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The role of working memory and declarative memory in trace conditioning

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Abstract

Translational assays of cognition that are similarly implemented in both lower and higher-order species, such as rodents and primates, provide a means to reconcile preclinical modeling of psychiatric neuropathology and clinical research. To this end, Pavlovian conditioning has provided a useful tool for investigating cognitive processes in both lab animal models and humans. This review focuses on trace conditioning, a form of Pavlovian conditioning typified by the insertion of a temporal gap (i.e., trace interval) between presentations of a conditioned stimulus (CS) and an unconditioned stimulus (US). This review aims to discuss pre-clinical and clinical work investigating the mnemonic processes recruited for trace conditioning. Much work suggests that trace conditioning involves unique neurocognitive mechanisms to facilitate formation of trace memories in contrast to standard Pavlovian conditioning. For example, the hippocampus and prefrontal cortex (PFC) appear to play critical roles in trace conditioning. Moreover, cognitive mechanistic accounts in human studies suggest that working memory and declarative memory processes are engaged to facilitate formation of trace memories. The aim of this review is to integrate cognitive and neurobiological accounts of trace conditioning from preclinical and clinical studies to examine involvement of working and declarative memory.

Keywords

Trace conditioning; Pavlovian; Working memory; Declarative memory; Hippocampus; Medial prefrontal cortex

1. Introduction

Translational assays of cognition are useful for bridging the gap between preclinical modeling of psychiatric neuropathology and clinical research. Indeed, behavioral-cognitive assays that are readily implemented in both lower animal species and also humans have the potential to facilitate fundamental cellular/molecular/genetic investigations, as well as systems level analysis of cognition and functional neuroanatomy within humans. To this end, Pavlovian associative learning has proved to be a fruitful tool for investigating basic

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cognitive processes in both laboratory animal and human studies (Delgado, Olsson, & Phelps, 2006; Maren, 2005; Rescorla, 1988; Woodruff-Pak, 2001).

An important aspect of Pavlovian associative learning is that it can be implemented in alternative ways such that the neural substrates that mediate learning are different. A commonly implemented “cued” form of conditioning, delay conditioning has been used to model implicit memory processes (Squire & Zola, 1996; Woodruff-Pak, 1993). During delay conditioning, a conditioned stimulus (CS) is presented, and after a delay, an overlapping unconditioned stimulus (US) is presented with both stimuli co-terminating. Interestingly, a slight modification to the temporal organization of the CS and US during conditioning results in a dramatic shift in the neural substrates that are recruited. More specifically, trace conditioning is typified by the insertion of a temporal gap, or trace interval, between presentation of a CS and US (Fig. 1). Initially noted by Pavlov, the insertion of a trace interval between CS and US presentations alters the strength of the association and as the length of the trace period increases, conditioned responding (CR) decreases (Pavlov, 1927). Additionally, trace conditioning requires an increased number of trials for CR learning to occur compared to delay conditioning (Beylin et al., 2001). Thus, while delay and trace conditioning result in a similar behavioral output indicating formation of a CS-US associative memory, they appear to engage different learning mechanisms in the formation of the CS-US association.

This review aims to discuss clinical and pre-clinical work investigating the mnemonic processes, specifically working memory and declarative memory, that may be recruited for trace conditioning. This review will limit its scope to discussing the role of the prefrontal cortex (PFC) and the hippocampus as both of these regions appear necessary for working memory and declarative memory, respectively (Baddeley & Warrington, 1970; Bechara et al., 1995; Brito, Thomas, Davis, & Gingold, 1982). However, the boundaries of this review are not meant to suggest that other cortical or subcortical regions are not functionally involved in these memory processes or trace conditioning more generally. In sum, this literature review seeks to examine behavioral and neurobiological overlap between trace conditioning and the memory domains of working and declarative memory, which is critical for understanding the translational value of trace conditioning.

A number of excellent reviews have discussed trace conditioning, but have tended to focus on either specific brain regions, such as the hippocampus (Shors, 2004) or PFC (Weiss & Disterhoft, 2011), or address literature in a paradigm specific fashion, i.e., trace fear (Gilmartin, Balderston, & Helmstetter, 2014; Raybuck & Lattal, 2014) or trace eyeblink conditioning (Christian & Thompson, 2003; Woodruff-Pak & Disterhoft, 2008). Thus, an important goal of this review is to integrate data from both fear and eyeblink domains and assess evidence that trace conditioning uniquely engages a set of learning processes, working and declarative memory. This discussion is important as it is now clear that hippocampal and PFC memory systems interact to support working memory and declarative memory (Godsil, Kiss, Spedding, & Jay, 2013; Preston & Eichenbaum, 2013; Sigurdsson & Duvarci, 2016). As such, trace conditioning may be an ideal assay to assess learning that recruits PFC/working memory and hippocampus/declarative circuitry. Therefore, determining the construct validity of trace conditioning is vital to its usefulness in modeling

complex cognition dependent on multiple neurobiological memory systems. All of which may be particularly useful, as psychiatric disorders become clustered by common dysregulated behavioral/cognitive outputs (Lapiz-Bluhm et al., 2008; Morilak & Frazer, 2004). Indeed, clustering by neuropsychological parameters, such as aspects of cognition or well-conserved neurobiological memory systems, necessitates understanding the overlap between pre-clinical *in vivo* behavioral assay read-outs and human cognitive measures.

1.1. Fear and eyeblink conditioning

Two forms of Pavlovian conditioning, fear and eyeblink conditioning, have been the most frequently examined in the field of neuroscience. During fear conditioning, the cue and/or context becomes associated with an aversive stimulus. When, a subject is re-exposed to a fear associated CS, the CS elicits a fear response that can be measured by startle magnitude, heart rate, or freezing behavior. Similarly, eyeblink conditioning involves an association between a US that elicits an eyeblink reflex and a CS, leading to eyeblink CR. Both fear and eyeblink conditioning have allowed for detailed analysis of underlying learning circuitry in animal models, while providing useful translational value in human studies.

1.1.1. Essential fear circuitry—Early non-human studies showed that the amygdala is a region critical for emotional processing, as amygdala lesions in rodents and primates result in decreased emotional responsiveness and increased passiveness (Goddard, 1964). Building upon this work, it has become well established that the amygdala is important for innate, as well as conditioned fear (Caroline & Blanchard, 1972; Davis, 1992; LeDoux, Cicchetti, Xagoraris, & Romanski, 1990). Specifically, CS and US information pathways converge on the lateral amygdala, where consolidation occurs for delay and trace fear memories (Bailey, Kim, Sun, Thompson, & Helmstetter, 1999; Kwapis, Jarome, Schiff, & Helmstetter, 2011; Romanski, Clugnet, Bordi, & LeDoux, 1993). Similarly, human imaging has observed activation of the amygdala during implicit and explicit fear learning paradigms (Knight, Waters, & Bandettini, 2009; Morris, Öhman, & Dolan, 1998). Work with rats showed that the lateral amygdala receives sensory information via the thalamus (LeDoux, Farb, & Ruggiero, 1990) and lesions of the medial geniculate nucleus disrupts auditory delay fear conditioning (LeDoux, Sakaguchi, Iwata, & Reis, 1986). Similarly, humans show increased thalamic activation during trace and delay fear conditioning (Knight, Cheng, Smith, Stein, & Helmstetter, 2004). These findings outline a basic fear learning circuit, necessary for delay fear conditioning, in which sensory information is sent from thalamus to amygdala where a CS-US association is consolidated. In turn, the amygdala projects to the hypothalamus and brain stem areas, regions implicated in expression of fear and anxiety (Davis, 1992; Krettek & Price, 1978).

1.1.2. Essential eyeblink circuitry—A large volume of pre-clinical data has elaborated the brain regions necessary for eyeblink conditioning, including the thalamus, pontine nucleus and cerebellum (Christian & Thompson, 2003; Gould, Sears, & Steinmetz, 1993; Halverson, Poremba, & Freeman, 2008; Steinmetz, Rosen, Chapman, Lavond, & Thompson, 1986; Thompson, 1986). Similar to the role that the amygdala plays in fear conditioning, the cerebellum is necessary for consolidation and expression of eyeblink conditioning (Gould & Steinmetz, 1996; McCormick & Thompson, 1984; Steinmetz et al., 1986; Woodruff-Pak,

Lavond, & Thompson, 1985). Pre-clinical work from rabbits and rodents has been critical in identifying essential eyeblink circuitry. During delay eyeblink conditioning, CS sensory information is sent from the thalamus to pontine nuclei (Halverson et al., 2008). Similarly, humans show delay eyeblink learning-related thalamic activity (Blaxton et al., 1996). In turn, pontine nuclei send CS information via mossy fiber inputs to the cerebellum, which also receives US information via climbing fibers from inferior olive (Gould et al., 1993). CS and US information converge within the interpositus nucleus of the cerebellum where critical plasticity occurs (Steinmetz et al., 1986). Imaging work in humans supports these data, showing increased cerebellar response in both delay and trace eyeblink conditioning (Cheng, Disterhoft, Power, Ellis, & Desmond, 2008).

1.1.3. Common trace circuitry—As described above, both fear and eyeblink circuitry involve convergence of CS and US pathways in the amygdala or cerebellum, respectively. Thus, these circuits are sufficient when CS and US signals temporally overlap during delay conditioning. However, during trace conditioning, CS and US information does not overlap, thus additional circuits are engaged to bridge the interval and facilitate formation of a CS-US association. Thus, while delay fear and eyeblink conditioning are dependent on different brain regions, trace forms of both fear and eyeblink paradigms similarly recruit PFC and hippocampus to facilitate learning (Fig. 2). Lesions of the hippocampus have no effect on acquisition of delay conditioning (Phillips & LeDoux, 1992; Schmaltz & Theios, 1972). In contrast, lesions of the hippocampus result in robust deficits in trace fear and eyeblink acquisition (McEchron, Bouwmeester, Tseng, Weiss, & Disterhoft, 1998; Solomon, Vander Schaaf, Thompson, & Weisz, 1986). Similarly, lesions or inactivation of the PFC can disrupt trace, but not delay fear or eyeblink conditioning (Corcoran & Quirk, 2007; Gilmartin & Helmstetter, 2010; Morgan & LeDoux, 1995; Weible, McEchron, & Disterhoft, 2000). Human imaging from trace fear and eyeblink studies supports pre-clinical data, with increased activation of the PFC and hippocampus (Cheng et al., 2008; Haritha, Wood, Hoef, & Knight, 2012; Knight et al., 2004). Therefore, this review aims to integrate data from trace fear and eyeblink paradigms, because while differences exist between these two paradigms, fundamental attributes of trace conditioning appear conserved. Moreover, such conservation suggests that trace conditioning is mediated by a unique set of learning rules and processes.

2. Working memory and trace conditioning

Pavlov initially suggested that formation of an association between the CS and US during trace conditioning depends upon a persistent neural representation of the CS across the trace interval (Pavlov, 1927). The “trace hypothesis” follows from the theoretical perspective that contiguity is highly important for associative learning, and therefore overlap between a CS memory trace and the US is essential for trace conditioning (Gormezano, Kehoe, & Marshall, 1982). In support, increasing the length of the trace interval leads to decreased trace fear conditioning, indicating that the CS memory trace may be strongest immediately after its termination and tapers off over time (Kamin, 1961). Interestingly, decrements in trace conditioning due to increased trace interval length are similar to performance decrements in delayed match-to-sample, an assay that also implements a temporal gap. In delayed match-to-sample a subject is presented with a sample stimulus, and after temporal

interval, the subject is required to select an identical match from an additional set of stimuli. Critically, as the temporal interval between sample and match increases, task performance decreases (Penetar & McDonough, 1983). The ability to retain information about the sample stimulus across the delay period is understood as a critical component of working memory (Goldman-Rakic, 1995). This suggests that working memory may similarly be important to provide a bridging signal or encode CS-related information during the trace interval facilitating contiguity (Clark, Manns, & Squire, 2002; Kalmbach, Ohyama, Kreider, Riusech, & Mauk, 2009).

To be clear, a learning theory of contiguity is not sufficient to explain all aspects of conditioning (Rescorla, 1988). For example, trace autoshaping performance in pigeons was decreased when the interval between the offset of the US and the onset of the next trial, the intertrial interval, was close in time irrespective of trace interval (Balsam, 1984). Thus, trace conditioning depends upon the relative proximity of the CS and US within the temporal context of the training session. (Balsam, 1984; Kaplan, 1985). As a result, trace conditioning paradigms are optimized for robust learning with short trace intervals and sufficiently long intervals between trials (Shors, 2004). In addition, numerous studies have shown that insertion of an additional “gap filling” stimulus within the trace interval facilitates trace conditioning (Bolles, Collier, Bouton, & Marlin, 1978; Kamin, 1965; Kaplan, 1984; Rescorla, 1982). One way a gap filling stimulus may facilitate trace conditioning is via second-order serial conditioning in which the CS is associated with the gap filling stimulus, which is associated with the US, or by changes in contextual learning (Rescorla, 1982; Shors, 2004). Interestingly, a cue inserted throughout the entire trace interval facilitates learning to a greater degree than presentation during only half of the temporal interval (Rescorla, 1982), possibly suggesting gap filling cues might to some degree facilitate learning by altering the perception of CS-US contiguity.

Working memory has been defined as a cognitive mechanism for short-term storage, processing, and manipulation of information (Baddeley, 1992). For example, in a classic rodent spatial working memory task, the radial 8-arm maze, a correct choice depends upon not repeating a previous selection after a temporal interval (Olton, Collison, & Werz, 1977; Olton & Samuelson, 1976). Thus, working memory can be viewed as an active memory buffer in which information is temporarily kept “online” over short periods of time to facilitate adaptive responding to new information. Such a buffer would hypothetically be ideal to mediate a bridging signal during trace conditioning. Indeed, a number of computational models of trace learning incorporate working memory-like storage buffer modules to model formation of trace CS-US associations (Kryukov, 2012; Larrauri & Schmajuk, 2008; Rivest, Kalaska, & Bengio, 2009). Further, as will be discussed in detail in Section 2.2, overlap exists in the prefrontal neural substrates involved in both trace conditioning and working memory (Gilmartin & McEchron, 2005a, 2005b; Knight et al., 2004, 2009), and manipulations of working memory alter trace conditioning (Carter, Hofstötter, Tsuchiya, & Koch, 2003). Therefore, working memory may play an important role in trace conditioning by maintaining a representation of the CS across the trace interval.

2.1. Working memory and the PFC

The PFC has long been implicated higher-order cognitive function, including working memory processes (Jacobsen & Nissen, 1937). Indeed, early work with primates showed that the PFC mediates working memory via sustained neural activity, which has been observed during temporal intervals in delay alternation tasks (Compte et al., 2003; Fuster & Alexander, 1971). As a result, the PFC has been a region of intense research in both human and non-human animal models of working memory. Functional and anatomical evidence overwhelmingly suggests that prefrontal cortical regions, in both primates and lower species, play a critical role in working memory. However, there has been debate regarding the homology of the primate PFC and prefrontal regions of lower species, such as in rodents (Seamans, Lapish, & Durstewitz, 2008; Uylings, Groenewegen, & Kolb, 2003; Vogt & Paxinos, 2012; Wise, 2008). Of particular importance, the primate PFC is typified by a granular region, including the dorsolateral PFC (dlPFC), which is involved in working memory and executive function (Preuss, 1995; Wise, 2008). As such, dlPFC activation is a neural correlate for working memory processes in primates (Curtis & D'Esposito, 2003; Manoach et al., 1997). In contrast, non-primate animals have a relatively less developed frontal cortex that lacks a direct homologue to the primate dlPFC. However, both the primate PFC and non-primate medial prefrontal cortex (mPFC) receive mediodorsal thalamic inputs (Uylings et al., 2003), and functional and anatomical data suggest that the mPFC may serve many similar functions as the primate PFC, including working memory processes (Godsil et al., 2013; Uylings et al., 2003; Vertes, 2004).

The mPFC in non-primates is important for working memory function, as well as other higher order cognitive processes, such as decision making and emotional control (Euston, Gruber, & McNaughton, 2012; Morgan & LeDoux, 1995; Uylings et al., 2003; Walton, Bannerman, & Rushworth, 2002). Similar to the primate PFC, the rodent mPFC is implicated in sustained working memory-related neural activity (Chang, Chen, Luo, Shi, & Woodward, 2002; Wang, 2001); thus the mPFC could support trace conditioning by maintaining a representation of the CS across the trace interval. For example, prior work has found that neurons within the mPFC of rats exhibited persistent firing during the delay between choice and reward outcomes in a spatial alternation task (Horst & Laubach, 2012). These findings suggest that neurons within mPFC are intrinsically capable of facilitating learning when events are temporally separated. Thus, sustained firing of mPFC neurons during the trace interval could support working memory processes that facilitate formation of CS-US trace associations.

2.1.1. Trace conditioning recruits neural activity within the PFC consistent with working memory processing—

Rodent and rabbit investigations of trace conditioning have demonstrated sustained firing in the mPFC during trace learning (Takehara-Nishiuchi & McNaughton, 2008) and, importantly, during the trace interval (Fig. 3) (Gilmartin & McEchron, 2005b; Siegel, Kalmbach, Chitwood, & Mauk, 2012). For example, one study found that during a trace fear conditioning procedure, 30% of cells sampled in the mPFC showed sustained firing during a 2 s trace interval, and a subset of “delay cells” increased firing during the trace interval (Baeg et al., 2001). Moreover, a persistent increase in mPFC activity after CS presentation during trace eyeblink conditioning

has been demonstrated as well (Siegel & Mauk, 2013). In compliment to these pre-clinical findings, human fear conditioning work has found increased BOLD response during the trace interval within the PFC (Haritha et al., 2012; Knight et al., 2004). In contrast to these data, cells recorded from the hippocampus in rats have not shown similar trace interval sustained firing, suggesting that the PFC provides a unique trace interval working memory signal (Gilmartin & McEchron, 2005a; Green & Arenos, 2007). Importantly, anatomical work in rodents and rabbits demonstrates that the mPFC projects to both the pontine nuclei, a brain stem region critical for eyeblink conditioning that projects to the cerebellum (Gould et al., 1993; Siegel et al., 2012), and the amygdala (Buchanan, Thompson, Maxwell, & Powell, 1994), a subcortical structure critical for fear conditioning (McDonald, 1998). Thus, the PFC may not only maintain a representation of the CS across the trace interval, but may relay sustained CS information to critical neural substrates for fear and eyeblink conditioning.

A number of findings also indicate learning related changes in neural activity in the PFC of human and rodents during delay fear conditioning (Baeg et al., 2001; Furlong, Cole, Hamlin, & McNally, 2010; Gilmartin et al., 2014; Knight, Smith, Stein, & Helmstetter, 1999; Knight et al., 2004). For example, single unit recordings of cells in the mPFC of rats found that a majority of cells showed learning related changes in firing to the CS (Baeg et al., 2001). Interestingly, Baeg et al. (2001) found that a subset of cells increased firing from the onset of the delay CS until the expected US timepoint. Therefore, some mPFC cells may process temporal information related to delay CS-US presentations during delay conditioning. Such findings from delay fear conditioning are unsurprising for two reasons. First, the PFC is responsive to emotionally relevant stimuli (Ono, Nishino, Fukuda, Sasaki, & Nishijo, 1984) and therefore might not necessarily differentiate a delay CS from a trace CS. Second, evidence suggests that the PFC is highly involved in fear expression and inhibition (Gilmartin et al., 2014; Sierra-Mercado, Padilla-Coreano, & Quirk, 2011). Thus, changes in firing in response to the CS may indicate CR related processing. For example sustained firing within the rat mPFC was correlated with freezing behavior (Burgos-Robles, Vidal-Gonzalez, & Quirk, 2009).

2.1.2. Prelimbic region is involved in acquisition of trace conditioning—The mPFC is divisible along the dorsal/ventral axis, with the dorsal medial regions, including the prelimbic region (PL), important for cognitive behaviors including working memory (Euston et al., 2012; Heidbreder & Groenewegen, 2003; Vertes, 2004). In contrast, the infralimbic region (IL) is more closely associated with fear and behavioral inhibition (Peters, Kalivas, & Quirk, 2009). Similarly, during trace fear conditioning, single unit recordings from PL showed sustained increased firing during the trace interval (Gilmartin & McEchron, 2005b), but not in the ventral IL. Much work suggests that the PL is engaged by trace conditioning, as pre-training pharmacological inactivation of the PL disrupts trace, but not delay fear conditioning (Corcoran & Quirk, 2007; Gilmartin & Helmstetter, 2010). Similarly, lesions of the PL retarded acquisition of trace, but not delay eyeblink conditioning (McLaughlin, Skaggs, Churchwell, & Powell, 2002). In addition, optogenetic silencing of PL neurons during the trace interval disrupted trace fear conditioning (Gilmartin, Miyawaki, Helmstetter, & Diba, 2013). However, the specificity of the role of PL in trace vs. delay fear

conditioning is complicated, as the PL projects to the basal nucleus of the amygdala and is important for fear expression (Peters et al., 2009; Sierra-Mercado et al., 2011). In support, other rodent work has found that delay conditioning induced increased levels of c-fos within the PL, indicating changes related to CS expectancy (Furlong et al., 2010). These data may suggest that the PL is normally engaged during fear learning, but is only necessary during trace. However, specific blockade of PL NR2A containing NMDA receptors disrupted both delay and trace fear conditioning, but blockade of PL NR2B containing receptors resulted in trace specific disruption (Gilmartin, Kwapis, & Helmstetter, 2013). Therefore, delineation between the role the PL plays in trace vs. delay fear conditioning may rest on differentiating two processes, working memory and fear expression, co-mediated by the PL. Interestingly, optogenetic inactivation during the CS+trace interval or trace interval did not alter freezing during training, but did result in a recall deficit (Gilmartin, Miyawaki, et al., 2013), indicating that these are dissociable processes. Further, it has been suggested that because prefrontal NR2B containing NMDARs are necessary for working memory and confer a wider activation window, they may be specifically involved in working memory processes necessary for trace conditioning (Gilmartin et al., 2014). In total, these results indicate the PL may be important for multiple aspects of delay and trace fear conditioning including working memory and fear expression. However, PL NR2B-containing neurons may contribute to working-memory involvement in acquisition of trace fear conditioning.

In short, clinical and pre-clinical evidence show that the PFC is functionally recruited in a fashion consistent with a working memory role during acquisition of trace conditioning (Table 1). That is to say, by maintaining sustained activation during the trace interval, the PFC may support trace conditioning via working memory-like processes across the trace interval. These findings contrast with some theoretical accounts that suggest the hippocampus maintains a representation of the CS via recurrent loops during trace conditioning (Moustafa et al., 2013; Rodriguez & Levy, 2001). Interestingly, the mPFC, (PL and IL) is directly innervated by neurons originating in the VH (Hoover & Vertes, 2007) and these projections appear to be involved in modulating hippocampal-PFC theta coupling during working memory (O'Neill, Gordon, & Sigurdsson, 2013). Therefore, the PFC and hippocampus may interact to engage trace interval working memory. In addition, the PFC projects to subcortical structures critical for fear and eyeblink conditioning, respectively the amygdala and cerebellum. Thus, the PFC is well placed to provide sustained CS information to these substrates, facilitating an association with a temporally discontinuous US.

2.2. Disruptions of working memory impact trace conditioning

Behavioral work in humans indicates that trace conditioning is highly sensitive to changes in working memory cognitive load, with increasing load resulting in disruptions in trace conditioning (Carter et al., 2003). To probe working memory the n-back task has been used because it robustly recruits the PFC, including the dlPFC (Owen, McMillan, Laird, & Bullmore, 2005). Specifically, Carter et al. (2003) found that increasing cognitive demands, via an n-back working memory task, resulted in deficits in two different variations of trace conditioning; single cue and differential trace fear conditioning. Subjects were asked to perform the n-back task during the conditioning procedure by pressing a key every time a number was presented that matched the one presented previously (1-back) or to the one

before the previous number (2-back). Learning was assessed by measuring skin conductance response (SCR) during un-reinforced trials. During single cue conditioning, only one CS is presented and paired with a US. In contrast, differential fear conditioning involves two different CS cues; one is associated with the US (CS+) and the other acts as a safety cue (CS-) indicating no US. Interestingly, Carter et al. (2003) found that delay differential fear conditioning was impacted by an n-back working memory task to a lesser degree than trace conditioning. For example, a 1-back task resulted in deficits in trace differential conditioning, but not in delay differential conditioning. However, a 2-back task caused deficits in both delay and trace differential fear conditioning. Considering n-back tasks engage PFC dependent processes, such deficits indicate greater competition for common resources during trace conditioning. Indeed, imaging work in humans indicates that trace, but not delay conditioning, recruits PFC activation (Knight et al., 2004). Furthermore, Carter et al. (2003) showed that even a 0-back task, essentially a simple signal detection task with minimal working memory load, could prevent normal trace single cue fear conditioning. Additionally, individuals performing the more difficult 2-back task showed intact delay single cue conditioning while individuals performing the same working memory task showed a complete lack of trace conditioning. Thus, delay and trace conditioning are differentially sensitive to working memory load. Considering that even mild working memory loads resulted in deficits in trace conditioning, this suggests that PFC-dependent working memory is important for trace conditioning in humans.

2.3. Trace conditioning engages the ACC and is sensitive to increases in attentional load

Attention is thought to share overlapping neural substrates with working memory including the PFC (Corbetta, Kincade, & Shulman, 2002; Fuster, 2008; Mayer et al., 2007). For example, in rats, top-down attention caused neurons within the PL and anterior cingulate (ACC) to synchronize (Totah, Jackson, & Moghaddam, 2013). Thus, changes in attentional demands may alter working memory by creating competition for common prefrontal cognitive reserves (Feng, Pratt, & Spence, 2012; Mayer et al., 2007; West, 2013). In mice, trace fear conditioning was disrupted when a flashing light distractor was presented during training. Starting 1 min before the first tone-shock pairing and ending 1 min after the final pairing, the light distractor was administered in 3 s bursts (250 ms on/off) pseudorandomly every 5–20 s. In contrast, the distractor had no effect on delay conditioning (Han et al., 2003). The same study found increased c-fos in within the ACC after trace conditioning compared to delay conditioned mice, and pre-training lesions of the ACC disrupted trace, but not delay fear conditioning. These data suggest a trace specific role for the ACC in mice. The dorsal mPFC of the rodent, which includes the PL and ACC, shares homology with human ACC (Seamans et al., 2008; Vogt & Paxinos, 2012). In humans, the ACC shows increased activation during anticipation (Murtha, Chertkow, Beauregard, Dixon, & Evans, 1996) and expression of conditioned fear (Milad et al., 2007). A role for the ACC in trace conditioning is further supported by work that found pre-training blockade of NR2B containing NMDARs within the ACC disrupted trace fear in mice (Descalzi et al., 2012). Similar to the PL, the rodent ACC also sends excitatory projections to the amygdala and thus may alter fear expression directly (Bissière et al., 2008). In support, mice with pre-training ACC inactivation showed initial deficits in fear acquisition in a delay fear paradigm

(Bissière et al., 2008), conversely humans showed increased ACC activation during both delay and trace fear conditioning (Knight et al., 2004; Milad et al., 2007).

Since the ACC projects to the amygdala and may alter fear expression, trace eyeblink studies are useful because they do not depend on fear expression as the dependent measure. Rabbit trace eyeblink conditioning lesion studies generally support a role for the ACC in trace conditioning (McLaughlin et al., 2002; Oswald, Knuckley, Mahan, Sanders, & Powell, 2006; Weible, Weiss, & Disterhoft, 2007). In intact rabbits, single neurons in the ACC during trace eyeblink conditioning showed a learning dependent decrease in firing (Hattori, Yoon, Disterhoft, & Weiss, 2014), suggesting that the ACC is initially recruited to maintain attention to conditioning stimuli prior to the formation of a CS-US association when stimuli are ambiguous. This may be more important during trace conditioning, compared to delay, as the trace interval makes the CS less predicative of the US (Marlin, 1981). Thus, the ACC may be recruited during trace conditioning via pre-stimulus attentional processing in response to arousing/noxious stimuli. Currently, it is still unclear if or how ACC and PL activity interact during trace conditioning, but one possibility is that ACC activation in anticipation of CS/US onset elicits sustained PL activity during the trace interval.

Work by Han et al. (2003), which suggests that trace conditioning is sensitive to attentional distraction, is supported by work with humans, where subjects performing an attentional distracting digit matching task showed a decrease in single-cue trace eyeblink conditioning (Manns, Clark, & Squire, 2000). Similarly, brain imaging during human trace fear conditioning shows activation of ACC with greatest activation during CS presentation and just prior to US presentation during the trace interval (Knight et al., 2004). However, not all findings are in agreement. For example, in humans, attentional distraction (silent movie or verbal shadowing) had no effect on either single cue delay or trace eyeblink conditioning (Carrillo, Gabrieli, & Disterhoft, 2000). In contrast, this same study found that attentional manipulation disrupted delay differential conditioning. This suggests that differential conditioning of a CS+ and CS-, regardless of the insertion of a trace interval, may require a greater degree of attentional processing compared to single cue conditioning (however, see Clark & Squire, 1998). One possible explanation for variability in the effect of attentional distraction on trace conditioning in humans may be that disruptions in learning are dependent on the subject's contingency awareness. For example, in the study by Carrillo et al. (2000), in which distraction had no effect, the majority of subjects were aware of the CS-US contingency during single cue trace conditioning. As will be discussed later, contingency awareness may be necessary for trace conditioning in humans. For example, Manns et al. (2000) demonstrated that contingency awareness was positively correlated with CR's. Interestingly, one study found that activation of ACC during trace conditioning was greatest to a CS+ when the subject was aware of the CS+ contingency (Knight et al., 2009). Therefore, trace conditioning appears to be particularly sensitive attentional distractor. However, in human subjects this sensitivity may be related to changes in contingency awareness.

In conclusion, these behavioral data indicate that trace conditioning requires attentional processes to facilitate learning. This is supported by neurobiological work showing that the ACC in humans and dorsal mPFC, including PL and ACC, in non-primate animals is

engaged during trace conditioning. In contrast under delay conditioning parameters when stimuli are contiguous, working memory and attention appear less critical. These data support previously described work showing that trace conditioning involves sustained neural firing within the mPFC across the trace interval. Further, the effects of attentional distraction in humans appear to be a function of contingency awareness. This is consistent with work that will be described later that suggests that trace conditioning involves declarative mnemonic processes.

3. PFC: A role beyond working memory

The role of the PFC in trace conditioning appears to extend beyond a purely working memory role. Evidence suggests that it also functions to consolidate and store trace associations. For example, post-training blockade of Mek1/2 (ERK) within the mPFC of rats impaired retention of trace fear memory, while having no effect on trace acquisition (Runyan, Moore, & Dash, 2004). Considering that the ERK-mitogen activated protein kinase signaling cascade is known to be important for synaptic plasticity and some forms of long-term memory (Martin et al., 1997; Orban, Chapman, & Brambilla, 1999), this suggests the mPFC facilitates storage of the CS-US memory trace. Similarly, pre-training infusion of muscimol into the PL disrupted trace fear 2 days after conditioning in rats (Blum, Hebert, & Dash, 2006). Additionally, NMDARs in the mPFC, particularly NR2B-containing receptors, have been shown to be important for acquisition of trace fear conditioning in rats (Gilmartin & Helmstetter, 2010; Gilmartin, Kwapis, et al., 2013). It is well established that NMDARs are critical for consolidation and formation of long-term memories (Kalisch et al., 2009; Manahan-Vaughan, von Haebler, Winter, Juckel, & Heinemann, 2008). Thus, in addition to working memory, the PFC may be recruited to maintain stable memory networks. This is consistent with the view that cortical regions that mediate sensory processing may also encode long-term memory traces (Weinberger, 2004). For example, because the PFC is recruited to process sensory stimulus information via thalamocortical pathways during acquisition, trace memories may be encoded and consolidated within the PFC. Therefore, the PFC may be important for formation of stabilized memory networks necessary for retrieval of trace memories.

Stable trace memory networks formed by the PFC may become increasingly important for recall in a time-dependent manner consistent with systems consolidation. Systems consolidation is a phenomenon in which memories that initially require the hippocampus for retrieval gradually become less dependent on the hippocampus and increasingly dependent on cortical structures over time (Clark, 2011; Wiltgen, Brown, Talton, & Silva, 2004). For example, in rats, post-training lesions of the mPFC 1 day after training had no effect on trace fear recall, but lesions of the mPFC made at remote time points (30 and 200 days) disrupted trace fear recall (Beeman, Bauer, Pierson, & Quinn, 2013; Quinn, Ma, Tinsley, Koch, & Fanselow, 2008). Conversely, these same studies found that lesions of the hippocampus 1 day after training resulted in immediate recall deficits, while hippocampal lesions at remote time points had no effect on trace fear recall. A similar time-dependent pattern was seen in trace eyeblink conditioning, with lesions of the mPFC made 1 day after acquisition having no effect on trace eyeblink CR retention, while mPFC lesions made 2 weeks after acquisition resulted in trace eyeblink CR deficits (Takehara, Kawahara, & Kirino, 2003).

These effects may depend on changes in neural excitability and plasticity, as chronic blockade of NMDARs within the mPFC after trace eyeblink conditioning resulted in recall deficits 42 days after training (Takehara-Nishiuchi, Nakao, Kawahara, Matsuki, & Kirino, 2006). Further, a recording study by Takehara-Nishiuchi and McNaughton (2008) found that cells in the mPFC produce temporally graded increased firing in response to a trace conditioned CS independent of new training. Such changes in the intrinsic properties of prefrontal neurons may represent a shift from hippocampal to PFC dependent memory. Alternatively, these data may suggest a continuation of immediate consolidation processes described previously. Interestingly, lesions of the hippocampus 1 day after trace fear conditioning did not result in deficits when testing occurred 30 days later (Beeman et al., 2013). Thus, the mPFC may facilitate recall at remote time points independent of hippocampal processes. Further, time-dependent effects of mPFC lesions are not always observed, as lesions of the mPFC resulted in disrupted recall of trace eyeblink as early as 6 and 24 h (Simon, Knuckley, Churchwell, & Powell, 2005). Thus, the mPFC appears important for recall of trace memories, but the temporal shift in its role for recall is still unclear.

Some data indicate that the PFC plays a role in recall of trace memory at early time points, while other data suggest the mPFC only becomes important for recall of remote trace memories. For example, Blum et al. (2006) found decreased freezing in response to inactivation of the PL 2 days after conditioning. In contrast, Quinn et al. (2008) did not find an early trace fear deficit with mPFC lesions made 1 day after training, but did observe a deficit when lesions were made 200 days after conditioning. However, some of this discrepancy, with regard to trace fear conditioning, may be related to the involvement of the PL in fear expression (Chan et al., 2011). Indeed, pre-testing inactivation of the PL decreased fear expression 1 day after hippocampus-independent delay fear conditioning (Sierra-Mercado et al., 2011). Thus, inactivation of PL, as seen in Blum et al. (2006), may cause decreased expression of conditioned fear, independent of alteration of trace memory recall *per se*. In contrast, the lesions used in Quinn et al. (2008) encompassed the PL and IL. Considering, the PL and IL appear to act in opposition to control fear expression (Burgos-Robles et al., 2009; Sierra-Mercado et al., 2011), PL/IL destruction might severely disengage prefrontal control of fear, making recall completely hippocampus-dependent. Thus, further delineation of the role of mPFC subregions in emotional control and trace consolidation is necessary.

In sum, in addition to evidence that suggests the PFC plays a critical role in acquisition of trace conditioning via sustained neural firing during the trace interval, the PFC appears to play a role in consolidation and storage of trace memories. While the interval is unclear, after some period of time the PFC appears to become involved in recall of trace memories. A recent study found that new hippocampal learning accelerated the shift from hippocampal to mPFC dependent recall in hippocampus-dependent contextual fear learning in rats (Haubrich et al., 2016). Therefore, future work might investigate the conditions under which recall of trace memory becomes mPFC dependent. Next, we will review the role of declarative memory in trace conditioning.

4. Declarative memory and trace conditioning

4.1. Temporal-lobe declarative memory deficits are associated with trace conditioning deficits

At its least granular scale, long-term memory has been organized into two domains, declarative (explicit) and non-declarative (implicit) memory. Declarative memory is commonly understood to encompass explicit conscious recollection of information and events (Cohen & Squire, 1980; Eichenbaum & Cohen, 2014; Lovibond & Shanks, 2002; Squire & Zola, 1996). Inasmuch as mnemonic constructs should be dissociable by anatomy as well as by cognitive characteristics (Squire & Zola, 1996; Tulving, 1992), individuals with anterograde amnesia have been instrumental in identifying brain regions necessary for declarative memory function. In particular, neuropsychological patients with lesions of the hippocampus show massive anterograde memory deficits for information about facts and events (Cohen & Squire, 1980; Eichenbaum & Cohen, 2014; Tulving & Markowitsch, 1998). In contrast, non-declarative memory, including procedural, motor, and non-associative learning, remain largely intact in such individuals.

Processes that underlie declarative memory have also been proposed to be critical for trace conditioning (Clark & Squire, 1998; Woodruff-Pak & Disterhoft, 2008). Support for this view is found in the clinic, as individuals with temporal-lobe lesions with deficits in declarative memory also show deficits in trace eyeblink conditioning (Clark & Squire, 1998; McGlinchey-Berroth, Carrillo, Gabrieli, Brawn, & Disterhoft, 1997; Woodruff-Pak, 1993). In contrast, delay eyeblink conditioning was not disrupted in individuals with temporal-lobe amnesia (Daum, Channon, & Canavan, 1989; Gabrieli, McGlinchey-Berroth, Gluck, Cermak, & Disterhoft, 1995). Interestingly, temporal-lobe lesions have also been associated with working memory deficits (Sidman, Stoddard, & Mohr, 1968). However, Clark and Squire (1998) suggest that trace eyeblink deficits in temporal-lobe amnesiacs are not explained by perturbations of working memory since amnesiac individuals show immediate memory capacity within the temporal range of the trace intervals used, i.e., up to 1000 ms (Cave & Squire, 1992; Nichols, Kao, Verfaellie, & Gabrieli, 2006). Further, work by Clark and Squire (1998), found that amnesiac individuals with hippocampal damage failed to demonstrate CRs during a trace differential eyeblink conditioning task, indicating a failure to form a CS+/US association. However, these same individuals did not show deficits in delay eyeblink conditioning. These findings strongly suggested that trace conditioning uniquely relies on temporal-lobe neural substrates, including the hippocampus, that support declarative memory.

4.2. The hippocampus is critical for learning trace CS-US associations

The previous clinical findings, along with much other work, has implicated the hippocampus as a critical region involved in encoding and storage of long-term declarative memory (for review see Eichenbaum, 2004). Thus, a critical issue in discussing the role of declarative memory in trace conditioning is the role of the hippocampus. Indeed, there is a large body of work that has shown that trace conditioning is a hippocampus-dependent form of learning (Bangasser, Waxler, Santollo, & Shors, 2006; Chowdhury, Quinn, & Fanselow, 2005; Kim, Clark, & Thompson, 1995; McEchron, Tseng, & Disterhoft, 2000; Moyer, Deyo, &

Disterhoft, 1990; Quinn, Oommen, Morrison, & Fanselow, 2002; Wanisch, Tang, Mederer, & Wotjak, 2005). For example, hippocampectomized rabbits demonstrated deficits in acquisition of trace eyeblink conditioning, with reduced CRs and increases in non-adaptive CRs (Moyer et al., 1990). Similarly, rats with hippocampal lesions also showed deficits in trace fear conditioning (McEchron et al., 1998).

It should be noted that there appears to be some difference in hippocampal processing between trace fear and eyeblink paradigms. For example, in trace fear conditioning, lesions of the hippocampus led to deficits with a trace interval of 20 s, however no disruption was found with trace intervals of 1 or 3 s (Chowdhury et al., 2005). In contrast, lesions of the hippocampus prevented trace eyeblink conditioning when the trace interval was 0.25 s (Tseng, Guan, Disterhoft, & Weiss, 2004). Paradigm specific sensitivity to the temporal interval is likely due to the differing substrates that mediate fear vs. eyeblink conditioning, i.e., amygdala and cerebellum. Additionally, fear and eyeblink conditioning occur on vastly different timescales. For example, eyeblink conditioning assays in rabbits and rodents may implement a CS duration of <1.5 s and US of <0.2 s. Furthermore, eyeblink conditioning requires extended training and can consist of multiple sessions occurring over many days, each consisting of ~90 CS-US trials per session (Clark, Manns, & Squire, 2001; Moyer et al., 1990; Woodruff-Pak, 2003). In contrast, fear conditioning in rodents can involve presentation of a discrete CS for 15–30 s (or longer) and a US duration of 0.05–5 s (Gould & Higgins, 2003; Phillips & LeDoux, 1992; Quinn et al., 2002), and conditioning can occur with as little as a single CS-US trial (Bevins, Rauhut, McPhee, & Ayres, 2000). Critically however, regardless of learning type, trace conditioning is hippocampus-dependent.

Evidence suggests that the hippocampus plays a critical role in acquisition of trace CS-US associations. For example, rats with pre-training lesions of the hippocampus showed disrupted trace fear conditioning (Bangasser et al., 2006). However, when trace conditioning was augmented such that, in addition to presentation of a CS followed by a trace interval, the CS was again presented simultaneously with the US, lesioned rats showed learning (Bangasser et al., 2006). This result suggests that the hippocampus initially facilitates bridging temporally discontinuous events. Interestingly, the hippocampus is not critical for trace conditioning once a CS-US association has been made. For instance, when rats were trained in delay eyeblink conditioning and later receive hippocampal lesions, they could maintain conditioned responding if shifted to trace conditioning, even if the interstimulus interval, the time elapsed between CS offset and US onset, was altered (Beylin et al., 2001; Shors, 2004). Similarly, patient H.M., who showed robust deficits in declarative memory, had normal CRs during trace eyeblink conditioning after successfully acquiring delay eyeblink conditioning (Woodruff-Pak, 1993). Thus, once an association is formed with a specific CS, adaptive responding to changes in CS-US contiguity are not dependent on the hippocampus. All together, these data suggest that the hippocampus is important for establishing a CS-US association when stimuli are initially discontinuous. As will be discussed, the hippocampus may provide a temporal prediction signal during trace that is not required once a CS-US association has been established.

Precisely how trace conditioning recruits hippocampal circuitry is still being investigated, but the process appears different from that associated with the mPFC (Gilmartin &

McEchron, 2005a; Green & Arenos, 2007). As previously discussed, behavioral evidence suggests that the hippocampus is involved in acquisition of trace fear conditioning by bridging the trace interval, i.e., Bangasser et al. (2006). However, single unit recordings of cells in dentate gyrus and CA1 region of the hippocampus showed that while firing rates changed in response to CS presentation, there was little learning-related responding during the trace interval (Gilmartin & McEchron, 2005a). Therefore, the role of the hippocampus, with respect to sustained activation during the trace interval appears different from that of the mPFC (Gilmartin & McEchron, 2005b). In contrast to the mPFC, which shows sustained firing during the trace interval, the hippocampus appears to be involved in processing CS and US information (Gilmartin & McEchron, 2005b; Siegel et al., 2012). In support, Gilmartin and McEchron (2005a) found changes in neural firing in DG and CA1 to the CS and US after repeated training, indicating learning related changes (Fig. 3). Considering the differing neural firing patterns of the mPFC and the hippocampus during trace conditioning, exactly how the mPFC and hippocampus integrate CS information during trace conditioning is not clear. However, Gilmartin and McEchron (2005b) have suggested that the hippocampus sends CS-US information to the mPFC to facilitate consolidation of trace conditioning. Moreover, these substrates share connectivity and trace fear conditioning may involve communication between them (Adhikari, Topiwala, & Gordon, 2010; Hoover & Vertes, 2007). Thus, it is possible that such connectivity allows for CS information to be relayed from the hippocampus to modify mPFC activity (Laroche, Davis, & Jay, 2000). Further, evidence suggests that the hippocampus may facilitate acquisition of trace conditioning by encoding temporal information (Solomon et al., 1986). In support, single unit recordings from CA1 found neuron subpopulations increased firing specifically to the CS or US during trace eyeblink conditioning (Weible, O'Reilly, Weiss, & Disterhoft, 2006). Importantly, during retention testing of trace fear conditioned rabbits, CA1 neurons showed increased firing after CS presentation at time points coinciding with presentation of the US during training (McEchron, Tseng, & Disterhoft, 2003). Thus, CA1 hippocampal cells may encode an expectancy or prediction of the CS-trace interval-US temporal order. Such findings from trace conditioning studies are consistent with work that suggests that the CA1 region is important for learning temporal ordering information (Farovik, Dupont, & Eichenbaum, 2010; Honey, Watt, & Good, 1998). Finally, considering that temporal information is intrinsic to episodic declarative memory, evidence suggesting that hippocampus-dependent temporal learning processes are involved in trace conditioning supports a declarative mnemonic function for trace conditioning.

4.3. Trace conditioning engages the dorsal hippocampus

While there is robust evidence that the hippocampus is critical for trace conditioning, trace conditioning has been shown to differentially engage the hippocampus along its rostral/caudal axis. It is well supported that the hippocampus is functionally divisible into dorsal and ventral regions in rodents, and corresponding posterior and anterior regions in primates (for review see Fanselow & Dong, 2010). Generally speaking, findings suggest that the dorsal hippocampus (DH) mediates cognitive functioning and the ventral hippocampus (VH) is important for emotional processing (Kjelstrup et al., 2002; Moser, Moser, & Andersen, 1993). For example, lesions of the DH produced pronounced deficits in spatial learning, but VH lesions did not (Moser et al., 1993). This delineation of function is also reflected in

fMRI work in humans. For example, increased activation of the posterior hippocampus, compared to the anterior region, was associated with episodic memory recall (Greicius et al., 2003), and activation of the posterior hippocampus during encoding has been shown to positively correlate with performance in episodic recall (Fernández et al., 1998). Further, a resting-state connectivity analysis found greater cortical connectivity with the posterior hippocampus in humans (Qin et al., 2015). Thus, DH function may be critical for cognition in rodents and declarative memory in humans. Moreover, consistent with overlapping of declarative and trace conditioning processes, evidence strongly suggests that the DH is necessary for trace conditioning. For example, pre-training lesions of the DH have been shown to disrupt trace fear conditioning (Burman, Starr, & Gewirtz, 2006; McEchron et al., 2000, however see Yoon & Otto, 2007), but not delay fear conditioning. Furthermore, pharmacological manipulations of the DH extend such lesion studies. Inactivation of the DH with pre-training infusions of the GABA agonist muscimol also resulted in trace fear conditioning deficits, while sparing delay conditioning (Esclassan, Coutureau, Di Scala, & Marchand, 2009). Thus, the DH appears necessary for acquisition of trace fear memories. Additionally, the overlap in the role of DH in declarative memory and trace conditioning suggests common substrates.

Glutamate signaling at NMDARs, a critical mediator of long-term memory and synaptic plasticity, is recruited within the DH during both acquisition and recall of trace conditioning. For example, blockade of DH NMDARs prior to training disrupted acquisition of trace fear conditioning (Czerniawski, Ree, Chia, & Otto, 2012; Misane et al., 2005; Wanisch et al., 2005). These studies suggest that NMDARs are critical for consolidation of trace memories and are consistent with the well-established role of NMDARs in long-term potentiation, the putative physiological process underlying long-term memory (Yashiro & Philpot, 2008). In addition, hippocampal NMDARs are also involved in trace conditioning recall (Kishimoto, Nakazawa, Tonegawa, Kirino, & Kano, 2006). For example, antagonism of NMDARs in the DH prior to testing also caused deficits in trace fear conditioning recall (Quinn, Loya, Ma, & Fanselow, 2005). Thus, NMDARs within the DH appear to be involved in recall in addition to consolidation. However, recall may also engage the VH. For example, another study found that pre-testing blockade of NMDARs in the VH, but not the DH resulted in disrupted trace fear recall (Czerniawski et al., 2012). It is not clear why this discrepancy was found. However, one possibility is that the effects of hippocampal pharmacological manipulations on trace conditioning are highly dependent on target region. Indeed, one study found that blockade of DH AMPA receptors within the dentate gyrus, but not CA1, disrupted trace fear retrieval (Pierson, Pullins, & Quinn, 2015). Therefore, to better understand the role of the hippocampus in trace conditioning, close attention will not only need to be paid to dorsal/ventral regional differences, but also to spatially relevant inputs to the trisynaptic circuit.

While the DH appears critical for formation of trace memories, the role of the VH in trace conditioning may be related to emotional processing. For example, pre-training VH lesions resulted in acquisition deficits and post-training lesions led to deficits in expression of trace fear conditioning (Rogers, Hunsaker, & Kesner, 2006; Yoon & Otto, 2007). However, such lesions also resulted in a decrease in fear response across all conditions at testing, i.e., intertrial interval, CS, and post-CS, suggesting a non-associative effect on fear expression. In addition, inactivation studies largely support such non-associative decreases in fear

expression found in VH lesion studies (Cox, Czerniawski, Ree, & Otto, 2013; Esclassan, Coutureau, Di Scala, et al., 2009). Anatomically, the VH has direct connections to the amygdala, a critical structure in fear learning and expression (Pitkänen, Pikkarainen, Nurminen, & Ylinen, 2000; Yoon & Otto, 2007) and lesions of the VH reduced expression of innate fear behavior (Kjelstrup et al., 2002). Thus, the VH may play a critical role in trace fear conditioning by modulating emotional fear processing; however, VH function may be less involved in processing CS-US association relevant information. Work from eyeblink conditioning is useful in parsing apart the role of the VH, as it is not a form of fear conditioning, and thus emotional processing is likely less important. Indeed, work from Weible et al. (2006) demonstrated that neural firing rates only modestly increased in VH CA1 pyramidal neurons compared to DH during trace eyeblink conditioning. This finding is consistent with trace fear conditioning data indicating that the DH is more important for trace CS-US association, while the VH is preferentially involved in less specific emotional processing. However, considering that the VH sends projections to the mPFC, while the DH does not (Hoover & Vertes, 2007), further investigation of VH involvement in trace conditioning is necessary.

In sum, these data suggest that trace conditioning differentially engages DH/VH hippocampal processes, with pre-clinical studies finding a critical role for the DH in acquisition and consolidation of trace conditioning. The reason trace learning engages DH processes may be related to differences in cortical input and/or intrinsic cellular properties along the dorsal-ventral axis of the hippocampus. The hippocampus receives highly processed sensory information via the entorhinal cortex (EC) (Canto et al., 2008), and pre-training lesions of the EC have been shown to disrupt trace fear, but not delay fear conditioning in rats (Esclassan, Coutureau, Scala, & Marchand, 2009). Similarly, EC lesions disrupted trace eyeblink acquisition in rabbits (Ryou, Cho, & Kim, 2001). However, the DH and VH receive differential input from the entorhinal cortex along the dorsal/ventral axis, with the dorsolateral band of the medial entorhinal cortex (dlMEC) primarily projecting to the DH. The dlMEC is connected to visual and somatosensory cortical areas and contains cells that respond to spatial location (grid cells) with finer resolution than cells in ventral MEC (Fyhn, Molden, Witter, Moser, & Moser, 2004; Kerr, Agster, Furtak, & Burwell, 2007). Similarly, in contrast to the VH, the DH has a greater density of place cells (Jung, Wiener, & McNaughton, 1994), and has been observed to synchronize with the lateral EC during associative learning (Igarashi, Lu, Colgin, Moser, & Moser, 2014). While place cells are notable for their contribution to spatial learning (O'Keefe, 1976), it has been suggested that the intrinsic ability of such cells to integrate into multiple representational networks indicates a possible role in declarative memory (Moser, Rowland, & Moser, 2015). In addition to mapping (and remapping) spatial information, cells in the DH have also been shown to fire in response at temporal intervals. These "time cells" have been shown to activate in temporally specific intervals during memory task delays (MacDonald, LePage, Eden, & Eichenbaum, 2011), and similar to place cells, can shift firing as temporal contingencies are altered. Moreover, in a study using two-photon calcium imaging, CA1 cells in the DH showed time-tuned firing in trace eyeblink conditioning between CS onset and US termination (Modi, Dhawale, & Bhalla, 2014). These data suggest that the hippocampus facilitates trace learning by mapping temporal information, which is consistent

with trace learning-related hippocampal firing patterns previously described (Gilmartin & McEchron, 2005a; Knight et al., 2004; McEchron et al., 2003; Weible et al., 2006). Moreover, these specific attributes suggest that the DH plays a critical role in processing spatial-temporal information, which is consistent with a role on episodic/declarative memory processes. Finally, as previously noted, the posterior hippocampus, which is homologous to the rodent DH, is implicated in episodic memory and DH mechanisms recruited by trace might reflect a similar conserved process. Thus, future work might investigate if differential anatomical recruitment of the hippocampus during trace conditioning is also found in humans.

4.4. Awareness predicts trace conditioning

In humans, a critical distinction between declarative and non-declarative memory is conscious awareness in the former and lack of awareness in the later (Squire & Zola, 1996). Thus, if trace conditioning depends upon declarative memory processes, then contingency awareness should be a necessary condition for human trace conditioning. Consistent with this prediction, Clark and Squire (1998) demonstrated that differential trace eyeblink conditioning was impaired in amnesia patients with hippocampal damage. Indeed, such individuals reported being unaware of the CS-US contingency. Moreover, using a post-task true/false questionnaire, control subject's awareness of the CS-US contingency was also assessed, and individuals judged as unaware showed decreased CRs under the longer 1 s trace period and a deficit in CS discrimination to the shorter 0.5 s trace period. In contrast to these disruptions in trace conditioning, no difference was observed between unaware and aware individuals in differential delay eyeblink conditioning. This delay vs. trace awareness dichotomy has been proposed as evidence that trace and delay conditioning are fundamentally different forms of learning within the dual-process memory model (Lovibond & Shanks, 2002). To test this idea further, Clark et al. (2001) performed an eyeblink experiment in which the CS was reinforced 50% of the time. Based upon the phenomenon of the gamblers fallacy, subjects should increase their expectation of a US delivery after receiving a series of unreinforced CS presentations. Critically, Clark et al. (2001) found that this expectation had an effect on CR within trace eyeblink conditioning, but not delay eyeblink conditioning. Therefore, conscious expectation appears to modulate trace conditioning, further supporting the notion that trace conditioning is dependent on declarative memory. This proposal is further supported by a number of additional studies that have found *no* relationship between awareness and delay eyeblink conditioning (Frcka, Beyts, Levey, & Martin, 1983; Manns, Clark, & Squire, 2002; Papka, Ivry, & Woodruff-Pak, 1997; Smith, Clark, Manns, & Squire, 2005). Conversely, when contingency awareness was manipulated via a distractor (silent movie presented throughout conditioning) the level of conditioning was correlated with awareness in trace eyeblink conditioning (Manns et al., 2000), indicating that awareness is critical for trace conditioning. Thus, simple delay associations may be formed via a non-declarative hippocampus-independent memory processes for which awareness is not critical, and trace conditioning associations depend upon hippocampus-dependent declarative processes (Clark & Squire, 1998; Manns et al., 2002).

In contrast to the view that trace conditioning uniquely depends upon conscious awareness, others have suggested a single-process model of associative learning in which all conditioning is dependent upon declarative or propositional memory (Lovibond, Liu, Weidemann, & Mitchell, 2011; Mitchell, De Houwer, & Lovibond, 2009). Indeed, there has been a long-standing debate regarding the importance of contingency awareness in delay conditioning (Dawson & Reardon, 1973; Lovibond & Shanks, 2002), and a number of reports indicate that contingency awareness may be necessary for delay eyeblink conditioning (Carrillo et al., 2000; Knutten, Power, Preston, & Disterhoft, 2001; Lovibond et al., 2011). Lovibond and Shanks (2002) criticized Clark and Squire (1998) on the basis that they may have misclassified individuals who were aware as unaware as a result of a liberal threshold, which could possibly result in seemingly unaware conditioning. In response, using a more strict cutoff of 9 questions out of 17, it was reported that the effect seen in Clark and Squire (1998) was replicated (Manns et al., 2002). Additionally, Lovibond and Shanks (2002) criticized the use of a post-assay questionnaire assessment of awareness used by Clark and Squire (1998). An important concern was that although CRs were measured by objective means, awareness measured by post-testing self-report could be confounded, i.e., forgetting and interference. More specifically, Clark and Squire (1998) administered 28 prior contingency awareness relevant questions, a number of the questions were redundant, and that a correct “true” answer only occurred in 4 out of 17 questions. However, when knowledge of contingency was assessed within session after 10, 60, and 120 trials with a briefer 7 question true/false questionnaire, awareness was related to trace, but not delay conditioning (Manns, Clark, & Squire, 2001). Lovibond and Shanks (2002) also raised the issue of participant age. Indeed, the mean age of healthy control subjects from Clark and Squire (1998) was 67, similar to the age of the amnesia patients. Importantly, older individuals are observed to be worse at both delay and trace eyeblink conditioning, compared to younger adults; thus the effects of age and awareness may potentially interact, resulting in exaggerated effects (LaBar & Disterhoft, 1998). However, acquisition of differential trace and delay eyeblink conditioning, when subjects were exposed to a movie distractor during conditioning, was found to be dependent on awareness in both young and aged individuals (Knutten et al., 2001). These results suggest that differential conditioning may be particularly sensitive to changes in awareness. Similarly, using a complex masking task where participants engaged in simultaneous one-back and go/no-go tasks, which depended upon attending to the CS and US respectively, differential delay eyeblink conditioning was disrupted (Weidemann, Satkunarajah, & Lovibond, 2016), suggesting that attention to the CS and US is not sufficient to facilitate delay differential eyeblink conditioning, but that awareness of the contingency is. Thus, differential conditioning, which is more difficult than single-cue conditioning, may be more dependent on awareness (LaBar & Disterhoft, 1998). However, using a false pretense masking task, involving reporting letter cues at a similar volume as CS volume, awareness was found to be critical for acquisition of both delay and trace single-cue eyeblink conditioning (Weidemann, Best, Lee, & Lovibond, 2013). Therefore, while trace conditioning appears to critically depend on awareness, data regarding the role of awareness in delay conditioning appears more equivocal. Interestingly, when unaware subjects were conditioned with a soft CS they poorly learned differential delay eyeblink conditioning compared to aware subjects, but unaware subjects conditioned with a loud CS showed no difference in conditioning to similarly conditioned aware

individuals (Huang et al., 2014). This finding speaks to the importance of methodological and procedural factors that likely play a key part in unraveling the role of awareness in delay conditioning.

Studies using fear conditioning procedures also suggest that trace conditioning is dependent upon awareness. For example, work by Weike, Schupp, and Hamm (2007) found that contingency unaware individuals, assessed by post-experimental interview, showed normal fear conditioned potentiated startle under delay conditioning, but unaware individuals did not show trace fear potentiated startle or SCR. Interestingly, Weike et al. (2007) found that awareness in both delay and trace was necessary for conditioned SCR. This was similar to a previous observation where differential delay fear conditioning was expressed in unaware individuals (no interference, post-task questionnaire), but unaware individuals did not show SCR to the CS+ (Hamm & Vaitl, 1996). These data suggest that SCR and startle CRs are mediated by separate memory systems. However, when a masking task was used, unaware individuals failed to show delay conditioned fear potentiated startle (Purkis & Lipp, 2001). Importantly, methodological differences may again play a key role in such divergent effects, specifically masking tasks could alter conditioning acquisition via interference (Weike et al., 2007).

In response to a methodological criticism of the post-task questionnaire posed by Lovibond and Shanks (2002), work by Knight et al. (2009) assessed awareness within a fear conditioning session. Knight et al. (2009) argued that a within session assessment of awareness addresses much of the criticisms offered by Lovibond and Shanks (2002). Thus, using a within training US expectancy rating system, in which each subject rated the likelihood of the US occurring on each trial, it was found that expectancy awareness was necessary for trace fear conditioning. For example, subthreshold CS presentations, which were not perceived by the subjects and thus could not be expected, did not result in a conditioned SCR. Functional brain imaging shows a potential physiological mechanism underlying this finding (Knight et al., 2009). When a US was correctly expected, subjects showed increased bilateral activation of the hippocampus in response to the CS. In contrast, an increased response in the right amygdala was observed during presentation of the CS in both aware and unaware conditions (Knight et al., 2009). Moreover, this data supports the view that, in contrast to the hippocampus, the amygdala encodes implicit emotional memory. Overall, this corroborates a dual-system model and indicates that trace conditioning is hippocampus-dependent and involves declarative-associated contingency awareness in humans.

One interesting discrepancy in the relationship between contingency awareness and trace conditioning is related to CS modality. For example, a study using human faces as the CS modality demonstrated that individuals could learn differential trace conditioning without contingency awareness (assessed within session) (Balderston, Schultz, Baillet, & Helmstetter, 2014). Interestingly, this study found that amygdala activation was likely involved in bridging the trace gap. This finding indicates that trace conditioning can occur without awareness via neural substrates not implicated in declarative function (or working memory). However, the use of face stimuli likely makes this a unique finding. For example, it has been shown that novel faces may act as “prepared stimuli” and strongly activate a

response in the amygdala even when the facial expression is neutral (Balderston, Schultz, & Helmstetter, 2011). Therefore, some cues may be privileged such that non-declarative processes may facilitate trace learning.

Briefly summarized, human behavioral data strongly suggests that trace conditioning requires contingency awareness. In contrast, data from delay conditioning have been mixed, with some examples showing that learning can occur without contingency awareness, while others have documented failure to learn. One likely possibility is that delay and trace conditioning are dependent on multiple memory systems that overlap. In support, while delay conditioning is generally robust to manipulations of the hippocampus, rodents presented deficits in delay eyeblink conditioning after hippocampal lesioning when a long CS (1500 ms) was used (Beylin et al., 2001). Further, delay fear conditioning elicits increased hippocampal activity as measure by c-Fos and Zif268 in mice (Weitemier & Ryabinin, 2004). Indeed, differing methodological manipulations such as masking task, single-cue vs. differential conditioning, and CS modality all likely alter the memory systems recruited during delay conditioning. In contrast, trace conditioning appears to consistently depend upon awareness-related declarative memory systems.

In conclusion, evidence from humans suggests that trace conditioning recruits declarative memory processes and associated temporal-lobe brain regions. Further, individuals with temporal lobe lesion-associated deficits in declarative memory also demonstrate deficits in trace conditioning that are not explained by differences in working memory ability. Similarly, hippocampal lesions result in trace conditioning deficits in rodents and rabbits. Clinical and pre-clinical data appear in agreement that the hippocampus does not facilitate trace conditioning by providing a bridging signal across the CS-US interval. Rather, learning-related changes in neural activity in response to conditioning stimuli indicate that the hippocampus processes temporal information. Moreover, both clinical and pre-clinical work suggest the hippocampus is critical during the initial formation of the trace CS-US association, but is not once a CS-US association has been formed. Pre-clinical data specifically implicates the DH as the locus of trace-dependent hippocampal processes, however it is not known if similar differential engagement of the hippocampus occurs in humans. Lastly, trace conditioning in humans is generally dependent on contingency awareness indicating the necessity of explicit conscious understanding of the CS-US relationship in order to form an association. While awareness is not something readily modeled in lower species, it may be plausible to assess overlap between functional anatomy in aware humans and brain regions in lower species. For example, learning related activation of hippocampus and parahippocampal cortex was observed in aware trace fear conditioning subjects (Knight et al., 2009). Therefore, trace conditioning-associated hippocampal processes may represent a conserved declarative memory system that can be investigated at clinical and pre-clinical levels.

5. Conclusion

Much behavioral work suggests that trace conditioning recruits working memory and declarative mnemonic processes. Furthermore, neurobiological studies indicate that trace conditioning recruits the hippocampus and mPFC in order to mediate these cognitive

processes. While this review has discussed these two regions as independent neural substrates, it should be acknowledged that they likely function together. For example, the VH makes direct monosynaptic glutamatergic connections with the mPFC, and the mPFC may communicate indirectly to the hippocampus via midline thalamus (Chudasama, Doobay, & Liu, 2012; Dégenétais, Thierry, Glowinski, & Gioanni, 2003; Li et al., 2015; Vertes, 2002). Therefore, their roles in trace conditioning are likely intertwined. Indeed, work indicates hippocampal projections make synaptic modifications within the mPFC during working memory tasks (for review see; Laroche et al., 2000). Thus, during acquisition of trace conditioning the hippocampus may act in concert with the mPFC to bridge the trace interval via forwarding stimulus information to the mPFC. Moreover, such cooperation is supported by findings in which mPFC shows sustained neural firing during the trace interval and enhanced theta power during trace acquisition (Gilmartin & McEchron, 2005b; Paz, Bauer, & Paré, 2008; Takehara-Nishiuchi & McNaughton, 2008). Furthermore, prefrontal neurons in rodents have shown phase-locking with combined DH/VH theta oscillations and mPFC VH/DH synchrony has been positively correlated with performance in another hippocampus-dependent form of learning, spatial working memory (O'Neill et al., 2013; Siapas, Lubenov, & Wilson, 2005; Sigurdsson, Stark, Karayiorgou, Gogos, & Gordon, 2010). In sum, this review has discussed work that generally provides support for the view that working memory and declarative memory processes underlie trace conditioning.

6. Future studies

The studies discussed here clearly provide evidence that trace conditioning depends upon memory processes mediated by both the PFC and hippocampus. However, it is less well understood if or how these regions act together to support trace conditioning. One possibility is that the PFC and hippocampus act in parallel and serve a redundant function during tasks with temporally discontinuous events. For example, a study investigating hippocampus-dependent spatial memory found that inactivation of the hippocampus disrupted spatial learning with a 5 min, but not a 10 s intertrial interval (Lee & Kesner, 2003). However, when muscimol was infused into the mPFC of hippocampal lesion animals, these subject then showed deficits with 10 s intertrial intervals (Lee & Kesner, 2003). These data suggest that under some conditions mPFC processing can support hippocampus-dependent learning of discontinuous events. One interesting question, considering differences between mPFC and hippocampal neural firing during trace, is how PFC and hippocampus mediate bridging temporal intervals together via different neural processing. Work suggests that normal cognitive functioning requires a bidirectional PFC-hippocampal circuit (Chudasama et al., 2012; Sigurdsson & Duvarci, 2016). Thus, future studies may seek to directly examine how hippocampal and PFC processes interact during trace conditioning.

A particular challenge to investigating a hippocampus-PFC circuit is cell population specificity. Specifically, neurons in the VH are heterogenous and project to either the mPFC or the basolateral amygdala, while some VH neurons send projections to both of these regions (Ishikawa & Nakamura, 2006). Thus, investigating the role of a hippocampal-mPFC circuit in trace conditioning will require specific manipulation of mPFC projecting cells, while leaving other projections unperturbed. In contrast to pharmacological techniques,

newer genetic approaches with increased cell subpopulation specificity, such as designer receptors exclusively activated by designer drugs and optogenetics, will be useful in addressing such questions. For example, pathway specific manipulation may be achieved using two vectors by infusing a retrograde canine adenovirus-2 into a target region (e.g., mPFC) to deliver Cre-recombinase and an adeno-associated virus carrying a designer receptor into a target region that projects to the first region (e.g., VH) (Boender et al., 2014). Likewise, optogenetics also allows for similar pathway specific manipulation (Li et al., 2016; Walsh et al., 2012). The temporal resolution provided by optogenetics may be particularly useful given the defined CS-US onset-offset parameters of trace conditioning. For example, Gilmartin et al. (2013) turned off cells within the mPFC exclusively during the trace interval. Future work might investigate the effects of modulating hippocampal neurons projecting to the PFC during different phases of the trace conditioning.

Understanding of trace conditioning and its implication as a model of working and declarative memory will also benefit from investigating hippocampal-PFC neural synchronization during trace conditioning. In primates, evidence points to learning-related hippocampal-PFC interactions during working memory (Böhner et al., 2015) and declarative memory (Brincat & Miller, 2015), while psychiatric disorders, including schizophrenia, post-traumatic stress disorder, and depression are associated with disrupted PFC-hippocampal connectivity (Godsil et al., 2013). A benefit to investigating functional connectivity is the ability to corroborate non-invasive primate work with more invasive techniques in experimental animal models, e.g., phase locking and coherence analysis (Sigurdsson & Duvarci, 2016). Connectivity analysis could examine to what degree the hippocampus and PFC interact during encoding, consolidation, and recall as well as the directionality of this connectivity.

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Fig. 1.

Temporal arrangement of stimuli in delay and trace conditioning paradigms (a) delay conditioning occurs when there is a delay between CS onset and US onset, but the CS and US co-terminate and (b) trace conditioning occurs when the CS and US are not contiguous. The CS is followed by a trace interval prior to presentation of the US.

Fig. 2.

Hypothetical schematic of brain regions recruited during eyeblink and fear conditioning paradigms. Black arrows indicate projections involved when stimuli are contiguous (delay conditioning). Regions in blue depict core circuitry required for trace and delay conditioning. During eyeblink conditioning auditory sensory information is passed via cochlear nucleus to thalamus (Th), pontine nuclei (Pn), and then Cerebellum (Cer) (Halverson et al., 2008). Critical plasticity occurs within interpositus nucleus of the Cer, mediating CR's (Steinmetz et al., 1986). During fear conditioning CS and US is sent from thalamus to the amygdala where fear memories are encoded (Kim, Rison, & Fanselow, 1993; LeDoux et al., 1990). The amygdala (Amy) is also critical for mediating CR's (Phillips & LeDoux, 1992) (additional supporting literature is found in Section 1.1). Red arrows indicate theoretical information flow between regions recruited during trace conditioning. Orange regions indicate brain areas engaged during trace conditioning. During trace conditioning information may pass from the hippocampus via monosynaptic projections to the mPFC. Importantly, the mPFC projects to areas critical for learning-related plasticity, including the Amy (fear conditioning) and Pn, which provides direct input to the Cer (eyeblink conditioning). Thus, while core circuitry differs between fear and eyeblink conditioning, trace conditioning may recruit overlapping neural substrates to support learning. (A) Trace Fear Conditioning: The CS is processed and relayed to the mPFC via thalamic inputs. CS representation may be maintained within the mPFC via sustained neural activation. The dorsal hippocampus receives sensory information from the entorhinal cortex (EC) and processes CS-US temporal information. Direct connections between ventral hippocampus (VH) and amygdala may play an important role in trace fear expression. mPFC and VH signaling converge on amygdala (Amy). (B) Trace Eyeblink Conditioning: CS information is relayed via the Th to the mPFC. The hippocampus may encode and send temporal CS-US information to the mPFC and maintains sustained activation during trace interval. Finally, mPFC may relay CS information to Cer facilitating CS-US plasticity within the Cer (supporting literature is found in Sections 2 and 3).

Fig. 3.

Schematic of neural activity patterns observed during trace interval, PFC (Blue) and hippocampus (Orange). Pre-clinical and clinical data suggest differing roles for the PFC and hippocampus in trace conditioning. The PFC shows working memory-like sustained activity across the trace interval. In contrast, the hippocampus shows learning-related changes in activation to the CS and US, suggesting that the hippocampus processes CS-US temporal information (Haritha et al., 2012; Gilmartin & McEchron, 2005a; Knight et al., 2004; Gilmartin & McEchron, 2005b).

Table 1

Key findings indicating a working memory role for the PFC in trace conditioning.

Species/Region	Paradigm	Key findings	Refs
<i>Human</i>			
PFC (dlPFC, dmPFC)	Trace fear conditioning	Increased BOLD response during trace interval	Haritha et al. (2012)
PFC (dlPFC)	Trace fear conditioning	Increased BOLD within middle frontal gyrus during trace interval	Knight et al. (2004)
<i>Rabbit</i>			
mPFC	Trace eyeblink conditioning	Single unit recordings showed CS evoked persistent activity in mPFC during trace interval	Siegel et al. (2012)
mPFC	Trace eyeblink conditioning	Single unit recordings showed sustained neural firing during the trace is independent of cerebellar processes	Siegel & Mauk (2013)
<i>Rat</i>			
mPFC (PL & IL)	Trace fear conditioning	Single unit recordings found subset of cells that increased firing during CS and sustained across trace interval	Baeg et al. (2001)
mPFC (PL)	Trace fear conditioning	Single unit recordings found subpopulation of cells with sustained activity during trace interval	Gilmartin and McEchron (2005b)
mPFC (PL)	Trace fear conditioning	Pre-training local administration of muscimol and APV disrupted trace fear conditioning	Gilmartin and Helmstetter (2010)
mPFC (PL)	Trace fear conditioning	Optogenetic silencing of PL neurons during trace interval at training disrupted trace conditioning	Gilmartin et al. (2013)
mPFC (PL)	Trace fear conditioning	Selective role of NR2B NMDRs; pre-training blockade disrupts trace, but not delay fear conditioning	Gilmartin et al. (2013)
mPFC (PL)	Trace eyeblink conditioning	Single neuron recordings show a sub-population of cells with CS elicited firing during the trace interval	Takehara-Nishiuchi and McNaughton (2008)

Abbreviations: 2-Amino Phosphonovaleric acid (APV), blood-oxygen level dependent (BOLD), N-methyl-D-aspartate receptor (NMDAR).