

Neonatal Amygdala Lesions Result in Globally Blunted Affect in Adult Rhesus Macaques

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The amygdala has been implicated in affective and social processing for more than a century. Animals with damage to the amygdala have altered affective and social behavior patterns, though the precise nature of these behavioral changes depends on a number of factors including lesion technique, age of the subject at the time of lesion, rearing, and housing environments. Interpretations of amygdala lesion studies are further complicated by the potentially confounded nature of affective and social stimuli (e.g., social interactions with a conspecific partner that is consistently aggressive). In the present study, we evaluated affective responding to affectively and socially evocative video stimuli in a group of rhesus macaques that received bilateral amygdala lesions as neonates. The stimuli were produced to vary independently in terms of their affective and social content. The responses of the amygdala-lesioned animals were compared with a group of age-matched controls and a group of animals that had sustained bilateral hippocampus damage as neonates. As compared with control animals, amygdala-lesioned animals had blunted responding to both positive and negative stimuli, regardless of social content, but did differentiate between levels of social content. Taken together, these findings suggest that early amygdala damage permanently compromises affective processing while leaving intact the ability to distinguish between socially meaningful contexts.

Keywords: amygdala, hippocampus, affect, emotion, nonhuman primate, *Macaca mulatta*, rhesus

It has long been known that regions in the temporal lobe, and in particular the amygdala, are important for normal affective and social processing (Brown & Schäfer, 1888; Rosvold, Mirsky & Pribram, 1954). A large human functional neuroimaging literature has demonstrated that the amygdala is active while subjects perceive affective and social stimuli such as facial depictions of emotion (e.g., Whalen et al., 1998; for a meta-analytic review see

Fusar-Poli et al., 2009) and while subjects engage in social interactions (e.g., Eisenberger, Gable, & Lieberman, 2007; Rilling et al., 2007). Much of what is known about the *critical* functions of the amygdala (those for which the amygdala is necessary) come from studies of animals, and in particular nonhuman primates, that have sustained experimental amygdala damage. These studies have demonstrated that adult macaques with amygdala damage respond inappropriately to discrete affective stimuli (e.g., snakes, spiders, novel objects; e.g., Aggleton & Passingham, 1981; Chudasama, Izquierdo & Murray, 2009; Izquierdo, Suda & Murray, 2005; Machado, Kazama & Bachevalier, 2009; Mason, Capitanio, Machado, Mendoza & Amaral, 2006; Meunier, Bachevalier, Murray, Málková & Mishkin, 1999; Stefanacci, Clark & Zola, 2003; Zola-Morgan, Squire, Alvarez-Royo & Clower, 1991) and during social interactions (e.g., Rosvold et al., 1954; Emery et al., 2001; Machado, Emery, Capitanio, et al., 2008). It is difficult to determine, however, whether the amygdala-lesioned animals have deficits in processing the affective content, the social content or a combination of the two because the discrete affective stimuli used to test amygdala function are often social (e.g., pictures of faces depicting “fear”) and social interactions are rarely neutral (e.g., social rejection is negative). To disentangle these stimulus properties, the present experiment used video stimuli in which the affective and social content could be easily manipulated. Such stimuli are more “life-like” than still objects commonly used in previous studies, potentially providing for a more robust and diverse behavioral repertoire to be generated by the experimental subjects. Not only are videos more life-like than objects, but their content can be easily controlled and consistently presented to all subjects, unlike the behavior of partner animals who typically

This article was published Online First October 10, 2011.

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We thank the veterinary and husbandry staff of the California National Primate Research Center for excellent care of the animal subjects. We also thank Dr. Pierre Lavenex, Jeffrey Bennett, and Pamela Tennant for assistance with surgical procedures and Jessica Toscano for help with data collection. This research was supported by a grant from the National Institute of Mental Health (R37MH57502) and by the base grant of the California National Primate Research Center (RR00169). This work was also supported through the Early Experience and Brain Development Network of the MacArthur Foundation. Portions of this data set were presented at the Society for Neuroscience Meeting in San Diego, California, November 2011.

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serve as “stimuli” in seminaturalistic social interaction tasks. To illustrate the critical importance of disentangling affective from social responding in the study of amygdala function, we presently review evidence implicating the nonhuman primate amygdala in affective and social processing.

The Nonhuman Primate Amygdala and Affective Processing

The amygdala has been historically studied in the context of understanding negative affective states (e.g., fear, anxiety, etc.). For example, the amygdala is critical for learning the threatening nature of stimuli via associative mechanisms (what is often called “fear” learning). Adult macaques with damage to the amygdala fail to learn the association between neutral stimuli and noxious stimuli presented concurrently (Antoniadis, Winslow, Davis, & Amaral, 2007; Antoniadis, Winslow, Davis, & Amaral, 2009), suggesting that they are incapable of learning what is threatening. Similarly, adult rhesus macaques with amygdala damage readily interact with potentially dangerous objects known to generate robust negative affective responses in neurologically intact animals (e.g., Aggleton & Passingham, 1981; Chudasama, Izquierdo & Murray, 2009; Izquierdo, Suda & Murray, 2005; Machado et al., 2009; Mason et al., 2006; Meunier et al., 1999; Stefanacci, Clark & Zola, 2003; Zola-Morgan et al., 1991). Neonatal damage restricted predominately to the amygdala (as opposed to complete medial temporal lobe damage) produces a nearly identical response to objects (Bliss-Moreau, Toscano, Bauman, Mason & Amaral, 2010, Bliss-Moreau, Toscano, Bauman, Mason & Amaral, 2011; Prather et al., 2001), indicating that the brain does not compensate for the amygdala’s affective function despite the substantial neural development that occurs after damage was sustained.

Accumulating evidence suggests that the amygdala may process positive stimuli as well. For example, the amygdala is active not only during learning about negative value (as discussed above) but also when stimuli predict the presence of reward (Belova, Paton, Morrison & Salzman, 2007; Paton, Belova, Morrison & Salzman, 2006; Hirai, Hosokawa, Inoue, Miyachi & Mikami, 2009). Similarly, macaques with selective amygdala damage are unable to modify their behavior based on changing reward values when those changes occur as a result of the animals’ own altered physiological state (i.e., when a food item is no longer rewarding because the animal has eaten it to satiety; Izquierdo & Murray, 2007; Málková, Gaffan & Murray, 1997). The importance of the amygdala in both negative and positive affective processing may help to explain the altered patterns of social behavior observed after damage to the amygdala. In this view, disruption of the amygdala may be responsible for an inability to accurately assess the affective properties of social stimuli or affective properties of the context in which social interactions occur, thus leading to inappropriate or abnormal social behavior.

The Nonhuman Primate Amygdala and Social Behavior

In the earliest report of social behavior after amygdala lesions, Rosvold and colleagues (1954) reported that two of three adult

amygdala-lesioned animals fell in the dominance hierarchy as indicated by a decreased competition for food dropped from a small feeder (that could only be accessed by one animal at a time). One possible explanation for this behavior is that the food reward no longer was valued by amygdala-lesioned animals and therefore not “worth” the competitive effort required to obtain the food. Lesioned animals were rated to be more aggressive when housed individually, suggesting that they were still capable of enacting the aggressive behavior that might have been necessary to maintain their dominance at the food dispenser (Rosvold et al., 1954). Contemporary studies also document perturbations of social behavior after amygdala damage. After neurotoxic lesions to the amygdala (which spare the fibers of passage through the amygdala) adult macaques were *more* socially engaged in dyadic (Emery et al., 2001) and tetradic (Machado, Emery, Capitanio, et al., 2008) interactions, indicated by greater numbers of prosocial behaviors (physical contact and grooming) and more time spent in proximity to their interaction partners. One interpretation of these data is that lesioned animals readily engage new social interaction partners because, in the absence of the amygdala, they fail to appreciate the possibility of social threat. This interpretation is consistent with data that suggest that pharmacologically increasing the activity of the amygdala activity leads to a reduction of social interaction (Málková et al., 2003).

Early damage to the amygdala also perturbs social behavior, although the pattern of effects appears to be related to early rearing contexts and lesion technique. Young, nursery-reared macaques with aspiration amygdala lesions initiate fewer social behaviors when paired with conspecifics at two and six months of age (Bachevalier, 1994). Research from our laboratory has also documented changes in social behavior resulting from early damage to the amygdala (Bauman, Lavenex, Mason, Capitanio & Amaral, 2004a, Bauman, Lavenex, Mason, Capitanio & Amaral, 2004b). Two-week-old rhesus macaques received ibotenic acid lesions (sparing the fibers of passage) to the amygdala or the hippocampus, or sham operations, and then were reared with their mothers with access to larger social “play groups” five days per week. These amygdala-lesioned monkeys did not differ from controls in the amount of time spent socially interacting (e.g., contacting, playing, grooming) with age-matched conspecifics during the first year of life. At this early time point, they were, however, more affectively expressive than controls and hippocampus-lesioned animals. Amygdala-lesioned animals generated more frequently behaviors related to “fear” (e.g., grimacing, screaming, crook-tail, etc.) in familiar social contexts. They also generated more behaviors related to positive affect (or “pro-social behavior”) such as cooing, grunting, lipsmacking, and so forth when interacting with novel age-matched peers (Bauman et al., 2004a). In contrast to the heightened affectivity described above, the amygdala-lesioned monkeys did not produce distress calls when separated from their mothers (Bauman et al., 2004a) and produced fewer behaviors associated with aggression during interactions with novel partners (Bauman et al., 2004b) and during food competition (Bauman, Toscano, Mason, Lavenex & Amaral, 2006). Taken together, these studies illustrate the complexity of social and affective behavioral changes after neonatal amygdala damage.

The Present Experiment

In the present study, we investigated the impact of neonatal damage to the amygdala on adult macaques global (both positive and negative) affective responding to salient video stimuli. Given the impact of amygdala lesions on affective processing and normal social behavior, we were interested in exploring affective responding to stimuli that varied both in terms of their affective content and their social content. To that end, monkeys viewed 30-s video clips that were positive, negative, or neutral in affective content. We varied social content across three levels—videos in which no other monkeys were present (“nonsocial”), videos in which other monkeys could be seen alone or interacting with other monkeys (“social nonengaging”), and videos in which monkeys were directing their activity toward the camera and thus appeared to be engaging the research subject (“social engaging”). This design allowed us to test whether behavioral deficits observed as a result of early amygdala damage were related to processing difficulties of affective content, social content, or both. To our knowledge, these properties have never been disentangled in the study of the amygdala’s role in nonhuman primates. We hypothesized that amygdala-lesioned animals would show blunted affective responding to evocative videos (i.e., positive or negative videos). It is important to note that videos of this sort readily capture adult macaques’ attention (Machado, Bliss-Moreau, Platt, & Amaral, in press; Capitanio, 2002) and have previously been paired with a food reward, in an experimental design similar to the present experiment, to index their value (Rudebeck et al., 2006). It was our hope that the use of dynamic attention capturing videos, rather than static stimuli, would create a context in which animals would engage their robust and diverse behavioral repertoires.

In addition to testing our cohort of adult animals that received bilateral neurotoxic lesions to the amygdala at 2 weeks of age and their neurologically intact control counterparts, we also tested age and rearing history matched animals that received bilateral hippocampus-lesions at 2 weeks of age. In addition to serving as an operated control group, these animals have allowed us to document the minimal impact of early hippocampus damage in affective responding across their development (e.g., Bliss-Moreau et al., 2010, Bliss-Moreau et al., 2011).

Method

All experimental procedures were developed in consultation with the veterinary staff at the California National Primate Research Center (CNPRC). All protocols were approved by the University of California Davis Institutional Animal Care and Use Committee.

Animals and Living Conditions

Subject selection and rearing history has been fully described in previous publications (Bauman et al., 2004a, Bauman et al., 2004b; Bliss-Moreau et al., 2010, Bliss-Moreau et al., 2011). Subjects for the present experiment were 23 adult rhesus macaque monkeys that received bilateral ibotenic acid lesions to either the amygdala (four females, three males) or hippocampus (five females, three males), or sham control operations (four females, four males). A male amygdala-lesioned animal died at approximately 1 year of

age because of a congenital heart defect and was subsequently replaced with an alternative amygdala-lesioned male who underwent surgery at the same time as the original cohort and was raised with his mother only for his first year of life. He became a subject in the present study at 1 year and 3 months of age. A female amygdala-lesioned animal died at approximately 3 years of age; she was not replaced as a subject. The cause of both animals’ deaths was unrelated to their lesion condition.

Surgical procedures. Lesion surgeries were performed at 12–16 days after birth. The surgical procedures summarized below are described in greater detail in previous publications (Bauman et al., 2004a, Bauman et al., 2004b). On the day of surgery, each animal was anesthetized with ketamine hydrochloride (15 mg/kg i.m.) and medetomidine (30 μ g/kg), and then placed in an MRI-compatible stereotaxic apparatus (Crist Instruments Co., Inc., Damascus, MD). The animal’s brain was imaged using a General Electric 1.5 T Gyroscan MRI, T1-weighted Inversion Recovery Pulse sequence with a slice thickness of 1 mm ([TR] = 21, [TE] = 7.9, NEX 3, FOV = 8 cm, Matrix, 256 \times 256). Ibotenic acid injection coordinates for the amygdala or hippocampus were calculated from these images. A stable level of anesthesia was maintained using a combination of isoflurane (1.0% - varied as needed to maintain an adequate level of anesthesia) and intravenous infusion of fentanyl (7–10 μ g/kg/hour). A midline incision was made on the scalp, the skin was laterally displaced to expose the skull, two craniotomies were made over the amygdala or the hippocampus, depending on the predetermined lesion condition, and the dura was reflected to expose the surface of the brain. Ibotenic acid (IBO, Biosearch Technologies Inc., Novato, CA, 10 mg/ml in 0.1 M phosphate buffered saline) was injected simultaneously bilaterally into the amygdala or hippocampus using 10 μ l Hamilton syringes (26 gauge beveled needles) at a rate of 0.2 μ l/min. Sham-operated controls underwent the same presurgical preparations and received a midline incision to expose the skull. The control animals were maintained under anesthesia for the average duration of the lesion surgeries, and the fascia and skin were sutured in two separate layers. After the surgical procedure, all infants were monitored by a veterinarian and returned to their mothers once they were fully alert.

Lesion analysis. The animals are continuing behavioral testing and therefore have not been euthanized. T2-weighted MR images acquired 10 days after surgery were used to examine the extent of the edema associated with the lesion. Images were collected using a General Electric 1.5 T Gyroscan magnet; 1.5-mm-thick sections were taken using a T2-weighted Inversion Recovery Pulse sequence (TR = 4000, TE = 102, NEX 3, FOV = 8 cm, Matrix, 256 \times 256). The hyper-intense T2-weighted signal for each of the 16 lesion animals (eight amygdala lesion, eight hippocampus lesion) was evaluated to confirm the general target and extent of the lesions (i.e., amygdala lesion sparing the hippocampus or hippocampus lesion sparing the amygdala). T2-weighted images of coronal sections through the mid portion of the amygdala are illustrated in previous publications (Bauman et al., 2004a, Bauman et al., 2004b), providing substantial reassurance that the ibotenic acid was injected and was focused in the amygdaloid complex or hippocampal formation. Additionally, lesion extent was further characterized in T1-weight MRI images when animals were four years of age (Machado, Snyder, Cherry, et al., 2008). On average, amygdala tissue was reduced in volume by

72.00% ($SD = 4.34\%$) in animals with amygdala lesions while of hippocampal volume was reduced by 76.65% ($SD = 7.46\%$) in animals with hippocampus lesions. The extent of the targeted lesion was confirmed using histological evaluation in the one amygdala-lesioned animal that died as a result of an unrelated illness (see Bauman et al., 2004a, Bauman et al., 2004b; Bliss-Moreau et al., 2010, Bliss-Moreau et al., 2011).

Animal housing. All animals were returned to their mothers after surgery and housed in standard home cages (61 cm W \times 66 cm D \times 81 cm H). While housed indoors, animals were maintained on a 12-hr light/12-hr dark schedule. Throughout the course of infancy, all subjects and their mothers participated in socialization groups for three hours, five times per week. Each playgroup included six subjects (two from each lesion condition) and an adult male. An adult female was added to the group when the subjects were weaned and separated from their mothers at six months of age. Beginning at one year of age, all animals were housed 24 hours per day in their socialization groups in large indoor chain-link enclosures (2.1m W \times 3.3m D \times 2.4m H). At 3.5 years of age, female subjects were moved into large outdoor enclosures (4.9 m W \times 4.3 m D \times 2.4 m H) in groups. Each social group consisted of one female from each lesion group and one adult male with which the females had no prior experience. Males were relocated into smaller (2.5 m W \times 4.8 m D \times 2.1 m H) outdoor enclosures and maintained in same-sex pairs. At approximately 6.5 years of age, animals were moved indoors and maintained in male–female pairs. At the time of testing, all but two animals (one control male and one hippocampus-lesioned male) were housed in stable male–female pairs. Each animal was allowed complete access to his or her pair-mate and his or her cage each for a minimum of 8 hours per day, 5 days a week. Testing in the current study occurred when animals were on average 7.73 years old ($SD = .11$ year).

Behavioral Testing

Experimental overview. To evaluate the impact of early amygdala damage on responsiveness to affective and social stimuli, all animals completed a *Video Responsiveness Task* during which they viewed a series of videos that varied in terms of both affective and social content. The structure of each trial in the Video Responsiveness Task was similar to that of tasks these animals had previously completed (Bliss-Moreau et al., 2010, Bliss-Moreau et al., 2011) and to tasks typically used to assess macaques' responsiveness to salient stimuli (e.g., Aggleton & Passingham, 1981; Mason et al., 2006; Machado et al., 2009). Specifically, during each 30-s video presentation, animals were concurrently presented with a desired food reward placed near the video screen. The length of time required for each animal to retrieve each food reward is thought to be an index of how interesting/engaging/salient the concurrently presented stimulus is. In this view, food retrieval latencies are long when the stimuli are very salient, because animals either spend a long period of time inspecting the stimulus or avoid it (and the food reward) altogether. Given the importance of food retrieval, we first determined which food items animals preferred during *Food Preference Testing*, and then ensured that the animals would retrieve the food items in the testing cage in the presence of a control video during the *Test Cage Acclimation*. Specific details of these phases are detailed below.

Food preference testing. Before the start of video testing, animals' preference for three different food rewards was assessed in their home-cages. Each animal completed five trials on each of four test days. On each trial, a grape, a banana chip, and a mini marshmallow were placed in individual wells of an ice-cube tray. The ice-cube tray was held in front of an opening on the cage through which the animals could easily reach the food item (presentation time = 30 seconds maximum). Placement of the food items (left to right) in the ice-cube tray was counterbalanced across trials and days. The order that animals retrieved food items was recorded. The food item that animals selected most frequently was used during the responsiveness testing phase. Data are available upon request.

Testing apparatus. All behavioral testing occurred in a large, modified laboratory care cage in which the animals had previously undergone testing (Bliss-Moreau et al., 2010, Bliss-Moreau et al., 2011). The cage had a clear plastic front with two small openings through which the animal could reach. In front of the clear plastic front was an opaque guillotine door that could be raised and lowered between trials to occlude the animal's view of the room. A small table sat directly in front of the clear window and held a 17" flat screen TV encased in a clear Plexiglas box. Food rewards were placed in a small depression in the table, directly in front of the TV. Two experimenters sat diagonally approximately 2 m in front of the cage.

Test cage acclimation. Animals were acclimated to the test cage before behavioral testing. During each acclimation day, animals were placed individually in the test cage. There were 10 30-s trials during which a "baseline" video (PC screen saver) was played on the TV and a desired food reward was presented on the platform. Each 30-s trial began when the opaque guillotine door was lifted and ended when the opaque door was closed. Animals were considered acclimated and allowed to move to the task phase when they retrieved the food item within 30 seconds during eight of 10 trials on two consecutive days.

Video responsiveness task. On each of eight testing days, animals completed seven trials during which a video was shown on the TV and a food reward was placed in the food well. The first trial was considered a "warm-up" and data from it were discarded. Each test day began with a trial during which the "baseline" PC screen saver video was shown and the same "baseline" video was subsequently shown before each experimental video.

Video stimuli were created such that they varied on three levels of social content and three categories of affective content. "Non-social" videos included footage of nature scenes (e.g., leaves blowing in the wind, clouds) and included no images of other monkeys. "Social nonengaging" videos included footage of monkeys interacting with each other (e.g., two monkeys grooming), or alone (e.g., playing in gravel), but in no cases were the pictured monkeys directly looking at the camera or engaging the person recording the video. "Social engaging" videos included footage where a monkey was directly engaging the camera (e.g., threatening, lipsmacking). The content for positive videos included objects believed to be pleasant (i.e., the nonsocial videos; e.g., granola pouring into a bin), affiliative interactions (i.e., the social nonengaging videos; e.g., monkeys grooming and mounting), or a monkey directing an affiliative signal to the observer (i.e., the social engaging videos; e.g., lipsmacking). The content for negative videos included objects believed to be unpleasant (i.e., the nonsocial

cial videos; e.g., monkey catcher net waving), aggressive/antagonistic interactions (i.e., the social nonengaging videos; e.g., monkeys fighting), or a monkey directing a clear aggressive/unpleasant signal to the observer (i.e., the social engaging videos; e.g., threatening). Finally, the content for neutral videos included objects believed to have no affective content—scenes from nature (i.e., the nonsocial videos), monkeys not engaged in interactions (i.e., the social nonengaging videos; e.g., monkeys playing in gravel), and finally monkeys looking directly at the camera but not making any sort of facial expressions (i.e., the social engaging videos; e.g., monkey staring at camera). Each category had at least two videos (see Table 1). A trained observer recorded a number of behaviors using an established ethogram or catalogue of behaviors (see Table 2) during each 30-s trial using The Observer (Noldus Information Technology; Leesburg, VA).

Data processing. Behavior frequency was summed across each behavioral class (see Table 2) for each individual video. Means were then computed for each video category. Duration and latency data were also averaged across each video category. Data were log transformed in cases where they were not normally distributed (as indicated below); in these cases, raw data are presented in tables for ease of interpretation (transformed data are available upon request). Data were subjected to repeated measures analysis of variance (ANOVA) with lesion condition (i.e., 3 groups: amygdala, hippocampus or control) as the between-

subjects factor and social (i.e., 3 levels: nonsocial, social nonengaging, social engaging) and affective content (i.e., 3 levels: positive, negative, neutral) as the two repeated measures. Mauchly's test of sphericity was used to assess whether the data violated the assumption of sphericity. In those cases, degrees of freedom were Greenhouse-Geisser corrected. After omnibus tests, the overall effect of lesion group on each trial type (e.g., positive nonsocial videos, negative social engaging videos, etc.) was computed using univariate ANOVAs with lesion group as the between-subjects factor. When the p value associated with the omnibus F test was significant ($p < .05$) or trend ($p < .08$), p values from significant LSD post hoc comparisons are presented in the figures (and were verified using t tests). We elected to report post hoc comparisons after marginally significant omnibus tests because the effect sizes were moderate. Marginal means from those trial specific ANOVAs were assessed, the data were visually inspected, and in cases where the marginal means suggested a difference between two groups (e.g., amygdala v. control), t tests were performed comparing just those groups. Results from those t tests are reported in the figure legends. In cases where the effect of lesion was assessed across multiple trial types, specific lesion group differences were computed using either paired or independent samples t tests. Levene's test for equality of variances was used to evaluate the variance structure for t tests; corrected degrees of freedom are reported in cases where there were unequal group variances. For the sake of

Table 1
Video Library

Social content	Affective content	Video description
Nonsocial	Positive	Popcorn popping from popcorn maker into bin Granola pouring into pan
	Negative	Capture net waving in air Room cleaning squeegee moving along floor
	Neutral	Leaves blowing in the wind Dandelion blowing in the wind Feather in grass Cage gravel Sky with clouds
Social non-engaging	Positive	Male and female engaging in consortship behavior Young animals playing
	Negative	Monkeys engaging in aggression Monkeys engaging in subordination
	Neutral	Young animal orally exploring cage Female sleeping Young animal chewing on plastic Male orally exploring cage
Social engaging	Positive	Male "lipsmacking" Female "presenting rump" with species typical sexual swelling
	Negative	Male "threatening" Female "threatening"
	Neutral	Male looking at camera Female looking at camera

Table 2
Behavioral Ethogram

Behavior	Description
Affective expressions	
Bark*	Low pitched, sharp, guttural sound.
Crooktail	Stiff-legged strut and tail held in stiff “?” shape
Grimace	Exaggerated grin with teeth.
Repetitive grimace	Multiple instance of a grimace occurring within 3 seconds after the first instance.
Grunt	Deep, muffled, low-intensity vocalization.
Lipsmack	Rapid lip movements with pursed or puckered lips.
Repetitive lipsmack	Multiple instance of a lipsmack occurring within 3 seconds after the first instance.
Present mount	Rigid posture with rump and tail elevated and oriented toward another (may or may not occur in the context of sex).
Scream*	High-pitched vocalization with extreme high intensity; usually sounds like “eeeeeee.”
Threat	Scored when one or more of these components are present: open mouth stare, head bobbing, ear flaps, bark vocalizations, or lunges.
Repetitive threat	Multiple instance of a threat occurring within 3 seconds after the first instance.
Tooth grind	Repetitive, audible rubbing of upper and lower teeth.
Exploratory behavior	
Cage pick*	Animal picks at or fiddles with cage.
Manual exploration	Animal physically touches TV.
Take food	Animal takes food reward.
Stereotypies	
Backflip	Animal flips backwards at least 2 times in a row.
Bounce *	Repetitive hopping or bouncing in the same place (must occur more than 3 times in a row to score).
Extended pace	The animal makes at least another 2 complete revolutions around the experimental cage once the initial pace event is scored
Feces smear*	Wiping feces on or around cage walls or floor.
Head-twist	Animal twists neck in a dramatic display; often seen when turning at corners and/or in conjunction with pacing.
Other stereotypy	Repetitive motor pattern not described by any of the above definitions.
Pace	Repetitive undirected pacing with the same path repeated (must last longer than 3 seconds to score).
Rock*	Rhythmic movement back and forth.
Salute	Animal covers hand over eye or holds hand over eye.
Self-bite	Biting oneself.
Self-clasp*	Unusual holding of body part or limb with another body part.
Spin*	Repetitive twirling or spinning for at least 2 rotations
Swinging	Repetitive swinging in the same place (must last at least 3 seconds to score).
Miscellaneous	
Cage shake	Vigorous shaking of cage bars, or animals slams body against cage.
Freeze	Scored when animal maintains rigidly fixed body position for at least 3 seconds.
Scratch	Animal scratches own body.
Self-groom	Grooming oneself.
Self-sex	Anogenital exploration of self.
Self-shake	Vigorous shaking of own body.
Yawn	Open mouth, exposing teeth.
Position in cage and looking direction	
Back, facing away from TV	The animal’s head is positioned in the rear of the cage with its face directed away from the front of the cage for at least 3 seconds.
Back, facing towards TV	The animal’s head is positioned in the rear of the cage with its face directed towards the front of the cage for at least 3 seconds.
Front, facing away from TV	The animal’s head is positioned in the front of the cage with its face directed away from the front of the cage for at least 3 seconds.
Front, facing towards TV	The animal’s head is positioned in the front of the cage with its face directed towards the front of the cage for at least 3 seconds.
Nonspecific activity	Animal does not remain in the front or rear of the cage. Default state in which each sample is started.

* Behavior was not scored for any monkey during entire study.

brevery, only significant behavioral results are discussed. Additional analyses are available upon request.

Results

Test Cage Acclimation

On average, animals passed acclimation after 5.73 days ($SD = 2.00$). One control male was removed from the sample because he did not pass acclimation after 17 days. Once this male was removed from the sample, experimental groups did not differ in the number of acclimation days required to reach criterion, $F(2, 21) = 1.41, p < .267, \eta_p^2 = .130$ (amygdala-lesioned animals: $M = 5.0, SD = 0$; hippocampus-lesioned animals: $M = 5.5, SD = 1.4$; control animals: $M = 6.7, SD = 3.1$).

Video Responsiveness Task

Retrieval of food reward. All animals retrieved food on all baseline trials. There were no effects of social or affective video content, or lesion condition on the frequency to retrieve the food item during all nonbaseline video trials (log transformed). Animals retrieved the food item on nearly every trial.¹

There was no difference in animals' speed of food retrieval on baseline trials, $F(2, 19) = 1.85, p < .185, \eta_p^2 = .163$. Lesion groups did not differ in terms of how quickly they retrieved foods during the nonbaseline videos, $F(2, 19) = .01, p < .992, \eta_p^2 = .001$. Food retrieval did differ significantly based on social content, $F(2, 4) = 8.92, p < .001, \eta_p^2 = .319$, but not affective content, $F(1.52, 28.97) = 1.38, p < .263, \eta_p^2 = .068$, such that all animals retrieved food fastest on trials with nonsocial content and slowest on trials with videos with social engaging content regardless of affective content (log transformed). Finally, there were no significant interactions: affective content \times lesion, $F(4, 38) = 1.12, p < .360, \eta_p^2 = .106$; social content \times lesion, $F(2, 38) = .17, p < .954, \eta_p^2 = .017$; affective content \times social content, $F(4, 76) = 1.81, p < .136, \eta_p^2 = .087$; affective content \times social content \times lesion $F(8, 76) = .49, p < .856, \eta_p^2 = .050$ (see Figure 1).

Frequency of "expressions." The "expressions" category includes all indexed behaviors which are thought to signal general affective or specific emotional states (e.g., grimacing, lipsmacking, grunting) as well as communicative social behaviors (e.g., presenting "rump"). Across all videos, amygdala-lesioned animals were the least expressive and control animals were the most expressive, $F(2, 19) = 3.68, p < .044, \eta_p^2 = .279$ (see Figure 2). Amygdala-lesioned animals produced significantly fewer expressions than control animals, $t(12) = 3.01, p < .011$, but did not differ significantly from hippocampus-lesioned animals, $t(13) = .54, p < .597$. Controls tended to be more expressive than hippocampus-lesioned animals, $t(13) = 1.79, p < .096$.

Overall, animals were most expressive toward the social-engaging videos compared with social nonengaging and nonsocial videos, $F(1.16, 22.02) = 40.82, p < .0001, \eta_p^2 = .682$. The effect of social content (main effect) did not differ across lesion conditions, $F(2.32, 22.02) = 1.52, p < .239, \eta_p^2 = .138$. On average, animals were equally expressive in the presence of positive, negative, and neutral videos, $F(1.61, 30.65) = 1.23, p < .299, \eta_p^2 = .061$. Lesion condition did not impact the influence of affective

content on expressiveness, $F(3.23, 30.65) = 2.02, p < .117, \eta_p^2 = .138$.

Social and affective content together influenced expressivity, $F(2.74, 52.10) = 7.90, p < .0001, \eta_p^2 = .294$. When content was positive or negative, animals were most responsive to the social engaging videos and equally responsive to the nonsocial and social nonengaging videos. In contrast, when the video content was neutral, animals were differentially expressive across social content categories—specifically, animals were most responsive to the social engaging videos and least responsive to nonsocial videos with an intermediate level of responsivity to social nonengaging videos. The interaction between social and affective content varied for the different lesion groups, $F(5.48, 52.10) = 3.23, p < .011, \eta_p^2 = .254$. Compared with control animals, amygdala-lesioned animals were less expressive during both positive and negative social-engaging videos. Control and amygdala-lesioned animals displayed comparable levels of expressivity when the social-engaging video content was neutral; hippocampus-lesioned animals were less expressive than both control and amygdala-lesioned animals during neutral social-engaging videos.

Given that all animals were most responsive to the social-engaging videos, we evaluated responsivity to those videos only by lesion condition. Amygdala-lesioned animals were equally expressive when content was positive, negative, or neutral, $F(2, 12) = 2.31, p < .142, \eta_p^2 = .278$. In contrast, hippocampus-lesioned and control animals were not consistently responsive across affective categories. Control animals were most responsive to videos with positive content and least responsive to videos with negative content, although the omnibus test did not reach conventional levels of significance, $F(1.13, 6.81) = 4.25, p < .077, \eta_p^2 = .414$. Responsivity to positive videos was significantly greater than to neutral videos, $t(6) = 2.863, p < .029$, and tended to be greater than to negative videos, $t(6) = 2.042, p < .087$. Responsivity to neutral and negative videos did not differ, $t(6) = .891, p < .407$. Hippocampus-lesioned animals were most responsive to videos with positive content and least responsive to videos with neutral content (with negative content as the intermediate), $F(2, 14) = 4.891, p < .025, \eta_p^2 = .411$. They were significantly more responsive to videos with positive content as compared with videos with neutral content, $t(7) = 2.871, p < .024$.

Discussion

Neurologically intact control animals responded robustly to videos with affective and social content by generating many communicative signals while watching the video clips. As such, they appear to be engaging the video stimuli on the TV as if they are "real" stimuli. Neonatal damage to the amygdala resulted in remarkably reduced affective responding to all stimuli. Compared

¹ Lesion conditions did not differ across videos, $F(2, 19) = 1.859, p < .183, \eta_p^2 = .164$. Overall, food retrieval frequency did not vary based on videos' social content, $F(1.48, 28.18) = 1.97, p < .167, \eta_p^2 = .094$, nor affective content, $F(2, 38) = 1.35, p < .272, \eta_p^2 = .066$. Similarly, no interactions were significant: affective content \times lesion, $F(4, 38) = 2.085, p < .102, \eta_p^2 = .180$; social content \times lesion, $F(4, 38) = 1.85, p < .140, \eta_p^2 = .094$; affective content \times social content, $F(4, 76) = .774, p < .545, \eta_p^2 = .039$; affective content \times social content \times lesion, $F(8, 76) = .891, p < .529, \eta_p^2 = .086$. Means available upon request.

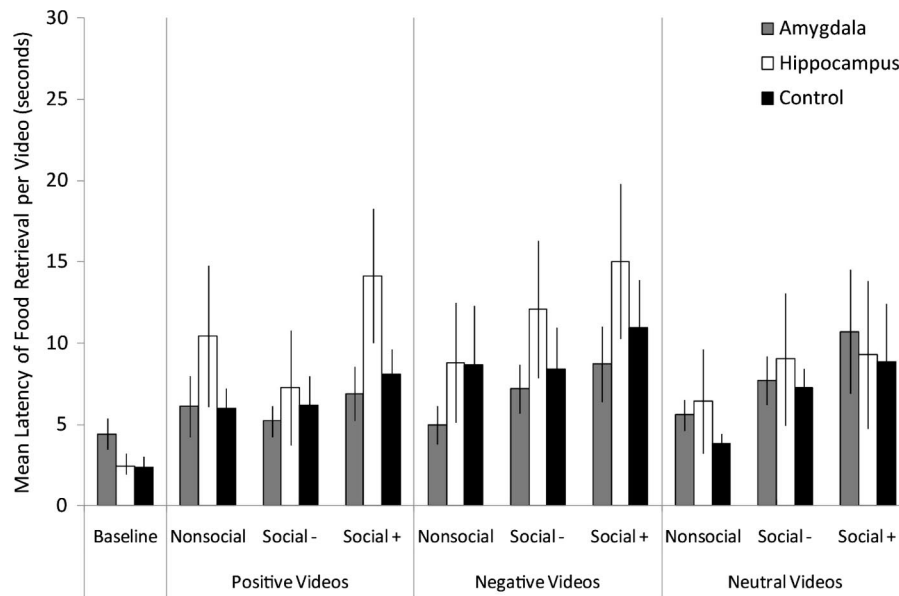


Figure 1. Food retrieval latency. Data columns depict the average time to retrieve food per video type; error bars represent standard errors of the means. Note that the figure uses raw data for the ease of interpretation, although log transformed data were analyzed. *Amygdala*: amygdala-lesioned animals; *Hippocampus*: hippocampus-lesioned animals; *Control*: control animals. *Baseline*: baseline trials with screen saver video. *Affective Content Categories—Positive*: videos with positive affective content; *Negative*: videos with negative affective content. *Neutral*: videos with neutral affective content. *Social Content Categories—Nonsocial*: Nonsocial videos. *Social-*: Social nonengaging videos. *Social+*: Social engaging videos. There were no significant, or marginally significant, lesion group differences in the latency to retrieve food within each specific stimulus type positive nonsocial videos, negative social engaging videos, and so forth).

with control monkeys, monkeys that received bilateral neurotoxic lesions of the amygdala at two weeks of age generated significantly fewer communicative signals (i.e., “affective expressions”) while watching videos with social and nonsocial affective content. Despite the overall reduction in amygdala lesioned animals’ affective responding, amygdala lesioned animals did respond most robustly to social engaging stimuli and least robustly to nonsocial stimuli. In other words, amygdala lesioned animals resembled control monkeys in their ability to differentially respond to stimuli based on social content but differed from control monkeys in their overall level of affective responding. Taken together, these findings suggest that early damage to the amygdala causes a global blunting of affective responding in adulthood, while leaving intact the ability to assess the intensity of social stimuli and to respond appropriately to them.

It is important to note that in the present study, we elected to equate “affective responding” with the generation of both affiliative and aggressive signals, as well as body postures that convey social meaning (e.g., presenting rump). We elected to use this analysis strategy to account for individual differences in affective signaling between monkeys and the expectation that we could not a priori determine what “appropriate” responding was for each category. For example, when faced with a large male monkey generating a threat facial signal, it might be appropriate to threaten the animal if the perceiving animal is also a large, dominant, male monkey. In contrast, the advantageous response for a small, submissive female monkey might be to generate submissive expressions such as lipsmacking or present rump. This approach to the

data seemed to be the most appropriate given that the experimental animals are heterogeneous in terms of size, sex, and rank. In fact, there was a good deal of variation in terms of specific signals generated within a given video category. Unpacking specific deficits in positive or negative affective responding related to amygdala-damage is a potentially fruitful avenue for future research.

The effect of early amygdala damage on affective responding to discrete nonsocial stimuli has been remarkably consistent over time. When the animals in the present study were tested at approximately 9, 18, and 36 months of age in the presence of novel and threat-provoking objects, amygdala-lesioned animals did not generate species typical responses to the objects (e.g., avoidance) and rather interacted with them readily (Bliss-Moreau et al., 2010, Bliss-Moreau et al., 2011). One interpretation of these findings is that interaction with the objects was made possible by a lack of species-typical fear, anxiety, or neophobia—in other words, a lack of, or blunted, negative affect. The present findings build upon that previous work by demonstrating that the amygdala-lesioned animals’ blunted affect is not restricted to the processing of negative, threatening, or fear-provoking stimuli, but instead encompasses processing of both positive and negative stimuli. An avenue for future analysis will be to map these animals’ deficits in responding to discrete affective stimuli to positive and negative social responsiveness across their lives.

Amygdala-lesioned animals’ responses, like control animals’ responses, did vary based on social content. All animals were most responsive to the social engaging videos and least responsive to the

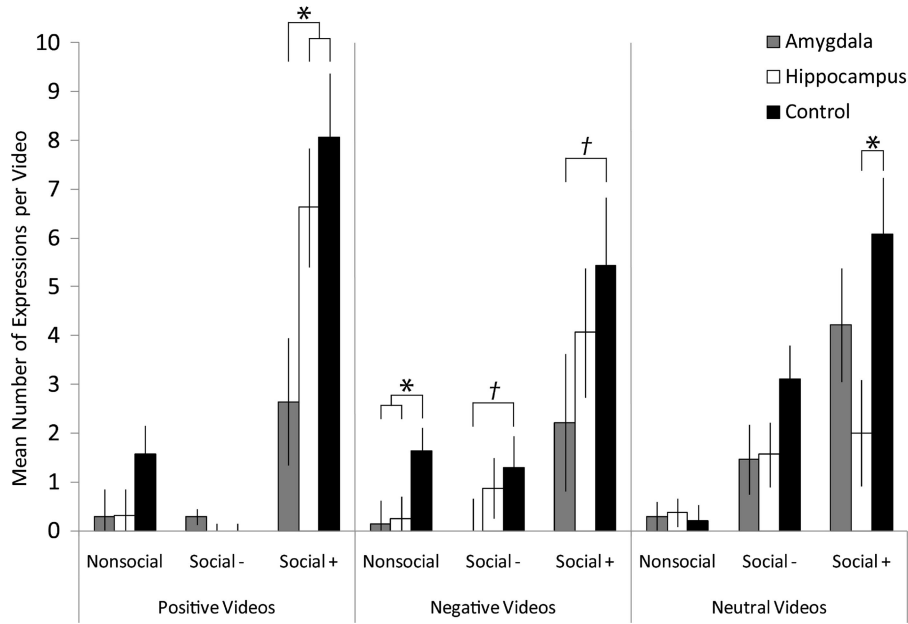


Figure 2. Expressions directed toward video. Data columns depict the mean number of expressions per video type; error bars represent standard errors of the estimated marginal means. *Amygdala*: amygdala-lesioned animals; *Hippocampus*: hippocampus-lesioned animals; *Control*: control animals. *Baseline*: baseline trials with screen saver video. *Affective Content Categories*—*Positive*: videos with positive affective content; *Negative*: videos with negative affective content. *Neutral*: videos with neutral affective content. *Social Content Categories*—*Nonsocial*: Nonsocial videos. *Social-*: Social nonengaging videos. *Social+*: Social engaging videos. * Indicates significant between group differences based on post hoc LSD comparisons or *t* tests. † indicates marginally significant (trend) between group differences based on post hoc LSD comparisons or *t* tests. Amygdala-lesioned animals were significantly less responsive to *positive social engaging* videos than hippocampus-lesioned and control animals, $F(2, 22) = 4.68, p < .023, \eta_p^2 = .330$ (amygdala-lesioned < hippocampus-lesioned, control, $p < .05$). Amygdala- and hippocampus-lesioned were marginally less responsive than controls to *negative nonsocial* videos, $F(2, 22) = 3.01, p < .07, \eta_p^2 = .245$ (amygdala-lesioned, hippocampus-lesioned < control, $p < .05$). Post hoc tests after a marginally significant effect of lesion condition on responsivity *neutral social engaging* videos $F(2, 22) = 3.279, p < .06, \eta_p^2 = .257$, revealed that hippocampus-lesioned animals were significantly less responsive than controls ($p < .05$). Amygdala-lesioned animals were marginally less responsive than controls to *negative social nonengaging* videos, $t(6) = 2.12, p < .08$, and *negative social engaging* videos $t(12) = 2.12, p < .06$.

nonsocial videos. This overall effect was influenced by affective content as well, such that for positive and negative affective content, animals were most responsive to positive and negative social engaging stimuli and equally lowly responsive to social nonengaging and nonsocial stimuli. In contrast, responsivity to neutral information was calibrated with sociality insofar as that animals were most responsive to social engaging stimuli, least responsive to nonsocial stimuli, with social nonengaging stimuli as an intermediate. This pattern held for the amygdala-lesioned and control animals, but not for the hippocampus-lesioned animals. These findings highlight two important points—first, that hippocampus-lesioned animals' affective responses differed from control animals' responses in some contexts and second, that stimuli with “neutral” content (on the basis of human assessment) were not necessarily perceived to be neutral by the rhesus monkey subjects.

As discussed above, the present findings also suggest that early hippocampus damage does influence affective processing, although not to the extent that early amygdala damage does. Hippocampus-lesioned animals' number of expressions were typ-

ically intermediate between amygdala-lesioned and control animals (even if the differences were not significant), and the magnitude of their responses decreased monotonically across affective categories (from positive to negative to neutral). The one notable exception to that pattern is their response to neutral, social-engaging stimuli—hippocampus animals were significantly less responsive to those stimuli as compared with amygdala-lesioned and control animals. Over the course of these animals' lives, we have observed inconsistent patterns of affective deficits resulting from hippocampus damage. For example, at 9 months of age, hippocampus-lesioned animals behaved just like control animals in the presence of novel and threat-related stimuli insofar as they did not touch the objects (Experiment 1; Bliss-Moreau et al., 2010). Yet at 18 months of age, they physically explored threat-related objects that were similar to those with which they had experience (e.g., a toy snake) much like amygdala-lesioned animals (Experiment 2; Bliss-Moreau et al., 2010). Finally, at approximately 36 months of age, they once again behaved like controls in the presence of threat-related objects (Bliss-Moreau et al., 2011). The

inconsistency within the hippocampus-lesioned group is mirrored in the adult lesion literature in which some groups have found affective responding deficits resulting from hippocampus damage (e.g., Chudasama et al., 2009; Chudasama, Wright & Murray, 2007) while other groups have not (e.g., Zola-Morgan et al., 1991). Additional research is needed to further characterize the affective deficits of the current hippocampus-lesioned experimental group. Further, histological examination of these animals' brains will allow us to characterize the neural reorganization that may underlie their affective deficits.

A second interesting finding from the present study is that control and amygdala-lesioned animals generated robust responses to "neutral" social engaging stimuli. The stimuli were selected because the human experimenters detected no inherent affective signal generated from the monkeys that were filmed (i.e., no facial expressions or communicative signals). One interpretation of these findings is that even though the stimuli appeared to be neutral (to the human experimenters), they actually did have subtle affective meaning. This is consistent with the idea that a stimulus' affective meaning (or affective "value") can be indexed by the response that it generates in the perceiver (Barrett & Bliss-Moreau, 2009). In this view, clear and directed social stimuli (e.g., conspecifics looking directly at the subject) are inherently valued even if the conspecifics in those stimuli are not generating an affective response themselves. Future research is needed to investigate what specific properties of social stimuli are necessary to generate an affective response in the observer.

The present findings have important implications for understanding the etiology of disorders characterized by a lack of affective responding. One possible source of such blunted affect may be related to a poorly functioning amygdala from birth. This conclusion is consistent with both the structural and functional neuroimaging literatures in psychiatric neuroscience which point to altered amygdala volumes and abnormal amygdala functioning in a host of psychiatric disorders ranging from bipolar disorder to autism (for reviews: Price & Drevets, 2010; Schumann, Bauman, & Amaral, 2011). Further investigation is warranted to determine whether the affective deficits documented in the present study relate to variation in naturalistic social interactions, the ability to build or maintain social relationships, or variation daily affective experience.

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Received March 29, 2011

Revision received August 22, 2011

Accepted August 26, 2011 ■

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