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Research Focus

The uncertainty of it all

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The amygdala is clearly implicated in the processing of biologically relevant stimuli, particularly those that can lead to a state of fear. A new study by Herry, Bach and colleagues using both mouse and human subjects seemingly throws a wrench in the spokes by demonstrating that the amygdala is sensitive to non-biologically relevant stimuli (i.e. tones) when they occur in an unpredictable fashion. The implications of this finding for understanding the role of the amygdala in vigilance, threat assessment and anxiety are considered here.

Fear is important. Without that rush of fear you felt the first time the subway train roared by, you might not remember crucial things, such as standing behind the yellow line rather than in front of it. But as important as fear is, it is the primary emotion that visits us the least often [1]. Even if you include horror movies, you can probably count the number of times in your life you have been 'scared out of your wits' on your fingers and toes. So what do brain areas important for fear-processing 'do' the rest of the time?

There is much research to support the notion that the amygdala, a brain structure buried deep within the temporal lobes, is a key player in your fear response [2]. Bolstered in large part by studies of aversive Pavlovian conditioning, the amygdala is known to be a key player in both the acquisition and expression of learned fear responses. The question remains – what role exactly does the amygdala have in the complex chain of events that includes monitoring the environment, detecting a stimulus, registering it as threatening, feeling afraid and devising a plan of action? Is increased amygdala activity the source of your feeling of fear, or is this increased activity observed because a fear state is a good time to learn a few things?

The recent study by Herry, Bach and colleagues [3] provides a glimpse of the amygdala as a clear learner of environmental contingencies before it takes on its role in emotional response. In their study, both mouse and human subjects were exposed to a simple repeating tone. Sometimes the tone occurred predictably (e.g. every 200 ms) and at other times the tone occurred unpredictably (e.g. at a variable interval with a mean of 200 ms). When segments of time comprising unpredictable tones were compared with segments comprising predictable tones, the amygdala was more responsive during the unpredictable tones, measured as c-fos changes in the mice and fMRI responses in the humans. Thus, unpredictability *per se*, even for events that are not biologically relevant, is enough to engage the amygdala. But what is the purpose of this system that is apparently tuned to environmental coherence? Is this role ultimately connected to the amygdala's known role in threat assessment?

Fortunately, Herry, Bach and colleagues' study has a second phase that offers an answer. Unpredictable and predictable tones were then set in the background while subjects engaged in tasks purported to be classic tests of anxiety in the mouse and human, respectively. The mice were exposed to the dreaded elevated plus maze test, in which anxious mice are highly avoidant of the open runways. The human subjects viewed angry and neutral faces and pressed a button when a dot appeared in a spatial location previously held by one of the faces (i.e. a dot-probe paradigm). Prior data show that anxious subjects show shorter reaction times when the dot replaces the angry face compared with replacement of the neutral face (when both faces are presented together). Remarkably, when unpredictable tones played in the background, both the mouse and human subjects behaved more like anxious subjects during these tasks. That is, compared with the predictable tone condition, the mice were more avoidant of the elevated, open runways and the human subjects showed an even greater reaction-time disparity between angry and neutral faces. Thus, a simple manipulation shown to induce greater amygdala reactivity in response to uncertainty (i.e. unpredictable tones) modulated responses to ensuing biologically relevant events in a way that was similar to the canonical performance of anxious subjects.

The take-home messages from this elegant study are numerous. Mice and humans behave similarly during an anxiety-related behavioral manipulation with a comparable supporting neural circuitry. Also, the amygdala is not only responsive to biologically relevant events [4]. Unpredictability in its own right engages the amygdala. These findings expand on data derived from aversive- [5] as well as appetitive-conditioning [6] paradigms specifically implicating the amygdala in associative orienting, defined as a reaction to the detection of predictive uncertainty concerning environmental events that increases vigilance to facilitate new learning. Neuroimaging data support a similar role for the human amygdala in response to facial expressions that are ambiguous with respect to the outcomes that they predict [7,8]. For example, the human amygdala is responsive to fearful and surprised facial expressions whose 'wide-eyes' signal the occurrence of a significant, but as yet, unidentified environmental event. Amygdala sensitivity to ambiguity is also observed in more-complex tasks, such as during gambling decisions in which the degree of risk is ambiguous [9]. The findings of Herry, Bach and colleagues offer new data showing that unpredictability biases an organism towards greater sensitivity to negativity. Future research could determine whether this is necessarily so, or

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whether the detection of environmental uncertainty might also prime processing of positivity.

The transient hyper-vigilance induced by exposure to unpredictable tones suggests that healthy subjects can end up looking a lot like anxious subjects when exposed to the right situations. Perhaps this basic vigilance function in response to uncertainty is quite similar across anxious and healthy individuals, at least initially. What might differ between these individuals is how the prefrontal cortex handles the calculation of actual danger when environmental uncertainty is encountered. Those without a disorder might not cross a diagnosable line because, when appropriate, they are able to counter with a prefrontal cortical response that overrides, regulates and ultimately quells this initial amygdala hyper-responsiveness [8,10–13]. Indeed, this regulatory function appears compromised in pathological anxiety [14]. In short, at least a portion of the healthy amygdala acts as if it has an anxiety disorder – searching for threat in response to uncertainty. This design enables the amygdala to operate based on principles that are more primal and rigid [2,15] while the more educated and flexible prefrontal cortex possesses the ability to bend these rules. Overt behavior ends up being the balance struck between these processes and therein lies a basis for individual differences.

For those specifically interested in amygdala function, the study by Herry, Bach and colleagues reminds us that although amygdala output has an important role in emotional responding, the associative functions of the amygdala are primary and ubiquitous in nature. That is, the influence of the amygdala is constant as it monitors the environment for events that have predicted clear outcomes in the past. If clear predictive signals are lacking, the amygdala can boost vigilance (e.g. lower sensory thresholds throughout sensory cortex [5]) in response to uncertain events, in an attempt to help determine any causal relationships between such events [7]. When appropriate, the amygdala (via extensive efferent circuits) can then give rise to an emotional-state change [2,5,6]. In the human subjects studied by Herry, Bach and colleagues, amygdala response to unpredictable tones did not evoke a measured change in emotional state in its own right, but it did modulate emotional behavior during subsequent biologically-relevant situations. Thus, higher amygdala activity can precipitate, but might not necessarily dictate, a change in your emotional state. This should be comforting news. You are not a prisoner of your emotions. In the face of uncertainty, the amygdala just gives you a jump-start. What you do with it is what makes you... 'you.'

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Letters

Combining electrophysiology and functional imaging – different methods for different questions

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The integration of functional magnetic resonance imaging (fMRI) and electrophysiological methods, such as electroencephalography (EEG) or magnetoencephalography (MEG), is highly attractive to the cognitive neuroscientist, because it promises a temporospatial resolution that cannot be obtained with either technique alone. In fMRI-constrained source analysis, the task-related spatial information from the fMRI is used to weight or constrain

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