Journal Club

Editor's Note: These short, critical reviews of recent papers in the *Journal*, written exclusively by graduate students or postdoctoral fellows, are intended to summarize the important findings of the paper and provide additional insight and commentary. For more information on the format and purpose of the Journal Club, please see http://www.jneurosci.org/misc/ifa_features.shtml.

The Role of the Bed Nucleus of the Stria Terminalis in Learning to Fear

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Review of Duvarci et al.

Determining how the brain regulates fear and anxiety is critical to developing appropriate treatments for the wide range of human anxiety disorders. The extended amygdala is a macrostructure in the forebrain that includes three key players in fear and anxiety-like behaviors: the basolateral nucleus of the amygdala (BLA), central nucleus of the amygdala (CeA), and bed nucleus of the stria terminalis (BNST). The BLA sends excitatory projections to both CeA and BNST, which in turn project to brainstem structures involved in the expression of fearful behaviors. In Pavlovian fear conditioning, animals learn to associate a previously neutral conditioned stimulus (CS) with an aversive unconditioned stimulus (US) (e.g., shock). Lesion or temporary inactivation of either the BLA or the CeA, but not the BNST, before conditioning disrupts the expression of fear-related behaviors such as potentiation of the startle reflex, freezing, and increased autonomic responses during a recall test (Walker et al., 2003).

Although the BNST does not seem to be involved in learning to fear an explicit stimulus (e.g., a tone or a light presented only in the presence of the aversive stimulus), it is involved in learning to fear more general, long-lasting cues (Walker et al., 2003; Davis et al., 2009). For example, disruption of the BNST impairs learning to fear the context in which shock was presented (Sullivan et al., 2004). In addition, Walker and Davis (2008) have recently shown that rats can be trained to fear an 8 min auditory CS for its full duration, but that fear to the late, sustained component of CS presentation is blocked by inactivation of the BNST. Based on such experiments, it has been suggested that the BNST preferentially responds to diffuse long-duration stimuli resulting in anxiety or "sustained" fear (Walker and Davis, 2008; Davis et al., 2009).

In a recent study in *The Journal of Neuroscience*, Duvarci et al. (2009) sought to further define the role of the BNST in fear and anxiety behaviors by examining whether this structure contributes to fearful learning about a neutral conditioned stimulus that is never directly paired with an aversive stimulus (CS−). To this end, Duvarci et al. (2009) trained Lewis rats in a differential auditory fear conditioning paradigm in which rats were first presented with two auditory stimuli, one that was paired with shock (CS+) and another that was not (CS−). Testing for contextual fear memory took place in the same chamber as training (context A). Further testing for fear of the auditory stimuli was done in a second context (context B). During both tests, time spent freezing was used as the measure of learning.

As would be expected in this type of experiment, freezing was consistently observed both in context A and in the presence of the CS+, indicating that animals had learned to fear both these stimuli. Interestingly, the animals showed a considerable amount of variability in their responses to the CS−. Although it was never paired with shock, some animals learned to fear the CS− as much as the CS+. These same animals also showed more context conditioning and increased anxiety on the elevated plus maze. To investigate the role of the BNST in these behaviors, Duvarci et al. (2009) performed the same experiments in a group of rats with bilateral BNST lesions. When compared to animals with sham BNST lesions, lesion animals demonstrated reduced freezing to context A but normal levels of freezing when the CS+ was presented, consistent with previously published experiments (Walker et al., 2003; Sullivan et al., 2004). Additionally, virtually none of the BNST lesion animals learned to fear the CS−, suggesting that the BNST is involved in learning this inappropriate behavior.

What do these results tell us about the role of the BNST in auditory cue fear conditioning? Duvarci et al. (2009) suggest that, in the subset of animals that learned to fear the CS−, increased activity in the BNST during fear conditioning decreased cue selectivity in the amygdala, causing the animals to learn to fear both the CS+ and the CS−. Learning about the CS− therefore occurred because of stimulus

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generalization; that is, the animals did not discriminate between the CS+ and the CS− during the training and/or test. According to this account, neural projections from the BNST to the amygdala determine how selective the amygdala is during the learning process.

In addition to the conclusion presented by Duvarci et al. (2009), another interpretation of the data exists. Animals responding to the CS− may have done so because fearful learning about this stimulus occurred in the BNST. In this case, fear of the CS− was not due to the disruption of learning processes in the amygdala by the BNST, but instead to separate instances of learning about the CS+ and the CS− in the amygdala and BNST, respectively. Although it may seem counterintuitive that learning about the CS−, a short-duration cue, occurred in the BNST, this could be possible if the CS− was perceived as a diffuse, contextual cue. When one considers that the majority of the relatively limited experience the animals had with the CS− occurred in the context where shock was presented and that the shock and CS− were presented during the same training session, it is easy to see how this cue could become associated with the context itself.

This alternative interpretation is consistent with the results of Duvarci et al. (2009). Importantly, lesion of the BNST eliminated freezing to the CS−. In addition, the positive correlation between fear of the CS− and fear of the context implies that these behaviors are mediated by similar substrates. As discussed above, it has already been established that context conditioning is a BNST-mediated behavior (Walker et al., 2003; Sullivan et al., 2004). BNST-mediated CS− learning is also consistent with the hypothesis of Davis and colleagues that the BNST responds to generalized, nonspecific stimuli (Walker and Davis, 2008; Davis et al., 2009).

Regardless of which interpretation of the data proves true, the results of Duvarci et al. (2009) are relevant to the study of anxiety in rodents and humans. For example, another way to view the inappropriate fear to the CS− expressed by some animals is as a failure to inhibit fear during CS− presentation, or as a failure to learn that the CS− signaled a period of safety from shock. The results of Duvarci et al. (2009) are therefore relevant to literature on conditioning of safety signals (i.e., conditioned inhibition) (Rescorla, 1969). Learning to view a cue as a safety signal is an active process that is mediated by suppression of neural activity in the lateral amygdala (Collins and Paré, 2000; Rogan et al., 2005). The fact that BNST lesions correct the failure to learn in CS− responders could be interpreted to mean that BNST activity interferes with this learning process. Because the current study used only five training trials, it is impossible to know whether all of the animals would have eventually learned to inhibit fear to the CS−. Repeating this experiment with more trials would reveal whether BNST activity is completely preventing or merely slowing conditioning of the CS− as a safety signal.

Because clinical anxiety is often thought of as an inability to appropriately inhibit fear, and because interventions that facilitate the ability of patients to inhibit fear offer an effective strategy for the treatment of anxiety (Davis et al., 2006), the findings of Duvarci et al. (2009) might also be important for understanding the origins of anxiety in humans. Increased freezing to the CS− in anxious rats offers a striking parallel to the finding that posttraumatic stress disorder (PTSD) patients exhibit increased fear to the context and to a neutral CS− (Grillon and Morgan, 1999). A similar pattern has also recently been described for patients with panic disorder (Lissek et al., 2009). The individual differences in anxiety behavior in the inbred strain of Lewis rats described by Duvarci et al. (2009) may therefore prove to be a useful model for studying the neural substrates of PTSD and panic disorder. Finally, it is clear that future treatments targeting the BNST may be particularly helpful in the treatment of human anxiety disorders.

In summary, the differential fear conditioning paradigm used by Duvarci et al. (2009) is poised to offer fresh insights about the role of the BNST in inappropriate learning about a neutral CS−. Duvarci et al. (2009) propose that the BNST interferes with the ability of the amygdala to discriminate between the CS+ and CS−. The alternative conclusion presented here hypothesizes that the CS− is perceived as a retrieval cue for the context in which shock occurred and the BNST therefore directly mediates its association with shock presentation. Careful testing should be done to discriminate between these two hypotheses, to shed light on a behavior that may be a hallmark of some human anxiety disorders.

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