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Cold-Induced Impairment of Delayed Matching in Rats

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Exposure to moderate, nonhypothermic cold temperature has been reported to affect a variety of behavioral and neural functions. To elucidate the effects of mild cold stress on short-term (working) memory, Long-Evans rats were exposed to an ambient temperature of either 2° or 23°C while performing a delayed matching task. At the beginning of each trial, rats were required to respond on one of two levers cued by a light. Following a delay of 2, 8, or 16 s, a response on the lever previously cued produced food reinforcement. Relative to performance at 23°C, exposure to 2°C occasioned no change in matching accuracy at the 2-s delay, a modest decrement at the 8-s delay, and a larger decrement at the 16-s delay. The cold exposure did not decrease colonic temperature. In addition to accuracy decrements, matching response times were consistently shorter during cold exposures. Cold-induced impairments were absent during removal of the memory component from the task, indicating the observed cold effects on memory were not due to impaired attentional, sensory, or motor processes. These data suggest that mild cold stress may impair active maintenance of information in working memory but not processes related to reference memory. © 1991 Academic Press, Inc.

In humans, exposure to moderate levels of cold temperature has profound effects on neural function (Brooks, 1983; VanOrden, Ahlers, Thomas, House, & Schrot, 1990). Of particular interest is the impairment of short-term memory reported in individuals during cold stress when hypothermia is not present (Pozos, 1986). Several investigators have described cold-induced memory degradation in humans, often with relatively brief, apparently nonhypothermic, cold exposures (Baddeley, Cuccaro, Egstrom, Weltman, & Willis, 1975; Bowen, 1968; Coleshaw, VanSomeren, Wolff, Davis, & Keatinge, 1983; Davis, Baddeley, & Hancock, 1983). This report was supported by Naval Medical Research and Development Command Research and Technology Work Units 61153N.MR04120.00B.1058 and 61152N.MR00001.001.1383. The opinions and assertions contained herein are those of the authors and are not to be construed as official or reflecting the views of the Navy Department or the Naval Service at large. Please address all correspondence and requests for reprints to Dr. John R. Thomas, Behavioral Neuroscience Division, Environmental Medicine Department, Naval Medical Research Institute, Bethesda, MD 20889-5055.
None of these studies evaluated specific components of short-term or working memory affected by cold. Although extensive literature exists on specific cold-induced memory impairments in animal models, this research has been almost exclusively concerned with profound hypothermia (e.g., Andjus, Knopfel, Russell, & Smith, 1956; Beitel & Porter, 1968; Riccio, Hodges, & Randall, 1968; Jacobs & Sorenson, 1969; Nagy, Anderson, & Mazzaferrri, 1976; Richardson, Guanowsky, Ahlers, & Riccio, 1984). Moreover, much of the existing literature using animals has focused on effects of hypothermia on long-term memory rather than on short-term or working memory processes.

The interest of the present study was the assessment of moderate, nonhypothermic cold exposure on working memory in rats. A delayed matching task was used to assess effects of cold temperature on working memory as moderate cold exposure has been shown to affect matching accuracy in humans (Thomas, Ahlers, House, & Schrot, 1989). The delayed matching task was procedurally similar to delayed conditional discrimination tasks previously used with rats (Dunnett, 1985; Dunnett, Badman, Rogers, Evenden, & Iversen, 1988; Kirk, White, & McNaughton, 1988), but differed in that the matching task in the present study contained both explicit working (matching response) and reference memory (sample response) components for assessment of selective effects on memory (cf. Olton, 1985). A delayed matching task with three delay intervals (2, 8, and 16 s) was employed to examine accuracy at varying delays within a single session. If cold exposures show selective effects at longer delay intervals compared to shorter intervals, performance deficits could be more easily attributable to specific memory impairment. To study the effects of cold exposure on matching performance, the rats were exposed to an ambient temperature of 2°C which did not induce core hypothermia.

METHODS

Subjects

The subjects were four male Long-Evans rats maintained over the course of the study at 80% of their free-feeding weight of approximately 340 g. The animals were individually housed in hanging cages in an air-controlled unit. Water was available continuously in the home cage.

Apparatus

The subjects performed in a rat test cage 24.1 by 30.4 by 26.6 cm. Two response levers were mounted on the front wall, 5.0 cm above the grid floor and 3.8 cm from either of the side walls. A food tray was mounted 1.2 cm above the grid floor and in the center of the front wall equidistant from each of the levers. The tray was connected by a short tube to a pellet feeder located behind the front wall which could dispense 45 mg
food pellets. A small light with a white lens cover was mounted 5.0 cm above both the right and the left levers. A third response lever with a light located above it was located on the back wall, 5.0 cm above the floor. A speaker located behind the front wall was used for presentation of a 2800-Hz tone at approximately 40 dB. A house light was mounted on the top of the front wall. All baseline and cold exposure sessions were conducted with the rat cage housed inside a temperature-controlled environmental chamber with internal dimensions of 61.0 by 71.1 by 121.9 cm. Experimental events were controlled and recorded by a microcomputer system.

**Matching Procedure**

Sessions were conducted 5 days per week (M–F) with sessions terminating after completion of 180 trials or 60 min, whichever occurred first. The house light was illuminated during all sessions. At the start of each trial the correct lever was cued by illumination of the light over one of the two levers on the front wall (sample light). The rat was required to press the lever under the illuminated light. A response on the lever under the sample light turned off the light and started a delay interval. A response on the lever not under the sample light also turned off the light but was followed by a 5-s intertrial interval and the start of the next trial. A trial occurrence was recorded only if the rat correctly responded on the lever under the sample light. At the start of the delay interval the light was illuminated over the single lever on the back wall. The delay interval was either 2, 8, or 16 s. A random order of delay intervals was presented in each session with the following constraints. Within a block of 60 trials, each delay interval appeared 20 times. Half of the trials at a particular delay interval began with the left light illuminated on the front wall and the other half began with the right light illuminated. No more than two trials with the same delay could occur consecutively. The first response on the back wall lever following the completion of the delay interval resulted in turning off the back wall light, sounding a 2800-Hz tone, and illuminating both lights over the two front wall levers. Responding during the delay interval was maintained on a fixed-interval schedule. The value of the fixed-interval schedule was that of the nominal delay interval. As a response was required on the back wall lever at the end of a delay interval, the actual obtained intervals were slightly longer than the nominal times of 2, 8, and 16 s. The average obtained delay intervals were 2.5, 8.5, and 16.6 s. The maintenance of responding on the back wall lever functioned to prevent the development of position bias or the adoption of simple mediating response patterns, such as standing in front of the appropriate front wall lever. The fixed-interval requirement also ensured that the rat was always positioned centrally in the back of the chamber at the termination of the delay interval. Following
illumination of the two front wall lights and tone onset, a response on the front wall lever previously associated with the sample light was recorded as a correct matching response. A correct matching response produced a food pellet and turned off both front panel lights. If a response was made on the front panel lever not previously associated with the sample light (an incorrect matching response), both front panel lights were turned off. Following either a correct or an incorrect matching response, a 5-s intertrial interval preceded the beginning of the next trial. During the intertrial interval only the house light was illuminated. Four months of daily sessions were conducted to establish stable performance on the matching procedure.

Control Procedure

Following several cold exposures in which the effect of cold on working memory was examined (detailed below), the subjects were exposed to approximately 6 weeks of a control procedure. This procedure was identical to the matching procedure except that following the delay interval only the light over the correct front wall lever was illuminated. By removing the explicit memory component from the task, this control procedure assessed the effects of cold on attention and on general sensory and motor processes. After several cold exposures, the subjects were again returned to the matching baseline for an additional cold exposure.

Cold Exposures

Rats were placed into the chamber 30 min before the start of each session. During this presession time all lights in the chamber were off. At the end of this 30-min period, the house light was illuminated and the session started. The 30-min presession placement in the chamber was in effect for all sessions, both cold and noncold. During all noncold sessions the environmental chamber was programmed at 23°C. The subjects were cold exposed once a week (either W or Th) for 2 weeks with the environmental chamber programmed at 2°C. The session immediately before a cold exposure session served as a 23°C baseline comparison session for that exposure. Following two separate cold exposures for each subject, they were placed on the control procedure (see above) for several weeks. They were again exposed, while on the control procedure, to 2°C once per week for 3 consecutive weeks. Finally, the subjects were returned to the original matching procedure and allowed to restabilize for several weeks. They were then exposed to 2°C while performing on the matching procedure for a third time. At the termination of each cold exposure session and at each immediately preceding baseline session the core temperature of the subjects was measured with a rectal probe inserted 3.5 cm.
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RESULTS

Matching Response Accuracy

The data are presented as the mean of three test sessions at each condition as there were no systematic changes observed as a function of the number of cold treatments. Figure 1 shows the response accuracy on the matching procedure for both cold (2°C) and baseline (23°C) conditions at each of the three delay intervals. A significant decline in overall matching response accuracy was obtained with increasing delay intervals ($F(2, 6) = 26.22, p < .01$). Analysis indicated that increasing delay intervals significantly reduced matching response accuracy at 23°C ($F(2, 6) = 24.75, p < .01$) and also at 2°C ($F(2, 6) = 24.68, p < .01$). Matching response accuracy was significantly lower during the 2°C exposure sessions than during the 23°C sessions ($F(1, 3) = 62.96, p < .01$). A significant interaction was obtained between exposure condition and delay interval ($F(2, 6) = 6.72, p < .05$) in that lower accuracy was observed at the longer delays during cold exposure. Pairwise analysis at each delay interval indicated that matching response accuracy was not decremented at the 2-s delay during exposure to 2°C. Accuracy was significantly lower during cold sessions at both the 8-s ($t(3) = 3.92, p < .05$) and 16-second delay ($t(3) = 7.16, p < .01$) than during 23°C.

Figure 2 shows the matching response accuracy on the control procedure for both cold and baseline conditions at each of three delays. No systematic changes were observed in matching response accuracy on the control procedure at any delay or as the result of cold exposure.
Matching Response Accuracy on Control Procedure at Three Delay Intervals (2, 8, and 16 s) at 2°C and 23°C. Data points are means and standard deviations are smaller than the size of the symbols.

**Matching Response Time**

Figure 3 shows time (in seconds) from the end of the delay interval until the occurrence of either a correct or incorrect response (matching response time) for both cold and baseline conditions. No systematic differences in matching response times were observed for the three delays. However, the matching response times were consistently shorter during cold exposures than during 23°C sessions ($F(1, 3) = 15.12, p < .05$).

The matching response times during the control procedure for both cold and baseline conditions at each delay are shown in Fig. 4. Control matching response times were also shorter during exposure to 2°C than during exposure to 23°C ($F(1, 3) = 26.01, p < .05$). Overall control response times did not differ systematically across delay intervals and did not differ from matching response times.

**Sample Response Performance**

Accuracy of responses under the illuminated sample light at the beginning of each trial was not affected by cold exposures in either the matching or the control procedure. Sample response durations also were not systematically affected by cold exposures in either matching or control procedures.

**Core Temperature**

Although slightly lower, the mean core temperature of the rats following cold exposure sessions (37.5 ± 0.6) was not significantly different from the mean temperature following 23°C sessions (38.2 ± 0.6).
COLD IMPAIRMENT OF DELAYED MATCHING

2.30
2.10
1.90
1.70
1.50
0 4 8 12 16
Delay Interval

Fig. 3. Matching response time (in seconds) on delayed matching procedure at three delay intervals (2, 8, and 16 s) at 2°C (■) and 23°C (□). Data points are means and brackets indicate standard deviations.

DISCUSSION

The present study demonstrates that even relatively moderate cold exposure that does not induce core hypothermia can impair working memory in rats. Specifically, disruption in working memory by cold exposure reflects a selective alteration in the maintenance of information over a relatively brief interval rather than a disruption in the acquisition of information. During exposure to ambient temperature of 23°C a gradual decrease in performance over the delay interval was observed such that

2.30
2.10
1.90
1.70
1.50
0 4 8 12 16
Delay Interval

Fig. 4. Matching response time (s) on control procedure at three delay intervals (2, 8, and 16 s) at 2°C (■) and 23°C (□). Data points are means and brackets indicate standard deviations.
accuracy of matching during noncold sessions was highest for the shortest delay and lowest for the longest delay, reflecting normal rate of forgetting of information in working memory. The differential accuracy as a function of delay interval was comparable to performance reported in studies with rats employing similar procedures and delay values (Dunnett, 1985; Dunnett et al., 1988; Kirk et al., 1988).

Importantly, an interaction was demonstrated between cold exposure and delay intervals in that, relative to the performance in 23°C, cold produced no decrement in accuracy at the 2-s delay, a modest decrease at 8 s, and the largest decrease at 16 s. The interaction may be interpreted to indicate that cold selectively affected retention of information in working memory. That is, cold had the most profound effect on accuracy at the longer delay interval during which a greater period of maintenance of information is required. The 2-s delay, not affected by cold, requires only minimal temporal maintenance of information. The lack of any cold-induced accuracy decrement at the 2-s delay also shows that cold did not have an effect upon the acquisition of information. Under the conditions of the present study, cold leads to more pronounced impairment in the maintenance of information in working memory with increasing delay. It should be noted that a caveat in the interpretation of an interaction between cold exposure and increasing delay intervals is that at the 2-s delay condition performance is constrained by a ceiling effect. It is possible that such an interaction would not be observed with less accurate performance levels, across all delays.

Cold-induced impairments were absent during removal of the memory component from the task (control procedure), indicating that cold did not impair attentional, sensory, or motor processes. The lack of cold effect on the control procedure also supports the view that impairment of response accuracy on the matching task was due to alterations in the active maintenance of information during the delay interval rather than effects of processes related to reference type memory. That cold produced a selective effect on working memory is also strengthened by the absence of any systematic cold effect on sample response accuracy. Accuracy in responding on the lever under the illuminated sample light at the beginning of each trial was not systematically affected by cold exposures in either the matching or the control procedure.

In addition to the selective decrements in matching response accuracy, cold also affected another performance aspect of the task in that matching response times were consistently shortened during cold exposures. However, unlike matching accuracy, the cold-induced decrease in response time was not specific to the matching condition. Response times were also shorter during cold sessions than during noncold sessions with the control procedure in which the memory component was removed. As the matching response time effect was similar in both matching and control procedures,
the shortening of response times during cold exposures appears to be more of a general cold effect on performance. The shortening of response times by rather moderate cold temperature is a pattern that has been observed during cold exposures with human subjects (Ellis, Wilcock, & Zaman, 1985; Enander, 1987; Thomas et al., 1989) and may reflect a cold-induced increase in specific neural functioning (VanOrden et al., 1990).

It is of interest to consider what aspects of the observed impairments in working memory may be related to nonhypothermic cold exposure. Because shorter response times were obtained during cold exposure regardless of whether the animals were performing on the matching or control procedure, the effect of cold on working memory would appear to result from a fairly nonspecific increase in neural activity. Such a general increase in activity might accelerate the rate of decay of information held in working memory by increasing the rate at which information is processed. Alternatively, however, it is possible that cold exposure may have increased interference and thereby impaired retention. There is an extensive literature demonstrating that presentation of events in the interpolated delay interval can substantially impair retention of working memory, i.e., retroactive interference, especially at longer delay intervals (Roberts & Grant, 1978; White, 1985; Worsham & D'Amato, 1973). Although the present experiment does not lend itself to unequivocal distinction between retroactive interference and decay interpretations of cold-induced memory decrements, several lines of evidence would suggest that increased interference per se does not account for the observed acceleration of forgetting. First, in most demonstrations of retroactive interference the interfering event is presented during the delay interval, whereas in the present study the animal was continually exposed to cold for 30 min prior to the test session and during the entire procedure. Thus, cold exposure was not a novel event introduced during the delay interval, but an event that was continually present immediately before and during the test session. Second, since the procedure employed in the present study required the animal to respond on the lever on the back wall between the sample and test interval, there was little opportunity for the animal to engage in additional activity during the delay interval. For these reasons it would appear more likely that the effect of cold on working memory is the result of an increased rate of decay of information rather than an increased retroactive interference. Similarly, it is also unlikely that the decrement in working memory stemmed from an increase in proactive interference. In general, increased proactive interference tends to produce a parallel downward shift in the rate of decay for all retention intervals rather than a decrease at longer delay intervals (cf. Roitblat & Harley, 1988; White, 1985). However, the contribution of interference, either retroactive or proactive, to the memory impairment observed during cold
exposure cannot be completely ruled out as an influential factor until manipulations of specific delayed matching parameters are undertaken.

In addition to the above possibilities, cold exposure may induce impairments in memory through quite different mechanisms. It is known, for example, that profound cold exposure produces changes in brain function reflected in modulations of normal wave form, frequency, and amplitude of neural activity (Beitel & Porter, 1968; Horsten, 1949). More specifically, cold exposure has been reported to induce increased neural activity in the hippocampus and amygdala and the modified activity has been related to memory impairments (Gehres, Randall, Riccio, & Varvaris, 1973). Interestingly, if cold-induced increases in neural activity in these regions are blocked pharmacologically, no memory impairment occurs (Gehres et al., 1973). Thus, cold-induced memory impairments observed in the present study may be associated with subtle temperature gradients in subcortical structures important to memory. Such subtle temperature gradients in selective brain regions induced by cooled blood have been proposed to underlie cold-induced performance decrements observed in humans (Pozos, 1986).

Last, it is possible that the effects of cold on working memory may be associated with cold-induced changes in stress hormones. That changes in levels of stress hormones are capable of memory modulation is well established (McGaugh, 1989). It has been shown, for example, that memory may be profoundly affected by increases in peripheral catecholamines (Gold, 1984; McGaugh, Liang, Bennett, & Sternberg, 1984). Importantly, sustained cognitive activity in a moderate cold environment can significantly increase plasma epinephrine levels to a degree not observed with cold alone (Thomas, Ahlers, House, Schrot, VanOrden, Winsborough, Hesslink, & Lewis, 1990). Additionally, large elevations in peripheral norepinephrine levels are a classic hallmark of cold stress. Changes in such peripheral catecholamine levels or in other stress-related hormones, as a result of exposure to cold stress, may be involved in the selective memory impairments observed in the present study. The extent to which alterations in information decay function, interference, brain temperature gradients, or stress hormones may underlie the effect of cold exposure on working memory remains to be determined.

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