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The Role Of Basal Forebrain Cholinergic Neurons In Fear and Extinction Memory

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Abstract

Cholinergic input to the neocortex, dorsal hippocampus (dHipp), and basolateral amygdala (BLA) is critical for neural function and synaptic plasticity in these brain regions. Synaptic plasticity in the neocortex, dHipp, ventral Hipp (vHipp), and BLA has also been implicated in fear and extinction memory. This finding raises the possibility that basal forebrain (BF) cholinergic neurons, the predominant source of acetylcholine in these brain regions, have an important role in mediating fear and extinction memory. While empirical studies support this hypothesis, there are interesting inconsistencies among these studies that raise questions about how best to define the role of BF cholinergic neurons in fear and extinction memory. Nucleus basalis magnocellularis (NBM) cholinergic neurons that project to the BLA are critical for fear memory and contextual fear extinction memory. NBM cholinergic neurons that project to the neocortex are critical for cued and contextual fear conditioned suppression, but are not critical for fear memory in other behavioral paradigms and in the inhibitory avoidance paradigm may even inhibit contextual fear memory formation. Medial septum and diagonal band of Broca cholinergic neurons are critical for contextual fear memory and acquisition of cued fear extinction. Thus, even though the results of previous studies suggest BF cholinergic neurons modulate fear and extinction memory, inconsistent findings among these studies necessitates more research to better define the neural circuits and molecular processes through which BF cholinergic neurons modulate fear and extinction memory. Furthermore, studies determining if BF cholinergic neurons can be manipulated in such a manner so as to treat excessive fear in anxiety disorders are needed.

Keywords

nucleus basalis; magnocellular; fear conditioning; contextual conditioning; inhibitory avoidance; fear extinction; extinction recall

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1. Introduction

Decades of research have demonstrated that cholinergic neurons in the basal forebrain (BF) serve as an extra-thalamic relay of sensory information (Jones, 2003), contribute to arousal (Fournier, Materi, Semba, and Rasmusson, 2004; Jones, 2003; Manns, Alonso, and Jones, 2000a; 2000b; 2003), attentional processing (Baxter and Chiba, 1999; Chiba, Bucci, Holland, and Gallagher, 1995; Kozak, Bruno, and Sarter, 2006; McGaughy, Kaiser, and Sarter, 1996; St Peters, Demeter, Lustig, Bruno, and Sarter, 2011), cortical sensory plasticity (Ashe, McKenna, and Weinberger, 1989; Conner, Culberson, Packowski, Chiba, and Tuszynski, 2003; Ramanathan, Tuszynski, and Conner, 2009), place field re-mapping in the dorsal hippocampus (dHipp) (Ikonen, McMahan, Gallagher, Eichenbaum, and Tanila, 2002), and spatial learning and memory (McGaughy, Koene, Eichenbaum, and Hasselmo, 2005; Winters and Bussey, 2005). These findings demonstrate that BF cholinergic input to the neocortex and dHipp modulate neural plasticity in these brain regions and are critical for mediating psychological function that are dependent on these brain regions.

The medial prefrontal cortex (mPFC), dHipp, ventral Hipp (vHipp) and basolateral complex of the amygdala (BLA) are critical for fear and extinction memory (see below). Given that BF cholinergic neurons project to these brain regions (Mesulam, Mufson, Levey, and Wainer, 1983a; Mesulam, Mufson, Wainer, and Levey, 1983b; Woolf and Butcher, 1982; Woolf, Eckenstein, and Butcher, 1983; 1984; Zaborszky, Pang, Somogyi, Nadasdy, and Kallo, 1999), one would expect BF cholinergic neurons to have an important role in modulating fear and extinction memory. Indeed, BF cholinergic neurons were included in early neural circuits believed to be critical for fear memory (LeDoux, 1992; Weinberger, 1998; Weinberger and Bakin, 1998). While studies have revealed a role for BF cholinergic neurons in fear and extinction memory, a number of other studies have reported that manipulation of cholinergic input to the neocortex, Hipp, and the BLA have no effect on fear memory. Possibly, these inconsistent findings have dampened enthusiasm for a thorough investigation of the role BF cholinergic neurons in mediating fear and extinction memory.

In this article I review studies that have examined the role of BF cholinergic neurons in fear and extinction memory. First, I define fear and extinction memory and then, briefly, the BF cholinergic system. I then review studies that have examined the effects of selective BF cholinergic manipulation on fear and extinction memory using a variety of dependent variables (e.g. startle, freezing, conditioned suppression) and experimental methods (e.g. selective lesion, pharmacological manipulation, optogenetics). Together, these studies demonstrate that different clusters of BF cholinergic neurons have different roles in mediating fear and extinction memory. However, the variable effects BF cholinergic manipulations have on fear and extinction memory, rather than raise questions about their involvement in fear and extinction memory, have the potential to inform us about the neurobiology of fear memory, novel ways fear extinction can be disrupted, and neural plasticity that modulates fear and extinction memory.

2. Definition of fear and extinction memory

Fear memory is almost always measured in relatively simple behavioral paradigms where a neutral stimulus such as a tone or a light is paired with an aversive event (Davis and Whalen, 2001; Fanselow, 2000; Lang, Davis, and Ohman, 2000; LeDoux, 2000; Maren, 2001). In the majority of experiments, the neutral stimulus, referred to as the conditioned stimulus (CS) is paired once or several times with an unconditioned aversive stimulus (UCS, typically a footshock) in order to induce a fear memory. If the CS co-terminates with the UCS this is referred to as cued or delayed fear conditioning (Maren, 2001). If there is an interval between the offset of the CS and onset of the UCS, this is referred to as trace fear conditioning (Marchand, Luck, and Di Scala, 2004). In many experiments that examine the neurobiology of fear and extinction memory, the CS can also be a distinct space or arrangement of objects (e.g. type of background noise, odor, or texture places into a distinct space) that form a context (but for a detailed review and complete definition of a context see (Bouton, Westbrook, Corcoran, and Maren, 2006; Maren, Phan, and Liberzon, 2013)). When the CS is a context, fear conditioning is referred to as contextual fear conditioning (Bouton et al., 2006; Fanselow, 2000; Maren, 2001; Maren et al., 2013; Rudy, Huff, and Matus-Amat, 2004).

Behavioral responses indicative of fear-like states (e.g. freezing, potentiated startle) are used to measure fear learning. The change in fear-like behavior induced by the CS after pairing with the UCS is used as an index of fear memory, which can be conceptualized as a CS-UCS association. Thus, for virtually all behavioral paradigms, pairing the CS and UCS comprises the fear learning phase. Fear memory is usually tested a day later by presenting the CS alone. High levels of conditioned responding during this test are indicative of a robust fear memory. Three common variables used to measure fear memory are freezing, potentiated startle, and avoidance (Cahill and McGaugh, 1998; Davis and Whalen, 2001; Lang et al., 2000; Maren, 2001; 2005; McGaugh, 2004; Williams and Clayton, 2001). In the freezing paradigm, which we will refer to as Pavlovian fear conditioning, freezing behavior induced by CS presentation is used to measure fear learning and memory (Blanchard and Blanchard, 1972; Fanselow, 1994). In the fear potentiated startle (FPS) paradigm a brief white noise (i.e. startle probe) is used to elicit a startle reflex in the absence or presence of the CS. After fear conditioning, the startle reflex in the presence of the CS is enhanced, and this enhancement is used as the measure of fear learning and memory (Davis, 1992a; b). Another behavioral paradigm is inhibitory avoidance (IA), which is comprised of a well-lit chamber and a dark chamber joined together and connected by a doorway. Typically, when the animal is placed in the light chamber, it avoids the brightly lit chamber by entering the dark chamber. Upon entering the dark chamber, animals experience a footshock. On the following day, animals are again placed in the well-lit chamber, but typically take a longer time to enter the dark chamber, because the dark chamber was paired with a footshock on the previous day. This increase in avoidance is used to index fear memory (for examples see Gold, van Buskirk, and McGaugh, 1975; Introini-Collison, Saghafi, Novack, and McGaugh, 1992; Power and McGaugh, 2002b; Williams and McGaugh, 1993). Another paradigm used to study fear memory is the suppression of operant responses (for examples see Amorapanth, Nader, and LeDoux, 1999; Estes and Skinner, 1941; Killcross, Robbins, and Everitt, 1997; Milad,

Rauch, Pitman, and Quirk, 2006; Sierra-Mercado, Corcoran, Lebron-Milad, and Quirk, 2006), though this is less common than the other variables mentioned above. In this paradigm, animals are first trained to press a bar for a reward. After training they are then presented with the CS-UCS stimulus set (i.e. fear conditioning). After conditioning, cessation in bar pressing occurs with CS presentation. This change in bar pressing is used to index fear memory.

After fear conditioning, presentation of the CS in the absence of the UCS results in a decrease in conditioned responding (Bouton et al., 2006; Estes and Skinner, 1941; Milad et al., 2006; Orsini and Maren, 2012; Pavlov, 1927; Quirk, 2002; Quirk, Garcia, and Gonzalez-Lima, 2006; Rescorla, 2004; Rothbaum and Davis, 2003). This inhibition in conditioned fear responding is referred to as fear extinction. This inhibition in conditioned fear responding does not only represent suppression of behavior, forgetting, or erasure of the fear memory, but also represents acquisition of a new memory (i.e. CS predicts no UCS) (Bouton et al., 2006; Milad et al., 2006; Orsini and Maren, 2012; Pavlov, 1927; Quirk, 2002; Quirk et al., 2006; Rescorla, 2004; Rothbaum and Davis, 2003). This new extinction memory can be examined in all of the behavioral fear paradigms mentioned above. Extinction memory is typically tested one day after induction of fear extinction by presenting the CS alone. Low levels of conditioned fear responding during the extinction test are indicative of robust extinction memory. In this review, extinction training refers to the repeated presentation of CSs without reinforcement, acquisition of extinction refers to the decrease in conditioned fear responding that typically occurs with non-reinforced CS presentation, and the ability to inhibit conditioned fear responding during an extinction test is indicative of robust extinction memory.

Cued and contextual fear and extinction memory can be examined in Pavlovian fear conditioning, FPS, and conditioned suppression, but only contextual fear and extinction memory can be examined in IA. These behavioral paradigms and how they are used to measure fear and extinction memory are illustrated in Figure 1.

3. BF Cholinergic Neurons

There are excellent reviews and empirical studies about BF cholinergic neurons (Jones, 2004; Mesulam et al., 1983a; Mesulam et al., 1983b; Semba, 1991; Woolf and Butcher, 1982; Woolf et al., 1983; 1984; Zaborszky et al., 1999). This section is not meant to be a comprehensive description of BF cholinergic neurons or cholinergic receptor pharmacology. Instead, the goal of this section is to provide the reader with brief definitions of different BF cholinergic clusters and summarize the cholinergic synapse within fear and extinction circuits.

BF cholinergic neurons are located on the base of the brain and can be found in clusters from the olfactory tubercle to the rostral end of the lateral geniculate bodies. At the anterior pole of the BF are cholinergic neurons in the medial septum and diagonal band of Broca (MS/DBB). These cholinergic neurons project to the Hipp (Mesulam et al., 1983b; Woolf et al., 1984) and midline cortical structures such as the posterior anterior cingulate cortex, retrosplenial cortex (RSC), and mPFC (Mesulam et al., 1983b; Woolf et al., 1984), including

the infralimbic cortex (IL) (Knox and Keller, 2015). Thus, in the MS/DBB there are septohippocampal as well as corticopetal cholinergic neurons. At the posterior pole of the BF are cholinergic neurons in the nucleus basalis of Meynert (NBM, including substantia innominata). NBM cholinergic neurons project to dorsolateral surfaces of the cortical mantle, PFC, and BLA (Mesulam et al., 1983b; Woolf et al., 1984). Thus, in the NBM there are corticopetal and amygdalopetal cholinergic neurons. Other BF corticopetal cholinergic neurons that project predominantly to anterior medial cortical regions (e.g. mPFC) and the olfactory tubercle can be found in the medial preoptic area, lateral preoptic area, and the horizontal limb of the diagonal band of Broca (hDBB) (Mesulam et al., 1983b; Woolf et al., 1984).

Upon membrane depolarization and Ca^{2+} influx into the axon terminal, acetylcholine (ACh) is released from the axon terminal (Birks and Fitch, 1974; Collier, Tandon, Prado, and Bachoo, 1993). Termination of ACh actions on receptors is accomplished by metabolism of ACh by acetylcholinesterase (AChE) (Chatonnet and Lockridge, 1989). Choline is then taken back up into the axon terminal via the high affinity choline transporter (Bazalakova and Blakely, 2006; Ferguson, Savchenko, Apparsundaram, Zwick, Wright, Heilman, Yi, Levey, and Blakely, 2003), though there is low affinity choline and ACh transport as well (Cooper, Bloom, and Roth, 1996). This choline is then used to synthesize ACh at the axon terminal (Bazalakova and Blakely, 2006; Ferguson et al., 2003); a reaction catalyzed by choline acetyltransferase (ChAT) (Benishin and Carroll, 1983). ACh is then packaged into synaptic vesicles via the vesicular acetylcholine transporter (VAChT) (Prado, Roy, Kolisnyk, Gros, and Prado, 2013).

Cholinergic neurons signal through metabotropic muscarinic receptors (mAChRs) and ionotropic nicotinic receptors (nAChRs) (Cooper et al., 1996). There are five broad types of mAChRs with m1AChR and m3-5AChRs being post synaptic and m2AChR being presynaptic (Cooper et al., 1996; Levey, 1993; Quirion, 1993). Activation of mAChRs lead to stimulation of phosphoinositol synthesis and or inhibition of cAMP synthesis (Bonner, 1989) and changes in the permeability of the neuronal membrane to K^+, Ca^{2+}, and Cl^- channels (Schimerlik, 1989). NAChRs are pentameric ion channels comprised of α and β subunits in different configurations (Cooper et al., 1996). There are at least 11 variants of the α subunit and eight variants of the β subunit (Decker, Brioni, Bannon, and Arneric, 1995). The two most common types of nAChRs in the brain comprise of α4β2 subunits and α7 subunits exclusively (Davis and Gould, 2007; Decker et al., 1995). Furthermore, even though nAChRs form a non-specific cation pore, receptors with different subunits can have selectivity for different types of cation species (McGehee, 1999).

In addition to expression Trk class of receptors that bind neurotrophic factors (Steininger, Wainer, Klein, Barbacid, and Palfrey, 1993), BF cholinergic neurons also express the p75 receptor (Heckers, Ohtake, Wiley, Lappi, Geula, and Mesulam, 1994) and are the only known neuronal group in the BF that express this receptor (Frick, Kim, and Baxter, 2004; Heckers et al., 1994). Figure 2 illustrates BF cholinergic neurons and summarizes the cholinergic synapse in the central nervous system.

4. BF Cholinergic Neurons In Fear and Extinction Memory

4.1 NBM amygdalopetal cholinergic neurons

4.1.1 Fear Memory—By infusing excitotoxins in the NBM that preferentially destroy BF amygdalopetal cholinergic neurons (Mallet, Beninger, Flesher, Jhamandas, and Boegman, 1995), a previous study has shown that BF amygdalopetal cholinergic lesions disrupt IA (Power and McGaugh, 2002b). Furthermore, memory deficits induced by BF amygdalopetal cholinergic lesions are attenuated by mAChR agonism in the BLA immediately after IA (Power and McGaugh, 2002b), which suggests BF amygdalopetal cholinergic neurons are critical for contextual fear memory consolidation in IA. BF amygdalopetal cholinergic lesions also disrupt Pavlovian contextual fear conditioning (Power and McGaugh, 2002a) and mAChR agonism in the BLA enhances consolidation of Pavlovian contextual fear conditioning (Power and McGaugh, 2002a). Systemic administration of histaminergic agents that decrease ACh levels in the BLA disrupt Pavlovian contextual fear conditioning (Passani, Cangioli, Baldi, Bucherelli, Mannaioni, and Blandina, 2001). The complementary effects that BF amygdalopetal excitotoxic lesions, direct BLA mAChR manipulation, and decreasing BLA ACh levels have on IA and Pavlovian contextual fear conditioning suggest that BF amygdalopetal cholinergic input to mAChRs in the BLA are critical for acquisition and consolidation of contextual fear memory.

Non-specific excitotoxic lesions in the NBM have no effects on cued FPS (Schauz and Koch, 1999), but studies using optogenetic and pharmacological methods in the Pavlovian fear conditioning paradigm suggest that BF amygdalopetal cholinergic neurons are critical for cued fear memory (Jiang, Kundu, Lederman, Lopez-Hernandez, Ballinger, Wang, Talmage, and Role, 2016). Optogenetic-induced inhibition of BF amygdalopetal cholinergic input to the BLA has no effect on acquisition, but disrupts expression, of cued fear memory (Jiang et al., 2016). MAChR antagonism in the BLA has no effect on cued Pavlovian fear conditioning (Baysinger, Kent, and Brown, 2012; Jiang et al., 2016), but simultaneously antagonizing mAChRs and nAChRs during fear conditioning disrupts expression of cued fear memory (Jiang et al., 2016). Interestingly, mAChR antagonism in the lateral amygdala (LA) disrupts trace fear conditioning (Baysinger et al., 2012), which does raise the possibility that BF amygdalopetal cholinergic input to mAChRs in the BLA are selectively critical for trace fear memory.

4.1.2. Extinction memory—MAChR agonism in the BLA enhances contextual extinction memory consolidation in the Pavlovian fear conditioning paradigm (Boccia, Blake, Baratti, and McGaugh, 2009), which raises the possibility that BF amygdalopetal cholinergic neurons may modulate consolidation of contextual extinction memory. While a previous study has shown that activation of BF amygdalopetal cholinergic input to the BLA during fear conditioning has effects on acquisition and maintenance of fear extinction (Jiang et al., 2016), no study to date has selectively examined the role of BF amygdalopetal cholinergic neurons in cued extinction memory.

4.1.3. Neurobiological mechanism—Neural plasticity in the LA and BLA is critical for acquisition, consolidation, and retrieval of cued and contextual fear memory (Davis and

Whalen, 2001; Maren, 1998; 2001; 2005; Pare, Quirk, and Ledoux, 2004; Phillips and LeDoux, 1992). Specifically, a fairly large amount of empirical data suggests that convergence of neural activity representing the CS and UCS onto BLA neurons increase the responsivity of BLA neurons to the CS via LTP-like mechanisms, which helps drive fear expression with CS presentation (Fanselow and LeDoux, 1999; Isoardi, Martijena, Carrer, and Molina, 2004; Maren, 2001; Pare et al., 2004). The BLA is also critical for the memory modulating effects adrenal hormones have on fear memory (Cahill and Alkire, 2003; Cahill and McGaugh, 1998; Cahill, Prins, Weber, and McGaugh, 1994; Gold et al., 1975; Introini-Collison et al., 1992; McGaugh, 1966; 2004; Williams and Clayton, 2001). Based on these observations one would expect BF amygdalopetal cholinergic neurons to be critical for cued and contextual fear memory. Previous findings support this assertion, though it remains unknown why BF amygdalopetal cholinergic neurons are critical for cued fear memory in Pavlovian fear conditioning, but not FPS (Baysinger et al., 2012; Boccia et al., 2009; Jiang et al., 2016; Power and McGaugh, 2002a; b; Schauz and Koch, 1999).

Through what neurobiological mechanisms might BF amygdalopetal cholinergic neurons facilitate contextual and trace fear memory? A previous study has shown that optogenetic-induced stimulation of NBM cholinergic axons in the BLA has two specific types of effects on principal neurons. When principal neurons fire at a low frequency, stimulation of NBM cholinergic axons inhibit the activity of principal neurons via m1AChRs. However, when principal neurons fire at a high frequency, stimulation of BF cholinergic axons enhance the after depolarization of principal cells, which enhances the excitability of these neurons (Unal, Pare, and Zaborszky, 2015). This excitability may have a role in facilitating types of learning where occurrence of conditioned and unconditioned stimuli are not optimal for learning (Unal et al., 2015). In trace fear conditioning, presentation of the CS is removed in time from presentation of the UCS. During the course of trace fear conditioning, BF amygdalopetal cholinergic input to BLA neurons could help sustain excitability of weak CS-responses in BLA neurons, and by doing this, allow synaptic plasticity critical for trace fear memory. Similarly, in contextual fear conditioning it is thought that binding of elements of an environment into a context occurs in the hippocampus, while association of that context with an aversive outcome occurs in the BLA (Bouton et al., 2006; LeDoux, 2000; Maren, 1998; 2001; Maren et al., 2013; Phillips and LeDoux, 1992). BF amygdalaopetal cholinergic input to BLA neurons could help sustain weak BLA neuron responses to the emerging context early in contextual fear learning, which would facilitate synaptic plasticity critical for associating a context with an aversive outcome. However, it should be noted that one study has observed that BF amygdalopetal cholinergic input to the BLA excites principal neurons in the BLA and this excitation is driven by nAChRs (Jiang et al., 2016). Furthermore, the results of this same study observed that BF amygdalopetal cholinergic input to the BLA potentiates glutamatergic neural transmission in the BLA and cortical input onto BLA neurons. The authors propose that these effects go on to facilitate cued fear memory formation in the Pavlovian fear conditioning paradigm (Jiang et al., 2016).

BF amygdalopetal cholinergic neurons are critical for contextual fear memory consolidation (see above) and this occurs via mAChRs. While molecular mechanisms remain undefined, there are a number of possibilities. M1AChR expression is enhanced after fear conditioning while m2AChR expression is downregulated (Ortega, del Guante, Prado-Alcala, and

Aleman, 1996). Activation of m2AChRs tend to lead to inhibition of ACh release (Quirion, Richard, and Wilson, 1994). Thus, if upregulation of m1AChRs coupled with downregulation of m2AChRs occur after fear conditioning, this could lead to potentiation of m1AChR activation and signaling cascades coupled to this receptor. These include increased intracellular Ca^{2+} levels driven by inositol triphosphate (IP_3) binding to receptors on the endoplasmic reticulum (Abe, Sugihara, Nawa, Shigemoto, Mizuno, and Nakanishi, 1992; Power and Sah, 2002), increased protein kinase C (PKC) activity driven by diacylglycerol (DAG) synthesis and enhanced intracellular Ca^{2+} levels (Newton, 2001; Sun and Alkon, 2010), or inhibition of K^+ channels driven by decreased phosphoinositol diphosphate levels in the neuronal membrane upon IP_3 synthesis (Brown, 2010; Brown and Adams, 1980). Further research is needed to determine which of the above processes, if any, are relevant for the role of BF amygdalopetal cholinergic neurons in contextual fear memory consolidation. BF amygdalopetal cholinergic input to BLA nAChRs, in conjunction with mAChRs, are critical for cued fear memory in Pavlovian fear conditioning (Jiang et al., 2016). How might activation of BLA nAChRs facilitate cued fear memory? BF amygdalopetal cholinergic input to nAChRs during fear memory formation could enhance Ca^{2+} conductance in BLA principal neurons, which drives plasticity critical for fear memory (Bauer, Schafe, and LeDoux, 2002; Davis, 1992b; Davis and Whalen, 2001; Pare et al., 2004). This hypothesis is consistent with the observation that the subunit composition of nAChRs in fear and extinction circuits (i.e. α7 and β4 subunits) allow for relatively specific conductance of Ca^{2+} currents (Marks, Stitzel, and Collins, 1989; Seguela, Wadiche, Dineley-Miller, Dani, and Patrick, 1993)

The BLA is also critical for acquisition and consolidation of cued and contextual extinction memory (Berlau and McGaugh, 2006; Boccia et al., 2009; Chhatwal, Myers, Ressler, and Davis, 2005; Herry, Trifilieff, Micheau, Luthi, and Mons, 2006; Laurent and Westbrook, 2008). Specifically, ventromedial prefrontal cortex (vmPFC) input to the intercalated cell clusters of the amygdala are critical for inhibiting neural activity in the BLA (Cho, Deisseroth, and Bolshakov, 2013; Likhtik, Popa, Apergis-Schoute, Fidacaro, and Pare, 2008; Milad and Quirk, 2002; Royer and Pare, 2002). The finding that the BLA is critical for acquisition and consolidation of extinction memory raises the possibility that BF amygdalopetal cholinergic neurons would be critical for extinction memory. While, BF amygdalopetal cholinergic input to mAChR receptors in the BLA may be critical for contextual extinction memory (see above), no study to date has examined the role of these neurons in cued extinction memory.

How might NBM amygdalopetal cholinergic input to mAChRs in the BLA be important for both contextual fear and extinction memory? Many molecular processes critical for fear memory are also critical for extinction memory (Orsini and Maren, 2012), so it is not surprising that BLA mAChRs modulate contextual fear and extinction memory. However, an important difference between fear conditioning and extinction training is levels of arousal and/or stress (Maren and Chang, 2006; Orsini and Maren, 2012). Indeed, if levels of arousal/stress are high prior to extinction training, extinction memory is impaired (Maren and Chang, 2006). It is possible that BLA mAChR function changes with levels of arousal/stress, where if arousal/stress is high, then these receptors facilitate neural plasticity critical for fear memory, but when arousal/stress levels are low, mAChRs help formation of the new

extinction memory. Of course, there are a number of neurobiological processes through which NBM amygdalopetal cholinergic neurons could modulate consolidation of contextual extinction memory (Bouton et al., 2006; Chhatwal et al., 2005; Herry et al., 2006; Lee and Kim, 1998; Maren et al., 2013; Orsini and Maren, 2012), and thus, more research is needed to identify the molecular processes through which BF amygdalopetal cholinergic input to BLA mAChRs modulate contextual fear and extinction memory.

In addition to receiving cholinergic input from the NBM, the BLA also receives cholinergic input from the lateral parabrachial nucleus (LPN) (Mesulam et al., 1983b; Woolf et al., 1984), which means care has to be taken when interpreting studies that have only employed cholinergic pharmacological manipulation in the BLA. This applies to trace fear memory and contextual extinction memory (Baysinger et al., 2012; Boccia et al., 2009). While LPN input to the central nucleus of the amygdala does modulate cued fear memory (Watabe, Ochiai, Nagase, Takahashi, Sato, and Kato, 2013), no study to date has implicated LPN input to the BLA as critical for fear or extinction memory. As a result, it is likely that BF amygdalopetal cholinergic neurons facilitate trace fear memory and contextual extinction memory, though further studies empirically demonstrating this are needed. Neurobiological mechanisms through which BF amygdalopetal cholinergic neurons could facilitate emotional memory are illustrated in Figure 3.

4.2. NBM corticopetal cholinergic neurons

Many studies investigating the role of NBM corticopetal cholinergic neurons in mediating fear and extinction memory have utilized the selective cholinergic immunotoxin 192 IgG saporin to induce permanent NBM corticopetal cholinergic lesions. This toxin does not affect NBM amygdalopetal cholinergic neurons and has minimal effects on non-cholinergic neurons (Conner et al., 2003; Frick et al., 2004; Heckers et al., 1994). Thus, when this toxin is infused into the NBM, selective corticopetal cholinergic neuronal loss can be induced. However, with this treatment residual cholinergic input to the mPFC remains and cholinergic input to posterior midline cortical systems (e.g. RSC) is unaffected (Knox and Berntson, 2008; Stowell, Berntson, and Sarter, 2000; Torres, Perry, Blockland, Wilkinson, Wiley, Lappi, and Dunnet, 1994).

4.2.1. Fear memory—NBM corticopetal cholinergic lesions attenuate cued and contextual fear conditioned suppression (Knox and Berntson, 2006; 2008; Stowell et al., 2000), though operant performance is not affected, and animals with NBM corticopetal cholinergic lesions can still display operant suppression to footshocks (Knox and Berntson, 2008; McGaughy et al., 1996; Stowell et al., 2000). These findings strongly suggest that NBM corticopetal cholinergic neurons are critical for fear memory. Surprisingly, complete BF or NBM corticopetal cholinergic lesions have no effect on cued or contextual Pavlovian fear conditioning (Conner et al., 2003; Frick et al., 2004; Knox and Berntson, 2006; Knox and Keller, 2015; Tronson, Schrick, Guzman, Huh, Srivastava, Penzes, Guedea, Gao, and Radulovic, 2009) and non-specific excitatory lesions in the NBM have no effects on FPS (Schauz and Koch, 1999).

There are a number of reasons why NBM corticopetal cholinergic lesions have robust effects on fear memory in the conditioned fear suppression paradigm only. In Pavlovian fear conditioning and FPS, animals show fear behaviors to CS presentation after the CS is paired with a UCS (i.e. CS-UCS memory). In the conditioned suppression paradigm, animals change their learned operant responses based on acquisition of a fear memory (i.e. CS-UCS). This parameter of the conditioned suppression paradigm could be critical in making fear memory in this paradigm sensitive to NBM corticopetal cholinergic manipulation. It should be noted that previous studies have observed differences between the neurobiology of conditioned freezing and suppression (Amorapanth et al., 1999; Killcross et al., 1997), which supports the hypothesis that the neurobiology of fear memory is different in the conditioned suppression paradigm when compared to other paradigms.

One study has reported that NBM cholinergic input to the auditory cortex is critical for auditory Pavlovian fear conditioning (Letzkus, Wolff, Meyer, Tovote, Courtin, Herry, and Luthi, 2011). The results of this study suggest that cholinergic input (via nAChRs) to the auditory cortex inhibit GABAergic neurons in layers I and II, which lead to activation of neurons in the layers 2/3 of the auditory cortex and via this mechanism, conditioning to the auditory CS. It is important to note that other studies have shown that complete BF cholinergic deafferentation of the neocortex has no effect on auditory fear conditioning (Conner et al., 2003; Frick et al., 2004; Knox and Berntson, 2006). The discrepancy between this study and several others could be due to a number of reasons. Letzkus et al. (2011), used complex auditory stimuli, but most other studies used single frequency tones (Conner et al., 2003; Frick et al., 2004; Knox and Berntson, 2006). Letzkus et al., used mice as experimental subjects, but in other studies subjects were rats (Conner et al., 2003; Frick et al., 2004; Knox and Berntson, 2006). Finally, rodents have interneurons in the neocortex that secrete ACh (Bayraktar, Staiger, Acsady, Cozzari, Freund, and Zilles, 1997; von Engelhardt, Eliava, Meyer, Rozov, and Monyer, 2007), and it is possible that these neurons, not NBM corticopetal cholinergic neurons, are critical for complex auditory Pavlovian fear conditioning.

Two previous studies have reported that contextual fear learning in IA is sensitive to NBM corticopetal cholinergic lesions. However, instead of disrupting IA, NBM corticopetal cholinergic lesions enhance IA (Pizzo, Thal, and Winkler, 2002; Torres et al., 1994). This is quite perplexing as it would appear the same experimental manipulation (i.e. NBM corticopetal cholinergic lesions) can disrupt contextual fear memory in one behavioral paradigm (i.e. conditioned suppression), have no effect in another behavioral paradigm (i.e. Pavlovian fear conditioning), and inhibit contextual fear memory formation in yet another paradigm (i.e. IA). It should be noted that another study has reported that NBM corticopetal cholinergic lesions have no effects on IA, but instead is critical for the enhancing effects norepinephrine release in the BLA has on contextual fear memory in IA (Power, Thal, and McGaugh, 2002). Norepinephrine release in the BLA is critical for the enhancing effects adrenal hormones have on contextual fear memory consolidation (Cahill and Alkire, 2003; Cahill and McGaugh, 1998; Power et al., 2002; Williams and Clayton, 2001). Thus, NBM corticopetal cholinergic neurons may be critical for mediating the enhancing effects adrenal hormones have on contextual fear memory consolidation, but not contextual fear memory

per se (Power et al., 2002). To resolve the discrepancies observed with NBM corticopetal cholinergic manipulation on contextual fear memory in IA, further research is needed.

4.2.2. Extinction memory—One study to date has investigated the effects of NBM corticopetal cholinergic lesions on cued extinction memory in the Pavlovian fear conditioning paradigm and found that these lesions have no effects on extinction memory (i.e. CS-no UCS memory) (Knox and Keller, 2015). MAChR antagonism in the IL attenuates extinction memory consolidation (Santini, Sepulveda-Orengo, and Porter, 2012), which suggests that ACh in the IL is critical for extinction memory consolidation. NBM cholinergic neurons project to the mPFC, but these projections may specifically terminate in the ACC and PL (Knox and Keller, 2015). Cholinergic neurons in the MS/DBB project to the mPFC as well, and may specifically project to the IL (Knox and Keller, 2015). Given that MS/DBB cholinergic neurons are critical for extinction memory (see below) it is possible that MS/DBB cholinergic input to the IL is critical for extinction memory formation.

4.2.3. Neurobiological mechanisms—Unlike NBM amygdalopetal cholinergic neurons, NBM cholinergic neurons project to a wide range of neocortical systems, some of which have been implicated in fear memory. The prelimbic cortex (PL) modulates expression of cued and contextual fear memory (Corcoran and Quirk, 2007), the anterior cingulate cortex (ACC) is critical for the formation and expression of weak cued fear memory (Bissiere, Plachta, Hoyer, McAllister, Olpe, Grace, and Cryan, 2008) and contextual fear memory consolidation (Einarsson and Nader, 2012; Frankland, Bontempi, Talton, Kaczmarek, and Silva, 2004). Given these findings, one would expect NBM corticopetal cholinergic neurons to be critical for fear memory. NBM corticopetal cholinergic neurons are critical for fear memory, but this only applies to the conditioned fear suppression paradigm (Baysinger et al., 2012; Boccia et al., 2009; Conner et al., 2003; Frick et al., 2004; Knox and Berntson, 2006; 2008; Power and McGaugh, 2002a; b; Schauz and Koch, 1999; Stowell et al., 2000), which is somewhat surprising.

How might NBM corticopetal cholinergic neurons facilitate fear memory in the conditioned suppression paradigm? During acquisition of contextual fear conditioned suppression there is a decrease in slow wave components (1-4Hz) of the PFC local field potential (LFP), and this decrease appears critical for contextual fear conditioned suppression (Knox and Berntson, 2008). NBM corticopetal cholinergic lesions increase slow wave PFC LFP at baseline and attenuate decreases in slow wave PFC LFP that occur during acquisition of contextual fear conditioned suppression (Knox and Berntson, 2008). These findings suggest that NBM cholinergic input to the PFC is critical for mediating fear conditioned suppression, though exact regions of the PFC and electrophysiological mechanisms that underlie changes in slow wave PFC LFP remain unknown. The PL and ACC are critical for fear memory (Bissiere et al., 2008; Corcoran and Quirk, 2007; Einarsson and Nader, 2012; Frankland et al., 2004), which raises the possibility that NBM corticopetal cholinergic input to these regions of the PFC are critical for fear memory in the conditioned suppression paradigm.

During fear conditioning enhanced arousal results in the release of adrenal hormones, which can modulate fear memory formation (Cahill and McGaugh, 1998; Cahill et al., 1994; McGaugh, 2004). NBM corticopetal cholinergic neurons could facilitate the modulatory effect adrenal hormones have on the PFC LFP during acquisition of fear memory and via this mechanism modulate fear memory. Pharmacologically enhancing arousal by systemic epinephrine administration enhances sensory evoked LFPs in the PFC and RSC (Berntson, Shafi, Knox, and Sarter, 2003b; Knox, Sarter, and Berntson, 2004) and both NBM cholinergic lesions and blockade of α1 noradrenergic receptors in the NBM attenuate these effects (Berntson et al., 2003b; Knox et al., 2004). Locus coeruleus neurons could secrete norepinephrine onto NBM corticopetal cholinergic neurons during acquisition of fear memory, which would cause an increase in ACh release in the PFC that is critical for fear memory formation in the conditioned suppression paradigm (LC➔NBM➔PFC). This hypothetical model has been previously proposed as critical for anxiety (Berntson, Sarter, and Cacioppo, 1998; 2003a), but could be important for fear memory as well.

Neurons in the central nucleus of the amygdala (CeA) project to the NBM (Jolkkonen, Miettinen, Pikkarainen, and Pitkanen, 2002; McDonald, 1991; Petrovich and Swanson, 1997; Price and Amaral, 1981), and given the role of the CeA in conditioned fear memory (Goosens and Maren, 2001; Wilensky, Schafe, Kristensen, and LeDoux, 2006), CeA input to NBM cholinergic neurons could stimulate ACh release in the PFC and induce plasticity critical for fear memory in the conditioned suppression paradigm (i.e. CeA➔NBM➔PFC) (Kapp, Supple, and Whalen, 1994; Weinberger, 1998). CeA neurons predominantly terminate on GABAergic neurons in the NBM (Jolkkonen et al., 2002), which suggests for the CeA➔NBM➔PFC circuit to be valid, CeA input to the NBM would have to act via GABAergic NBM neurons (Jolkkonen et al., 2002). Neurobiological mechanisms through which NBM corticopetal cholinergic neurons could facilitate fear memory in the conditioned suppression paradigm are illustrated in Figure 4.

Unfortunately, no previous study has examined the role of BF cholinergic neurons in mediating extinction memory in the conditioned suppression paradigm, even though these neurons are critical for fear memory (see above), which raises the possibility that they may be critical for extinction memory. More research is needed to identify neural circuitry, pharmacological mechanisms, and molecular mechanisms through which NBM corticopetal cholinergic neurons mediate emotional memory in the conditioned suppression paradigm, and address why the neurobiology of fear memory seems to be different in this paradigm when compared to other paradigms.

4.3 MS/DBB Cholinergic Neurons

MS/DBB contains cholinergic neurons project to the Hipp, but there are neurons in the MS/DBB that also project to the mPFC as well (Knox and Keller, 2015; Woolf et al., 1983). While much of the studies covered in this section focus on MS/DBB hippocampal cholinergic neurons, we do try to identify where MS/DBB corticopetal cholinergic neurons may be critical for emotional memory.

4.3.1. Fear memory—Research measuring ACh levels in the dHipp, pharmacologically manipulating cholinergic receptors in the dHipp, or optogenetic activation of MS/DBB cholinergic neurons suggest that MS/DBB hippocampal cholinergic neurons are critical for mediating Pavlovian contextual fear conditioning. It should be noted that MS/DBB cholinergic input to the Hipp is virtually the exclusive source of ACh in the Hipp (Mesulam et al., 1983a; Mesulam et al., 1983b; Woolf et al., 1983; 1984). As a result, pharmacological manipulation of cholinergic receptors in the Hipp directly manipulates MS/DBB cholinergic input to the Hipp.

Hipp ACh levels are enhanced during Pavlovian contextual fear conditioning (Calandreau, Trifilieff, Mons, Costes, Marien, Marighetto, Micheau, Jaffard, and Desmedt, 2006; Nail-Boucherie, Dourmap, Jaffard, and Costentin, 2000) and blockade of mAChRs in the dHipp disrupts acquisition (Rogers and Kesner, 2004; Wallenstein and Vago, 2001) and consolidation (Izquierdo, da Cunha, Rosat, Jerusalinsky, Ferreira, and Medina, 1992; Wallenstein and Vago, 2001) of Pavlovian contextual fear conditioning. Physiostigmine is an AChE inhibitor, and local AChE inhibition in distinct brain regions increases ACh levels (Messamore, Warpman, (Rogers and Kesner, 2004). nAChR agonism in the dHipp enhances Pavlovian contextual fear conditioning (Davis, Kenney, and Gould, 2007; Kenney, Raybuck, and Gould, 2012), although nAChR antagonism in the dHipp has no effect on Pavlovian contextual fear conditioning (Raybuck and Gould, 2010). Interestingly, nAChR agonism in the vHipp also disrupts Pavlovian contextual fear conditioning (Kenney et al., 2012), which suggests MS/DBB cholinergic input to nAChRs in the dHipp and vHipp are critical for Pavlovian contextual fear conditioning, though they may have different roles. Finally, optogenetic stimulation of MS/DBB cholinergic neurons enhances contextual fear conditioning in mice (Hersman and Fanselow, 2015). Together, these findings suggest that MS/DBB hippocampal cholinergic neurons are critical for contextual fear memory.

Research using direct measurement of ACh in the dHipp and direct pharmacological methods to manipulate AChRs in the dHipp suggests that MS/DBB hippocampal cholinergic neurons are critical for contextual fear memory in IA. ACh levels in the dHipp are enhanced during IA and drug treatments that enhance IA also enhance ACh levels in the dHipp (Kart, Jocham, Muller, Schlomer, Brandao, Huston, and de Souza Silva, 2004; Nail-Boucherie, Dourmap, Jaffard, and Costentin, 1998; Qi and Gold, 2009). Disrupting IA by inhibiting MS neural activity is reversed by enhancing ACh release in the dHipp (Degroot and Parent, 2001). MAChR antagonism disrupts acquisition (Khakpai, Nasehi, Haeri-Rohani, Eidi, and Zarrindast, 2012; Nail-Boucherie et al., 1998; Qi and Gold, 2009) and consolidation (Zarrindast, Ardjmand, Ahmadi, and Rezayof, 2012) of IA, as well as long-term contextual fear memory in IA (Parfitt, Campos, Barbosa, Koth, and Barros, 2012).

NAChRs have also been implicated in contextual fear memory in IA. Non-selective nAChR antagonism in the dHipp disrupts acquisition, consolidation, and retrieval of contextual fear memory (Marti Barros, Ramirez, Dos Reis, and Izquierdo, 2004) and nAChR agonism in the dHipp enhances IA (Marti Barros et al., 2004). NAChRs are also critical for long-term contextual fear memory in the IA paradigm (Parfitt et al., 2012) and the homomeric α7 nAChR is critical for reconsolidation of IA (Boccia, Blake, Krawczyk, and Baratti, 2010).

Cholinergic manipulation in the dHipp modulates trace fear conditioning. Nicotine administration in the dHipp enhances trace fear conditioning, and β2 containing nAChRs appear critical for this effect (Davis and Gould, 2007; Raybuck and Gould, 2010). MAChR antagonism in the dHipp also disrupts trace fear conditioning (Pang, Kim, Kim, Kim, Kim, and Choi, 2010).

While the studies using pharmacological and optogenetic manipulation of MS/DBB hippocampal cholinergic neurons suggest these neurons are critical for contextual fear memory, results of studies employing selective MS/DBB cholinergic lesions suggest otherwise. MS/DBB cholinergic lesions have no effects on contextual Pavlovian fear conditioning (Craig, Hong, Kopp, and McDonald, 2009; Frick et al., 2004; Pizzo et al., 2002; Tronson et al., 2009) or IA (Pizzo et al., 2002; Torres et al., 1994). However, MS/DBB cholinergic lesions disrupt contextual fear memory discrimination (Knox and Keller, 2015). If animals are fear conditioned in one context, then tested for fear memory in a novel context, contextual fear expression is observed in this novel context in rats with MS/DBB cholinergic lesions, even though this context was never paired with a UCS (Knox and Keller, 2015).

There are several possible explanations for the discrepancies observed when using pharmacological manipulation in the dHipp vs. MS/DBB cholinergic lesion with regard to contextual fear memory. One reason could be due to cholinergic regeneration that occurs after cholinergic deafferentation of the dHipp (Gage, Buzsaki, and Armstrong, 1990). The ACh content could be somewhat normalized if cholinergic terminal regeneration were to occur after cholinergic lesions in the dHipp, which may render MS/DBB cholinergic lesions ineffective in disrupting contextual fear memory. A previous study has shown that MS/DBB cholinergic lesions attenuate ACh levels in the dHipp by 60% relative to controls (Chang and Gold, 2004). This finding suggests that residual ACh levels may be sufficiently high in the dHipp to mediate contextual fear memory after MS/DBB cholinergic lesions.

In spite of discrepancies observed with pharmacological and optogentic manipulation vs. permanent selection lesions, it is very likely that MS/DBB hippocampal cholinergic neurons modulate contextual fear memory, given the extensive data set supporting this hypothesis. The finding that MS/DBB cholinergic lesions disrupt contextual fear memory discrimination is consistent with this hypothesis.

4.3.2. Extinction memory—MS/DBB cholinergic lesions disrupt acquisition of contextual fear extinction in the Pavlovian fear conditioning paradigm (Tronson et al., 2009) and induce deficits in acquisition of cued extinction memory (Knox and Keller, 2015). These two findings suggest that MS/DBB cholinergic neurons are critical for extinction memory.

4.3.3. Neurobiological mechanisms—MS/DBB cholinergic neurons project to the dHipp, vHipp, RSC, and IL and these neural substrates have been implicated in fear and extinction memory. The RSC has been implicated in recent and long-term contextual fear memory (Corcoran, Donnan, Tronson, Guzman, Gao, Jovasevic, Guedea, and Radulovic, 2011), while the dHipp is critical for contextual fear memory (for reviews see Jadhav, Kemere, German, and Frank, 2012; Maren et al., 2013; Phillips and LeDoux, 1992; Quinn,

Loya, Ma, and Fanselow, 2005), as well as trace fear memory (Beeman, Bauer, Pierson, and Quinn, 2013; Kent and Brown, 2012; Raybuck and Lattal, 2011), and contextual control of extinction memory retrieval (Bouton et al., 2006; Corcoran and Maren, 2004). The IL and vHipp are critical for extinction memory (Lebron, Milad, and Quirk, 2004; Milad et al., 2006; Quirk et al., 2006; Quirk, Pare, Richardson, Herry, Monfils, Schiller, and Vicentic, 2010; Sierra-Mercado et al., 2006; Sierra-Mercado, Padilla-Coreano, and Quirk, 2011; Vidal-Gonzalez, Vidal-Gonzalez, Rauch, and Quirk, 2006). Given these observations, it is not surprising that MS/DBB cholinergic neurons are critical for contextual fear memory, trace fear memory, and extinction memory.

How might MS/DBB cholinergic input to the dHipp facilitate contextual and trace fear memory? During IA, mAChR antagonism disrupts ERK phosphorylation (Giovannini, Pazzagli, Malmberg-Aiello, Della Corte, Rakovska, Cerbai, Casamenti, and Pepeu, 2005), which is the last kinase in the MAPK pathway (RAF➔MEK➔ERK). Given that MAPK signaling is critical for fear memory consolidation (Cammarota, Bevilaqua, Ardenghi, Paratcha, Levi de Stein, Izquierdo, and Medina, 2000; Schafe, Atkins, Swank, Bauer, Sweatt, and LeDoux, 2000; Schafe and LeDoux, 2000; Schafe, Nadel, Sullivan, Harris, and LeDoux, 1999; Walz, Roesler, Quevedo, Sant'Anna, Madruga, Rodrigues, Gottfried, Medina, and Izquierdo, 2000) these findings raise the possibility that during contextual and trace fear conditioning, mAChR activation in the dHipp leads to enhanced MAPK signaling, which then contributes to neural plasticity in the dHipp critical for contextual and trace fear memory. However, mechanisms by which mAChR activation leads to enhanced MAPK signaling during contextual (and possibly trace) fear memory formation remain undefined.

MS/DBB cholinergic input to dHipp nAChRs also contribute to contextual and trace fear memory (Davis and Gould, 2007; Davis et al., 2007; Kenney et al., 2012; Marti Barros et al., 2004; Parfitt et al., 2012; Raybuck and Gould, 2010) and this could occur via increased conductance of Ca^{2+} currents upon nAChR activation. Sustained depolarization of the neuronal membrane leading to enhanced Ca^{2+} entry into the neuron is believed to trigger a number of events that are critical for neural plasticity that mediates fear memory (Bauer et al., 2002; Davis, 1992a; Davis and Whalen, 2001; Pare et al., 2004). MS/DBB cholinergic input to nAChRs during contextual and trace fear memory formation could enhance Ca^{2+} conductance in dHipp neurons, which drives plasticity critical for both types of fear memory. This hypothesis is consistent with the observation that the subunit composition of nAChRs in the dHipp (α7 and β4 subunits) allows for relatively specific conductance of Ca^{2+} currents (Marks et al., 1989; Seguela et al., 1993).

Tronson et al., observed that MS/DBB cholinergic lesions disrupted increases in ERK phosphorylation in CA1 during contextual fear extinction training, which raises the possibility that cholinergic input to CA1 mediates contextual extinction memory via MAPK signaling, though it is not clear if this is initiated by mAChR or nAChR activation. Similar to what was observed for BF amygdalopetal cholinergic neurons, it would appear that the same signaling pathway initiated by AChR activation facilitates contextual fear and extinction memory. As mentioned previously, a difference between fear conditioning and extinction training is levels of arousal/stress, and this could serve as a discriminating signal for cholinergic input to the dHipp. High levels of arousal/stress could bias AChRs in the dHipp

to facilitate plasticity critical for contextual and trace fear memory, but low levels of arousal/stress could then bias these receptors to facilitate plasticity critical for contextual extinction memory. Of course, further research is needed to test this hypothesis.

MS/DBB cholinergic lesions disrupt contextual fear memory discrimination (Knox and Keller, 2015), and this effect may be linked to cued extinction memory deficits induced by MS/DBB cholinergic lesions. Formation of distinct ensemble of neurons that respond to and represent specific contexts within the dHipp is critical for pattern separation and discriminating one spatial context from another (Frankland, Cestari, Filipkowski, McDonald, and Silva, 1998; Guzowski, Knierim, and Moser, 2004; McHugh, Jones, Quinn, Balthasar, Coppari, Elmquist, Lowell, Fanselow, Wilson, and Tonegawa, 2007). MS/DBB cholinergic lesions have no effect on place field formation in the dHipp, but inhibit place field re-organization when a rat is moved from a familiar context to a novel context (Ikonen et al., 2002). This raises the possibility that MS/DBB cholinergic neurons may facilitate contextual fear memory discrimination by facilitating the formation of ensembles of neurons in the dHipp that represent distinct contexts. Because fear conditioning always precedes extinction training, deficits in discriminating the fear and extinction contexts could lead to enhanced representation of the fear context. If the fear generated from this contextual representation was resistant to extinction (i.e. deficit in contextual fear memory discrimination and contextual fear extinction), then persistent contextual fear expression would occur, which would then prime cued fear expression (i.e. disrupt cued extinction memory) (Bouton et al., 2006).

Another mechanism via which MS/DBB cholinergic neurons may facilitate extinction memory is via a feedforward positive loop with IL neurons. Previous studies suggest that PFC input to BF cholinergic neurons can drive increased ACh release in the PFC and other neocortical regions (Nelson, Sarter, and Bruno, 2005; Sarter, Hasselmo, Bruno, and Givens, 2005) and this mechanism is believed to be important for attentional processing (Nelson et al., 2005; Parikh, Kozak, Martinez, and Sarter, 2007; Sarter et al., 2005; Zaborszky et al., 1999). Thus, PFC neurons (in particular in the IL and possibly PL) could drive MS/DBB cholinergic neurons to secrete ACh in the dHipp, RSC, and mPFC. In turn, this enhancement in ACh may facilitate formation of contextual memory and neural plasticity critical for extinction memory. Consistent with this hypothesis, mAChR antagonism in the IL disrupts extinction memory formation (Santini et al., 2012). However, more research is needed to explicitly test the hypothesis that MS/DBB cholinergic neurons facilitate extinction memory via a feedforward excitatory loop with neurons in the mPFC. This is particularly so, because mPFC stimulation results in complex single unit responses in BF cholinergic neurons and mPFC neurons do not make direct synapses with BF cholinergic neurons (Gyengesi, Zaborszky, and Detari, 2008). Neurobiological mechanisms via which MS/DBB cholinergic neurons could facilitate fear and extinction memory are illustrated in Figure 5.

5. Clinical Relevance

The finding that BF cholinergic neurons are critical for fear and extinction memory may have relevance to anxiety disorders in humans. Changes in fear and extinction memory have been implicated in post traumatic stress disorder (PTSD) and specific phobia (Milad et al.,

2006; Pitman, Sanders, Zusman, Healy, Cheema, Lasko, Cahill, and Orr, 2002; Quirk et al., 2006; Rothbaum and Davis, 2003). Neuroscience theories posit that PTSD can stem from enhanced fear conditionability (Rothbaum and Davis, 2003) and/or deficits in extinction memory (Milad et al., 2006; Pitman et al., 2002; Quirk et al., 2006; Quirk et al., 2010), while persistent fear in specific phobia may stem from deficits in extinction memory (Hofmann, Pollack, and Otto, 2006). It may be possible to enhance extinction-based therapies (e.g. exposure therapy, cognitive behavioral therapy) by targeting BF cholinergic systems. Because a number of drugs that increase ACh levels already exist and are in current clinical use, this line of research has high translational value and could have a significant impact on how excessive fear is treated in anxiety disorders such as specific phobia and PTSD.

6. Conclusion

Previous studies that have used a variety of experimental methods (e.g. pharmacological manipulation, selection lesion, direct measurements of acetylcholine in restricted brain regions, optogenetic stimulation) in a number of different behavioral paradigms (e.g. Pavlovian fear conditioning and IA) suggest that BF cholinergic neurons can facilitate fear and extinction memory. However, we still do not have a sufficiently comprehensive understanding of how BF cholinergic neurons modulate these mnemonic processes. In particular, identification of neural circuitry by which clusters of BF cholinergic neurons modulate fear and extinction memory remains undefined. Teasing apart the neural circuitry via which BF cholinergic neurons contribute to fear and extinction memory can be greatly facilitated by optogenetics, since the technology to use light to selectively stimulate or inhibit BF cholinergic efferents in target brain regions (e.g. dHipp vs. RSC) exist (Brown, Tan, O'Connor, Nikonenko, Muller, and Luscher, 2012; Hersman and Fanselow, 2015; Jiang et al., 2016; Unal et al., 2015). In spite of these gaps in knowledge, research conducted to date has demonstrated that BF cholinergic neurons are critical for mediating fear and extinction memory.

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Highlights

- BF cholinergic neurons are critical for emotional memory
- Different BF cholinergic neuronal clusters have different roles in emotional memory
- BF cholinergic function in emotional memory changes with behavioral paradigm
- BF cholinergic neurons are a critical component of emotional memory systems

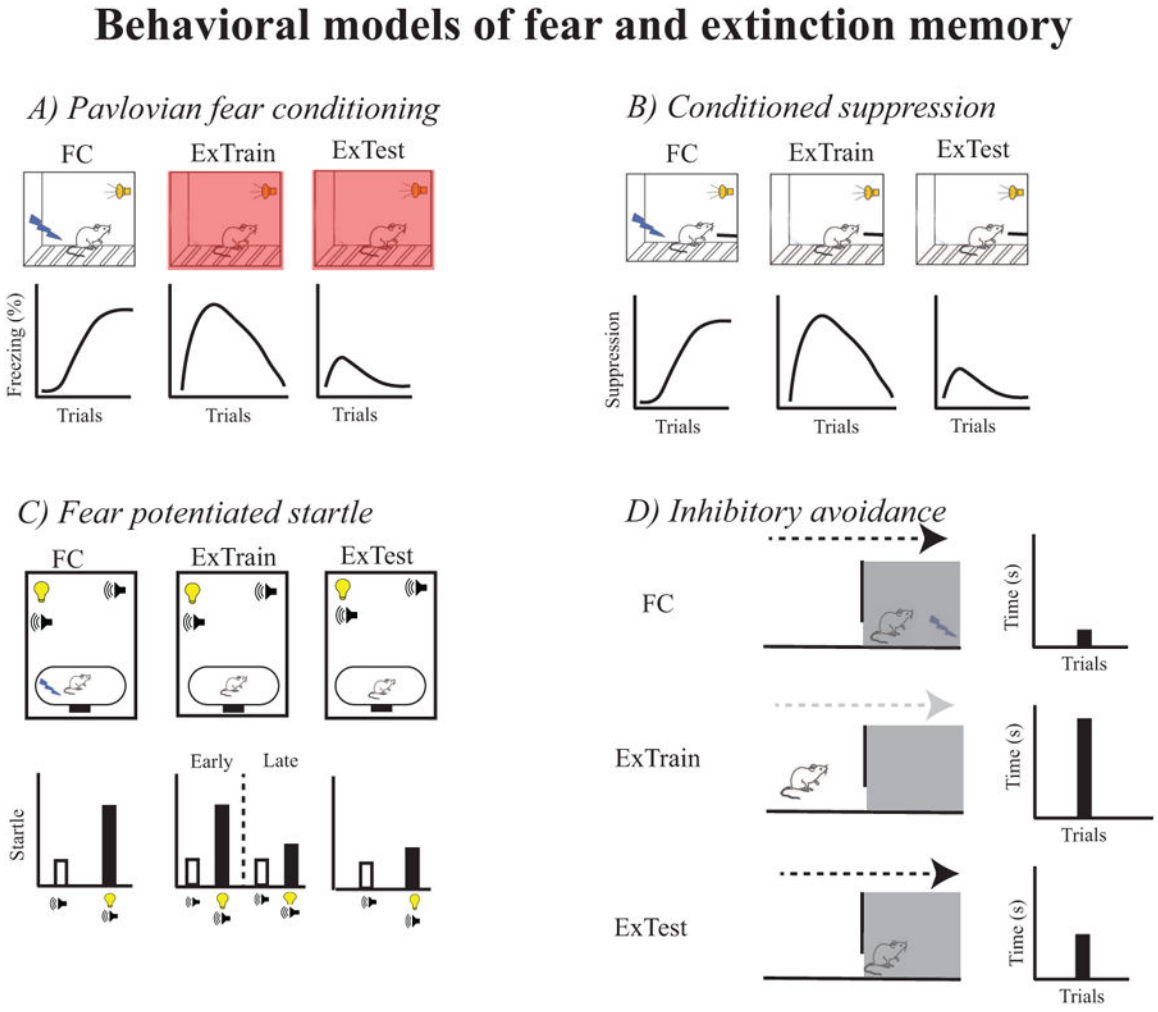

Figure 1.

Behavioral paradigms used to examine emotional memory (fear and extinction) in neuroscience experiments. Cartoons illustrate the paradigm and graphs adjacent to the cartoons illustrate the change in fear behavior during fear conditioning (FC), extinction training (ExTrain), and extinction testing (ExTest). A) Pavlovian fear conditioning. Freezing is used as the measure of fear in this paradigm. Often the conditioning and extinction contexts are different in this paradigm (represented by change in color), which can allow for separate measurement of cued and contextual fear and extinction memory. B) Conditioned fear suppression. In this paradigm, changes in operant performance are used as the measure of fear behavior, but a context shift is not typically used. C) Fear potentiated startle. This paradigm involves presentation of a white noise burst to elicit a startle reflex, which is typically measured by an accelerometer that transduces movement into an electrical signal. During conditioning and in the presence of the conditioned stimulus (CS) the startle reflex is enhanced. D) Inhibitory avoidance. This paradigm involves placing the animal in a light compartment that is connected to a dark compartment. Upon entering the dark compartment the animal then receives a footshock. Avoidance of the dark compartment after conditioning is the measure of fear behavior.

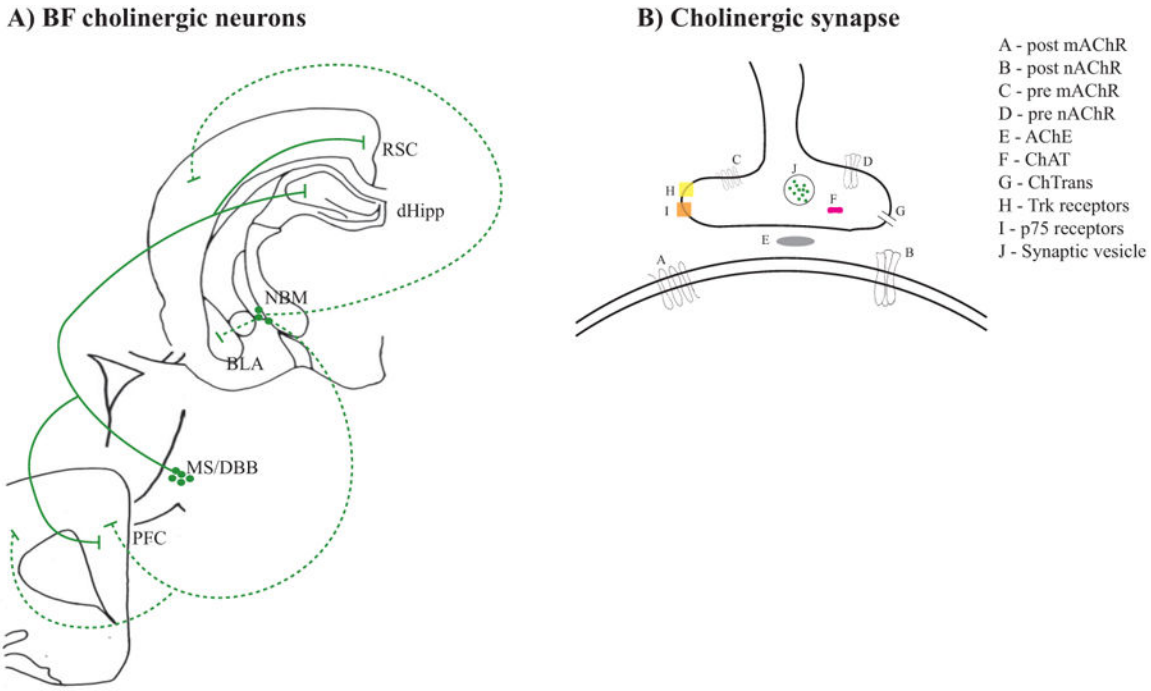

Figure 2.

A) Schematic of the basal forebrain (BF) cholinergic neurons that project to fear and extinction circuits. BF neurons in the preoptic area are not being shown, because these neurons are rarely manipulated in studies that examine the effects of BF cholinergic manipulation on fear and extinction memory. NBM neurons are showed in dashed lines while MS/DBB neurons are showed in solid lines. B) Summarized schematic of the cholinergic synapse in fear and extinction circuits. Post and pre prefixes refer to whether receptors are pre or post synaptic. ChTrans – choline transporter,

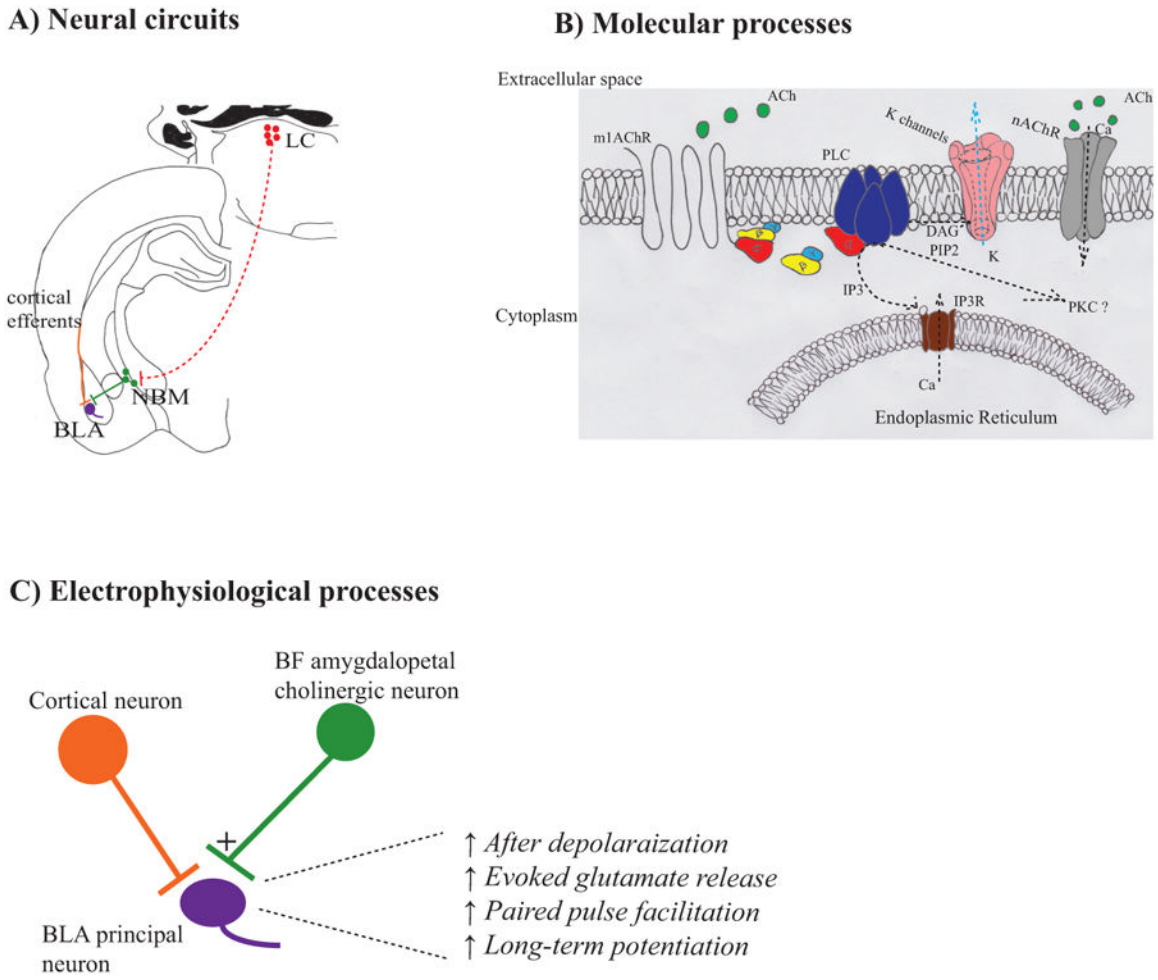

Figure 3.

Neurobiological processes via which BF amygdalopetal cholinergic neurons modulate emotional memory. A) Hypothetical circuit. Circles in red illustrate locus coeruleus neurons, green represent BF amygdalopetal cholinergic neurons, purple represent BLA principal neurons, and orange represent cortical input to BLA principal neurons. Components of the circuit that need verification are shown in dashed lines. B) Molecular processes by which BF amygdalopetal cholinergic neurons modulate emotional memory. Unknown mechanisms are shown as question marks or dashed lines. Decreased signaling is indicated by light blue arrows. C) Fear relevant electrophysiological processes by which BF amygdalopetal cholinergic neurons modulate BLA principal neurons. LC – locus coeruleus. m1AChR – muscarinic receptor type 1, nAChR – nicotinic receptor, IP3 – inositol triphosphate, IP3R – IP3 receptor, DAG – diacylglycerol, PIP2 – phosphatidylinositol biphosphate, PKC – protein kinase C.

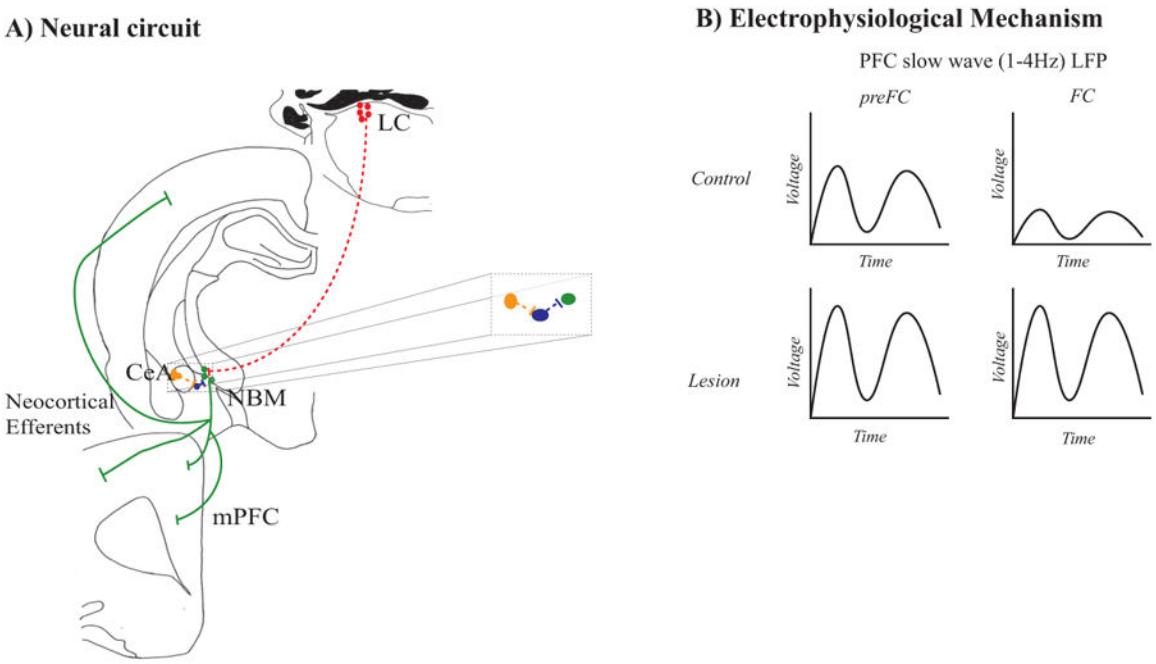

Figure 4.

Neurobiological processes via which NBM corticopetal cholinergic neurons modulate emotional memory. A) Neural circuits. NBM cholinergic neurons are in green, LC neurons are in red, central amygdala (CeA) neurons are in yellow, and NBM GABAergic neurons are in purple. Components of the neural circuit that need verification are shown in dashed lines. B) Electrophysiological mechanisms. NBM corticoptal cholinergic input to the PFC increases the slow-wave components (1-4Hz) of the PFC local field potential (LFP) and may disrupt decreases in slow wave PFC LFP during fear conditioning. These effects may mediate the disruptive effect NBM corticopetal cholinergic lesions have on fear memory in the conditioned suppression paradigm. preFC – pre fear conditioning.

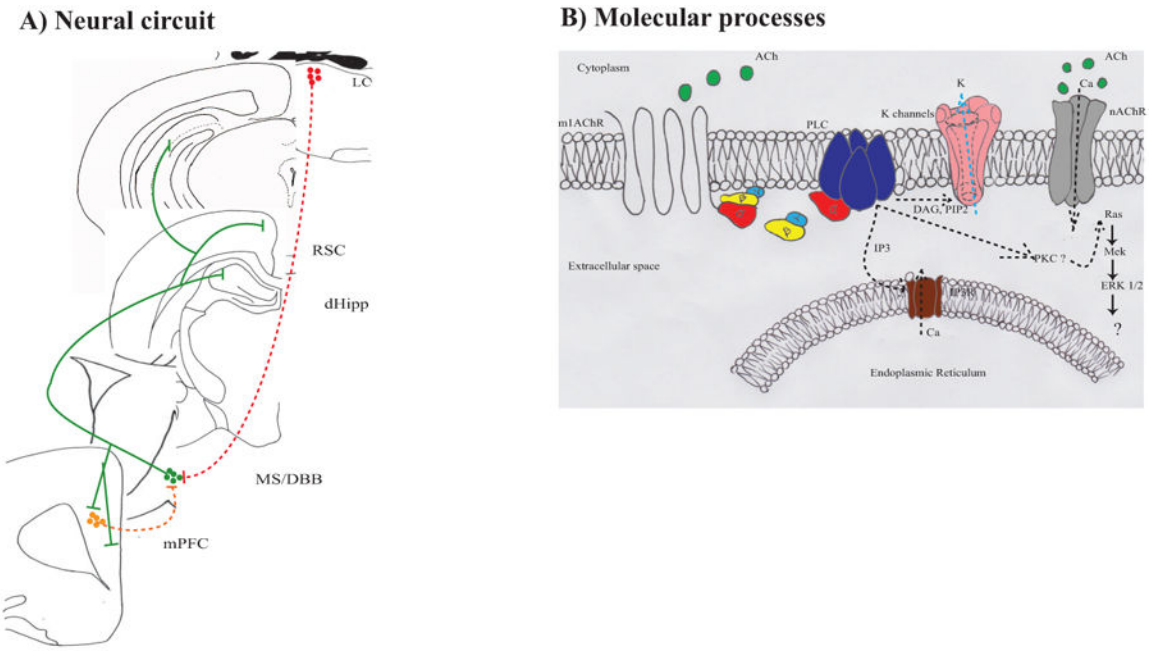

Figure 5.

Neurobiological processes via which MS/DBB cholinergic neurons modulate emotional memory. A) Hypothetical circuit. Components of the circuit that need verification are shown in dashed lines. B) Molecular processes by which MS/DBB cholinergic neurons modulate emotional memory. Unknown mechanisms are shown as question marks or dashed lines. Decreased signaling is indicated by light blue arrows.