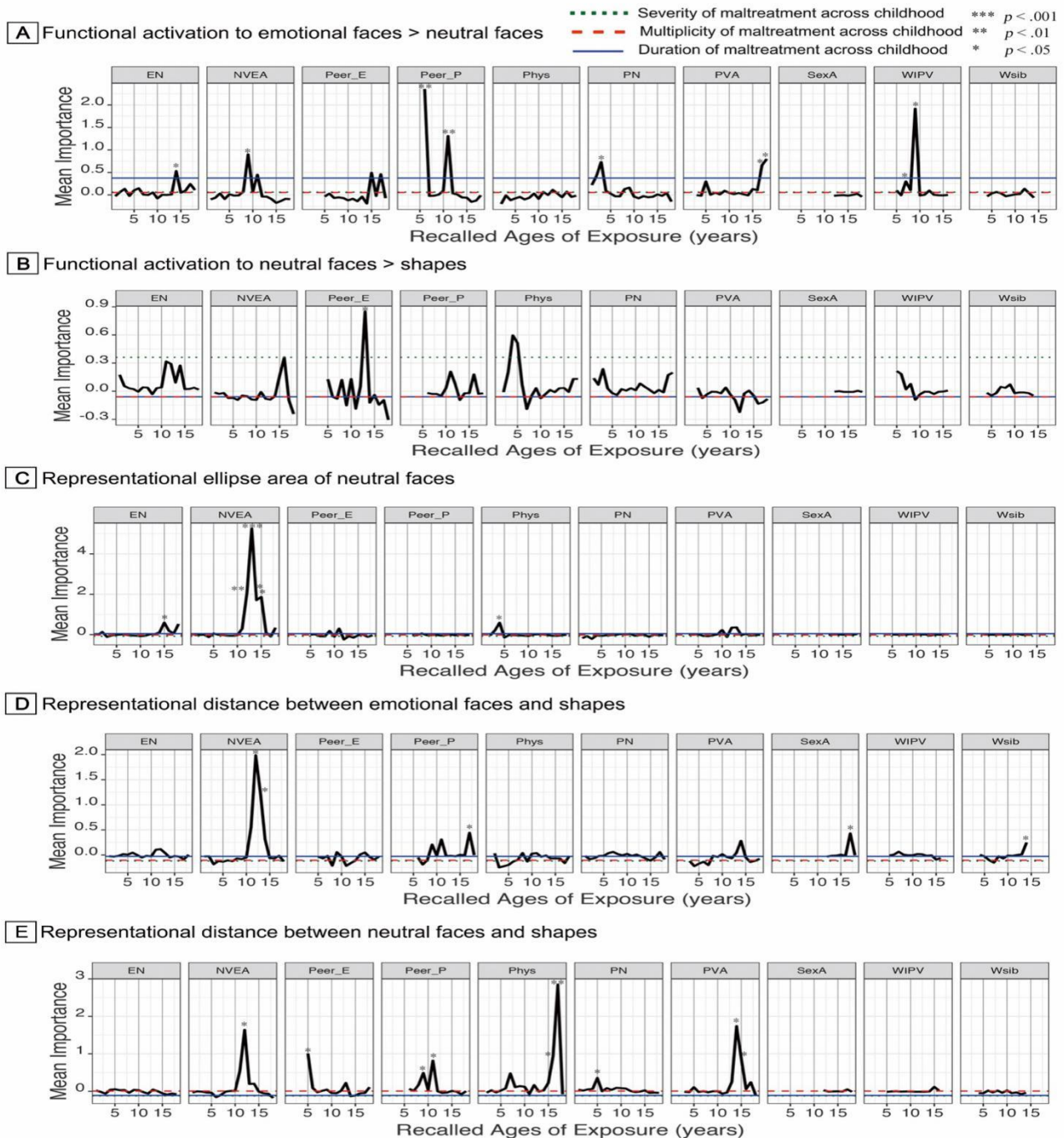
Type	Predictors	Random Forest Regression		Response Prediction
		Importance	<i>p</i> Value	Direction
Emotional faces > Shapes	Peer_E age 15	1.83	0.006	↑
	Phys age 4	1.27	0.023	↓
	Peer_E age 13	1.07	0.031	↑
	PVA age 17	0.90	0.021	↑
	Peer_P age 6	0.76	0.012	↓
	Phys age 3	0.74	0.046	↓
	NVEA age 9	0.73	0.033	↓
Emotional faces > Neutral faces	PVA age 17	0.66	0.039	↑
	PVA age 18	0.80	0.034	↑
	NVEA age 9	0.90	0.024	↓
	WIPV age 7	0.30	0.043	↓
	WIPV age 9	1.92	0.002	↓
	Peer_P age 6	2.36	0.001	↓
	Peer_P age 11	1.31	0.009	↑
	EN age 14	0.53	0.036	↑
	PN age 3	0.73	0.017	↓
Neutral faces > shapes	Peer_E age 13	0.85	0.038	↑

Abbreviations: EN, Emotional Neglect; NVEA, Parental Non-verbal Emotional Abuse; Peer_E, Peer Emotional Bullying; Peer_P, Peer Physical Bullying; Phys, Parental Physical Abuse; PN, Physical Neglect; PVA, Parental Verbal Abuse; SexA, Sexual Abuse; WIPV, Witnessing Interparental Violence.

eTable 3. Identification of Important Predictor Variables. Predictors identified using random forest regression with conditional inference trees followed by comparison between participants with exposure to the predictor versus participants without exposure.

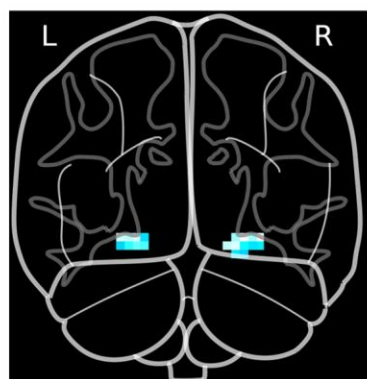
Representational type	Maltreatment type	Random Forest Regression		Two Group t Test				
		Importance	P value	Unexposed		Exposed		P value
				NO. of Subject	Mean (SD)	NO. of Subject	Mean (SD)	
Ellipse area of emotional faces	NVEA age 12	2.03	0.006	79	0.64 (0.37)	123	0.21 (0.13)	<.001
	NVEA age 13	5.94	<0.001	73	0.91 (0.59)	129	0.25 (0.15)	<.001
	Phys age 4	2.68	0.001	136	0.29 (0.18)	66	1.41 (1.05)	<.001
	EN age 10	0.54	0.044	100	0.37 (0.16)	102	0.37 (0.39)	.999
	EN age 15	0.41	0.049	91	0.70 (0.45)	111	0.22 (0.12)	<.001
	EN age 18	1.49	0.009	91	0.52 (0.29)	111	0.22 (0.12)	<.001
Ellipse area of Neutral faces	NVEA age 12	2.06	0.005	79	0.79 (0.42)	123	0.33 (0.17)	<.001
	NVEA age 13	5.26	<0.001	73	1.03 (0.63)	129	0.41 (0.21)	<.001
	NVEA age 14	1.71	0.017	69	0.81 (0.44)	133	0.48 (0.21)	<.001
	NVEA age 15	1.87	0.011	64	1.09 (0.72)	138	0.48 (0.28)	<.001
	EN age 15	0.59	0.048	91	0.78 (0.53)	111	0.28 (0.16)	<.001
	Phys age 4	0.59	0.046	136	0.31 (0.21)	66	1.52 (0.75)	<.001
The distance between Emotional and neutral faces	NVEA age 14	1.28	0.011	69	1.47 (1.02)	133	1.28 (0.58)	.011
	Peer_E age 5*	0.49	0.038	179	0.98 (0.71)	23	0.75 (0.64)	.024
	Peer_E age 6	3.35	0.001	159	1.10 (0.77)	43	1.89 (0.75)	<.001
	Peer_E age 8	1.27	0.023	122	1.16 (0.88)	80	1.67 (0.81)	<.001
	Peer_E age 9	1.21	0.020	107	0.72 (0.48)	95	2.78 (0.90)	<.001
	Peer_E age 13	1.39	0.016	89	1.94 (0.77)	113	0.80 (0.39)	<.001
	EN age 16	1.18	0.009	89	1.70 (1.08)	113	1.63 (0.94)	.448
	EN age 18*	0.70	0.038	91	1.17 (0.93)	111	2.33 (0.94)	<.001
	PN age 1	0.94	0.024	127	0.86 (0.55)	75	3.29 (1.52)	<.001
	PN age 2	3.09	0.003	127	0.82 (0.64)	75	3.06 (1.27)	<.001
	PN age 3	1.76	0.002	136	0.72 (0.48)	66	2.78 (0.90)	<.001
The distance between emotional faces and shapes	SexA age 17	0.43	0.026	187	1.59 (1.99)	15	2.12 (2.88)	.119
	NVEA age 12	1.99	0.015	79	2.46 (2.57)	123	4.44 (2.15)	<.001
	NVEA age 13	1.25	0.028	73	2.21 (2.44)	129	4.21 (2.31)	<.001
	WSib age 14	0.25	0.017	192	1.27 (0.91)	10	2.10 (1.66)	<.001
	Peer_P age 17	0.44	0.018	188	1.88 (1.98)	14	1.74 (1.49)	.984
	The distance between neutral faces and shapes	PVA age 14	1.74	0.012	111	1.78 (1.03)	91	4.73 (3.02)
PVA age 15		0.88	0.026	112	2.12 (1.99)	90	3.50 (2.38)	<.001
NVEA age 12*		1.64	0.014	79	3.30 (2.34)	123	2.85 (2.21)	.030
Phys age 16		0.94	0.008	167	1.85 (1.20)	35	3.06 (1.38)	<.001
Phys age 17		2.85	0.001	172	1.58 (2.14)	30	2.59 (1.35)	<.001
Peer_E age 5		1.01	0.021	179	2.09 (2.43)	23	0.95 (0.84)	<.001
Peer_P age 9		0.49	0.034	184	1.79 (1.26)	18	0.37 (0.38)	<.001
Peer_P age 11		0.82	0.022	174	1.29 (1.03)	28	1.98 (1.02)	<.001
PN age 5	0.36	0.045	145	2.48 (1.48)	57	1.78 (1.14)	<.001	

Abbreviations: EN, Emotional Neglect; NVEA, Parental Non-verbal Emotional Abuse; Peer_E, Peer Emotional Bullying; Peer_P, Peer Physical Bullying; Phys, Parental Physical Abuse; PN, Physical Neglect; PVA, Parental Verbal Abuse; SexA, Sexual Abuse; WSib, Witnessing Violence toward Siblings.
 * These significant predictors produced group differences in the opposite direction of the expected prepubertal / postpubertal contrast. However, they showed the expected directionality based on random forest prediction.

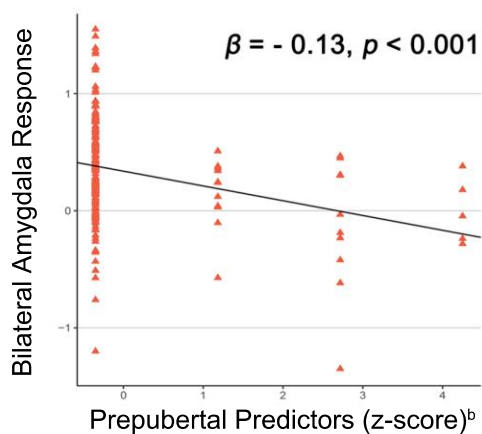


eFigure 1. Sensitive Periods. Random forest regression with conditional trees indicating the importance of ten types of childhood maltreatment across ages on bilateral amygdala function during emotional face matching task.

Abbreviations: EN, Emotional Neglect; NVEA, Parental Non-verbal Emotional Abuse; Peer_E, Peer Emotional Bullying; Peer_P, Peer Physical Bullying; Phys, Parental Physical Abuse; PN, Physical Neglect; PVA, Parental Verbal Abuse; SexA, Sexual Abuse; WIPV, Witnessing Interparental Violence; Wsib, Witnessing Violence toward Siblings.



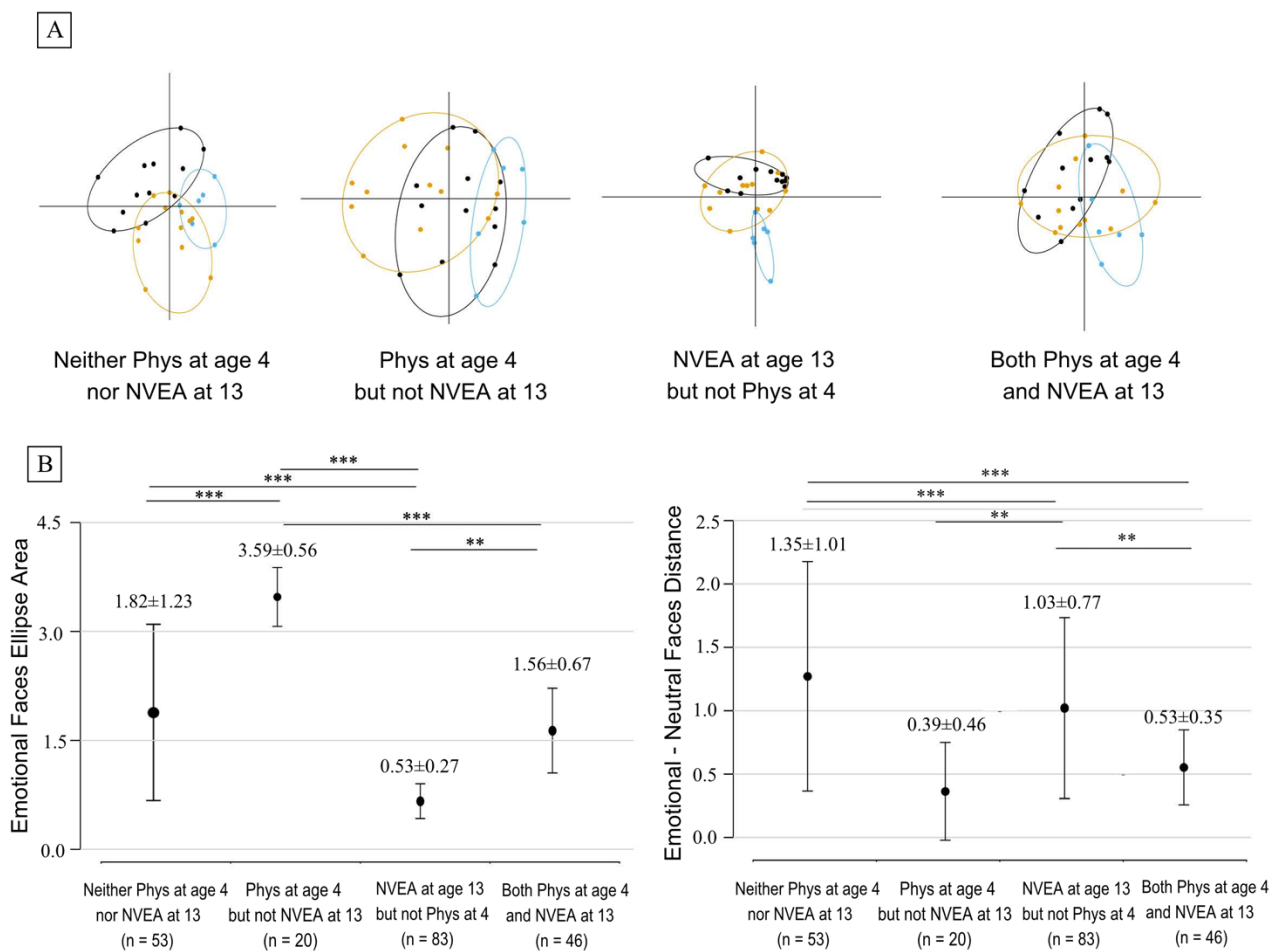
Hypoactive clusters^a



eFigure 2. Prepubertal Exposure and BOLD fMRI. Relationship between severity of exposure to prepubertal response predictors and bilateral amygdala activity to emotional faces > neutral faces

^a All clusters in the glass brain are corrected for false display rate across bilateral amygdala ROI ($p < .05$).

^b Severity of prepubertal predictors is the sum of peer physical abuse at age 6 and witnessing interparental violence at age 9.



eFigure 3. Graphs for Combined Prepubertal and Postpubertal Exposure

A, Representaionl geometry for subjects exposed to parental physical abuse (Phys) at age 4 or parental non-verbal abuse (NVEA) at 13. X and Y axis are scaled the same for all graphs and range from: X -1.74 to 1.35 and Y: -1.72 to 1.45.

B, Group comparison for the means and standard deviations of emotional faces ellipse area and emotional-neutral faces d' distance.

** $p < .01$, *** $p < .001$

References

1. Teicher MH, Parigger A. The 'Maltreatment and Abuse Chronology of Exposure' (MACE) Scale for the Retrospective Assessment of Abuse and Neglect During Development. *PLoS One*. 2015;10(2):e0117423.
2. Brogden HE. The Rasch model, the law of comparative judgement and additive conjoint measurement. *Psychometrika*. 1977;42:631-634.
3. Bond T, Fox CM. *Applying the Rasch Model: Fundamental Measurement in the Human Sciences*. 2 ed. Mahwah, NJ: Lawrence Erlbaum; 2007.
4. Dale AM, Fischl B, Sereno MI. Cortical surface-based analysis: I. Segmentation and surface reconstruction. *Neuroimage*. 1999;9(2):179-194.
5. Fischl B, Salat DH, Van Der Kouwe AJ, et al. Sequence-independent segmentation of magnetic resonance images. *Neuroimage*. 2004;23:S69-S84.
6. Breiman L. Random Forests. *Machine Learning*. 2001;45:5-32.
7. Liaw A, Wiener M. Classification and Regression by randomForest. *R News*. 2002;2/3:18-22.
8. Khan A, McCormack HC, Bolger EA, et al. Childhood Maltreatment, Depression, and Suicidal Ideation: Critical Importance of Parental and Peer Emotional Abuse during Developmental Sensitive Periods in Males and Females. *Front Psychiatry*. 2015;6:42.
9. Teicher MH, Anderson CM, Ohashi K, et al. Differential effects of childhood neglect and abuse during sensitive exposure periods on male and female hippocampus. *Neuroimage*. 2018;169:443-452.
10. Strobl C, Boulesteix AL, Zeileis A, Hothorn T. Bias in random forest variable importance measures: illustrations, sources and a solution. *BMC Bioinformatics*. 2007;8:25.
11. Pechtel P, Lyons-Ruth K, Anderson CM, Teicher MH. Sensitive periods of amygdala development: the role of maltreatment in preadolescence. *Neuroimage*. 2014;97:236-244.
12. Dannlowski U, Stuhrmann A, Beutelmann V, et al. Limbic scars: long-term consequences of childhood maltreatment revealed by functional and structural magnetic resonance imaging. *Biol Psychiatry*. 2012;71(4):286-293.
13. Grant MM, Cannistraci C, Hollon SD, Gore J, Shelton R. Childhood trauma history differentiates amygdala response to sad faces within MDD. *J Psychiatr Res*. 2011;45(7):886-895.
14. Banny AM, Cicchetti D, Rogosch FA, Oshri A, Crick NR. Vulnerability to depression: a moderated mediation model of the roles of child maltreatment, peer victimization, and serotonin transporter linked polymorphic region genetic variation among children from low socioeconomic status backgrounds. *Dev Psychopathol*. 2013;25(3):599-614.
15. Maheu FS, Dozier M, Guyer AE, et al. A preliminary study of medial temporal lobe function in youths with a history of caregiver deprivation and emotional neglect. *Cogn Affect Behav Neurosci*. 2010;10(1):34-49.
16. Tottenham N, Hare TA, Millner A, Gilhooly T, Zevin JD, Casey BJ. Elevated amygdala response to faces following early deprivation. *Dev Sci*. 2011;14(2):190-204.
17. Bogdan R, Williamson DE, Hariri AR. Mineralocorticoid receptor Iso/Val (rs5522) genotype moderates the association between previous childhood emotional neglect and amygdala reactivity. *Am J Psychiatry*. 2012;169(5):515-522.
18. White MG, Bogdan R, Fisher PM, Munoz KE, Williamson DE, Hariri AR. FKBP5 and emotional neglect interact to predict individual differences in amygdala reactivity. *Genes Brain Behav*. 2012;11(7):869-878.

19. Guru Rajan D, Shirey K, Ostermann J, Whetten R, O'Donnell K, Whetten K. Child and Caregiver Concordance of Potentially Traumatic Events Experienced by Orphaned and Abandoned Children. *Vulnerable Child Youth Stud.* 2014;9(3):220-233.
20. Gray CL, Pence BW, Ostermann J, et al. Gender (in) differences in prevalence and incidence of traumatic experiences among orphaned and separated children living in five low- and middle-income countries. *Glob Ment Health (Camb).* 2015;2.
21. Gray CL, Pence BW, Ostermann J, et al. Prevalence and Incidence of Traumatic Experiences Among Orphans in Institutional and Family-Based Settings in 5 Low- and Middle-Income Countries: A Longitudinal Study. *Glob Health Sci Pract.* 2015;3(3):395-404.
22. Raaska H, Lapinleimu H, Sinkkonen J, et al. Experiences of school bullying among internationally adopted children: results from the Finnish Adoption (FINADO) Study. *Child psychiatry and human development.* 2012;43(4):592-611.
23. Pitula CE, Thomas KM, Armstrong JM, Essex MJ, Crick NR, Gunnar MR. Peer victimization and internalizing symptoms among post-institutionalized, internationally adopted youth. *J Abnorm Child Psychol.* 2014;42(7):1069-1076.
24. Berger JM. False memory syndrome and therapist liability to third parties for emotional distress injuries arising from recovered memory therapy: a general prohibition on liability and a limited liability exception. *Spec Law Dig Health Care Law.* 2002(275):9-41.
25. Brown LS. The recovered memory/false memory debate. Comment. *Conscious Cogn.* 1995;4(1):130-132.
26. Porter S, Yuille JC, Lehman DR. The nature of real, implanted, and fabricated memories for emotional childhood events: implications for the recovered memory debate. *Law Hum Behav.* 1999;23(5):517-537.
27. Bernstein DP, Fink L. *Childhood Trauma Questionnaire Manual.* San Antonio, TX: The Psychological Corporation; 1998.
28. Sanders B, Becker-Lausen E. The measurement of psychological maltreatment: early data on the Child Abuse and Trauma Scale. *Child Abuse Negl.* 1995;19(3):315-323.
29. Bland JM, Altman DG. Agreement between methods of measurement with multiple observations per individual. *J Biopharm Stat.* 2007;17(4):571-582.
30. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet.* 1986;1(8476):307-310.
31. Straus MA, Hamby SL. Measuring physical and psychological maltreatment of children with the Conflict Tactics Scales. In: Kantor K et al., ed. *Out of the darkness: contemporary perspectives on family violence.* Thousand Oaks, CA: Sage; 1997:119–135.
32. Finkelhor D. Current information on the scope and nature of child sexual abuse. *Future Child.* 1994;4(2):31-53.
33. Berger KS. Update on bullying at school: Science forgotten? *Developmental Review.* 2007; 27(1):90–126.
34. Teicher MH, Ohashi K, Khan A, et al. Does sleep disruption mediate the effects of childhood maltreatment on brain structure? *Eur J Psychotraumatol.* 2017;8(Suppl 7):1450594.
35. Usher JA, Neisser U. Childhood amnesia and the beginnings of memory for four early life events. *J Exp Psychol Gen.* 1993;122(2):155-165.
36. Lyons-Ruth K, Pechtel P, Yoon SA, Anderson CM, Teicher MH. Disorganized attachment in infancy predicts greater amygdala volume in adulthood. *Behav Brain Res.* 2016;308:83-93.

37. McLaughlin KA, Sheridan MA, Tibu F, Fox NA, Zeanah CH, Nelson CA, 3rd. Causal effects of the early caregiving environment on development of stress response systems in children. *Proc Natl Acad Sci U S A*. 2015;112(18):5637-5642.
38. Choi J, Jeong B, Polcari A, Rohan ML, Teicher MH. Reduced fractional anisotropy in the visual limbic pathway of young adults witnessing domestic violence in childhood. *Neuroimage*. 2012;59(2):1071-1079.
39. Jensen SK, Dickie EW, Schwartz DH, et al. Effect of Early Adversity and Childhood Internalizing Symptoms on Brain Structure in Young Men. *JAMA Pediatr*. 2015;169(10):938-946.