

Is the Amygdala a Locus of “Conditioned Fear”? Some Questions and Caveats

Viewpoint

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Since the publication of Weiskrantz' seminal paper, widely interpreted as suggesting that amygdala lesions impair the formation of stimulus–reinforcement associations (Weiskrantz, 1956), extensive research in many laboratories has attempted to determine the role(s) of the amygdala in learning and memory. In recent years, many studies have investigated amygdala participation in Pavlovian “fear conditioning” in rats. The findings of such studies have suggested that the amygdala may be an essential link in a subcortical circuit mediating the formation and permanent (or “indelible”) storage of “conditioned fear” (reviewed by LeDoux, 1995; Maren and Fanselow, 1996; Davis, 1997). Succinctly put, interpretations of the findings have suggested that “...attaching ‘fear’ to the previously neutral stimulus and remembering it is what the amygdala does” (Stevens, 1998). Evidence from many studies is consistent with the hypothesis that the amygdala—in particular, the lateral/basolateral (L/BL) nuclei—encodes and permanently stores learned fear. However, there is also evidence that challenges this hypothesis. Evaluation of the hypothesis and the supporting evidence requires consideration and clarification of several critical issues.

The first issue concerns interpretation of the effects of L/BL lesions on the expression of “conditioned fear.” It is well established that L/BL lesions impair the expression of conditioned fear, indexed either by “freezing” in the presence of a cue previously paired with footshock or by startle to a tone in the presence of a cue previously paired with footshock (fear-potentiated startle or FPS) (LeDoux, 1995; Maren and Fanselow, 1996; Davis, 1997). Indeed, excitotoxic lesions of the L/BL impair freezing and FPS even when induced 1 month after the conditioning (Lee et al., 1996; Maren et al., 1996). Such impairments are generally interpreted as evidence that L/BL lesions block *conditioned* fear. However, when using lesions to study the role of a brain region in memory, it is absolutely essential to distinguish the lesion's effects on memory from other influences on performance (the well-known “learning/performance” distinction). The conclusion that a brain lesion impairs memory requires evidence that the lesion does not simply disrupt the animal's ability to make the specific response(s) that are used as evidence of memory. Thus, Richard Thompson and colleagues (Thompson et al., 1998), for example, began their investigation of the role of the deep cerebellar nuclei in Pavlovian eyelid conditioning by demonstrating convincingly that lesions of these nuclei did not

affect performance of the unconditioned eyelid response.

In the case of the L/BL and “conditioned fear,” there are no demonstrations of which we are aware in which L/BL lesions impaired conditioned freezing or FPS while unconditioned freezing or FPS remained intact. Indeed, there is considerable evidence indicating that an intact L/BL is necessary for the expression of *unconditioned* freezing and FPS (Walker and Davis, 1997; see also Davis, 1997, for a review of much of the relevant literature). Therefore, critical additional evidence must be provided to exclude the very real possibility that the impairing effects of L/BL lesions are due simply to an impaired ability of rats to express freezing or FPS, whether it is conditioned or unconditioned. Clearly, until such evidence is provided, it is premature to conclude on the basis of results of lesion studies that the L/BL is necessary for the acquisition and expression of *conditioned* fear.

The second issue concerns interpretation of the effects of intraamygdala infusions of NMDA antagonists on Pavlovian “fear conditioning.” Several studies have reported that Pavlovian conditioned freezing or FPS is attenuated by NMDA antagonists infused into the amygdala (directed at the L/BL) prior to conditioning (see LeDoux, 1995; Maren and Fanselow, 1996; Davis, 1997). Such findings are consistent with the hypothesis that induction of NMDA-dependent long-term potentiation (LTP) within the L/BL may be the neural substrate of “conditioned fear” (Rogan et al., 1997). However, in entertaining this hypothesis, it is essential to provide evidence that excludes non-mnemonic effects of NMDA antagonists that might disrupt acquisition, such as effects on attentional or motivational processes. Furthermore, and more importantly, an unambiguous demonstration that intra-L/BL infusions of NMDA antagonists impair learning would not address the critical tenet of the hypothesis that the L/BL is the permanent storage site for “conditioned fear.” Such findings would be completely consistent with the possibility that activation of NMDA receptors in the L/BL influences short-term memory processes within the L/BL and/or alters L/BL activity regulating long-term memory storage in other brain regions (McGaugh et al., 1984; Cahill and McGaugh, 1998).

A final issue concerns interpretation of electrophysiological changes in the L/BL associated with “fear conditioning.” Recent findings suggest, for example, that LTP develops in the L/BL during Pavlovian “fear conditioning” (Rogan et al., 1997). However, it is well established that, within regions of the medial geniculate nucleus known to project to these same amygdala regions, Pavlovian “fear conditioning” induces specific, associative changes in neuronal responses to the CS used to induce conditioning (for discussion, see Ryugo and Weinberger, 1978; Weinberger, 1998). Additionally, convergence of auditory and noxious sensory stimulation is known to occur in the medial geniculate nucleus (Wepic, 1966; Love and Scott, 1969). Finally, recent evidence suggests that electrophysiological changes in the amygdala related to auditory classical conditioning result

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from increased input to the L/BL from the medial geniculate, rather than from plasticity *within* the L/BL (McKernan and Shinnick-Gallagher, 1997). The well-established evidence of "upstream" plasticity in the medial geniculate during "fear conditioning" suggests that considerable caution is required in interpreting electrophysiological changes detected in the L/BL as evidence of the formation and storage there of "conditioned fear."

Evidence from studies of human subjects also needs careful consideration. For example, it has been shown that nonconscious, conditioned emotional responses (including galvanic skin responses) can be formed in the complete absence of an amygdala (Tranel and Damasio, 1993). Also, functional magnetic resonance imaging (fMRI) studies suggest that the amygdala is active during acquisition of "conditioned fear" but not after it is acquired (Buchel et al., 1998; LaBar et al., 1998). This time-limited involvement of the amygdala in "fear conditioning" in humans is very difficult to reconcile with the view that the conditioned associations are permanently stored there. If it can be shown that the amygdala requires less blood flow to respond to a CS after conditioning than during it, then it may be possible to reconcile the fMRI findings with the "conditioned fear" view. However, the fMRI findings fit very well with other evidence of a time-limited role of the amygdala in memory storage (Cahill and McGaugh, 1998).

It remains possible that the L/BL is both a site critical for the generation of unconditioned fear and a site where "conditioned fear" is formed and permanently stored. What kinds of experiments could provide clear and compelling evidence for or against this possibility? One useful approach is to examine the effects of L/BL lesions on retention of "conditioned fear" using indices of the association other than freezing or FPS. Demonstrations that a Pavlovian conditioned association is retained in L/BL-lesioned rats despite deficits in conditioned freezing, for example, would provide strong evidence against the view that the L/BL is necessary for acquisition and permanent storage of the association. In fact, such findings have recently been reported (Vazdarjanova and McGaugh, 1998). Additional behavioral experiments providing a more exact understanding of how selective L/BL lesions do, or do not, affect Pavlovian "fear conditioning" are clearly warranted.

Evidence from many studies leaves little doubt that the amygdala, in particular the L/BL, is *involved* in the storage of emotionally arousing events such as those that evoke fear (McGaugh et al., 1984; Cahill and McGaugh, 1998). Recent findings indicate, for example, that L/BL stimulation modulates consolidation of Pavlovian "fear conditioning" (Vazdarjanova and McGaugh, 1999). However, the question of whether the L/BL is a site where memories of Pavlovian "fear conditioning" are formed and permanently stored (LeDoux, 1995; Maren and Fanselow, 1996; Davis, 1997; Stevens, 1998), or even the question of whether the L/BL is necessary for such memories (Tranel and Damasio, 1993; Vazdarjanova and McGaugh, 1998), remains open, pending further experimental inquiry. New evidence addressing the issues we have raised here might well provide convincing support for the hypothesis that "conditioned fear" is formed and permanently stored in amygdala nuclei. But, it might not. Until such convincing evidence is provided, caveat emptor.

References

- Buchel, C., Morris, J., Dolan, R.J., and Friston, K.J. (1998). Brain systems mediating aversive conditioning: an event-related fMRI study. *Neuron* 20, 947-957.
- Cahill, L., and McGaugh, J.L. (1998). Mechanisms of emotional arousal and lasting declarative memory. *Trends Neurosci.* 21, 273-313.
- Davis, M. (1997). Neurobiology of fear responses: the role of the amygdala. *J. Neuropsychol. Clin. Neurosci.* 9, 382-402.
- LaBar, K.S., Gatenby, J.C., Gore, J.C., LeDoux, J.E., and Phelps, E.A. (1998). Human amygdala activation during conditioned fear acquisition and extinction: a mixed-trial fMRI study. *Neuron* 20, 937-945.
- LeDoux, J.E. (1995). Emotion: clues from the brain. *Annu. Rev. Psychol.* 46, 209-235.
- Lee, Y., Walker, D., and Davis, M. (1996). Lack of a temporal gradient of retrograde amnesia following NMDA-induced lesions of the basolateral amygdala assessed with the fear-potentiated startle paradigm. *Behav. Neurosci.* 110, 836-839.
- Love, J.A., and Scott, J.W. (1969). Some characteristics of the cells of the magnocellular division of the medial geniculate body of the cat. *Can. J. Physiol. Pharmacol.* 130, 313-328.
- Maren, S., and Fanselow, M.S. (1996). The amygdala and fear conditioning: has the nut been cracked? *Neuron* 16, 237-240.
- Maren, S., Aharonov, G., and Fanselow, M. (1996). Retrograde abolition of conditional fear after excitotoxic lesions in the basolateral amygdala of rats: absence of a temporal gradient. *Behav. Neurosci.* 110, 718-726.
- McGaugh, J.L., Liang, K.C., Bennett, C., and Sternberg, D.B. (1984). Adrenergic influences on memory storage: interaction of peripheral and central systems. In *Neurobiology of Learning and Memory*, G. Lynch, J.L. McGaugh, and N.M. Weinberger, eds. (New York: The Guilford Press), pp. 313-332.
- McKernan, M., and Shinnick-Gallagher, P. (1997). Fear conditioning induces a lasting potentiation of synaptic currents in vitro. *Nature* 390, 607-611.
- Rogan, M.T., Staubli, U.V., and LeDoux, J.E. (1997). Fear conditioning induces associative long-term potentiation in the amygdala. *Nature* 390, 604-607.
- Ryugo, D.R., and Weinberger, N.M. (1978). Differential plasticity of morphologically distinct populations in the medial geniculate body of the cat during classical conditioning. *Behav. Biol.* 22, 275-301.
- Stevens, C.F. (1998). A million dollar question: does LTP = memory? *Neuron* 20, 1-2.
- Thompson, R.F., Thompson, J.K., Kim, J.J., Krupa, D.J., and Shinkman, P.G. (1998). The nature of reinforcement in cerebellar learning. *Neurobiol. Learn. Mem.* 70, 150-176.
- Tranel, D., and Damasio, A.R. (1993). The covert learning of affective valence does not require structures in the hippocampal system or amygdala. *J. Cogn. Neurosci.* 5, 79-88.
- Vazdarjanova, A., and McGaugh, J.L. (1998). Basolateral amygdala is not critical for cognitive memory of contextual fear conditioning. *Proc. Natl. Acad. Sci. USA* 95, 15003-15007.
- Vazdarjanova, A., and McGaugh, J.L. (1999). Amygdala modulates consolidation of memory for classical fear conditioning. *J. Neurosci.*, in press.
- Walker, D.L., and Davis, M. (1997). Double dissociation between the involvement of the bed nucleus of the stria terminalis and the central nucleus of the amygdala in startle increases produced by conditioned versus unconditioned fear. *J. Neurosci.* 17, 9375-9383.
- Weinberger, N.M. (1998). Physiological memory in primary auditory cortex: characteristics and mechanisms. *Neurobiol. Learn. Mem.* 70, 226-251.
- Weiskrantz, L. (1956). Behavioral changes associated with ablation of the amygdaloid complex in monkeys. *J. Comp. Physiol. Psychol.* 49, 381-391.
- Wepic, J.G. (1966). Multimodal sensory activation of cells in the magnocellular medial geniculate nucleus. *Exp. Neurol.* 15, 299-318.