



## The amygdala: is it an essential component of the neural network for social cognition?

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### Abstract

Observations from human subjects with focal brain lesions and animal subjects with experimental lesions have implicated a variety of brain regions in the mediation of social behavior. Previous studies carried out in the macaque monkey found that lesions of the amygdala not only decrease emotional reactivity but also disrupt normal social interactions. We have re-investigated the relationship between amygdala lesions and social behavior in cohorts of mature and neonatal rhesus monkeys who were prepared with selective and complete bilateral ibotenic acid lesions of the amygdaloid complex. These animals display clear alterations in emotional and social behavior. We interpret these changes as due to a loss of the ability to evaluate environmental stimuli as potential threats. However, adult animals with bilateral lesions of the amygdala demonstrate normal, and even increased, social interactions with conspecifics. Moreover, neonatal animals, prepared with amygdala lesions at 2 weeks of age, also demonstrate species typical social behaviors such as the generation of facial expressions, grooming and play behavior. These results argue against the idea that the amygdala is essential for the interpretation of social communication or for the expression of social behavior. Because it does appear to participate in the evaluation of the “safety” of social interactions, we believe that it does have a role in modulating the amount of social behavior in which an organism will participate. However, our current answer to the question posed in the title of this paper is no!

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It has been known for more than a century that damage to the temporal lobe in non-human primates is associated with dramatic changes in socioemotional behavior [3]. Macaque monkeys with these lesions typically are more tame, demonstrate abnormal food preferences and have alterations of sexual behavior [11,12]. Subsequent studies with more selective lesions provided evidence that damage restricted to the region of the amygdala can produce most of these changes in behavior [1,18].

One of the earliest studies explicitly designed to evaluate changes in social behavior in macaque monkeys following amygdala damage was carried out by Rosvold et al. [15]. They established artificial social groups of male rhesus monkeys and studied the dominance hierarchy that emerged. They then carried out two-stage bilateral destructive lesions

of the amygdala of the most dominant animals and studied the dominance hierarchy as the group reorganized. The common finding was that the lesion led to a decrease in social dominance with the lesioned animal typically falling to the most subordinate position of the group.

A more extensive group of studies was carried out by Kling and coworkers in a variety of primate species in both captive and free ranging environments [6–10]. In a classic study, Dicks et al. [4] retrieved rhesus monkeys from social troops on the island of Cayo Santiago. These animals were subjected to bilateral amygdectomy and then returned to their social groups. While it was difficult to follow the minute-to-minute interactions of the lesioned animals, the typical finding was that they were invariably ostracized and would often perish without the support of the social group.

From the results of these and similar studies carried out by several laboratories, Brothers [2] formalized the view that the amygdala is one of a small group of brain regions that form the neural substrate for social cognition. This

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view predicts that the amygdala is essential for certain aspects of the interpretation and production of normal social gestures such as facial expressions, body postures, etc. It also predicts that damage to the amygdala would invariably lead to a decrease in the amount, or quality of, conspecific social interactions.

While the evidence in favor of a prominent role for the amygdala in social function is substantial, there are also a number of problems with the way in which many of the earlier non-human primate studies were conducted. Virtually, all of the lesion studies involved destructive lesions of the amygdala that not only damaged cells within the amygdala itself, but also damaged fibers that travel through and around the amygdala from other brain regions. Many of the lesions also directly involved surrounding brain regions. Some of the lesions in the study by Rosvold et al. [15], for example, heavily involved the temporal polar cortex. Another problem is that most of the studies of post-surgical alterations in social behavior were qualitative or anecdotal. It was rare that a full array of primate interactions was evaluated and even rarer that the frequency or duration of behaviors was quantified. In some cases, lack of social interaction could be explained due to reasons other than the brain damage. For example, in the matrilineal social system of macaque monkeys, young, male monkeys often emigrate from their natal troops to other troops. This has the obvious merit of maintaining genetic diversity in the population. If a male who emigrates attempts to return to its natal troop, however, it is typically rebuffed. Therefore, it is not clear in some of the naturalistic studies whether the amygdala lesioned animals were ostracized due to the effects of the lesion or because the troop had interpreted that the animal was an émigré.

We have re-investigated the contribution of the macaque monkey amygdala to social behavior using a more controlled and quantitative approach both to the production of the lesions and to the subsequent behavioral observations. A complete account of the effects of amygdala lesions on dyadic social interactions in the mature macaque monkey has been published recently [5]. A preliminary report on the effects of neonatal amygdala lesions on the emergence of social behavior has also been published [14]. In the remainder of this article, we will briefly summarize the major findings of these studies and then comment on the implications of these findings for considering the amygdala an essential component of the network for social cognition.

Male rhesus monkeys with bilateral ibotenic acid lesions of the amygdala, and age- and sex-matched control monkeys were observed during a variety of social encounters. All monkeys were born and raised in different outdoor cages and had comparable ranks in their respective dominance hierarchies. The neurotoxic lesion technique has the merit of removing the neurons of the amygdala while sparing fibers that pass through it. Fig. 1 illustrates the near complete loss of neurons in the amygdala at a mid rostrocaudal level in one of the subject animals.

We will summarize below some of the data from dyadic interactions in which the amygdala lesioned animals and age-, sex- and dominance-matched control animals interacted with “stimulus monkeys” (two males and two females). A variety of both affiliative (groom, present sex, etc.) and agonistic (aggression, displace, etc.) behaviors were quantitatively recorded using the Observer program (Noldus) while animals interacted in a large (18 ft × 7 ft × 6.5 ft—shown in Fig. 2) chain link enclosure. Each experimental animal interacted with each stimulus animal for 6 and 20 min periods

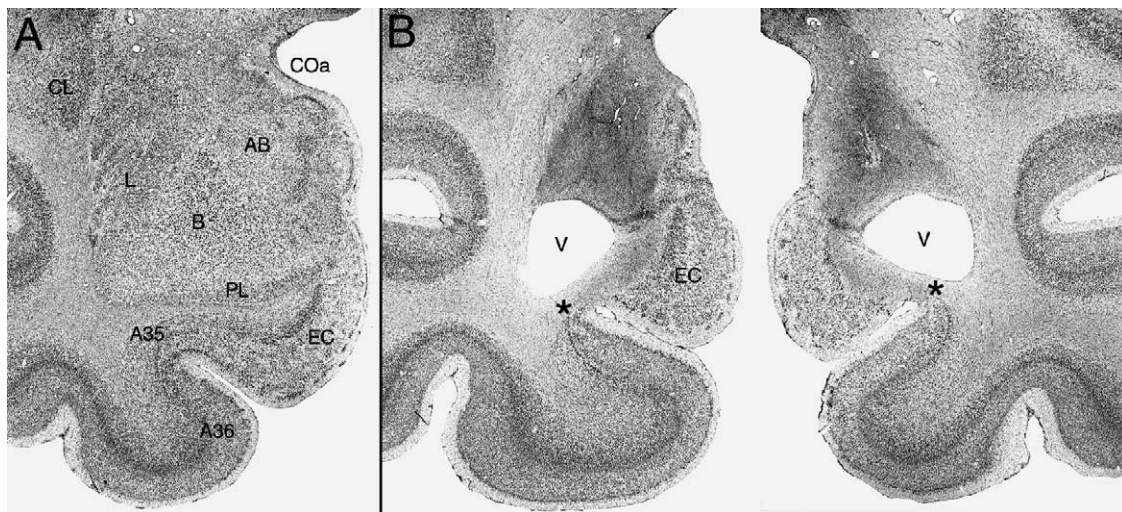


Fig. 1. Photomicrographs of Nissl-stained coronal sections through a mid rostral caudal level of the macaque monkey amygdala. Panel (A) shows the left side in a control brain and panel (B) shows the left and right sides in one of the animals that had received a bilateral ibotenic acid lesion of the amygdala. The amygdala in the lesioned animals has shrunk substantially, shows few viable neurons, and the subjacent ventricle has expanded. Abbreviations: A35, A36, areas 35 and 36 of the perirhinal cortex; AB, accessory basal nucleus; B, basal nucleus; CL, claustrum; COa, anterior cortical nucleus; EC, entorhinal cortex; L, lateral nucleus, PL, paralamina nucleus; V, ventricle; asterisk marks minor damage of area 35 of the perirhinal cortex in the lesioned brain.

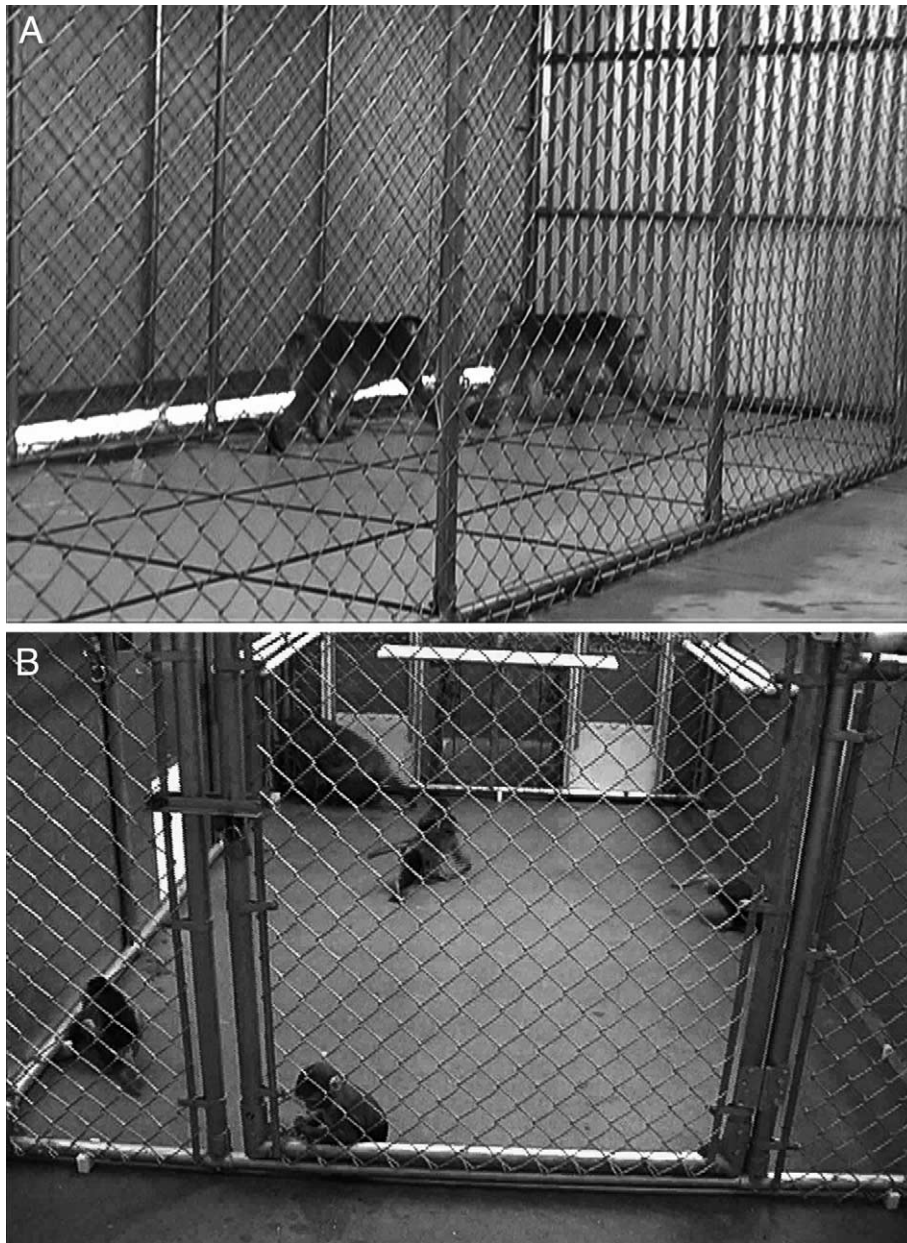


Fig. 2. (A) Still images derived from videotapes of adult monkeys participating in a dyadic social interaction to show the enclosure that was constructed for analyses of social behavior in macaque monkeys. (B) Still images derived from video tapes of post-weaning infants (approximately 8 months of age) participating in a socialization period with five other infants and one adult male. Observations on their social behaviors were carried out during these group interactions as well as in more controlled dyadic interactions.

in what we called the unconstrained dyad format. In another test of dyadic social interaction (round robin format) each of the experimental animals interacted with each of the other 11 experimental animals for 1 and 20 min episode. The results from both tests of dyadic interaction were striking. The amygdala lesioned monkeys generated significantly greater amounts of affiliative social behavior towards the stimulus monkeys or towards the other experimental monkeys. The lesioned monkeys appeared to be socially uninhibited in that they did not go through the normal period of evaluation of the social partner before engaging in social interactions.

One unexpected result was how the control animals interacted with the lesioned monkeys. One could imagine that the early and inappropriate forwardness of the lesioned monkeys towards the control monkeys might have been interpreted as “pathological” by the controls and could have resulted in them shunning the lesioned animals. In stark contrast to this outcome, the control monkeys actually found the lesioned animals more “attractive” in that they generated more affiliative social behaviors towards them than towards the control animals. Even when the animals had only 120 min period of social interaction in the round

robin format, the control animals immediately identified the amygdala lesioned animals as different and generated more social behavior towards them.

The inevitable conclusion from this study is that in dyadic social interactions, monkeys with extensive bilateral lesions of the amygdala can interpret and generate social gestures and initiate and receive more affiliative social interactions than normal controls. They are clearly not critically impaired in carrying out social behavior. We would suggest that the lesions have produced a socially uninhibited monkey since their normal reluctance to engage a novel animal appears to have been eliminated. This, as well as other evidence, has led us to the hypothesis that a primary role of the amygdala is to evaluate the environment for potential threats. Without a functioning amygdala, the animals do not respond to one another as if conspecifics are potentially dangerous and whatever system(s) are involved in mediating social interactions run in the default mode of engagement.

The same group of animals has also been tested for their responsiveness to a variety of stimuli including novel objects (Mason et al., unpublished observations). Some of the objects, such as rubber replicas of snakes, provoke fear responses in normal monkeys. In one such study, the latency to retrieve a food reward (usually a grape or piece of another type of fruit) from in front of the stimulus items was measured (Fig. 3). For normal animals, the latency to retrieve the food reward depended on whether there was a stimulus present or not and on the fear provoking qualities of the stimulus. With the amygdala lesioned animals, in contrast, fear eliciting stimuli such as a rubber snake did not appreciably increase the latency to retrieve the food. The lesioned animals would even tactually explore objects such as rubber snakes which the normal animals were never observed to touch. These observations were consistent with the notion that the amygdala lesions impair a system that is normally

engaged in evaluating environmental stimuli for potential threats or dangers.

One caveat of the conclusion that the amygdala is not essential for social behavior is that these experiments were carried out in mature monkeys. One might argue that while the amygdala is not necessary for generating social behavior, perhaps it is essential for learning appropriate social behaviors. There is precedent for this in the role of the hippocampal formation and memory. The hippocampal formation is clearly essential for the establishment of long-term episodic memories. However, analysis of well-known amnesic patients, such as H.M., who have marked bilateral damage to the hippocampal formation indicate that it is not essential for the retrieval of memories stored prior to the hippocampal damage which must be therefore stored in brain regions other than the hippocampal formation [16].

We have carried out a series of studies in which the amygdala is lesioned bilaterally in primates at 2 weeks of age [14]. This is at a point in time when infant macaque monkeys are mainly found in ventral contact with their mothers and there is virtually no play or other types of social interactions with other animals. It is important to note that strategies were developed to allow the post-surgical return of the infant to its mother for rearing. Moreover, all mother–infant pairs engaged in daily 3 h-long “play groups” with five other mother–infant pairs and an adult male. We took these steps to promote normal social development and to avoid the behavioral pathologies associated with nursery rearing.

We found that the interactions of the lesioned animals with their mothers was similar to that of control animals. Moreover, we found that, like adult animals with bilateral amygdala lesions, they showed little fear of normally fear-provoking objects such as rubber snakes. However, they showed increased fear, as indicated by more fear grimaces, more screams and less social interactions, in novel dyadic social interactions. An intriguing, yet unsolved puzzle with

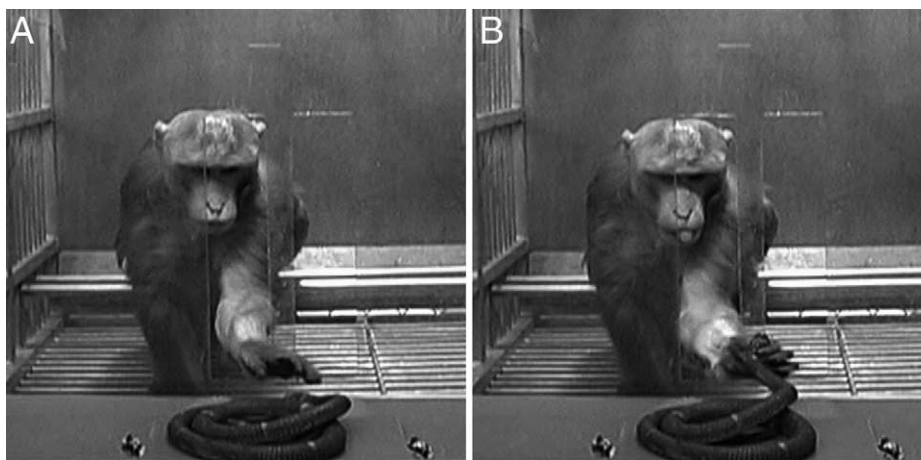


Fig. 3. Still images derived from a videotape of adult monkeys participating in a test of responsiveness to a series of novel objects. The animal in these images has received a bilateral lesion of the amygdala. The animal immediately reached for the grape in front of the rubber snake replica (A) but, after putting the grape in his mouth, began tactually exploring the rubber snake (B). Normal animals would typically not approach the rubber snake and never tactually explore it.

this finding, is the elucidation of which brain region is subserving the social fear since the amygdala was entirely eliminated. More germane to this discussion, however, is the finding that the lesioned animals generated substantial social behavior that could not be distinguished from age-matched controls. The quality and quantity of social interactions of the neonatally lesioned animals in a number of social formats is currently being investigated. While the amygdala lesioned animals may demonstrate subtle differences in their social interactions, the inescapable conclusion from observation of these animals is that there are none that are markedly impaired in generating species typical social behaviors such as grooming, play and facial expressions (Prather et al., unpublished observations).

Given that the amygdala appears not to be essential either for the mediation of appropriate social behavior in mature macaque monkeys nor for the development of species-typical social interactions in immature monkeys, our current hypothesis is that the amygdala is not an essential component of the neural system involved in social cognition. This conclusion is consistent with the emerging information from analyses of human subjects with bilateral amygdala lesions. As described by Adolphs and coworkers (personal communication), patient S.M. who, due to Urbach–Wiethe syndrome, has bilateral cystic lesions of the amygdala, is perfectly capable of normal daily life. Her primary deficit appears to be an inability to interpret signs of danger in other people such as expressions of fear or the level of “trustworthiness” they convey. There do not appear to be any human cases in the literature in which the amygdala has been selectively damaged at birth to compare with our neonatal lesion experiments.

This is not to say that the activity of the amygdala does not have a modulatory role on social behavior. If, as we suspect, a prominent function of the amygdala is threat detection, it would tend to inhibit social interaction while evaluation of the social environment is under way. If the amygdala was dysregulated and hyperactive, social behavior could potentially be greatly inhibited. There is intriguing evidence that this may be the case in social phobia. Tillfors et al. [17] found increased cerebral blood flow, relative to controls, in the amygdala of individuals with social phobia as they anticipated giving a public presentation.

Before concluding, it is important to raise one caveat about much of the data presented in this paper. All of the data presented from our non-human primate studies and conclusions reached from patients such as S.M. are based on permanent, destructive lesions of the amygdala. As with any lesion study, damage to one brain region has consequences for all of the brain regions that share afferent or efferent connections with it. We have interpreted the lack of dramatic change in social behavior after amygdala damage as evidence that the amygdala is not essential for near normal social behavior. However, the lesion study does not negate the possibility that the amygdala may normally be involved in social behavior. Perhaps there is redundancy in the brain systems involved in organizing social behavior and remain-

ing systems can compensate for the functions normally subserved by the amygdala when it is damaged. Or, perhaps the loss of the amygdala induces another brain region that is normally not involved in social behavior to take over this function. Other techniques will be needed to resolve these issues and further refine the function of the amygdala and define the neural network underlying social cognition. One exciting technique has recently been described by Lechner et al. [13]. Using viral transfection techniques, these investigators have inserted the gene for a *Drosophila* hormone receptor, the allostatin receptor, into the ferret central nervous system. Since there is no endogenous ligand for the receptor, it lies dormant in the brain. However, by administering the allostatin hormone, the G protein coupled receptor activates potassium channels and leads to hyperpolarization of the transfected neurons. In essence, the neurons are transiently turned off. As the hormone is eliminated through metabolic processes, the neurons come back on line. One can imagine, therefore, that in the very near future, destructive lesions with their concomitant potential for brain reorganization will no longer be needed. Using different molecular transient deactivators, different brain regions and even different cell types will be able to be turned off at will while behavioral observations, such as those described in our non-human primate studies, could be carried out. These types of studies, along with non-invasive imaging studies, will go some way towards confirming or refuting the speculations that we have raised based on our lesion studies of the macaque monkey.

To conclude, therefore, we have directly evaluated the role of the amygdala in the learning and production of conspecific social behavior in the macaque monkey. The amygdala does not appear to be essential for either of these functions. Rather, selective bilateral lesions of the amygdala in mature macaque monkeys results in a lack of fear responses to inanimate objects and a “socially uninhibited” pattern of behavior. These results imply that the amygdala functions as a protective “brake” on engagement of objects or organisms while an evaluation of potential threat is carried out. While not directly involved in the control of social interaction, the amygdala might modulate the amount of social behavior an organism would generate based on an evaluation of the safety of the social context.

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