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Types of Memory or Attention? Impairments After Lesions of the Hippocampus and Limbic Ventral Tegmentum

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OADES, R. D. *Types of memory or attention? Impairments after lesions of the hippocampus and limbic ventral tegmentum*. BRAIN RES. BULL. 7(2) 221–226, 1981.—An animal with an unimpaired "reference" memory can distinguish between alternatives that belong to a rewarded set and those that are unrewarded. An animal with an unimpaired "working" memory can distinguish between alternatives where it has been rewarded (e.g., food has been eaten and not replaced) and those where it will be rewarded. Olton *et al.* [19] proposed that rats with fimbria-fornix or hippocampal damage showed a lasting deficit specific to "working" memory. This hypothesis has been tested for animals with damage to the hippocampus, limbic ventral tegmentum, neocortex and for intact and operated controls on a task where food pellets must be found in four of 16 holes in a "hole-board" arena. Only the first two groups were impaired in acquiring this task. The impairment was marked for both types of "memory." It is proposed that the deficit may, in part, be accounted for by deficits in the selective mechanisms related to attention.

"Working" memory "Reference" memory Attention Fimbria-fornix Hippocampus
Ventral tegmental area Hole-board Dopamine Noradrenaline

SEVERAL hypotheses for an involvement of hippocampal function in cognitive activity have been proposed in the last 12 years. The hippocampus has been said to generate internal of response inhibition [3, 4, 10], form cognitive maps [20], process temporal information [29] and contain attention-related mechanisms [14,15]. Recently Olton *et al.* [19] postulated a specific role for the hippocampus in the formation and use of a "working" memory. They examined the performance of rats with fornix lesions in 8- and 17-arm radial mazes in which several arms were baited with food. Following the working definitions of Hönig [5] an analysis was made of the probability of responding to an arm in the baited set ("reference,' memory) and the probability of responding to an arm in the baited set that still had food in it ("working" memory). They found that lesioned animals showed impairments of both types of memory at first. But after 30 tests only the "working" memory remained impaired.

These results are of interest because the impairment specific to "working" memory appears after selective damage to the fornix-fimbria system and the hippocampus [8, 9, 18, 19]. Further the distinction between "working" and "reference" memory parallels the distinction that has been made by psychologists between "episodic" and "semantic" memory [30]. The distinction could be important because the former is said to be more liable to interference [30] and may be more impaired in humans amnesics [11].

Few experimental designs in use, apart from the radial maze, are suitable to test the hypothesis of Olton *et al.* [19]. Here I report results from a "hole-board' search task where the generality of this hypothesis can be tested. In this task the proportion of visits that rats make to baited and non-baited holes may be compared to the visits made to baited and non-baited arms in the maze of Olton [19].

It is emphasised that the generality of Olton's hypothesis can be tested. The tasks differ in two important ways. In the radial maze long training sessions have been used [18]. The constraint of finding the correct alleys in a prescribed sequence appears to be relatively difficult for rats to acquire. In the hole board, where rats are able to choose their hole-visit sequence, learning apparently occurs more rapidly (100 trials). A second difference is that rats in the radial maze are forced to make discrete choices after confinement to an area in the middle of the maze. In the hole-board choices are less "discrete" in that after each hole visit (4 of 16 holes are rewarded) they can choose to move in any direction toward any hole.

The prediction from the work of Olton is that rats with hippocampal damage will show no improvement of performance according to the measure of "working" memory alone. The data show that both types of memory are disturbed after extensive hippocampal damage and after large lesions of the ventral tegmentum that projects to the septo-hippocampal axis.

METHOD

The subjects were hooded rats that weighed 200–300 g (80% of preoperative weight) during testing. They were in-

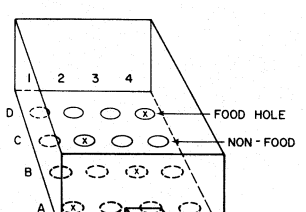

FIG. 1. A schematic drawing of the test apparatus—a 16-hole board—is shown. The numbers and letters designate the rows and columns in the arena. The x-symbol in holes A1, B3, C2 and D4 shows where food pellets are placed.

dividually housed, but were kept in visual, auditory and olfactory contact on a 12 hr light/dark cycle at 23±2°C. They had free access to water outside the test arena.

Six animals were unoperated controls (C_1), 7 received bilateral hippocampal (plus neocortical) lesions (H) and 7 received bilateral lesions of the neocortex overlying the hippocampus (N) by aspiration. At the end of the experiment the rats were perfused with saline followed by 10% Formalin solution. The brains were then frozen and 20 μm sections were cut and stained with thionin. These procedures resulted in bilateral lesions which involved 60–90% of the hippocampus as well as the removal of part of the overlying posterior neocortical surface. The lesions were comparable with those produced in the same laboratory (e.g., [33]). All animals had received saline injections (SC) prior to test sessions 4–10 as controls for drug-treated groups not reported here (for full details, see [17]).

Eight animals received bilateral lesions of the ventral tegmental area (VTA) extending ventrally from the mesencephalic grey to the superior border of the interpeduncular nucleus, caudally from the posterior mamillary body (spared) to the nucleus linearis caudalis (damaged). Lateral limits of damage were marked by the border between the A9 and A 10 dopaminergic nuclei [2] ventrally; more dorsally the nucleus ruber received some damage. Coagulation was made by the implantation of 22 gauge cannulae into the VTA and the removal/replacement of stylets extending 0.5 mm beyond the cannulae (histology figure, [16]). Eight control animals were implanted with cannulae but received no coagulation (C_2). These animals were tested as a pilot study for investigations following the intracerebral injection of drugs.

The test apparatus consisted of a hole-board arena (70×70 cm). There were 16 holes (3.5 cm diameter) in the floor, 10 cm apart (Fig. 1). After recovery from operation (10 days) all animals spent half an hour on 5 consecutive days in the arena. On the first two days no food was available in the arena; on the next three days one Noyes food pellet (35 mg) was placed in each hole. Thus the animals were habituated to the arena and used to visiting all holes to eat food. During the following test week one pellet was placed consistently in each of 4 holes (Fig. 1). A test session consisted of 10 trials. During the inter-trial interval (30–40 sec) the floor was cleaned with a wet and dry cloth. On each trial the rat entered the arena from the start box and ate all food pellets. A test session was performed in the morning and afternoon of 5 successive days. During the intersession interval (>4 hr) the floor, the holes and the start box were washed.

For groups C_1, N and H an eleventh session was performed on the third day after the tenth session. This allowed the effects of drug-treatment (not reported here) to wear off. Thus data were retained solely for the behavior before [3], at the start of [4], at the end of [10] and after treatment had ended [11]. Only data from these sessions could be reanalysed for this report. Testing of C_2 and VTA groups ended after session 9 in the morning as the brains were required for biochemical analysis.

Comparisons between the performance of the groups on a given session were made by the Kruskal Wallis analysis of variance (KW). The within group changes were analysed by the Wilcoxon matched pairs test (W) and the comparison between changes was made with a two-tailed Mann Whitney U test (MW) [26].

RESULTS

Lesion Size

Against expectations no overt relationship existed between the extent of the lesion and the degree of behavioral change recorded. In contrast, inspection of Figs. 2–4 shows that for animals with hippocampal or VTA lesions the SEM was less than for the control groups. This is remarkable in the case of the VTA group where it has been found (unpublished results) that small blood clots (<1 mm) can cause as much behavioral change on the recorded measures as a larger lesion (2 mm). This is less surprising in the case of hippocampal lesions where the extent of damage lay well over 60% [17, 31, 33]; however, differences were recorded where damage was subsequently shown to have affected the thalamus. These animals were not included in the subsequent analysis.

"Reference" Memory

The score for reference memory measured the number of visits to the correct set (total food-hole visits) in relation to the number of visits to the incorrect set of holes (total non-food hole visits). The term "total" refers to the first visit to a food-hole and further visits when it was empty. For the control groups (C_1, C_2 and N) this ratio more than doubled between the third and last session (Fig. 2, respectively, $p<0.05$, $>p>0.02$, $p<0.02$, W). For both lesioned groups (H, VTA) the improvement was significant, but the increase was less than 50% (Fig. 2, respectively, $p<0.02$, $p<0.05$, W). The increase was significantly larger for C_1 and N than for the H group ($p<0.001$, U=0, MW). From session 3 on the scores were higher for the C_1 and N than for the H group (session 3, N>H, $p<0.01$, H=6.7, C>H $0.02<p<0.05$, H=4.1; session 10, N>H, $0.01>p>0.001$, H=9.7, C>H $p<0.001$, H=19.3, KW). On sessions 3, 4 and 9 the scores were higher for the C_2 than for the VTA group ($p<0.01$, H=7.7–9, KW). There was no difference between the C_2 and VTA group on the first session (C_2, 0.475±0.054; VTA, 0.433±0.019).

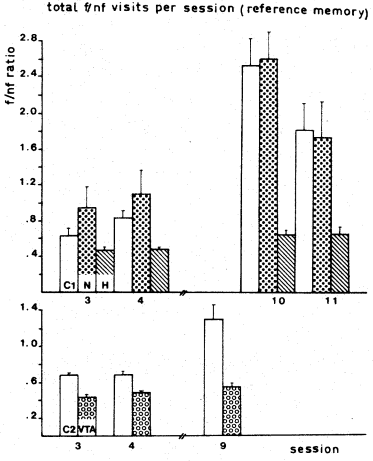

FIG. 2. This bar diagram shows the performance according to the measure of "reference" memory (total visits to food holes: total visits to non-food holes) of the following groups of rats with hippocampal lesions (H), neocortical lesions (N), ventral tegmental lesions (VTA); also for intact controls (C_1) and operated (implanted) controls (C_2). S.E.M. bars are shown. Data are presented for sessions 3, 4, 9 (last session for VTA and C_2), 10 and 11 (last session for C_1, N and H groups). All comparisons between C_1, C_2, N and VTA, H groups are significant (<5%); (e.g., session 3; N, $p<0.01$, H=6.7; C_1, $0.05>p>0.01$, H=4.1; C_2, $p<0.01$, H=7.7; session 10; N, $0.001<p<0.01$, H=9.7; C_1, $p<0.001$, H=19, session 9, C_2, $p<0.01$, H=9; KW).

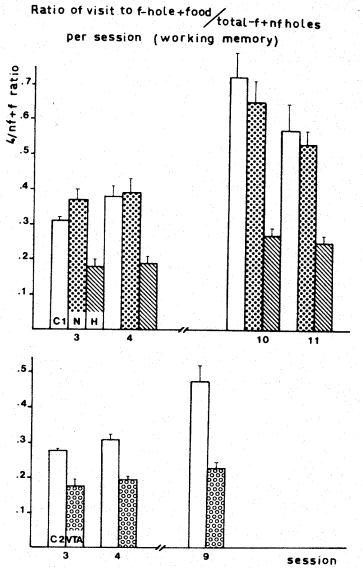

FIG. 3. This bar diagram shows the performance according to the measure of "working" memory (food-rewarded hole-visits: total hole visits) for 5 groups of rats (see legend for Fig. 2). Data are presented for session 3, 4, 9 (last session or C_2 and VTA), 10 and 11 (last session for C_1, N and H groups). S.E.M. bars are shown. All comparisons between C_1, C_2 N and H, VTA groups are significant (<5%). (session 3: N, $0.001<p<0.01$, H=8.1; C_1 $0.01<p<0.02$; C_2, $p<0.01$, H=8.4; session 10, N, $0.001<p<0.01$, H=9.7; C_1, $0.001<p<0.01$, H=9; session 9, C_2 $p<0.01$, H=8.6; KW).

"Working" Memory

The score for "working" memory measured the proportion of visits to correct holes that contained food (i.e., 4) in relation to the total number of hole visits (food and non-food holes) on a given trial. For control groups, (C_1, C_2 and N) this ratio approximately doubled (Fig. 3, respectively, $p<0.05$, $p<0.02$, $p<0.02$, W). Both lesioned groups (H and VTA) showed a slight increase that only reached significance for the H group (Fig. 3, $p<0.05$, W). The increase was significantly larger for the C_1 and N than or the H group (respectively, $p<0.002$, U=1; $p<0.01$, U=5, MW) and larger for the C_2 than for the VTA group ($p<0.04$, U=10, MW). From session 3 on the scores were higher for the C_1 and N than for the H group (session 3, C>H, $0.02>p>0.01$, H=6.3, N>H, $0.01<p<0.001$, H=8.1; session 10, C>H, N>H, $0.01>p>0.001$, H=9–9.7, KW. On sessions 3, 4 and 9 the scores were higher for the C_2 than for the VTA group ($p<0.01$, K=8.4–8.6, KW). Even on session 1 the C_2 group performed slightly better than the VTA group (C_2, 0.208±0.015; VTA, 0.168±0.013, $p<0.05$, K=4.3, KW).

DISCUSSION

It is clear that animals with hippocampal and ventral tegmental damage, when tested on the hole-board search task, are severely impaired on measures of both "reference" and "working" memory in comparison with unoperated, operated and lesioned (neocortex) control animals. These impairments remained significant even after the animals had performed over 100 trials. Olton *et al.* [19] reported an initial

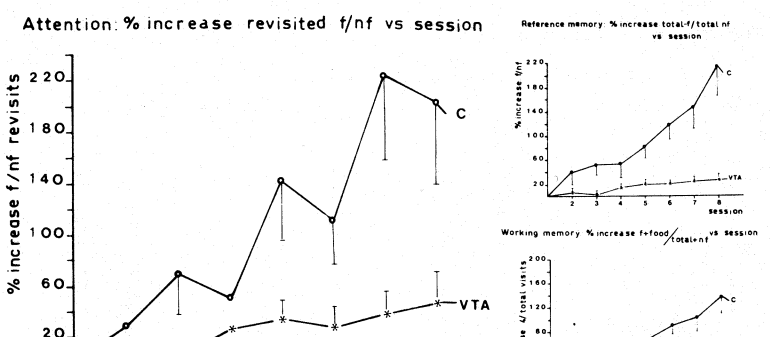

FIG. 4. For rats with ventral tegmental lesions (VTA) and for operated controls (C) the left-hand diagram shows the percentage increase of the attention-related indicator (re-visited food-holes: re-visited non-food holes) on successive test sessions with respect to session 1. The changes between morning and afternoon session (3–4, 5–6, 7–8) contrast with the percentage increases of performance according to "working" and "reference" memory shown in the two right-hand diagrams. (S.E.M. bars illustrate where significant differences appear between the two groups).

impairment on both measures for animals with fimbria-fornix damage on the radial maze task. however there was a rapid improvement after 30 tests on the measure of "reference" memory.

Secondly there is a striking similarity between the performance of animals with hippocampal damage and those with damage to the limbic midbrain, that sends afferent fibres to the lateral septum, entorhinal cortex and dentate gyrus [2, 12, 23, 27].

What could explain the differences between the previous results [8, 9, 18, 19] and those reported here for animals with extensive hippocampal damage? First, Olton [19] suggested that cutting the fimbria-fornix system would be functionally equivalent to a large hippocampal lesion. As the H group of the present study had large lesions (60–90%), this assumption may not hold. However Jarrard [8,9] has claimed similar results to the studies of Olton [18,19] following restricted dorsal hippocampal damage. Thus the reason for the differences may lie elsewhere. A second potential explanation may be found in the way the two experiments were conducted. The radial maze test of Olton consists of sequences of discrete trials for rats that are required to make discrete choices. In the hole-board test, by contrast, a rat makes a large number of choices on each trial. One might speculate that the discrete trial situation allows more time for an animal to consolidate "reference" memory but introduces as much interference as the hole-board test for holding a "working" memory. In this case the nature of the task (radial maze vs hole board) limits the generality of Olton's hypothesis.

A further difference is that, in contrast to the present report, previous studies concerned animals that had received some preoperative training. Winocur [32] conducted radial maze tests with hippocampally damaged rats and found that performance errors were increased for both cued and non-cued conditions. He reported that preoperative training on the cued test was particularly disadvantageous for animals tested postoperatively on the non-cued test. All animals in this report had exclusively postoperative experience of the hole board.

Although I emphasize that both forms of memory were severely impaired on the hole-board task, there was a tendency, in agreement with previous studies, for the performance according to "reference" rather than "working" memory to improve slightly in all experimental animals. According to the measure of "working" memory the VTA group showed a slight impairment with respect to the C_2 group at the end of the first test session.

Lastly, it should be pointed out that a deeper problem remains for the interpretation of these results. What is the nature of the mechanism(s) affected (cf. [1])?

Animals with hippocampal damage [6] and mesolimbic damage [16,28] are capable of learning simple tasks. This implies that simple memorial mechanisms may still be available after lesion damage. Let me offer an example. Lesioned rats learn to reduce the number of empty holes visited on the way to the first food pellet in the hole-board as well as controls [16]. Further, all animals develop a preference for the first hole they visit on leaving the start box. The specific hole is different for individual animals [16,17]. The frequency of

preference changes between sessions is the same for lesioned and control rats [16]. However, within a session the preference is not repeated by lesioned animals on as many trials as it is by controls. This suggests that simple memory mechanisms are intact, but on a given trial a lesioned animal is likely to be distracted. Increased distractibility has been noted in animals with lesions of the dopaminergic ventral tegmentum [28] and the noradrenergic locus coeruleus [13, 14, 15]. As would be expected, a lack of distractibility was found after hippocampal lesions [31], which contains terminals from fibres originating in these monoaminergic nuclei. In each case simple runway tests were performed and the results have been interpreted in terms of lesion-induced changes of attentional mechanisms [13, 14, 15, 28].

Oades [16] has proposed an indicator for the performance of attention-related mechanisms. This is the ratio of *re*-visited food-holes to *re*-visited non-food-holes. This indicator is based on the idea that attention-related functions involve the decision between relevant and irrelevant stimuli [7, 15, 29]. *Re*-visits are recorded as these tend to occur when uncertainty is high and thus the decision crucial (for example when rats experience difficulty in finding the last food pellet). One characteristic in favor of this indicator, where operated controls show an improved performance with respect to lesioned animals (Fig. 4), is that the performance of controls is better on the morning than on the afternoon sessions. Performance is better when arousal and general activity is higher. Whereas dopamine and serotonin levels are likely to be similar on the two sessions, noradrenaline levels are likely to be higher in the morning [21,22]. Many experiments have implied that noradrenaline plays a role in the function of attention-related mechanisms [13, 15, 24, 25]. In contrast the data for the two types of memory show no morning or afternoon changes (Fig. 4). A disadvantage for the measure of "relevance" is that any indicator based on repeated choices of animals will involve a memorial component.

In conclusion, the performance of animals with damage either to the hippocampus or the limbic ventral tegmentum was examined on a hole-board in order to test how widely a distinction between "working" and "reference" memory function in animals with hippocampal damage could be applied. The generality of the suggestion of Olton [18,19] that there is a long-lasting deficit restricted to "working" memory is not supported from results obtained using a different task. It remains unclear whether the difference can be attributed to dissimilarities in the nature of the radial maze and holeboard tasks and the way in which these tasks were conducted. The impairments seen on measures of both "reference" and "working" memory, recorded from the holeboard, may support an interpretation in terms of an increased influence of interference after damage to the limbic system. However it is proposed that in the light of the differences seen according to the measure of "relevance" that this may reflect an impairment of the selective characteristics associated with attention-related mechanisms.

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