Genes, Brain and Behavior (2003) **2:** 295–302

Review

The amygdala and autism: implications from non-human primate studies

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Received 19 June 2003, revised 25 August 2003, accepted for publication 26 August 2003

Brothers (1990) has proposed that the amygdala is an important component of the neural network that underlies social behavior. Kemper and Bauman (1993) identified neuropathology in the amygdala of the postmortem autistic brain. These findings, along with recent functional neuroimaging data, have led Baron-Cohen *et al*. (2000) to propose that dysfunction of the amygdala may be responsible, in part, for the impairment of social behavior that is a hallmark feature of autism. Recent data from studies in our laboratory on the effects of amygdala lesions in the adult and infant macaque monkey do not support a fundamental role for the amygdala in social behavior. If the amygdala is not essential for the component processes of social behavior, as seems to be case in both non-human primates and selected patients with bilateral amygdala damage, then it is unlikely to be the primary substrate for the impaired social behavior of autism. However, damage to the amygdala does have an effect on a monkey's response to normally fear-inducing stimuli, such as snakes, and removes a natural reluctance to engage novel conspecifics in social interactions. These findings lead to the conclusion that an important role for the amygdala is in the detection of threats and mobilizing an appropriate behavioral response, part of which is fear. Interestingly, an important comorbid feature of autism is anxiety (Muris *et al*. 1998). If the amygdala is pathological in subjects with autism, it may contribute to their abnormal fears and increased anxiety rather than their abnormal social behavior.

Keywords: Amygdaloid complex, anxiety, lesion, rhesus monkey, social behavior

How has the amygdala come to be implicated in the pathophysiology of autism?

Autism is a lifelong neurological disorder that typically manifests by three years of age. Individuals with autism are severely impaired in reciprocal social interaction, cognitive development and verbal and non-verbal communication. Other difficulties may include gross motor problems, unusual fear or anxiety, hyper-orality and the inability to modulate sensory input. Since Leo Kanner (1943) initially described the disorder 50 years ago, the definition of the autism spectrum has evolved and now encompasses a wide range of social and emotional abnormalities with varying levels of cognitive and linguistic functioning. Almost simultaneously with Kanner, Hans Asperger (1944) described a group of children as having 'autistic psychopathy'. These children had a narrow range of interests similar to high functioning autism, but their language skills appeared to develop normally. Although several studies have provided biological clues in the last 10 years, the cause(s) of autistic spectrum disorders remain unknown. Currently there is no clear relationship between structural abnormalities in the brain and autism. However, some recent literature has suggested a possible link between autism and abnormal development of the amygdala (Baron-Cohen *et al*. 2000; Sweeten *et al*. 2002). These reviews primarily site evidence from post-mortem qualitative observations of autistic brain tissue and structural magnetic resonance imaging (MRI) studies of live subjects with autism vs. controls.

Neuropathology of the amygdala in autism

To date, less than 40 human post-mortem autistic cases have been described in the literature (Bailey *et al*. 1998-Coleman *et al*. 1985; Kemper & Bauman 1993; Ritvo & Freeman 1984; Rodier *et al*. 1996; Williams *et al*. 1980). One of the largest studies consisted of six autistic brains and was the only report of abnormalities in the microscopic organization of the amygdala (Kemper & Bauman 1993). Nissl stained sections of brain tissue from autism cases were

doi: 10.1046/j.1601-183X.2003.00043.x

compared to age-matched controls in which corresponding areas were viewed side-by-side under a microscope at the same magnification. Their report indicated that neurons in the amygdala of autism cases appeared unusually small and more densely distributed than age-matched controls. This was most pronounced in the cortical, medial and central nuclei, whereas the lateral nucleus generally appeared to be comparable to controls. The basal nucleus of the amygdala also showed an intermediate degree of involvement. Kemper and Bauman (1993) suggest that densely distributed neurons in the amygdala may manifest during an early stage of maturation, a time at which the neuronal size and complexity of neuropil have not reached adult proportions. These changes can be characterized as a curtailment of normal maturation.

These results are complicated by the fact that four of the six cases studied by Kemper and Bauman (1993) also had seizure disorders. Studies focusing on cases of epilepsy without autism indicate a reduction in amygdala volume of 10–30%, with neuronal cell loss reported in the lateral and basal nuclei of the amygdala (Pitkanen *et al*. 1998). To date, the only other neuropathological study of the amygdala in autism examined six post-mortem cases, four of which had a seizure disorder, and failed to report any significant differences from controls (Bailey *et al*. 1998). Both studies on the amygdala included a wide age range of subjects and therefore cannot address any possible age-related changes throughout development. In addition, none of these studies presented quantitative data.

Structural magnetic resonance imaging studies

To date, no consistent findings have been reported for MRI studies of volumetric abnormalities of the amygdala in individuals with autism. Some studies have reported decreased volume (Aylward *et al*. 1999; Pierce *et al*. 2001), others increased volume (Howard *et al*. 2000; Sparks *et al*. 2002), or decreased anterior volume and increased posterior volume (Abell *et al*. 1999), and still others show no significant differences (Haznedar *et al*. 2000). A number of factors may contribute to the contradictory reports, including differences in diagnostic and exclusionary criteria, the age group of subjects measured, methods of image processing and anatomical definition of the amygdala.

Many studies have included a wide age range of subjects. Aylward *et al*. (1999) manually traced the amygdala in 14 cases of high functioning autism with ages ranging from 11 to 37 years of age, and reported decreased amygdala volume in autism subjects compared to age-matched control cases. Pierce *et al*. (2001) analyzed six cases of high functioning autism with ages ranging from 23 to 41 years, also reporting amygdala volumes to be significantly smaller by approximately 15% relative to controls.

Howard *et al*. (2000) employed both manual tracing and stereological point counting in 10 males with high functioning autism and Asperger's syndrome ranging from 15 to 40 years of age. They reported the volume of the amygdala to be larger in subjects with autistic spectrum disorder relative to controls. Abell *et al*. (1999) took a different approach to analyzing structural images by employing a voxel-based whole brain analysis in 15 high functioning autism and Asperger's syndrome subjects with an average age of 28 years. Subjects with a diagnosis on the autistic spectrum showed decreased gray matter volume in the area of the anterior amygdala, but increased gray matter volume in more posterior portions.

Sparks *et al*. (2002) measured the amygdala in males of 36–56 months of age and found it to be larger by 16% on the right and 13% on the left, in autism subjects relative to controls. The authors suggest that arrested development or increased apoptosis throughout development in individuals with autism may contribute to differing results found in studies of early childhood vs. adulthood.

MRI studies measuring the volume of the amygdala in normal controls also suggest that the size of the amygdala typically increases in males from 5 through 15 years of age (Giedd *et al*. 1996). These results support the hypothesis that age related changes in the amygdala occur throughout development and may account for some of the variability seen in various MRI studies, in addition to differences in diagnostic and image processing methods.

Functional imaging studies of the amygdala in autism

During a task that requires subjects to judge from images of a person's eyes what that person might be feeling or thinking, individuals with high functioning autism or Asperger's syndrome show significantly less amygdala activation than control subjects (Baron-Cohen *et al*. 1999). Others have found that the amygdala in high-functioning subjects with autism demonstrates a blunted activation when implicitly judging facial emotion (Critchley *et al*. 2000). Schultz *et al*. (2003) have provided evidence that the amygdala, along with regions such as the fusiform face area, is activated by a social attribution task involving the perception of human–like interactions among three simple geometric shapes. Howard *et al*. (2000) also provided evidence of a role for the amygdala in autism. They found that people with high-functioning autism show selective impairment in the recognition of facial expressions of fear, perception of eye-gaze direction and recognition memory for faces, characteristic of the effects of amygdala damage. Moreover, using quantitative MRI analysis techniques, they found that the same individuals also show bilaterally enlarged amygdala volumes. They proposed that developmental malformation of the amygdala might underlie the social-cognitive impairments characteristic of autism. While these data would appear to be compelling evidence for the notion that the amygdala is involved in the interpretation of socially relevant stimuli, a number of methodological concerns have been raised (Davidson & Slagter 2000). For example, given that subjects with

autism are reluctant to make eye contact, it is not clear that they are examining face stimuli or other socially relevant stimuli in the same manner as normal controls. One can raise the question therefore, of whether the altered brain activation reflects abnormal brain functional organization or altered behavior during the imaging session.

Medial temporal lobe lesions in macaque monkeys

Brown and Shaffer (1888), followed by Kluver and Bucy (1939), first reported that large lesions of the temporal lobe, including the amygdala, result in profound changes in the emotional behavior of non-human primates. Macaque monkeys with temporal lobe lesions develop a compulsive interest in objects, abnormal food preferences, as well as behavioral changes in tameness and sexual behavior. Subsequent lesion studies indicated that these changes in emotional behavior could be produced by complete lesions of the amygdala alone (Aggleton & Passingham 1981; Weiskrantz 1956). The role of the amygdala in social behavior was first established in a classic experiment by Rosvold (Rosvold *et al*. 1954). In this study, the most dominant members of a group of eight male rhesus monkeys received bilateral amygdala lesions. Behavioral observations indicated that two of the three formerly high ranking individuals developed submissive behaviors and fell to the bottom of the dominance hierarchy following the amygdala lesions, while the third developed pronounced aggression. These results indicate that amygdala lesions result in profound changes in social behavior production, as well as alterations in social rank. The role of the amygdala in social behavior was further examined in a series of experiments by Kling and colleagues using a variety of non-human primate species in both laboratory and free-range testing conditions (Kling 1992). The collective results from these studies indicated that bilateral amygdala lesions disrupt species-typical social behavior, generally resulting in decreased affiliative behavior and subsequent social isolation when tested in socially complex environments (Steklis & Kling 1985). For instance, seven free-range rhesus monkeys who were captured, given bilateral amygdalectomies and then returned to their social groups displayed social indifference, became solitary and were unable to reestablish themselves with their former group (Dicks *et al*. 1968). The lack of social communication reported in these early amygdala lesion studies led to the proposal that the amygdala was an essential component of the neural circuitry underlying social behavior, a theory formalized in a review by Brothers (1990).

Recently, the amygdala lesion technique has been applied to developmental studies in an attempt to identify the neural structures underlying developmental disorders such as autism (Bachevalier 2000; Machado & Bachevalier 2003). Bachevalier and colleagues conducted a series of experiments on the effects of neonatal amygdala lesions on social behavior development, using peer-reared infant macaques with bilateral amygdala lesions (Bachevalier 1994). When tested with control subjects at two months of age the amygdala-lesioned subjects displayed inactivity and less exploration of their environment. Alterations in social behavior were first reported at six months of age, with the amygdala-lesioned subjects demonstrating less initiation of social contact and more social withdrawal than control subjects. At this age, both amygdala-lesioned subjects and controls demonstrated stereotypic behaviors. More extensive lesions of the medial temporal lobe, including the amygdala, hippocampus and ventromedial temporal cortex produced a more profound effect on social interactions, including 'lack of social skills', flat affect and increased stereotypic behaviors. Given that impaired social communication and a lack of social interest are the hallmarks of autism, the authors proposed that lesions of the medial temporal lobe, specifically the amygdala, might provide an animal model of autism.

How have recent non-human primate and human studies questioned a role for the amygdala in autism?

Early maternal deprivation can markedly influence primate social behavior

In order to evaluate previous studies on the effects of amygdala lesions in neonatal non-human primates, it is important to note that virtually all of the animals in the earlier studies were deprived of normal maternal rearing. There is reason to believe that this manipulation, which is standard animal husbandry procedure at many primate facilities, is sufficient to produce animals with profound social/emotional disturbances. There is evidence, for example, that pair rearing leads to socioemotional pathologies such as excessive clinging (Novak & Sackett 1997). Sackett and colleagues (2002) have recently demonstrated, in fact, that extraordinary measures are needed in order to partially mitigate the deleterious effects of nursery rearing. Early non-maternal rearing situations also negatively impact an animal's ability to respond to environmental challenges (Suomi 1991). Moreover, Parr and colleagues (2002) demonstrated that peer-reared rhesus monkeys have higher baseline levels of fear potentiated startle than mother-reared age-matched controls. This would suggest that there is a fundamental alteration of neural systems that regulate emotional responsivity. In addition, Wallen (1996) has pointed out that the ability to express species typical sexual behavior 'results from hormonally induced predispositions to engage in specific patterns of juvenile behavior whose expression is shaped by the specific social environment experienced by the developing monkey.' Rearing conditions have also been shown to have a profound influence on the development of monoaminergic systems (Clarke *et al*. 1996) leading these authors to conclude that primate mothers influence the psychobiological development of central nervous system neurotransmitter systems in their infants. Finally, Coe and colleagues (Lubach *et al*. 1995) have

produced overwhelming evidence that rearing in the absence of the mother severely affects several aspects of cellular immunity. For example, nursery reared monkeys have significantly lower proportions of CD8 cells and lower natural killer cell activity than mother reared monkeys. These studies have influenced our decision to return infant macaques to their mothers following the neurosurgical intervention and to insure that they receive species typical social stimulation on a daily basis throughout development.

Lesions of the amygdala do not decrease social behavior in adult or neonatal rhesus monkeys

We first examined the effects of selective amygdala lesions in a group of socially experienced adult rhesus males who had previously lived in a seminaturalistic field cage environment (Emery *et al*. 2001). Unlike previous adult amygdala lesion studies, we found that amygdala-lesioned subjects were capable of communicating with conspecifics through a variety of species-typical social cues. When observed in dyadic interactions, the adult macaques without an amygdala actually engaged in greater amounts of social interaction, particularly early in a social encounter, because they apparently lacked the normal reluctance to engage another conspecific before it is determined to be safe to do so. These results indicated that amygdala lesions in mature subjects do not alter the component processes of social behavior (i.e., production/interpretation of social signals and social interest). However, amygdala lesions may indirectly alter social behavior by disrupting the ability to evaluate potential danger (i.e., an unfamiliar social partner) and respond appropriately (Fig. 1).

Although it did not appear that the amygdala was essential for the production of adult macaque social behavior, it remained possible that the amygdala was needed to acquire these social tools at earlier developmental timepoints. To address this question, we produced selective amygdala lesions in two-week-old infant rhesus monkeys and systematically examined their behavioral development (Bauman *et al*. 2003; Prather *et al*. 2001b). We reared the infants with their mothers and provided daily access to a social group consisting of five other mother–infant pairs and one adult male. This enriched rearing environment mimics many features of naturally occurring macaque social organization (Berman 1980). Thus alterations in social behavior can be more reasonably ascribed to the effects of the lesion rather than a side-effect of the rearing environment.

Our results indicate that maternally reared infant monkeys with selective bilateral amygdala lesions develop a complete repertoire of species-typical social signals, including facial expressions, vocalizations and body postures. We have observed no indication of flattened affect, motor stereotypies or the absence of social skills in the first year of development. Moreover, the amygdala-lesioned infants display 'social interest' in conspecifics. Measures of eye gaze frequency reveal that both amygdala and control infants look toward conspecifics with the same frequency (Prather

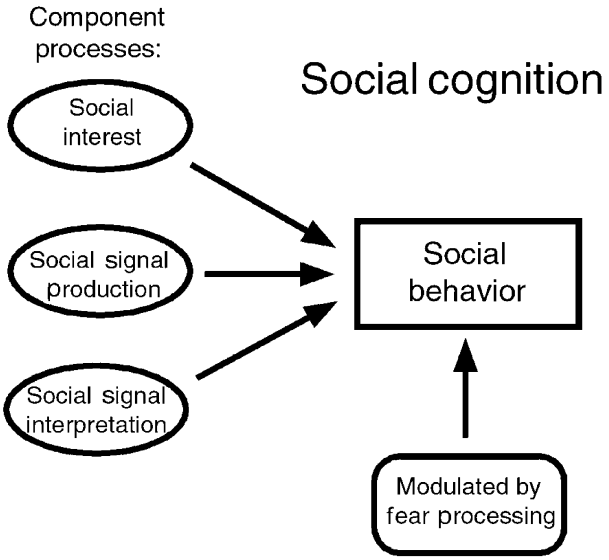

Figure 1: Social Cognition Model. Component processes required for social behavior are potentially modulated by fear processing.

et al. 2001a). Under certain testing conditions, the amygdala-lesioned subjects actually demonstrate heightened social interest in novel conspecifics (e.g., higher frequency of following their social partner; Bauman *et al*. 2003). Although the motivation for this heightened social interest is not yet understood, it is clear that the maternally reared amygdala-lesioned subjects do not display flattened affect or disinterest in conspecifics.

The fact that these fundamental aspects of social behavior are preserved in infant monkeys without an amygdala calls into question the validity of the proposed amygdala theory of autism. DSM-IV criteria for autism diagnosis must include a qualitative impairment in social interaction, including two of the following characteristics:

1 marked impairment in the use of non-verbal behaviors that regulate social interactions

2 failure to develop peer relationships

3 a lack of spontaneous seeking to share enjoyments, interests or achievements

4 lack of social or emotional reciprocity (APA 1994).

Not all aspects of these complex social behaviors can be modeled in non-human primates. However, we are able to study fundamental aspects of macaque social behavior, including development and use of social communication signals, social interest and relationships with conspecifics. Our results indicate that infant rhesus monkeys with bilateral amygdala lesions develop species-typical non-verbal communication,

including frequency of eye gaze, facial expressions and body postures, as well as social interest and an ability to form relationships with conspecifics. Moreover, the behavioral abnormalities that we do observe in the amygdala-lesioned infants appear more consistent with deficits in fear processing rather than impaired social communication. For instance, infant macaques without an amygdala demonstrate an impaired ability to correctly evaluate dangerous vs. benign stimuli, as indicated by a lack of fear response when exposed to normally fear-inducing objects, such as a rubber snake, and an over expression of fear behaviors (i.e., more frequent fear grimaces and screams than control subjects) when paired with an unthreatening conspecific (Prather *et al*. 2001b). This consistent finding of heightened social fear in neonatal amygdala-lesioned subjects (Thompson *et al*. 1969; Thompson 1981) offers an alternative explanation for the changes in social behavior Bachevalier and colleagues observed in the amygdala-lesioned infant monkeys (Bachevalier 1994). It is plausible that the absence of social interaction observed by Bachevalier was not the result of 'autistic like' symptamotolgy, but rather due to the abnormal social fear response that is characteristic of amygdala-lesioned monkeys. This explanation is consistent with the view that the amygdala is not essential for fundamental aspects of social behavior, such as producing social signals and interacting with conspecifics. However, the amygdala may indirectly modulate social behavior by detecting danger within a social context and orchestrating an appropriate behavioral response.

Human subjects with focal lesions of the amygdala are not autistic

Human patients with amygdala lesions are rare. One exceptional subject, patient S.M., is one of the most extensively studied individuals with a selective and complete bilateral amygdala lesion (Adolphs *et al*. 1994; Bechara *et al*. 1995). Her lesion developed during adolescence from Urbach-Wiethe disease, resulting in space occupying what would normally be the amygdala. Despite her lack of amygdala function, patient S.M.'s social behavior remains relatively intact. She has a High School education, lives independently, and has normal IQ, linguistic ability and executive function. She is married, raising children and is able to hold down a job. Although she has a deficit in recognizing emotions in facial expressions, primarily fear, she does not display any autistic symptomotology based on DSM-IV (APA 1994) criteria from which the diagnosis of autism relies. Patient S.M. is able to carry out a fairly normal social life and there are no reports in the literature that she shows any impairment in reciprocal social interaction. Neither she nor any other patients with amygdala lesions display any type of restricted, repetitive or stereotyped patterns of behavior, interests or activity.

Although human patients with amygdala lesions are clearly not autistic, some may display impairments also seen in autism. Both patients with amygdala lesions (Adolphs 2003) and individuals with autism (Adolphs *et al*. 2001; Critchley *et al*. 2000) appear to have deficits in recognizing complex emotions in facial expressions. However, the role of the amygdala in making complex judgments about visual stimuli may not be restricted to social stimuli (Adolphs & Tranel 1999). Instead, it may play a broader role in danger detection and this function may be recruited for many cognitive processes in humans.

The role of the amygdala in processing stimuli related to potential threat may extend to complex judgments on the basis of which we approach or trust other people. In a recent study (Adolphs *et al*. 1998), patients with bilateral amygdala damage, including patient S.M., were impaired in judging how much to trust another person from viewing their face. They all judged other people to look more trustworthy and more approachable than did normal viewers. Adolphs *et al*. (2001) recently carried out an analogous task in subjects with autism. They found that the autism subjects performed similarly to amygdala lesion patients. However, both subject groups were able to give a verbal description of untrustworthiness and, when read a story, were able to judge character appropriately. A limitation of this study is that it is not clear if subjects were examining face stimuli in the same manner as normal controls. However, both the amygdala lesion subjects and autism subjects were able to judge that a person was trustworthy and approachable, but were impaired in judging if they were untrustworthy and unapproachable.

Although S.M. has normal declarative memory (Bechara *et al*. 1995), both she and patients with unilateral left amygdala lesions appear to have impairments in long-term declarative memory for emotionally arousing stimuli (Adolphs *et al*. 1997; Adolphs *et al*. 2001). The amygdala has direct connections with the hippocampus (Amaral 1986) and its potential role as a danger detector may influence or modulate how strongly an event may be stored in memory (Cahill & McGaugh 1998; Packard & Cahill 2001). Individuals with autism also appear to have normal, and in some cases exceptional, declarative memory. However, so-called emotional memory has not been well studied. The amygdala, through abnormal anxiety or impaired recognition of threatening stimuli, may indirectly affect this aspect of autism and suggests a direction for future research.

Another extraordinary human subject, patient H.M., provides further evidence that the amygdala is not essential for normal social behavior. Patient H.M. had bilateral temporal lobecomies for intractable seizures, which completely removed the amygdala and rostral half of the hippocampal formation (Corkin *et al*. 1997). While H.M. is clearly amnesic, he is capable of normal reciprocal social interaction. Neither he nor patient S.M. demonstrates typical autistic symptomotology. These patients support the contention that damage to the amygdala does not necessarily lead to abnormal social or autistic behavior.

If the amygdala is not responsible for social deficits in autism, what other feature might a pathologic amygdala influence?

Pathology of the amygdala may contribute to comorbid anxiety in autism

In Kanner's (1943) original report on autism, he described language and social impairments, but he also emphasized that his cohort of children exhibited substantial anxious behavior. Although the presence of anxiety has been noted in descriptions (APA 1994) and classifications of autism (Wing & Gould 1979), the characteristics and pervasiveness of this have not been well studied. However, recent studies are suggestive that anxiety is an extremely common feature of the autism spectrum disorders.

Muris and colleagues (Muris *et al*. 1998) examined the presence of co-occurring anxiety symptoms in 44 children with autism spectrum disorder. The sample included 15 children with autism and 29 with pervasive developmental disorder, not otherwise specified (PDD-NOS). They found that 84.1% of the children met criteria for at least one anxiety disorder. In descending order, the percentage of children meeting diagnostic criteria for an anxiety disorder were as follows: simple phobia (63.6%), agoraphobia (45.5%), separation anxiety (27.3%), overanxious (22.7%), social phobia (20.5%), avoidant disorder (18.2%), obsessive-compulsive disorder (11.4%) and panic disorder (9.1%). While the authors raised the caveat that anxiety symptoms were assessed via parental interview, they noted that parents often underreport internalizing symptoms, such as anxiety.

More recently, Gillott *et al*. (2001) compared high-functioning children with autism to two control groups including children with specific language impairment and normally developing children on measures of anxiety and social worry. Children with autism were found to be more anxious on both indices. In fact, four of the six factors on the anxiety scale were elevated, with obsessive-compulsive disorder and separation anxiety showing the highest elevations.

A number of recent studies have provided evidence that the amygdala may be dysregulated in emotional disorders such as anxiety (Davidson *et al*. 1999; Fredrikson & Furmark 2003; Rauch *et al*. 2003). Recently, Thomas *et al*. (2001) used fearful faces as probes for functional MRI analysis and demonstrated that the amygdala of anxious children showed heightened activity. De Bellis (De Bellis *et al*. 2000) also showed that the right amygdala of children with generalized anxiety disorder was larger than age matched controls. These findings are consistent with the results of our studies in non-human primates in that removal of the amygdala produced animals that were less fearful of inanimate objects.

Conclusions

The amygdala has been proposed to play an essential role in the production of normal social behavior. While there are intriguing neuroimaging and behavioral data indicating that the human amygdala is responsive to a variety of social signals, amygdala lesion studies both in rhesus monkeys and human subjects indicate that the amygdala is not essential for the expression of species-typical social interaction. As with all lesion studies, our data do not completely 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 remaining 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. However, there is clear evidence across species that the amygdala plays a prominent role in detecting threats in the environment. Thus, we interpret the bulk of available evidence as indicating that it is unlikely that dysfunction of the amygdala provides the substrate for the impairments of social interaction that are a hallmark feature of autism. However, if the amygdala is indeed dysfunctional in autism, this could contribute to the abnormalities of fear and anxiety that appear to be a common comorbid feature of autism.

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Acknowledgments

The original research described in this paper was supported by a grant from the National Institute of Mental Health (#RO1MH57502) and by the base grant of the California National Primate Research Center (#RR00169). This work was also supported through the Early Experience and Brain Development Network of the MacArthur Foundation.