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Review

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.

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 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;

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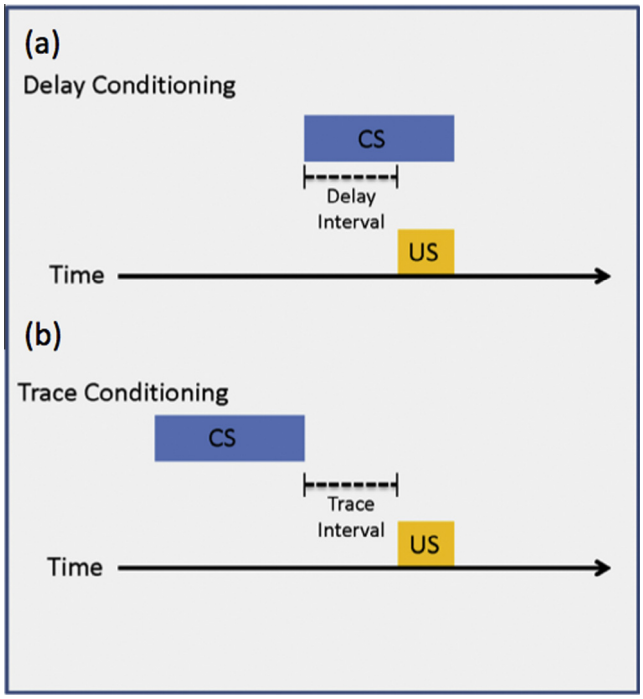

Fig. 1. Temporal arrangement of stimuli in delay and trace conditioning paradigms (a) delay conditioning occurs when there is a delay between CS onset and US onset, but the CS and US co-terminate and (b) trace conditioning occurs when the CS and US are not contiguous. The CS is followed by a trace interval prior to presentation of the US.

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). Preclinical 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 interpositous nucleus of the cerebellum where critical plasticity occurs (Steinmetz et al., 1986). Imaging work in humans supports these data, showing increased cerebellar