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Magnitude and Timing of Conditioned Responses in Delay and Trace Classical Conditioning of the Nictitating Membrane Response of the Rabbit (*Oryctolagus cuniculus*)

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The present experiment characterized conditioned nictitating membrane (NM) movements as a function of CS duration, using the full range of discernible movements (>.06 mm) rather than movements exceeding a conventional criterion (>.50 mm). The CS–US interval was fixed at 500 ms, while across groups, the duration of the CS was 50 ms (trace), 550 ms (delay), or 1050 ms (extended delay). The delay group showed the highest level of acquisition. When tested with the different CS durations, the delay and extended delay groups showed large reductions in their responses when their CS was shortened to 50 ms, but the trace group maintained its response at all durations. Timing of the conditioned movements appeared similar across all manipulations. The results suggest that the CS has both a fine timing function tied to CS onset and a general predictive function tied to CS duration, both of which may be mediated by cerebellar pathways.

Keywords: conditioning, timing, rabbit, trace conditioning, delay conditioning

Delay conditioning and trace conditioning were first identified by Pavlov (1927). In delay conditioning, the conditioned stimulus (CS) fills the interstimulus interval (ISI) between CS onset and onset of the unconditioned stimulus (US), whereas in trace conditioning, CS offset occurs before US onset. Operationally, these names only roughly denote the range of manipulations. Trace conditioning includes both brief CSs that are tiny fractions of the ISI and longer CSs that occupy nearly the entire ISI. In delay conditioning, CS offset may coincide with US onset, coincide with US offset, or even occur after US offset.

It is a matter of considerable interest whether and how the two paradigms engage different processes (e.g., Clark & Squire, 1998). In eyeblink conditioning, they differentially engage cerebellar and cerebral pathways, depending on a variety of factors, particularly the ISI (Walker & Steinmetz, 2008). For short ISIs (<300 ms), only cerebellar pathways are needed regardless of CS duration, although the exact pathways may vary (Woodruff-Pak & Disterhoft, 2008). For midrange ISIs (e.g., 500 ms), delay conditioning requires only cerebellar pathways, but trace conditioning requires both cerebellar and cerebral (hippocampal and prefrontal cortex) pathways (Moyer, Deyo, & Disterhoft, 1990; Solomon, Vander Schaaf, Weisz, & Thompson, 1986; Walker & Steinmetz, 2008; Woodruff-Pak & Disterhoft, 2008). For long ISIs (e.g., 1400 ms), both types of pathway appear needed for both paradigms (Beylin et al., 2001).

Despite differences in their neural mechanisms, delay and trace conditioning appear behaviorally continuous. Kehoe and Schreurs (1986) demonstrated that for an ISI of 800 ms, the rate and asymptote of conditioned response (CR) acquisition in the rabbit nictitating membrane (NM) preparation increased as the CS duration was manipulated across values of 50, 200, and 800 ms. Moreover, the timing of eyeblink CRs has appeared similar across the two paradigms. Eyelid closure starts around the midpoint of the ISI, and peak closure occurs around the time of US presentation (Claflin, Garrett, & Buffington, 2005; Kehoe & Macrae, 2002; Schneiderman, 1966; Smith, 1968).

As a result of this behavioral continuity, models of eyeblink conditioning at both the behavioral level (Buhusi & Schmajuk, 1999; Grossberg & Schmajuk, 1989; Kirkpatrick & Church, 1998; Machado, 1997; Sutton & Barto, 1990; Vogel, Brandon, & Wagner, 2003) and the neural level (Buonomano & Mauk, 1994; Gluck, Reifsnider, & Thompson, 1990; Medina, Garcia, Nores, Taylor, & Mauk, 2000) depict delay and trace conditioning in virtually the same way. These models originated in Pavlov's (1927, pp. 103–104) explanation of "inhibition of delay," in which extending a CS caused progressive delays in the CR such that it remained near US onset. Pavlov (1927) proposed that the CS produces a series of stimulus elements, each of which acquires its own associative strength depending on its proximity to the US.

If CR timing is primarily mediated by cerebellar pathways, then the behavioral similarity between delay conditioning and trace conditioning is not surprising. Nevertheless, there remains the possibility of an undetected difference. Along these lines, the present experiment was conducted to compare delay conditioning and trace conditioning on the basis of recent fine-grained analyses of rabbit NM conditioning (Kehoe, Ludvig, Dudeney, Neufeld, &

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Sutton, 2008; Kehoe, Olsen, Ludvig, & Sutton, 2009). These analyses examined the entire range of NM movements, including small but detectable movements—less than .50 mm—that have not usually been counted as CRs and hence largely ignored (e.g., Garcia, Mauk, Weidemann, & Kehoe, 2003).

These fine-grained analyses revealed that movements as small as .10 mm showed orderly timing. These observations, however, were obtained using an atypical delay paradigm in which the CS was extended well past the US. By using this extension, the CS duration on CS-alone test trials was constant across ISIs, and the NM movement could occur without interruption by CS offset. Hence, the main empirical aim of the present experiment was to determine whether or not a similar pattern of timing in smaller and larger movements would appear in more typical delay and trace paradigms. To do so, two manipulations were conducted.

First, during initial training, the ISI was fixed at 500 ms, and across three groups, the duration of the CS was either 50, 550, or 1050 ms, thus creating a conventional trace paradigm, a conventional delay paradigm, and an extended delay paradigm. The 500-ms ISI was chosen, because it falls in the range in which delay and trace conditioning diverge most noticeably in their engagement of cerebellar and cerebral pathways.

Second, after initial training, all groups were administered tests with all three CS durations to determine whether or not movements of all sizes were sensitive to alterations in CS duration. Kehoe and Napier (1991) found that, using the conventional criterion for CRs (>.50 mm), asymmetric effects appeared after delay and trace conditioning. When a 400-ms delay CS was truncated, CR likelihood was dramatically reduced, and the latencies of the CR showed a small increase of approximately 100 ms. In contrast, extension of a 25-ms trace CS yielded only tiny reductions in CR likelihood and tiny increases in CR latencies. However, there was no way of knowing whether this asymmetry would appear if smaller movements were included in the data. The reduction in CR likelihood in the delay condition may have been an artifact of using the .50-mm criterion, which could mask small but discernible conditioned movements.

Method

Subjects and Apparatus

The subjects were 24 female, albino rabbits, 70–80 days old, weighing around 1.5 kg on arrival. With apparatus based on that of Gormezano (1966), the CS was an 83-dB (SPL, C scale) tone superimposed on white noise (76 dB SPL, C scale). The US was a 50-ms, 3-mA, 50-Hz AC current delivered via wound clips 10 mm behind the dorsal canthus of the right eye and 15 mm below the eye. No eye straps were used, and the transducer was coupled to a loop of surgical silk sutured into the right NM under local anesthetic (proxymetacaine hydrochloride; Gormezano & Gibbs, 1988). All procedures were approved under relevant ethics legislation.

Procedure

After 60 min of adaptation to the apparatus, the rabbits were assigned randomly to three groups ($n = 8$) designated as Trace, Delay, or Extended, using CS durations of 50, 550, and 1050 ms, respectively. For all groups, the ISI (CS onset – US onset) was 500 ms. (One rabbit was removed from Group Delay because of an eye infection.)

Stage 1 contained 16 sessions, each divided into six blocks of nine CS–US trials followed by one CS-alone test trial using the group's CS duration. Stage 2 contained four sessions, each containing a mixture of 30 CS–US trials and 30 CS-alone trials, 10 each of 50, 550, and 1050 ms in duration. The mean intertrial interval (ITI) was 60 s (uniformly distributed over 50–70 s).

Statistical Tests

Planned statistical contrasts used a Type I error of .05 (O'Brien & Kaiser, 1985). Effect size was measured by partial eta squared (η_p^2), which equals the proportion of explained variance ($SS_{effect}/(SS_{effect} + SS_{error})$; Cohen, 1973). According to Cohen (1988), $\eta_p^2 = .010$, .059, and .138 imply small, medium, and large effects, respectively.

Results

Stage 1

Panel A of Figure 1 shows the mean magnitude of NM movements on CS-alone trials for each day in Stage 1. Magnitude was defined as the largest closure on each trial, including trials with movements of zero. To see the fine-grained changes in NM magnitude across training, particularly for smaller movements, in Panels B, C, and D, we plot the $\log_{10}$ magnitude of each movement on successive CS-alone trials by all animals in each group. (Because there is no logarithm for zero, movements of zero could not be plotted.)

As can be seen in all the panels, each group showed a progressive growth in magnitude. This growth, however, was accompanied by considerable variability, consistent with previous observations in the rabbit (Kehoe et al., 2008) and other species (Gallistel, Fairhurst, & Balsam, 2004). Despite this variability, Group Delay showed significantly greater growth than did the other two groups, $F(1, 20) = 5.11$, $p < .05$, $\eta_p^2 = .204$.

The magnitude measure appeared more sensitive than did the conventional method of splitting the range of magnitudes into CRs and non-CRs. Using a conventional criterion of .50 mm, Groups Delay, Extended, and Trace showed similar rates of acquisition and similar terminal likelihoods of 86%, 79%, and 88% CRs (SEM = 9%), respectively. Any apparent differences were not statistically significant (all ps $> .10$).

Panel E shows the mean onset latency and peak latency for each group for Days 9–16, by which time most of the growth in magnitude had occurred. Onset latency was the time between CS onset and the initiation of NM closure that departed from the baseline by more than .06 mm (Marshall-Goodell, Schreurs, & Gormezano, 1982). Peak latency was defined as the time from CS onset to the point of maximum closure. All three groups showed similar onset and peak latencies (all ps $> .10$).

Panels F, G, and H show the onset latencies (open circles) and peak latencies (solid circles) for each trial for all animals in each group plotted as a function of $\log_{10}$ magnitude. Movements as small as .06 mm were included in the plots. The onset and peak latencies appeared similar across the entire range of movement.

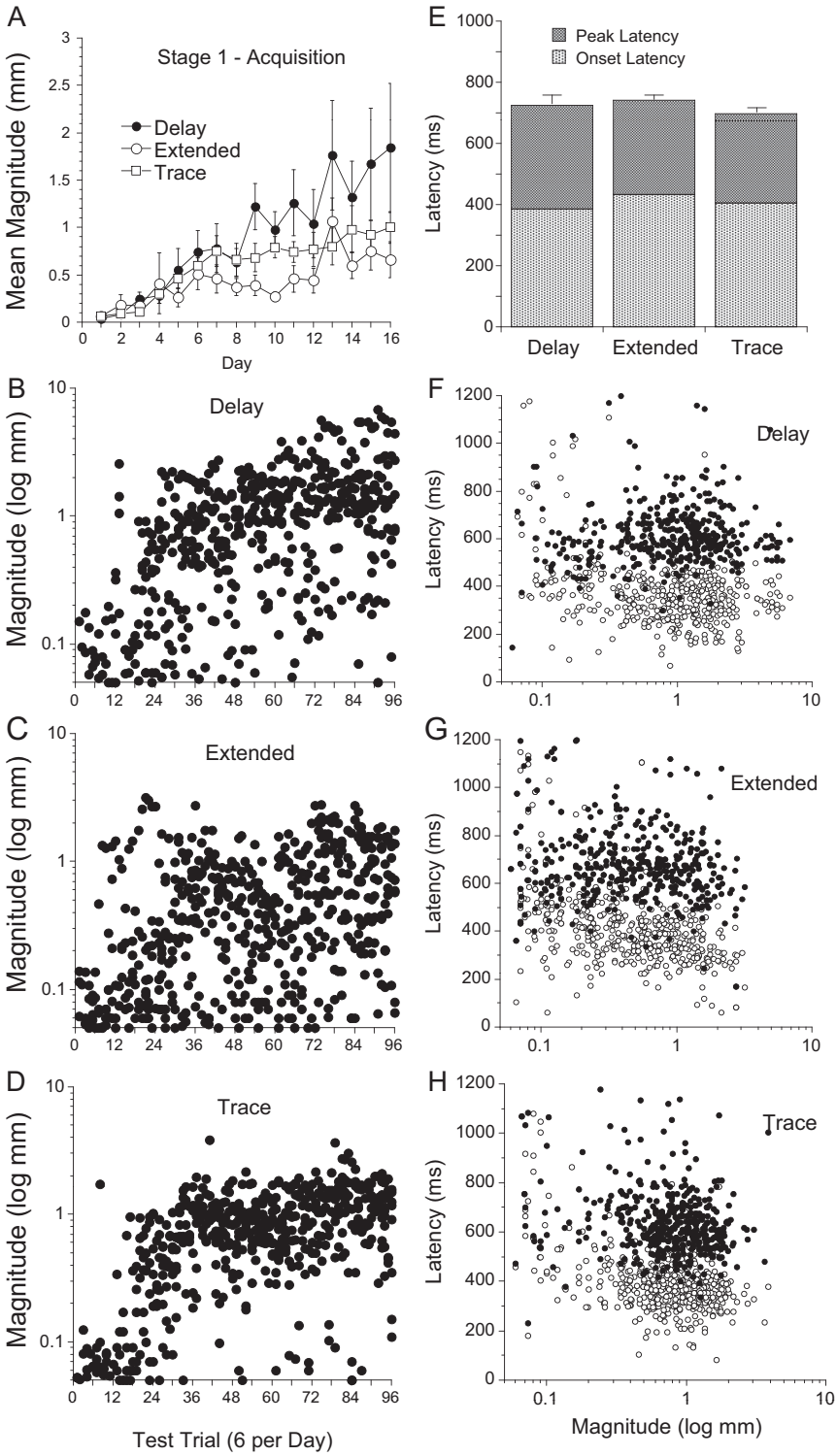

Figure 1. Panel A shows the mean magnitude of nictitating membrane (NM) movements on Test CS trials as a function of days of training. In Groups Delay, Extended, and Trace, the duration of the conditioned stimulus (CS) was 550, 1050, and 50 ms, respectively. Error bars represent the standard error of the mean. Panels B, C, and D plot the magnitude of all detectable NM movements (>.06 mm) as a function of successive CS-alone test trials in Stage 1 for all the animals in each group. Panel E shows the mean onset latency and peak latency across all days of Stage 1. Panels F, G, and H plot the onset latencies (open circles) and peak latencies (solid circles) as a function of their magnitude in Stage 1 in each group. Note that magnitudes in Panels B–H are plotted on a logarithmic scale.

The contribution of spontaneous movements to these plots was small. Specifically, in 1200-ms periods during the ITIs of Day 1, the likelihood of a spontaneous movement ≥.06 mm was .07 (*SD* = .13). For progressively larger criteria of .125, .25, and .50 mm, the likelihood of spontaneous movement declined to .02, .01, and .01, respectively (*SD*s = .02, .01, and .01).

Stage 2

Panel A of Figure 2 plots the mean magnitude of the NM movements on CS-alone trials for each group as a function of the Test CS duration in Stage 2. Test CS duration had a profound effect in Groups Delay and Extended. Group Delay showed very small movements when tested with the 50-ms CS, and these were significantly smaller than the responses to the 550-ms CS used in acquisition, $F(1, 20) = 38.31$, $p < .01$, $\eta_p^2 = .657$. The 1050-ms CS increased the magnitude of the movements in Group Delay only by a small, nonsignificant amount, $F(1, 20) = 3.50$, $p = .08$, $\eta_p^2 = .149$. Group Extended showed a similar pattern, despite its movements being smaller than those of Group Delay. Specifically, Group Extended showed smaller movements to the 50-ms CS than to the 550-ms CS, $F(1, 20) = 9.07$, $p < .01$, $\eta_p^2 = .312$, which in turn did not discernibly differ from the 1050-ms CS ($F < 1$). In contrast to Groups Delay and Extended, Group Trace displayed similar magnitudes to all three Test CSs (*F*s <1).

Panel B of Figure 2 depicts the percentage CRs calculated by using the criterion of .50 mm for counting a NM movement as a CR. The pattern of results paralleled that obtained with the magnitude measure. Likewise, statistical tests confirmed that Groups Delay and Extended both showed a significantly lower likelihood of a CR to the 50-ms CS than to the 550-ms CS, *F*s(1, 20) = 118.53, 62.07, *p*s < .01, $\eta_p^2 = .856, .756$. Any other apparent differences within groups were not statistically significant.

Notwithstanding the large impact of CS duration on the magnitude of movements in Groups Delay and Extended, timing ap-

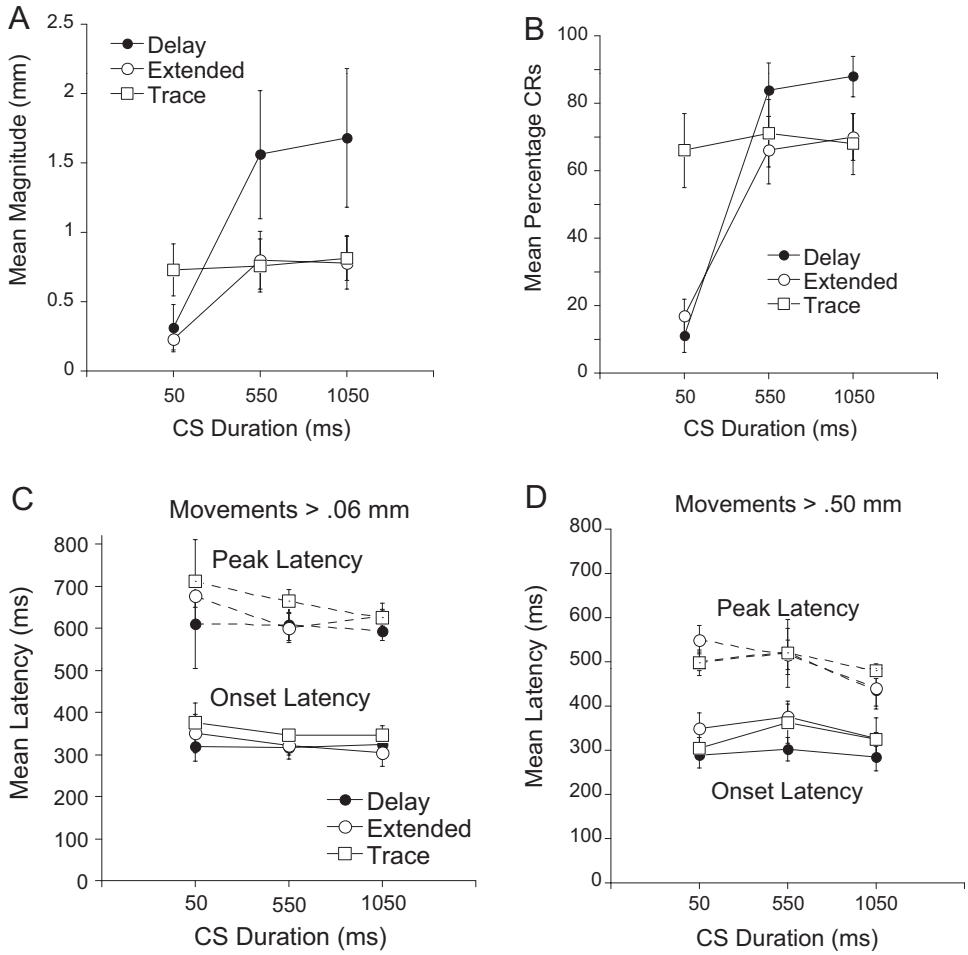

Figure 2. Results from Stage 2 plotted as a function of the durations of the Test CS (conditioned stimulus). Panel A shows the mean magnitude of nictitating membrane (NM) movements. Panel B shows the mean percentage of trials containing a "conditioned response (CR)" when defined as a NM movement greater than .50 mm. Panels C and D each show the mean onset latency (solid connecting lines) and mean peak latency (dashed connecting lines) for, respectively, all discernible NM movements (>.06 mm) and NM movements greater than .50 mm, the conventional criterion for a "CR." Error bars represent the standard error of the mean.

peared largely unaffected. The lower panels of Figure 2 show the mean onset and peak latencies for all discernible movements (>.06 mm, Panel C) and for movements greater than the .50-mm criterion (Panel D). For each latency measure, any apparent differences among groups or durations were not significant (all ps $> .10$). A comparison between the panels reveals that when all discernible movements are included (Panel C), the mean of the peak latencies was significantly longer than for those movements that exceeded a .50-mm criterion (Panel D), $F(1, 20) = 135.48$, $p < .01$, $\eta_p^2 = .871$. In the latter case, the overall mean peak latency was 469 ms (SEM = 36 ms), which is consistent with previous observations that the CR peak occurs near the US (Kehoe & Macrae, 2002).

Discussion

The present experiment was aimed at characterizing the magnitude and timing of conditioned NM movements in conventional delay and trace conditioning paradigms when all discernible movements were included. In brief, the results confirmed and extended the previous fine-grained analyses based on an extended delay paradigm. Specifically, in Stage 1, the magnitude of NM movements grew in an orderly fashion across training, and a similar pattern of timing appeared across the range of discernible movements (≥.06 mm). The results also confirmed observations obtained using only larger movements that, for a given ISI, conventional delay conditioning proceeds more rapidly and to a higher asymptote than do either trace conditioning (Kehoe & Schreurs, 1986; Schneiderman, 1966; Schneiderman & Gormezano, 1964) or extended delay conditioning (Schneiderman & Gormezano, 1964; but see Kehoe, 2000).

For Stage 2, the results confirmed that there is an asymmetry between delay conditioning and trace conditioning (Kehoe & Napier, 1991). Truncation of a delay CS dramatically reduced the magnitude of the movements, and a corresponding extension of a trace CS did not discernibly alter their magnitude. In both cases, the timing of the movements remained intact. The present results revealed that this pattern was not an artifact of excluding movements smaller than the conventional criterion for counting CRs.

The present results cannot directly identify which neural structures mediate the timing of CRs in delay conditioning versus trace conditioning. However, the results do help refine our picture of what theoretical processes of timing underpin the two paradigms. ISI studies have consistently shown that the timing of CRs, now including tiny ones, is consistent with spectral timing models (Kehoe et al., 2009). These models assume that CR acquisition and timing is mediated by the progressive activation of elements initiated by the CS (e.g., Desmond & Moore, 1988; Grossberg & Schmajuk, 1989; Ludvig, Sutton, Verbeek, & Kehoe, 2009; Machado, 1997). Each element is assumed to develop associative strength in proportion to its level of activation during the US. During subsequent presentations of the CS, the magnitude of a CR at any point in time reflects the summation of the associative strengths of the elements active at that moment. Hence, a CR's peak tends to occur near the time of US delivery, when there had been the greatest overlap of elements with the US.

At a neural level, a spectrum of elements may arise from the progressive time delays introduced as CS input is spread through the cerebellar cortex via the synapses among mossy fibers, granule cells, parallel fibers, and Purkinje cells (Buonomano & Mauk, 1994; Mauk, Medina, Nores, & Ohyama, 2000 Moore & Choi, 1997). More specifically, timing may be explained by the planar nature of Purkinje cells coupled with their dendritic morphology (Ito, 1984; Steuber & Willshaw, 2004). The first inputs from the parallel fibers activated by a CS would converge near the base of Purkinje cells. Succeeding inputs would then ascend the dendritic tree as time elapses. Recently, ISI-dependent activity has been observed in individual Purkinje cells (Jirenhed, Bengtsson, & Hesslow, 2007).

Although these models generally account for the acquisition and timing of conditioned movements, they have not addressed possible differences between trace and delay conditioning. Indeed, other than the slower and lower acquisition often seen in trace conditioning, there has been little evidence of behavioral differences in NM conditioning. However, the results of Stage 2 in the present experiment plus those of Kehoe and Napier (1991) reveal that durational features of the CS affect the expression of conditioning as well as its acquisition.

As a basic assumption, all available models assume that a stimulus change—most importantly, CS onset[1]—is the major source of the internal stimulus sequence. The continuing portion of CS has been thought to be either a source of additional stimulus elements (Gormezano & Kehoe, 1981; Sutton & Barto, 1990) or the basis of an enduring *on* element (Ludvig et al., 2009). Both these approaches effectively increase the intensity of longer CSs, which explains the greater acquisition in conventional delay conditioning relative to trace conditioning. However, these approaches differ in their predictions concerning (a) the relatively low level of acquisition in extended delay conditioning and (b) the asymmetric effects of truncating a delay CS versus extending a trace CS.

Added-elements hypotheses are well supported by the present results, but not entirely. Like the onset-generated elements, the elements generated during the CS are assumed to have discrete time courses and gain associative strength in proportion to their overlap with the US. Truncating a delay CS would eliminate those elements, eliminate activation of their associative strengths, and as seen, reduce the magnitude of the CR. Conversely, extending a trace CS would add elements, but these elements would have no associative strength and, as seen, would not affect the CR.

So far so good, but an added-elements hypothesis cannot easily explain the maintenance of timing seen when a delay CS is truncated. The added elements, being closer to the US, should play a major role in governing the peak of the CR. Their elimination should especially reduce the magnitude of later portions of a CR. Hence, the peak during a truncated CS should not only be smaller but earlier. In fact, there is no evidence for such a shift in timing: The present results failed to show any shift, while Kehoe and Napier (1991), who recorded only larger movements, observed a shift in the opposite direction.

Given the large role that elements added during the CS may play in generating the overall CR versus their negligible role in timing, they may effectively serve as an undifferentiated *on* element that persists throughout the CS. A continuing *on* element could gain

[1] The offset of a stimulus can also serve as a CS separate from its onset, but in trace conditioning of the rabbit NM preparation, this effect emerges only when the CS is several hundred milliseconds or longer (Desmond & Moore, 1991; Kehoe & Weidemann, 1999; Kehoe & Macrae, 2002).

substantial associative strength but leave control of the timing to the differentiated elements generated at CS onset (Ludvig et al., 2009). The duration of the *on* element may also explain the greater CR acquisition in conventional delay conditioning in relation to both trace conditioning and extended delay conditioning. For the trace CS, the *on* element would not outlast its 50-ms duration, would not overlap the US, and would gain no associative strength. Hence, only the spectrum of elements generated at CS onset would gain associative strength. For the conventional delay CS, the *on* element would persist up to the US and add to the total intensity of the CS, thus facilitating acquisition of associative strength throughout the CS. Finally, for the extended delay CS, its duration after the US would expose its associative strength to extinction, which would reduce the net positive associative strength of the *on* element.

If an *on* element does exist, its function and neural substrates need delineation. Its function in conditioning may vary with the ISI. For shorter ISIs, in which accurate timing occurs, it may play little role; hence the similarity between trace and delay conditioning at the shorter ISIs. However, as the ISI lengthens and accurate timing declines, an *on* element may allow the CS to continue to provide a general predictive function for an impending US, up to some outer limit. The presence of an *on* element in delay conditioning but not in trace conditioning may also help explain why these two procedures apparently rely on different cerebellar pathways (Woodruff-Pak & Disterhoft, 2008).

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