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Amygdala: Eyes Wide Open

A new study sheds light on how the amygdala contributes to social interactions by providing direct evidence for specialized visual neurons that selectively respond to seeing the eyes of another individual or making eye contact with them.

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The eyes convey privileged social information in primates [1]. Numerous studies to date have reported a specialized role for the amygdala in processing information about the eyes in primates. In a patient known as S.M., bilateral damage to amygdala caused a deficit in perceiving the emotional states of others by viewing their faces, and this impairment stemmed from reduced exploration of the eyes [2]. A welter of neuroimaging studies has found that viewing the eyes of others strongly activates the amygdala, and this activity is related to the angle subtended by the eyes, typically with greater activation for direct eye contact [3,4]. One study [4] found that a specific region within the right amygdala in humans is specifically engaged during direct eye contact. The importance of the amygdala in signaling information about the eyes of others appears to extend to actively making eye contact: patient S.M. shows difficulty making direct eye contact during social interactions, and instead pays much more attention to the mouths of her social partners [5].

Despite this strong evidence for an important role for the amygdala in sensing and potentially making eye contact with others, however, direct physiological evidence that neurons in amygdala actually respond to eyes has been elusive. As they report in this issue of *Current Biology*, using a more ethological way of testing neuronal selectivity in the amygdala [6], Mosher *et al.* [7] have now shown that there are distinct classes of visual neurons in the amygdala that

selectively respond when monkeys view the eyes of other monkeys. Notably, a subset of eye-fixation cells are specialized for detecting when monkeys in movie clips looked at the camera, resulting in eye contact with the subject monkey [7]. These findings suggest the amygdala — a collection of brain nuclei long associated with emotion, punishment, reward, and attention — contains neuronal specializations for processing some of the most important, emotionally-arousing, and meaningful biological stimuli in our environment, namely the eyes of others.

Foraging for Social Information with the Eyes

Foraging is one of the most important and fundamental behaviors controlled by the nervous system. Foraging is usually considered in the context of acquiring food, but the computational principles that guide foraging behavior [8] can be applied more generally, and in particular they offer insights helpful for understanding how the nervous system organizes social behavior [9]. For highly visual animals such as primates and humans, eye movements may be considered behaviors aimed at foraging for valuable information, including information about others — and in primates and humans, such information can be gained from looking at the eyes of conspecifics [1]. The direction of gaze, for example, conveys social information [1], signaling intentions, promoting cooperation and directing the attention of others to important objects and events [10].

Following the gaze of others is an adaptive response to their use in

foraging for visual information, and is found in gregarious primates and other social animals [10]. Gaze-following behavior is foundational for joint attention and theory of mind, and may be critical for developing language [10]. These observations invite the hypothesis that the primate brain may have evolved neuronal specializations for detecting and responding to the eyes of others.

Social Behavior and the Amygdala

In their classic 1939 paper, Klüver and Bucy [11] described the behavioral deficits caused by bilateral temporal lobectomy in rhesus macaques. Monkeys with amygdectomy showed profound social impairments. They tended to lose social rank and were often excluded from their troops, sometimes leading to their deaths [12]. Many of these social impairments were attributable to loss of amygdala functions. In addition to social impairments, amygdala lesions are also associated with alterations in nonsocial behaviors, including loss of fear in response to physical threats (for example, from a snake or human), especially in novel and unfamiliar settings [13]. Thus, social processing is just one of many operations carried out by the amygdala that appear to orient the organism to critical objects and events in the environment.

Though often discussed as if it were a single, homogeneous nucleus, the amygdala is actually a heterogeneous region composed of multiple nuclei that receive inputs from all sensory modalities, with particularly strong visual inputs in primates [14]. The amygdala is ideally situated anatomically to integrate multiple sources of information from both central and peripheral sources [14]. This may allow the amygdala to compute the state of the brain with respect to the rest of the body. The amygdala is also involved in learning and decision-making: neuronal activity

in the amygdala tracks signed reward values, in which either appetitive or aversive outcomes are signaled by distinct but anatomically-intermingled populations of neurons [15]. Amygdala lesions impair, but do not abolish, reward value coding by neurons in prefrontal cortex [16]. Converging evidence from humans and other animals suggests that reward-related computations are tightly associated with social behavior [9,17]. Although it remains unclear how amygdala neurons integrate reward and social context during interactions with others, communication between amygdala and prefrontal cortex may play a key role [18].

Eye-contact Cells in Amygdala

Mosher *et al.* [7] report that about a quarter of amygdala neurons that respond specifically to seeing the eyes of others (eye-fixation cells) showed significantly greater activity when making direct eye contact — the monkeys in the movies were looking directly at the camera — compared to when looking at the eye region of a monkey with averted gaze (Figure 1). Although most cells in amygdala were not selective for eye contact *per se*, the presence of these specialized cells constrains models of the role of amygdala in social behavior. It remains to be determined whether all or just a subset of socially-informative stimuli are encoded in a privileged manner in the amygdala. Other types of social information, such as grooming or threatening facial expressions, may also be processed by specialized populations of cells.

Mosher *et al.* [7] further showed that eye-fixation cells, which were not anatomically confined to one nucleus, have visually-modulated responses similar to those of the canonical visual cells in the amygdala (Figure 1), which were previously characterized by the same authors [19]. Precisely how such visual cells in the amygdala become specialized to eye fixation or eye contact is an intriguing computational question to be explored in the future. It is important to note that the responses of these cells were not specific to viewing naturalistic movies; rather, these cells responded similarly when viewing static images of other monkeys [7]. Finally, the amygdala is one of the regions influenced by social network size in rhesus macaques [20]. It remains to be

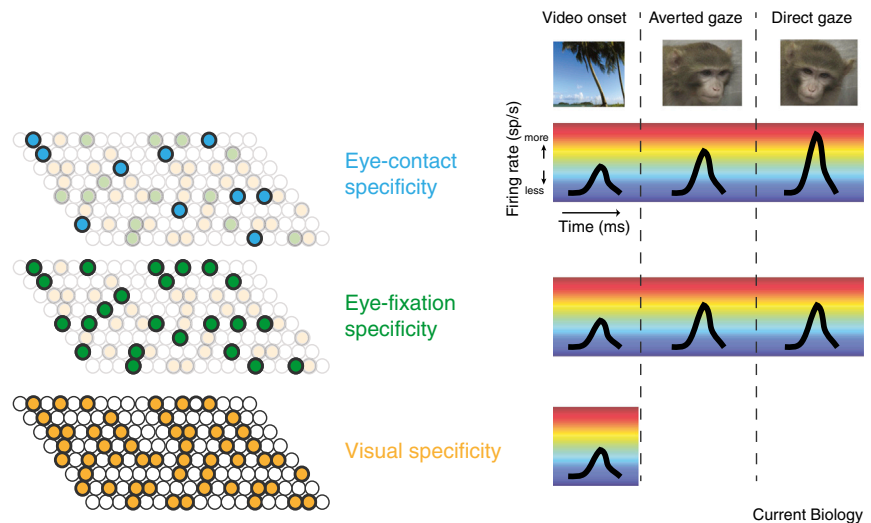


Figure 1. Neuronal encoding of eye-fixation and eye-contact in amygdala.

Right: neural network illustrations show the nested properties of the eye-fixation and eye-contact cells within the visually-sensitive amygdala population. Out of all amygdala cells (black circles), cells with generic visual specificity emerge (orange). Within this population, a subset of the cells shows eye-fixation specificity (green). Finally, within the cells with eye-fixation specificity, a subset of the cells further shows eye-contact specificity (blue). Left: firing rate illustrations of different visual classes of amygdala cells upon the event of generic visual stimulation, looking at the eyes with an averted gaze, and looking at the eyes with a direct gaze of a social partner. Artificial heatmaps are overlaid to demonstrate the magnitude of spiking activity.

seen how much of the changes in the amygdala volume due to the increased social network size translates to a more robust processing of information from the eyes.

Do the eyes have it? We believe so. The eye-fixation and eye-contact neurons found by Moser and colleagues in the amygdala endorse this conclusion. We appear to be one step closer to understanding mechanistically what Klüver and Bucy observed [11] on the notable relationship between amygdala and social behavior.

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Biofilms: Five-Star Accommodations for the Aerobically Challenged

The human microbiome contains a diverse array of microbes that affect human health. A recent study finds that fungal biofilms are capable of supporting growth of anaerobic bacteria, suggesting that these fungi can promote bacterial growth in otherwise toxic environments.

Robert A. Cramer

Environmental oxygen levels have changed significantly over the course of Earth's history and consequently organism oxygen requirements vary throughout the tree of life [1,2]. Oxygen serves as the key electron acceptor in the generation of chemical energy via mitochondrial respiration in most eukaryotes and is essential for biosynthesis of macromolecules such as sterols and porphyrins. Oxygen is also the source of toxic reactive oxygen species that can damage cells and tissue. In fact, many prokaryotic and eukaryotic microbes live anaerobic lifestyles and do not rely on oxygen to grow. For many of these anaerobes, exposure to oxygen is lethal. As a result, oxygen levels are an important factor in determining the composition of a microbial community.

Pioneering research on microbial communities of the human body, collectively termed the microbiome, has revealed the importance of microbes in human health [3,4]. While the majority of human microbiome research has focused on identifying and quantifying bacterial species, it is becoming clear that fungi are also significant components of these microbial communities [5]. As bacteria and fungi are present together in many ecological niches in the human body, a rich opportunity exists for cross-kingdom microbial interactions [6]. Important ongoing research on these cross-kingdom interactions in

various compartments of the human body strongly suggests their impact on human health is significant [7]. A particularly clinically relevant question is whether fungal–bacterial interactions can alter the ability of microbes to colonize specific environments of the human body. If so, the spectrum of disease, and subsequent treatments of those diseases, could be directly impacted.

In this issue of *Current Biology*, a report by Fox *et al.* [8] shows that fungal biofilms can support the growth of anaerobic bacteria that would otherwise be too oxygen-rich for these anaerobes (Figure 1). Fox *et al.* focus on *Candida albicans*, a common fungal commensal of mammalian mucosal surfaces including the gastrointestinal (GI) tract [8]. *C. albicans* is well known for its ability to grow as yeast, pseudohyphae or hyphae depending on environmental conditions [9]. In otherwise healthy individuals, *C. albicans* is not often a major agent of infectious disease. However, perturbations to the host immune system and/or microbiome can lead to disease caused by *C. albicans* [10]. As one example, studies in mice reveal that alterations in the microbiome result in increased susceptibility to disease caused by *Candida* [11]. Perhaps more commonly experienced, it is documented that antibiotic usage can increase yeast growth in the female reproductive tract. Consequently, it is clear that bacterial–fungal interactions play a critical role in human health [6,7].

A major feature of *C. albicans* biology that impacts human health resides in its ability to form biofilms [12]. Biofilms are complex, heterogeneous communities of microbes encased in a polysaccharide-rich extracellular matrix that attaches to biotic and abiotic surfaces [13,14]. Their association with human disease is significant as up to 80% of human microbial infections are suspected to result from biofilms according to the National Institutes of Health. Biofilms are often resistant to antimicrobial therapies and provide sources for dissemination of pathogenic microbes throughout the human body. Importantly, biofilms contain complex microenvironments that influence the metabolism and biology of the resident cells, which often consist of multiple species of microbes [15].

While it has previously been shown that bacterial biofilms can promote growth of different bacteria, Fox *et al.* [8] report for the first time that fungal biofilms can also support growth of two obligate anaerobes found in the human GI tract, *Clostridium perfringens* and *Bacteroides fragilis* [16]. As *C. perfringens* and *B. fragilis* are anaerobes with differing degrees of tolerance to oxygen, the authors' hypothesized that *C. albicans* biofilms contain regions of reduced oxygen levels, or hypoxic microenvironments. Previous studies on bacterial biofilms have shown the presence of hypoxic microenvironments within the biofilm, yet in fungal biofilms this has remained speculative. Gene expression and examination of genetic null mutants in *Candida* species forming biofilms has strongly suggested that fungal biofilms contain regions with low oxygen tension, and moreover it has also been shown that key transcriptional regulators of the fungal hypoxia response contribute to biofilm formation [17,18].