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Issue: *The Year in Cognitive Neuroscience***What does the amygdala contribute to social cognition?**

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The amygdala has received intense recent attention from neuroscientists investigating its function at the molecular, cellular, systems, cognitive, and clinical level. It clearly contributes to processing emotionally and socially relevant information, yet a unifying description and computational account have been lacking. The difficulty of tying together the various studies stems in part from the sheer diversity of approaches and species studied, in part from the amygdala's inherent heterogeneity in terms of its component nuclei, and in part because different investigators have simply been interested in different topics. Yet, a synthesis now seems close at hand in combining new results from social neuroscience with data from neuroeconomics and reward learning. The amygdala processes a psychological stimulus dimension related to saliency or relevance; mechanisms have been identified to link it to processing unpredictability; and insights from reward learning have situated it within a network of structures that include the prefrontal cortex and the ventral striatum in processing the current value of stimuli. These aspects help to clarify the amygdala's contributions to recognizing emotion from faces, to social behavior toward conspecifics, and to reward learning and instrumental behavior.

Keywords: amygdala, emotion, fear, face processing, saliency, social cognition, reward learning

Introduction

Work on the amygdala is fractured into several domains, and relating these in a consistent account of amygdala function is not straightforward. In terms of functional topics, one can identify three broad themes: social behavior, emotion, and reward learning. The classic studies by Kluver and Bucy (in the 1930s), and before them Brown and Schafer (in the 1880s), perhaps emphasized mostly the first, although they were also relevant for the second and third. The late 1990s and early 2000s saw an explosion of work on emotion, in particular in relation to the processing of facial expressions. And earlier work on issues related to reward learning has now led to a host of studies using single-unit electrophysiology in animals as well as fMRI in humans. Complementing the diversity of functional topics is a diversity of species in which the amygdala has been investigated. Until about 1994 this was almost exclusively research conducted in rodents, with a small number of laboratories tackling the challenge of work in monkeys. Although that work has con-

tinued (and indeed is thriving), it has been to some extent overshadowed by a plethora of fMRI studies in humans, many investigating psychiatric illness.

At the outset it is important to keep in mind that the amygdala is a complex collection of 13 nuclei in primates¹ (indeed, there has been some controversy about the concept of "the amygdala" as a single entity²) (Fig. 1). These are typically distinguished in studies in nonhuman animals, but rarely in humans because of the limited spatial resolution afforded by techniques commonly used, such as fMRI (see Box 1). The amygdala is extensively connected with many other cortical and subcortical structures, and so accounts of its function will need to do justice to its location in this dense web of connections. Finally, it has become apparent that there are substantial individual differences in the amygdala (the extremes of which may contribute to many psychiatric illnesses), as well as substantial effects of context and stimulus history, all of which makes it essential to look at individual and trial-wise details which can get obscured in group-level effects and meta-analyses.

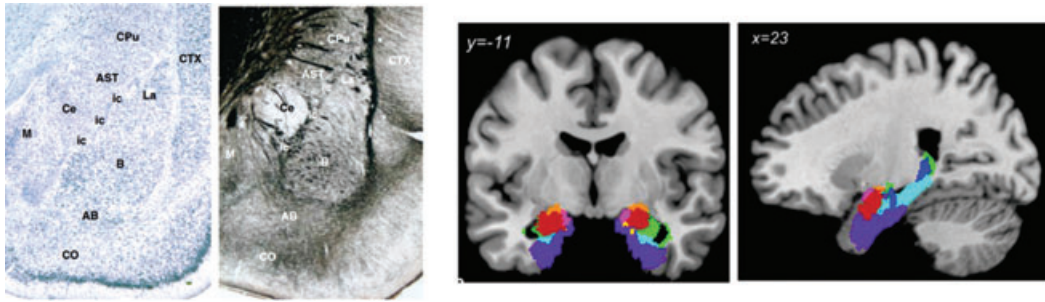


Figure 1. The amygdala and its nuclei. On the left is a Nissl stain, which stains cell bodies, and a silver stain that stains fibers coursing through the amygdala, showing the rat amygdala. On the right are a coronal and parasagittal MRI scan onto which probabilistic locations of amygdala nuclei in humans have been mapped. From Refs. 87 and 137. Abbreviations of amygdala areas: AB, accessory basal; B, basal nucleus; Ce, central nucleus; ic, intercalated cells; La, lateral nucleus; M, medial nucleus; CO, cortical nucleus. Nonamygdala areas: AST, amygdalo-striatal transition area; CPu, caudate putamen; CTX, cortex. Copyright acknowledgment: two lefthand panels: reproduced from Ref. 87 with permission from Elsevier; two righthand panels: reproduced from Ref. 137 with permission from Springer Science+Business Media.

Some disclaimers are in order to help circumscribe this review, because one could easily write a book on the amygdala (and several have been written^{3,4}). First, the focus will be on social-emotional functions of the amygdala in primates with an emphasis on humans. Second, I will not review the amygdala's role in psychiatric illness here, although

insights into its functional role from the studies discussed earlier are of course highly relevant for understanding psychiatric illnesses as well, ranging from mood disorders to autism. Third, I will highlight lesion studies together with some electrophysiological studies while minimizing review of functional imaging studies (which have been

Box 1: BOLD fMRI of the amygdala

By far the largest number of studies on the human amygdala use BOLD fMRI as the approach. Although this is revealing a wealth of data and is certain to continue to constitute the method of choice for practical reasons at least for the next several years, it is worth reiterating the caveats associated with BOLD fMRI. Aside from the flurry of recent attention to concerns about statistical reliability and generalizability,^{135,136} all of which can be addressed in studies cognizant of these caveats, there are technical difficulties in obtaining and localizing signal in and around the amygdala due to susceptibility artifacts. Optimized imaging parameters have largely solved the problem of weak signal, and many researchers now obtain B0 field maps to correct for geometric distortion. Another tricky issue is that BOLD responses to particular psychological or objective stimulus dimensions may be nonlinear—for instance, nonlinear responses have been noted both to trustworthiness in faces⁶⁴ as well as to valence in odors.⁷⁰ A more

fundamental limitation is the spatial resolution of BOLD fMRI together with individual variations in amygdala morphology, limiting conclusions about exact boundaries and nuclei within the amygdala to probabilistic statements.¹³⁷ Even worse is the issue of temporal resolution as we noted earlier, because this definitely conflates a number of distinct processes that occur on the timescale of a few milliseconds rather than the seconds of BOLD signal integration. Perhaps the most worrisome aspect of BOLD fMRI concerns its physiological basis. Not only is the hemodynamic response function in the amygdala rather different in shape than what is found in cortex, but as with all BOLD fMRI, it remains uncertain what precisely is driving the observed signal. Possibilities range from inputs from distal targets to intrinsic processing to little neuronal activity at all and mere distal regulation of hemodynamics.¹³⁸ While researchers are acutely aware of these issues and more, it remains the case that definitive findings will require convergent results from multiple approaches—ideally electrophysiology, fMRI, and lesion studies.

reviewed to some extent elsewhere^{5,6}). Finally, studies reviewed and citations will emphasize the most recent work, following the theme of this book series.

Lesion studies of social behavior in monkeys

Kliver and Bucy's classic studies in the 1930s described the behavioral consequences of large bitemporal lesions in monkeys,^{7,8} which included a propensity to shift rapidly in exploring different objects ("hypermetamorphosis"), to approach, ingest, and mount many stimuli indiscriminately, and to show a profound lack of behavioral regulation on the basis of the emotional and social meaning of stimuli ("psychic blindness"). Monkeys with such lesions were not blind or deaf—they just no longer had access to the value of what they saw and heard.⁹ A well-known shortcoming of these early experiments was the nonselectivity of the lesions, which included not only the entire medial temporal lobe but also substantial portions of lateral and posterior temporal cortex as well as subjacent white matter, making it impossible to assign the deficits specifically to the amygdala. Nonetheless, their observations set the stage for subsequent work using more selective aspiration¹⁰ and pharmacological lesions of the amygdala.^{11–14} Current lesion studies favor lesions made by injecting the drug ibotenic acid, a neurotoxin which can be quite selective for neurons, sparing both fibers of passage as well as surrounding structures if the injection is sufficiently focal (typically verified by structural MRI). Reversible lesions can also be made by injecting drugs such as muscimol, a GABA-A receptor agonist that temporarily silences the electrical activity of neurons through inhibition. The advent of optogenetic methods will no doubt lead to a large number of studies examining the reversible activation and inactivation of specific neuronal sub-populations in the amygdala in the very near future.¹⁵ The studies so far have generally revealed a subset of the full-blown Kliver–Bucy syndrome, the subset becoming more restricted the more selective the lesions. This likely arises from the fact that many of the structures proximal to the amygdala, such as perirhinal and entorhinal cortices and temporal polar cortex, also participate in social behaviors to some extent. When the amygdala is more selectively lesioned, there is disproportionate

impairment in particular in the normal cautiousness and distrust with which monkeys approach novel or frightening objects, or people. For instance, monkeys with amygdala lesions show less caution in approaching potential predators like snakes to which they normally have an innate fear response¹⁴ and show less initial avoidance of human strangers.¹² These behaviors are especially notable in circumstances of novelty and unfamiliarity, where healthy monkeys typically exercise substantial caution in approaching unknown objects or unfamiliar people—an issue we will return to when discussing insights obtained from functional imaging and lesion studies in humans that are pointing toward a role for the amygdala in processing unpredictability or ambiguity.

The behavior of amygdalotomized monkeys toward other monkeys is more complex to quantify, due to the reciprocity of the social interaction. Earlier lesions that were nonselective resulted in severe impairments in social behavior with the result that the monkeys lost their social status¹⁶ and were ostracized by the group, resulting in death in the wild.¹⁷ Selective neurotoxic lesions resulted in more subtle impairments that were quite complex and depended on other factors. One study found that the amygdalotomized monkeys showed more prosocial cues and less avoidance behaviors toward other (healthy) monkeys when in dyadic interactions, with the result that they were actually approached more and groomed more by other monkeys.¹¹ They also showed more approach behavior toward unfamiliar humans, consistent with their increase in prosocial behaviors (Fig. 2). However, in more complex groups (the lesioned monkey together with three healthy monkeys in a tetrad) these effects were not seen, and instead a quite subtle increase in avoidance and stress behaviors was shown by other monkeys toward the amygdalotomized monkey.¹³ Further complexities arise if the lesions are made neonatally: for instance, exaggerated social fear (yet with the typically diminished fear of novel objects) has been reported in such lesioned monkeys,¹⁸ although this profile appears to change as the monkeys age.¹⁹

Two important take-home messages from the monkey lesion studies are that the amygdala's effect on social behavior is not rigid and universal, but context dependent and susceptible to individual differences; and that even complete lesions of

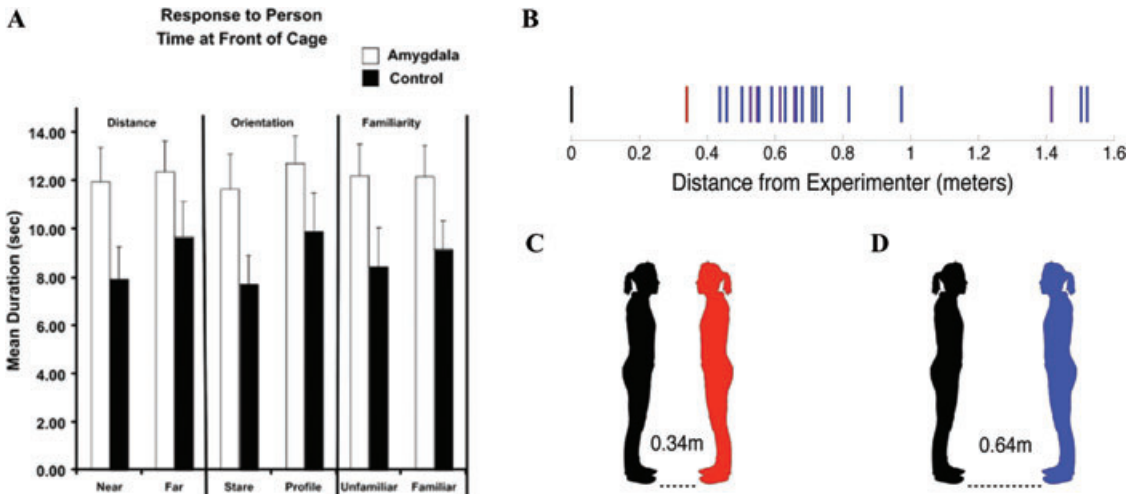


Figure 2. Social approach behavior following amygdala lesions. (A): Monkeys with amygdala lesions show less fear towards predators and less timidity towards humans. One measure quantifying this is that they spend more time at the front of the cage when there is an unfamiliar person standing there. (B): Approach behavior in patient SM (red bar) compared to control subjects (purple bars) in relation to the experimenter (black bar). Whereas SM had a preferred interpersonal distance of 0.34 meters (C), controls had a distance of 0.64 meters (D). Copyright acknowledgment: A: reproduced from Ref. 12 with permission from the American Psychological Association; (B-D): modified from Ref. 37 with permission from Nature Publishing Group.

the amygdala appear to leave the repertoire of social behaviors as such largely intact—they just are not elicited in a context-appropriate way.²⁰ For instance, monkeys with amygdala lesions can still respond normally to social stimuli such as a human stare, even though they show blunted avoidance responses to potential predators such as a snake.¹⁴ Although the socioemotional changes in monkeys with amygdala lesions appear to constitute a stable behavioral change that can be thought of as a trait change in personality,¹² it is neither a change in the ability to show the full repertoire of social behaviors²⁰ nor a change in mood as such.²¹ Rather, it is probably best thought of as a consistent change in the way that context-dependent situations (stimuli in the context of an emotionally significant or socially significant setting) modulate motivated behavior. Part of the complexity in accounting for the amygdala's effects on social behavior, and the reason for the rather nuanced explanation just offered, will become more apparent in the sections later: they arise from the fact that the amygdala is connected to a host of other structures whose function it modulates.

Lesion studies of social behavior in humans

Several etiologies can produce amygdala lesions in humans. Probably the most common is epilepsy, which can result in medial temporal sclerosis if severe and untreated. More relevant for the present review, medically refractory epilepsy is occasionally treated neurosurgically, by ablation of parts of the medial temporal lobe on one side. The late famous patient HM had bilateral medial temporal lobe lesions, including bilateral lesions of the amygdala, for the treatment of epilepsy with the consequence that he became severely amnesic due to his bilateral hippocampal damage. Nowadays, the surgery is essentially always unilateral and involves variable extents of resection of the hippocampus, the amygdala, and surrounding medial temporal and temporal polar cortices. The consequences of such lesions on social cognition are impossible to attribute selectively to the amygdala, although they are likely due in good part to amygdala damage because they bear some resemblance to what is observed following selective amygdala lesions (*e.g.*, impaired Pavlovian

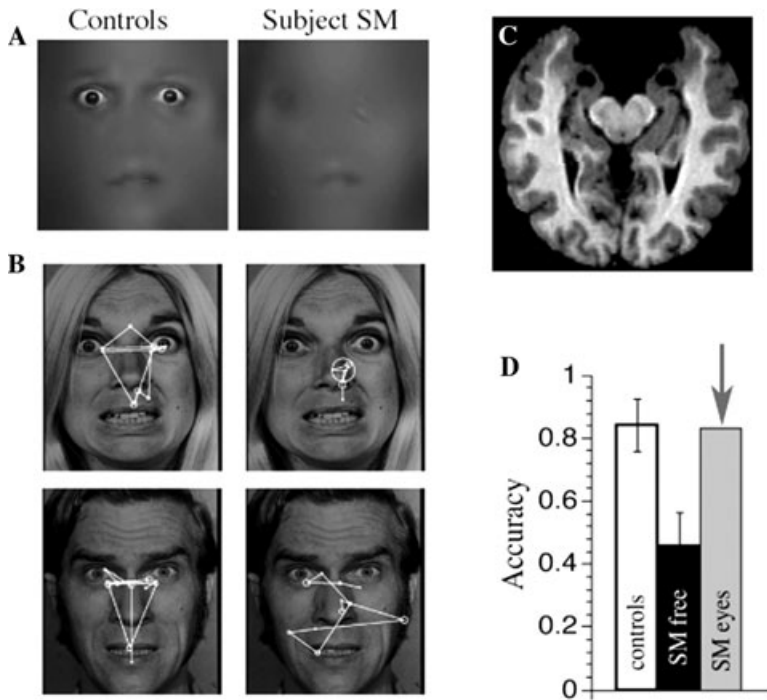


Figure 3. The brain and face processing of patient SM. Bilateral amygdala lesions impair the use of the eyes and gaze to the eyes during emotion judgment. (A) A patient with bilateral damage to the amygdala made significantly less use of information from the eye region of faces when judging emotion. (B) While looking at whole faces, the patient (*right column* of images) exhibited abnormal face gaze, making far fewer fixations to the eyes than did controls (*left column* of images). This was observed across emotions (free viewing, emotion judgment, gender discrimination). (C) MRI scan of the patient's brain, whose lesion was relatively restricted to the entire amygdala, a very rare lesion in humans. The two round black regions near the top middle of the image are the lesioned amygdalae. (D) When the subject was instructed to look at the eyes ("SM eyes") in a whole face, she could do this, resulting in a remarkable recovery in ability to recognize the facial expression of fear. The findings show that an apparent role for the amygdala in processing fearful facial expressions is in fact more abstract, and involves the detection and attentional direction onto features that are socially informative. Modified from Ref. 162. Copyright acknowledgment: reproduced from Ref. 162 with permission from Nature Publishing Group.

fear conditioning²²). They are milder than the impairments seen with bilateral amygdala damage,^{23,24} as would be expected, and there is some indication that damage to the right amygdala may disrupt aspects of social cognition more than damage to the left amygdala.²⁵

A second possible cause of amygdala lesions in humans is encephalitis, which can result in large bitemporal lesions approaching those made by Klüver and Bucy in monkeys. Patients with such lesions do show severe impairments in processing emotional and social information,^{26,27} although not generally to the degree that Klüver and Bucy observed in monkeys, and like Klüver and Bucy's studies they

suffer the same nonspecificity of the lesion to the amygdala.

The most specific bilateral lesions of the amygdala result from very rare constellations of damage (*e.g.*, a combination of neurosurgical and/or vascular^{28,29}) or from Urbach-Wiethe disease.^{30,31} Urbach-Wiethe disease, also called lipoid proteinosis, is an extremely rare genetic disease,^{32,33} although a few studies with samples of 10 or more subjects have now been published.^{34,35} We have studied in detail a patient, SM, who has complete bilateral amygdala lesions due to Urbach-Wiethe disease (Fig. 3) with minimal damage to surrounding structures and with IQ in the low normal range.³⁶ She

Table 1. Summary of findings from subject SM

Impaired in recognizing fear from static facial expressions ³⁸
Gives abnormally low ratings of intensity to fearful faces ¹⁴⁷
Impaired conditioned autonomic responses in Pavlovian fear conditioning ¹⁴⁸
Impaired emotional modulation of declarative memory ¹⁴⁹
Abnormally positive judgments of trustworthiness and approachability from faces ¹⁵⁰
Cannot judge arousal in negatively valenced stimuli ¹⁵¹
Abnormally positive preferences for abstract visual stimuli ¹⁵²
Can discriminate between emotions normally ¹⁵³
Can recognize fear from voice prosody ¹⁵⁴ but not music ¹⁵⁵
Impaired in the Baron-Cohen eyes task ¹⁵⁶
Less impaired in recognizing emotions in scenes when faces are erased ¹⁵⁷
Mildly impaired also in recognizing sadness, but not happiness ¹⁵⁸
Impaired in fixating and using information from the eye region of faces ⁵⁵
Impaired emotional memory for gist but not details ¹⁵⁹
Lack of experience of negatively valenced emotions in real life ¹²⁵
Fixates the mouth instead of the eyes in conversations with real people ¹⁶⁰
Has diminished BOLD signal in medial prefrontal cortex during reward expectancy ¹⁰⁶
Can recognize fear from body posture and pointlight walkers ¹⁶¹
Lacks a sense of personal space ³⁷
Performs normally on rapid detection and nonconscious processing of fear faces ⁵⁴

is a 43-year-old woman with a high-school education whose lesions encompass the entire amygdala plus subjacent white matter and anterior entorhinal cortex. This lesion was likely developmental; although the precise age at which it was acquired is unknown, it is likely to have occurred sometime in childhood or adolescence, and it is possible that it was congenital. A series of studies in this patient has documented a remarkably specific impairment in recognizing fear from facial expressions, together with impairments in a variety of social judgments from faces, discussed in more detail in the next section (see Table 1 for a summary).

With respect to social behavior, SM is notably disinhibited and shows a propensity to approach and engage with others that has occasionally resulted in social difficulties in real life.³⁶ Although her social behavior and social decision-making appears somewhat abnormal, and in the same direction as what one might hypothesize on the basis of the lesion studies in monkeys reviewed earlier, this is difficult to quantify. We recently undertook a first laboratory study to quantify aspects of her social behavior toward others.³⁷ In this study, we asked participants to indicate their preferred distance in standing facing an experimenter, together with rating their feeling

of uncomfortableness when this preferred distance was narrowed and their personal space was violated. Although there is of course considerable contextual and individual variation in interpersonal distance in real life, the distances obtained in our laboratory context were remarkably consistent and hovered around 0.6 m with a long-tailed distribution. When people were approached close to 0.4 m, we reliably encountered the wall of personal space. By contrast, SM appeared to have no feeling of personal space whatsoever: her mean preferred interpersonal distance in this experiment was smaller than that of any control subject, she occasionally walked all the way up to touching the experimenter, and in all circumstances endorsed no feeling of uncomfortableness when personal space was violated (Fig. 2).

These findings in humans with amygdala lesions bear some resemblance to what we saw in monkeys with bilateral amygdala lesions earlier: a lack of the normal cautionary brake on behavior with an increase in approach and prosocial behaviors (Fig. 2). It is also consistent with a broader function for the amygdala in processing salient or relevant stimuli, perhaps especially when these signal unpredictability or potential threat, a function reviewed in more detail later. It is noteworthy that

subject SM still appears to have rank-ordering of interest in other people: she is not completely indiscriminate in putting an equal value on everyone. For instance, she exhibits concern and maternal emotions toward her children. Interestingly, female monkeys with neonatal amygdala lesions have a notably reduced interest in infant monkeys, suggesting that aspects of maternal behavior in monkeys are disrupted.¹⁹

Processing information from faces

The initial finding that bilateral lesions to the human amygdala impair recognition of emotion from facial expressions^{38,39} was quickly followed up with functional imaging using PET⁴⁰ and has since then spawned a veritable industry of fMRI studies investigating responses to faces and other social stimuli (see Ref. 4 for a sampling). The results from the neuroimaging studies have been complex and to some extent inconsistent. Although earlier studies found evidence that the amygdala responded more to fearful faces than expressions of other emotions,⁴⁰ more recent studies support the idea that the amygdala responds to all faces,⁴¹ perhaps especially on the left side,⁴² and with complex modulations depending on their social meaning for a particular individual in a particular context.^{43,44} There are now many examples of large individual differences in amygdala responses to faces, differences that have been tied to differences in gender,⁴⁵ in mood and personality (ranging from anxiety⁴⁶ to extraversion⁴⁷), as well as in genotype.^{48,49}

In the patient with bilateral lesions, SM, who was described earlier, we studied her processing of emotional faces in great detail. Two recent conclusions have emerged from this work. One is a conclusion about the stage(s) in processing at which the amygdala might come into play. Based on a number of prior findings, notably auditory fear conditioning in rats⁵⁰ as well as a few neuroimaging studies⁵¹ together with a theoretical view,⁵² it was generally thought that the amygdala comes into play early in processing, and therefore participates importantly in automatic and nonconscious rapid processing of stimuli that signal danger. Although the amygdala may still participate to some extent in such a function, this view ought to be revised in light of several new findings, as argued elsewhere.⁵³ The amygdala's role appears to be much broader than the older view

would suggest, and seems unlikely to be restricted to processing only stimuli related to threat or danger. It also appears to be inessential for many aspects of rapid and nonconscious processing of such stimuli. One recent study in subject SM demonstrated this latter finding: SM showed a normal ability to detect fearful faces in visual search or rapid discrimination, and a normal ability for fearful faces to overcome binocular suppression that would render them nonconscious.⁵⁴ These findings do not rule out some role for the amygdala in rapid and nonconscious processing related to orienting, but together with other findings they shift the view toward a more modulatory, temporally extended role for the amygdala in perception and recognition. They also shift the anatomical substrate of processing away from a subcortical route of visual input to the amygdala via the superior colliculus and pulvinar thalamus to amygdalo-cortical interactions.

A second broad conclusion from findings in subject SM and from other recent studies has been the idea that the amygdala allocates processing resources (such as attention) to salient stimuli, or features within stimuli. In regard to SM's impaired recognition of fear from facial expressions, this appears to arise from her inability to make spontaneous use of information from the eye region of faces: she fails to direct her gaze toward this region in faces, fails to benefit from it when it is shown in isolation, and improves when instructed to fixate the eye region (Fig. 3).⁵⁵ When shown sparsely sampled faces (using a method called "bubbles"⁵⁶ to reveal only small random parts of an underlying face), people normally benefit from having the eyes in the face revealed when they are asked to discriminate fear from other emotions,⁵⁷ but SM shows no such benefit. SM also generally does not fixate the eyes in faces (either in whole faces or in the bubbles faces), in many cases staring straight at the center of the face without moving her eyes over the face at all. Yet she is able to make use of the eye region of faces to help her discriminate fear when her visual attention is explicitly directed toward the eyes. These findings fit with a role for the amygdala in vigilance, ambiguity resolution, and uncertainty resolution: it modulates other brain structures to enhance the processing of stimuli about which more information needs to be acquired.^{58,59} Both of the earlier findings are in line with the idea that the amygdala modulates cortical processing to implement selectivity for

biologically relevant stimuli, just as it does, for example, in modulating hippocampal-dependent memory consolidation.⁶⁰

The amygdala's role in processing information about the eye region of faces, put together with its presumptive function in disambiguating stimuli, has been borne out also by two recent functional neuroimaging studies (Fig. 4). One study⁶¹ showed subjects' fearful faces (as well as neutral, happy, and angry faces) briefly presented at locations where the preceding fixation cross either coincided with the eye region of faces, or with the mouth region of faces. The authors then collected BOLD signal from the amygdala and also measured eye movements. When the data were analyzed with the direction of the eye movement as a regressor (either moving down toward the mouth when the eyes had been fixated, or up toward the eyes when the mouth had been fixated), a significant effect was found in the amygdala specifically to fear faces (Fig. 4, left). The effect amounted to a significant correlation between BOLD signal evoked in the amygdala and the propensity to direct gaze to the eye region of the face when the mouth had been fixated initially. These findings provide strong support for the idea that the amygdala serves to direct gaze toward the eyes in fearful faces to obtain disambiguating information. Another fMRI study found that the amygdala was differentially activated by fearful compared to neutral faces even when the eye region of the face was masked⁶² (Fig. 4, right), also consistent with the idea that the amygdala is not necessarily responding to the eyes as such, but rather directing processing resources toward disambiguating that region of the face to figure out its social meaning (a mechanism that could engage even more so when the eyes are covered in an attempt to glean whatever information possible from that region).

There are several remaining puzzles about the type of visual information processed by the amygdala. A subcortical route of input would put emphasis on low spatial frequencies; yet patient SM has impairments rather selective for high spatial frequencies. Some fMRI studies have suggested that low spatial-frequency information is most effective in driving the amygdala,⁶³ whereas others have found evidence for both high and low spatial frequency.⁶⁴ In the case of our studies with SM on the bubbles task, the data are quite specific in show-

ing that she fails to make use selectively of high spatial-frequency information from the eyes while low spatial frequencies are preserved. The relationship between visual fields and amygdala response is also somewhat puzzling. Some human fMRI studies have now provided evidence that amygdala activation correlates better with presentation of salient stimuli in the ipsilateral visual field,⁶⁵ and we have preliminary findings that unilateral amygdala lesions impair processing of the eye region shown on the side of the stimulus face that is ipsilateral to the side of the lesion.

The amygdala codes salience or relevance

The earlier notion that the amygdala may be specialized for fear-related processing and later ideas that it comes into play when stimuli are unpredictable or ambiguous have a related theme: both situations involve a need to gather additional information from the environment. The physiology of facial expressions of fear is such that they maximize visual and olfactory intake of information—adaptive in circumstances where an unknown potential predator needs to be detected.⁶⁶ Yet it has been elusive to quantify this aspect of information processing in terms of a single parameter or psychological dimension. It does not neatly fit the concept of “arousal” if by that one means autonomic arousal as classically conceived; however, it could be related to a more information-processing concept of arousal that construes it as interruption of ongoing processing to gather new information (more aligned with orienting).

There have been hints for some time that the amygdala must process a stimulus dimension that is more abstract than the traditional concepts of valence or arousal alone. Several studies have found that the amygdala is activated by both negatively as well as positively valenced stimuli,⁶⁷ leading to the common view that it tracks emotional arousal (and that prior claims about specialization for fear, threat, or negative valence were simply derivative to the higher arousal of such stimulus categories).⁶⁸ This emphasis on the amygdala as processing arousal also fit with a view that emerged from the literature on emotional memory.⁶⁹ However, this looks unlikely to be the final story. One study investigating the intensity and valence of odorants argued that a conjunction of valence and intensity (in those studies

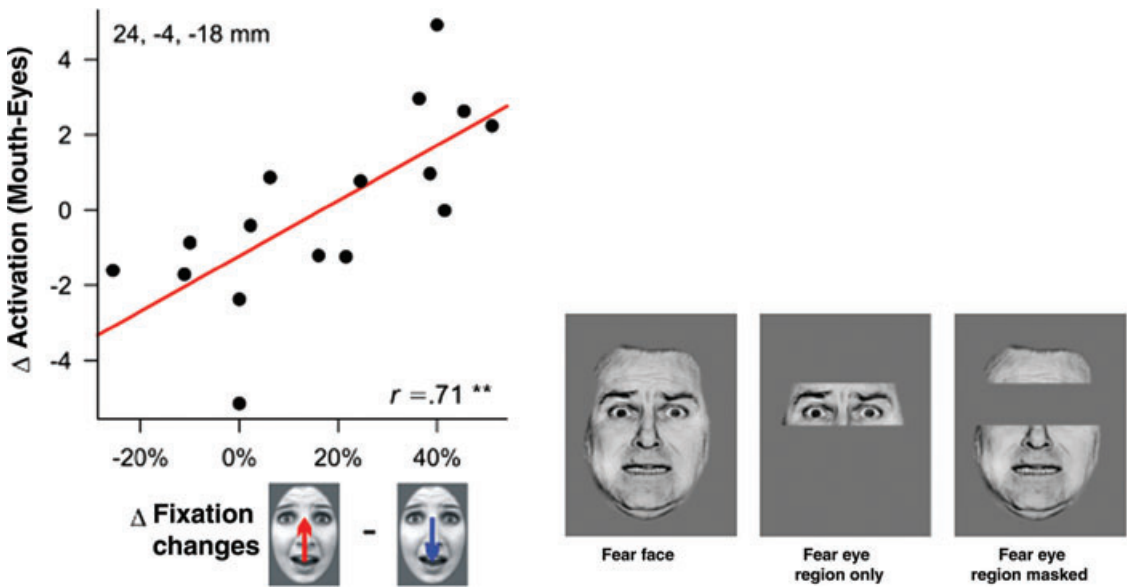


Figure 4. The amygdala helps direct gaze to eyes in faces. *Left:* data from an fMRI study that plots the response in the amygdala as a function of how often people shift their gaze from the mouth up to the eyes.⁶¹ The amygdala is not activated so much as a consequence of fixating the eyes, but rather in preparation for fixating the eyes. A similar conclusion was obtained in another fMRI study, which found equivalent amygdala activation to fear faces even when the eye region itself was erased (*right*).⁶² Copyright acknowledgment: reproduced from Ref. 61 with permission from the Society for Neuroscience (*left*), and from Ref. 62 with permission from Elsevier (*right*).

a proxy for arousal) may be what the amygdala cares about: stimuli that are both arousing/intense and emotional (either positively or negatively valenced).⁷⁰ Another study found amygdala activation not only to both negatively and positive-valenced stimuli of high arousal, but also to stimuli that were not so much arousing as they were interesting or bizarre.⁷¹ It is difficult to know from these studies what psychological construct would best capture whatever it is that is engaging the amygdala.

One study explicitly investigated psychological dimensions other than “arousal” or “valence,” and found that even when these were held relatively invariant, the amygdala showed a further differential activation as a function of “impact,”⁷² the subjective significance or relevance of a stimulus. Although this construct is correlated with arousal, it is not perfectly correlated. This finding is consistent with some other attempts to assign to the amygdala a more abstract and ecological role in processing “relevance,” a concept from psychological appraisal theory that stresses the contextual and goal-dependent value of a stimulus within a personal situation.^{73,74}

Constructs such as impact and relevance also pave the way for investigating individual differences in amygdala function, because they are patently subjective and dependent on each person’s contextual interpretation of a stimulus in the sense that they are individual rather than entirely universal.

Several electrophysiological studies in both humans and monkeys have led to a conceptually parallel view: on the one hand, the amygdala appears to respond to a broad class of social stimuli and to reward value or arousal as such; on the other hand, neurons within it can show highly selective responses to specific social stimuli that are relevant for that person or monkey. In monkeys, electrophysiological responses in the amygdala have been found that precede skin-conductance responses,⁷⁵ a ubiquitous index of orienting and arousal that can be elicited by any salient or novel stimulus. A number of recordings from the amygdala and adjacent cortex in monkeys have found responses to faces^{76,77} and to other complex social stimuli,⁷⁸ in several cases showing selectivity for identity, emotion, or social status of the stimulus. Several recent

studies have also investigated responses to reward value. In humans, responses to emotional faces⁷⁹ and complex social scenes⁸⁰ have been recorded from depth electrodes in the amygdala in neurosurgical patients, and some categorical coding to emotions such as threat or disgust have been extracted.⁸⁰ Highly selective and abstract responses to the identity of specific people have also been found at the single-unit level—in some cases with generalizability across viewpoints, kinds of depictions (photos or caricatures), and even whether the image is a photo or the written name of a famous person.⁸¹ It should be noted, however, that such responses are not unique to the amygdala, and similar response profiles are often encountered in nearby cortex and hippocampus.

It would be useful to probe the amygdala's response on a battery of heterogeneous stimuli that span a range of saliency or relevance to test the hypothesis that these dimensions are what is driving the amygdala. Although no such study has yet been undertaken, there is evidence to support this prediction from the tasks so far: the amygdala is activated by salient images including faces, by increasing amplitudes of sound (arguably an auditory analog of the most salient visual stimulus type, optic flow to signal collision),⁸² and even by cognitive indicators of saliency such as the mere belief that another person is approaching to stand close, when that person cannot actually be seen.³⁷ The related concepts of unpredictability and ambiguity seem to be two potential underlying (but perhaps not exhaustive) factors that could influence saliency and hence the amygdala. Ambiguity aversion in monetary gambles (*i.e.*, gambling when the risks are unknown and uncertainty is therefore highest) is correlated with amygdala activation.⁸³ Amygdala activation in humans, as well as electrophysiological responses within the amygdala in rodents, have been linked to temporal unpredictability in sequences of auditory stimuli.⁸⁴ In this latter study, a potential cellular mechanism was suggested: temporally unpredictable stimuli result in less habituation of amygdala responses. This differential habituation, together with a generally rapid habituation to stimuli that have become predictable and hence less salient in some way,⁸⁵ may underlie some of the amygdala's response to novel and unpredictable stimuli. Taken together, the recent studies point toward a revised view of the type of stimulus cat-

egory, and the kind of psychological dimension, that the amygdala helps process. The challenge now is to translate these constructs into a computational framework that would allow one to formulate parametrically quantitative hypotheses. Here, approaches from reinforcement learning and neuroeconomics may help, a topic we briefly review next.

The amygdala in reward learning

There is a huge and well-known literature on fear conditioning and the amygdala, mostly from work in rodents. This has shown that the amygdala is necessary for at least some and possibly all aspects of fear conditioning,⁸⁶ that prominently the lateral as well as the central nucleus⁸⁷ are the key components, and that specific subpopulations of neurons within the amygdala can be identified as a possible neuronal substrate.⁸⁸ There is still plenty of debate about details in this picture. But there are now an ever-growing number of studies that examine the amygdala's role in processing stimulus value in a much broader way than only fear conditioning.

Ever since earlier lesion studies showing that the amygdala plays a role in appetitive as well as aversive conditioning, evidence has been accumulating that linking the amygdala to "fear" is too simple a story. There is now a substantial literature from electrophysiological studies in animals showing that amygdala neurons respond both to rewarding and punishing stimuli or their predictors. In fact, there is a bewildering variety of neuronal response types in the amygdala, with neurons that encode rewards intermixed with those coding punishment and no apparent evidence of any segregation or topography.⁸⁹ Some neurons respond both to aversive and rewarding conditioned stimuli,⁹⁰ suggesting a more abstract coding of predictors for emotional arousal or saliency. In general, the lesion and electrophysiology literature from studies in animals has made a strong argument that the amygdala codes the abstract reward value of stimuli or their predictors, rather than their sensory properties or the particular instrumental actions required for obtaining or avoiding them.⁹¹ This has led to the view that the amygdala codes a continuously updated and flexibly deployed representation of stimulus value.⁹² Somewhat at odds with such a role in abstract value representations are other electrophysiological

studies in both human^{81,93} and nonhuman⁷⁷ animals that argue there is also coding for stimulus identity. Plausibly, the conjunction of a dynamic coding of stimulus value together with coding stimulus identity would serve a key role in social behavior: the need to keep track of the social value of conspecifics through time.

Although the amygdala appears essential for Pavlovian fear conditioning and is clearly involved in reward learning, this latter role is nuanced. There are many tasks that ostensibly involve aspects of reward learning for which complete bilateral lesions of the amygdala, if selective, result in essentially no impairment.^{94,95} This revision is reminiscent of how our picture of the amygdala's role in social behavior has evolved from early highly nonselective ablation studies through selective ibotenate lesions in modern day. What selective ibotenic acid lesions of the amygdala do seem to impair is learning in tasks where information about stimulus value is essential, such as in devaluation studies.⁹² In such studies, the animal is asked to choose the exact same stimulus before and after a devaluation such as satiation, which changes the reward value of the stimulus without changing any of its sensory properties or associations. These tasks require a flexible updating of the value associated with a stimulus based on integration of its outcome with the physiological state of the animal (*e.g.*, when satiated on a particular food, that food loses its reward value even though its sensory properties remain unchanged). Lesions of the amygdala abolish the change in behavior that would indicate that the reward value of the stimulus has been updated by the satiation, suggesting the amygdala is critical to maintain current representations of reward value—a conclusion in line also with functional imaging studies in humans.⁹⁶

The importance of context and of individual differences is emerging in studies of reward learning and decision-making as well. One example has been highlighted in a study that examined the so-called framing effect from economics.⁹⁷ In this study, participants were first given some money, and then asked to choose between two options. One option was to keep a fixed amount of this money (say, \$20 out of an initial endowment of \$50); the other option was to gamble with some probability of keeping or losing all of the initial endowment (say, 2/5 chance of keeping all of it and 3/5 chance of losing

all of it). Importantly, the expected value of the sure amount and the gamble were identical. The trick in this study was that the sure amount was presented in two frames: a “loss frame” in which it was described as “you lose \$30 of your original \$50,” and a “gain frame” in which it was described as “you win \$20 of your original \$50.” This resulted in a well-known effect from economics called the framing effect; subjects chose the gamble with the positive frame over the one with the negative frame, even though both state the same outcome. This framing effect correlated profoundly with activation of the amygdala. Moreover, there were substantial individual differences on the task and in brain activation. This story has recently been linked to genetic variation in the serotonin reuptake transporter as well⁹⁸ (a polymorphism with a rapidly growing literature linking it to individual differences in amygdala response⁹⁹).

These findings from the reward learning literature, which have only been reviewed very briefly here, complement the studies on face processing and social behavior, which also emphasize the highly dynamic and context-sensitive role that the amygdala must play in evaluating stimuli. For instance, the actual task of judging the positive or negative qualities of famous faces strongly modulates amygdala activation to those faces¹⁰⁰; and the mere assignment to a social group in an experiment is sufficient to drive amygdala responses to faces that discriminate people within one's assigned experimental group from those outside the group.¹⁰¹ Taken together, the reward learning and social neuroscience literature hold out promise to provide a computational framework in which amygdala function could be formally modeled. Such a framework would be expected to draw from neuroeconomics and decision science and might provide a unified view of what are now a huge number of somewhat disparate findings on the amygdala's role in social cognition. That view would articulate the amygdala's role in integrating internal and external sensory signals to continuously monitor the physiological value of a stimulus, and it would play this role also extended to complex social stimuli. However, a complete model of such a function requires we consider what other structures interact with the amygdala, and what regions of the brain might receive signals from the amygdala that can be used to implement aspects of cognition and behavior.

Interaction with other structures

Investigating the amygdala's interaction with other structures as a component of a network for processing the reward value of stimuli is a currently hot topic. Who are the other players? Highlighted have been the orbitofrontal cortex and other sectors of the prefrontal cortex, the striatum, and the nucleus accumbens.¹⁰² Lesions that disconnect the amygdala with some of these structures have documented the importance of their interaction. For instance, disconnection of the amygdala and orbitofrontal cortex results in deficits on reward learning tasks as severe as lesions to either structure in isolation.¹⁰³ Similarly, disconnection of the amygdala from the nucleus accumbens disrupts instrumental behavior toward rewards.¹⁰⁴ A technically and conceptually challenging issue concerns the order in processing at which different structures come into play. The issue is technically difficult because it generally requires concurrent electrophysiological recording; it is conceptually challenging because the structures are reciprocally connected and participate in processing over some extended duration that would permit multiple iterations of feedback. Nonetheless, some headway has been made even here. For instance, in the aforementioned interaction between amygdala and nucleus accumbens, there is evidence that the amygdala can come into play early and convey information about particular sensory cues to the nucleus accumbens to guide instrumental behavior. A similar story has been proposed from lesion studies of the amygdala in humans: one study reported a lack of loss aversion following amygdala lesions, interpreted as an amygdala-dependent signal that was passed to the striatum¹⁰⁵; another study found reduced signal related to reward prediction in the prefrontal cortex when the amygdala was lesioned, a finding also interpreted as evidence for a reward-related signal that would normally be passed from the amygdala to the prefrontal cortex to guide behavioral choice.¹⁰⁶ In all these cases, the actual route of information transfer is unknown: for instance, it appears likely that the amygdala influences the prefrontal cortex both through a strongly driving indirect route via the dorsomedial thalamus as well as a direct but diffusely modulatory input¹⁰⁷ (somewhat the converse of what one might have guessed intuitively). Electrophysiological recordings from amygdala and orbitofrontal cortex in rats bear out this

overall picture: the amygdala acquires the requisite associations related to the current reward value of a stimulus, and the orbitofrontal cortex uses this signal to guide choice,¹⁰⁸ a finding consistent with human fMRI data as well.¹⁰⁶ An important future direction will be to dissect in detail how processing between the two structures evolves in time during the decision-making process.

In terms of sensory inputs to the amygdala, these hail from all sensory modalities, including interoceptive information that would include information about internal states such as hunger or satiety. In regard to vision, the primate amygdala receives strong inputs from anterior temporal neocortex; there is also a hypothesized subcortical route of visual input that, as we noted above, is both anatomically and functionally unclear.⁵³ It has been known for some time that the connections of the amygdala with visual cortices show both reciprocal and nonreciprocal feedback projections from the basal amygdala to all regions of visual cortex in the temporal lobe, and indeed all the way back to primary visual cortex in the occipital lobe (a finding so far documented only in monkeys¹⁰⁹ and cats¹¹⁰). The functional significance of this feedback architecture remains unclear, although it has been shown to modulate processing in temporal cortex of emotional facial expressions¹¹¹ and may play a role particularly in conscious evaluation of such stimuli.¹¹² The sensory inputs to the amygdala are gated by at least two mechanisms. One is a dopamine-mediated enhancement of sensory inputs to the amygdala; a second is a prefrontal-mediated inhibition via projections from the prefrontal cortex.¹¹³ Both of these mechanisms show individual differences, which may be correlated substantially with individual differences related to mood.¹¹⁴ The connections between amygdala and the prefrontal cortex in particular have been highlighted in regard to genetic polymorphisms and susceptibility to psychiatric illness.¹¹⁵ Of great interest has been a polymorphism in the promoter region of the serotonin reuptake transporter (5HTTLPR), which is associated with risk of depression, as well as with changes in BOLD signal within the amygdala while processing emotional facial expressions⁹⁹ in humans, and associated with individual differences in anxious temperament and scanpaths to faces in monkeys.¹¹⁶ More recently, a number of studies have found that the polymorphism is associated also with systematic changes in

the strength of both structural and functional connectivity between amygdala and medial parts of the prefrontal cortex,^{49,117} with consequences for psychopathology,⁴⁹ trait anxiety,¹¹⁸ as well as for aspects of decision making that take into account context and framing effects we discussed earlier.⁹⁸ There are also well-known projections from the amygdala to the nucleus accumbens to modulate dopaminergic responses related to reward learning. In fact, the basolateral amygdala together with prefrontal cortex appear essential to provide such dopaminergic neurons with stimulus and context-related information that can be used to predict reward,^{119,120} emphasizing the tight relationship between amygdala, prefrontal cortex, and ventral striatum in reward learning.

The amygdala projects to a host of other structures (see Ref. 1 for review), and the functional consequences of these projections remain to be fully understood. In addition to the projections to components of the basal ganglia that influence instrumental learning and choice, and to the prefrontal cortex to modulate decision making as noted earlier, the amygdala also projects to structures such as the hippocampus to modulate consolidation of emotional declarative memories, to the basal forebrain to modulate attention and other aspects of memory, and to the retrosplenial cortex¹²¹ where it may influence self-directed versus externally directed attention. All of these connections can likely be understood at least in part as a modulation that provides some kind of processing selectivity based on value, saliency, and relevance. It is likely that such modulation takes place at multiple temporal scales, ranging from long-term trait-like effects to moment-by-moment effects on specific items encountered.¹²²

Future directions

One big open question concerns the amygdala's role in the conscious experience of emotion and motivation. Although functional imaging studies generally have supported such a role correlatively, few have investigated it explicitly. One study found a correlation between real-life emotional experience and the magnitude of amygdala activation to visual stimuli.¹²³ Yet a lesion study argued that the amygdala was inessential for the experience of fear,¹²⁴ although this was based on a limited questionnaire

measure. We have examined the issue to some extent in subject SM as well, who on clinical interview comes across as having an abnormally low level of negative emotions in her experience.¹²⁵ The topic remains to be explored with a detailed, rich battery of probes including realistic elicitors of strong emotions like fear—something ethically difficult to do in humans.

A technically challenging question concerns the temporal dynamics of when the amygdala comes into play during information processing, and how it does so in interaction with other structures such as the prefrontal cortex and striatum, a topic we hinted at earlier. The theme of context-dependent amygdala evaluation of stimuli as part of evaluating the relevance of stimuli fits also within certain psychological appraisal theories that incorporate time as an explicit dimension of interest. For instance, Klaus Scherer's component-process framework to emotion posits a number of temporally and informationally sequential "stimulus evaluation checks" that correspond to degrees of evaluation and disambiguation.¹²⁶ Which of these relies on the amygdala? This question finds some parallel to questions about whether the amygdala subserves rapid, coarse, preattentive processing or slower, more fine-grained processing that should be considered fully "cognitive" (a neuroanatomical equivalent of a long historical debate about the primacy of emotion and cognition within psychology^{127,128}). Such levels of processing are not always carefully distinguished from the point in time at which they unfold, two distinct issues. Related to the temporal dynamics issue is the topic of amygdala habituation, of interest both mechanistically and in terms of relevance to psychiatric illness. The emerging view of the amygdala's role in many psychiatric disorders is that it is not modulated or habituated appropriately, resulting in exaggerated or context-inappropriate amygdala responses in those disorders. For instance, there is recent evidence from studies in autism that the amygdala fails to habituate to the sight of faces.¹²⁹ Clearly, better tools to measure neuroanatomical engagement with millisecond accuracy will help tremendously in mapping out precisely which processes the amygdala contributes to; right now we are generally blurring with a very wide temporal window. The ever-increasing number of electrophysiological studies of the human amygdala in surgical patients holds out great promise for tackling this issue.

A final topic of great current interest is the amygdala's role in development as well as aging (see Box 2). The amygdala has been implicated in developmental disorders and undergoes substantial changes in morphometry throughout adolescence, in both human^{130,131} and nonhuman animals.¹³² There is some evidence this developmental trajectory is altered in autism, even though the adult volume may be normal.¹³³ We briefly noted earlier that the consequences of amygdala lesions in monkeys can be quite different if the lesions are made in adulthood or neonatally¹³⁴ and that subject SM may have amygdala lesions best described as developmental.

Box 2: The amygdala in development

Structural changes in the amygdala are evident throughout adolescence in both human and non-human animals.^{130–132} In parallel with structural development, there are important functional changes in emotional behaviors thought to depend on the amygdala. From early adolescence (4 weeks old) through early adulthood (8 weeks old), mice show a variety of changes in emotional responsiveness.¹³⁹ Pavlovian fear conditioning is more generalized¹⁴⁰ and enhanced¹³⁹ in early adolescence as compared to early adulthood, a change that appears to arise mostly from an increased plasticity within synapses arising from the thalamus in the younger mice.¹⁴¹ Findings in even younger rodents have shown that 3-week-old rats completely erase conditioned fear after extinction,¹⁴² whereas adult animals have long been known to show spontaneous recovery and reinstatement, a phenomenon of great interest also to understanding traumatic memories in humans. The long-term nature of fear memories appears to depend in particular on the basolateral amygdala.¹⁴³ Very young rat pups have shown that fear conditioning can even lead to opposite behavioral effects from those seen in adults: 10-day-old rat pups are attracted to odors associated with shock, unlike the normal behavioral avoidance seen in older animals. This surprising effect depends on differences in release of glucocorticoids and dopamine release within the amygdala, and it has been speculated that it evolved to mediate unconditional attachment in altricial animals where the young are helpless.¹⁴⁴ There are also substantial differences in amygdala-mediated behaviors between infant and older monkeys,¹³⁴

as well as differences during development in humans.^{145,146} All of these findings stress the need to take into account changing socio-emotional functions throughout the lifespan.

Related to this topic is the question of which aspects of value and saliency might be coded in the amygdala already at birth, and which are acquired through experience—and how easily they can be extinguished or changed, a very important topic for understanding disorders such as posttraumatic stress syndrome or phobias that can be remarkably resistant to extinction.

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Conflicts of interest

The author declares no conflicts of interest.

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