TRACE FEAR CONDITIONING: A ROLE FOR CONTEXT?

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INTRODUCTION

Several recent studies of fear conditioning are based on trace-conditioning, which allows manipulations of the balance between conditioning to explicit and background contextual cues (55). However, because in trace conditioning a temporal gap (the trace interval) separates the conditioned stimulus (CS) from the unconditioned stimulus (US), trace conditioning remains a challenge to most association theories which require contiguity between the events to be associated (21). While already puzzling when limited to trace intervals of a few hundred milliseconds, as in conditioning of the nictitating membrane (31), this question becomes unavoidable when dealing with extremely long trace intervals (hours) as in taste aversion learning (18). We will focus on the intermediate case of fear conditioned responses (CRs) which can be obtained over trace intervals of one minute or more (28, 46). Through a brief survey of the literature relevant to trace fear conditioning, this article explores the idea that background contextual cues might provide the missing link between the temporally separate CS and US.

LACK OF SPECIFICITY OF TRACE CONDITIONED RESPONSES.

Fear conditioning is obtained in many species by pairing an initially neutral CS (often auditory) with an aversive US such as a mild electric shock. The resulting internal state of "fear", induced by presentation of the CS alone, is characterized by the activation of several response systems, both physiological and behavioural (15), although fear is usually evaluated by conditioned suppression (28) or freezing (6). Fear responses constitute a distinct class of CRs since they are rapidly acquired and allow relatively long CS-US intervals (33). To account for trace conditioning, Pavlov (52) postulated the existence of a stimulus "trace" in the nervous system which did not stop with the physical stimulus, but persisted for long enough to allow associations between this trace and a subsequent US.

The notion of persistent stimulus traces raises the question of when trace CRs will occur. Conditioned responses obtained under a delay protocol (US occurring just at the end of the CS) are known to display a maximum near the expected time of occurrence of the US (13, 50, 60). With a trace protocol, the temporal specifici-

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ty of CRs is less well known (12), except in the case of nictitating membrane responses (30). Experiments with cardiac fear responses conditioned to auditory stimuli have shown that the duration and temporal parameters of responses are not, as some theories would predict (19), proportional to the CS-US interval (37). Rather, CRs tend to follow one of two privileged shapes (Fig. 1). In particular, responses obtained with trace intervals of 7 sec and 15 sec were identical. Similar characteristics of trace CRs were observed by McEchron *et al.* (44). These results suggest that during trace conditioning, the timing of US occurrence may be encoded in a categorical (short/long) rather than in a proportional manner. This issue would require investigation with longer trace intervals and different measures of fear.

Conditioned responses acquired under a trace protocol have other peculiarities. Pavlov (52) was the first to report that trace responses conditioned to a given stimulus were prone to generalize to a variety of novel stimuli, including some from other sensory modalities. More recently, Honey and Hall (27) confirmed that discriminative fear conditioning appeared more slowly under a trace protocol than under a delay protocol. A similar result was obtained with cardiac CRs (36). Furthermore, Marchand and Kamper (37) observed more generalization of cardiac responses following conditioning with a trace interval of 7 to 15 sec than with a trace interval of 3 sec. These results argue in favour of the existence of both a short stimulus trace capable of sustaining specific responses and of a longer type of trace which allows generalization between stimuli. Interestingly, generalization of audito-
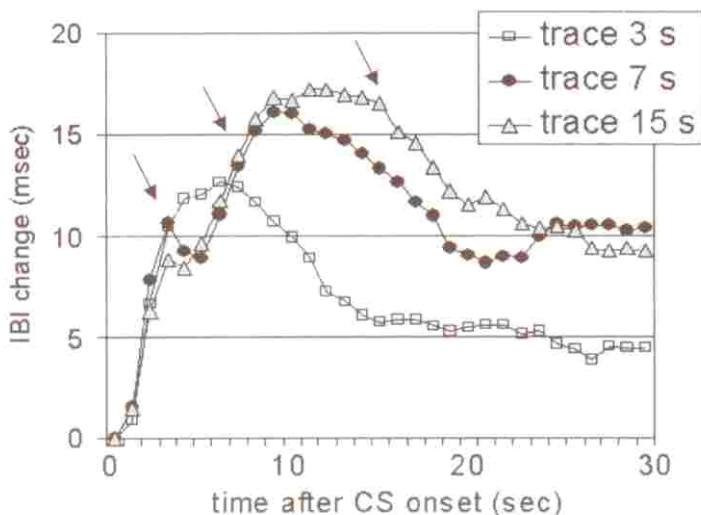

Fig. 1. - *Time course of cardiac trace responses during CS alone trials.*

Increases in the inter-beat interval (IBI) following CS onset correspond to conditioned bradycardia. Rats were submitted to trace pairings of a 0.5 sec auditory CS with a tail shock US. CS-US intervals were 3, 7 or 15 sec. The peak bradycardiac response did not occur at the expected time of US occurrence (arrows), nor at a time proportional to the CS-US interval. Adapted from Marchand and Kamper (37).

ry-cue fear responses has been studied by Rudy and Pugh (63), although in a delay protocol with freezing as the fear measure. These authors proposed that generalized fear responses shared similar mechanisms with fear conditioned to contextual cues.

ANALOGIES BETWEEN TRACE FEAR RESPONSES AND CONTEXTUAL FEAR.

This raises the possibility that trace conditioning could involve conditioning to background contextual cues, which are necessarily present throughout the experiment and in particular during the "empty" trace interval. Fear to contextual cues is known to develop when no explicit CS is present to signal shocks. This has led to a number of investigations in rodents (40) using various measures of contextual fear (2). Contextual conditioning is thought to require an unifying process between a number of tonically present stimuli with low salience (16, 62). Assuming that these contextual stimuli are represented by a low level of activity in the nervous system, a stimulus trace could have similar properties: not only is it present for long periods of time, but also it is likely to elicit far less activity than the CS itself.

With trace conditioning, there is evidence that CRs can develop to both the CS and the context. Actually, a trace conditioning protocol is one of the conditions used to favour contextual conditioning (38, 74). Although the contextual stimuli are always present at the time of US occurrence, in a delay protocol conditioning to the CS may occur with much less contextual conditioning than in a trace protocol (38, 39). This overshadowing of the context by the explicit CS results in a balance between conditioning to the two stimuli (58). On the other hand, to the extent that trace conditioning depends upon contextual conditioning, there should be no balance between conditioning to the context and conditioning to the CS in this condition (38) (Fig. 2). Indeed, rats conditioned with a long trace interval (30-60 sec) may display more conditioning to the context than rats conditioned with a short trace interval (0-10 s), without displaying less conditioning to the CS (55, 74, 75). In other studies, conditioning of CS and context showed a balance (25, 46, 51, 66). In these studies, the trace response to the CS is usually measured during the CS itself. However, when tested with a long CS, trace responses do not appear homogeneous, the early part of freezing responses showing much less freezing than the later part (38). Moreover, a measure after the CS could yield different results. Quinn *et al.* (55) actually reported that marked levels of freezing were present after presentation of the CS and even in a group conditioned with a backward (US-CS) protocol, which would be expected to prevent conditioning to the CS. Similar observations were made by Marchand *et al.* (39) with trace procedures and an explicitly unpaired procedure, as compared with conditioning with unsignaled shocks. These observations suggest that fear responses to the context and after the CS may occur under similar conditions, and are consistent with the idea that context and CS become associated during trace conditioning (55).

A second line of evidence in favour of a link between trace conditioning and contextual conditioning comes from lesion, pharmacological and developmental studies. Lesions of the dorsal hippocampus, for instance are known to disrupt contextual conditioning when performed either before (54, 66) or after conditioning (1, 32,
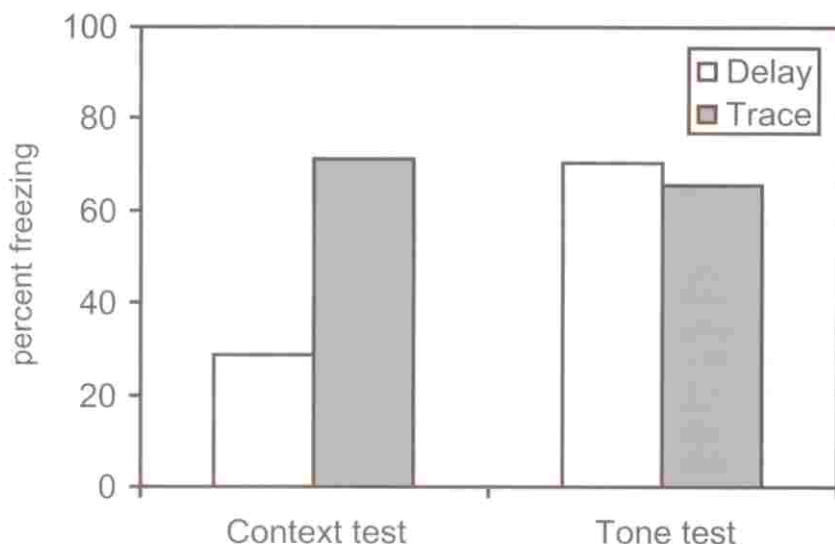
Fig. 2. - *Trace conditioning may not show a balance between CS and context.*

Freezing responses in rats averaged during 8 min of context test or 2 min of tone test in a different context respectively 24 h and 48 h following conditioning with 6 pairings of a 15 sec CS and a footshock US. Trace interval was 0 (delay) or 50 sec (trace). Adapted from Marchand *et al.* (38).

41). Interestingly, hippocampal lesions also impair trace but not delay conditioning in nictitating membrane experiments (5, 67) and fear conditioning (44). Few experiments have explicitly compared the effects of lesions in contextual and trace fear conditioning, but impairments in both tasks have been reported following surgical or neurotoxic lesions performed either before (43, 44) or after conditioning (55). Similarly, infusions of alcohol prior to conditioning impair contextual and trace but not delay fear conditioning (73). Finally, unlike delay conditioning which is already present in 15-18 days-old rats, both contextual (61) and trace (49) fear conditioning develop during the third and fourth weeks of the rat's life.

ASSOCIATIVE LEARNING THEORIES AND TRACE CONDITIONING.

There are basically three classes of theoretical accounts for trace conditioning: timing models, multiple-time-scale models and conditioning of secondary cues. Actually, some major models of associative learning do not explicitly address trace conditioning (53, 58). According to timing models (9, 17, 64, 75), any association embodies a representation of the timing between events, so that trace conditioning is not different in nature from simple delay conditioning. The trace interval should not prevent the establishment of an association because time itself is encoded and not the residual trace of a particular stimulus. These models are specified to various degrees, the most elaborate being the scalar expectancy theory (SET) and rate estimation theory (RET) models (11, 17). However, these models become rather com-

plex when applied to trace conditioning. In particular, they appear to require a decision process that examines the distribution of USs relative to a time marker (17, p. 31). Besides, because of their scalar timing properties, these models do not predict the existence of privileged responses shapes as found in cardiac studies (37). In addition, RET incorporates a principle of parsimony which minimizes the number of predictors in a competition situation. As a result, it is not clear how these models allow conditioning both to the CS and to the context in the same subject. Nevertheless, timing models have received support from a series of experiments demonstrating that subjects (rats) learn the intervals between events during conditioning, at least within a range of 10 sec (3, 12, 65).

However satisfactory timing models may be from a theoretical and empirical viewpoint, they do not easily map onto a biological implementation. The processes needed to measure, subtract or otherwise compare temporal intervals do not emerge in a straightforward manner from the basic properties of neurons or neural networks. More biologically oriented models of conditioning have been proposed, which accommodate both delay and trace conditioning. Early models were mostly extensions of conditioning theories assuming that a CS was followed by a single trace (68, 69). Wagner's SOP model (71) was a little more elaborate, involving a primary CS trace decaying with a fixed time course and leading to excitatory conditioning insofar as it overlapped the primary US trace. A secondary US trace was involved in the expression of the conditioned response. In these single trace models, both learning and expression of the conditioned response are essentially constrained by the dynamics of the trace. Actually, Wagner introduced an affective extension of his model which accounted for long CS-US intervals involved in fear conditioning (72). Later models allowed multiple traces so that time could be to some extent embodied into the association (30). They constitute a class of connexionist models called multiple-time-scale models or spectral models (10). These models assume that any sensory event elicits multiple parallel patterns of activity or traces in the central nervous system, each trace having a particular time course. Traces may be triggered by the CS onset or offset (14) but not necessarily maintained during the CS (7). In this way, time elapsed since the event is uniquely represented by the pattern of active traces, and this pattern can become associated with the US (8). Moreover, the same traces which are associated with the US during conditioning are also responsible for the expression of the conditioned response (Fig. 3). In this way, during conditioning with short trace intervals, most traces should become associated with the US so that the response may appear early. However, long traces would largely be active after the US and thus become inhibitory, preventing the development of responses of long duration. Conversely, during conditioning with long trace intervals, long traces become associated with the US but short traces are never active during the US. They may become inhibitory, resulting in responses being delayed. As a result, the peak of the conditioned response is expected to approximate the time of US occurrence. This type of model has been developed in various forms (7, 14, 22, 77), with a related class of models relying on behaviour as a support for timing (34). These models appear quite successful within a time range of one or two seconds as in delay and
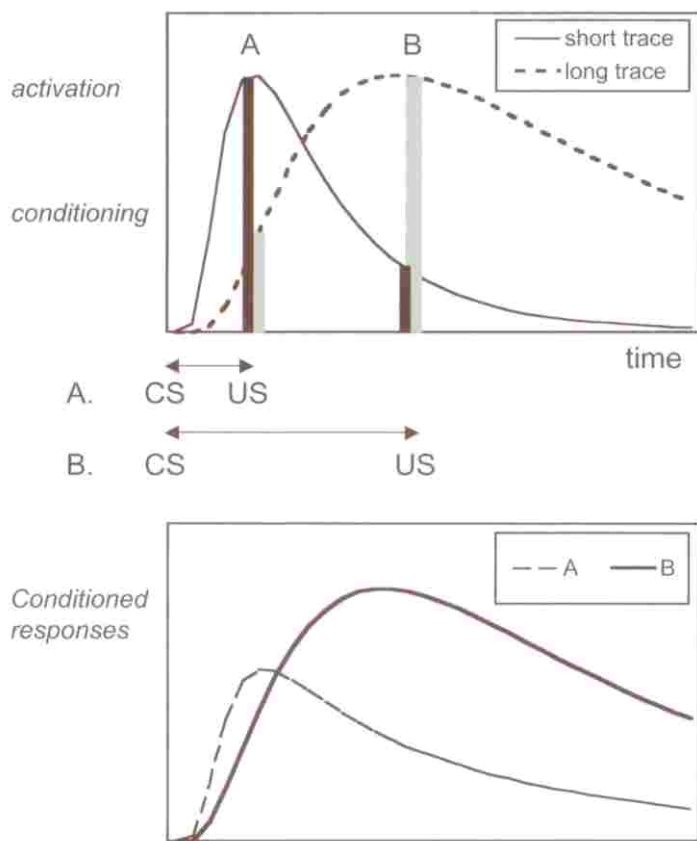
Fig. 3. - *Schematic represen-tation of a multiple-time-scale model with only two traces.*

Upper panel: CS onset acti-vates both a short and long trace, with distinct dynamics. Each trace will be condi-tioned (bars) as a function of its activation at the time of US occurrence. For simplici-ty, inhibitory conditioning is not represented. Lower panel: The shape of the CR is a weighted average of the con-ditioned traces (bar height x activation). Responses condi-tioned to short CS-US inter-vals (A) are dominated by the short trace dynamics whereas responses conditioned to long CS-US intervals (B) are dom-inated by the long trace dynamics.

trace conditioning of the nictitating membrane (23). However, they have not often been matched with fear conditioning experiments (7), which may involve trace intervals of up to one minute. Furthermore, the nature and diversity of prolonged trace activity required by these models still awaits firm biological support. Actually, if only a small number of trace dynamics are available, it would reduce the tempo-ral selectivity of the conditioned response in a manner compatible with some of the observed data (37).

A third way to account for trace conditioning is to assume that the CS somehow becomes associated to other stimuli, that we may call secondary cues, which can bridge the temporal gap between CS and US. Since it is impossible to eliminate sec-ondary cues during the trace interval, this possibility must be considered. Unfortunately, this issue has seldom been addressed (20, 29, 56), and it is not clear whether an intervening cue ("marking" the CS) facilitates trace fear conditioning or simply improves discrimination (24). Indirect evidence for an unitary representation of context and CS may be found in some experiments with delay conditioning in a first context, showing that further conditioning of the CS in a second, distinct con-

text enhances fear to the first context (35). Besides, two mechanisms for condition-
ing via secondary cues are sometimes contrasted, second-order conditioning and
within-event learning (42, 57). In the following section, we will see how a theory
involving an unitary representation of the CS trace and the context explains some of
the intriguing data about trace fear conditioning and may be used to generate new
predictions.

TRACE FEAR CONDITIONING: AN HYPOTHESIS.

We propose that trace fear conditioning may be best described in the framework
of a theory proposed by McLaren *et al.* (47). According to this theory, each stimu-
lus is composed of a set of elements which become associated together as long as
they are simultaneously presented. This first process is one of unification. On the
other hand, separate presentation of elements leads to the elaboration of distinct rep-
resentations through inhibitory mechanisms in a second stage. Since we are dealing
with stimuli present for extended periods of time, inhibitory learning should depend
not only upon the discriminability of stimuli, but also upon their duration rather than
number of presentations. A brief, salient CS should be quickly discriminated from
the context. On the other hand, a prolonged stimulus trace may be assumed to con-
sist of few elements which are active simultaneously with background contextual
cues. It should at first undergo the unification process and become embedded into a
unified representation of the context. Generalization may be described in terms of
response to stimulus elements which are common to various CSs. Thus, a long stim-
ulus trace may include mainly common elements and may support discrimination
less easily than a short stimulus trace (37). Moreover, the initial part of the response
may be dominated by the short stimulus trace and may differ from the later part.

The consequences of such an interpretation are that trace fear conditioning should
first generate CRs to both the context and the CS trace, and that these CRs ought to
be mainly apparent after rather than during CS presentation. This should also be the
case following explicitly unpaired CSs and USs, because unification only depends
on the CS being presented in context. This unification process may allow associa-
tions across long trace intervals although the CS trace may not be immediately iden-
tified as a relevant cue. In a second stage of conditioning, the behaviour of an ani-
mal should reflect the discrimination of "safe" periods (Fig. 4). Thus, responses to
the context should disappear in trace-conditioned subjects, because the US always
occur during the trace and never during presentation of the context alone (39). If,
instead, the CS-US interval exceeds the duration of the trace, which amounts to
unpairing the two stimuli, the US will occur during presentation of the context alone,
and responding after the CS, i.e. during the trace, may extinguish. However, this
may require a number of CS presentations in order to cumulate a sufficient extinc-
tion time for the trace. One may therefore predict that unless extensive trace condi-
tioning is conducted, a response after the CS in very long trace or explicitly unpaired
groups may be present (55).

This interpretation leads to a number of predictions which remain to be tested:
Firstly, unification implies that at an early stage of conditioning, altering the asso-
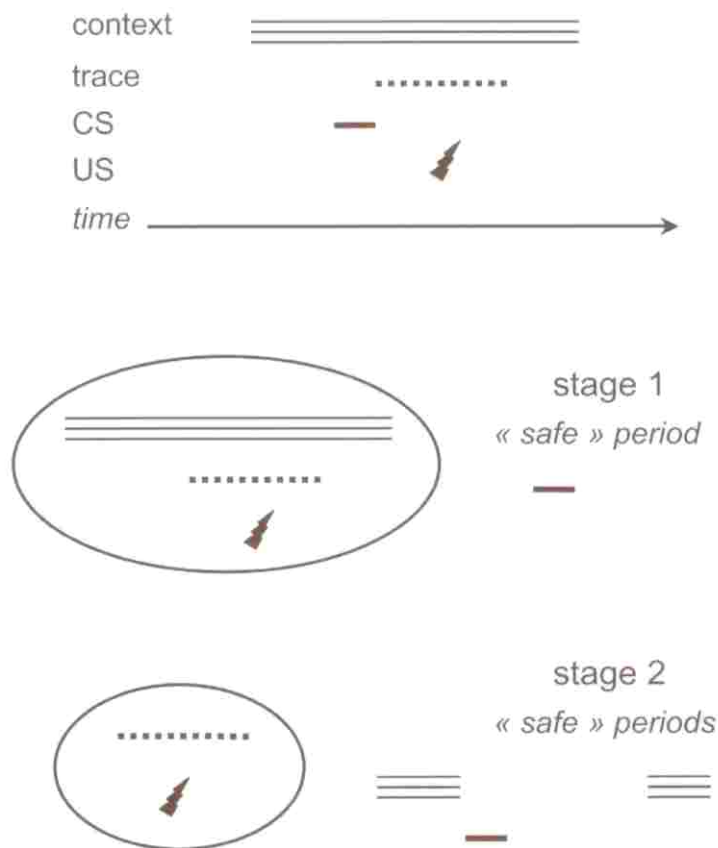
Long-trace conditioning

Fig. 4. - *Unification and discrimination of trace fear conditioned responses.*

Events occurring together during the conditioning session (upper panel) tend to be integrated into a unified representation (stage 1). This representation (oval) integrates the context and the CS long trace, but not the CS itself or the short trace (not shown). In stage 2, a "safe" period where shocks do not occur is identified, corresponding to context-alone (without trace). This stage depends on the discriminability of the trace and the cumulated time of context-alone exposure.

ciative status of one of the stimuli (CS or context) should also affect responses to the other stimulus. Secondly, discrimination processes should depend both on the discriminability of the trace and on the total time of unreinforced exposure to the to-be-extinguished phase (trace or context alone). Moreover, prior training of a discrimination between the trace and the context should facilitate the appearance of selective responses to the context or to the trace CS.

NEURONAL RESPONSES AS SUPPORTS FOR THE TRACE.

These theoretical considerations leave open the question of what constitutes a stimulus trace of long duration. There is ample evidence for neuronal responses which outlast a stimulus for several seconds in several brain regions such as the auditory cortex (64), the prefrontal cortex (4), or the perirhinal cortex (76) and the

hippocampus (45). Some authors have suggested that these long traces may be elaborated by chains of neurons in the perirhinal cortex projecting to the lateral amygdala (70), and that very long persistent activity could be sustained by recurrent chains of neurones. Responses in the hippocampus are of special interest in the light of lesion studies. A recent work by McEchron *et al.* (45) suggests that neuronal trace fear responses in the CA1 region of the hippocampus can be temporally selective. In addition, evidence for a convergence of auditory fear CRs onto hippocampal cells encoding spatial context has recently been presented (48). Finally, studies of the molecular correlates of trace fear conditioning are also now developing (26). Trace fear conditioning thus represents a challenging task which may require the potentialities of the hippocampus as an associator and a temporal encoder (59). It is an active research area where combined psychological, physiological and computational approaches can lead to significant advances.

S U M M A R Y

Fear conditioning can be rapidly obtained over long trace intervals, but its specificity with respect to both time and stimulus is uncertain. Long-trace fear conditioning often parallels contextual conditioning, and it is sensitive to hippocampal lesions. These properties of trace conditioning are not directly addressed by timing models and multiple-time-scale models of conditioning. It is proposed that during early stages of conditioning, a joint representation of the context and the stimulus trace may underlie conditioned responses, and that discriminative processes allow the emergence of specific responses in a later stage.

R E F E R E N C E S

1. ANAGNOSTARAS, S.G., MAREN, S., AND FANSELOW, M.S. Temporally graded retrograde amnesia of contextual fear after hippocampal damage in rats: Within-subjects examination. *J. Neurosci.*, **19:** 1106-1114, 1999.
2. ANTONIADIS, E.A. AND McDONALD, R.J. Discriminative fear conditioning to context expressed by multiple measures of fear in the rat. *Behav. Brain Res.*, **101:** 1-13, 1999.
3. ARCEDIANO, F., ESCOBAR, M., AND MILLER, R.R. Temporal integration and temporal backward associations in human and nonhuman subjects. *Learn. Behav.*, **31:** 242-256, 2003.
4. BAEG, E.H., KIM, Y.B., JANG, J., KIM, H.T., MOOK-JUNG, I., AND JUNG, M.W. Fast spiking and regular spiking neural correlates of fear conditioning in the medial prefrontal cortex of the rat. *Cereb. Cortex*, **11:** 441-451, 2001.
5. BEYLIN, A.V., GANDHI, C.C., WOOD, G.E., TALK, A.C., MATZEL, L.D., AND SHORS, T.J. The role of the hippocampus in trace conditioning: Temporal discontinuity or task difficulty? *Neurobiol. Learn. Mem.*, **76:** 447-461, 2001.
6. BLANCHARD, R.J. AND BLANCHARD, D.C. Crouching as an index of fear. *J. Comp. Physiol. Psychol.*, **67:** 370-375, 1969.
7. BUHUSI, C.V. AND SCHMAJUK, N.A. Timing in simple conditioning and occasion setting: a neural network approach. *Behav. Processes*, **45:** 33-57, 1999.

8. BUONOMANO, D.V. AND MAUK, M.D. Neural network model of the cerebellum: temporal discrimination and the timing of motor responses. *Neural Comput.*, **6**: 38-55, 1994.

9. CHURCH, R.M. Quantitative models of animal learning and cognition. *J. Exp. Psychol.: Anim. Behav. Processes*, **23**: 379-389, 1997.

10. CHURCH, R.M. Evaluation of quantitative theories of timing. *J. Exp. Anal. Behav.*, **71**: 253-256, 1999.

11. CHURCH, R.M., MECK, W.H., AND GIBBON, J. Application of scalar timing theory to individual trials. *J. Exp. Psychol.: Anim. Behav. Processes*, **20**: 135-155, 1994.

12. COLE, R.P., BARNET, R.C., AND MILLER, R.R. Temporal encoding in trace conditioning. *Anim. Learn. Behav.*, **23**: 144-153, 1995.

13. Davis, M., Schlesinger, L.S., and Sorenson, C.A. Temporal specificity of fear conditioning: Effects of different conditioned stimulus-unconditioned stimulus intervals on the fear-potentiated startle effect. *J. Exp. Psychol.: Anim. Behav. Processes*, **15**: 295-310, 1989.

14. DESMOND, J.E. AND MOORE, J.W. Altering the syncrony of stimulus trace processes: test of a neural-network model. *Biol. Cybern.*, **65**: 161-169, 1991.

15. FANSELOW, M.S. What is conditioned fear. *T. I. N. S.*, **78**: 460-462, 1984.

16. FANSELOW, M.S. Contextual fear, gestalt memories, and the hippocampus. *Behav. Brain Res.*, **110**: 73-81, 2000.

17. GALLISTEL, C.R. AND GIBBON, J. Time, rate, and conditioning. *Psychol. Review*, **107**: 289-344, 2000.

18. GARCIA, J., ERVIN, F.R., AND KOELLING, R.A. Learning with prolonged delay of reinforcement. *Psychonomic Science*, **5**: 121-122, 1966.

19. GIBBON, J. Scalar expectancy theory and Weber's law in animal timing. *Psychol. Review*, **84**: 279-325, 1977.

20. GIBBS, C.M., KEHOE, E.J., AND GORMEZANO, I. Conditioning of the rabbit's nictitating membrane response to a CSA-CSB-US serial compound: manipulations of CSB's associative character. *J. Exp. Psychol.: Anim. Behav. Processes*, **17**: 423-432, 1991.

21. GORMEZANO, I. AND KEHOE, E.J. Classical conditioning and the law of contiguity. In HARZEM, P. AND ZEILER, M.D. (Eds.). *Predictability, Correlation and Contiguity*. John Wiley & Sons. 1981, 1-45.

22. GROSSBERG, S. AND MERRILL, J.W.L. A neural network model of adaptively timed reinforcement learning and hippocampal dynamics. *Cognitive Brain Res.*, **1**: 3-38, 1992.

23. GROSSBERG, S. AND SCHMAJUK, N.A. Neural dynamics of adaptive timing and temporal discrimination during associative learning. *Neural networks*, **2**: 79-102, 1989.

24. HALL, G. AND HONEY, R.C. Poststimulus events in discrimination learning with delayed reinforcement: Role of distraction and implications for "marking". *Learn. Motiv.*, **24**: 242-254, 1993.

25. HALL, J., THOMAS, K.L., AND EVERITT, B.J. Cellular imaging of zif268 expression in the hippocampus and amygdala during contextual and cued fear memory retrieval: selective activation of hippocampal CA1 neurons during the recall of contextual memories. *J. Neurosci.*, **21**: 2186-2193, 2001.

26. HAN, C.J., O'TUATHAIGH, C.M., VAN TRIGT, L., QUINN, J.J., FANSELOW, M.S., MONGEAU, R., KOCH, C., AND ANDERSON, D.J. Trace but not delay fear conditioning requires attention and the anterior cingulate cortex. *Proc. Natl. Acad. Sci. U.S.A*, **100**: 13087-13092, 2003.

27. HONEY, R.C. AND HALL, G. CS memory after trace conditioning. *Learn. Motiv.*, **23**: 145-155, 1992.

28. KAMIN, L.J. Temporal and intensity characteristics of the conditioned stimulus. In PROKASY, W.F. (Ed.) *Classical Conditioning: A Symposium*. New York, Appleton-Century-Crofts. 1965, 118-147.

29. KAPLAN, P.S. AND HEARST, E. Bridging temporal gaps between CS and US in autoshaping: insertion of other stimuli before, during, and after CS. *J. Exp. Psychol.: Anim. Behav. Processes*, **8**: 187-203, 1982.

30. KEHOE, E.J., HORNE, P.S., MACRAE, M., AND HORNE, A.J. Real-time processing of serial stimuli in classical conditioning of the rabbit's nictitating membrane response. *J. Exp. Psychol.: Anim. Behav. Processes*, **19**: 265-283, 1993.

31. KEHOE, E.J. AND WEIDEMANN, G. Within-stimulus competition in trace conditioning of the rabbit's nictitating membrane response. *Psychobiology*, **27**: 72-84, 1999.

32. KIM, J.J. AND FANSELOW, M.S. Modality-specific retrograde amnesia of fear. *Science*, **256**: 675-677, 1992.

33. LENNARTZ, R.C. AND WEINBERGER, N.M. Analysis of response systems in Pavlovian conditioning reveals rapidly versus slowly acquired conditioned responses: support for two factors, implications for behavior and neurobiology. *Psychobiology*, **20**: 93-119, 1992.

34. MACHADO, A. Learning the temporal dynamics of behavior. *Psychol. Review*, **104**: 241-265, 1997.

35. MAES, J.H.R., FIDLER, T.L., AND LoLORDO, V.M. Contextual fear after signalled versus unsignalled shocks: effect of extent of prior experience with context and signal. *Q. J. Exp. Psychol. B*, **49B**: 148-173, 1996.

36. MARCHAND, A.R. Integration of cardiac responses to serial stimuli after Pavlovian conditioning in rats. *Anim. Learn. Behav.*, **30**: 132-142, 2002.

37. MARCHAND, A.R. AND KAMPER, E. Time course of cardiac conditioned responses in restrained rats as a function of the trace CS-US interval. *J. Exp. Psychol.: Anim. Behav. Processes*, **26**: 385-398, 2000.

38. MARCHAND, A.R., LUCK, D., AND DI SCALA, G. Evaluation of an improved automated analysis of freezing behaviour in rats and its use in trace fear conditioning. *J. Neurosci. Meth.*, **126**: 145-153, 2003.

39. MARCHAND, A.R., LUCK, D., MELGIRE, M., AND DI SCALA, G. Overshadowing of context by an auditory CS in trace fear conditioning assessed by freezing behavior in rats. *In preparation*, 2004.

40. MAREN, S. Neurobiology of Pavlovian fear conditioning. *Annu. Rev. Neurosci.*, **24**: 897-931, 2001.

41. MAREN, S., AHARONOV, G., AND FANSELOW, M.S. Neurotoxic lesions of the dorsal hippocampus and Pavlovian fear conditioning in rats. *Behav. Brain Res.*, **88**: 261-274, 1997.

42. MARLIN, N.A. Second-order conditioning using a contextual stimulus as S1. *Anim. Learn. Behav.*, **11**: 290-294, 1983.

43. McECHRON, M.D., BOUWMEESTER, H., TSENG, W., WEISS, C., AND DISTERHOFT, J.F. Hippocampectomy disrupts auditory trace fear conditioning and contextual fear conditioning in the rat. *Hippocampus*, **8**: 638-646, 1998.

44. McECHRON, M.D., TSENG, W., AND DISTERHOFT, J.F. Neurotoxic lesions of the dorsal hippocampus disrupt auditory-cued trace heart rate (fear) conditioning in rabbits. *Hippocampus*, **10**: 739-751, 2000.

45. McECHRON, M.D., TSENG, W., AND DISTERHOFT, J.F. Single neurons in CA1 hippocampus encode trace interval duration during trace heart rate (fear) conditioning in rabbit. *J. Neurosci.*, **23**: 1535-1547, 2003.

46. McKINZIE, D.L. AND SPEAR, N.E. Ontogenetic differences in conditioning to context and CS as a function of context saliency and CS-US interval. *Anim. Learn. Behav.*, **23**: 304-313, 1995.

47. McLAREN, I.P.L., KAYE, H. AND MACKINTOSH N.J.. An associative theory of the representation of stimuli: Applications to perceptual learning and latent inhibition. In MORRIS, R.G.M. (Ed.). *Parallel Distributed Processing: Implications for Psychology and Neurobiology*. London, New York, Oxford University Press, 1989, 102-130.

48. Moita, M.A., Rosis, S., Zhou, Y., LeDoux, J.E., and Blair, H.T. Hippocampal place cells acquire location-specific responses to the conditioned stimulus during auditory fear conditioning. *Neuron,* **37:** 485-497, 2003.

49. Moye, T.B. and Rudy, J.W. Ontogenesis of trace conditioning in young rats: dissociation of associative and memory processes. *Dev. Psychobiol.,* **20:** 405-414, 1987.

50. Olton, D.S., Meck, W.H., and Church, R.M. Separation of hippocampal and amygdaloid involvement in temporal memory dysfunctions. *Brain Research,* **404:** 180-188, 1987.

51. Parkinson, J.A., Robbins, T.W., and Everitt, B.J. Selective excitotoxic lesions of the nucleus accumbens core and shell differentially affect aversive pavlovian conditioning to discrete and contextual cues. *Psychobiology,* **27:** 256-266, 1999.

52. Pavlov, I. P. *Conditioned reflexes.* London, Oxford University Press. 1927.

53. Pearce, J.M. A model for stimulus generalization in Pavlovian conditioning. *Psychol. Review,* **94:** 61-73, 1987.

54. Phillips, R.G. and LeDoux, J.E. Differential contribution of amygdala and hippocampus to cued and contextual fear conditioning. *Behav. Neurosci.,* **106:** 274-285, 1992.

55. Quinn, J.J., Oommen, S.S., Morrison, G.E., and Fanselow, M.S. Post-training excitotoxic lesions of the dorsal hippocampus attenuate forward trace, backward trace, and delay fear conditioning in a temporally specific manner. *Hippocampus,* **12:** 495-504, 2002.

56. Rescorla, R.A. Effect of a stimulus intervening between CS and US in autoshaping. *J. Exp. Psychol.: Anim. Behav. Processes,* **8:** 131-141, 1982.

57. Rescorla, R.A. Simultaneous second-order conditioning produces S-S learning in conditioned suppression. *J. Exp. Psychol.: Anim. Behav. Processes,* **8:** 23-32, 1982.

58. Rescorla, R.A. and Wagner, A.R. A theory of Pavlovian conditioning: variations in the effectiveness of reinforcement and nonreinforcement. In Black, A.H. and Prokasy, W.F. (Eds.) *Classical Conditioning II: Current Research and Theory.* New York, Appleton-Century-Crofts. 1972, 64-99.

59. Rodriguez, P. and Levy, W.B. A model of hippocampal activity in trace conditioning: Where's the trace? *Behav. Neurosci.,* **115:** 1224-1238, 2001.

60. Rosas, J.M. and Alonso, G. Temporal discrimination and forgetting of CS duration in conditioned suppression. *Learn. Motiv.,* **27:** 43-57, 1996.

61. Rudy, J.W. Contextual conditioning and auditory cue conditioning dissociate during development. *Behav. Neurosci.,* **107:** 887-891, 1993.

62. Rudy, J.W. and O'Reilly, R.C. Contextual fear conditioning, conjunctive representations, pattern completion, and the hippocampus. *Behav. Neurosci.,* **113:** 867-880, 1999.

63. Rudy, J.W. and Pugh, C.R. A comparison of contextual and generalized auditory-cue fear conditioning: Evidence for similar memory processes. *Behav. Neurosci.,* **110:** 1299-1308, 1996.

64. Sakurai, Y. Cells in the rat auditory system have sensory-delay correlates during the performance of an auditory working memory task. *Behav. Neurosci.,* **104:** 856-868, 1990.

65. Savastano, H.I. and Miller, R.R. Time as content in Pavlovian conditioning. *Behav. Processes,* **44:** 147-162, 1998.

66. Selden, N.R., Everitt, B.J., Jarrard, L.E., and Robbins, T.W. Complementary roles for the amygdala and hippocampus in aversive conditioning to explicit and contextual cues. *Neuroscience,* **42:** 335-350, 1991.

67. Solomon, P.R., Van der Schaaf, E.R., Thompson, R.F., and Weisz, D.J. Hippocampus and trace conditioning of the rabbit's classically conditioned nictitating membrane response. *Behav. Neurosci.,* **100:** 729-744, 1986.

68. Sutton, R.S. and Barto, A.G. Towards a modern theory of adaptive networks: expectation and prediction. *Psychol. Review,* **88:** 135-170, 1981.

69. Tesauro, G. Simple neural models of classical conditioning. *Biol. Cybern.,* **55:** 187-200, 1986.

70. TIEU, K.H., KEIDEL, A.L., MCGANN, J.P., FAULKNER, B., AND BROWN, T.H. Perirhinal-amygdala circuit-level computational model of temporal encoding in fear conditioning. *Psychobiology,* **27:** 1-25, 1999.

71. WAGNER, A.R. SOP: A model of automatic memory processing in animal behavior. In SPEAR, N.E. AND MILLER, R.R. (Eds.). *Information Processing in Animals: Memory Mechanisms.* Hillsdale, NJ, Erlbaum. 1981, 5-47.

72. WAGNER, A.R. AND BRANDON, S.E. Evolution of a structured connectionist model of Pavlovian conditioning (AESOP). In KLEIN, S.B. AND MOWRER, R.R. (Eds.). *Contemporary Learning Theories: Pavlovian Conditioning and the Status of Traditional Learning Theory.* Hillsdale, Lawrence Erlbaum Associates. 1989, 149-189.

73. WEITEMIER, A.Z. AND RYABININ, A.E. Alcohol-induced memory impairment in trace fear conditioning: a hippocampus-specific effect. *Hippocampus,* **13:** 305-315, 2003.

74. WILKINSON, L.S., HUMBY, T., KILLCROSS, S., ROBBINS, T.W., AND EVERITT, B.J. Dissociations in hippocampal 5-hydroxytryptamine release in the rat following Pavlovian aversive conditioning to discrete and contextual stimuli. *Eur. J. Neurosci.,* **8:** 1479-1487, 1996.

75. WILLIAMS, D.A. AND LOLORDO, V.M. Time cues block the CS, but the CS does not block time cues. *Q. J. Exp. Psychol. B,* 48B: 97-116, 1995.

76. YOUNG, B.J., OTTO, T., FOX, G.D., AND EICHENBAUM, H. Memory representation within the parahippocampal region. *J. Neurosci.,* **17:** 5183-5195, 1997.

77. ZIPSER, D. A model of hippocampal learning during classical conditioning. *Behav. Neurosci.,* **100:** 774-776, 1986.