

Affect, Action, and Ambiguity and the Amygdala-Orbitofrontal Circuit. Focus on “Combined Unilateral Lesions of the Amygdala and Orbital Prefrontal Cortex Impair Affective Processing in Rhesus Monkeys”

Geoffrey Schoenbaum

University of Maryland School of Medicine, Department of Anatomy and Neurobiology, Baltimore, Maryland 21201

You startle awake. Was that the dog? Palms sweaty, heart rate up, anxious—you strain to listen for clues. Then you hear the tinkle of breaking glass from downstairs. Although your physiological response is similar, now you're scared. As you reach for your Louisville Slugger, you wonder about the differences in the neural circuitry underlying anxiety and fear. Well you're in luck! A report by Izquierdo and Murray (this issue p. 2023–2039) on the effects of lesions to the amygdala and outflow areas in the orbitofrontal cortex may shed some light on this question.

Although the amygdala is thought to be central to mediating both anxiety and fear, different outflow pathways may be critical to generating these emotions and their attendant reactions (Davis 2000). Moreover recent evidence suggests that within the amygdala there is dissociation between systems that mediate affective responses to definite outcomes, characterized by goal-directed actions, and systems that mediate affective responses when consequences are more ambiguous, characterized by elevated attention and vigilance. A number of investigators have proposed that the basolateral complex is particularly important for the former function whereas the central nucleus, extended amygdala, and basal forebrain cholinergic system may be more important for the latter (Davis 2000; Holland and Gallagher 1999; Whalen et al. 2001). In this issue, Izquierdo and Murray (2004) report an interesting dissociation between the effects of combined, unilateral lesions of amygdala and orbitofrontal cortex on affective behavior that may reflect the involvement of these different systems.

These researchers made unilateral lesions of amygdala and orbitofrontal cortex in monkeys and tested them on a battery of four tests. Two of these tests involved learning to respond appropriately to arbitrary cues (visual objects) associated with unambiguous appetitive outcomes (food rewards). The third and fourth tests, which required no new learning, assessed appropriate responding to innately aversive cues (plastic snakes and hairy spiders) and an ambiguous social cue (neutral human observer). The authors compared performance in monkeys with lesions in the right or left hemisphere to identify hemispheric specialization for affective processing.

They observed no differences in affective processing between hemispheres, however they found that unilateral lesions to this circuit produced mild but significant impairments compared to the performance of monkeys without lesions. Monkeys with lesions to the amygdala-orbitofrontal circuit in either hemisphere exhibited inappropriate responses in discrimina-

tion tasks when the identity of the predicted outcome was switched in a “reversal” or when the predicted outcome was “devalued” by selective over-feeding. These deficits resembled in mild form the impairments caused by bilateral lesions of either amygdala or orbitofrontal cortex alone (Gallagher et al. 1999; Hatfield et al. 1996; Izquierdo and Murray 2000; Jones and Mishkin 1972; Malkova et al. 1997; Schoenbaum et al. 2003). These monkeys also responded inappropriately to the innately aversive snake cue. They were less fearful and more willing than controls to interact with the fake snake and showed shorter latencies when reaching for objects in the vicinity of the snake; again deficits similar to those that have been reported after bilateral lesions of either structure (Butter et al. 1970; Kalin et al. 2001; Meunier et al. 1999).

That these animals were impaired relative to controls on these tests suggests that the functions supported by the amygdala-orbitofrontal circuit can be sufficiently sensitive as to require intact processing in both hemispheres. As Izquierdo and Murray note, this is typically not the case when the effects of unilateral lesions of other brain regions are assessed in monkeys. However it is also interesting that the lesioned monkeys behaved normally when confronted with a neutral human observer. Why is defensive behavior observed in this setting and not when the monkeys were confronted with a threatening item in the snake test? What is the difference?

Although there are several possible explanations, one critical difference may be that snakes (and the cues in the discrimination tasks) are associated with a clear outcome; the human intruder, presumably, is not. Humans may be innately threatening but, for these monkeys, they have a history of providing rewards and humane treatment, along with the occasional scary object. Outflow from amygdala to prefrontal areas, including the orbitofrontal cortex, may be more critical for taking action in response to the snake and the cues in the discrimination tasks, where the likely outcomes are clear, whereas projections from central nucleus to subcortical areas may be more critical for increased vigilance in response to the novel human, where the likely outcome is uncertain. Since unilateral lesions to amygdala and orbitofrontal cortex damage the former circuit more extensively, such a lesion might be expected to have a greater impact on appropriate responding when a cue is directly associated with an outcome and requires action than when information is incomplete or ambiguous and greater attention is warranted. This might be particularly true in the human intruder paradigm, which assesses information acquired before the lesions were sustained, since within these circuits the amygdala appears to be particularly important for encoding associations, which may then be stored and used by downstream regions (McGaugh 2002; Pickens et al. 2003). Such

Address for reprint requests: G. Schoenbaum, University of Maryland School of Medicine, Department of Anatomy and Neurobiology, 685 W Baltimore St, HSF-1, Rm 280K, Baltimore, MD 21201. (E-mail: schoenb@schoenbaumlab.org).

speculation is consistent with the results of Kalin et al. (2001) who found that the defensive reactions in the human intruder paradigm to be unaffected even after bilateral amygdala lesions.

Of course most situations involve both ambiguity and the need for action, but the balance may determine which system is dominant in generating behavior. To return to our story, you don't know what woke you up, so you activate amygdalar outflow through basal forebrain to promote vigilance. When the source of the sound becomes clear, you recruit prefrontal mechanisms to respond to the threat. But as you creep downstairs with your bat in hand, you wonder—is the bat big enough to fight off all those plastic snakes and hairy spiders?

REFERENCES

- Butter CM, Snyder SH, and MacDonald JA.** Effects of orbital frontal lesions on aversive and aggressive behaviors in rhesus monkeys. *J Comp Physiol Psychol* 72: 132–144, 1970.
- Davis M.** The role of the amygdala in conditioned and unconditioned fear and anxiety. In: *The Amygdala: A Functional Analysis*, edited by Aggleton JP. Oxford: Oxford University Press, 2000, p. 213–287.
- Gallagher M, McMahan RW, and Schoenbaum G.** Orbitofrontal cortex and representation of incentive value in associative learning. *J Neurosci* 19: 6610–6614, 1999.
- Hatfield T, Han JS, Conley M, Gallagher M, and Holland P.** Neurotoxic lesions of basolateral, but not central, amygdala interfere with Pavlovian second-order conditioning and reinforcer devaluation effects. *J Neurosci* 16: 5256–5265, 1996.
- Holland PC and Gallagher M.** Amygdala circuitry in attentional and representational processes. *Trends Cog Sci* 3: 65–73, 1999.
- Izquierdo AD and Murray EA.** Bilateral orbital prefrontal cortex lesions disrupt reinforcer devaluation effects in rhesus monkeys. *Soc Neurosci Abstr* 26: 978, 2000.
- Izquierdo AD and Murray EA.** Combined unilateral lesions of the amygdala and orbital prefrontal cortex impair affective processing in rhesus monkeys. *J Neurophysiol* 91: 2023–2039, 2004.
- Jones B and Mishkin M.** Limbic lesions and the problem of stimulus-reinforcement associations. *Exp Neurol* 36: 362–377, 1972.
- Kalin NH, Shelton SE, Davidson RJ, and Kelley AE.** The primate amygdala mediates acute fear but not the behavioral and physiological components of anxious temperament. *J Neurosci* 21: 2067–2074, 2001.
- Malkova L, Gaffan D, and Murray EA.** Excitotoxic lesions of the amygdala fail to produce impairment in visual learning for auditory secondary reinforcement but interfere with reinforcer devaluation effects in rhesus monkeys. *J Neurosci* 17: 6011–6020, 1997.
- McGaugh JL.** Memory consolidation and the amygdala: a systems perspective. *Trends Neurosci* 25: 456–461, 2002.
- Meunier M, Bachevalier J, Murray EA, Malkova L, and Mishkin M.** Effects of aspiration versus neurotoxic lesions of the amygdala on emotional responses in monkeys. *Eur J Neurosci* 11: 4403–4418, 1999.
- Pickens CL, Setlow B, Saddoris MP, Gallagher M, Holland PC, and Schoenbaum G.** Lesions of orbitofrontal cortex and basolateral amygdala differentially impair the use of previously acquired outcome representations to guide responding after devaluation. *J Neurosci* 23: 11078–11084, 2003.
- Schoenbaum G, Setlow B, Nugent SL, Saddoris MP, and Gallagher M.** Lesions of orbitofrontal cortex and basolateral amygdala complex disrupt acquisition of odor-guided discriminations and reversals. *Learn Mem* 10: 129–140, 2003.
- Whalen PJ, Shin LM, McInerney SC, Fischer H, Wright CI, and Rauch SL.** A functional MRI study of human amygdala responses to facial expressions of fear versus anger. *Emotion* 1: 70–83, 2001.