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Review

Bridging the interval: Theory and neurobiology of trace conditioning

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ABSTRACT

An early finding in the behavioral analysis of learning was that conditioned responding weakens as the conditioned stimulus (CS) and unconditioned stimulus (US) are separated in time. This "trace" conditioning effect has been the focus of years of research in associative learning. Theoretical accounts of trace conditioning have focused on mechanisms that allow associative learning to occur across long intervals between the CS and US. These accounts have emphasized degraded contingency effects, timing mechanisms, and inhibitory learning. More recently, study of the neurobiology of trace conditioning has shown that even a short interval between the CS and US alters the circuitry recruited for learning. Here, we review some of the theoretical and neurobiological mechanisms underlying trace conditioning with an emphasis on recent studies of trace fear conditioning. Findings across many studies have implications not just for how we think about time and conditioning, but also for how we conceptualize fear conditioning in general, suggesting that circuitry beyond the usual suspects needs to be incorporated into current thinking about fear, learning, and anxiety.

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Contents

1. Introduction

A key feature of associative learning is its sensitivity to the temporal arrangement of stimuli. In Pavlovian conditioning procedures, research has focused on the temporal relation between the conditioned stimulus (CS) and the unconditioned stimulus (US). Pavlov (1927) noted that as the trace interval, the interval between CS offset and US onset, was increased, responding during the CS decreased. This pattern of results is a textbook finding that has been replicated across many different Pavlovian preparations (e.g., Ellison, 1964; Kamin, 1961). The study of trace conditioning has had a major impact on theories of learning and timing, and has revealed novel neurobiological mechanisms of learning and memory. In this review, we focus primarily on trace fear conditioning, where a subtle change in the interval between the CS and US results in the recruitment of distinct neurobiological circuitry.

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Trace conditioning has been studied with multiple behavioral approaches that reveal common and unique characteristics. At a behavioral level, trace conditioning procedures generally slow the rate of acquisition of a behavioral response and lead to less behavior during subsequent tests, relative to delay conditioning procedures. As with delay procedures, however, trace conditioning often results in the emergence of response patterns consistent with precise timing of the CS–US relation (e.g., Balsam, 1984) and this timing is stimulus and contingency specific (e.g., Kehoe et al., 2009; Woodruff-Pak and Disterhoft, 2008). There is a growing literature from neurobiological studies of trace fear conditioning suggesting that the neural, molecular, and biochemical mechanisms that support long-term learning and anxiety may differ in trace and delay conditioning (Raybuck and Lattal, 2011).

2. Theoretical mechanisms of trace fear conditioning

In trace fear conditioning, the CS and US are temporally discontiguous. Thus, CS offset and US onset are separated by a stimulus-free interval. During subsequent testing, responding is weaker compared to that of delay conditioned subjects, where the CS and US co-terminate, thus overlapping in presentation. This is a robust behavioral difference that occurs after relatively few or many trials (Ellison, 1964; Kamin, 1961; Pavlov, 1927). The difference between trace and delay conditioning has led to different theoretical accounts that have focused on three potential mechanisms. These mechanisms include differences in associative strength (which has been the theoretical focus of most neurobiological studies of trace fear conditioning), inhibitory learning, or temporal pattern of responding.

2.1. Weakened associative strength

One obvious interpretation of the behavioral differences between trace and delay conditioning is that increasing the trace interval weakens the relation between the CS and US, resulting in poorer associative learning compared to when there is no trace interval (Pavlov, 1927). Thus, according to this interpretation, the difference in conditioned freezing between delay and trace fear conditioning demonstrates a deficit in learning; the two groups differ in terms of the associative strength of the CS. This may occur because in delay conditioning, the CS is a better predictor of the US compared to trace conditioning, where the CS does not immediately predict the US. Indeed, the term “trace” originated in this way of thinking, with the idea being that residual activation of the CS center in the brain was what was paired with US delivery (Pavlov, 1927). In modern approaches, this “trace” is most associated with the idea of a memory trace that decays as a function of time, resulting in a weaker CS representation paired with the US. The primary evidence for this account comes from simple differences in behavior during the CS. When a different stimulus intervenes between CS and US, the associative linking of the CS and US may be strengthened (e.g., Bolles et al., 1978; Rescorla, 1982). This bridging effect itself may occur through various mechanisms that include not just strengthened CS–US learning, but conditioned reinforcement and occasion setting (Rescorla, 1982; Thomas et al., 1989; Williams, 1991). The challenge, of course, for a weakened associative strength account is to demonstrate that weakened conditioned responding in the presence of the CS reflects weakened associative learning about the CS–US contingency (e.g., Lockhart, 1966; Smith et al., 2007). Experiments describe below suggest that weak behavioral responses after trace conditioning are not necessarily indicative of weak associative learning.

2.2. CS as safety signal

A second account of the difference in behavior induced by trace and delay conditioning focuses not on the effects on excitatory learning that occur during conditioning, but instead on the possibility that inhibitory learning causes reduced responding to the CS. According to this account, as the trace interval increases, the CS comes to signal the explicit absence of the US; i.e., the animal learns that the US will not occur when the CS is present (e.g., Kalat and Rozin, 1973; Moscovitch and LoLordo, 1968). Indeed, as the trace interval is lengthened, the trace conditioning procedure effectively becomes an explicitly unpaired procedure, in which the CS and the US have no contiguous relation (Smith et al., 2007). In these cases, there is more ongoing behavior in the absence of the CS, because the context alone better predicts the US (Marlin, 1981). Consistent with this idea, Huerta et al. (2000) found that a 30-s trace interval during conditioning resulted in a high level of freezing in the absence of the CS. This was followed by a depression of freezing with CS onset, followed by a resumption of freezing after CS termination. This suggests that the CS may act as a safety signal in trace fear conditioning, signaling the explicit absence of shock. However, the inhibitory nature of this learning, the time course over which this learning develops, and the procedural variations necessary to generate it remain to be determined.

2.3. Timing

A third theoretical account is that excitatory learning is maintained, even with increased trace intervals, but responses are timed to US presentation. Although the measured response in the presence of the CS is attenuated, the CS still retains the ability to signal to the animal when the US will occur. Thus, the weak responding in the presence of the CS after trace conditioning does not reflect what the animal learns, but rather, responding (or some other measure of learning) needs to be assessed at the time of US expectancy.

An examination of responding in fine temporal blocks sometimes reveals that responding begins low during the CS, but rises gradually to peak around the time of the previous US presentations (e.g., Drew et al., 2005; Huerta et al., 2000). With more conditioning, this peak becomes sharper, suggesting that the CS acquires temporally specific excitatory learning. Thus, responding is low during the CS not necessarily because of its poor excitatory or strong inhibitory association with the US. Instead, there is a strong excitatory association between the CS and the time of US presentation that is revealed by responding that peaks at the time of expected US presentation (Balsam, 1984).

The best evidence for timing of the conditioned response in trace conditioning comes from studies of eyeblink conditioning, which have revealed that as trace conditioning progresses, peak response shifts toward the time of US occurrence. This temporal learning is stimulus specific and shows selectivity in extinction (Joscelyne and Kehoe, 2007; Kehoe and Joscelyne, 2005). In fear conditioning, which involves much longer intervals, there is some evidence that rapidly learned CS–US associations result in a conditioned response being timed to coincide with the time at which the US is expected (e.g., Burman and Gewirtz, 2004; Drew et al., 2005). To account for the difference in response strength between trace and delay fear conditioning, timing would have to develop rapidly, because differences in trace and delay fear conditioning often occur after a single trial. The evidence for timing, as measured as peak responding at the time of expected footshock during a post-conditioning test, is mixed (see Bevins and Ayres, 1995; Davis et al., 1989; Lattal and Abel, 2001). Based on this examination of behavior during the CS, it appears that temporal response patterns do occur, but may require extensive training to develop (see also Delamater and Holland, 2008).

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