The Development of Social Behavior Following Neonatal Amygdala Lesions in Rhesus Monkeys

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Abstract

■ We examined the role of the amygdala in the development of nonhuman primate social behavior. Twenty-four rhesus monkeys received bilateral ibotenic acid lesions of either the amygdala or the hippocampus or received a sham surgical procedure at 2 weeks of age. Subjects were reared with their mothers and were provided daily access to social rearing cohorts. The subjects were weaned at 6 months of age and then observed while paired with familiar conspecifics at 6 and 9 months of age and with unfamiliar conspecifics at 1 year of age. The subjects were also observed during daily cohort socialization periods. Neither amygdala nor hippocampus lesions altered fundamental aspects of social behavior development. All subjects, regardless of lesion condition, developed a species-typical repertoire of social behavior and displayed interest in conspecifics during social encounters. The amygdala lesions, however, clearly affected behaviors related to fear processing. The amygdala-lesioned subjects produced more fear behaviors during social encounters than did control or hippocampus-lesioned subjects. Although the heightened fear response of the amygdala-lesioned subjects was consistent across different testing paradigms and was observed with both familiar and novel partners, it did not preclude social interactions. In fact, the amygdala-lesioned subjects displayed particular social behaviors, such as following, cooing, grunting, presenting to be groomed, and presenting to be mounted more frequently than either control or hippocampus-lesioned subjects. These findings are consistent with the view that the amygdala is not needed to develop fundamental aspects of social behavior and may be more related to the detection and avoidance of environmental dangers. ■

INTRODUCTION

Human patients with bilateral damage of the amygdala demonstrate subtle impairments in identifying facial expressions (Adolphs, Tranel, Damasio, & Damasio, 1994), evaluating the trustworthiness of faces (Adolphs, Tranel, & Damasio, 1998), and processing complex social information (Stone, Baron-Cohen, Calder, Keane, & Young, 2003). Nonhuman primates prepared with destructive bilateral amygdala lesions display decreased affiliative behavior and increased social isolation (Steklis & Kling, 1985; Kling, Lancaster, & Benitone, 1970; Kling & Cornell, 1971; Dicks, Myers, & Kling, 1968). Although the precise behavioral outcome following amygdala damage depends on the species, lesion extent, testing environment, and group composition (Kling, 1992; Rosvold, Mirsky, & Pribram, 1954), consistent deficiencies in social behavior have led to the suggestion that a functional amygdala is essential for the normal production and interpretation of social signals (Kling, 1992) and that the amygdala is an essential component of a neural system underlying social behavior (Brothers, 1990). Recent nonhuman primate research, however, which employs selective lesioning techniques paired with quantified behavioral measures indicates that mature rhesus monkeys with bilateral amygdala lesions are quite capable of producing species-typical social signals and interacting with conspecifics (Emery et al., 2001). The behavioral changes observed in these amygdala-lesioned subjects appear more closely related to deficits in fear processing rather than fundamental aspects of social behavior, thus calling into question the role of the amygdala in the production of species-typical social behavior (Amaral, Bauman, Capitanio, et al., 2003).

While mature nonhuman primates may not need a functional amygdala to engage in social behavior, it remains possible that the amygdala is essential for gaining social knowledge during development. One might predict, therefore, that lesions of the amygdala at an early age, prior to extensive socialization, might massively impair an animal's ability to carry out normal social behavior, as previously reported by Bachevalier (1994). Preliminary findings from our program of research, however, have indicated that maternally reared infant monkeys who received neurotoxic amygdala lesions at 2 weeks of age are capable of producing species-typical social signals and interacting with conspecifics (Prather et al., 2001). These results are consistent with

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the hypothesis that the amygdala is not needed for the development of fundamental aspects of social behavior. This study, however, had a relatively small number of subjects and did not include an appropriate comparison group with lesions of another brain region. The current study was designed to replicate and extend the findings of Prather et al. (2001).

Despite the apparently normal repertoire of social behavior seen in the animals studied by Prather et al. (2001), the amygdala-lesioned subjects produced heightened fear responses during social interactions similar to those reported by Thompson, Schwartzbaum, and Harlow (1969) and Thompson (1981). These data suggest that, to the extent that lesions of the amygdala alter social behavior, this may be due to an impairment of systems involved in evaluating environmental dangers rather than in the systems involved in learning and implementing a species-specific repertoire of social behavior.

We have examined the development of social behavior of rhesus monkeys who received bilateral ibotenic acid lesions of the amygdala or the hippocampus or were sham-operated at 2 weeks of age. We have expanded our original study to include more subjects ($N = 24$), a hippocampus-lesioned control group and a naturalistic social rearing environment. Subjects were raised by their mothers and provided daily 3-hr access to a social cohort to approximate the features of macaque social organization (Berman, 1980) that appear necessary for the development of species-typical behavior (Bastian, Sponberg, Suomi, & Higley, 2003; Winslow, Noble, Lyons, Sterk, & Insel, 2003; Parr, Winslow, & Davis, 2002; Shannon, Champoux, & Suomi, 1998; Anderson & Mason, 1974; Mason, 1960; Mason & Sponholz, 1963). The subject animals were permanently separated (weaned) from their mothers at 6 months of age, but continued daily socialization with their original rearing cohort, a familiar adult male and an adult female. The subjects were observed alone, in dyads with familiar subjects from their rearing cohort at 6 and 9 months of age and with unfamiliar subjects from a separate rearing cohort at 1 year of age (Table 1). Subjects were also observed during their daily cohort socialization periods.

We predicted that if the amygdala is essential for the development of normal social behavior, then we would observe a lack of social interest in conspecifics and/or significant impairments in the animal's ability to carry out component processes of social behavior such as producing and responding appropriately to social signals.

Table 1. Summary of Behavioral Observations

Observations	*Sampling Method*	*Description*
Solo		
Home cage	10-sec focal samples[a]	216 observations per subject in individual cages
Six-month solo	5-min focal samples[b]	4 observations per subject in group cage
Nine-month solo	5-min focal samples[b]	4 observations per subject in group cage
Dyad		
Six-month familiar dyad	5-min focal samples[b]	20 observations per subject in group cage
Nine-month familiar dyad	5-min focal samples[b]	20 observations per subject in group cage
Twelve-month novel dyad	5-min focal samples[b]	72 observations per subject in group cage
Social Group		
	5-min focal samples[b]	30 observations per subject in group cage

[a]One–zero behavior scoring.

[b]Duration and frequency behavior scoring.

RESULTS

Magnetic Resonance Imaging and Histological Evaluation of Lesions

The subjects in the current study are continuing behavioral testing and therefore their lesions have not been evaluated histologically. However, we did obtain T2-weighted magnetic resonance (MR) images 10 days after surgery to confirm the general location of the lesion. The exact relation between the T2 hyperintense signal and the actual lesion extent is somewhat controversial (Nemanic, Alvaro, Price, Jackson, & Bachevalier, 2002; Shelton, Oakes, & Kalin, 2002; Malkova, Lex, Mishkin, & Saunders, 2001). However, this technique does provide a means of initial lesion confirmation prior to euthanizing the subjects. The T2 hyperintense signal for each of the 16 lesioned subjects (8 amygdala and 8 hippocampus) 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). Given the histological analysis that we have carried out on one of the lesioned animals (see below), we suspect that the T2-weighted signal may overestimate the actual extent of the lesion. However, we do believe that this change in signal provides substantial reassurance that the ibotenic acid was injected (there was not a failure in the injection procedure) and that the lesion was focused in the amygdaloid complex or the hippocampal formation (Figure 1).

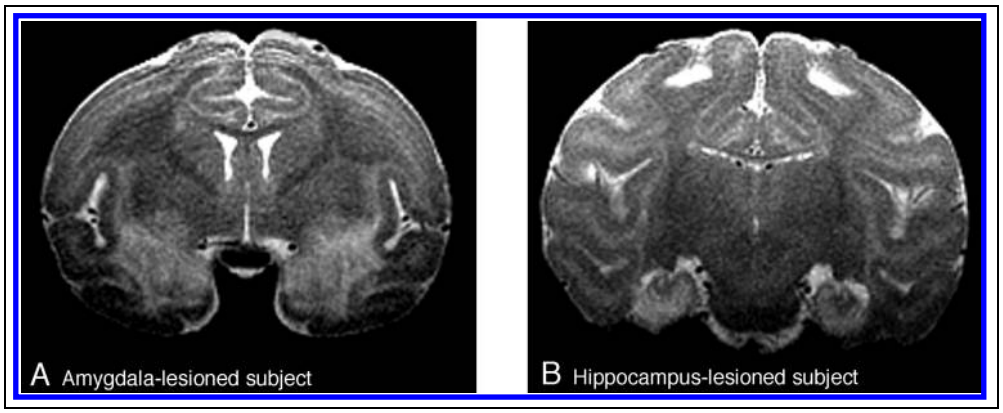

Figure 1. T2-weighted MR images obtained 10 days after injection of ibotenic acid. The T2 hyperintense signal was used to confirm that ibotenic acid was injected and that the lesion target (amygdala or hippocampus) was in the central region of the edema. (A) T2-weighted MR image of an amygdala-lesioned subject. (B) T2-weighted MR image of a hippocampus-lesioned subject.

One amygdala-lesioned subject was euthanized after behavioral testing for health reasons unrelated to the lesion surgery, thus enabling histological evaluation of the lesion (Figure 2). The region of actual neuronal damage was more confined to the amygdala than suggested by the extent of the postlesion edema visualized by the T2 MR images. The subject sustained substantial bilateral amygdala damage, with residual cell patches limited to the medial surface of the amygdala, including the amygdalo-hippocampal area, the nucleus of the lateral olfactory tract, and the ventromedial aspect of the parvicellular division of the basal nucleus. Collateral damage was limited to focal damage in the sulcus of the superior temporal gyrus, ventral claustrum, and the most rostral portions of the hippocampal formation, primarily the subiculum.

Behavioral Definitions and Statistical Analyses

Thirty-nine species-typical behaviors were recorded and analyzed during observations of the subjects alone (solo), in pairs (dyad), and in social groups (Table 2). Behaviors that occur for a measurable length of time (duration behaviors), such as grooming, physical contact, and play, were evaluated for both duration and frequency of occurrence. Behaviors without a measurable time component (frequency behaviors), such as facial expressions and vocalizations, were only analyzed for their frequency. Most of the lesion effects that we observed involved the frequency of behaviors initiated by the focal subject. These are listed in Tables 4–7 and described in detail below. Differences in duration are not included in the tables and are only reported in the text when significant.

Although each behavior was recorded and analyzed separately, we grouped the most commonly produced behaviors into broad categories (affiliative, fearful, aggressive) based on descriptions in the literature (Hinde & Spencer-Booth, 1967; Hansen, 1966; Rowell & Hinde, 1962) to facilitate presentation of our findings. Several of the behaviors fit into more than one behavioral category, and these were therefore grouped according to the context in which they were most frequently observed. For example, crook tails in mature macaque monkeys are usually considered a display of dominance. However, in infant macaques, we have observed that this behavior is associated with high levels of arousal or distress. Given that the crook-tail postures were typically produced in concert with fear behaviors (i.e., fear grimaces, flees, and screams), we believe that it is reasonable to group this behavior with the fear responses.

Analysis of variance (ANOVA) followed by Fisher's protected least significant difference (PLSD) post hoc tests (with a significance level of $p < .05$) was used for data analyses. Two-factor ANOVA (Focal Subject Lesion × Partner Lesion) was used to analyze data from social interactions consisting of only two partners (familiar and novel dyads). In the results, what we call a ''partner effect'' indicates a situation where the likelihood of a behavior occurring is dependent on the animal (amygdala- or hippocampus-lesioned or control) with which the focal animal is paired. Two factor ANOVA (Focal Subject Lesion × Behavior Recipient) was used to analyze data from social interactions consisting of multiple partners (social groups). The recipient of behavior indicates the identity of the subject that the behaviors were directed to (amygdala- or hippocampus-lesioned or control). Thus, behavior recipient effects indicate the frequency in which a particular behavior was directed to members of a specific experimental group. In appropriate cases, repeated measures ANOVAs and paired t tests were performed, with a significance level set at $p < .05$.

Overview of Behavioral Findings

Subjects from all experimental groups were capable of producing social behaviors that are typical for this species at the ages observed (Hinde & Spencer-Booth, 1967; Hansen, 1966) (Table 2). There were very few instances of stereotypies, tantrums, or self-directed

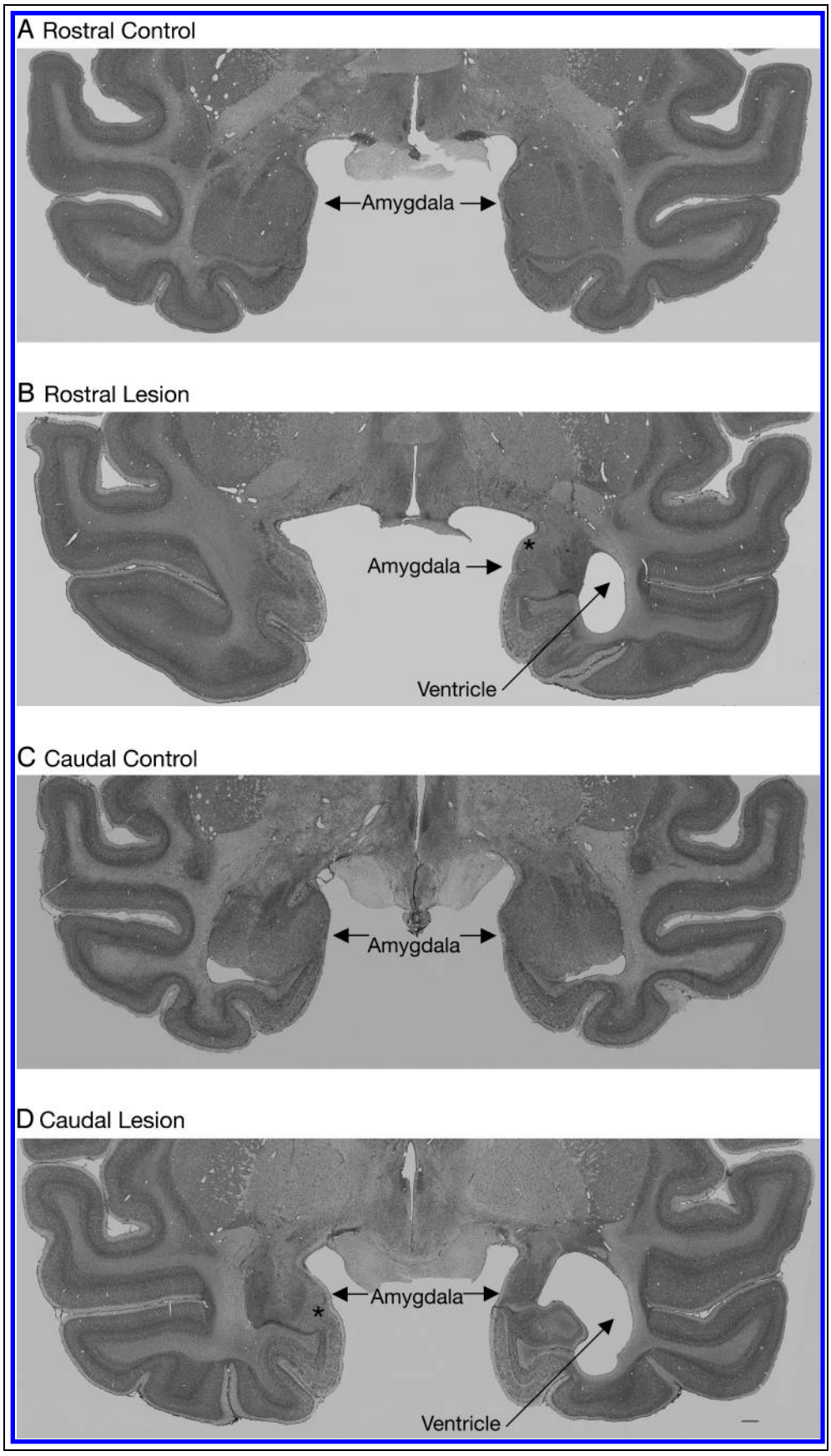

Figure 2. Nissl-stained coronal sections through two levels of the amygdala in an adult control animal used in another study (A and C) and one of the amygdala-lesioned subjects sacrificed at 1.5 years of age (B and D). (A) Rostral level of the amygdala illustrated in the control subject. (B) Rostral level of the amygdala-lesioned subject showing an expanded ventricle and substantial amygdala damage on the right side and cell damage to the rostral portion of the amygdala on the left side. The asterisk indicates sparing in the medial portion of the accessory basal nucleus and the periamygdaloid cortex. (C) Caudal level of the amygdala illustrated in the control subject. (D) Caudal level of the amygdala-lesioned subject showing an expanded ventricle and nearly complete cell loss on the right side and substantial cell damage on the left side. The asterisk indicates sparing in a small, ventomedial portion of the parvicellular division of the basal nucleus on the left side.

Table 2. Behavioral Ethogram (6–12 Months of Age)

Behaviors	*Description*
Duration Behaviors	
Extended play	Play behavior lasting for more than 3 sec
Extended negative	Aggressive encounters lasting more than 3 sec
Groom	Picking or licking another monkey's fur for more than 3 sec
Proximity	Within arm's reach of another subject for more than 3 sec
Nonsocial active	Active behavior (head up/exploring) out of proximity for more than 3 sec
Nonsocial inactive	Passive behavior (head down/not exploring) out of proximity for more than 3 sec
Physical contact	Physical contact with another subject for more than 3 sec
Sleep	Eyes closed, no activity for more than 3 sec
Social activity	Alternating proximity and contact within a group for more than 3 sec
Frequency Behaviors	
Aggression	Grab, hit, bite, or slap
Anogenital explore	Sniffing, touching, or licking genital area of another subject
Approach	Directed movement into arm's reach of another subject
Bark	Sharp, guttural vocalization
Cage shake	Dominance display involving shaking the cage
Chase	Quick, directed movement after another subject lasting more than 3 sec
Coo	High-pitched, soft vocalization
Crook tail	Tail is held in a stiff "?" formation
Displacement	Scored when another subject approaches and "takes the place" of the other subject
Fear grimace	Upper and lower lips retracted, exposing teeth
Flee	Rapid movement away from another subject
Follow	Slow, deliberate movement after another subject lasting for more than 3 sec
Freeze	No movement for more than 3 sec (note: only scored for novel dyads)
Grunt	Soft, guttural sound produced in affiliative encounters
Incomplete mount	One or two of the following: double foot clasp, partner positioning, or thrusting
Lipsmack	Rhythmic lip movements, often with pursed lips
Manual explore	Use of hands to explore physical environment
Mount	Includes double foot clasp, appropriate partner positioning, and thrusting
Oral explore	Use of mouth to explore physical environment
Social play	Rough and tumble play, grappling
Present groom	Rigid presentation of body part for grooming
Present mount	Stiff, four point stance, tail up, rump toward partner
Scratch	Rapid hand movements, using fingers to scratch own body
Scream	High-pitched, high-intensity vocalization indicating fear or distress
Self clasp	Grasping own body
Stereotypic movement	Abnormal motor movements, including circling, back flipping, spinning, or pacing
Tantrum	Shaking/spasms of body, often accompanied by gecker vocalization
Tooth grind	Audible rubbing of lower premolars and upper canines
Threat	One or more of the following: open mouth stare, head bob, lunge
Withdraw	Movement out of arm's reach of another subject
Yawn	Fully open mouth, lips retracted, and teeth showing

behaviors that can be associated with abnormal rearing conditions (Mason & Green, 1962; Mason & Sponholz, 1963). In addition, there were no consistent differences among experimental groups in the amount of time spent in contact, proximity, extended play behaviors, extended negative behaviors, nonsocial activity, and inactivity. The lesion groups did, however, differ in the frequency of certain specific behaviors that are described in detail below.

Table 3. Home Cage Observations: One–Zero Scoring

	AMY	*CON*	*HIP*	*Lesion Effect*	*Post Hoc*
Affiliative					
Coo	27.875 ± 4.365	77.125 ± 13.406	55.250 ± 10.333	$F(2,21) = 5.978$, $p = .0088$	C > A ($p = .0024$)
Grunt	24.875 ± 9.205	27.250 ± 7.333	28.375 ± 6.936	$F(2,21) = 0.051$, $p = .9501$	–
Lipsmack	29.500 ± 5.584	46.500 ± 10.836	52.125 ± 16.194	$F(2,21) = 1.013$, $p = .3801$	–
Present groom	15.000 ± 13.293	7.000 ± 3.333	8.750 ± 6.16	$F(2,21) = 0.235$, $p = .7926$	–
Present mount	0.250 ± 0.164	4.000 ± 3.162	3.625 ± 2.584	$F(2,21) = 0.766$, $p = .4774$	–
Fearful					
Fear grimace	23.250 ± 6.576	47.250 ± 11.365	32.875 ± 11.269	$F(2,21) = 1.462$, $p = .2545$	–
Freeze	12.750 ± 3.895	2.375 ± 0.944	2.625 ± 0.944	$F(2,21) = 6.201$, $p = .0077$	A > C ($p = .0056$) A > H ($p = .0066$)
Scream	3.375 ± .822	9.875 ± 1.747	3.875 ± 1.093	$F(2,21) = 7.975$, $p = .0027$	C > A ($p = .0017$) C > H ($p = .0033$)
Crook tail	8.875 ± 2.930	19.750 ± 6.516	15.125 ± 5.390	$F(2,21) = 1.116$, $p = .3464$	–
Aggressive					
Bark	6.875 ± 1.726	11.750 ± 3.629	10.625 ± 3.412	$F(2,21) = 0.703$, $p = .5062$	–
Threat	11.000 ± 07.339	2.625 ± 1.133	8.375 ± 3.530	$F(2,21) = 0.814$, $p = .4565$	–
Other					
Cage stereotypy	3.250 ± 2.007	17.500 ± 6.242	1.750 ± 1.473	$F(2,21) = 5.020$, $p = .0165$	C > H ($p = .0092$) C > A ($p = .0168$)
Crouch	8.250 ± 1.398	3.375 ± 0.981	6.625 ± 2.528	$F(2,21) = 1.986$, $p = .1622$	–
Self-groom	0.875 ± 0.639	1.000 ± 0.327	1.375 ± 0.375	$F(2,21) = 0.310$, $p = .7371$	–
Self-bite	1.375 ± 0.706	1.125 ± 0.350	0.625 ± 0.263	$F(2,21) = 0.634$, $p = .5402$	–
Self-clasp	5.500 ± 2.471	2.750 ± 1.130	3.250 ± 1.082	$F(2,21) = 0.753$, $p = .4834$	–
Self-play	9.500 ± 2.405	8.750 ± 1.810	6.500 ± 1.476	$F(2,21) = 0.651$, $p = .5320$	–
Sleep	0.000 ± 0.000	0.375 ± 0.263	0.375 ± 0.263	$F(2,21) = 1.016$, $p = .3791$	–
Tooth grind	0.500 ± 0.500	0.375 ± 0.375	0.250 ± 0.164	$F(2,21) = 0.112$, $p = .8943$	–

One–zero scoring was used for daily home cage observations; any behavior occurring within the 10-sec observation period received a score of 1 (even if the behavior was repeated), whereas behaviors that were not observed received a score of 0. The average number of 10-sec trials in which the behavior was observed (out of 216 total trials) ± *SEM* is shown for amygdala-lesioned subjects (AMY), sham-operated control subjects (CON), and hippocampus-lesioned subjects (HIP). ANOVA followed by Fisher's PLSD post hoc tests (with a significance level of $p < .05$) were used for data analysis (A = amygdala-lesioned subjects; C = sham-operated control subjects; H = hippocampus-lesioned subjects).

Home Cage Observations

Each subject was observed in its individual home cage approximately nine times per week between 6 and 12 months of age (Table 3). During these observations, controls appeared more agitated, as they produced more screams and cage stereotypies than either amygdala- or hippocampus-lesioned subjects. In addition, controls also produced more coos than amygdala-lesioned subjects. Amygdala-lesioned subjects froze more frequently than either control or hippocampus-lesioned subjects.

Social Group Observations

Each subject was observed on 30 separate occasions during daily group socialization with all members of their rearing cohort (two amygdala-lesioned subjects, two hippocampus-lesioned subjects, two sham-operated controls, one adult female, and one adult male). Lesion effects were found for certain affiliative behaviors (Table 4). Amygdala-lesioned subjects groomed other monkeys less frequently than controls. Hippocampus-lesioned subjects presented for grooming more frequently than either control or amygdala-lesioned subjects. The recipient of affiliative behaviors revealed lesion effects for lipsmack, presents for grooming, presents for mounting, physical contact, and proximity. In general, controls were more likely to receive these behaviors than were amygdala-lesioned subjects.

Consistent lesion effects were found for behaviors associated with fear (Table 4). Amygdala-lesioned subjects produced more fear grimaces and crook tails than either control or hippocampus-lesioned subjects. Amygdala-lesioned subjects also screamed more than hippocampus-lesioned subjects and fled more frequently than controls. There were no significant effects for the recipient of these fear behaviors, suggesting that fear behaviors were directed equally to subjects from all three experimental groups. Tantrums are another indicator of fear or extreme distress. Although the frequency of tantrums was very low, amygdala-lesioned subjects produced more tantrums than either control or hippocampus-lesioned subjects, $F(2,21) = 6.40$, $p = .0067$; $p = .0036$ and $p = .0088$, respectively. It should be noted, however, that amygdala-lesioned subjects produced an average of only 2.4 tantrums over a total of 150 min of observations, while hippocampus-lesioned subjects averaged 0.50 tantrums and controls averaged 0.25 tantrums.

A lesion effect was also found for displacements; controls displaced other subjects more frequently than amygdala-lesioned subjects did. There were no significant effects for the recipient of aggressive behaviors, suggesting that these behaviors were directed equally to subjects from all three experimental groups.

Lesion effects were also found for nonsocial behaviors, $F(2,21) = 6.47$, $p < .0064$; amygdala-lesioned subjects explored the cage orally less frequently than control or hippocampus-lesioned subjects ($p = .0029$ and $p = .0114$, respectively).

Six-month Solo Observations

During the 6-month solo observations, only oral exploration of the cage differed among experimental groups, $F(2,21) = 6.16$, $p = .0077$; amygdala-lesioned subjects orally explored the cage less frequently than did control ($p = .0028$) or hippocampus-lesioned subjects ($p = .0198$).

Six-month Familiar Dyad Observations

Lesion effects were found for several affiliative behaviors, including follows, coos, and grunts (Table 5). Amygdala-lesioned subjects followed and cooed more frequently than control or hippocampus-lesioned subjects and grunted more frequently than controls. Although the total time spent in physical contact did not differ between the experimental groups, $F(2,63) = 2.31$, $p = .1081$, the amygdala-lesioned subjects engaged in physical contact less frequently than controls. Partner effects were only found for the frequency of following, indicating that this behavior occurred more frequently when subjects were paired with a hippocampus-lesioned subject.

Consistent lesion effects were found for behaviors associated with fear, including fear grimaces, flees, and screams (Table 5). Amygdala-lesioned subjects produced more fear grimaces and fled more frequently than control or hippocampus-lesioned subjects, and screamed more frequently than controls. There were no partner effects, indicating that these fear behaviors were not produced more frequently when paired with individuals from a particular experimental group.

Lesion effects were also found for nonsocial behaviors, $F(2,63) = 10.73$, $p < .0001$; amygdala-lesioned subjects orally explored the cage less frequently than control or hippocampus-lesioned subjects ($p < .0001$ and $p = .0049$, respectively).

Nine-month Solo Observations

There were no lesion effects for any of the 39 species-typical behaviors.

Nine-month Familiar Dyad Observations

As was the case for the 6-month familiar dyads, lesion effects were found for affiliative behaviors at 9 months (Table 6). Amygdala-lesioned subjects followed their dyad partner more frequently than hippocampus-lesioned subjects, and cooed more frequently than controls. Amygdala-lesioned subjects also grunted more frequently than either control or hippocampus-lesioned

Table 4. Social Group Observations: Behavioral Frequency

	AMY	*CON*	*HIP*	*Lesion Effect*	*Post Hoc*	*Behavior Recipient Effect*	*Post Hoc*
Affiliative							
Approach	5.158 ± 0.850	4.421 ± 0.715	5.996 ± 0.818	$F(2,63) = 0.88, p = .4217$	–	$F(2,63) = 2.21, p = .1181$	–
Coo	0.096 ± 0.018	0.042 ± 0.015	0.104 ± 0.059	$F(2,63) = 0.51, p = .6020$	–	$F(2,63) = 0.29, p = .7475$	–
Groom	0.042 ± 0.018	0.112 ± 0.033	0.075 ± 0.026	$F(2,63) = 3.25, p = .0454$	C > A ($p = .0149$)	$F(2,63) = 0.14, p = .8715$	–
Grunt	0.104 ± 0.036	0.108 ± 0.035	0.133 ± 0.043	$F(2,63) = 0.45, p = .6418$	–	$F(2,63) = 0.35, p = .7079$	–
Follow	0.029 ± 0.020	0.037 ± 0.017	0.037 ± 0.016	$F(2,63) = 0.37, p = .6892$	–	$F(2,63) = 1.41, p = .2514$	–
Lipsmack	0.212 ± 0.049	0.204 ± 0.081	0.250 ± 0.048	$F(2,63) = 0.64, p = .5326$	–	$F(2,63) = 3.59, p = .0334$	C > A ($p = .0362$) H > A ($p = .0164$)
Mount	0.013 ± 0.009	0.167 ± 0.090	0.133 ± 0.066	$F(2,63) = 1.90, p = .1584$	–	$F(2,63) = 1.25, p = .2925$	–
Play	0.958 ± 0.229	1.267 ± 0.232	1.388 ± 0.091	$F(2,63) = 0.87, p = .4250$	–	$F(2,63) = 0.35, p = .7087$	–
Present groom	0.242 ± 0.116	0.083 ± 0.021	0.463 ± 0.078	$F(2,63) = 6.50, p = .0027$	H > A ($p = .0224$) H > C ($p = .0007$)	$F(2,63) = 3.74, p = .0291$	C > A ($p = .0082$)
Present mount	0.221 ± 0.080	0.121 ± 0.046	0.288 ± 0.088	$F(2,63) = 1.49, p = .2340$	–	$F(2,63) = 5.07, p = .0091$	C > A ($p = .0023$)
Physical contact	0.362 ± 0.090	0.250 ± 0.079	0.487 ± 0.096	$F(2,63) = 1.07, p = .3483$	–	$F(2,63) = 3.37, p = .0406$	C > A ($p = .0119$)
Proximity	0.442 ± 0.082	0.333 ± 0.059	0.471 ± 0.055	$F(2,63) = 0.13, p = .8802$	–	$F(2,63) = 7.34, p = .0014$	C > A ($p = .0003$) C > H ($p = .0257$)
Fearful							
Fear grimace	0.404 ± 0.172	0.029 ± 0.020	0.108 ± 0.034	$F(2,63) = 4.71, p = .0124$	A > C ($p = .0052$) A > H ($p = .0227$)	$F(2,63) = 0.07, p = .9329$	–
Flee	0.542 ± 0.131	0.171 ± 0.077	0.300 ± 0.060	$F(2,63) = 4.04, p = .0223$	A > C ($p = .0071$)	$F(2,63) = 2.28, p = .1111$	–
Scream	0.138 ± 0.047	0.071 ± 0.025	0.033 ± 0.017	$F(2,63) = 4.02, p = .0228$	A > H ($p = .0062$)	$F(2,63) = 2.19, p = .1210$	–
Crook tail	0.496 ± 0.165	0.121 ± 0.050	0.188 ± 0.050	$F(2,63) = 5.36, p = .0071$	A > C ($p = .0026$) A > H ($p = .0201$)	$F(2,63) = 1.82, p = .1707$	–
Aggressive							
Aggression	0.029 ± 0.008	0.092 ± 0.027	0.075 ± 0.031	$F(2,63) = 1.11, p = .3373$	–	$F(2,63) = 1.11, p = .3373$	–
Chase	0.071 ± 0.028	0.083 ± 0.035	0.092 ± 0.031	$F(2,63) = 0.52, p = .5982$	–	$F(2,63) = 2.98, p = .0582$	–
Displace	0.025 ± 0.012	0.100 ± 0.039	0.050 ± 0.017	$F(2,63) = 3.64, p = .0318$	C > A ($p = .0113$)	$F(2,63) = 0.87, p = .4257$	–
Threat	1.129 ± 0.268	1.554 ± 0.286	1.929 ± 0.230	$F(2,63) = 2.68, p = .0764$	–	$F(2,63) = 1.27, p = .2874$	–

Frequency of the most common social behaviors exhibited during social group observations. Average number of occurrence ± *SEM* per 5 min is shown for amygdala-lesioned subjects (AMY), sham-operated control subjects (CON), and hippocampus-lesioned subjects (HIP). Two-factor (Focal Subject Lesion × Behavior Recipient) ANOVAs followed by Fisher's PLSD post hoc tests (with a significance level of $p < .05$) were used for data analysis (A = amygdala-lesioned subjects; C = sham-operated control subjects; H = hippocampus-lesioned subjects).

Table 5. Six-month Familiar Dyads: Behavior Frequency

	AMY	*CON*	*HIP*	*Lesion Effect*	*Post Hoc*	*Partner Effect*	*Post Hoc*
Affiliative							
Approach	3.900 ± 0.763	3.462 ± 0.548	3.525 ± 0.427	$F(2,63) = 0.15, p = .8600$	–	$F(2,63) = 1.35, p = .2670$	–
Coo	11.469 ± 2.274	5.225 ± 1.626	5.631 ± 1.172	$F(2,63) = 9.97, p = .0002$	A > C ($p = .0002$) A > H ($p = .0005$)	$F(2,63) = 0.05, p = .9551$	–
Groom	0.063 ± 0.049	0.169 ± 0.047	0.069 ± 0.028	$F(2,63) = 3.0, p = .0572$	–	$F(2,63) = 0.63, p = .5372$	–
Grunt	4.212 ± 1.276	2.031 ± 0.269	3.431 ± 0.783	$F(2,63) = 3.79, p = .0278$	A > C ($p = .0086$)	$F(2,63) = 0.14, p = .8736$	–
Follow	0.706 ± 0.236	0.244 ± 0.106	0.150 ± 0.050	$F(2,63) = 4.78, p = .0116$	A > C ($p = .0174$) A > H ($p = .0057$)	$F(2,63) = 4.61, p = .0136$	H > A ($p = 0.0043$) H > C ($p = 0.0444$)
Lipsmack	1.169 ± 0.568	0.638 ± 0.082	0.625 ± 0.222	$F(2,63) = 1.67, p = .1957$	–	$F(2,63) = 0.03, p = .9733$	–
Mount	0.075 ± 0.062	0.669 ± 0.254	0.344 ± 0.174	$F(2,63) = 5.37, p = .0070$	A < C ($p < .0018$)	$F(2,63) = 0.55, p = .5778$	–
Play	0.038 ± 0.026	0.106 ± 0.041	0.131 ± 0.089	$F(2,63) = 1.41, p = .2525$	–	$F(2,63) = 1.67, p = .2025$	–
Present groom	0.319 ± 0.126	0.306 ± 0.140	0.294 ± 0.102	$F(2,63) = 0.16, p = .8487$	–	$F(2,63) = 0.75, p = .4776$	–
Present mount	0.319 ± 0.179	0.225 ± 0.077	0.813 ± 0.327	$F(2,63) = 3.45, p = .0379$	H > A ($p = .0376$) H > C ($p = .0193$)	$F(2,63) = 0.80, p = .4530$	–
Physical contact	0.225 ± 0.113	0.763 ± 0.126	0.525 ± 0.139	$F(2,63) = 3.30, p = .0435$	A < C ($p = .0156$)	$F(2,63) = 1.25, p = .2941$	–
Proximity	1.20 ± 0.271	0.975 ± 0.182	0.683 ± 0.055	$F(2,63) = 3.86, p = .0263$	A > H ($p = .0079$)	$F(2,63) = 1.38, p = .2581$	–
Fearful							
Fear grimace	1.10 ± 0.483	0.094 ± 0.055	0.069 ± 0.027	$F(2,63) = 7.49, p = .0012$	A > C ($p = .0016$) A > H ($p = .0012$)	$F(2,63) = 0.10, p = .9093$	–
Flee	0.581 ± 0.178	0.181 ± 0.081	0.163 ± 0.080	$F(2,63) = 6.30, p = .0032$	A > C ($p = .0049$) A > H ($p = .0021$)	$F(2,63) = 0.27, p = .7674$	–
Scream	2.044 ± 0.842	0.156 ± 0.071	0.931 ± 0.602	$F(2,63) = 4.90, p = .0105$	A > C ($p = .0028$)	$F(2,63) = 0.23, p = .7980$	–
Crook tail	0.569 ± 0.204	0.519 ± 0.181	0.475 ± 0.164	$F(2,63) = 0.05, p = .9512$	–	$F(2,63) = 1.25, p = .2923$	–
Aggressive							
Aggression	0.031 ± 0.013	0.119 ± 0.025	0.013 ± 0.008	$F(2,63) = 4.52, p = .0147$	C > H ($p = .0043$)	$F(2,63) = 0.83, p = .4395$	–
Chase	0	0	0	–	–	–	–
Displace	0	0.044 ± 0.020	0.031 ± 0.016	$F(2,63) = 2.68, p = .0766$	–	$F(2,63) = 1.88, p = .1607$	–
Threat	0.038 ± 0.018	0.169 ± 0.096	0.125 ± 0.055	$F(2,63) = 1.82, p = .1709$	–	$F(2,63) = 1.06, p = .3525$	–

Frequency of the most common social behaviors exhibited during the 6-month familiar dyad observations. Average number of occurrence ± *SEM* per 5 min is shown for amygdala-lesioned subjects (AMY), sham-operated control subjects (CON), and hippocampus-lesioned subjects (HIP). Two-factor (Focal Subject Lesion × Partner Lesion) ANOVAs followed by Fisher's PLSD post hoc tests (with a significance level of $p < .05$) were used for data analysis (A = amygdala-lesioned subjects; C = sham-operated control subjects; H = hippocampus-lesioned subjects).

Table 6. Nine-month Familiar Dyads: Behavior Frequency

	AMY	*CON*	*HIP*	*Lesion Effect*	*Post Hoc*	*Partner Effect*	*Post Hoc*
Affiliative							
Approach	2.956 ± 0.520	3.144 ± 0.436	3.031 ± 0.305	$F(2,63) = 0.19$, $p = .8263$	–	$F(2,63) = 0.84$, $p = .4369$	–
Coo	8.137 ± 2.454	2.862 ± 0.896	5.088 ± 1.154	$F(2,63) = 6.09$, $p = .0038$	A > C ($p = .0009$)	$F(2,63) = 0.08$, $p = .9224$	–
Groom	0.025 ± 0.019	0.075 ± 0.028	0.056 ± 0.032	$F(2,63) = 1.52$, $p = .2264$	–	$F(2,63) = 1.14$, $p = .3251$	–
Grunt	4.731 ± 1.715	1.406 ± 0.219	2.619 ± 0.447	$F(2,63) = 5.51$, $p = .0062$	A > C ($p = .0018$) A > H ($p = .0319$)	$F(2,63) = 0.88$, $p = .4208$	–
Follow	0.537 ± 0.220	0.213 ± 0.118	0.081 ± 0.030	$F(2,63) = 4.14$, $p = .0205$	A > H ($p = .0066$)	$F(2,63) = 1.62$, $p = .2058$	–
Lipsmack	0.950 ± 0.194	0.794 ± 0.150	1.125 ± 0.231	$F(2,63) = 0.71$, $p = .4963$	–	$F(2,63) = 0.11$, $p = .8991$	–
Mount	0.050 ± 0.034	0.412 ± 0.160	0.331 ± 0.189	$F(2,63) = 2.60$, $p = .0826$	–	$F(2,63) = 0.93$, $p = .3993$	–
Play	0.206 ± 0.110	0.475 ± 0.160	0.275 ± 0.132	$F(2,63) = 1.12$, $p = .3329$	–	$F(2,63) = 0.08$, $p = .9246$	–
Present groom	0.431 ± 0.175	0.306 ± 0.082	0.444 ± 0.209	$F(2,63) = 0.12$, $p = .8870$	–	$F(2,63) = 0.10$, $p = .3742$	–
Present mount	0.506 ± 0.251	0.344 ± 0.149	0.613 ± 0.232	$F(2,63) = 0.47$, $p = .6256$	–	$F(2,63) = 2.66$, $p = .0776$	–
Physical contact	0.181 ± 0.066	0.550 ± 0.126	0.369 ± 0.084	$F(2,63) = 3.87$, $p = .0260$	A < C ($p = .0072$)	$F(2,63) = 0.53$, $p = .5899$	–
Proximity	0.525 ± 0.118	0.519 ± 0.081	0.487 ± 0.078	$F(2,63) = 0.16$, $p = .8561$	–	$F(2,63) = 1.84$, $p = .1672$	–
Fearful							
Fear grimace	1.844 ± 0.875	0.063 ± 0.025	0.212 ± 0.082	$F(2,63) = 6.82$, $p = .0021$	A > C ($p = .0015$) A > H ($p = .0032$)	$F(2,63) = 0.87$, $p = .4251$	–
Flee	1.719 ± 0.483	0.487 ± 0.211	1.306 ± 0.236	$F(2,63) = 5.28$, $p = .0076$	A > C ($p = .0022$) H > C ($p = .0363$)	$F(2,63) = 0.48$, $p = .6215$	–
Scream	1.638 ± 0.577	0.294 ± 0.148	1.000 ± 0.639	$F(2,63) = 4.23$, $p = .0189$	A > C ($p = .0050$)	$F(2,63) = 0.58$, $p = .5622$	–
Crook tail	2.231 ± 0.910	0.350 ± 0.125	0.594 ± 0.168	$F(2,63) = 7.88$, $p = .0009$	A > C ($p = .0004$) A > H ($p = .0036$)	$F(2,63) = 0.12$, $p = .8858$	–
Aggressive							
Aggression	0.106 ± 0.053	0.269 ± 0.104	0.094 ± 0.073	$F(2,63) = 0.95$, $p = .3923$	–	$F(2,63) = 0.37$, $p = .6934$	–
Chase	0.119 ± 0.054	0.619 ± 0.268	0.356 ± 0.117	$F(2,63) = 3.78$, $p = .0281$	A < C ($p < .0078$)	$F(2,63) = 2.98$, $p = .0582$	–
Displace	0.063 ± 0.028	0.131 ± 0.080	0.094 ± 0.026	$F(2,63) = 0.83$, $p = .4392$	–	$F(2,63) = 1.38$, $p = .2599$	–
Threat	0.725 ± 0.289	0.788 ± 0.190	0.556 ± 0.187	$F(2,63) = 0.54$, $p = .5848$	–	$F(2,63) = 0.43$, $p = .6512$	–

Frequency of the most common social behaviors exhibited during the 9-month familiar dyad observations. Average number of occurrence ± *SEM* per 5 min is shown for amygdala-lesioned subjects (AMY), sham-operated control subjects (CON), and hippocampus-lesioned subjects (HIP). Two-factor (Focal Subject Lesion × Partner Lesion) ANOVAs, followed by Fisher's PLSD post hoc tests (with a significance level of $p < .05$) were used for data analysis (A = amygdala-lesioned subjects; C = sham-operated control subjects; H = hippocampus-lesioned subjects).

subjects. However, the amygdala-lesioned subjects engaged in physical contact with other monkeys less frequently than did controls. Partner effects for the frequency of affiliative behaviors were not significant. In contrast to the 6-month results, there was also a lesion effect for the duration of physical contact, $F(2,63) = 6.82$, $p = .0021$; controls spent more time in physical contact with their dyad partners than either the amygdala- or hippocampus-lesioned subjects ($p = .0014$ and $p = .0036$, respectively).

As for the 6-month familiar dyads, lesion effects were also found for behaviors associated with fear (Table 6). Amygdala-lesioned subjects produced more fear grimaces and crook tails than control or hippocampus-lesioned subjects. They also screamed more frequently than controls. Both amygdala- and hippocampus-lesioned subjects fled more frequently than controls. Partner effects were not significant, indicating that the fear behaviors were not differentially associated with partners of a particular experimental group.

Lesion effects were also found for nonsocial behaviors, $F(2,63) = 17.98$, $p < .0001$; amygdala-lesioned subjects explored the cage orally less frequently than control or hippocampus-lesioned subjects (all $p < .0001$).

Comparison of Six- and Nine-month Familiar Dyad Observations

The two rounds of familiar dyad observations were compared to evaluate potential changes in behavior between 6 and 9 months of age. Repeated measures ANOVAs comparing all subjects demonstrated that the frequency of affiliative behaviors was relatively consistent between the 6- and 9-month observations. Only the frequency of cooing differed between the two testing periods, $F(1,21) = 16.11$, $p = .0006$; more coos were produced at 6 months than at 9 months of age ($p = .0006$).

Repeated measures ANOVAs comparing all subjects demonstrated that the frequency of fear behaviors did not decline between the 6- and 9-month testing periods. Fleeing was the only behavior to demonstrate an age effect, $F(1,21) = 20.52$, $p = .0002$; more flees were produced at 9 months than at 6 months of age ($p = .0002$).

Twelve-month Novel Dyad Observations

Pairing the subjects with unfamiliar conspecifics revealed lesion effects for several affiliative behaviors (Table 7). Amygdala-lesioned subjects cooed, grunted, followed, lipsmacked, and presented for grooming more frequently than control or hippocampus-lesioned subjects, and they presented for mount more frequently than controls (Figure 3). No partner effects were found for affiliative behaviors with the exception of grooming and physical contact, which were produced more frequently when paired with amygdala-lesioned subjects as compared to control or hippocampus-lesioned subjects.

In spite of the higher frequency of affiliative behaviors produced by the amygdala-lesioned subjects, they did not spend significantly more time in reciprocal social interactions (i.e., contact, play, or proximity) than did subjects from the other experimental groups. There was no lesion effect for total duration of physical contact, $F(2,63) = 2.67$, $p = .0769$, no partner effect, $F(2,63) = 1.54$, $p = .2222$, or interaction between lesion condition and partner, $F(4,63) = 1.10$, $p = .3641$. Likewise, there was no lesion effect for total duration of extended play, $F(2,63) = 0.79$, $p = .4578$, and no partner effect, $F(2,631) = 1.68$, $p = .1947$, or interaction, $F(4,63) = 0.57$, $p = .6862$. The lesion effect for total duration of proximity was not significant, $F(2,63) = 2.08$, $p = .1335$, but the effect of partner, $F(2,63) = 4.73$, $p = .0122$, and the interaction between lesion condition and partner, $F(4,63) = 3.66$, $p = .0096$, were both significant. Interestingly, the controls spent more time in proximity with other controls than with amygdala- or hippocampus-lesioned subjects ($p = .0422$ and $p = .0251$, respectively). Amygdala-lesioned subjects spent more time in proximity with other amygdala-lesioned subjects than with control ($p = .0125$) or hippocampus-lesioned subjects ($p = .0030$). Hippocampus-lesioned subjects showed no partner effects.

Receiving groom was the only social interaction apparently influenced by the increased affiliative behaviors of the amygdala-lesioned subjects. Lesion effects were found for the frequency of grooming received, $F(2,63) = 5.34$, $p = .0072$, with amygdala-lesioned subjects receiving grooming more frequently than control or hippocampus-lesioned subjects ($p = .0284$ and $p = .0023$, respectively). The partner effect for receiving groom was not significant, $F(2,63) = 1.50$, $p = .2318$. Lesion effects were also found for the total duration of grooming that was received, $F(2,63) = 3.94$, $p = .0245$, with amygdala-lesioned subjects receiving grooming for longer durations than hippocampus-lesioned subjects ($p = .0076$).

As was the case for familiar dyads, lesion effects were also found for behaviors associated with fear, including fear grimaces, flees, freezes, screams, and crook tails (Table 7). Amygdala-lesioned subjects produced more fear grimaces, freezes, screams, and crook tails than control or hippocampus-lesioned subjects (Figure 4). Both amygdala- and hippocampus-lesioned subjects fled more frequently than controls. Unlike affiliative behaviors, which were consistently produced when paired with individuals from all three experimental groups, fear behaviors were produced more frequently when the dyad partner was a control or hippocampus-lesioned subject.

Although the amygdala-lesioned subjects produced more fear and affiliative behaviors than the other subject

Table 7. Novel Dyads: Behavior Frequency

	AMY	*CON*	*HIP*	*Lesion Effect*	*Post Hoc*	*Partner Effect*	*Post Hoc*
Affiliative							
Approach	2.095 ± 0.452	2.396 ± 0.240	2.786 ± 0.435	$F(2,63) = 1.49, p = .2330$	–	$F(2,63) = 1.27, p = .2882$	–
Coo	7.019 ± 2.159	2.431 ± 0.832	2.722 ± 0.904	$F(2,63) = 8.80, p = .0004$	A > C ($p = .0004$) A > H ($p = .0008$)	$F(2,63) = 0.15, p = .8603$	–
Groom	0.068 ± 0.039	0.115 ± 0.040	0.069 ± 0.020	$F(2,63) = 0.95, p = .3913$	–	$F(2,63) = 4.45, p = .0156$	A > C ($p = .0248$) A > H ($p = .0069$)
Grunt	4.052 ± 1.133	1.127 ± 0.400	1.181 ± 0.196	$F(2,63) = 14.78, p < .0001$	A > C ($p < .0001$) A > H ($p < .0001$)	$F(2,63) = 0.07, p = .9329$	–
Follow	0.252 ± 0.053	0.113 ± 0.027	0.127 ± 0.038	$F(2,63) = 5.72, p = .0052$	A > C ($p = .0032$) A > H ($p = .0075$)	$F(2,63) = 1.95, p = .1511$	–
Lipsmack	1.536 ± 0.417	0.597 ± 0.121	0.852 ± 0.126	$F(2,63) = 7.73, p = .0010$	A > C ($p = .0003$) A > H ($p = .0074$)	$F(2,63) = 0.79, p = .4601$	–
Mount	0.142 ± 0.108	0.359 ± 0.145	0.153 ± 0.049	$F(2,63) = 2.06, p = .1354$		$F(2,63) = 1.06, p = .3542$	–
Play	0.063 ± 0.036	0.203 ± 0.050	0.137 ± 0.048	$F(2,63) = 2.72, p = .0737$	–	$F(2,63) = 0.25, p = .7779$	–
Present groom	0.656 ± 0.144	0.276 ± 0.115	0.283 ± 0.077	$F(2,63) = 6.11, p = .0037$	A > C ($p = .0033$) A > H ($p = .0039$)	$F(2,63) = 0.97, p = .3863$	–
Present mount	0.878 ± 0.281	0.288 ± 0.120	0.679 ± 0.229	$F(2,63) = 3.44, p = .0383$	A > C ($p = .0123$)	$F(2,63) = 2.62, p = .0804$	–
Physical contact	0.264 ± 0.092	0.562 ± 0.124	0.401 ± 0.079	$F(2,63) = 3.10, p = .0519$	–	$F(2,63) = 4.06, p = .0220$	A > C ($p = .0124$) A > H ($p = .0223$)
Proximity	0.392 ± 0.086	0.323 ± 0.031	0.345 ± 0.068	$F(2,63) = 0.36, p = .7003$	–	$F(2,63) = 2.96, p = .0589$	–
Fearful							
Fear grimace	2.085 ± 0.457	0.163 ± 0.068	0.366 ± 0.084	$F(2,63) = 27.55, p < .0001$	A > C ($p < .0001$) A > H ($p < .0001$)	$F(2,63) = 6.98, p = .0018$	C > A ($p = .0004$) C > H ($p = .0366$)
Flee	1.451 ± 0.202	0.394 ± 0.073	1.083 ± 0.222	$F(2,63) = 16.61, p < .0001$	A > C ($p < .0001$) H > C ($p = .0005$)	$F(2,63) = 21.09, p < .0001$	C > A ($p < .0001$) H > A ($p < .0001$)
Freeze[a]	0.227 ± 0.024	0.031 ± 0.010	0.038 ± 0.010	$F(2,63) = 50.34, p < .0001$	A > C ($p < .0001$) A > H ($p < .0001$)	$F(2,63) = 15.91, p < .0001$	C > A ($p < .0001$) H > A ($p = .0033$) C > H ($p = .0122$)
Scream	1.142 ± 0.323	0.102 ± 0.035	0.214 ± 0.119	$F(2,63) = 17.69, p < .0001$	A > C ($p < .0001$) A > H ($p < .0001$)	$F(2,63) = 2.68, p = .0765$	–
Crook tail	3.127 ± 1.304	0.601 ± 0.115	1.045 ± 0.276	$F(2,63) = 8.94, p = .0004$	A > C ($p = .0002$) A > H ($p = .0018$)	$F(2,63) = 0.17, p = .8470$	–
Aggressive							
Aggression	0.036 ± 0.031	0.448 ± 0.162	0.158 ± 0.069	$F(2,63) = 6.53, p = .0026$	A < C ($p = .0008$) H < C ($p = .0159$)	$F(2,63) = 0.03, p = .9721$	–
Chase	0.059 ± 0.026	0.517 ± 0.124	0.589 ± 0.113	$F(2,63) = 17.40, p < .0001$	A < C ($p < .0001$) A < H ($p < .0001$)	$F(2,63) = 9.00, p = .0004$	H > A ($p = .0007$) H > C ($p = .0004$)
Displace	0.009 ± 0.005	0.259 ± 0.050	0.203 ± 0.053	$F(2,63) = 13.28, p < .0001$	A < C ($p < .0001$) A < H ($p = .0003$)	$F(2,63) = 2.90, p = .0623$	–
Threat	0.370 ± 0.141	0.826 ± 0.177	0.826 ± 0.230	$F(2,63) = 3.13, p = .0506$	–	$F(2,63) = 3.45, p = .0379$	A < C ($p = .0354$) A < H ($p = .0203$)

Frequency of the most common social behaviors exhibited during the novel dyad observations. Average number of occurrence ± *SEM* per 5 min is shown for amygdala-lesioned subjects (AMY), sham-operated control subjects (CON), and hippocampus-lesioned subjects (HIP). Two-factor (Focal Subject Lesion × Partner Lesion) ANOVAs, followed by Fisher's PLSD post hoc tests (with a significance level of $p < .05$) were used for data analyses (A = amygdala-lesioned subjects; C = sham-operated control subjects; H = hippocampus-lesioned subjects).

[a]Freeze was not scored during the familiar dyads or social group observations.

groups, they produced fewer behaviors associated with aggression (Table 7). Amygdala-lesioned subjects chased and displaced other subjects less frequently than did control or hippocampus-lesioned subjects. Partner effects suggested that chasing was most likely to be initiated when paired with a hippocampus-lesioned subject and threatening was more likely to be produced when paired with either control or hippocampus-lesioned subjects. Controls exhibited more aggressive behaviors (grabs, hits, bites, or slaps) than amygdala- or hippocampus-lesioned subjects. Lesion effects were not found, however, for receiving aggression, $F(2,63) = 0.03$, $p = .9677$, indicating that subjects from a particular experimental group were not selectively targeted for aggression.

Lesion effects were also found for nonsocial behaviors, $F(2,63) = 36.74$, $p < .0001$, with amygdala-lesioned subjects exploring the cage orally less frequently than control or hippocampus-lesioned subjects (all $p < .0001$).

Comparison of Nine-month Familiar Dyad and Twelve-month Novel Dyad Observations

Familiar dyads at 9 months of age were compared to novel dyads at 12 months of age to evaluate the effects of partner novelty and potential developmental changes. Because familiar dyads consisted of just two repetitions, only the first two repetitions of novel dyads were included for the comparison. Repeated measures ANOVAs revealed that affiliative behaviors remained relatively consistent between the 9-month familiar and 12-month novel dyads. Only the frequency of coos differed, $F(1,21) = 4.66$, $p = .0426$; more coos were produced with familiar subjects at 9 months, compared to unfamiliar subjects at 12 months ($p = .0426$).

The frequency of fear behaviors showed no differences between 9-month familiar and 12-month novel dyads for any of the experimental groups. These results suggest that fear behaviors were not affected by the familiarity or novelty of the social encounter, or by developmental changes between 9 and 12 months of age.

Comparison of Novel Dyad Periods

Novel dyads were repeated six times to assess possible behavioral changes as the subjects became more familiar with each other. For statistical analysis, the six sessions were grouped into three periods (first period = first two sessions; second period = middle two sessions; third period = final two sessions). Period effects were not found for any of the behaviors, with the exceptions of coos and grunts. The lesion effect for the frequency of coo failed to reach significance, $F(2,21) = 3.21$, $p = .0608$. The period effect was significant, however, $F(1,21) = 26.66$, $p < .0001$, reflecting the greater number of coos produced during the first period compared to the second and the third (all $p < .0001$), while the interaction between lesion condition and the testing period was not significant, $F(2,21) = 1.83$, $p = .1403$. The lesion effect for the frequency of grunt was significant, $F(2,21) = 5.67$, $p = .0107$; amygdala-lesioned subjects grunted more frequently than either control or hippocampus-lesioned subjects ($p = .0078$ and 0.0088, respectively). The effect of period was also significant, $F(1,21) = 10.45$, $p = .0002$, with more grunts produced during the first period compared to the second ($p = .0002$) and the third ($p = .0006$), while the interaction between lesion conditions and the testing period was not significant, $F(2,21) = 0.72$, $p = .5832$.

Novel Dyad Attitude Assessments

Following each novel dyad observation, the subjects were rated on a scale of 1 (*least*) to 7 (*most*) for level of confidence, nervousness, fear, and activity by observers who were blind to their lesion status. Definitions of the categories were based on personality assessments used for adult male macaque monkeys (Capitanio, 1999), modified for age appropriateness (Table 8). Significant lesion effects were found for all attributes: confidence: $F(2,21) = 34.62$, $p < .0001$; controls were judged more confident than either amygdala- or hippocampus-lesioned subjects ($p < .0001$ and $p = .0291$, respectively), and hippocampus-lesioned subjects were judged more confident than amygdala-lesioned subjects ($p < .0001$); nervousness: $F(2,21) = 16.64$, $p < .0001$; amygdala-lesioned subjects were judged more nervous than either control or hippocampus-lesioned subjects ($p < .0001$ and $p = .0018$, respectively), and hippocampus-lesioned subjects were judged more nervous than controls ($p = .0449$); fear: $F(2,21) = 25.97$, $p < .0001$; amygdala-lesioned subjects were judged more fearful than either control or hippocampus-lesioned subjects (all $p < .0001$); activity: $F(2,21) = 17.43$, $p < .0001$, hippocampus-lesioned subjects were judged more active than either control or amygdala-lesioned subjects ($p = .0112$ and $p < .0001$, respectively), and controls were judged more active than amygdala-lesioned subjects ($p = .0052$).

Summary of Experimental Group Differences

Amygdala-lesioned Subjects

The amygdala-lesioned subjects developed a species-typical repertoire of social behaviors. They displayed more affiliative behaviors, including follows, coos, and grunts during familiar and novel dyads. The amygdala-lesioned subjects also made more presentations for grooming and presentations for mounting during novel dyads. Despite the development of a normal social repertoire, the amygdala-lesioned subjects consistently produced more fear behaviors than either control or hippocampus-lesioned subjects during social group

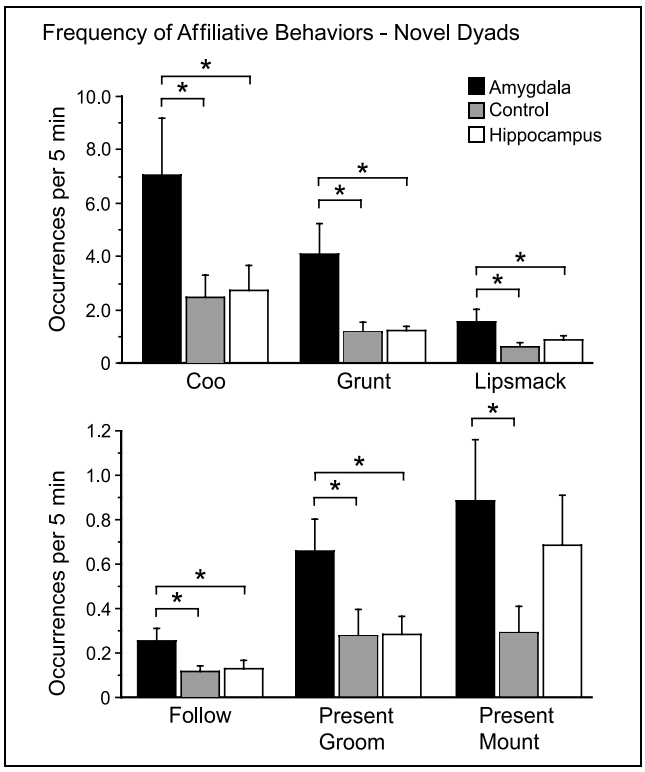

Figure 3. Amygdala-lesioned subjects produced more affiliative behaviors during novel dyadic interactions than did control or hippocampus-lesioned subjects. At 1 year of age, each subject participated in a series of 20-min dyadic interactions with one of six unfamiliar conspecifics (each partner was observed for two 5-min sample periods). Each combination of initially unfamiliar dyad partners was then repeated once a week for a total of 6 weeks, resulting in seventy-two 5-min observation periods for each subject. Each bar represents the average number of affiliative behaviors (± *SEM*) per 5-min observation period across all 72 observation periods. Asterisks denote significant post hoc Fisher PLSD tests ($p < .05$).

observations, familiar dyads, and novel dyads. Although the amygdala-lesioned subjects produced more affiliative and fear behaviors, they did not produce all behaviors more frequently. For example, the amygdala-lesioned subjects produced significantly fewer aggressive behaviors than controls during novel dyads (i.e., aggression, chase, and displace). However, the amygdala-lesioned subjects were capable of producing aggressive behaviors, and did not consistently differ from control or hippocampus-lesioned subjects in the frequency of these behaviors produced during familiar dyads or social groups.

No consistent differences were found in the amount of time spent in social interactions (play, proximity, grooming, and contact). However, the amygdala-lesioned subjects did engage in physical contacts less frequently than controls at 6 and 9 months of age. It is important to note that control subjects were found to spend more time in proximity with other control subjects than amygdala- or hippocampus-lesioned subjects during the novel dyad observations. Although this result was not consistent across other testing paradigms (familiar dyads and social groups) or social interactions (i.e., grooming, play, contact), it does raise the possibility that the control monkeys preferred to spend time in proximity with other controls due to subtle behavioral differences presented by the amygdala- and hippocampus-lesioned subjects.

Across all testing conditions, the amygdala-lesioned subjects orally explored the cage less frequently than either control or hippocampus-lesioned subjects, indicating that the hyperorality previously associated with adult amygdala-lesioned subjects (Emery et al., 2001; Meunier, Bachevalier, Murray, Malkova, & Mishkin, 1999; Kluver & Bucy, 1939) was not present in this population of subjects up to 1 year of age. The lack of hyperorality observed in the infant amygdala-lesioned subjects is consistent with recent reports that infants with neonatal medial or inferior temporal lobe ablations show no hyperorality (Meunier, Nalwa, & Bachevalier, 2003).

Hippocampus-lesioned Subjects

The hippocampus-lesioned subjects developed a species-typical repertoire of social behavior and were indistinguishable from controls for nearly all measures of social behavior. The one consistent difference displayed by the hippocampus-lesioned subjects was increased motor activity. Although locomotor movements were not specifically quantified in this study, the hippocampus-lesioned subjects were rated more active than either control or amygdala-lesioned subjects in the novel dyad attitude assessments. These results are consistent with quantified activity levels observed in this population of hippocampus-lesioned subjects immediately following weaning (Bauman, Lavenex, Mason, Capitanio, & Amaral, 2004) and increased locomotion reported in rats following neonatal hippocampus lesions (Sams-Dodd, Lipska, & Wienberger, 1997).

Although there were few differences in social behavior between the hippocampus-lesioned subjects and the controls, it is possible that the hyperactivity observed in the hippocampus-lesioned subjects may have influenced their behavioral profile. For example, the hippocampus-lesioned subjects did not consistently produce heightened fear responses. However, they were observed to flee more frequently than controls during the 9-month familiar and 12-month novel dyads. Given that the hippocampus-lesioned subjects did not produce any other fear behaviors (i.e., fear grimace, freeze, scream) more frequently than controls, it is possible that the hyperactivity of the hippocampus-lesioned subjects may have artificially increased the frequency of fleeing episodes that were scored (i.e., flee is defined as a rapid movement away from another subject).

Despite the seemingly normal social behavior of the hippocampus-lesioned subjects, it is possible that they displayed subtle behavioral deficits that eluded our

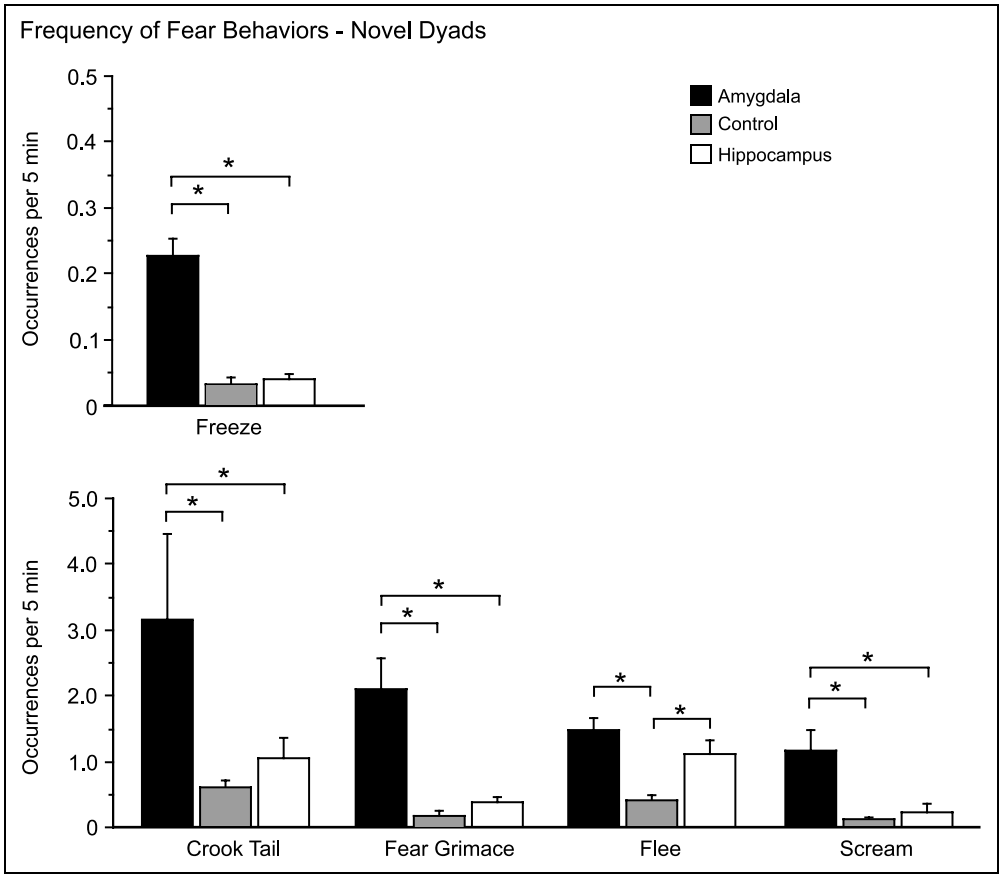

Figure 4. Amygdala-lesioned subjects produced more fear behaviors during novel dyadic interactions than did control or hippocampus-lesioned subjects. At 1 year of age, each subject participated in a series of 20-min dyadic interactions with one of six unfamiliar conspecifics (each partner was observed for two 5-min sample periods). Each combination of initially unfamiliar dyad partners was then repeated once a week for a total of 6 weeks, resulting in seventy-two 5-min observation periods for each subject. Each bar represents the average number of fear behaviors (± *SEM*) per 5-min observation period across all 72 observation periods. Asterisks denote significant post hoc Fisher PLSD tests ($p < .05$).

quantitative observations. Indeed, the control subjects were found to spend more time in proximity with other control subjects than with either amygdala or hippocampus-lesioned subjects during the novel dyads. This result was not consistent across other testing paradigms (i.e., familiar dyads and social groups) or other behavioral interactions (i.e., grooming, play, contact). However, it is possible that the control monkeys preferred to spend time in proximity with other controls due to subtle behavioral abnormalities presented by the hippocampus-lesioned subjects.

Sham-operated Controls

The sham-operated monkeys developed a species-typical repertoire of social behavior. Although they appeared more agitated during individual home cage observations, as indicated by more frequent vocalizations and cage stereotypies, they displayed very few behaviors indicative of abnormal development when observed in dyads or in social groups. The controls were relatively more aggressive than either amygdala- or hippocampus-lesioned subjects during novel, but not familiar dyads. Interestingly, the control subjects were found to spend more time in proximity with other control subjects than with amygdala- or hippocampus-lesioned subjects during the novel dyads.

DISCUSSION

Summary of Findings

The present set of experiments indicates that neither the amygdala nor the hippocampus is needed to develop fundamental aspects of social behavior. All experi-

Table 8. Attitude Assessment Ethogram

Assessment	*Description*
Active	Constantly moving around the cage and remains stationary only for short periods. The subject spends time in many different locations.
Fearful	Appears anxious in the presence of other animals; readily fear grimaces, flees, freezes, or screams. The subject gives in readily to others; submits easily.
Confident	Behaves in a positive assured manner, not restrained or tentative. The subject's attitude is characterized by free movement around the cage; the movements are fluid, not furtive.
Nervous	Uncomfortable, or tense with the situation. The subject's attitude is characterized by fidgeting, stereotypies, yawning, jerky movements, or heightened vigilance.

mental subjects, irrespective of lesion condition, developed a normal repertoire of social signals, demonstrated interest in conspecifics, and interacted in a variety of social contexts. We observed few behaviors indicative of maladaptive development, such as chronic stereotypies, prolonged tantrums, or habitual self-directed behaviors during the first year of development. We believe that the mother-rearing and daily social interactions that were important innovations in our protocol facilitated development of species-typical social behavior and avoided the behavioral pathology associated with alternative rearing strategies (Bastian et al., 2003; Winslow et al., 2003; Parr et al., 2002; Shannon et al., 1998; Anderson & Mason, 1974; Mason, 1960; Mason & Sponholz, 1963). Although previous studies have reported that neonatal aspiration lesions of the hippocampus result in minor disturbances in the initiation of social interactions (i.e., fewer approaches and more withdrawals) (Beauregard, Malkova, & Bachevalier, 1995; Bachevalier, 1994; Bachevalier, Alvarado, & Malkova, 1999), we did not observe consistent differences between control and hippocampus-lesioned subjects for any behavioral measures. Thus, the majority of our findings pertain to the amygdala-lesioned subjects.

Abnormal Fear Responses

Despite the development of a normal repertoire of social behavior, the amygdala-lesioned subjects consistently demonstrated more fear behaviors (i.e., fear grimacing, fleeing, freezing, screaming) during social interactions. The abnormal fear behavior remained a consistent feature of the amygdala-lesioned subjects throughout the entire observation period (6–12 months of age) and was manifest in various social contexts (daily socialization cohorts, familiar dyads, novel dyads). The amygdala-lesioned subjects were also rated as more nervous and fearful by observers who were blind to their lesion condition. Given that neither the control nor the hippocampus-lesioned subjects displayed heightened fearfulness, we propose that the abnormal fear behavior is attributable to neonatal damage of the amygdala.

It is important to note that the heightened fear behavior exhibited by the amygdala-lesioned subjects was not in response to behaviors that would be expected to elicit a fear response, such as aggression. Rather, the amygdala-lesioned subjects consistently displayed inappropriate fear behaviors in a variety of social interactions with unthreatening conspecifics. While the exact trigger of the abnormal fear response is unknown, subjects from all experimental groups did produce more fear behaviors in the presence of control or hippocampus-lesioned subjects than in the presence of amygdala-lesioned animals. Interestingly, the novelty of the social partner did not appreciably influence the frequency of fear behaviors. We found that the amygdala-lesioned subjects produced more fear behaviors than control and hippocampus-lesioned subjects in all social testing paradigms, including daily socialization periods with familiar individuals from their own rearing cohort. Taken together, these results suggest that the amygdala plays a critical role in regulating social fear responses early in development.

Sparing of Fundamental Social Behavior

In spite of their abnormal fear behavior, the social behavior of the amygdala-lesioned subjects was, in other respects, remarkably normal. Throughout development, they spent as much time in social interactions, including physical contact, proximity, and play, as the animals from the other experimental groups. The amygdala-lesioned subjects even displayed more affiliative behaviors (such as follows, coos, and grunts) than the control or hippocampus-lesioned subjects when paired with familiar conspecifics at 6 and 9 months of age. During novel dyad testing, the amygdala-lesioned subjects produced behaviors that generally serve to initiate social interactions (such as presenting for groom and presenting for mount) more frequently than control or hippocampus-lesioned subjects. Thus, neonatal amygdala lesions did not preclude development of fundamental aspects of social behavior, including interest in conspecifics and the ability to produce a species-typical repertoire of social signals. Although we were not able to directly evaluate how the amygdala-lesioned subjects interpreted social signals, they did not consistently differ from controls in the amount of time spent playing, grooming, in contact or proximity with other animals. These findings provide indirect evidence that the amygdala-lesioned subjects were able to respond to reciprocal social interactions. However, future research is needed to evaluate whether the amygdala-lesioned subjects are correctly interpreting and responding to specific social cues. This will necessitate a quantitative analysis of the micro-organization of sequences of behavioral interactions for which analytical tools are currently being developed.

Although the production of both heightened fear and affiliative behaviors by the amygdala-lesioned subjects may seem inconsistent, we see several possible explanations. First, it is possible that the amygdala-lesioned subjects were hyper-responsive to social interactions and overproduced all social signals. The fact that the amygdala-lesioned subjects actually produced fewer aggressive behaviors than control or hippocampus-lesioned subjects during novel dyads, however, would tend to argue against this interpretation. Second, it is also possible that the amygdala-lesioned subjects were simply more vigilant during social encounters, and produced affiliative behaviors in an attempt to ''appease'' the other subjects. Indeed, similar behavioral responses have been reported in lower ranking adult macaques that produce both affiliative and fearful

behaviors during challenging social interactions (Capitanio, 1999). Given that amygdala lesions have been associated with lower social rank in both mature (Rosvold et al., 1954) and immature subjects (Amaral, Toscano, et al., 2003), it is possible that the production of both fear and affiliative behaviors may reflect their low social rank. Third, it is possible that the amygdala-lesioned subjects were unable to correctly evaluate specific social signals and therefore responded inappropriately by producing both fear and affiliative behaviors. Although our data indicate that the amygdala-lesioned subjects engage in species-typical reciprocal social interactions (i.e., play and grooming), it is possible that they may not respond appropriately to all social signals. We plan to examine the response of the amygdala-lesioned subjects to specific social signals in future experiments.

Implications for an Animal Model of Autism

The sparing of basic aspects of social behavior that we have observed in maternally reared infant macaques with neurotoxic amygdala lesions differs from previous reports of infant macaques that received neonatal aspiration lesions of the amygdala and were peer-reared (Bachevalier, 1994). Unlike Bachevalier (1994), we did not observe deficits in social interactions in the amygdala-lesioned subjects during the first year of development. The reports of abnormal social development presented by Bachevalier were based primarily on observations that the amygdala-lesioned subjects ''displayed less initiation of social contact and more social withdrawal than controls.'' The authors (Bachevalier, 1994, 2000; Bachevalier, Malkova, & Mishkin, 2001) also found that more extensive lesions of the medial temporal lobe, including the amygdala, hippocampus, and ventromedial temporal cortex, produced more profound effects on social interactions, including flat affect and increased stereotypic behaviors. Given that impaired social communication and a lack of social interest is the hallmark of autism, the authors proposed that lesions of the medial temporal lobe, specifically the amygdala, might provide an animal model of autism (Bachevalier, 1994; Bachevalier et al., 2001). However, the consistent finding of heightened social fear in neonatal amygdala-lesioned subjects offers an alternative explanation of the changes in social behavior initially reported by Bachevalier. It is plausible that the absence of social interaction observed by Bachevalier was not the result of ''autistic like'' symptomatology, but rather due to the abnormal social fear response that is characteristic of amygdala-lesioned infant monkeys (Bauman et al., 2004; Prather et al., 2001; Thompson et al., 1969). Although fear behaviors were not explicitly scored by Bachevalier, it is possible that the behavior described as ''social withdrawal'' may actually reflect heightened fear responses, rather than social disinterest.

Moreover, methodological differences in lesion technique and rearing practices may have contributed to the different behavioral outcomes of the two studies. In contrast to the aspiration lesions used by Bachevalier and colleagues (Bachevalier, 1994; Bachevalier et al., 2001), the neurotoxic lesions used in the current study cause less damage to surrounding cortical regions (i.e., temporal polar cortex and anterior entorhinal cortex) and spare fibers passing through and around the amygdala, including fibers originating in inferior temporal cortical areas (Goulet, Dore, & Murray, 1998). It has recently been demonstrated that adult macaques with neurotoxic amygdala lesions demonstrate more mild changes in emotional reactivity than subjects prepared with aspiration amygdala lesions (Meunier et al., 1999). Thus, it is possible that unintended collateral damage associated with aspiration lesions may have contributed to the behavioral abnormalities reported by Bachevalier. Another methodological concern that is particularly important for developmental studies is the rearing conditions of the infants. We used mother-reared subjects that were provided daily access to large social groups, while Bachevalier utilized more restricted rearing conditions (i.e., peer-only rearing). Although peer-rearing results in fewer behavior abnormalities than isolate rearing (Sackett, Ruppunthal, & Davis, 2002), peer-reared subjects do develop substantial behavioral abnormalities (Bellanca & Crockett, 2002), including excessive mutual clinging and deficits in social play (Suomi, 1984). Although it is unknown how the behavioral abnormalities associated with restricted rearing may interact with the neonatal brain injury, it is a clear possibility that the restricted rearing environments may have contributed to the abnormal social development originally attributed to early amygdala damage (Bachevalier, 1994).

Although neonatal lesions of the medial temporal lobe, specifically the amygdala, have been proposed as an animal model of autism (Bachevalier, 1994; Bachevalier et al., 2001), the sparing of social behavior that we have observed in the current population of amygdala-lesioned monkeys argues against this model. Collectively, our results indicate that infant rhesus monkeys with bilateral amygdala lesions develop species-typical forms of social communication, including facial expressions, vocalizations, and body postures, as well as social interest and an ability to interact with conspecifics. The sparing of these fundamental aspects of social behavior does not support the hypothesis that early damage of the amygdala leads to impairments of social behavior that closely mimic autistic symptomatology. If the amygdala is not essential for the component processes of social behavior, then it is unlikely to be the primary cause of impaired social behavior of autism. This does not rule out the possibility that the amygdala might be pathological in autism. However, it suggests that dysfunction of the amygdala does not directly account for the profound impairments in social behavior that are the hallmark of

autism. Given the deficits in fear processing associated with amygdala damage, it is plausible that amygdala dysfunction may underlie anxiety disorders and may possibly contribute to comorbid anxiety in autism (Amaral, 2002; Amaral, Bauman, & Schumann, 2003).

Indeed, abnormal fear behaviors have now been reported in three separate populations of amygdala-lesioned infants (Bauman et al., 2004; Prather et al., 2001; Thompson et al., 1969; Table 9). The heightened fear behavior reported by Thompson et al. (1969) was not apparent immediately following surgery, but increased dramatically between 5 and 8 months of age. By 13 months of age, the fear responses of the amygdala-lesioned subjects were 100 times more pronounced than those of control subjects. Consequently, the social behavior of Thompson's amygdala-lesioned subjects was initially quite normal, but became increasingly abnormal over time as the amygdala-lesioned subjects exhibited fewer social interactions and became exceedingly submissive to conspecifics (Thompson & Towfighi, 1976; Thompson, Bergland, & Towfighi, 1977; Thompson, 1981). Although we have observed similar abnormalities in fear behaviors, we have not yet observed similar deficits in social behavior development. Methodological differences in lesion technique (neurotoxic vs. aspiration) and rearing environment (enriched vs. restricted) may account for these differences in social development. Given that the subjects in Thompson's study were reared in near isolation, it remains unknown if these abnormalities in social development are due to the aspiration amygdala lesions, the restricted rearing environment, or a combination of the two factors. However, another possibility is that the full effects of amygdala lesions may not become evident until the subjects reach maturity. Given the similarities between Thompson's initial observations and our own (i.e., heightened social fear), we will continue to observe our current population of amygdala-lesioned subjects into adulthood to assess the long-term effects of early amygdala damage on social development.

Developmental Role of the Amygdala

Whereas immature subjects that receive neonatal amygdala lesions produce heightened fear behaviors in all social testing paradigms, adult macaques with selective amygdala lesions do not show any indication of social fear, and in fact, do not demonstrate the species-typical reluctance to interact with novel conspecifics (Emery et al., 2001). Although immature and mature amygdala-lesioned subjects differ in their fear responses to social stimuli, both mature and immature amygdala-lesioned subjects consistently demonstrate a blunted fear of nonsocial stimuli, including novel, and potentially dangerous items, such as a rubber snake (Kalin, Shelton, Davidson, & Kelly, 2001; Prather et al., 2001; Meunier et al., 1999). Collectively, these results indicate that damage to the amygdala profoundly alters fear-processing capabilities for both social and nonsocial stimuli. Mature and immature amygdala-lesioned subjects both demonstrate blunted fear to nonsocial stimuli, suggesting that the amygdala has a similar function in evaluating nonsocial objects in development and adulthood. However, a key difference is observed between immature and mature amygdala-lesioned subjects in response to social stimuli (i.e., excessive vs. absent fear responses), suggesting that the amygdala may play a unique role in regulating social fear responses early in development.

Although it appears that infant macaques are ''hard-wired'' to produce fear responses to social stimuli (Sackett, 1966), social experience is likely to play a key role in refining fear responses. Indeed, infant monkeys reared in social isolation respond to social contact with seemingly innate fear responses, including submission and flight (Mason & Sponholz, 1963), presumably because they lack the social experience needed to regulate these fear reactions. Whereas adult macaques that receive amygdala lesions have years of acquiring social knowledge prior to lesion placement, the infant amygdala-lesioned subjects acquire little or no social experience prior to the lesion surgery at two weeks of age. If the amygdala is needed to correctly evaluate potential danger, then it is likely that damage to the amygdala early in development may interfere with the ability to learn from social experience which encounters are potentially dangerous and which are not. Our research lends support to this proposal by demonstrating that early damage to the amygdala results in profound social fear that is not observed in subjects receiving amygdala damage later in life. An interesting parallel from the human literature demonstrates that adults and children show different patterns of amygdala activation in response to viewing facial expression depicting fear (Thomas et al., 2001). Collectively, these studies suggest that the amygdala may have unique roles in coordinating behavior at different stages of development.

Conclusions

In summary, our results suggest that the amygdala is not directly involved in developing basic components of the social repertoire, but instead plays a more general role in developing appropriate fear processing. Our results are consistent with converging neurobiological evidence suggesting that an important function of the amygdala is to evaluate stimuli for potential danger and to coordinate an appropriate response. Lesions of the amygdala consistently disrupt fear processing abilities, as evidenced by blocked fear conditioning in rodents (LeDoux, 1998), altered fear behaviors in nonhuman primates (Emery et al., 2001; Kalin et al., 2001; Meunier et al., 1999), and impaired processing of fearful facial expressions in human patients (Adolphs

et al., 1994). While the exact behavioral profile following amygdala lesions shows great variability, disruption of fear processing remains one of the most consistent deficits associated with amygdala damage. This finding is further supported by functional imaging studies in human subjects demonstrating amygdala activation in response to a variety of dangerous or aversive stimuli, including pictures of phobia-related stimuli (Dilger et al., 2003), anticipation of aversive stimuli (Phelps et al., 2001), and threatening and fearful stimuli (Hariri, Mattay, Tessitore, Fera, & Weinberger, 2003).

The amygdala has generally been considered a central component of the brain circuitry involved with the production of fear behavior (LeDoux, 1998, 2000; Davis, 1992). One unresolved question brought forth from our study is which brain regions might support the amygdala-independent fear behavior that we observed in the amygdala-lesioned subjects. Walker, Toufexis, and Davis (2003) have suggested that the bed nucleus of the stria terminalis may mediate slow-onset, long-duration fear responses. However, given that the bed nucleus of the stria terminalis receives the majority of its input from the amygdala, it is most likely dependent on information from the amygdala to carry out its function (Amaral, Price, Pitkanen, & Carmichael, 1992). Although the bed nucleus is presumably still intact in the amygdala-lesioned subjects, it is also largely deafferented from the amygdala and therefore unlikely to mediate the fear responses that we have observed in the amygdala-lesioned subjects. At this point, we are not able to speculate as to which brain regions might be supporting the fear behavior that we observed in the neonatally lesioned animals. It is clear, however, that early permanent lesions of the amygdala may have markedly altered

Table 9. Summary of Previous Neonatal Amygdala Lesion Studies of Social Development

Study Description	*Social Behavior Summary*	*Fear Behavior Summary*	*Comments*
Thompson et al. (1969), Thompson and Towfighi (1976, 1977) and Thompson (1981) Aspiration lesions at 2–3 months of age Subjects reared without social contact	Abnormalities in social behavior were not initially apparent, however, the amygdala-lesioned subjects became increasingly subordinate over time.	Amygdala-lesioned subjects produced heightened fear behaviors in response to social interactions and blunted fear responses to nonsocial stimuli (a novel testing cage).	The amygdala-lesioned subjects consistently produced abnormal fear responses to both social and nonsocial stimuli. It is unclear if the deficits in social behavior are directly linked to the heightened social fear. It is also unclear to what extent the restricted rearing conditions and extensive aspiration lesions may have contributed to the abnormal social development.
Bachevalier (1994) Aspiration lesions at 2–3 weeks of age Subjects reared with peers only	Amygdala-lesioned subjects demonstrated inactivity at 2 months of age and reduced social interactions at 6 months of age.	No reports of abnormal fear behaviors.	Although behavioral abnormalities were attributed to deficits in social development, it is possible that the lack of social interactions may actually reflect heightened fear responses (which were not explicitly scored). It is unclear to what extent the restricted rearing conditions and extensive aspiration lesions may have contributed to the abnormal social development.
Bauman et al. (2004) and Prather et al. (2001) Neurotoxic lesions at 2 weeks of age Subjects reared with mothers (Prather et al., 2001) or with mothers and a larger social group (Bauman et al., 2004)	Amygdala-lesioned subjects developed a normal repertoire of social behavior, displayed interest in conspecifics and demonstrated species-typical social interactions with their mothers.	Amygdala-lesioned subjects produced heightened fear behaviors in response to social interactions and blunted fear responses to nonsocial stimuli (novel test cage and novel objects).	Despite consistent abnormalities in fear behaviors, the amygdala-lesioned subjects developed fundamental aspects of social behavior, including a normal repertoire of social signals, interest in conspecifics, and an ability to interact with conspecifics in different social contexts.

the subsequent brain development of these animals (Saunders, Kolachana, Bachevalier, & Weinberger, 1998; Bertolino et al., 1997). Thus, regions that may not normally be involved in fear processing may have assumed this function after the loss of the amygdala. We plan to investigate these issues in future studies using positron emission tomography.

The collective results from our research program indicate that the amygdala is not needed to produce social behavior in adult macaque monkeys (Emery et al., 2001) or to learn the fundamental components of social behavior early in development (Bauman et al., 2004; Prather et al., 2001). Our results do, however, suggest that the amygdala plays a critical role in evaluating potential danger, a function that may indirectly influence social behavior. The distinction between an essential role in social behavior and a modulatory role is not trivial, given that much of the theory linking the amygdala to behavioral disorders, such as autism, has relied on the assumption that the amygdala is essential for the production of the fundamental components of social behavior. Discerning the relative contributions of different structures implicated in social behavior is a first step to understanding the basic neurobiology of social behavior. This in turn will provide new insight into which brain structures are likely to underlie pathology of social cognition.

METHODS

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

Subjects and Living Conditions

Twenty-four infant rhesus monkeys (*Macaca mulatta*) naturally born of multiparous mothers were randomly assigned to one of three lesion conditions: (a) bilateral amygdala lesion (five females, three males), (b) bilateral hippocampus lesion (five females, three males), and (c) sham-operated control (four females, four males). All surgeries were performed at 12–16 days after birth. The infants were returned to their mothers following surgery and housed in standard home cages (61 cm W × 66 cm D × 81 cm H). Following a brief recovery period, each mother–infant pair was assigned to a socialization cohort consisting of six mother–infant pairs and one adult male. Cohort members were initially combined for a series of five 3-hr acclimation periods, while being continually monitored by a trained technician to ensure group acceptance of all members. Following this acclimation procedure, each socialization cohort met for a minimum of 3 hr/day, 5 days per week in a large group cage (2.13 m W × 3.35 m D × 2.44 m H). The four socialization cohorts were each composed of two amygdala-lesioned subjects and their mothers, two hippocampus-lesioned subjects and their mothers, and two sham-operated subjects and their mothers. The age range between the youngest and oldest subject within each cohort was approximately 2 months. Three of the socialization cohorts were comprised of one male and one female per lesion condition, and the fourth cohort consisted of two female amygdala-lesioned subjects, two female hippocampus-lesioned subjects, one male, and one female sham-operated subject. By 6 months of age, infant macaques demonstrate increasing independence from their mothers (Hansen, 1966). Infants in the current study were weaned from their mothers when the youngest member of each cohort reached 6 months of age. At that time, a new adult female was added to each socialization group to provide continued exposure to adult female social behavior.

Presurgical Preparations

Given the importance of providing naturalistic social rearing conditions, it was critical that the infants were reaccepted by their mothers following surgery. On postnatal days 4, 8, and 11, each infant was temporarily removed to accustom the mother to the separation procedure necessary for surgery. During these separations, the infant's head was shaved and scrubbed with Betadine and 70% ethanol to mimic the appearance and odor of presurgical preparations and familiarize the mother with these conditions. These procedures have resulted in 100% successful reunion rate for all neonatal surgeries conducted by our laboratory.

Presurgical Magnetic Resonance Imaging

Because of the variability in size and shape of the rhesus monkey head and brain, accurate lesions were facilitated by producing an individualized MR imaging stereotaxic atlas for each infant. On the day of surgery, the infants were initially anesthetized with ketamine hydrochloride (15 mg/kg im) and medetomidine (25–50 μg/kg), then placed in an MR imaging-compatible stereotaxic apparatus (Crist Instruments, Damascus, MD). Their brain was imaged using a General Electric 1.5-T Gyroscan magnet; 1.0-mm-thick sections were taken using a T1-weighted inversion recovery pulse sequence (TR = 21, TE = 7.9, NEX 3, FOV = 8 cm, matrix 256 × 256). From these images, we determined the location of the amygdala or hippocampus and calculated the coordinates for the ibotenic acid injections.

Surgical Procedures

All surgical procedures were performed under aseptic conditions at the California National Primate Research

Center. Infants were ventilated and vital signs were monitored throughout the surgery. A stable level of anesthesia was maintained with a combination of isoflurane (1.5%; varied as needed to maintain anesthesia) and intravenous infusion of fentanyl (7–10 μg/kg/hr). Following a midline incision, the skin was displaced laterally 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. We then performed electrophysiological recordings to confirm the dorsoventral coordinates of the injection sites. A tungsten microelectrode was lowered into the amygdala or hippocampus at a mid-rostrocaudal, mid-mediolateral position, and recordings from salient features of the amygdala or hippocampus were documented and used to adjust the injection coordinates. Ibotenic acid (10 mg/ml in 0.1 M phosphate-buffered saline; Biosearch Technologies, Novato, CA) was injected simultaneously bilaterally into the amygdala or hippocampus using 10-μl Hamilton syringes (26-gauge beveled needle) at a rate of 0.2 μl/min. Complete amygdala lesions required a total of 7–12 μl of ibotenic acid per amygdala. Each amygdala lesion consisted of two rostrocaudal injection planes, each with one to two mediolateral and two dorsoventral injection sites. Complete hippocampus lesions required 5.5–7 μl of ibotenic acid per hippocampus. Each hippocampus lesion consisted of six to seven rostrocaudal injection planes, each with one to two mediolateral and one dorsoventral injection sites. Following injections, the dura was sutured, the craniotomy filled with Gelfoam (Pharmacia & Upjohn, Peapack, NJ) and the fascia and skin sutured in two separate layers. The bone flaps were replaced and sutured for the hippocampus-lesioned subjects. Following the surgical procedure, the infants were monitored by a veterinarian and returned to their mothers once they were fully alert. Sham-operated controls underwent the same presurgical preparations, received a midline incision, and the skull was exposed. The control subjects were maintained under anesthesia for the average duration of the lesion surgeries, and the fascia and skin were sutured in two separate layers.

Lesion Analysis

Magnetic Resonance Imaging-based Lesion Evaluation

We obtained T2-weighted MR images 10 days after surgery to confirm the general location of the lesion (i.e., amygdala lesion sparing the hippocampus or hippocampus lesion sparing the amygdala) and to assess collateral damage (Figure 1). The brains of the amygdala- and hippocampus-lesioned subjects were imaged 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 × 256).

Histological Lesion Evaluation

One amygdala-lesioned subject was sacrificed after behavioral testing for health reasons unrelated to the lesion surgery, thus enabling histological evaluation of the lesion (Figure 2). The results of this histological evaluation are summarized in the Results section.

Experimental Design and Procedures

Home Cage Observations

Each subject was observed alone in its home cage on a daily basis in the morning and/or the afternoon for a minimum of 216 times between 6 and 12 months of age (approximately nine observations per subject per week). Trained observers who were blind to the assigned lesion conditions conducted observations in a predetermined pseudorandom order for 10-sec periods. At the onset of each observation, the observer approached to 1 m in front of the home cage and recorded behaviors using a checklist of one–zero behavioral sampling described by Altmann (1974). Behaviors observed included bark, coo, crook tail, fear grimace, freeze, grunt, lipsmack, crouch, present groom, present mount, scream, self-groom, self-bite, self-clasp, self-sex, self-play, sleep, cage stereotypies, threat, and tooth grind.

Behavioral Sampling Overview

Behavioral data were collected with The Observer software (Noldus, 1991) by trained observers demonstrating an interobserver reliability >90% (agreements/[agreements + disagreements] × 100). Observers remained blind to the lesion condition of the subjects for the duration of data collection. Focal animal samples (Altmann, 1974) were taken for each subject in a predetermined pseudorandom order using a catalog of 39 behaviors commonly used for this species (Table 1). In addition to frequency and duration of species-typical behaviors, observers also recorded the direction of the behavior (initiate or receive) and the identity of any other subjects directly interacting with the focal subject. Subjects were observed under three distinct levels of social complexity, defined by the number of other subjects present (Table 1): (1) solo observations (subject alone), (2) dyadic interactions (two subjects), and (3) social groups (six experimental subjects, one adult male, and one adult female).

Social Group Observations

Each cohort was assigned to one of four identical, large chain link cages (2.13 m W × 3.35 m D × 2.44 m H) where daily cohort socialization occurred. Subjects were observed between 6 months and 1 year of age during a 3-hr socialization period, which took place between 12 noon and 3 p.m. daily. Each socialization cohort

consisted of the focal subject and five other experimental subjects, one adult male, and one adult female. Five-minute focal observations were conducted on each subject in a predetermined pseudorandom order, with no more than two observations per subject per week for a total of 30 observations per subject.

Solo Observations and Familiar Dyads

Solo observations and familiar dyads (between subjects from the same rearing cohort) were conducted immediately following weaning, when the youngest monkey within a particular cohort reached 6 months, and was repeated when they reached 9 months of age. Testing took place in one of four identical large chain link group cages, unfamiliar to the animals (2.13 m $W \times$ 3.35 m $D \times$ 2.44 m H) between 9 a.m. and 12 noon for five consecutive days. First, each subject was observed alone (solo observations) to obtain a baseline behavior in the absence of a social partner. Two consecutive 5-min focal observations were conducted for each subject on the first day testing. Then, on the same day, each subject was observed during dyadic interactions, when two subjects from the same socialization cohort were allowed to interact freely for 20 min. Each subject participated in two dyads per day. Behavioral data were collected for the entire observation period, alternating the focal subject every 5 min. Each subject was tested twice (on separate days) with every other subject from the same cohort, according to a predetermined pseudorandom sequence. On the last day of testing, each subject was again observed alone (solo observations) for two 5-min periods to obtain another baseline of behavior.

Novel Dyads

Novel dyads were conducted when the average age of the subjects within a particular cohort reached 12 months. Unlike familiar dyads, novel dyads were composed of two unfamiliar subjects, from separate rearing cohorts who had never met. Testing took place in one of four identical large chain link group cages unfamiliar to both animals between 9 a.m. to 12 noon and 2 to 5 p.m. Each subject was observed with every subject from a separate rearing cohort (two amygdala-lesioned, two hippocampus-lesioned, and two sham-operated control subjects), according to a predetermined pseudorandom sequence. Each subject participated in two 20-min dyads per day, balanced for testing order and morning/afternoon sessions. Behavioral data were collected during the entire observation period, alternating the focal subject every 5 min. The complete rotation of dyads was then repeated for five more weeks, resulting in six interactions for each combination of dyad partners. At the conclusion of each novel dyad, subjects were rated on a seven-point scale for level of confidence, nervousness, fear, and activity.

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