

The amygdala: inside and out

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Abstract

Research at the interface of psychology, neuroscience, molecular biology, and genetics, focusing on the amygdala, has begun to reveal a rule book for emotional reactions. Variations in intrinsic and extrinsic factors tweak the sensitivity of the amygdala, giving rise to differences in behavior between individuals. At their most extreme, these variations may generate psychological disorders, and even our current rudimentary understanding of this brain region suggests novel strategies for the treatment of such disorders.

In this report, we provide an overview of the innovative approaches and subsequent findings that have contributed to the discovery of specific factors that elucidate how a relatively small portion of our brain called “the amygdala” can dictate a significant number of the behaviors that make up our emotional lives. The amygdala is a deep-brain structure that is uniquely positioned to filter the constant barrage of input from our external and internal worlds. It is the sensitivity of this structure that dictates how the rest of the brain will convert those signals into adaptive behavioral and physiological responses. Fundamentally, the amygdala is critical to detecting and initiating the learning that allows us to use environmental events to predict potential threats. Whether it is a rat in a cage learning that the tone it hears heralds a mild electric shock, or a human realizing that someone is coming up behind them because the person in front of them just widened their eyes, it is the amygdala that calls the “rest of the brain” into action so its smarter “parent” can decide what to do (or not to do) next. Abnormal variations in amygdala reactivity can lead to exaggerated reactions to both intrinsic (biological) and extrinsic (environmental) signals, leading to the disorders we experience as depression and anxiety. The past ten years have borne witness to remarkable progress in our understanding of

the intrinsic and extrinsic factors that modulate the responsiveness of the amygdala and its effects on behavior and physiology. These advances offer the beginnings of an understanding that addresses why different individuals respond to adversity and challenge in ways that range from submission to resilience. Critically, these studies have uncovered novel neurobiological targets for the treatment and even prevention of psychopathological states.

Intrinsic factors

Three complimentary strategies have proven particularly useful in identifying specific intrinsic factors that help shape the responsiveness of the human amygdala [1]. Each of these three approaches is based on the ability to accurately measure inter-individual differences in amygdala function through blood oxygen level-dependent functional magnetic resonance imaging (BOLD fMRI). In the first strategy, commonly referred to as pharmacologic fMRI, a drug that is a specific antagonist or agonist of a targeted neuromodulatory system is administered to subjects either shortly before or during BOLD fMRI. The effects of the drug on brain function are typically compared to the effects of a placebo. Ideally, a double-blinded design is employed so that neither the participants nor the investigators are aware which treatment is

being administered until all data have been collected. Any differences in brain function between the drug and placebo groups reflect a specific role in the brain circuitry for the neuromodulatory system under investigation. Such pharmacologic fMRI research has demonstrated that several neuromodulatory systems, including dopamine [2,3], serotonin [4,5], norepinephrine [6,7], GABA [8], endocannabinoids [9], and steroid hormones [10-12], affect the responsiveness of the human amygdala. Although pharmacologic fMRI studies like those noted above are useful for identifying specific systems that modulate the human amygdala, they do not identify inter-individual differences in the intrinsic functioning of these systems and the resulting variability in the responsiveness of the amygdala.

The second strategy addresses these shortcomings by combining BOLD fMRI with neuroreceptor positron emission tomography (PET). A significant number of molecules involved in neuromodulatory signaling cascades such as biosynthesis, release, reuptake, and cell-signaling can be assayed *in vivo* using PET ligands. By combining these PET-derived measures of brain chemistry with BOLD fMRI data in the same participants, intrinsic regional levels of specific neuromodulatory targets can be systematically related to brain function. Already, such multimodal PET/fMRI studies have identified predictive links between inter-individual differences in amygdala responsiveness and endogenous variability in the serotonin [13-15] and dopamine [16,17] systems. These effects are not only consistent with those observed in pharmacologic fMRI studies but also serve to establish how naturally occurring variability in these neuromodulatory systems shapes amygdala functioning.

The third complimentary research strategy, imaging genetics, seeks to establish connections between common genetic polymorphisms, variability in neuromodulatory systems and inter-individual differences in brain function. Thousands and possibly millions of common polymorphisms (i.e., those variations in a gene that are present in more than 1% of the population) exist across the entire human genome. By affecting the pathways between genes and their protein products, these polymorphisms can cause significant variability in the functioning of neuromodulatory systems between individuals. Combining information on these common functional genetic polymorphisms with BOLD fMRI data from the same group of participants, we can map the variability in neuromodulatory function associated with the polymorphisms onto differences in brain function between individuals. Many imaging genetic findings of amygdala function are consistent with patterns reported in pharmacologic fMRI and multimodal

PET/fMRI studies. This includes confirmation of the role of serotonin [18,19], dopamine [20-22], norepinephrine [23], endocannabinoids [24], and steroid hormones [25,26]. However, imaging genetics research has also broken new ground in identifying specific intrinsic factors that shape variability in amygdala responsiveness in the absence of a priori pharmacologic fMRI or multimodal PET/fMRI findings [27-29]. Unlike the first two research strategies, which are limited by the number of available drugs or ligands, respectively, imaging genetics offers the potential to explore the impact of any factor whose function may be affected by common variation in its genetic code. Thus, imaging genetics holds unique promise in identifying a broad array of intrinsic factors that contribute to inter-individual differences in the responsiveness of the human amygdala.

Regardless of the specific strategy, the intrinsic factors identified through the above research are largely consistent with the identified roles of the amygdala, the target neuromodulatory systems, and the genetic polymorphisms that have been implicated in the expression of normal emotional behavior as well as psychopathology (particularly mood and anxiety disorders). Moreover, these intrinsic factors, which modulate amygdala responsiveness, may be useful predictive markers of relative risk for psychopathology. Even more intriguingly, they suggest specific mechanisms for the development of individually tailored treatment and, ultimately, prevention strategies for psychopathology.

Extrinsic factors

Numerous studies have shown that increased amygdala responsiveness is critical to acquiring a learned state of fear during aversive conditioning [30]. During these learned states, the amygdala mediates common adaptive responses that allow the animal to learn best—examples of these responses are autonomic responses such as heart rate and respiration as well as somatomotor (movement-related) responses such as freezing [31-34]. Critically, the amygdala's role in mediating these behaviors is particularly important during learning when the outcome predicted by a particular stimulus is uncertain, be it (a) early in training, (b) when a particular contingency has changed, or (c) when a cue can lead to more than one outcome [33]. The key to elucidating the role of the amygdala during learning is to devise tasks that set aside a strong fear state that can overshadow the direct study of the amygdala. For example, while early studies aimed to present the human amygdala with stimuli that would produce strong emotional state changes, recent studies have opted to present more “emotionally subtle” stimuli to assess the amygdala's role in learning.

Photographs of facial expressions are often used as stimuli in this context because we can glean information about someone's internal emotional state, their intentions, and their reaction to events in our immediate environment from their expressions. Facial expressions of emotion have predicted important events for us in the past, and we can use these previous experiences to respond appropriately to expressions as we perceive them. In this way, facial expressions are naturally conditioned stimuli.

If the amygdala is constantly monitoring something as subtle as changes in facial expression then it is playing a fundamental role in modulating our moment-to-moment vigilance and learning [33]. The implications this perspective has for amygdala dysfunction are therefore enormous. Aberration in this system would lead to very basic interpersonal dysfunction that could lie at the heart of a host of psychological disorders. Indeed, facial expressions have been used as stimuli to identify abnormal amygdala responses in many disorders [35,36] and, more importantly, have been used to predict treatment outcomes in specific disorders including generalized anxiety disorder [37,38].

Recent advances

Some useful research concerning amygdala reactions to extrinsic events has addressed its role in processing explicit versus implicit emotional events. That is, those events and responses that we are consciously aware of, and those that we are not. Being aware of your emotional response to a particular environmental stimulus is clearly beneficial. For example, knowing that your ex-wife causes your blood to boil is a good thing to remind yourself of before heading to an extended family function. However, we are not always aware of the emotional "triggers" that set us off, for example, sometimes we are in the middle of a social situation and look down and realize that we are sweating. Numerous studies have now examined whether the amygdala is sensitive to these environmental events that escape our awareness. Much like the field of human memory, the study of human emotion is beginning to elucidate the importance of implicit versus explicit processing of emotional information.

The early human neuroimaging work addressing implicit emotion used a technique called backward masking to present fearful facial expressions in a way that increased amygdala activity without the participant being consciously aware of their presence [39,40], a technique derived from the seminal psychophysiological studies of Arne Öhman [41,42]. Perceptual illusions other than backward masking, such as binocular rivalry and

continuous flash suppression, have also been used to demonstrate similar implicit effects [43,44]. However, contrived experimental manipulations are not the only way such effects can be shown. It is probably more compelling to show such effects when subjects could have been aware of the trigger. Demos and colleagues [45] presented subjects with female faces and then told them that a single facial feature had been manipulated. Though none of the subjects were able to state what the change was, their amygdala did by discriminating between faces with large compared to small pupils. Since stimulation of the amygdala produces pupil dilation, this is an example of the amygdala showing sensitivity to an emotional response in others that it controls in one's self.

In another example, Mujica-Parodi and colleagues [46] presented their subjects with sweat samples from individuals who had either just completed their first sky dive or exercised on a treadmill. The subjects could not possibly have known which of the samples were from people experiencing their first sky dive, but their amygdala knew, showing a larger response to the samples derived from first-time sky divers. Therefore, if another person in my immediate environment is in an excitable state, even if I don't know the reason myself, perhaps I will have some sense for that and react accordingly.

Todorov and colleagues [47,48] provide one of our favorite examples of the utility of separating amygdala responses into "things I can explicitly tell you about" from "those that I cannot." Subjects were presented with many pictures of faces, all intended to have no discernable expression (i.e., neutral). The subjects were asked to tell the experimenters how trustworthy they thought each face was based on a gut reaction. As expected, each subject thought some of the faces were more trustworthy-looking, some were in the middle, and some were less trustworthy-looking. Not surprisingly, their amygdala responses to these faces also matched their verbal assessments. From a large number of varied ratings, the researchers computed a mean trustworthiness score for each face. Fascinatingly, although the test group's amygdala responses correlated with their own subjective verbal ratings of the faces, their amygdala responses showed an even stronger relationship with the consensus ratings for each face! The implications of this finding are many, but most importantly it means that "there are rules"—implicit rules about certain facial features that guide our amygdala reactions and, in turn, our behavior. Although we can modulate these reactions once we become aware of them, we have less control over their initiation.

Future directions

These examples of implicit emotional processing are sometimes passed off as “cute” novelties. But we suggest that they will be critical to fully understanding our emotional lives and their aberrations in psychopathology. Depression and anxiety are not explicit emotional behaviors—they are, at their core, exaggerated implicit emotional reactions that have not been properly regulated. Identification of the genetic signatures that predict these exaggerated reactions, as well as the compromised prefrontal function that yields to these exaggerations, will clarify the predisposition of particular individuals to psychopathology. Combining information gleaned from examining implicit and explicit emotional function with measurement of the genetic markers that help shape each individual’s “trigger” point, is one clear future direction that will yield benefits for the field.

Abbreviations

BOLD fMRI, blood oxygen level-dependent functional magnetic resonance imaging; PET, positron emission tomography.

Competing interests

The authors declare that they have no competing interests.

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