The Amygdala and Development of the Social Brain

DAVID SKUSE, JOHN MORRIS, AND KATE LAWRENCE

Behavioural and Brain Sciences Unit, Institute of Child Health, London, United Kingdom

ABSTRACT: The amygdala comprises part of an extended network of neural circuits that are critically involved in the processing of socially salient stimuli. Such stimuli may be explicitly social, such as facial expressions, or they may be only tangentially social, such as abstract shapes moving with apparent intention relative to one another. The coordinated interplay between neural activity in the amygdala and other brain regions, especially the medial prefrontal cortex, the occipitofrontal cortex, the fusiform gyrus, and the superior temporal sulcus, allows us to develop social responses and to engage in social behaviors appropriate to our species. The harmonious functioning of this integrated social cognitive network may be disrupted by congenital or acquired lesions, by genetic anomalies, and by exceptional early experiences. Each form of disruption is associated with a slightly different outcome, dependent on the timing of the experience, the location of the lesion, or the nature of the genetic anomaly. Studies in both humans and primates concur; the dysregulation of basic emotions, especially the processing of fear and anger, is an almost invariable consequence of such disruption. These, in turn, have direct or indirect consequences for social behavior.

KEYWORDS: social brain; amygdala; behavior; facial expression

FACE PROCESSING AND THE "SOCIAL BRAIN"

We gain critically important information about how to respond appropriately in social encounters by monitoring the expression on another's face. This observation provides us with information about that person's emotional state. In certain circumstances, another's emotional expressions can evoke that emotion in oneself—viewing an expression of great happiness is one obvious example. Haxby *et al.*[1] proposed that there are dedicated systems for processing emotional expressions in another's face, in which the amygdala and insula play a crucial role.

When we use our social cognitive capacity to interpret the emotional content of a face and its meaning to us, we take into account a wide range of visual cues. These include, whether we know the individual or not (face recognition memory), the facial configuration (e.g., whether the mouth is wide open or shut, whether the eyes are

Address for correspondence: David Skuse, M.D., FRCP, Institute of Child Health, Behavioural and Brain Sciences Unit, 30 Guilford St., London, UK WC1N 1EH. Voice: +44 20 7831 0975; fax: +44 20 7831 7050.
dskuse@ich.ucl.ac.uk

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wide open or narrowed), and, in particular, eye gaze (is this person looking at me, or at something/someone else?) Accurate perception of emotional expression involves the coordinated participation of regions for the visual analysis of expression and regions for representing and producing emotions, in which the amygdala plays a significant role.[2] Studies both from humans with congenital or acquired damage to their amygdalae[3] and from primates in which lesions have been induced[4] show that this subcortical structure influences our ability to gain and to maintain socially appropriate behavior by affecting domains of face-processing ability including face recognition memory, facial expression interpretation and eye-gaze monitoring. Whether its functional integrity is critical for normal social cognitive development in humans has not yet been determined.[5]

AMYGDALA RESPONSIVENESS IN FACE PROCESSING

We observe, from functional magnetic resonance imaging, that there is greater activation in the amygdala (in terms of a blood oxygen level depletion (BOLD) response) when we perceive *fear* compared with other emotional faces.[6] When the amygdala is bilaterally ablated the perception of fear is selectively impaired.[7] We do not fully understand why this is so, but recent evidence suggests that the amygdala responds specifically to eye contact in adults.[8] Behavioral studies in monkeys have shown that eye contact is a critical component of threatening and fear-related displays.[9] A simple stare is often the most effective stimulus in evoking a fight or flight response in nonhuman primates.[10] Consequently, direct eye contact elicits an instinctive "fear-response" in humans and primates that is detectable in terms of autonomic arousal (e.g., skin conductance response[11] (SCR)). The amygdala is an essential and central component of a threat-detection system, with extensive neocortical and subcortical connections that are crucial for the automatic nonconscious responses to a threatening stimulus (e.g., fight and flight).

Our social interactions require complex cortical processing of face stimuli and our reaction to direct eye contact is critically dependent on the social context in which it occurs. Our response to a stimulus that *could* be a threat is normally determined by a full evaluation of that stimulus, by means of complex neocortical connections.

Accordingly, the outcome of interactions between the activated amygdala and social cognition processing centers in the neocortex[12] permits appropriate responses in a social encounter. When patients have suffered amygdala damage, there is impairment in interpreting subtleties of mood from the eye region of others.[13] When eye contact is made, activity is elicited in both conscious (explicit) and nonconscious (implicit) neural pathways, in parallel, and it is the synthesis of perceptions carried by these separate pathways that allows the development of social cognition, based on visual information from faces. We propose that their normal functioning, and their mutual interaction, is essential for the development and maintenance of social cognitive skills.

Implicit Processing of Threat Cues by the Amygdala

Implicit processing of visual stimuli that could constitute a threat, including fearful expressions and other fear-related stimuli (such as snakes or spiders), engages

subcortical visual pathways that are routed directly to the amygdala, without passing through the visual cortex first.[6,14] Consequently, these stimuli can evoke a very rapid physiological response, before the neocortex has had time to process the information and initiate an appropriate course of action.[14]

The visual pathway from the larger cell bodies (magnocellular retinal ganglion cells) of the retina is differentially sensitive to movement and contrast rather than to detail.[15] They project to both the ventral and dorsal streams of visual processing. The superior colliculus receives its visual input primarily from these magnocellular retinal ganglion cells—which have large and rapidly conducting axons.[16] The principal projection of the magnocellular pathway from the superior colliculus is to the pulvinar and other nuclei in the posterior thalamus.[17] In turn, there are direct projections from the pulvinar nucleus to the amygdala in primates.[18] Activation of pulvinar and superior colliculus by fearful expressions has been shown to occur specifically with low-spatial frequency faces, suggesting that these subcortical pathways may provide coarse fear-related inputs to the amygdala.[19] It is notable the contrast of sclera to iris, and the width of the palpebral fissure, are far greater in humans than in any other primate,[20] thus exaggerating the contrast and impact of direct eye to eye contact.

Morris *et al*.[21] propose that this low-spatial resolution subcortical pathway provides a potential route by which neural responses to the threat posed by "fearful eyes" (and by implication, eye contact in general) can reach the amygdala independently of the geniculostriate neocortical system. They found, using chimerical faces as stimuli in an functional magnetic resonance imaging study, that fearful eyes alone are sufficient to evoke increased neural responses in this nonconscious circuit.[22] This circuit because of its importance for survival has been highly conserved in the evolution of different species, including humans, where its influence interacts with neocortical processes underlying complex social interactions.[10]

The ability to interpret emotions on other's faces is one aspect of our development that underpins our reactivity in social situations, particularly complex situations that demand rapid processing of facial expressions from several individuals simultaneously. Remarkably, our ability to process certain negative emotions—especially the accurate interpretation of the expression of "fear"—is closely correlated in women with face recognition memory, implying the same neural circuits may be used for both purposes in them.[23] Such a correlation is not found in men. Infants are able to discriminate their mother's face from that of a stranger as early as the newborn period,[24] although the ease with which they do so is dependent on the dissimilarity of their faces.[25] They are also especially interested in facial expressions that emphasize wide-open eyes, such as fearful expressions.[26]

Experiential Impact on the Maldevelopment of Face-Processing Systems

Seth Pollak has investigated the role that experience plays in the development of affective strategies, patterns of expressed emotion, and the ability to interpret the emotions of others. For many years, we have known that patterns of emotional expression and recognition are different in maltreated children from those who have not been maltreated.[27] He postulated a role for socioemotional experiences in the onset of brain organization, operationalizing the latter in terms of evoked response potentials (ERPs). In a remarkable series of studies, he found that traumatic

experiences during childhood could influence the attention paid by cortical circuits to the sorts of facial expressions associated with abusive experiences, in particular, the expression of anger.[27,28]

Pollak reports that the right frontal ERP component P3b has greater amplitude in maltreated children when they are asked to attend to an angry, as opposed to a fearful or happy face, compared with the equivalent P3b potential in nonmaltreated children. Angry faces may have different implications for maltreated children, for they would be more ambiguous in terms of possible outcomes. It is possible that they therefore command greater processing resources in formerly maltreated children. In a further set of studies Pollak and Kistler[29] found that the threshold for categorical discrimination of anger from other facial expressions (fear and sad) is lower among children who had been maltreated. Formerly maltreated children "over-interpret signals as threatening."

Amygdala-Cortical Connectivity and the Integrity of the Social Brain

Normally, the ability to make an accurate distinction between the facial expression of fear, and that of surprise, entails the interpretation of context. It is possible to distinguish these expressions accurately in an unfamiliar face, but studies of the mistakes made by adults rating the Ekman face series[30] show that fear is most frequently confused with surprise. We hypothesize that inhibitory circuits (probably originating in the ventromedial prefrontal cortex, possibly the anterior cingulate cortex[31,32]) enable us to respond appropriately to the facial expression of (pleasant) surprise—which would normally be encountered within a context that assists the distinction from fear. Obviously, a surprise that is unpleasant or threatening would lead to a fearful response, so the distinction from surprise would be irrelevant to the observer.

The distinction between surprise and fear would not presumably be relevant to any other primate. It is arguable that even our closest primate cousins would not be capable of inhibiting a fear-related social response, as has been suggested by some recent observations of David Amaral. He found, when selective lesions were made in the amygdalae of 2-week-old macaques, that, at 6 months or so of age, the lesioned animals were in adulthood less fearful of novel objects such as rubber snakes than controls, but they were substantially more fearful during dyadic social interactions.[33] Interestingly, this fear was expressed maximally when the animals were face to face with one another. When the animal with the lesion encountered another animal moving away (hence not making face to face contact), it was inclined to follow. That observation suggests the social anxiety was not generalized but was specifically engendered by face to face (or eye to eye) encounters. The finding of social fear in adulthood following lesions to the amygdala that were made in infancy is in striking contrast to his earlier work, which reported social disinhibition as the outcome for macaques whose amygdala lesions were induced in adulthood.[34] On the face of it, there is a paradox needing to be explained here.

We suggest that paradox may be resolved as follows. If a primitive response to social threat can be induced merely by eye contact, then direct contact with the eyes of a conspecific would produce an initial pattern of brain activation that responds as if they were the eyes of a predator. To use eye contact for social purposes, primates

have developed all sorts of cortical control mechanisms during evolution to modulate such arousal and harness it to other ends (e.g., social bonding). As discussed, our response to direct eye contact initially is processed by subcortical visual structures—superior colliculus and thalamic pulvinar nucleus. These subcortical responses are normally relayed to the amygdala, which also receives extensive neocortical inputs from sensory regions in temporal lobe and "executive" regions in the prefrontal lobe. Amygdala-mediated fear behavior depends on an integration of all these influences. It is possible that the 6–8-month-old macaques, whose amygdalae had been removed, showed less fear of novel objects, because this behavior depends on neocortical inputs to amygdala—it was a fear that had at least in part to be learned. The reason why they showed more fear of face to face social interactions was because the innate fear signals from collicular and pulvinar processing of eye contact could no longer be subject to prefrontal inhibitory modulation in amygdala, because it had been removed. The pulvinar projects directly to many subcortical and neocortical areas and the amygdala is bypassed. There is presumably sufficient plasticity in brain development at this age for the links between pulvinar and subcortical circuits that mediate stress responses to be enhanced, in the absence of the amygdala. Amaral comments (personal communication) that when the amygdala is removed in adult monkeys, the treated animals do not show the usual physiological response to a social stressor either. A normal monkey interacting for the first time with an unfamiliar animal would exhibit an increased cortisol secretion in the animals without an amygdala. Such a physiological response is not seen in animals whose amygdalae were removed in adulthood. In contrast to the consequences of neonatal lesions, the pulvinar–subcortical circuits that potentially mediate a social stress response are presumably incapable of enhancement, in the absence of the amygdala.

SEXUAL DIMORPHISM IN THE DEVELOPMENT OF "SOCIAL BRAIN"

There is increasing evidence that deficits in social cognitive competence are substantially more common in males than females.[35] The evolution of the sex chromosomes has caused unique mechanisms of regulation, so as to equalize gene expression between the sexes.[36] We hypothesize that imbalance in the expression of certain classes of X-linked genes could account for sexually dimorphic traits independent of the influence of sex steroids, although it is likely such systems would be interacting with hormonal regulators of gene expression. Specifically, we hypothesize that male vulnerability to the symptoms of autistic spectrum disorders, in those of normal intelligence, is influenced by relative haploinsufficiency for one or more X-linked genes that serve to protect females. The ratio of males to females identified with high-functioning (high IQ) autism is at least 10:1, a little-remarked upon yet intriguing observation which must have relevance for our understanding of the neural basis of that condition.[37]

In normal females, one of the two X-chromosomes is inactivated at random, to ensure equal expression of X-linked genes in male and female mammals.[58] Genes that escape X inactivation are found at the tips of the X and Y chromosome arms in the so-called pseudoautosomal regions, where the equivalent nucleotide sequence is

identical in both sex chromosomes, thus allowing meiotic recombination to take place. Surprisingly, many genes are now known to escape inactivation elsewhere on the X chromosome. These are nonrandomly distributed, they lie mostly on the short arm, and they do not necessarily have expressed Y homologues.[38] Persistence of a dosage imbalance in such genes, between males (46,XY) and females (46,XX), may be important for sex-specific functions.[36]

X Monosomy as a Developmental Model of Social-Cognitive Impairment

Turner syndrome females have a single X chromosome (45,X or X monosomy) and therefore are haploinsufficient for noninactivated X-linked genes, relative to normal females.[39] Turner syndrome (TS) is a chromosomal disorder, with a prevalence of 1 per 2,500 live female births, in which typically all or a substantial part of one X chromosome is missing because of nondisjunction or chromosome loss during early cleavage of the zygote. In 70% of monosomic (45,X) TS, the single X chromosome is maternally inherited,[40] the remainder being paternally inherited. In monosomy X, this single chromosome is never inactivated, although in normal 46,XX females one of the two X chromosomes is inactivated at random during the blastocyst stage of development. Dosage-sensitive genes that escape X inactivation may contribute to some features of TS if haploinsufficient in X monosomy. For example, SHOX[41] is now known to contribute to the short stature of the syndrome and is normally expressed from the pseudoautosomal region (PAR1) of both the X and Y chromosomes. Most cases of TS show normal verbal intelligence, but almost all have poor visuospatial abilities.[42] Recently, we have discovered the condition is associated with a substantially increased risk of autism (at least 200 times).[43]

We have studied the neural basis of the social-cognitive deficit in TS, which we suspected would be similar in quality to that found in autistic individuals with idiopathic disorders. We discovered reliable deficits in the recognition of faces, and in the identification of a "fearful" facial expression, among X-monosomic women of normal verbal intelligence.[44] Because these deficits were reminiscent of those reported in people with autism,[45] we hypothesized that TS women would possess other anomalies in socioperceptual skills. The processing of gaze was one such feature that interested us, because children with autism and those at risk for developing autism show less eye contact and a reduced ability to follow the gaze of another, especially when the attention of the other is directed to an event of social interest.[46] We confirmed that women with TS had difficulty ascertaining gaze direction from face photographs showing small lateral angular gaze deviations.[47] They also showed selective impairments in "reading the mind from the eyes" and face recognition memory.[44,47] These findings are indicative of an anomaly in the processing of facial information, in particular, that involving the eyes, and implicated functional anomalies in the amygdala and related circuitry of the "social brain."

In view of the parallels with deficits that have been reported in association with autism, we also assessed our 45,X subjects with a cartoon-based task that measures Theory of Mind skills.[48] Our hypothesis, that many 45,X women would score in the autistic range on aspects of this task, was supported. More than 50% scored at least 1 SD below the mean for normal female controls, with no significant association between performance and IQ in the X-monosomic sample.

We subsequently conducted a range of structural and functional imaging studies of the amygdala in TS, the results of which confirm the hypothesis that both the amygdala and its functional connections are abnormal in X-monosomic women. The structural studies show that the size of the amygdala is larger in this condition than in matched comparison 46,XX females.[49] Our functional imaging analyses are still undergoing analysis. In other (unpublished) findings of behavioral studies in TS, which focused on the amygdala's role in fear conditioning, we found most 45,X women had impaired habituation and excessive SCR responses in a well-studied conditioning paradigm.[6] The fact that a deficit in the perception of fear in another's face can be associated with excessive reactivity (rather than hyporeactivity) of the amygdala in fear conditioning is a remarkable dissociation that demands further analysis. The strong implication is that in this condition there is anomalous modulation by the amygdala of cortical circuits concerned with face processing and other aspects of social cognition, and of the amygdala itself by frontal cortical regions. We also have shown recently that the ability to classify fear in facial expressions is correlated with face recognition skill in women, but not in men.[23] This intriguing dissociation between the sexes may reflect sexual dimorphism in the mnemonic functions of the amygdala[50] and could, in turn, have relevance to the observation that males are more vulnerable to disorders of social cognition than females.[37]

Intriguingly, not all 45,X females shared these deficits in fear perception, gaze monitoring, and fear conditioning. About one-third were severely affected, and the remainder had a range of impairments distributed around a median that was low-normal. Examination of the data plotted graphically suggested a bimodal distribution. It is not at this stage clear just what mechanism or mechanisms relating to X monosomy are responsible for our findings. However, the implication is that, directly or indirectly, haploinsufficiency of X-linked genes that normally escape X inactivation (and are not imprinted) causes maldevelopment and dysfunction of the amygdala and related circuits that are essential for processes relating to social cognition.

There is now substantial replicated evidence that the amygdala is sexually dimorphic in structure, and there appears to be an inverse relationship between amygdala volume and the number of X chromosomes in broad terms. Several studies[51,52] have reported larger volumes among 46,XY males than 46,XX females. 47,XXY males have amygdalae of similar volume to 46,XX females, whereas the amygdalae of 47,XXX females are significantly smaller than either group.[53]

In X monosomy the deficit in specific social cognitive abilities is associated with abnormal structure of the amygdala and orbitofrontal cortex.[49] In a separate investigation of adult females who lack part of the short arm (Xp) of the X chromosome,[54] we have deletion-mapped the critical locus to a 5-Mb region at Xp11.3 (Ensembl v 15.33.1). In females who have deleted this region, deficits in performance in tasks of social cognition are similar to those seen in X monosomy (despite the fact that the remainder of the X chromosome is intact). In females who have deleted a more distal region of Xp, performance is similar to that of normal 46,XX females. Details of these experiments and their associated findings are reported in Good *et al*.[49]

Accordingly, close to the centromere on the short arm of the X chromosome lies a region that appears to contain one or more dosage-sensitive genes, which are critical for the normal development and function of the amygdala and its cortical connections. Within the critical region at Xp11.3 the monoamine oxidase (MAO) genes

are clearly contenders for a potential influence upon amygdala development. Borowsky *et al*.[55] showed that three of four members of a family of G protein–coupled receptors that are activated by trace amines, such as beta-phenylethylamine, are expressed exclusively in the human amygdala. Trace amines are exquisitely sensitive to the deaminergic actions of MAO genes (in the case of phenylethylamine it is especially MAOB). Accordingly, relatively low levels of MAOB activity consequent upon haploinsufficiency in males and 45,X females may lead to male-typical patterns of amygdala responsiveness, for example, in the context of emotional learning.[56] Unfortunately, proving that specific genes could contribute to the social-cognitive deficits of X monosomy is far from easy. There is heterogeneous expression from inactivated X-chromosome for some X-linked genes that escape inactivation outside the pseudoautosomal region, indicating there could be variability in X inactivation between tissues for the same genes, and even differences of inactivation patterns between individual females.[38]

Testing of somatic cell hybrids suggest some 5–15% of X-linked genes could escape X inactivation in females, despite the fact they lie outside the pseudoautosomal region. We are particularly interested in the possibility that MAOB and conceivably MAOA could escape X inactivation in some tissues (discussed in Good *et al*.[49]). If so, activity would be relatively lower in 45,X than 46,XX females (consistent with our observations), as well as being potentially sexually dimorphic with lower activity in males (also consistent with our findings). Such a mechanism could exacerbate sex differences in vulnerability to disorders affecting predominantly males that result from MAOA functional polymorphisms.[57]

CONCLUSIONS

The normal development of social-cognitive skills depends fundamentally on our genotype, but disorders of social cognition are substantially more common among males than females. This observation implies that sex-related biological factors increase male susceptibility, or reduce female vulnerability, or both. We have yet to identify the mechanisms involved, but when we do so we will be substantially closer to understanding the neural basis of disorders such as autism, in which social-cognitive deficits predominate. Increasingly, structural and functional anomalies of the amygdala are reported in autistic conditions. There is substantial evidence that this complex multinuclear structure plays a critical role in the modulation of social behavior in primate species, although it may not be essential for the emergence of species-typical social behaviors. The role played by the amygdala in determining primate reactions to potentially fear-inducing stimuli has been investigated by Skuse (in X-monosomic human females) and Amaral (in macaque monkeys). Both have found evidence for an abnormal response to potential threats, associated with congenital and acquired lesions, respectively. Both studies have found evidence that face to face contact induces abnormal responses in those whose amygdalae are dysfunctional. However, an abnormal physiological response to certain classes of face stimulus can be induced by environmental influences too. Pollak has demonstrated that the early experience of abuse can significantly alter children's perception of angry facial expressions, which may represent a threat to the child, long after the abuse has

ceased. The complementary findings from these strands of research emphasize the importance and subtlety of interactions that can occur between biological diathesis and environmental contingencies. When considering the roots of mental illness in children, here we have a fascinating example of how complementary strands from clinical and animal research come together to illuminate one aspect of the social brain and its disorders.

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