Does the basolateral amygdala store memories for emotional events?

In his recent article Stephen Maren advances LTP in the basolateral amygdala (BLC) as a mechanism for encoding and storing emotional memory[1]. He asserts that: (1) 'fear memories are formed and stored in the basolateral amygdala'; and that (2) 'fear conditioning induces LTP in the amygdala'. The first postulation has two major problems. First, it does not acknowledge many studies that have seriously questioned the role of the BLC as a permanent repository of memories for emotional events[2]. Second, in interpreting the data presented, the author relies on assumptions that are not supported by existing data.

Several studies provide strong evidence for spared memory of classical conditioning in rats with BLC lesions. A day after context–footshock conditioning, rats with permanent or temporary BLC lesions display impaired freezing compared with sham control rats, yet they selectively avoid a place previously paired with footshock[3–5]. Additionally, BLC lesions do not disrupt conditioned suppression, which also requires an association between neutral and aversive stimuli[6]. Furthermore, rats with BLC lesions show savings when retrained compared with naïve lesioned rats[7,8] or with lesioned rats that received training in a different environment[9]. In at least two studies[4,9], spared memory was evident in rats with nearly complete (>98%) BLC lesions, suggesting that spared tissue is not likely to account for the memory savings. Additionally, the deficits in some indices of learned fear, such as freezing, potentiated startle and hypoalgesia, following BLC lesions could be deficits in behavioral expression, that is, an inability of lesioned rats to perform these behaviors in response to fearful stimuli, both unlearned and learned[10–15].

Other evidence offered to support the claim that the BLC stores emotional memories is electrophysiological data that report the development of associative neuronal firing in the BLC when conditioned and unconditioned stimuli are paired. The interpretation of these data is based on two major assumptions: (1) increased associative neuronal firing represents memory; and (2) the BLC is the only place in the brain that exhibits such associative plasticity. The latter assumption is flawed: associative neuronal changes as a result of tone–footshock conditioning occur at all levels of the auditory system, as early as the cochlear nuclei[16], in the medial geniculate[17] and in the auditory cortex[18]. Furthermore, the associative firing of BLC neurons decreases over minutes and parallels the extinction of behavioral responses, whereas that in the auditory cortex persists over minutes, even weeks[18,19].

Finally, there is at least one case of clear dissociation between LTP in the basolateral amygdala and memory. Mice that lack RasGRF, a neuron-specific nucleotide-exchange factor activated by Ca^{2+}, lack LTP in the amygdala 30 min after an LTP-inducing theta burst stimulation that induces LTP in wild-type mice. Significantly, at the same time-point, mutant mice show normal memory for tone–footshock and context–footshock conditioning[20].

Clearly, the described findings do not warrant the conclusion that emotional memories are stored in the BLC and that LTP is the mechanism that represents the stored information. The well-documented LTP of BLC neurons might be necessary for the time-limited participation of the BLC in other aspects of memory processing and storage, such as memory consolidation in various other brain regions[2].

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Reply

In my recent article, I argue that Pavlovian fear memories are stored in the basolateral complex of the amygdala (BLC) and that synaptic plasticity mechanisms such as LTP might be involved in this process[1]. Vazdarjanova takes issue with this conclusion and suggests that BLC LTP does not subserve memory storage in the BLC, but might be involved in memory consolidation in other brain regions[2]. The suggestion that the BLC is not a memory storage site is essential to Vazdarjanova's view that LTP in the BLC is not a mechanism for memory storage.

Vazdarjanova presents four pieces of evidence that argue against a role for the BLC as a fear-memory storage site. First,

she states that rats with BLC lesions 'selectively avoid a place previously paired with footshock'. Although rats with such lesions do avoid a compartment associated with footshock, avoidance in the control animals is nonselective. That is, intact rats also avoid a compartment that has never been paired with shock[3]. Thus, avoidance in BLC rats cannot be attributed to a spared associative memory, insofar as avoidance in normal rats is apparently nonassociative. Second, Vazdarjanova states that rats with BLC lesions can acquire Pavlovian fear conditioning when conditioned suppression is used as a measure of learning. However, in this study many more conditioning trials were used than is typical for fear conditioning[4], and I have confirmed that extensive overtraining can mitigate the effects of BLC lesions made prior to training[5]. Importantly, extensive overtraining does not protect animals against the global amnesia for fear conditioning produced by posttraining BLC lesions. Third, Vazdarjanova states that rats with BLC lesions show savings (faster reacquisition) of conditional fear when retrained after an initial conditioning session. By contrast, I have found that rats with BLC lesions made after initial training, but before reacquisition training, do not show savings even after 75 conditioning trials[5]. Fourth, Vazdarjanova argues that fear-conditioning deficits in rats with BLC lesions might be due to an inability to perform fear responses. However, I have recently demonstrated that this explanation cannot account for the pattern of memory deficits in rats with BLC lesions[5]. Collectively, these and other data strongly favor a role for the BLC in the encoding and long-term storage of fear memories[6,7]. It is important to note that this does not imply, as Vazdarjanova suggests I did, that the BLC is the only locus of plasticity in the brain during fear conditioning. Indeed, fear conditioning establishes plasticity in many brain areas associated with the BLC.

As an alternative to a role for LTP in storing fear memories in the BLC, Vazdarjanova suggests that LTP in the BLC might be involved temporarily in memory consolidation in other brain areas. While BLC LTP might play this role for some forms of aversive learning[8], it does not appear to have a time-limited role in Pavlovian fear conditioning. For example, infusions of NMDA-receptor antagonists into the BLC before, but not immediately after, fear conditioning produce memory deficits[9]. Similarly, BLC lesions made up to one month after fear conditioning produce robust deficits in conditional fear[10,11]. Together with data indicating that rats with BLC lesions can express fear responses under some conditions[5], these results implicate the BLC in memory storage. Because fear conditioning induces electrophysiological changes in the BLC that are isomorphic to those associated with experimental LTP induction[12,13] and manipulations that impair BLC LTP also impair fear conditioning[14–16], I conclude that LTP in the BLC remains a candidate cellular mechanism for the storage of Pavlovian fear memories.

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