

Indiscriminate Amygdala Response to Mothers and Strangers After Early Maternal Deprivation

Aviva K. Olsavsky, Eva H. Telzer, Mor Shapiro, Kathryn L. Humphreys, Jessica Flannery, Bonnie Goff, and Nim Tottenham

Background: In altricial species, maternal stimuli have powerful effects on amygdala development and attachment-related behaviors. In humans, maternal deprivation has been associated with both “indiscriminate friendliness” toward non-caregiving adults and altered amygdala development. We hypothesized that maternal deprivation would be associated with reduced amygdala discrimination between mothers and strangers and increased parent report of indiscriminate friendliness behaviors.

Methods: Sixty-seven youths (33 previously institutionalized; 34 comparison; age-at-scan 4–17 years) participated in a functional magnetic resonance imaging experiment designed to examine amygdala response to mother versus stranger faces. In-scanner behavior was measured. Indiscriminate friendliness was assessed with parental report.

Results: Comparison youth showed an amygdala response that clearly discriminated mother versus stranger stimuli. Previously institutionalized youths, by contrast, exhibited reduced amygdala discrimination between mothers and strangers. Reduced amygdala differentiation correlated with greater reports of indiscriminate friendliness. These effects correlated with age-at-adoption, with later adoptions being associated with reduced amygdala discrimination and more indiscriminate friendliness.

Conclusions: Our results suggest that early maternal deprivation is associated with reduced amygdala discrimination between mothers and strangers, and reduced amygdala discrimination was associated with greater reports of indiscriminate friendliness. Moreover, these effects increased with age-at-adoption. These data suggest that the amygdala, in part, is associated with indiscriminate friendliness and that there might be a dose–response relationship between institutional rearing and indiscriminate friendliness.

Key Words: Affective salience, amygdala development, attachment, indiscriminate friendliness, institutional rearing, maternal deprivation

The impact of maternal deprivation in the formation of attachment-related behaviors has been explored in the animal (1–4) and human literature (5–8). Early maternal separation and institutional rearing (e.g., orphanages) has implications for mental health outcomes (9–12). One common outcome in previously institutionalized (PI) children is a behavior often called “indiscriminate friendliness,” which includes reduced reticence and atypical approach behaviors toward all adults, including strangers (13). It is important to note that the term is a misnomer, as the behavior in these children has been noted to be “neither ‘friendly’ nor ‘sociable’” (14). Tizard and Hodges (15) note that this behavior was the greatest source of complaints from teachers, because the children engaged in attention-seeking behaviors, attempting to engage in social approach toward teachers too frequently and at inappropriate times, in a way that disrupted the classroom environment. This common phenotype after deprivation might be associated with reactive attachment disorder, indiscriminate type (16), or might be present in the absence of dysfunctional attachment (17–20).

From the David Geffen School of Medicine (AKO); Semel Institute for Neuroscience and Human Behavior (AKO); and Department of Psychology (EHT, MS, KLH, JF, BG, NT), University of California at Los Angeles, Los Angeles, California.

Address correspondence to Aviva K. Olsavsky, M.D., Semel Institute for Neuroscience and Human Behavior at UCLA Psychiatry, 760 Westwood Plaza, Suite C8-193, Los Angeles, CA 90095; E-mail: aolsavsky@mednet.ucla.edu.

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Under most circumstances, the early human environment is highly constrained in that a caregiver will typically remain present. Caregiver presence is a necessary and species-expected environmental agent (21), which instantiates a developmental learning process that includes: 1) approaching the caregiver; 2) learning to recognize the caregiver; and 3) forming a preference for the caregiver and avoiding non-caregiver adults (2). Thus, experience with a primary caregiver facilitates a process whereby infants show preference for that caregiver over and above all other adults. In contrast, indiscriminate friendliness is characterized by attenuated affective discrimination between caregiver and strangers. Caregiver preference development is profoundly influenced by stability of care. Several factors work against this process in an institutional environment, including fluctuating staff, lack of caregiver sensitivity, and physical deprivation (22). If presence of a stable caregiver is required for typical attachment-related behaviors, including discrimination between mothers and strangers, then it is not surprising that PI children are at elevated risk for displaying indiscriminate behaviors (23).

Work in humans and nonhuman animals suggests that the amygdala plays an important role in representing affective relevance of the caregiver. Maternal absence alters the trajectory of amygdala development (24–26). In its broader role, the amygdala represents motivational salience of stimuli (27–31). For this reason, the amygdala might be well-suited to mediate affective discrimination of attachment figures (i.e., the role of the amygdala in detecting affective salience and motivating behavior might also serve to represent the importance of the maternal stimulus). Work in nonhuman primates has demonstrated that the amygdala is necessary for expression of caregiver preference; infants with amygdala lesions showed lack of maternal preference after maternal separation, despite initially demonstrating species-typical bonding behaviors with mothers (32,33). Similarly, the amygdala of the child is preferentially engaged by the mother

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stimulus over and above that for an unfamiliar adult, and this amygdala response has been found to mediate specific approach behaviors to caregivers (21). These findings suggest that amygdala response is associated with intense emotional relationships. The hypothesis that amygdala activity supports attachment-related behaviors is substantiated by findings that mothers also show increased amygdala activation to their own child, an effect that does not seem to merely reflect familiarity (34,35). Taken together, these data suggest a role for amygdala in the dyadic and intense interaction between mother and child, perhaps in recognizing affective salience of the primary caregiver.

Notwithstanding evidence for the involvement of the amygdala in human attachment representation, little is known about the mechanism by which deprivation-induced brain development gives rise to indiscriminate friendliness behaviors. Of note, PI children have been shown to have atypical amygdala development, with children adopted later having larger amygdala volumes, compared with early-adopted/non-adopted children (36,37). In addition, PI children have been shown to exhibit amygdala hyperactivation to emotionally arousing faces (38). These findings with human samples mirror the effects of maternal deprivation observed in several other altricial species (24,25,39,40).

We used a previously published functional magnetic resonance imaging (fMRI) paradigm (21) to examine neural responses to mother and stranger stimuli in PI youth and a typically raised comparison (Comp) group. Given the role of the amygdala in selectively representing affective/motivational salience of caregivers (21,41), we hypothesized that children with a history of maternal deprivation would show indiscriminate amygdala response to all social stimuli that would mirror the indiscriminate friendliness seen both by parents and in laboratory settings in this population. We predicted that, unlike typically raised children who show more robust amygdala response to their mothers relative to strangers (21), PI children would show reduced amygdala discrimination between mothers and strangers, a prediction based on previous work showing hyperactivity of the amygdala (38). We anticipated that amygdala reactivity would be atypically high to strangers in the PI group, despite the nonfearful nature of our stimuli. Moreover, we anticipated that children with less amygdala discrimination would exhibit more indiscriminate friendliness. On the basis of previous findings of age-at-adoption associations with indiscriminate friendliness (10,42), we hypothesized that children adopted at a later age would show more indiscriminate friendliness and less differential amygdala response to mothers and strangers.

Methods and Materials

Participants

Functional MRI data were collected from 75 youths. Comp youth ($n = 37$), living with biological parents, and PI youth ($n = 38$) with a history of institutional rearing and resultant deprivation were studied. All PI youths were adopted by families in the United States via international adoption. Although all youths in institutional care experience maternal deprivation (43), institutional care is also commonly associated with physical, nutritional, and sensory deprivation in addition to adverse prenatal exposures (43).

Of the 75 participants for whom data were collected, 67 were included in our study (Comp $n = 34$, mean age-at-scan = 11 ± 4 years, range 4–17 years; PI $n = 33$, mean age-at-scan = 10 ± 3 years, range 6–15 years). Twenty-five Comps have been

previously published (21), whereas all PI data have never been published. There was no significant difference in number excluded or reason for exclusion by group (Comp = 3, PI = 5, $p > .05$): motion artifacts (Comp = 0, PI = 1, $p > .05$); clinical imaging findings (Comp = 0, PI = 1, $p > .05$); imaging outliers (Comp = 3, PI = 2, $p > .05$)¹. Parents completed a series of questionnaires, including an indiscriminate friendliness questionnaire (detailed in the following), the Security Scale to assess attachment-related behaviors (44), the Child Behavior Checklist (45), and a telephone interview with regard to medical and psychiatric history. Relevant demographic data, including country of origin (Table 1) and age-at-orphanage/adoption (Table 2) were collected for each PI participant. To address variability in pre-adoption quality of care and possible prenatal exposure to alcohol, we included additional data (Figure S1 in Supplement 1) related to preadoption parameters in our PI population: 1) measures of orphanage quality of care (Table 2); and 2) prevalence of typical fetal alcohol dysmorphological facial features by photographs (Figure S1 in Supplement 1), that might suggest prenatal alcohol exposures. Modified version of the Hoyme criteria (46) as well as the Astley photographic scale (47) were used to quantify upper lip and philtrum characteristics on a scale of 1–5. However, no definitive Fetal Alcohol Syndrome diagnoses can be made on the basis of these data alone (47).

Youths with a history of serious medical illness, including head trauma, seizure disorder, or borderline intellectual functioning (IQ < 70) were excluded from the study. All participants were right-handed. Families had incomes above the US median annual household income (\$48,451) (United States Census Bureau, 2006). This study was approved by the University of California Los Angeles Institutional Review Board, and informed consent and assent were obtained.

Questionnaires

Indiscriminate Friendliness Scale. To examine stranger-related behaviors, we adapted indiscriminate friendliness measures of multiple laboratories (13,15,17,42), which have been shown to have convergent validity (19). Previous work has shown that parental report of indiscriminate friendliness correlates well with observation of children and families by clinical psychology staff (10). Parent-administered questionnaire (1–10 scale) assessed the following: 1) How likely do you think it is that your child would willingly go home with a stranger?; 2) How likely do you think it is that your child would wander off (and not be distressed)?; and 3) How trusting is your child with new adults?

Attachment Security. To examine mother-related behaviors in our sample, youths completed the Security Scale (44), which provides a continuous measure of their perception of security in parent-child relationships in middle childhood and early adolescence. Although frequency and intensity of caregiver-directed attachment-related behaviors decline after infancy, these behaviors continue to be observed during childhood and adolescence, particularly during stress (44). Items are rated on a 4-point scale, with higher scores signifying more secure attachment. The instrument provides scores for three subscales: 1) belief of the child that attachment figure is responsive and available; 2) reliance of the child on attachment figure in times of stress; and 3) ease and interest of the child in communicating with

¹In the supplemental analysis with anatomical region of interest (ROI), there were two additional imaging outliers from PI group excluded for >2.5 SD from mean.

attachment figure. Kerns *et al.* (48) demonstrated good internal consistency (Cronbach's $\alpha = .84$ and $.88$, respectively), and the measure was highly correlated ($p < .01$) with self-esteem of the child, peer acceptance, observer ratings of friendship quality, and behavioral conduct, but longitudinal studies have not been performed to test its concordance with infant measures of attachment security.

Additional Questionnaires. The Child Behavior Checklist (49) was used to examine anxiety, mood, and inattention symptoms of subjects (Table S1 in Supplement 1). Psychiatric disorders were reported via history by parents. The Wechsler Abbreviated Scale of Intelligence was also administered to participants over 5 years old (50).

Experimental Task

We used a previously published fMRI block-design task (21). Participants viewed color pictures of their mother (adopted or biological) and an age- and ethnicity-matched unfamiliar individual, who was the mother of another participant (stranger) in alternating 28-sec blocks. Mother² and stranger stimuli posed happy and neutral expressions, with one exemplar of each emotional state/stimulus set. These images were taken by the experimenter in a set location and were standardized for size and luminance. Color images had a vertical visual angle of approximately 15°. Participants were instructed to respond quickly (within 1500 msec) by pressing a button for happy expressions (regardless of model), which were presented 50% of the time with fixed random order. Thus, the task required responses for target expressions (happy) and inhibiting response for distracter (neutral). Four blocks each of mother and stranger and three fixation blocks were presented in alternation (+MSMS+SMSM+), counterbalanced across subjects. Each block contained 18 identical mother- or stranger-stimuli (with happy or neutral expressions), resulting in 144 total stimuli (72 mother, 72 stranger). Each stimulus was presented for 500 msec, followed by 1-sec fixation. Video goggles (model, VisuaStim Digital, Resonance Technology, Los Angeles, California) were used to present stimuli, and a response pad (model 932 fORP, Current Designs, Inc., Philadelphia, Pennsylvania) was used to record behavioral responses. The task lasted 4:54 min. Before scanning, participants were given the opportunity to practice to ensure that they understood and could perform the task.

Image Acquisition

Images were acquired with a Siemens Trio 3T MRI scanner (Malvern, Pennsylvania). Foam padding placed around the head reduced motion artifacts. Whole-brain, high-resolution structural T1 images were acquired as follows: magnetization prepared rapid acquisition gradient-echo; $1 \times 1 \times 1$ mm resolution; 256-mm field-of-view; 192 sagittal slices. Functional T2*-weighted echo-planar images were acquired during the behavioral task at 30° oblique angle as follows: 34 slices; 4-mm slice thickness (skip 0); repetition time = 2000 msec; echo time = 30 msec; flip angle = 90°; matrix 64×64 .

Procedure

Participants attended two sessions: 1) behavioral measures were collected, and participants were acclimated to the scanner

²One child viewed images of his father and an ethnically matched male stranger.

environment with an MRI replica; and 2) the fMRI task was administered.

Behavioral Data Analysis

Out of Scanner Behavioral Measures. Because total indiscriminate friendliness scores were skewed (skewness = 1.22), we log-transformed these values for analyses. To examine group differences in indiscriminate friendliness, we performed an analysis of covariance (ANCOVA) on total indiscriminate friendliness score, controlling for age-at-scan and IQ. To determine whether there was a dose-response effect of time spent in institutional care on level of indiscriminate friendliness, we correlated indiscriminate friendliness score and age-at-adoption, controlling for age-at-scan and IQ.

In-Scanner Behavioral Measures. Reaction time and behavioral response rates were analyzed in SPSS (SPSS, Chicago, Illinois). Average reaction times, correct hit rate, and false alarm rates were calculated for each group. Subjects (Comp = 4, PI = 5) were excluded from behavioral analysis for correct hit rate <50%. Because the task was employed mostly to ensure engagement (e.g., not sleeping), we justify these rather lenient compliance thresholds. No subjects were excluded from the imaging analysis on the basis of correct hit rate. Repeated-measures ANCOVAs for each variable (reaction time, false alarm rate, correct hit rate) were performed in SPSS with within-subject variable of stimulus type and between-subjects variable of group, with age-at-scan and mean reaction time (or false alarm or correct hit rate) as covariates.

fMRI Data Analysis

Preprocessing and Single-Subject Analysis. Functional imaging data were analyzed with AFNI software (51). All data with motion artifact of >2.5 mm in any direction were removed. Slice-timing correction Talairach spatial normalization (52) and smoothing with an anisotropic 6-mm Gaussian kernel were performed. Single-subject models included repeated measures for stimulus types (mother, stranger) as well as six motion parameters that were convolved with the hemodynamic response function. General linear model (GLM) was performed to fit beta weights to each regressor; modeling correlated drift with linear and quadratic factors within each voxel. Additionally, psychophysiological interaction analyses were performed with the functionally defined amygdala as a seed region (Methods in Supplement 1).

Group-Level Analysis. We performed a linear mixed effect voxel-wise whole-brain AFNI analysis, with within-subjects factor of stimulus type and between-subjects factor of group, with age-at-scan as a covariate. Correction for multiple comparisons was applied at cluster-level for the functionally derived left amygdala region of interest (ROI) after Monte Carlo simulations conducted in AFNI AlphaSim ($p < .01$). This method offers reasonable multiple-comparisons correction during group-level analyses in small ROIs (53).

Initial analyses to decompose the interaction in the AFNI GLM used cluster-level statistics, but correlation analyses were performed with an anatomical ROI (defined by a right amygdala mask in the Talairach-Tournoux atlas implemented in AFNI) to avoid redundancy (54). Extracted beta weights were analyzed with a repeated-measures ANCOVA with the within-subjects factor of stimulus type (mother, stranger) and between-subjects factor of age-at-adoption (values designated as 0 for Comps, to simulate a continuous rather than categorical variable), controlling for age-at-scan and IQ. To examine dose-response relationships, we correlated amygdala response and age-at-adoption,

Table 1. Region of Origin—PI Children

Region of Origin	% of PI Sample
Eastern Europe	76
East and South Asia	24

n = 4 missing data from previously institutionalized (PI) group.

controlling for age-at-scan, age-at-adoption, and IQ. We also correlated indiscriminate friendliness with differential amygdala response (mother–stranger).

Habituation analysis was performed by extracting beta weights from the functionally defined amygdala ROI during the first and second half of the experiment separately. Change scores were calculated (second – first block) for both stimulus types and subjected to a repeated-measures ANCOVA (age-at-scan, age-at-adoption, and IQ as covariates), with the within-subject factor of stimulus type.

Results

Participants

Among the 67 participants included in analyses, there was a trend for more PI female subjects ($p = .07$). There was no significant group difference in age-at-scan. There was a group difference in IQ, with Comps having higher IQ ($p < .05$); neither group had below-average IQ (Table 2). Region of origin data are provided in Table 1.

Behavioral Findings

Indiscriminate Friendliness Scale. Indiscriminate friendliness score differed between groups (controlling for age-at-scan and IQ) ($F = 4.33, p < .05$), with PI being more indiscriminately friendly per parent-report. There was a positive correlation between age-at-adoption and indiscriminate friendliness score (controlling for IQ and age-at-scan) ($r = .37, p < .05$)³, which became under-powered when we examined the PI group alone (Figure 1).

Attachment Security. There were no group differences in the Security Scale score (controlling for age-at-scan and IQ) ($p > .05$). The Security Scale score (controlling for age-at-scan and IQ) did not correlate with age-at-adoption ($r = -.39, p > .05$).

Behavioral Data Analysis

Four Comp and 5 PI subjects were excluded for low hit rates, which did not differ between groups ($p > .05$). Correct hits (to happy), errors of commission (to neutral), and reaction time (correct trials) were measured. There were no significant differences between groups for any of these variables. There was no effect of age except in the case of reaction time ($F = 8.23, p < .05$, partial $\eta^2 = .112$); age-at-scan was associated with faster reaction times.

fMRI Findings

Whole-Brain Analysis. Linear mixed effect analysis revealed a Group \times Stimulus Type interaction ($F = 4.003, p < .05$, small-volume-corrected): left amygdala $-27 -3 -19$; $k = 47$ (Figure 2A). Other activated regions are provided in Supplement 1 (Table S2 in Supplement 1).

³Of note, there was also a negative correlation of indiscriminate friendliness with time spent in adoptive families ($r = -.31, p < .05$).

Amygdala Response to Mothers and Strangers as a Function of Early Maternal Deprivation. We used predicted values from a repeated-measures GLM in SPSS with within-subjects factor of stimulus type and covariates of age-at-adoption, age-at-scan, and IQ to examine effects by stimulus and group. Post hoc *t* test showed that Comps exhibited higher amygdala signal for mother than stranger stimuli ($t = 7.00, p < .05$), whereas PI did not differ ($t = -.09, p > .05$) (Figure 2B). There was no significant difference in response to mothers between groups ($p > .05$), although PI children did exhibit increased response to strangers versus Comps ($t = -2.74, p < .05$)⁴.

Habituation Analysis. Repeated-measures GLM showed a main effect of group ($F = 5.42, p < .025$), such that Comps decreased amygdala response by late trials, but PI did not (Figure 3).

Psychophysiological Interaction Analysis. An ANOVA comparing the two groups in the difference between mothers and strangers revealed significant group differences in connectivity between the left amygdala and several cortical regions (Table S3 in Supplement 1), most notably the ventral anterior cingulate. This was the only region where amygdala connectivity was greater in the Comp group than in the PI group.

Correlations with Amygdala Discrimination. There was a negative correlation between age-at-adoption and values extracted from left anatomically defined amygdala (mother–stranger) in PI children, with those adopted later exhibiting attenuated amygdala discrimination ($r = -.39, p < .05$) (Figure 4). Finally, children with higher indiscriminate friendliness exhibited more attenuated amygdala (anatomically defined) discrimination between mothers and strangers ($r = .28, p < .05$), controlling for age-at-scan, age-at-adoption, and IQ (Figure 5). Indiscriminate friendliness correlations became underpowered

Table 2. Demographic Data

	Comp (<i>n</i> = 34)	PI (<i>n</i> = 33)	<i>p</i>
Age at Scan (Yrs), Mean (SD)	11 (4)	10 (3)	> .05
Range	4–17	6–15	
Months at Adoption, Mean (SD)	—	37 (31)	—
Range	—	6–120	—
Age Orphaned (Mo), Mean (SD)	—	12 (18) ^a	—
Range	—	0–72	—
Time (Mo) in Orphanage	—	26 (19) ^b	—
Range	—	5–65	—
Parent's Rating—Quality of Care	—	.93 (.86) ^c	—
Parent's Rating—Quantity of Care	—	1.11 (.80) ^c	—
Gender (% Male)	65%	42%	> .05
Mean Full-Scale IQ, Mean (SD)	110 (17) ^d	100 (15) ^e	< .05
Presence of Any Psych Dx, <i>n</i> (%)	1 (3%)	11 (34%) ^f	< .01

Comp, comparison subjects; PI, previously institutionalized; Psych Dx, psychological diagnosis.

^a*n* = 3 missing data from PI group.

^b*n* = 5 missing data from PI group.

^c*n* = 6 missing data from PI group. Rated on a scale of 1 to 10, 10 being highest level/quantity of care.

^d*n* = 8 missing data from Comp group.

^e*n* = 2 missing data from PI group.

^f*n* = 1 missing data from PI group.

⁴Of note, primary repeated-measures analysis was re-performed with gender as a factor and demonstrated no significant effect of this variable.

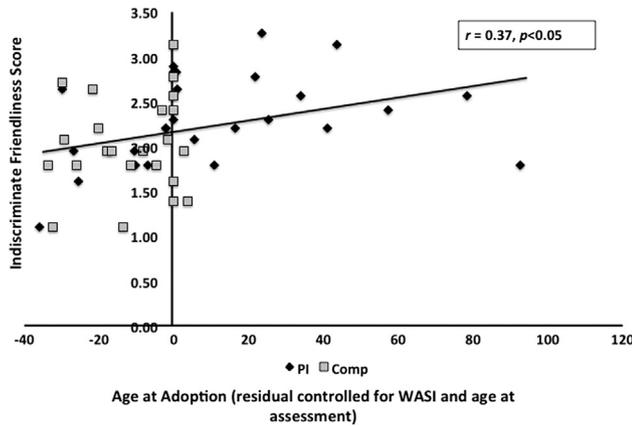


Figure 1. Older age-at-adoption was associated with higher parent report of indiscriminate friendliness (adjusted for IQ and age-at-scan). Pearson correlation ($r = .37, p < .05$). Missing indiscriminate friendliness data $n = 11$ from Comparison (Comp) group and $n = 4$ from previously institutionalized (PI) group. Total: $n = 40$. WASI, Wechsler Abbreviated Scale of Intelligence.

when examining only the PI group, due to missing data as noted in the figures. There was no relationship between amygdala discrimination and the Security Scale.

Discussion

We tested the hypothesis that early-life maternal deprivation would be associated with attenuated amygdala discrimination between mothers and strangers and parent-report of indiscriminate friendly behaviors. We focused on the amygdala because of its role in representing intense relationships (21,32,33,35). We observed that, relative to the typically raised Comp group, PI youth exhibited equivalent amygdala response to mothers and strangers, consistent with our predictions. This lack of discrimination was the result of atypically high amygdala response to strangers in PI youth, whereas responses to mother stimuli were equivalent across groups. Moreover, the amygdala response in PI youth did not attenuate over the course of the scan session as evidenced by habituation analysis and showed decreased functional coupling

with the ventral anterior cingulate. This prefrontal region has been associated with regulatory skill, suggesting that the current neural findings might support previous work associating indiscriminate behaviors with low inhibitory control abilities (10,55). Amygdala findings were associated with age-at-adoption, such that younger age-at-adoption was associated with more typical differentiation between mother and stranger stimuli and older age-at-adoption was associated with reduced discrimination. Additionally, PI demonstrated more parent-reported indiscriminately friendly behaviors, which correlated with amygdala discrimination; participants with reduced amygdala mother-stranger discrimination tended to be rated as exhibiting more indiscriminate friendly behaviors.

The association of amygdala response with indiscriminate affective behaviors in PI youth suggests that the amygdala detects affective salience appropriately (mother) and inappropriately (stranger), unlike typically raised Comp youth, who showed higher amygdala activation to mothers. The current findings suggest that highly affiliative behaviors directed toward unfamiliar adults might in part be explained by inappropriate amygdala response to strangers. Indiscriminate friendliness is observed during institutional care (23) and has been described as an adaptive behavior in that setting (perhaps eliciting maternal care from unfamiliar adults) (17). However, these behaviors often continue after adoption, and it has been suggested that, because of their enduring nature, they might be understood in terms of biological adaptations at the level of brain development (1).

The process of distinguishing primary caregivers and strangers typically occurs during a sensitive period soon after birth. In rat pups, maternal odor learning (56,57) has been shown to develop within the first 10 days of life. In humans, this process requires more ontological time, and typically the discrimination emerges within the first year (58,59). How this affective discrimination is then maintained over the course of development is not yet well-understood, although work in typical children and adults suggests that the amygdala plays an important role in representing the affective salience of intimate relationships (21,35,60) and might be part of the maintenance process. In the current study, we observed associations with age-at-adoption for both amygdala response to mothers versus strangers and indiscriminate friendliness behaviors, where earlier removal from institutional care was associated with more typical phenotypes. Therefore, it is possible

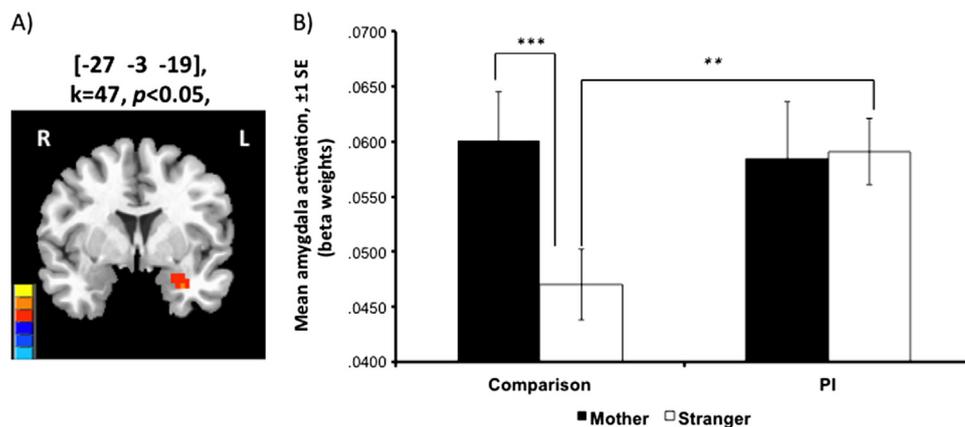


Figure 2. (A) Whole-brain linear mixed effect analysis revealed a Group \times Stimulus Type interaction ($F = 4.003, p < .05$, small-volume-corrected): left amygdala region of interest (peak $[-27 -3 -19]$; $k = 47$). (B) Unlike the Comparison (Comp) group, who showed greater amygdala signal for mother than stranger stimuli, the previously institutionalized (PI) group showed equivalent signal across stimuli (controlling for age-at-adoption, age-at-scan, and IQ). Asterisks indicate post hoc tests: Mother vs. Stranger—Comp: $***p < .001$, PI: $p > .05$; Comp vs. PI—Mother: $p > .05$, **Stranger: $p < .05$. L, left; R, right.

correlated with indiscriminate friendliness. Characterizing the pathophysiology of indiscriminate friendliness behaviors might provide important insight into understanding how early deprivation contributes to aberrant behaviors. By studying these pathways longitudinally, we might further describe the relationship between risk and resilience from a developmental perspective. Describing these basic processes is critical for implementing early intervention strategies to improve psychiatric outcomes in children.

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- Rutter M, O'Connor TG (2004): Are there biological programming effects for psychological development? Findings from a study of Romanian adoptees. *Dev Psychol* 40:81–94.
- Insel TR, Young LJ (2001): The neurobiology of attachment. *Nat Rev Neurosci* 2:129–136.
- O'Connor TG, Cameron JL (2006): Translating research findings on early experience to prevention: Animal and human evidence on early attachment relationships. *Am J Prev Med* 31:S175–S181.
- Sabatini MJ, Ebert P, Lewis DA, Levitt P, Cameron JL, Mirnics K (2007): Amygdala gene expression correlates of social behavior in monkeys experiencing maternal separation. *J Neurosci* 27:3295–3304.
- Bowlby J (1954): The effect of separation from the mother in early life. *Ir J Med Sci* 121–126.
- Bowlby J (1988): Developmental psychiatry comes of age. *Am J Psychiatry* 145:1–10.
- Ainsworth M, Boston M, Bowlby J, Rosenbluth D (1956): The effects of mother-child separation: A follow-up study. *Br J Med Psychol* 29:211–247.
- Beckett C, Brendenkamp D, Castle J, Groothues C, O'Connor TG, Rutter M (2002): Behavior patterns associated with institutional deprivation: A study of children adopted from Romania. *J Dev Behav Pediatr* 23:297–303.
- Colvert E, Rutter M, Beckett C, Castle J, Groothues C, Hawkins A, *et al.* (2008): Emotional difficulties in early adolescence following severe early deprivation: findings from the English and Romanian adoptees study. *Dev Psychopathol* 20:547–567.
- Rutter M, Colvert E, Kreppner J, Beckett C, Castle J, Groothues C, *et al.* (2007): Early adolescent outcomes for institutionally-deprived and non-deprived adoptees. I: Disinhibited attachment. *J Child Psychol Psychiatry* 48:17–30.
- Pinheiro P (2006): *World Report on Violence Against Children*. New York: UNICEF.
- Rutter M, Sonuga-Barke EJ, Castle J (2010): I. Investigating the impact of early institutional deprivation on development: Background and research strategy of the English and Romanian Adoptees (ERA) study. *Monogr Soc Res Child Dev* 75:1–20.
- Hodges J, Tizard B (1989): Social and family relationships of ex-institutional adolescents. *J Child Psychol Psychiatry* 30:77–97.
- O'Connor TG, Brendenkamp D, Rutter M (1999): Attachment disturbances and disorders in children exposed to early severe deprivation. *Infant Ment Health J* 20:10–29.
- Tizard B, Hodges J (1978): The effect of early institutional rearing on the development of eight year old children. *J Child Psychol Psychiatry* 19:99–118.
- O'Connor TG, Rutter M (2000): Attachment disorder behavior following early severe deprivation: Extension and longitudinal follow-up. English and Romanian Adoptees Study Team. *J Am Acad Child Adolesc Psychiatry* 39:703–712.
- Chisholm K (1998): A three year follow-up of attachment and indiscriminate friendliness in children adopted from Romanian orphanages. *Child Dev* 69:1092–1106.
- Smyke AT, Dumitrescu A, Zeanah CH (2002): Attachment disturbances in young children. I: The continuum of caretaking casualty. *J Am Acad Child Adolesc Psychiatry* 41:972–982.
- Zeanah CH, Smyke AT, Dumitrescu A (2002): Attachment disturbances in young children. II: Indiscriminate behavior and institutional care. *J Am Acad Child Adolesc Psychiatry* 41:983–989.
- American Psychiatric Association (1994): *Diagnostic and Statistical Manual of Mental Disorders: DSM-IV, 4th ed.* Washington DC: American Psychiatric Association.
- Tottenham N, Shapiro M, Telzer EH, Humphreys KL (2012): Amygdala response to mother. *Dev Sci* 15:307–319.
- van Ijzendoorn MH, Palacios J, Sonuga-Barke EJS, Gunnar MR, Vorria P, McCall RB, *et al.* (2011): I. Children in Institutional Care: Delayed Development and Resilience. *Monogr Soc Res Child Dev* 76:8–30.
- Bakermans-Kranenburg MJ, Steele H, Zeanah CH, Muhamderahimov RJ, Vorria P, Dobrova-Krol NA, *et al.* (2011): III. Attachment and Emotional Development in Institutional Care: Characteristics and Catch Up. *Monogr Soc Res Child Dev* 76:62–91.
- Ono M, Kikusui T, Sasaki N, Ichikawa M, Mori Y, Murakami-Murofushi K (2008): Early weaning induces anxiety and precocious myelination in the anterior part of the basolateral amygdala of male Balb/c mice. *Neuroscience* 156:1103–1110.
- Ali I, Salzberg MR, French C, Jones NC (2011): Electrophysiological insights into the enduring effects of early life stress on the brain. *Psychopharmacology (Berl)* 214:155–173.
- Moriceau S, Sullivan RM (2006): Maternal presence serves as a switch between learning fear and attraction in infancy. *Nat Neurosci* 9:1004–1006.
- Sander D, Grafman J, Zalla T (2003): The human amygdala: An evolved system for relevance detection. *Rev Neurosci* 14:303–316.
- Hamann S, Mao H (2002): Positive and negative emotional verbal stimuli elicit activity in the left amygdala. *Neuroreport* 13:15–19.
- Ousdal OT, Jensen J, Server A, Hariri AR, Nakstad PH, Andreassen OA (2008): The human amygdala is involved in general behavioral relevance detection: Evidence from an event-related functional magnetic resonance imaging Go-NoGo task. *Neuroscience* 156:450–455.
- Paton JJ, Belova MA, Morrison SE, Salzman CD (2006): The primate amygdala represents the positive and negative value of visual stimuli during learning. *Nature* 439:865–870.
- Adolphs R (2010): What does the amygdala contribute to social cognition? *Ann N Y Acad Sci* 1191:42–61.
- Bauman MD, Lavenex P, Mason WA, Capitanio JP, Amaral DG (2004): The development of social behavior following neonatal amygdala lesions in rhesus monkeys. *J Cogn Neurosci* 16:1388–1411.
- Bauman MD, Lavenex P, Mason WA, Capitanio JP, Amaral DG (2004): The development of mother-infant interactions after neonatal amygdala lesions in rhesus monkeys. *J Neurosci* 24:711–721.
- Swain JE, Lorberbaum JP, Kose S, Strathearn L (2007): Brain basis of early parent-infant interactions: Psychology, physiology, and in vivo functional neuroimaging studies. *J Child Psychol Psychiatry* 48:262–287.
- Leibenluft E, Gobbi MI, Harrison T, Haxby JV (2004): Mothers' neural activation in response to pictures of their children and other children. *Biol Psychiatry* 56:225–232.
- Tottenham N, Hare TA, Quinn BT, McCarry TW, Nurse M, Gilhooly T, *et al.* (2010): Prolonged institutional rearing is associated with atypically large amygdala volume and difficulties in emotion regulation. *Dev Sci* 13:46–61.
- Mehta MA, Golembo NI, Nosarti C, Colvert E, Mota A, Williams SC, *et al.* (2009): Amygdala, hippocampal and corpus callosum size following severe early institutional deprivation: The English and Romanian Adoptees study pilot. *J Child Psychol Psychiatry* 50:943–951.
- Tottenham N, Hare TA, Millner A, Gilhooly T, Zevin JD, Casey BJ (2011): Elevated amygdala response to faces following early deprivation. *Dev Sci* 14:190–204.
- Caldji C, Diorio J, Meaney MJ (2000): Variations in maternal care in infancy regulate the development of stress reactivity. *Biol Psychiatry* 48:1164–1174.
- Plotsky PM, Thrivikraman KV, Nemeroff CB, Caldji C, Sharma S, Meaney MJ (2005): Long-term consequences of neonatal rearing on central corticotropin-releasing factor systems in adult male rat offspring. *Neuropsychopharmacology* 30:2192–2204.
- Todd RM, Cunningham WA, Anderson AK, Thompson E (2012): Affect-biased attention as emotion regulation. *Trends Cogn Sci* 16:365–372.
- O'Connor TG, Marvin RS, Rutter M, Olrick JT, Britner PA (2003): Child-parent attachment following early institutional deprivation. *Dev Psychopathol* 15:19–38.

43. Gunnar MR, Bruce J, Grotevant HD (2000): International adoption of institutionally reared children: Research and policy. *Dev Psychopathol* 12:677–693.
44. Kerns KA, Aspelmeier JE, Gentzler AL, Grabill CM (2001): Parent-child attachment and monitoring in middle childhood. *J Fam Psychol* 15:69–81.
45. Achenbach TM, Edelbrock CS (1981): Behavioral problems and competencies reported by parents of normal and disturbed children aged four through sixteen. *Monogr Soc Res Child Dev* 46:1–82.
46. Hoyme HE, May PA, Kalberg WO, Kodituwakku P, Gossage JP, Trujillo PM, *et al.* (2005): A practical clinical approach to diagnosis of fetal alcohol spectrum disorders: Clarification of the 1996 institute of medicine criteria. *Pediatrics* 115:39–47.
47. Astley SJ (2006): Comparison of the 4-digit diagnostic code and the Hoyme diagnostic guidelines for fetal alcohol spectrum disorders. *Pediatrics* 118:1532–1545.
48. Kerns KA, Klepac L, Cole AK (1996): Peer relationships and preadolescents' perceptions of security in the mother-child relationships. *Dev Psychol* 32:457–466.
49. Achenbach TM, Ruffle TM (2000): The Child Behavior Checklist and related forms for assessing behavioral/emotional problems and competencies. *Pediatr Rev* 21:265–271.
50. Clements GR (1965): An abbreviated form of the Wechsler Intelligence Scale for Children. *J Consult Psychol* 29:92.
51. Cox RW (1996): AFNI: Software for analysis and visualization of functional magnetic resonance neuroimages. *Comput Biomed Res* 29:162–173.
52. Talairach J, Tournoux P (1988): *Co-Planar Stereotaxic Atlas of the Human Brain: An Approach to Medical Cerebral Imaging*. New York: Thieme Medical Publishers.
53. Phan KL, Fitzgerald DA, Nathan PJ, Tancer ME (2006): Association between amygdala hyperactivity to harsh faces and severity of social anxiety in generalized social phobia. *Biol Psychiatry* 59:424–429.
54. Poldrack RA, Mumford JA (2009): Independence in ROI analysis: Where is the voodoo? *Soc Cogn Affect Neurosci* 4:208–213.
55. Roy P, Rutter M, Pickles A (2004): Institutional care: associations between overactivity and lack of selectivity in social relationships. *J Child Psychol Psychiatry* 45:866–873.
56. Moriceau S, Sullivan RM (2005): Neurobiology of infant attachment. *Dev Psychobiol* 47:230–242.
57. Moriceau S, Sullivan RM (2004): Unique neural circuitry for neonatal olfactory learning. *J Neurosci* 24:1182–1189.
58. Carlson EA, Sampson MC, Sroufe LA (2003): Implications of attachment theory and research for developmental-behavioral pediatrics. *J Dev Behav Pediatr* 24:364–379.
59. Ainsworth MD, Bell SM (1970): Attachment, exploration, and separation: Illustrated by the behavior of one-year-olds in a strange situation. *Child Dev* 41:49–67.
60. Todd RM, Evans JW, Morris D, Lewis MD, Taylor MJ (2011): The changing face of emotion: Age-related patterns of amygdala activation to salient faces. *Soc Cogn Affect Neurosci* 6:12–23.
61. Gleason MM, Fox NA, Drury S, Smyke A, Egger HL, Nelson CA 3rd, *et al.* (2011): Validity of evidence-derived criteria for reactive attachment disorder: Indiscriminately social/disinhibited and emotionally withdrawn/inhibited types. *J Am Acad Child Adolesc Psychiatry* 50:216–231. e3.
62. Smyke AT, Zeanah CH Jr, Fox NA, Nelson CA 3rd (2009): A new model of foster care for young children: The Bucharest early intervention project. *Child Adolesc Psychiatr Clin N Am* 18:721–734.