Review

Role of the bed nucleus of the stria terminalis in aversive learning and memory

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Surviving threats in the environment requires brain circuits for detecting (or anticipating) danger and for coordinating appropriate defensive responses (e.g., increased cardiac output, stress hormone release, and freezing behavior). The bed nucleus of the stria terminalis (BNST) is a critical interface between the "affective forebrain"—including the amygdala, ventral hippocampus, and medial prefrontal cortex—and the hypothalamic and brainstem areas that have been implicated in neuroendocrine, autonomic, and behavioral responses to actual or anticipated threats. However, the precise contribution of the BNST to defensive behavior is unclear, both in terms of the antecedent stimuli that mobilize BNST activity and the consequent defensive reactions. For example, it is well known that the BNST is essential for contextual fear conditioning, but dispensable for fear conditioning to discrete conditioned stimuli (CSs), at least as indexed by freezing behavior. However, recent evidence suggests that there are circumstances in which contextual freezing may persist independent of the BNST. Furthermore, the BNST is involved in the reinstatement (or relapse) of conditioned freezing to extinguished discrete CSs. As such, there are critical gaps in understanding how the BNST contributes to fundamental processes involved in Pavlovian fear conditioning. Here, we attempt to provide an integrative account of BNST function in fear conditioning. We discuss distinctions between unconditioned stress and conditioned fear and the role of BNST circuits in organizing behaviors associated with these states. We propose that the BNST mediates conditioned defensive responses—not based on the modality or duration of the antecedent threat or the duration of the behavioral response to the threat—but rather as consequence the ability of an antecedent stimulus to predict when an aversive outcome will occur (i.e., its temporal predictability). We argue that the BNST is not uniquely mobilized by sustained threats or uniquely involved in organizing sustained fear responses. In contrast, we argue that the BNST is involved in organizing fear responses to stimuli that poorly predict *when* danger will occur, no matter the duration, modality, or complexity of those stimuli. The concepts discussed in this review are critical to understanding the contribution of the human BNST to fear and anxiety disorders.

The bed nucleus of the stria terminalis (BNST) is a diverse cluster of neuronal nuclei located within the ventral forebrain of humans and other animals (Dumont 2009). The connectivity of the bilateral BNST (or sometimes BST) is extensive and far-reaching—the BNST is interconnected with the amygdala, dorsal raphe, hippocampus, hypothalamus, medulla, nucleus accumbens, periaqueductal gray, prefrontal cortex, thalamus, ventral tegmental area, among others (for recent reviews, see Avery et al. 2016; Lebow and Chen 2016). As a result of this connectivity, it is perhaps not surprising that the BNST has been implicated in a number of functions and behaviors relevant to psychiatric disorders, including the acquisition and expression of Pavlovian fear conditioning, reinstatement of drug seeking, negative affect in pain, compulsivity, the expression of social defeat and learned helplessness, social attachment and reproductive behaviors, and regulation of the stress axis (Davis et al. 2010; Hammack et al. 2012; Crestani et al. 2013; Petrulis 2013; Adhikari 2014; Coria-Avila et al. 2014; Stamatakis et al. 2014; Takahashi 2014; Fox et al. 2015; Kash et al. 2015; Minami and Ide 2015; Avery et al. 2016; Daniel and Rainnie 2016; Gungor and Paré 2016; Lebow and Chen 2016; Mantsch et al. 2016; Waraczynski 2016; Laman-Maharg and Trainor 2017; Vranjkovic et al. 2017). Moreover, a growing body of research links BNST function (and its dysfunction) to a number of human pathological disorders such as anxiety and addiction (Fox et al. 2015; Avery et al. 2016; Lebow and Chen 2016)—disorders that are widespread, extremely costly to the individual, and often comorbid (Kessler et al. 2005a,b; Koob 2009; McEwen 2012; Whiteford et al. 2013; DiLuca and Olesen 2014; Gonzalez and Martinez 2014). Accordingly, the BNST represents an important target for therapeutic interventions aimed at treating various psychopathologies.

Within the realm of aversively motivated behaviors, early studies suggested a limited role of the BNST in fear conditioning to only certain stimulus modalities (e.g., LeDoux et al. 1988). It has been suggested that temporal factors (either in terms of the duration of the antecedent stimulus or consequent behavioral response) explain BNST's selective function in learned fear (e.g., Davis et al. 2010). Further, it is now understood that different populations of neurons within the BNST can bidirectionally regulate various unlearned anxiety-like responses (Jennings et al. 2013; Kim et al. 2013; Crowley et al. 2016; Marcinkiewcz et al. 2016; Mazzone et al. 2016). Despite this progress, we still lack an updated and integrated view of BNST function that accounts for its diverse contributions to aversive learning and memory. Accordingly, the purpose of this review is to dissect the current literature in an effort to provide a cohesive analysis of BNST function in Pavlovian fear

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conditioning and how this might relate to its roles in stress- and anxiety-like behaviors. While this review focuses primarily on animal studies, we also examine recent and relevant developments in human BNST research. We will begin by addressing the fundamentals of aversive learning, followed by a review of the BNST's relationship with other conditioned fear-regulating regions of the brain. In subsequent sections, we will address the role of the BNST in the conditioning and expression of fear in detail. Finally, we will consider how these results may be unified under an updated model of conditioned fear-related BNST function. Based on a growing and converging data set, we argue that an overarching function of the BNST in humans and other animals is to generate defensive behaviors to unpredictable threats independent of their modality or duration.

Learning to fear

Pavlovian conditioning is the process through which animals learn associations between stimuli (Pavlov 1927). For aversive events, *Pavlovian fear conditioning* models how humans and other animals learn about threats in their environment (Rescorla 1988; LeDoux 2000; Maren 2001; Phelps and LeDoux 2005). Importantly, the conditioning, extinction, and relapse of fear may contribute to and interact with trauma-related psychopathologies such as posttraumatic stress disorder (PTSD) (Jovanovic and Ressler 2010; Mahan and Ressler 2012; Milad and Quirk 2012; Goswami et al. 2013; Gonzalez and Martinez 2014; VanElzakker et al. 2014; Careaga et al. 2016; also, see LeDoux 2012, 2014, 2017; LeDoux and Pine 2016; LeDoux and Brown 2017).

In specific terms, Pavlovian fear conditioning is a process through which a salient cue (e.g., a tone or light source) is paired with an unavoidable and noxious outcome (e.g., electric shock). Exposure to the shock (the *unconditioned stimulus*, or US) induces various species-specific "circa-strike" defensive responses (termed *unconditioned responses*) (e.g., escape, defensive fighting, etc.; Bolles 1970; Bolles and Fanselow 1980; Fanselow 1980, 1994). Through the process of conditioning, the cue comes to predict the aversive outcome (hence, termed the *conditioned stimulus*, or CS), and with one or more pairings with the US, a "post-encounter" *conditioned response* (e.g., freezing and autonomic activity in rodents) to the CS alone emerges. In addition to freezing in the presence of a shock-paired CS, animals will suppress instrumental responses for food (a phenomenon termed *conditioned suppression*; e.g., Waddell et al. 2006, 2008) and will increase the magnitude of their startle responses to other loud acoustic stimuli (termed *fear-potentiated startle*; e.g., Lee and Davis 1997). In humans, conditioned fear is often indexed using physiological measures, including skin conductance, heart rate, and pupil dilation (Lonsdorf et al. 2017). Fear conditioning can occur in the absence of a discrete CS (the US is "unsignaled"); in this case, the environment or "context" serves as the CS (and is referred to as *contextual conditioning*; Rudy et al. 2004; Curzon et al. 2009; Maren et al. 2013; Urcelay and Miller 2014). Standard conditioning procedures to a discrete CS often result in at least some concurrent contextual conditioning as the discrete CS may not fully acquire all of the associative strength of the US (Rescorla and Wagner 1972).

In contrast to conditioning, repeated presentations of the CS in the absence of the US will ultimately lead to a reduction in conditional responding, a process termed *extinction* (Pavlov 1927; Myers and Davis 2002; Chang et al. 2009). Numerous studies indicate that extinction results in a new inhibitory memory that suppresses conditional fear in a context-dependent manner (Maren 2011). Specifically, fear to an extinguished CS will return when that CS is presented outside of the extinction context, a fundamental form of "relapse" termed *renewal* (Bouton and Bolles 1979a). Renewal is not the only way in which fear can relapse: fear *reinstates* after reexposure to the US (Rescorla and Heth 1975; Bouton and Bolles 1979b; Bouton and King 1983; Westbrook et al. 2002; Morris et al. 2005; Goode et al. 2015a) and fear can *spontaneously recover* after a passage of time in the absence of the CS (Pavlov 1927; Rescorla 2004). Distinct mechanisms are thought to underlie these and other various forms of relapse (and are examined elsewhere in detail: Bouton 2002, 2004; Vervliet et al. 2013; Goode and Maren 2014; Haaker et al. 2014; McConnell and Miller 2014; Maren and Holmes 2016), but it should be noted that contextual information is thought to be critical for many of these phenomena (Bouton et al. 2006).

Neural circuits for aversive learning and memory

Originally considered a subregion of the "extended amygdala" (Johnson 1923; Alheid and Heimer 1988; Alheid et al. 1998; Alheid 2003), the BNST has numerous direct connections with other areas of the brain that are involved in Pavlovian fear conditioning, including the amygdala, hippocampus, and prefrontal cortex (PFC). Brain circuits for the acquisition and expression of conditioned fear as well as for its extinction and relapse have received considerable attention over the years (Fendt and Fanselow 1999; LeDoux 2000; Maren 2001; Maren and Quirk 2004; Quirk and Mueller 2008; Herry et al. 2010; Orsini and Maren 2012; Furini et al. 2014; Izquierdo et al. 2016). In brief, CS and US signals converge on the lateral nucleus (LA) of the amygdala and plasticity within this nucleus is vital for the acquisition, consolidation, and expression of conditioned fear (Rogan et al. 1997; Maren 1999a, 2005; Johansen et al. 2011). Output from the amygdala, via the central nucleus of the amygdala (CeA), targets downstream structures such as the periaqueductal gray (PAG) and hypothalamus to engage freezing and stress responses (respectively) in the presence of conditioned cues (LeDoux et al. 1988; Behbehani 1995; McLemore et al. 1999; Keifer et al. 2015; Tovote et al. 2015). Additionally, the hippocampus—by way of its connections with the PFC and amygdala—fundamentally regulates the acquisition and expression of contextual fear in a time-dependent manner (Kim and Fanselow 1992; Phillips and LeDoux 1992; Maren et al. 1998, 2013; Fanselow 2000; Fanselow and Dong 2010; Xu et al. 2016). Furthermore, PFC has been shown to drive or impair extinction via its projections to fear-promoting or -inhibiting neurons within the amygdala (Vertes 2004; Quirk et al. 2006; Hoover and Vertes 2007; Herry et al. 2008; Knapska et al. 2012; Senn et al. 2014; Adhikari et al. 2015; Rozeske et al. 2015; Giustino and Maren 2015; Gourley and Taylor 2016)—processes that are regulated by the hippocampus (Ji and Maren 2007, 2015a,b; Goosens 2011; Maren et al. 2013; Orsini et al. 2011; Xu et al. 2016).

The BNST is well positioned to integrate information from the amygdala, hippocampus, and PFC (Weller and Smith 1982; Sun et al. 1991; Canteras and Swanson 1992; McDonald et al. 1999; Dong et al. 2001a; Reynolds and Zahm 2005; Jalabert et al. 2009; deCampo and Fudge 2013; Torrisi et al. 2015; Lebow and Chen 2016; Oler et al. 2017; Reichard et al. 2017), and BNST subregions may have differential roles in this process (for recent reviews, see Lebow and Chen 2016; Gungor and Paré 2016). Nevertheless, the functions of these circuits in fear conditioning are not well characterized. BLA activity appears to be required for BNST-dependent fear behaviors in most cases, insofar as BLA lesions block both phasic and long-lasting fear responses even with the BNST intact (Maren et al. 1996; Maren 1999b; Davis et al. 2010; but, see overtraining studies: Poulos et al. 2010; Zimmerman and Maren 2011). However, it is not yet clear if neurons required for BNST-dependent or -independent conditioned fears are distinct

or overlapping within the BLA (Davis et al. 2010). Furthermore, it is unclear if direct projections from the BLA are required for BNST-dependent aversive learning and memory, particularly because photostimulation of these afferents produces nonassociative anxiolytic effects (Kim et al. 2013; Crowley et al. 2016).

The CeA also densely innervates the BNST, but the role of the CeA in BNST-dependent defensive behaviors has been an area of debate. There is evidence that these structures mediate different aspects of conditioned fear (Walker and Davis 2008; Walker et al. 2009; Davis et al. 2010), although others have suggested that their roles in these processes are similar (Fox et al. 2015; Gungor and Paré 2016; Shackman and Fox 2016, also, see Gorka et al. 2017). That said, there are some recent and compelling data indicating that the CeA is required for BNST-dependent conditioned fears. For example, Asok and colleagues (2017) demonstrated that optogenetic silencing of central amygdala CRF-positive afferents in the BNST during training blunts fear expression to a shock-associated context, at least in the later portion of the retrieval (note that it is possible that other circuits may be involved and at different stages). The anxiogenic functions of the BNST are generally attributed to its anterior regions, (see Crown et al. 2000; Kocho-Schellenberg et al. 2014) a region targeted by CeA (and BLA) neurons (Gungor and Paré 2016).

Beyond the amygdala, the significance of hippocampal inputs to the BNST in the context of aversive learning is not well understood. The hippocampus exerts inhibitory control over stress hormone release (via the hypothalamic–pituitary–adrenal [HPA] axis) through its glutamatergic projections to the BNST (Cullinan et al. 1993; Forray and Gysling 2004). Thus, projections from the hippocampus to the BNST may modulate anxiety (and perhaps BNST-dependent fear) not by driving defensive responses per se but by reducing stress responses in particular contexts (Glangetas et al. 2017; also, see Gorka et al. 2017). The PFC, particularly the infralimbic (IL) region of the PFC, projects strongly to the BNST —this circuit (along with BNST-projecting cells from the neighboring orbitofrontal cortex) may be involved in both reward (Jalabert et al. 2009; Reisiger et al. 2014) and threat processing (Spencer et al. 2005; Fox et al. 2010; Motzkin et al. 2015). Nonetheless, a role for IL projections to the BNST in conditioned fear has not been explored. The prelimbic (PL) region of the PFC has been shown to play important roles in contextual conditioning (e.g., Corcoran and Quirk 2007; Ye et al. 2017), but its direct projections to the BNST are sparse. Outside of these circuits, recent work on serotonergic inputs to the BNST has implicated dorsal raphe afferents in enhanced fear conditioning (Marcinkiewcz et al. 2016).

BNST efferents extensively target the CeA, but moderately to sparsely terminate in the PFC, BLA, and hippocampus (Dong et al. 2000, 2001b, Dong and Swanson 2003, 2004a,b, 2006a,b,c; Gungor et al. 2015; Krüger et al. 2015; Dabrowska et al. 2016; Kaufling et al. 2017; Oler et al. 2017); little is known regarding the roles of these circuits in aversive memories. BNST efferents are largely GABAergic, with a smaller portion consisting of glutamatergic neurons (Tovote et al. 2015; Vranjkovic et al. 2017; also, see McElligott et al. 2013; Avery et al. 2014; Kaufling et al. 2017). BNST subregions are highly interconnected (Turesson et al. 2013), suggesting that BNST-dependent behavioral responses reflect an integration of activity within these areas (Kim et al. 2013; Gungor and Paré 2016). Outside of its connections with the amygdala, PFC, and hippocampus, the BNST is positioned to elicit defensive behavior via direct projections to the hypothalamus and PAG (Holstege et al. 1985; Gray and Magnuson 1992; Nagy and Paré 2008). Finally, it is worth noting that in humans (Allen and Gorski 1990; Chung et al. 2002) and rodents (Hines et al. 1985; Hines et al. 1992), the male BNST is generally larger than in females (also, see Avery et al. 2014). It is not yet clear if this sexual dimorphism impacts BNST function in aversive learning, but (perhaps relatedly) male rodents generally express greater levels of contextual (but not discretely cued) freezing when compared with females (Maren et al. 1994; Markus and Zecevic 1997; Pryce et al. 1999; Gupta et al. 2001; Barker and Galea 2010; Nagaya et al. 2015; Acca et al. 2017; Bangasser and Wicks 2017; also, see Gruene et al. 2015; Pellman et al. 2017). With these connections in mind, we will now explore the various factors that may account for the roles of the BNST in conditioned fear.

BNST function in response to unconditioned aversive stimuli

Exposure of animals to aversive events—including both physical (e.g., unsignaled footshock, restraint) and psychological stressors (e.g., open or elevated spaces, bright lights, predator odors, alarm pheromones)—readily engage or influence signaling within the BNST (Rosen et al. 2015; Daniel and Rainnie 2016; Gungor and Paré 2016). Currently, it is understood that BNST neurons do not react uniformly to these various stressful stimuli. For example, the BNST has been shown to exhibit alterations (albeit, increases or decreases depending on the study) in immediate early gene expression in its anterolateral and anteroventral regions after restraint alone, inescapable tailshock, or predator odor (Lino-de-Oliveira et al. 2001; Day et al. 2005; Christianson et al. 2011; Butler et al. 2016). Electrophysiological studies have further shown that aversive footshock exposure can rapidly recruit and modify activity in BNST neurons (Marcinkiewcz et al. 2016; also, see Daldrup et al. 2016). In turn, BNST lesions often reduce or eliminate the behavioral and physiological changes (termed *unconditioned fear* responses) that come with direct exposure to these aversive stimuli. For example, BNST lesions block freezing responses in the presence of predator odors (Fendt et al. 2003, 2005). Additionally, stress (in the form of extensive footshock exposure) can potentiate acoustic startle in a separate context; lesions of the BNST block this effect (Gewirtz et al. 1998; also, see Hammack et al. 2004; Meloni et al. 2006). In cases where BNST lesions fail to alter unconditioned stress responses (e.g., Treit et al. 1998), it is thought that this may be due to the disruption of both stress-promoting and -attenuating circuits within the BNST (Adhikari 2014; Luyck and Luyten 2015). Nevertheless, the BNST functions, in part, to generate unconditioned stress responses and to mediate stress-induced sensitization.

Along these lines, BNST manipulations can also *induce* unconditioned stress and fear- or anxiety-like responses in a subregion-specific and neurotransmitter system-dependent manner (Levita et al. 2004; Hammack et al. 2009b; Daniel and Rainnie 2016). For example, increasing CRF, calcitonin gene-related peptide (CGRP), or serotonin signaling within the BNST can potentiate acoustic startle in the absence of any other training, and tends to increase anxiety in other tasks in the short term (Lee and Davis 1997; Sahuque et al. 2006; Lee et al. 2008; Sink et al. 2011, 2013b; Mazzone et al. 2016). Similarly, β-adrenergic agonism in the BNST or induction of pituitary adenylate cyclase-activating polypeptide (PACAP) signaling within the BNST promotes stress and anxiety-like responses (Deyama et al. 2008; Hammack et al. 2009a, 2010; Naka et al. 2013; Hammack and May 2015). Increasing nitric oxide production within the BNST has also been shown to induce unconditioned freezing in a novel arena (Faria et al. 2016; also, see Deyama et al. 2017). Furthermore, stimulation or inhibition of select BNST circuits, including BLA→BNST and BNST→VTA neurons, can increase or decrease avoidance (or modulate stress responding) without any prior learning (Jennings et al. 2013; Kim et al. 2013; Crowley et al. 2016; Marcinkiewcz et al. 2016; Mazzone et al. 2016).

Stress may lead to plasticity in the BNST that will ultimately affect circuit function during future stressors or tasks. For example, acute restraint stress significantly alters plasticity in the BNST in response to PFC-dependent input (Glangetas et al. 2013). Chronic stress in the form of multiday unpredictable shock exposure generally increases serotonin release in the BNST and alters serotonin receptor expression in the BNST (Hazra et al. 2012). Additionally, it has been shown that stress-enhancement of trace eyeblink conditioning in rats (through the use of restraint and tail shock) is mediated by the BNST (Bangasser et al. 2005; Bangasser and Shors 2008). From a translational perspective, and in light of pathologies in which patients may have experienced a significant degree of stress, these data are important to consider when examining unconditioned anxiety- and (perhaps) conditioned fear-related function in the BNST. Indeed, circuit-specific manipulations often occur in animals where stress history is minimal (Belzung et al. 2014). As such, important questions remain as to whether the effects seen in the circuit-selective studies (Jennings et al. 2013; Kim et al. 2013; Crowley et al. 2016; Marcinkiewcz et al. 2016; Mazzone et al. 2016) remain true following a history of stress and whether plasticity in the BNST shifts the phenotypic function of any of these circuits (also, see Conrad et al. 2011). In total, the BNST processes unconditioned aversive stimuli, but it is important to consider that negative outcomes may occur in a distinct place and in the presence of particular cues, which may foster associative learning.

BNST function in fear conditioning: stimulus modality and duration

BNST lesions (whether permanent or temporary) do not universally blunt somatic, autonomic, or hormonal responses during fear conditioning. Rather, several studies have now demonstrated a necessary role for the BNST in the learning and/or expression of *contextual*—but not discretely *cued*—fear, as indexed by freezing, conditioned suppression, potentiated startle, and stress hormone release (LeDoux et al. 1988; Hitchcock and Davis 1991; Lee and Davis 1997; Gewirtz et al. 1998; Sullivan et al. 2004; Waddell et al. 2006; Resstel et al. 2008; Duvarci et al. 2009; Poulos et al. 2010; Zimmerman and Maren 2011; Hott et al. 2012, 2017; Sink et al. 2013a; Davis and Walker 2014; Goode et al. 2015b; Hammack et al. 2015; Asok et al. 2016). Relatedly, electrical stimulation of the BNST can either increase or decrease conditioned contextual fear (as assessed by freezing or startle amplitude), effects that depend on the location, intensity, and frequency of the stimulation (Luyck et al. 2017; also, see Baas et al. 2014; Luyck and Luyten 2015). Disrupting BNST signaling does not appear to impair discrimination between two nonaversive contexts per se (e.g., given the persistence of context-dependent renewal in BNST-lesioned animals in the study by Goode et al. 2015b), suggesting that contextual representations (e.g., spatial/visual properties, etc.) are processed upstream of the BNST in the hippocampus. It has not yet been demonstrated whether unconditional fear- and stress-attenuating circuits of the BNST (Jennings et al. 2013; Kim et al. 2013; Crowley et al. 2016; Marcinkiewcz et al. 2016; Mazzone et al. 2016) (or BNST neurons in general) play any fundamental role in the extinction of conditioned fear to cues or contexts (also, see Ranjan et al. 2017).

Some of the aforementioned studies involved pretraining permanent lesions of the BNST, making it difficult to determine whether the BNST's role in context fear is specific to acquisition, consolidation, expression, or some combination of these processes (granted, there are few studies published that specifically examine the role of the BNST in the acquisition or consolidation of fear). However, there are a handful of studies using temporary or post-training lesions (or inhibitors of protein synthesis) that implicate BNST function in the acquisition (Davis and Walker 2014; also, see Asok et al. 2017), consolidation (Poulos et al. 2010), and expression of context fear (Sullivan et al. 2004; Zimmerman and Maren 2011; Goode et al. 2015b; but, see Davis and Walker 2014). Consistent with these ideas, cued or contextual conditioning increases immediate early gene expression (e.g., c-fos) in the BNST (Passerin et al. 2000; Ranjan et al. 2017), as does the expression of contextual fear (Beck and Fibiger 1995; also, see Luyten et al. 2012). Furthermore, the BNST has been shown to be important for consolidation of contextual fear in overtrained animals if the BLA is lesioned (this consolidation effect is eliminated if the BLA remains intact; Poulos et al. 2010; Zimmerman and Maren 2011). These effects on acquisition and consolidation suggest that BNST afferents (e.g., Asok et al. 2017) or perhaps BNST neurons themselves are at least *in part* a node for BNST-dependent fear memory in certain cases. However, overtraining studies suggest that the BNST is not an alternative locus for standard fear conditioning (Poulos et al. 2010; Zimmerman and Maren 2011). Thus, it is not yet clear whether plasticity within the BNST serves to store BNST-dependent conditioned fear memories and/or if the BNST is simply recruited by learning-dependent plasticity in other regions in the presence of particular conditioned stimuli. Collectively, these findings suggest a unique role for the BNST in contextual fear conditioning, but why the BNST is selective for contextual fear is unclear.

Conditioned contexts and discrete CSs not only differ in terms of their modality, but they also often differ in duration. To determine which factor is more relevant to BNST function, Hammack et al. (2015) tested whether the duration of context exposure prior to US onset in a context conditioning procedure influenced the role of the BNST in the task. Specifically, Hammack et al. (2015) placed rats in a context where unsignaled footshock occurred either 1 or 10 min after animals entered the chamber. Rats were removed from the chambers 30 sec after shock offset (thereby, the groups differed on both the timing of shock onset as well as total context exposure). After several training sessions, rats were tested in the absence of shock to the context. The results revealed that contextual fear was only affected by the BNST lesions in the context in which shock occurred at a 10-min delay; rats with BNST lesions conditioned normally to the context in which shock occurred at a 1-min delay. Importantly, these data suggest that contextual fear can be independent of the BNST under some conditions (which may also have interesting implications for context fear-induced reinstatement). Consistent with these findings, an earlier report by Waddell et al. (2006) demonstrated that lesions of the BNST attenuated conditioned suppression in the presence of a long-duration (10 min), but not a short-duration (1 min), auditory CS. Based on these results, the authors (Waddell et al. 2006; Hammack et al. 2015) argued that it was stimulus duration, not modality or response duration, that determined whether the BNST was recruited during fear conditioning procedures.

However, stimulus duration alone may not fully account for the recruitment of the BNST during fear conditioning. For example, BNST lesions prevent fear reinstatement to short-duration CSs (Waddell et al. 2006, 2008; Goode et al. 2015b). Likewise, shock-induced reinstatement of extinguished fear to a discrete CS is associated with increased activity in the human BNST (Scharfenort and Lonsdorf 2016). Furthermore, BNST lesions can enhance discrimination between a CS+ and CS− (Duvarci et al. 2009; Radke 2009) by attenuating fear to the CS− (also, see Botta et al. 2015; De Bundel et al. 2016; Sanford et al. 2017). Thus, the BNST may also be involved in the generalization of conditioned fear to both discrete cues and contexts (also, see Jasnow et al. 2017). Similarly, serotonin in the BNST during training to a phasic CS has been shown to increase fear responding to that same CS

when tested off-drug in a familiar but different context (Ravinder et al. 2013; however, it is unclear if these effects are confounded by enhanced contextual fear on top of the tone response at test; also, see Marcinkiewcz et al. 2016). In total, there are many circumstances in which the BNST regulates fear to unimodal or even discrete stimuli.

BNST function in fear conditioning: response duration

Early and seminal research on the role of downstream targets of the BLA in aversive learning demonstrated a double dissociation in the roles of the BNST and CeA in sustained and phasic fear responses, respectively (Lee and Davis 1997; Walker and Davis 1997; but, see Sullivan et al. 2004). In particular, CRF- and unconditioned light-enhanced startle—paradigms associated with long-duration fear-like responses—were shown to be mediated by the BNST (and not the CeA); conversely, fear-potentiated startle, which involves a phasic CS-evoked fear response, was attenuated by CeA lesions (and not the BNST) (Lee and Davis 1997). In this framework, the BNST was argued to be necessary to maintain long-lasting fear responses, whereas the CeA drives rapid, phasic fear responses (Davis 1998, 2006; Davis and Shi 1999; Walker et al. 2009; Davis et al. 2010; Rodríguez-Sierra et al. 2016; also, see Herrmann et al. 2016; Brinkmann et al. 2017a).

Nevertheless, a growing body of evidence indicates that the BNST mediates both rapid and sustained fear responses at least in some cases (also, see Nagy and Paré 2008). For example, work in humans has revealed that the BNST can exhibit rapid and short-lived neural responses to phasic images of an approaching tarantula or to relatively brief unpredictable threats of shock (Mobbs et al. 2010; Choi et al. 2012; Klumpers et al. 2015; Shackman and Fox 2016; also, see Schlund et al. 2013). At the behavioral level, post-training lesions or inactivation of the BNST rapidly attenuate freezing responses to an aversive context (e.g., as early as within the first minute; Zimmerman and Maren 2011; Goode et al. 2015b)—these effects coincide with rapid prevention of reinstatement to the onset of discrete extinguished CSs. Other studies examining the effects of various neuromodulators or neurosteroids within the BNST have also shown rapid alterations in behavioral responding upon return to a conditioned context (Nagaya et al. 2015; Acca et al. 2017). At the physiological level, Resstel et al. (2008) demonstrated that blockade of neurotransmitter release within the BNST (via the infusion of cobalt chloride) prevented the immediate increase in mean arterial pressure and heart rate that coincided with being placed in a previously conditioned context. Intra-BNST administration of NMDA antagonists or nNOS inhibitors also blocks these rapid physiological changes (Hott et al. 2017). These data suggest that the BNST does not selectively mediate sustained fear responses.

BNST function in fear conditioning: state-dependence

Recently, it has been observed that intra-BNST infusions of the neurosteroid allopregnanolone (ALLO, a progesterone metabolite that potentiates $GABA_A$ receptors) produce state-dependent retention deficits of contextual fear (Nagaya et al. 2015; Acca et al. 2017). In other words, animals trained *or* tested after ALLO infusions exhibit impaired contextual freezing, however animals trained *and* tested after ALLO infusions exhibit robust freezing. This suggests that the BNST not only processes environmental (i.e., exteroceptive) conditioned contexts, but might also be involved in representing interoceptive contexts (such as hormonal states). Moreover, state-dependence is not observed when ALLO is infused into the BLA, suggesting that the effects of ALLO on state-dependence relates to its actions within the BNST (Acca et al. 2017). However, it is not yet clear if other drugs that are commonly used to assess BNST function also induce state-dependence via the BNST, or if other brain areas might mediate these state-dependent effects. For example, infusions of NBQX (an AMPA receptor antagonist) or muscimol (a GABA receptor agonist) into the BNST did not cause renewal of fear to an extinguished CS as might be expected if there was a drug-induced shift in the animals interoceptive context (i.e., interoceptive renewal; Goode et al. 2015b). Nevertheless, when examining the role of the BNST in conditioned fear, it is important to consider the role of interoceptive contexts that may be associated with the aversive event; a change in interoceptive context might induce state-dependent generalization decrements.

Temporal unpredictability in BNST-dependent aversive learning and memory

Up to this point, we have reviewed studies that suggest that the BNST (1) is particularly attuned to aversive (US-like) stimuli, (2) is implicated in acquisition, expression, reinstatement, and at times consolidation of conditioned fear, (3) *does not* mediate all forms of contextual fear, (4) mediates fear to unimodal or multimodal stimuli, (5) can respond to phasic or sustained cues, (6) can exhibit phasic or sustained neural responses in the presence of threats, (7) may be involved in aversive learning to interoceptive states, and (8) can rapidly mediate defensive behaviors. What unifies these properties and what may account for BNST's selectivity in fear conditioning? We propose that the BNST is specifically recruited to aversive learning by *temporally unpredictable events* (Fig. 1).

By this view, the BNST is not involved in aversive *contextual* conditioning or expression per se, rather it becomes engaged by stimuli (whether cues or exteroceptive/interoceptive contexts) that are associated with *temporally* unpredictable USs (even if the probability that the US will occur is 100%). In other words, the BNST is recruited when the animal cannot reliably predict the onset of shock. This account of BNST function explains its diverse roles in conditioning to stimuli of various modalities or durations. For example, the BNST mediates fear to long CSs (whether unimodal or multimodal) because long CSs are poor predictors of when the aversive US will occur during presentation of the stimulus (e.g., Waddell et al. 2006; Hammack et al. 2015; also, see Fig. 1E, G). Conversely, discrete CSs (whether contexts or cues) that are trained with near immediate shock (Fig. 1A,B) allow the animal to reliably predict US onset and thereby do not require the BNST. However, the BNST is required for conditioning to relatively short, unimodal CSs if those CSs are trained as poor predictors of when a US occurs (Fig. 1C; Lange et al. 2016). This interpretation of BNST function is perhaps specific to its role in aversive learning—that is, temporal uncertainty of a US may foster BNST-dependence to various CSs, whereas nonassociative stressors (serving as USs) may engage the BNST for reasons not necessarily related to timing. Nevertheless, time as a factor in unconditioned stress is plausible (e.g., bright lights may signal a degree of vulnerability during which the animal is uncertain of the time in which a direct threat or predator will appear), but such possibilities are still in need of exploration.

One possibility is that unpredictable threats operate to produce sustained fear as the animal has learned that the risk of US onset is nearly continuous throughout presentation of the CS—these sustained fear responses have been argued to require the BNST (e.g., Walker and Davis 2008; Walker et al. 2009; Davis et al. 2010). However, temporally predictable CSs (albeit, massed) or contexts (e.g., Hammack et al. 2015) can also produce long-lasting and sustained fear responses, such as freezing behaviors, that do

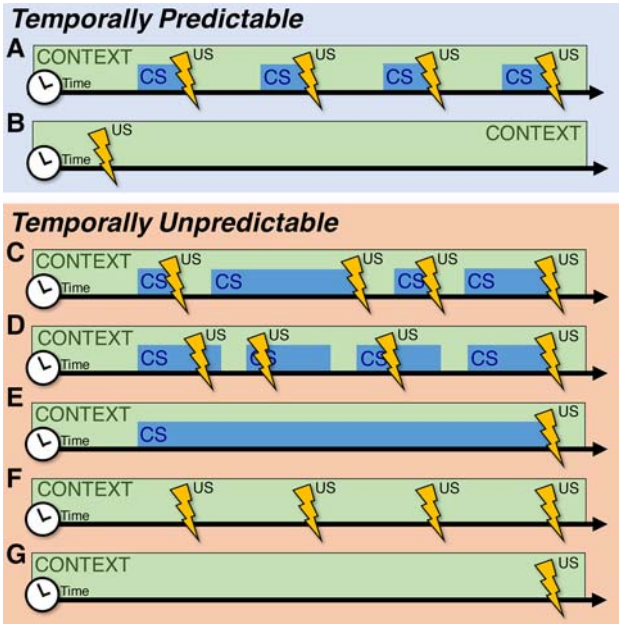

Figure 1. Temporally predictable and unpredictable aversive conditioning procedures. Standard fear conditioning procedures produce temporally predictive discrete CSs that do not require the BNST—fear to the conditioning context may be BNST-dependent given that the context is a poor predictor of shock onset (*A*). Contextual conditioning with early—but not necessarily immediate—shock onset, however, is temporally predictive of the US, and may therefore be BNST-independent (this procedure may require multiple training sessions and may not necessarily require extensive context exposure post-shock) (*B*). Temporally unpredictable conditioned stimuli can be generated by varying the duration of the CS across conditioning trials (*C*), randomizing the onset of shock during presentation of a CS (*D*), extending the duration of the CS to exhibit remote shock onset (*E*), or conditioning a context with multiple unsignaled and temporally unpredictive shocks (*F*) or late shock onset (*G*). BNST circuitry has been implicated in all of these cases of temporally unpredictable aversive stimuli (outside of example *D*, which has not yet been tested).

not require the BNST (e.g., Zimmerman and Maren 2011). Hence, it is possible that neither the duration of the fear response nor the duration of the CS is the determinant of when or whether the BNST is recruited to mediate conditioned fear responses.

Of course, there is considerable variability in animals and individuals in terms of how accurately they time the onset of aversive events (also, see Buhusi and Meck 2005). Thus, the role of the BNST in temporal predictability may need to be addressed by comparing responses to temporally predictable (Fig. 1A,B) and unpredictable antecedents of aversive outcomes (Fig. 1C–E). The number of studies utilizing temporally uncertain discrete CSs are limited (e.g., Daldrup et al. 2015; Lange et al. 2016; Seidenbecher et al. 2016), but they often train the CS with components of both immediate and delayed US onset (thereby contributing to its temporal uncertainty). Fear to these stimuli is then tested to a continuous presentation of the CS over the course of several minutes. Only the late phases of CS presentation appear to require the BNST (Davis et al. 2010; also, see Meloni et al. 2006). Accordingly, we argue that in these cases these early phases of retrieval are akin to temporally predictable CSs, whereas the later times of CS exposure are temporally unpredictable of US onset. By training the CS with early shock onset (as well as late onset), the animals have learned that CS onset could possibly predict immediate shock—only after sustaining the CS does the uncertainty arise regarding when the US might occur. Along these lines, if the CS is paired with temporally certain shock (i.e., early shock onset), its retrieval is BNST-independent and does not elicit sustained responding. Thus, we propose that temporal uncertainty, which may produce sustained fear, accounts for the BNST's diverse contributions to aversive learning and memory. Note that other forms of unpredictability—such as CS–US contingency (e.g., Davies and Craske 2015)—might also interact with temporal unpredictability (also, see Alvarez et al. 2011; Robinson et al. 2012; Schmitz and Grillon 2012).

It is not yet clear if the conditioning of temporally uncertain stimuli relies on plasticity within and/or upstream of the BNST, but recent studies comparing predictable and unpredictable threats have implicated the amygdala (e.g., Herry et al. 2007), amygdalar afferents to the BNST, and activity/endocannabinoid signaling within the BNST itself in the response to temporally unpredictable threats (Davis et al. 2010; Lange et al. 2016). Additionally, pharmacological or optogenetic inhibition of the dorsal hippocampus has been shown to attenuate fear to temporally unpredictable (but not predictable) auditory CSs (e.g., Fig. 1D; Amadi et al. 2017)—manipulations that also disrupt contextual fear.

In total, we propose that the BNST mediates learned fear when the *timing* of an aversive event is uncertain, even in the face of certainty that the event will happen. Indeed, this interpretation is consistent with other recent accounts of BNST broader functions. For example, the BNST has been proposed to be involved in "valence surveillance" (Lebow and Chen 2016), which includes monitoring positive and negative stimuli and initiating appropriate behavioral and physiological reactions. Unpredictable stressors (such as temporally unpredictable CSs) may require ongoing monitoring via the BNST—such hypervigilance to threat of shock has been associated with activity in the BNST in anxious humans (Somerville et al. 2010). Ultimately, the role of the BNST in mediating fear responses to temporally unpredictable threats is likely an important factor in the role of the BNST in human anxiety, given that ambiguity is thought to be a core component of anxiety (Foa et al. 1992; Bouton et al. 2001; Grillon 2002a,b, 2008; Perusini and Fanselow 2015). Notably, there have been several recent advances in imaging techniques of the human BNST, which will help to better characterize the role of the BNST in aversive learning and in clinical psychopathologies (Fox et al. 2015; Torrisi et al. 2015; Avery et al. 2016; Brinkmann et al. 2017a,b; Pedersen et al. 2017; Sladky et al. 2017; Theiss et al. 2017). On a final note, an emphasis on temporal uncertainty might have implications for BNST's additional roles in drug seeking behaviors (Shaham et al. 2003; Flavin and Winder 2013; Silberman and Winder 2013), given that footshock exposure can induce both fear and drug reinstatement (e.g., Erb and Stewart 1999; Erb et al. 2001; Shalev et al. 2001). All of this considered, future experiments will hopefully shed light on the precise circumstances and circuits by which conditioned and unconditioned stimuli engage the BNST.

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