EPISODIC-LIKE MEMORY: RATS REMEMBER WHEN EVENTS OCCURRED

by

WENYI ZHOU

(Under the Direction of Jonathon D. Crystal)

ABSTRACT

Episodic memory refers to memories of unique past events, which are grounded in a temporal framework. It has recently been argued that episodic-like memory in rats may be qualitatively different from human episodic memory because, rather than remembering when an earlier past event occurred, rats used the cue of how long ago it occurred. In this study, rats were tested in the morning and afternoon, on separate days. A distinctive flavor (chocolate) replenished at a daily-unique location at only one of these times. The retention interval between study and test was constant to render the how-long-ago cue irrelevant. Rats solved the task using time of day rather than using the cue of how long ago an event occurred. Two lines of evidence suggest that at the time of test, rats remembered the time at which the distinctive event occurred, similar to human episodic memory.

INDEX WORDS: Episodic-like memory, Episodic memory, How long ago cue, Time of day, Phase shift, Transfer test, Conflict test,

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CHAPTER 1

INTRODUCTION

People remember when an event occurred within a past temporal framework that spans hours, days, or years (1). It has been argued that retrieval from episodic memory includes the experience of travelling back in time to remember specific events from one's personal past (2-4). An earlier definition focused on the content of episodic memory – information about what, where, and when a specific event occurred (5). Clayton and Dickinson (6) introduced the term episodic-like memory to emphasize that behavioral studies in animals focus on the content of episodic memory rather than subjective experiences.

A number of recent studies with non-human animals (6-18) suggest that animals remember specific episodes from their past (i.e., what-where-when memories). However, controversy has emerged about the comparability of episodic-like memory in rodents and episodic memory in humans (17). Roberts (2, 17) suggested that memory for when an event occurred suggests an ability akin to mentally travelling in time to locate an event within a temporal framework; such an ability would be similar to human episodic memory in which people reconstruct past experiences using an absolute temporal dimension (1, 19, 20). By contrast, a judgment of how long ago an event occurred is quite different from human episodic memory, and may be solved with a simpler interval timing mechanism.

The objective of this research was to determine, at the time of memory assessment, if rats can remember when an earlier distinctive event occurred, in addition to what and where

information about that event. The approach was to eliminate the usefulness of how long ago an event occurred as a temporal cue. The rationale for this approach is that Roberts (17) showed that rats used how long ago cues under conditions in which both when and how long ago cues are available. The behavioral task in these types of experiments (13-17) required rats to enter four randomly selected arms on an eight-arm radial maze in daily trials; three of the arms provided standard reward pellets, and one randomly selected study arm contained a distinctive flavor (e.g., chocolate). After a retention interval, the rats were returned to the maze for a test phase with all eight arms open. The arms previously closed during the study phase provided standard reward pellets, and the arms that had contained pellets in the study phase were empty at test. The distinctively baited location replenished (or not) according to a temporal rule, and evidence for what-where-when memory comes from documenting that the rats learned the temporal contingency for the location that recently provided the distinctive flavor (13-17). Thus, rats should revisit the distinctive location at the time at which this location would replenish.

Given the important role that a rodent model of episodic memory can play in investigations of models of human disorders of memory (21), we sought evidence for remembering when an event occurred by making how-long-ago cues irrelevant. We investigated whether rats remembered the time of day at which they had recently encountered a distinctive food type (chocolate). Rats were tested in the morning and afternoon, on separate days, but chocolate replenished at a daily-unique location at only one of these times (counterbalanced across rats). We made the interval between study and test irrelevant by using a constant retention interval in morning and afternoon sessions. The rats adjusted their revisits to the chocolate location at the different times of day (Experiment 1). Next, we used a phase shift of light onset in the colony (22, 23) to determine whether the rats used time of day or the interval since light

onset (Experiment 2). Under conditions in which predictions for time of day and an interval cue were dissociated, we observed revisits to the chocolate location based on time of day. Finally, we used two techniques to determine whether, at the time of test, the rats were remembering when the study episode occurred rather than discriminating the time of day at test. To determine whether the rats used the study time of day to guide revisits, we introduced 7-hr retention intervals that maintained the familiar times of day at study but used novel times of day at test (Experiment 3). Under these transfer test conditions, the rats immediately transferred (i.e., without feedback) their chocolate revisit strategy to the novel situation (i.e., when tested at a novel time of day, they used their earlier experience with the chocolate contingency based on the familiar study time of day). To determine whether revisits were based on study or test times of day, we conducted a conflict test in which a trial began at the usual time of a late study phase and terminated at the usual time of an early test (Experiment 4). Under these conditions, in which predictions for study and test time revisits were dissociated, we observed revisits to the chocolate location based on when the study occurred rather than when the test occurred. In both Experiments 3 and 4, revisits to the chocolate location were guided by the study time of day. Our results suggest that, at the time of memory assessment, rats remember when earlier study events occurred (in addition to what and where information), which represents a qualitative similarity to human episodic memory.

CHAPTER 2

RESULTS

Experiment 1. The design of Experiment 1 is shown in Figure 2.1. The morning or the afternoon was randomly selected for presentation of study and test phases, separated by an approximately

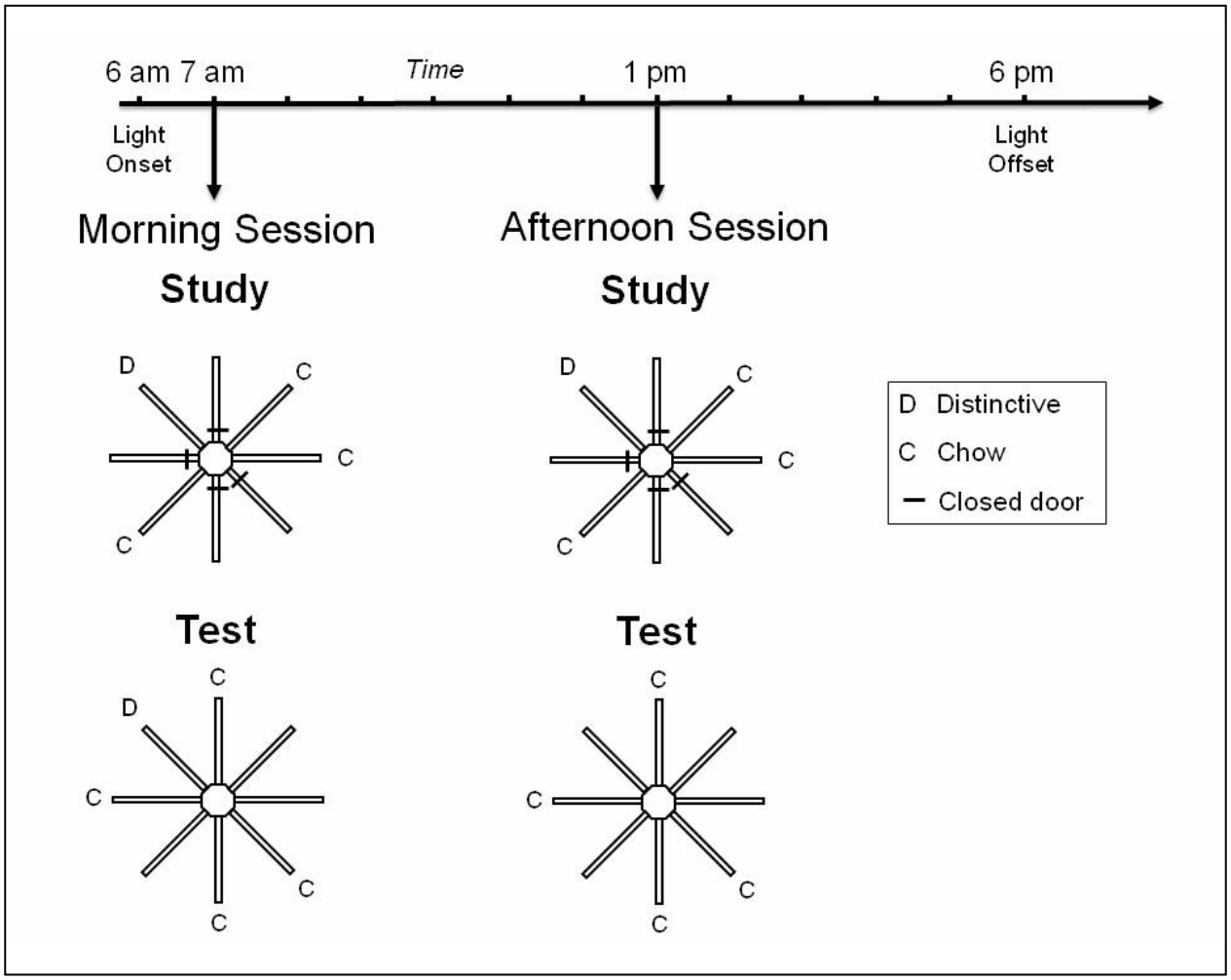

Figure 2.1: *Design of Experiment 1*

2-min retention interval. Chocolate was encountered at a randomly selected location in the study phase and sometimes replenished at that location in the test phase. For some rats, the replenishment of chocolate occurred if the study-test sequence occurred in the morning, and non-replenishment of chocolate occurred in the afternoon; this arrangement was reversed for the remaining rats. The rats preferentially resisted the chocolate location when it was about to replenish. The probability of revisiting the chocolate location in the test phase during the first

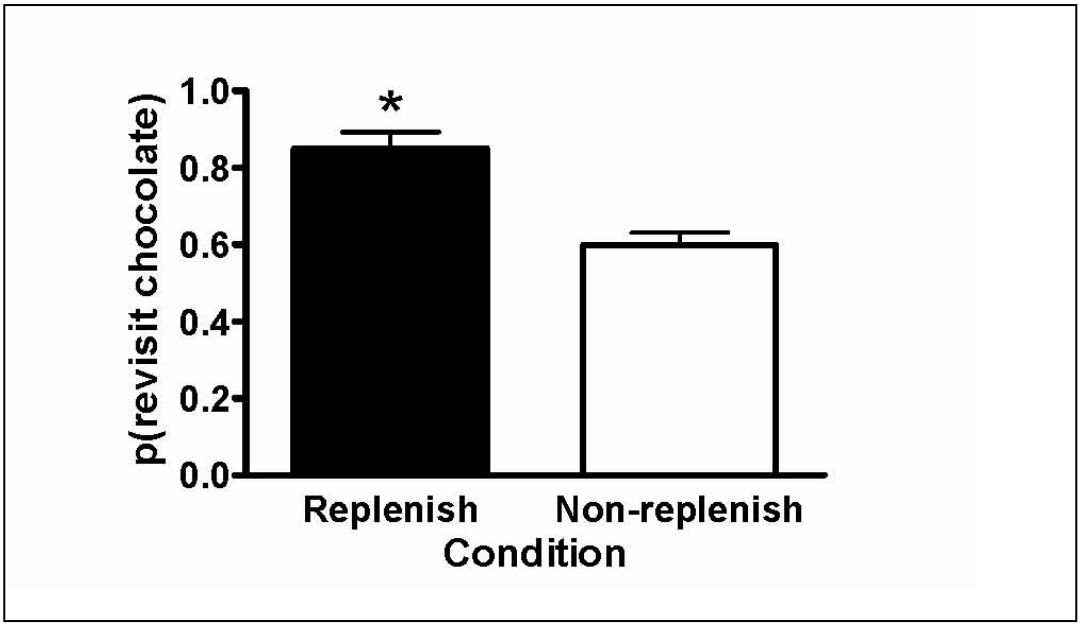

Figure 2.2: *Rats preferentially revisit the chocolate location when it is about to replenish. The probability of a revisit to the chocolate location in the first four choices of a test phase is shown for replenishment and non-replenishment conditions; replenish and non-replenish sessions were presented in random order. Error bars indicate S.E.M. * P < 0.001 difference between conditions. The probability expected by chance is 0.41.*

Table 2.1: *Accuracy* in avoiding revisits to depleted chow-flavored locations*

Procedure	Mean ± S.E.M.
Experiment 1 Block testing	0.77 ± 0.01
Experiment 1 Mixed testing	0.72 ± 0.03
Experiment 2	0.80 ± 0.05
Experiment 3 Initial	0.73 ± 0.04
Experiment 3 Terminal	0.70 ± 0.01
Experiment 4	0.75 ± 0.04

** Accuracy was measured as the proportion correct in the first four choices excluding the chocolate location in a test phase. Note: This analysis of the first four choices was restricted to the seven non-chocolate arms. Accuracy expected by chance (i.e., random arm entries) is 0.46. Block testing refers to consecutive sessions with the replenishment or non-replenishment contingency; mixed testing refers to testing of replenish and non-replenish sessions in random order.*

four arm entries was higher during the replenishment time of day than during the non-replenishment time of day ($t(15) = 4.3$, $P < 0.001$), see Figure 2.2. Because the interval between study and test phases was constant in morning and afternoon sessions, the cue of how long ago the study occurred provided no useful information about the forthcoming replenishment or non-replenishment of chocolate. The differential rates of revisiting chocolate-flavored locations were

accomplished while the rats accurately avoided revisits to depleted chow-flavored locations (see Table 2.1).

Experiment 2. Experiment 1 suggests that the adjustment of revisits to the location recently baited with chocolate in Figure 2.2 may be based on time of day (i.e., morning vs. afternoon). However, a residual interval was available to solve this task. As noted in Figure 2.1, light onset in the colony occurred at 6 a.m. in Experiment 1. Because morning and afternoon sessions occurred 1 and 7 hr after light onset, respectively, an alternative explanation for the chocolate-revisit data in Figure 2.2 is that the rats used the interval between light onset and the daily session as a cue to adjust revisit rates. In Experiment 2, we put predictions for time-of-day and interval hypotheses in conflict by shifting the light onset to 12 a.m. The probe study-test session occurred at 7 a.m., which was 7 hr after 12 a.m., as shown in Figure 2.3. Consequently, we sought to determine whether the rats treated the probe as a 7 a.m. morning session (which would suggest time of day) or as a 1 p.m. afternoon session (which would suggest timing 7 hr from light onset).

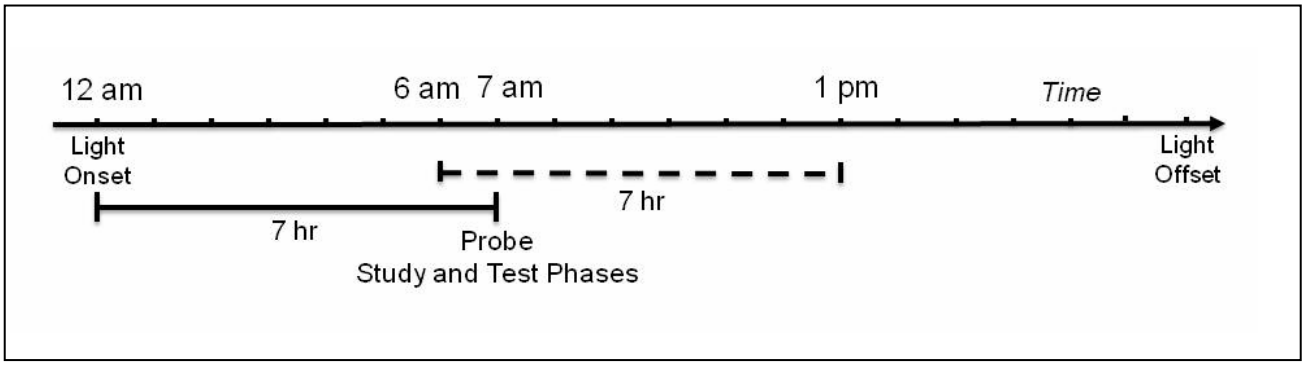

Figure 2.3: *Phase-shift design of Experiment 2*

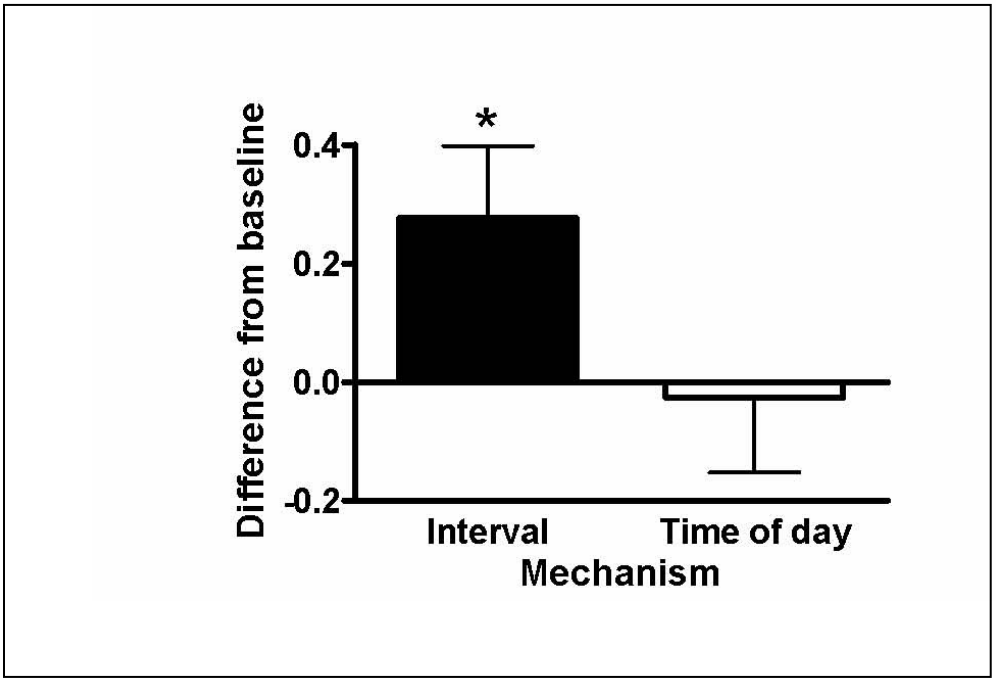

Figure 2.4: *Rats used time of day, rather than how long ago, to adjust revisit rates at the probe in Experiment 2. The rats treated the probe as a morning session, suggesting the use of time of day rather than the use of an interval-timing mechanism. The figure plots the difference between probe and baseline revisit rates. For the bar labeled interval, the baseline was the probability of revisiting chocolate in the afternoon; thus, the significant elevation above baseline shown in the figure suggests that the rats did not use an interval mechanism. For the bar labeled time of day, the baseline was the probability of revisiting chocolate in the morning; thus, the absence of a significant elevation above baseline in the figure is consistent with the use of time of day. The horizontal line corresponds to the baseline revisit rate to the chocolate location from Experiment 1. Positive difference scores correspond to evidence against the hypothesis indicated on the horizontal axis. Error bars indicate S.E.M. * $P < 0.04$ different from baseline.*

The rats adjusted revisit rates based on the time of day at which the session occurred rather than using the interval between light onset and the session. Figure 2.4 shows data from the probe session relative to baseline data according to interval and time-of-day hypotheses; the baseline data come from Figure 2.2. The probe data was significantly different from the baseline for the interval hypothesis ($t(15) = 2.3$, $P < 0.04$), suggesting that the rats did not time the interval between light onset and study-test sessions. The probe data was not reliably different from the time-of-day hypothesis ($t(15) = -0.03$, $P > 0.8$), consistent with the proposal that the rats adjusted their revisit rates to chocolate based on the time of day at which study-test sessions occurred.

Experiment 3. The phase-shift manipulation of light onset in Experiment 2 suggests that the rats were using time of day to adjust revisit rates to the chocolate location in morning and afternoon sessions. However, these data do not tell us whether the rats were using the time of day at the study phase or the time of day at the test phase to produce this adjustment in revisits. It is

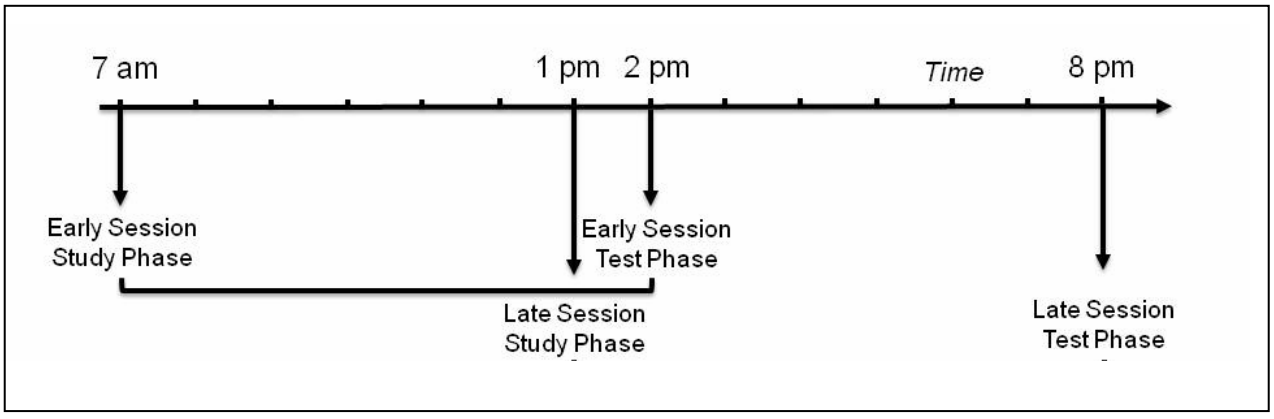

Figure 2.5: *Transfer-test design of Experiment 3*

important to note that the 2-min separation between the time of day at study and at test is too small for the rats to discriminate (22, 24). Yet, it is critically important to determine whether the rats were, at the time of test, remembering the time of day at which the study episode occurred; an alternative hypothesis is that at the time of test the rats may discriminate time of day and adjust revisit rates based on this information without remembering the time of day at study. With a 2-min retention interval, these two hypotheses may not be separately evaluated. Consequently, in Experiment 3 we introduced 7-hr retention intervals. The time of day at which study episodes occurred was the same as in Experiment 1 (i.e., 7 a.m. and 1 p.m. for early and late study phases,

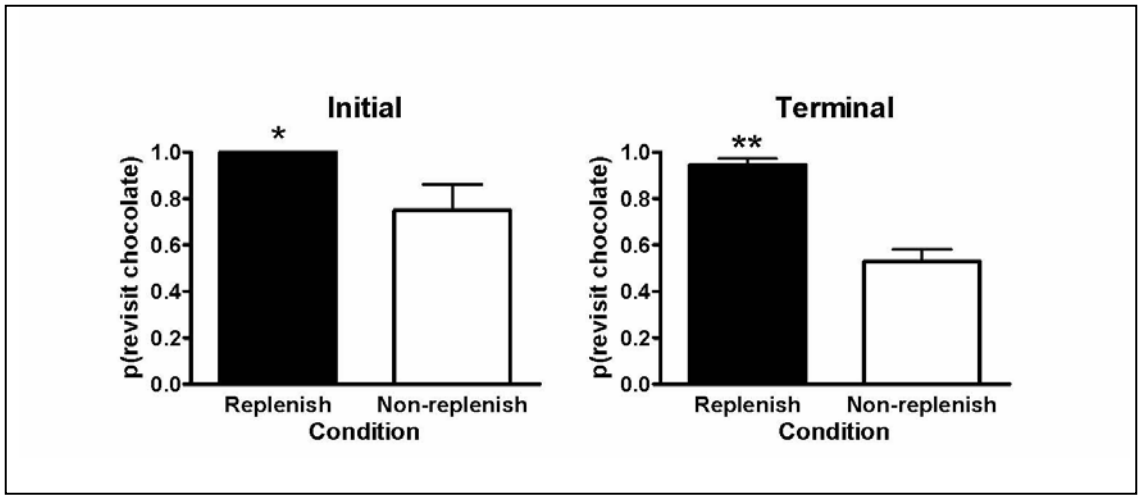

Figure 2.6: *Rats preferentially revisit the chocolate location when it is about to replenish when the study, but not the test, time of day was familiar. The probability of a revisit to the chocolate location in the first four choices of a test phase is shown for first replenishment and first non-replenishment conditions (left panel; initial) and for subsequent sessions (right panel; terminal). Error bars indicate S.E.M. * P < 0.04 and ** P < 0.0001 difference between conditions. The probability expected by chance is 0.41*

respectively). However, the introduction of 7-hr retention intervals between study and test phases produced test phases that occurred at 2 p.m. and 8 p.m. for early and late sessions, respectively, as shown in Figure 2.5. Thus, the study times were familiar (i.e., from Experiment 1) and the test times were novel. Consequently, in this transfer test design, we would expect that the rats would continue to differentially revisit chocolate locations more in the replenishment condition than in the non-replenishment condition if they were adjusting revisit rates based on the time of day at which study episodes occurred. Alternatively, if the rats were adjusting revisit rates based on the time of day at which test phases occurred, there is no basis for the rats to know that a higher revisit rate should occur at the novel times of 2 p.m. or 8 p.m. It is important to note that the strongest version of these predictions comes from the very first transfer test to novel early and late times (i.e., before receiving feedback from extended training with the new test times). Consequently, the critical data for evaluating the above hypotheses comes from the very first early and late sessions.

On the very first replenish and non-replenish trials (i.e., before feedback with the new test times), the rats were more likely to revisit the chocolate location in the replenishment condition than in the non-replenishment condition ($t(15) = 2.24$, $P = 0.04$), see Figure 2.6 (left panel). These data strongly suggest that, at the time of test, the rats remembered the time of study and adjusted chocolate revisit rates based on the time of day at study. As expected, when additional training under the new regime was extended (Figure 2.6, right panel), the rate of revisiting chocolate continued to be higher in the replenishment condition compared to the non-replenishment condition ($t(15) = 6.8$, $P < 0.0001$).

Experiment 4. To provide a converging line of evidence for memory of the time at which the study episode occurred, we conducted a novel test that put predictions based on time at study and time at test in conflict. To dissociate predictions from study and test times of day, the study phase began as in a late session, at 1 p.m., and the test phase began as in an early session, at 2 p.m., as shown in Figure 2.7. If at the time of test, the rats remember when the study phase occurred, then the rats should revisit chocolate (or not) at the same rates that usually occur at 8 p.m. (i.e., the usual test phase after a 1 p.m. study phase). Alternatively, if the rats use time of day at test, then the rats should revisit chocolate (or not) at the same rates that usually occur at a 2 p.m. test (i.e., the current time of day), which usually occurs after a 7 a.m. study phase. It is important to note that the rats had never received this sequence of 1 and 2 p.m., and that the data were collected before any feedback occurred with respect to replenishment or non-replenishment of chocolate.

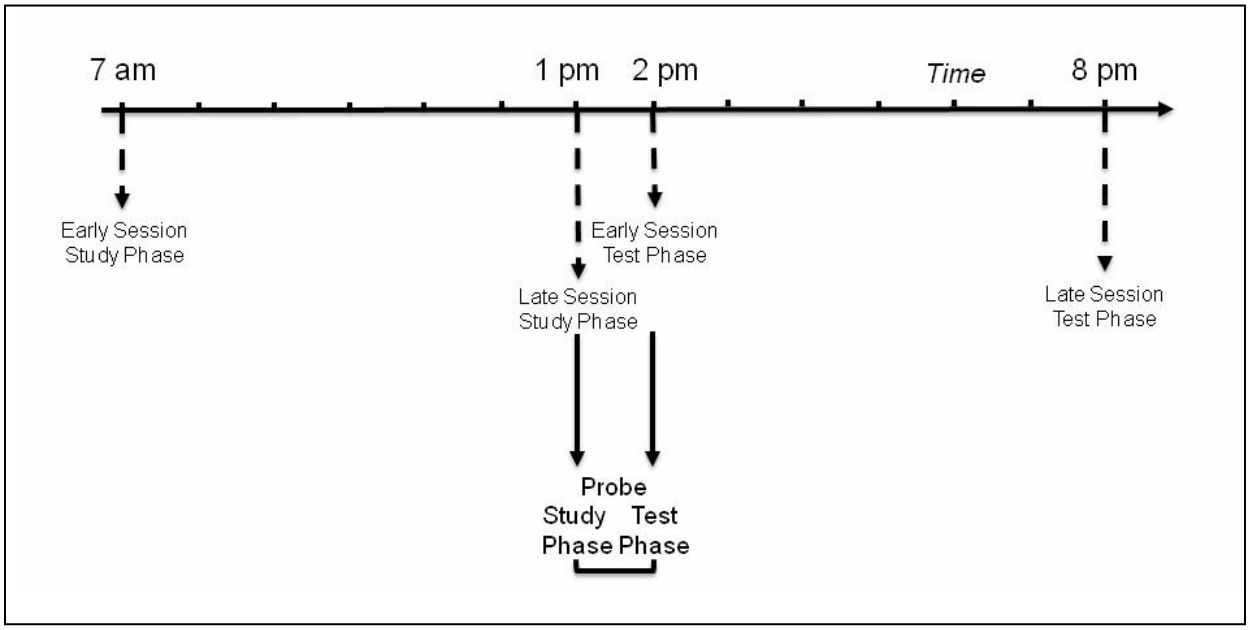

Figure 2.7: *Conflict-test design of Experiment 4*

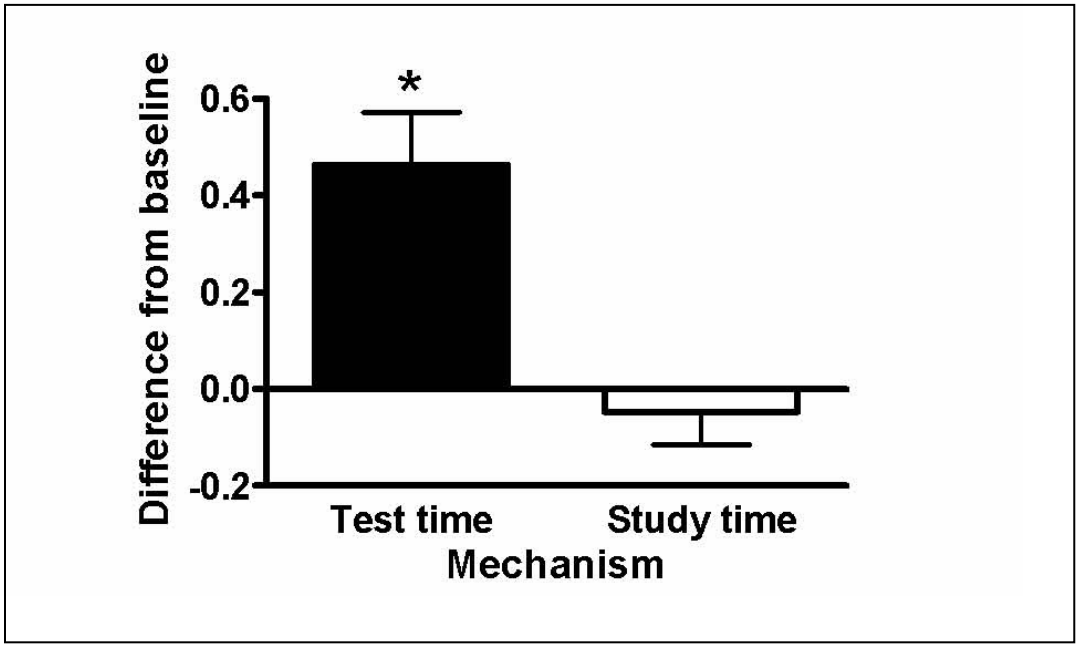

Figure 2.8: *Rats remembered the time of day at which the study episode occurred in the probe in Experiment 4. The rats treated the probe as a late-session test phase, suggesting memory of the time of day at study rather than discriminating time of day at test. The figure plots the difference between probe and baseline revisit rates. For the bar labeled test time, the baseline was the probability of revisiting chocolate in the early-session test phase in Experiment 3; thus, the significant elevation above baseline shown in the figure suggests that the rats did not use the time of day at test to modulate revisit rates. For the bar labeled study time, the baseline was the probability of revisiting chocolate in the late-session test phase in Experiment 3; thus, the absence of a significant elevation above baseline in the figure is consistent with memory of the time of day at study. The horizontal line corresponds to the baseline revisit rate to the chocolate location from Experiment 3 (terminal). Positive difference scores correspond to evidence against the hypothesis indicated on the horizontal axis. Error bars indicate S.E.M. * P < 0.001 different from baseline.*

The rats adjusted chocolate revisit rates based on the time of day at which the study phase occurred, rather than using the time of day at which the test phase occurred. Figure 2.8 shows data from the probe session relative to baseline data according to the time of day at study or time of day at test hypotheses; baseline data come from Figure 2.6 (right panel). The probe data was significantly different from the baseline for the test time hypothesis ($t(15) = 4.2$, $P < 0.001$), suggesting that the rats did not use the time of day at the test phase to adjust chocolate revisit rates. The probe data was not reliably different from the study time hypothesis ($t(15) = -0.7$, $P > 0.5$), consistent with the proposal that, at the time of test, the rats remembered the time at which the study episode occurred.

CHAPTER 3

DISCUSSION

Rats encountered chocolate, at a daily unique location, which sometimes replenished in a subsequent test phase. The replenishment depended on the time at which chocolate had been initially encountered. Optimal performance is to revisit the chocolate location at test when replenishment is imminent but to reduce this tendency when the chocolate replenishment is not forthcoming. Solving this task requires knowledge about what and where events occurred (chow-flavored locations from study phases never replenished in test phases) in addition to information about when the critical events occurred. Because the interval between study and test was constant within each experiment, how long ago a chocolate encounter occurred could not be used to predict replenishment.

In a series of manipulations, we documented that the rats solved this task by remembering when the study episode occurred. First, we ruled out timing the interval between light onset and the study-test sequence by shifting light onset to an earlier time that put interval and time-of-day predictions in conflict. Presumably, the estimate of time of day comes from an endogenous circadian oscillator; because a characteristic feature of such a system is that adjustment to phase shifts of the light cycle is gradual (25, 26), the representation of time of day would be unaffected by a single manipulation of light onset. The rats did not use the interval between light onset and the session, which suggests that they used time of day. Second, we sought evidence that the rats used the time of day at study, rather than the time of day at test, by

introducing a 7-hr retention interval (for both early and late sessions). The time of day at study, but not the time of day at test, was familiar to the rats from the earlier experiment. Thus, we infer that the rats used time of study rather than time of test to adjust revisit rates because the rats continued to revisit at a higher rate in the replenishment condition, compared to the non-replenishment condition. Third, we provided a novel test for the rats by beginning a session with a late study and ending the session with an early test phase; thus, we could determine if the rats adjusted revisits in the test phase based on the time of day at study or the time of day at test. The rats did not use the time of day at test, which suggests that they used the time of day at study. These experiments suggest that rats remember what-where-when under conditions in which how-long-ago cues were made irrelevant to performance.

In a series of elegant experiments, Roberts et al. (17) unconfounded time of day at study and the cue of how long ago the study episode occurred. In the Roberts et al. (17) study, the time of day at which study and test phases occurred and the retention interval between study and test were carefully arranged so that some rats received a consistent replenishment pattern with respect to time of study (referred to as the when group), retention interval (referred to as the how-long-ago group), or both (the when + how-long-ago group). The when group failed to learn the replenishment contingency whereas the other two groups adjusted revisit rates to the replenishment contingency. Roberts proposed that these results suggest that episodic-like memory may be qualitatively different from human episodic memory. It should be noted that rats in the when group received inconsistent feedback (i.e., replenishment) after short and long retention intervals. Thus, an alternative explanation of these data is the hypothesis that when both when and how-long-ago information are available, rats appear to rely on how-long-ago (or learn about it more rapidly); this may be a form of overshadowing under conditions of cue competition

(27). This hypothesis does not preclude the possibility that time of study may be encoded, but different experimental techniques might be necessary to reveal remembering of when the study episode occurred.

Roberts et al. (17) concluded that rats remember only how much time has elapsed since a significant event occurred. Because the data of Roberts et al. suggest that how-long-ago dominates when multiple temporal cues are available, we sought to evaluate what-where-when memories under conditions in which how-long-ago cues were irrelevant to predicting replenishment. When how-long-ago was rendered irrelevant in the current studies, we found evidence for remembering when an earlier study episode occurred, in addition to the content of what and where did the episode occur.

People can describe when earlier events occurred using calendar-date-time systems, i.e., a representational system that retains the time of occurrence of earlier events (19). Our data suggest that, at the time of memory assessment, rats remember when specific events occurred in time. Moreover, these experiments provide insight into the type of temporal representational systems that rats may use to support episodic-like memory, namely a timing system that retains the time of occurrence of earlier events.

CHAPTER 4

METHODS

Sixteen male Long-Evans rats (*Rattus norvegicus*; Harlan, Madison, WI; 76 days old and 269 g, on average, at the start of the experiment) were individually housed with light onset and offset in the colony at 7 a.m. and 7 p.m. EST, respectively. They received 45-mg chow and chocolate pellets (F0165 and F0299, respectively; Bio-Serv, Frenchtown, NJ) during experimental sessions and 15-20 g/day of 5001-Rodent-Diet (Lab Diet, Brentwood, MO) after completing each session. Water was available ad lib, except during brief testing periods. All procedures were approved by the institutional animal care and use committee and followed the guidelines of the National Research Council *Guide for the Care and Use of Laboratory Animals*.

The 8-arm radial maze (described in (13, 14)) had a central hub and 8 guillotine doors and arms. A food trough and a 45-mg pellet dispenser were located at the distal end of each arm. A photobeam in the trough detected head entries. Additional photobeams were 3.8 and 5.1 cm from guillotine doors. White noise masked outside noise. Experimental events (guillotine doors and food) were computer controlled from an adjacent room. Data (photobeam breaks) were recorded (10-ms resolution) with MED-PC software (version 4.0). Throughout all experiments, maze arms were cleaned with Nolvasan (Fort Dodge Animal Health, Fort Dodge, IA) after each rat was removed from the maze. Chow and chocolate pellets were placed beside the filled pellet dispensers (i.e., food odors were constant throughout all parts of the experiment).

Experiment 1. Pretraining permitted the rats to explore the maze in three 20-min daily session, in which chow pellets were placed in seven arms and corresponding troughs and one randomly chosen arm and trough contained chocolate pellets. During initial training, rats were individually placed in the central hub beginning at 7 a.m. for half the rats and 1 p.m. for the remaining rats (within each subset, rats were tested in a consistent order each day throughout all experiments to establish approximately constant times of day); all eight doors were then opened. A visit was defined by the interruption of a food-trough photobeam; interruption of the photobeam near the guillotine door was required before the next interruption of a food-trough photobeam counted as a visit. Food was dispensed into a trough contingent upon interrupting the photobeam located in that trough. Each arm containing chow dispensed one pellet per day. The arm containing chocolate (randomly selected each day) could dispense three pellets per visit. Rats could revisit locations with distinctive foods up to five times and receive three pellets per visit (additional food was not available after the fifth visit). Fifteen daily sessions ended when food was earned at each location or 10 min had elapsed.

In block testing, four blocks of 15-20 morning and afternoon sessions alternated (73 sessions overall). For half of the rats, the chocolate location replenished in the morning but not in the afternoon session (designated as replenish and non-replenish conditions, respectively). This contingency was reversed for the other rats. Each session consisted of a study phase and a test phase, separated by a retention interval of 1.71 ± 0.05 min (mean ± SEM). Rats were individually placed in the central hub. In the study phase, four doors (randomly chosen for each rat each day) were opened, with the restriction that one arm dispensed three chocolate pellets; all other accessible arms dispensed one chow pellet. Pellet(s) were delivered to accessible troughs contingent on the first interruption of the trough photobeam. When food had been dispensed at

each accessible location, the study phase ended and the rat was removed. Each animal was returned to the hub for a test phase with all doors open. In the test phase, chow-flavored food was available at each arm not previously accessible at study. Additionally in test phases, the study-phase chocolate location provided three chocolate pellets per visit for up to five visits in the replenishment (but not in the non-replenishment) condition. The test phase ended when food had been dispensed at each of the baited locations (i.e., after 4 or 5 different arms had provided food in non-replenish and replenish conditions, respectively). On any given day, a morning or an afternoon session (but not both) was conducted.

In mixed testing, replenish and non-replenish sessions (24 overall) were conducted in random order, using blocks of 6 sessions (3 trials of each type), with the constraint that no more than 3 consecutive sessions of the same type occurred (see Figure 2.1). In all other respects, mixed testing was the same as block testing.

Experiment 2. Light onset occurred at 12:00 a.m. instead of 6 a.m., and a morning session was conducted as described in Experiment 1; light offset was as in Experiment 1, and each rat was presented with the early light onset only once (see Figure 2.3). The manipulation was presented to the rats in two subsets because typical session times could only be preserved if half the rats were tested in the morning. Consequently, half of the rats received this manipulation immediately after completion of Experiment 1. The other rats were placed in a nearby colony for one night with the Experiment-1 light cycle, and they were not tested for one day; next these rats were returned to the original colony, they received 4 days of additional mixed testing (in case moving the rats disrupted performance), and then they received the manipulation described above.

Experiment 3. Experiment 3 began after the rats were not tested for 5-10 days. Study-test sequences were identical to Experiment 1 except the retention interval was 7 hr. Consequently, a session had a study and test occur, respectively, at 7 a.m. and 2 p.m. (designated as an early session) or at 1 p.m. and 8 p.m. (designated as a late session); see Figure 2.5. The first two sessions were replenish and non-replenishment conditions, respectively (the order was determined randomly). The subsequent 16 sessions were presented in random order as described in mixed testing of Experiment 1. In all other respects, the experiment was as in Experiment 1.

Experiment 4. A study phase started at 1 p.m. and a test phase started at 2 p.m. (see Figure 2.7). Testing was again conducted for two subsets (as in Experiment 3), except that the order of testing subsets was reversed and one day of mixed testing occurred before the second subset was tested.

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