COMMENTARY

Conditioning, Awareness, and the Hippocampus

Kevin S. LaBar[1] and John F. Disterhoft[2]*

[1]*Cognitive Neurology and Alzheimer's Disease Center and Department of Neurology, Northwestern University Medical School, Chicago, Illinois*
[2]*Institute for Neuroscience and Department of Cell and Molecular Biology, Northwestern University Medical School, Chicago, Illinois*

ABSTRACT: For the past 50 years, psychologists have wrestled with questions regarding the relationship between conscious awareness and human conditioned behavior. A recent proposal that the hippocampus mediates awareness during trace conditioning (Clark, Squire, Science 1998;280:77–81) has extended the awareness-conditioning debate to the neuroscience arena. In the following commentary, we raise specific theoretical and methodological issues regarding the Clark and Squire study and place their finding into a broader context. Throughout our discussion, we consider the difficulties in assessing subjective awareness, the importance of establishing necessary and sufficient conditions for cognitive mediation effects, the influence of conditioned response modality, and the nature of hippocampal requirements across conditioning protocols. It is clear that trace eyeblink conditioning is a hippocampal-dependent task, but whether awareness is a necessary component of trace conditioning is not definitively proven. We propose that future functional neuroimaging studies and behavioral experiments using on-line measures of awareness may help clarify the relationship among classical conditioning, awareness, and the hippocampus. *Hippocampus 1998;8:620–626.*
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INTRODUCTION

Simple classical (Pavlovian) conditioning is a form of associative learning that has been classified as implicit or nondeclarative, meaning that conscious recollection and the integrity of the hippocampus are not required for successful performance (Squire and Zola, 1996). As the processing demands of the experimental task increase in complexity, however, the hippocampus appears to make a critical contribution to conditioned learning (e.g., Ross et al., 1984; Port et al., 1986; Solomon et al., 1986; Moyer et al., 1990; Phillips and LeDoux, 1992). Specifying the conditions where the hippocampus becomes essential to conditioned behavior has remained an evasive but important scientific question, one

that may help us to understand the role of the hippocampus in other learning tasks and the mechanisms underlying various forms of conditioning.

In a recent eyelid conditioning study, Clark and Squire (1998) found that amnesic patients exhibited intact delay discrimination conditioning but impaired trace discrimination conditioning. In the delay paradigm, subjects were given one auditory conditioned stimulus (the CS+) that coterminated with an airpuff to the eye (the unconditioned stimulus, or US), whereas another auditory cue (the CS−) was explicitly unreinforced. Subjects showed greater conditioned responses (CRs) to the CS+ than the CS−, thereby indicating intact differential learning. The trace paradigm was similar to the delay paradigm, except that a 1-s interval separated the offset of the CS+ from the onset of the US. In this case, the amnesic patients did not exhibit differential conditioning. In the control group, Clark and Squire reported that some subjects conditioned successfully and others did not. Using a postexperimental questionnaire as a probe of verbal awareness of the CS-US contingency and other aspects of the training session, Clark and Squire found a correlation between the control subjects who scored high on the declarative memory questionnaire and those that exhibited differential trace conditioning. The declarative memory questionnaire, however, was uncorrelated to performance on the delay discrimination paradigm. As expected, amnesic patients were impaired in their declarative knowledge of both tasks. Clark and Squire concluded that declarative awareness of the reinforcement contingency was a necessary prerequisite for successful conditioning on the trace but not the delay paradigm. They thus invoked a declarative memory account to understand the hippocampal contribution to more complex forms of conditioning-- specifically, that the hippocampus makes an essential contribution to conditioning only when declarative knowledge of the reinforcement contingency is required for successful performance.

The Clark and Squire (1998) result is interesting and provocative, and it adds a new dimension to the debate over the relationship between awareness and conditioning, which has a long and contested history. There is no doubt that trace eyeblink conditioning is a learned behavior that is hippocampal-dependent. However, there are several features of their study that we feel require discussion before the declarative memory theory of trace conditioning can be accepted unequivocally. In the present work, we raise specific issues concerning Clark and Squire's methodology and then expand the discussion to place their finding into a broader perspective on the relationship among conditioning, awareness, and hippocampal function. We hope that the following commentary will shed some light on the complexity of the issues at hand and suggest empirical strategies to resolve them.

SPECIFIC ISSUES WITH CLARK AND SQUIRE (1998)

Trace Discrimination Conditioning as a Paradigm

It must be stressed that the protocol Clark and Squire followed was a two tone trace discrimination conditioning procedure. Essentially all of the previous studies of trace eyeblink conditioning done in both animals and humans have used a single tone CS, separated from the air puff or shock US by an empty trace interval (e.g., Port et al., 1986; Solomon et al., 1986; Woodruff-Pak, 1993; McGlinchey-Berroth et al., 1997). We are not aware of any eyelid conditioning studies that utilized the trace discrimination procedure. However, trace discrimination would be expected to be even more difficult than delay discrimination because single-cue trace conditioning is more difficult than single-cue delay conditioning (Solomon and Groccia-Ellison, 1996; Thompson et al., 1996). Ross and Nelson emphasize the added complexity involved in discrimination paradigms: "...In summary, some additional *cognitive* or *awareness processes*, which are sensitive to a variety of variables that do not affect single-cue conditioning, appear to be involved in differential conditioning...it appears to be necessary to distinguish carefully between single-cue and differential conditioning in discussing the effects of cognitive factors and awareness." (Ross and Nelson, 1973, p. 92, original italics). Note that Ross and Nelson were discussing discrimination procedures in which the CSs were presented in a delay configuration, i.e., overlapping and coterminating with the US. More recently, work in our laboratory showed that performance of a verbal shadowing task or watching a silent movie (Charlie Chaplin's "Gold Rush", the same movie used by Clark and Squire) had a significant detrimental effect on simultaneous acquisition of two tone discrimination delay conditioning (and its reversal) in normal young adult humans (Carrillo et al., 1996). These manipulations had no effect on acquisition of either delay or trace conditioning with a single, pure tone CS. The use of the discriminative trace procedure by Clark and Squire may have increased the power of their manipulations and made the awareness effect more obvious than experi-

ments using a single CS would have done. It will be interesting to determine if awareness is as important a factor in single-cue trace eyeblink conditioning as Squire and Clark demonstrated it to be in the more complex trace discrimination paradigm with two auditory cues.

Effects of Aging on Learning

The subjects in the Clark and Squire study were amnesics and their age-matched controls. This was certainly the correct procedure but it is interesting to note that both the amnesics and their controls would be considered to represent aging subject populations (67.5 and 66.9 years old, respectively). It is well known that aging humans are impaired in their ability to do single tone delay (Woodruff-Pak and Thompson, 1988; Solomon et al., 1989) and trace eyeblink conditioning (Carrillo et al. 1996) as compared to young adult subjects. Aging subjects should definitely be impaired in the more difficult trace discrimination procedure. It is not clear how age-associated learning deficits interact with awareness. It is possible that the relation between awareness and learning ability observed by Clark and Squire is present only in aging subjects, or that the awareness effect would be severely attenuated in a younger subject population.

Movie Distracter Divides Attention

The participants were shown a silent movie to serve as a distracter while they were undergoing discriminative trace eyeblink conditioning. As noted by the authors, use of a silent movie distracter has become a standard practice in recent human eyeblink conditioning studies. But, as discussed above, we have shown that this procedure is not a neutral one, even for young adult subjects (Carrillo et al., 1996). We made a comparison between groups of subjects being trained in discrimination delay eyeblink conditioning under conditions of full attention, watching a silent movie, and doing a verbal shadowing task. There was a stepwise reduction both in the ability to acquire the basic discrimination task, and to reverse it, among the three training groups. The relevant points for this discussion are that the silent movie group was significantly impaired in acquisition as compared to the full attention group, and that this study was done with a group of young adult subjects using a delay, not a trace, discrimination task. Distraction also disrupts delay discrimination as measured by autonomic indices (e.g., Baer and Fuhrer, 1969). It would seem that the impact of the distracter task on attention, and consequently awareness, would be even larger in a population of aging subjects.

AWARENESS-CONDITIONING LINK

Shape of the Learning Curve

Martin and Levey discuss the potential role of conscious awareness in the final, speculative chapter in their monograph *The Genesis of the Classical Conditioned Response* (1969). They stress, as

we do here, that discussion of the role of awareness in humans who are undergoing eyeblink conditioning is complicated by the fact that several parallel systems are likely to be engaged simultaneously in the human during the acquisition of a relatively simple learning task. They suggest that humans, who are using their "second signaling system" of words and meaning early in the learning process, may show an unusually rapid rise in their acquisition curve. Although the detailed form of the response may be a bit less regular than that obtained only through the primary, sensory channel, the probability of a response occurring may rise very quickly once the "aha" insight has occurred. This would suggest that a detailed examination of both the form (latency, amplitude, overall shape) of the conditioned and unconditioned response as well as of the probability of conditioned response occurrence on a trial-by-trial basis should yield differences between aware and unaware subjects. These differences should be evident even in delay conditioning, which the unaware amnesics were able to perform normally (Clark and Squire, 1998). This approach might be one way to determine if trace conditioning in experimental animals such as rabbits or primates proceeds with the use of the same type of declarative memory as in humans. The prediction would be that the form of the acquisition curve and the detailed shape of the developing conditioned response would be similar in the unaware humans and animals, whereas the aware humans, with their ability to use language as an intermediary, might show a quite different ramping up early in the learning process.

On Measuring Awareness

The assessment of subjective awareness during human conditioning has proven to be more controversial than one might expect at first glance. Clark and Squire's use of a postexperimental questionnaire is subject to several difficulties, including that reconstruction of events may occur at the time of test and retrospective reports are sensitive to forgetting over time. Because subjects become aware of various features of the conditioning episode, it is not clear which components of the learning experience are relevant to test. Treating "awareness" and "conditioning" as dichotomous variables also poses the problem of establishing appropriate criteria with which to classify subjects. On-line measures of awareness provide a more accurate method of estimating when and if subjects became cognizant of the stimulus relationships during conditioning, though even in this case, different results can be obtained depending on the criteria of "awareness" (Biferno and Dawson, 1977). Furthermore, subjective probability estimates of the reinforcement contingency exhibit degrees of gradation across learning trials, which implies that awareness is not an all-or-none phenomenon (Furedy and Schiffman, 1973; Öhman et al., 1976; Furedy et al., 1982; K. Hugdahl, personal communication, April 27, 1998). Although on-line probing improves the temporal precision of awareness measurement, it also changes the task demands in a way that may not approximate "true" learning when such probing is not superimposed on the conditioning process. Under awareness monitoring conditions, subjects are more likely to pay attention to

and seek out information regarding the CS-US contingency (Baeyens et al., 1990); the task may induce higher baseline anxiety/arousal levels; and physiological responses can arise during contingency insight due to increases in orienting or motor activity when subjects indicate changes in their awareness levels (cf. Biferno and Dawson, 1977). All of these factors contribute to the difficulty in assessing awareness during conditioning tasks and need to be taken into consideration when evaluating studies claiming to find links between declarative knowledge and behavioral learning.

In their study, Clark and Squire conclude that awareness of the stimulus contingencies is essential for the development of trace but not delay discrimination learning. This result is consistent with previous studies of eyelid conditioning that have repeatedly failed to relate awareness and single-cue delay conditioning (Grant, 1973; Frcka et al., 1983; Papka et al., 1997). In contrast, a large body of evidence using autonomic indices has linked awareness and delay conditioning using both postexperimental questionnaires (e.g., Baer and Fuhrer, 1968, 1969, 1970) and on-line measures (e.g., Dawson and Biferno, 1973; Furedy and Schiffman, 1973; Biferno and Dawson, 1977; Schiffman and Furedy, 1977; Furedy et al., 1982). Thus, if the declarative memory hypothesis of conditioning is correct, one may need to take into consideration the particular response system studied. It is not yet clear, however, that awareness is *necessary* for autonomic delay conditioning because differential autonomic responses can be elicited when the CS is masked without overt recognition (Corteen and Wood, 1972; Dawson and Schell, 1982; Öhman et al., 1995; Büchel et al., 1998). The interdependence of declarative memory and conditioning systems, therefore, needs to be more firmly established, a theme that is elaborated in the following sections.

Awareness in Brain-Lesioned Patients

The implication of Clark and Squire's hypothesis is that hippocampal-diencephalic lesions should impair performance on conditioning paradigms in which awareness is deemed critical for successful learning. Determining these boundary conditions is formidable, considering the complications that have arisen in normal subjects regarding replications across experiments, the particular response system under investigation, and the definition of "awareness." In fact, the neuropsychological studies conducted to date have reported double dissociations between awareness and conditioning in patients with brain lesions. Using a delay discrimination paradigm and autonomic measures of conditioning, Bechara et al. (1995) found that a patient with bilateral hippocampal damage had intact CRs but impaired declarative knowledge, whereas a patient with bilateral amygdala damage showed the opposite dissociation. Given that awareness appears to mediate delay discrimination learning when autonomic measures of conditioning are employed (as explained earlier), the hippocampal result contradicts the extension of the declarative memory hypothesis to the autonomic domain. It may be argued, however, that the hippocampal patient did not exhibit intact conditioning because he tended to overgeneralize his CRs (Bechara et al., 1995,

p. 1117). Despite this observation, Bechara et al. (1995) interpreted their finding as indicating that declarative memory and conditioning depend on partially independent neural systems. In general, across a variety of tasks and dependent measures, conscious awareness is unrelated to CR acquisition when conditioning is intact following hippocampal-diencephalic damage (Claparède, 1911; Weiskrantz and Warrington, 1979; Daum et al., 1989; Daum et al., 1992; Woodruff-Pak, 1993; Daum and Ackermann, 1994; Bechara et al., 1995). Moreover, when declarative memory for the stimulus contingency is preserved in patients with partial medial temporal lobe lesions, it is insufficient to support the development of conditioning (Daum et al., 1991; LaBar et al., 1995; Phelps et al., 1998).

One problem with the majority of these studies is that awareness was assessed postexperimentally. Because amnesia is characterized by impaired memory function over time intervals of minutes, on-line measures are needed to confidently state that the patients were not aware of the stimulus relationships at the time of initial learning (see also Daum and Schugens, 1995). Clark and Squire (1998, p. 81) did probe awareness intermittently in an additional set of trials, which were not described in detail, but they claim that this did not yield improved memory or conditioning ability. As alluded to above, some of the studies may also be scrutinized in terms of methodology, interpretation, or failure to use complex protocols. Nonetheless, the bulk of the neuropsychological evidence does not yield an intimate relationship between phenomenological and behavioral aspects of conditioned learning. For a similar conclusion in cerebellar patients see Daum et al., 1993.

CORRELATION, CAUSATION, AND THE UNDERLYING PROCESSING MECHANISM

Clark and Squire postulate that declarative knowledge in trace paradigms is established via hippocampal-neocortical networks that influence neural circuitry mediating the CR. An alternative hypothesis is that declarative memory is a by-product of successful hippocampally-dependent behavioral conditioning and not a necessary prerequisite. Because awareness was probed postexperimentally by Clark and Squire, it is uncertain whether the declarative or neurobiological aspects of conditioning were established first. Even in studies where on-line knowledge of the stimulus contingency was shown to precede physiological learning, there is little correlation between the learning rate/degree of awareness and the learning rate/degree of conditioning (Furedy and Schiffman, 1973; Öhman et al., 1976; Furedy et al., 1982). Therefore, there is no clear sense that the awareness somehow "caused" the conditioning (Maltzman, 1987).

A more likely scenario is that the declarative and behavioral aspects of learning in a conditioning setting develop in parallel. Clark and Squire may be unveiling a hippocampal influence on both faculties during more complex conditioning tasks, but the underlying processing mechanism remains unspecified. There are several facets of conditioned learning that may require hippocampal input. First, the hippocampus may impart some degree of stimulus differentiation that allows the organism to respond flexibly and adaptively to changes in the relative salience of environmental cues. Stimulus differentiation and redundancy compression are characteristic features of computational models of hippocampal function (e.g., Eichenbaum et al., 1992; Gluck and Myers, 1993) and may account for the overgeneralization of differential CRs that occurs following hippocampal damage (Berger and Orr, 1983; Ross et al., 1984; Daum et al., 1991; Bechara et al., 1995). These characteristics of spatiotemporal binding may help to explain why simple stimulus associations are intact following hippocampal lesions but complex ones, including contextual and differential trace associations, are not. Second, the hippocampus may be important for signaling an organism's attention to relevant or novel stimuli in the environment. When subjects undergo associative learning under divided attention conditions, the hippocampus may be required to filter out irrelevant stimulation to yield appropriate behavioral output. Attentional factors have also been hypothesized to play a critical role in some complex conditioning tasks, including latent inhibition and blocking (e.g., Mackintosh, 1975; Buhusi and Schmajuk, 1996). But even within a single paradigm such as latent inhibition, hippocampal lesions can facilitate, impair, or have no effect on task performance, depending on slight variations in the experimental protocol (reviewed in Buhusi et al., 1998). This suggests that a simple explanation in terms of "awareness" or "attention" is insufficient. Third, the hippocampus may be important for interval/response timing or for generating conditional probability estimates of reinforcement, which have received increasing emphasis in theoretical models of associative learning (Pearce and Hall, 1980; Gibbon and Balsam, 1981; Gallistel, 1990; Wallenstein et al., 1998). When such computations are rendered more difficult, as in trace conditioning, the hippocampus may be recruited. For example, the hippocampus might be important for bridging smaller temporal intervals across multiple stimulus instantiations to achieve appropriately-timed responses during incremental learning. A hallmark of hippocampal damage is inappropriately-timed CRs (Orr and Berger, 1985; Port et al., 1985, 1986; Moyer et al., 1990; Christiansen and Schmajuk, 1992; McGlinchey-Berroth et al., 1997). This may explain why amnesics have difficulty with the short time intervals in trace conditioning but not in other memory tasks. The timing information modeled in hippocampal neurons may interact with circuitry in the cerebellum to form a hippocampal-cerebellar network that controls response timing when the CS-US interval is nonoptimal (Berger et al., 1986; Sears and Steinmetz, 1990; Weiss and Disterhoft, 1996).

Indeed, the contribution of the hippocampus to classical conditioning is likely to be multifunctional due to the extensive connectivity of the hippocampal region. Even if a correlation is mapped between conscious awareness and various conditioning protocols, a declarative memory account of conditioning leaves open the nature of the underlying process or processes that are critical for the development of conditioned responding in some

circumstances but not others. The degree to which spatiotemporal binding, attentional demands, and response/interval timing are relatively taxed may determine when the hippocampus makes an essential contribution to conditioned behavior. These hippocampal computations may lead to a quick "aha" insight that is readily verbalizable in humans. But such processes have to get transferred to other brain systems that control physiological CRs. If sensorimotor response systems are more sluggish than language systems with respect to their interface with the hippocampus, then it is not surprising that verbalization of CS-US contingencies can develop prior to behavioral learning. This does not necessarily imply a causal relationship, but instead may reflect differences in the neural control or operating characteristics of the two systems, such as their relative speed, reliability, or susceptibility to forgetting/interference over time.

SUMMARY

We conclude with several points that we feel are important to keep in mind when considering the relationship among awareness, conditioning, and brain systems.

(1) Clark and Squire's (1998) finding is provocative and renews an interest in the awareness-conditioning debate and in using conditioning paradigms to study hippocampal function. However, the fact that they employed a differential trace conditioning paradigm needs to be emphasized and further explored in younger subjects and animal models.

(2) The use of divided attention conditions may interact with differential conditioning, even in a delay paradigm. To make a specific case for the influence of the hippocampus on the trace aspect of the conditioning task, it should be tested under undivided attention conditions and in single-cue trace conditioning. Previous studies have shown deficits in amnesic patient performance on single-cue trace conditioning tasks. McGlinchey-Berroth et al. (1997) found that amnesics were impaired in single-cue trace conditioning, but awareness was not tested. Woodruff-Pak (1993) also reported impaired trace conditioning in the amnesic patient HM, since conditioning was only observed after extensive overtraining. Interestingly, HM showed savings for the conditioning procedure over a two-year interval that could not be attributable to intact declarative memory.

(3) "Awareness" is difficult to define and is problematic when probed postexperimentally. This is especially true in amnesic patients and elderly subjects, who are likely to forget the experimental contingencies over short time intervals. Therefore, on-line measures of awareness should be developed and tested in eyelid conditioning tasks (e.g., Baer and Fuhrer, 1982).

(4) Although cognitive factors certainly modulate behavioral learning, they may not be necessary or sufficient. Cognitive and neurobiological learning may develop in parallel with no causal linkage between the two. The hippocampus may mediate some aspects of the cognitive learning, the neurobiological

learning, or both. As with other measures of nondeclarative or implicit memory, there is often explicit "contamination" or conscious awareness of aspects of the learning experience that may contribute to task performance in human subjects. It may be possible to tease out this influence by examining the topography or timing characteristics of the CR (see Biferno and Dawson, 1977, for an attempt to do this with autonomic conditioning).

(5) A declarative memory account leaves the underlying computational mechanism unspecified. The degree to which spatiotemporal binding, attentional demands, or response/interval timing are taxed may determine the conditions under which the hippocampus becomes critical for classical conditioning. These considerations may be especially important when attempting to use nonhuman animals, who lack language capabilities, to study declarative memory.

We are currently in a scientific era where rapid advances in methodology have opened new avenues for exploring the neural bases of associative learning in humans. Some of the techniques that have already been applied to conditioning tasks include event-related potential indices (Lammers, 1995; LaBar, 1996), magnetoencephalographic recording (Wik et al., 1996), positron emission tomography (Molchan et al., 1994; Fredrikson et al., 1995; Logan and Grafton, 1995; Hugdahl et al., 1995; Blaxton et al., 1996; Timmann et al., 1996; Morris et al., 1997, 1998a, 1998b), and functional MRI (Büchel et al., 1998; LaBar et al., 1998). These studies have begun to reveal the brain systems involved in various aspects of human conditioned behavior, including those related to conscious awareness factors (Lammers, 1995; Morris et al., 1998b). In combination with on-line awareness measures in normal and brain-lesioned subjects, future studies employing these methods may help to clarify the relationship among declarative memory, conditioning, and specific brain systems.

Acknowledgments

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