Biological Psychology 12 (1981) 77–85
North-Holland Publishing Company

IMPAIRMENTS OF SEARCH BEHAVIOUR IN RATS AFTER HALOPERIDOL TREATMENT, HIPPOCAMPAL OR NEOCORTICAL DAMAGE SUGGEST A MESOCORTICOLIMBIC ROLE IN COGNITION

Robert D. OADES *
Department of Psychology, University of Florida, Gainesville, FL 32601, U.S.A.

Accepted for publication 5 May 1981

In a radial maze rats with fimbria-fornix or hippocampal damage are reported to show a lasting impairment of *working* but not *reference* memory (Olton, Becker and Handelman, 1979). On a 16-hole board, search task, rats with hippocampal damage showed deficits persisting over 100 trials on both measures: (4/16 holes contained food; *working* memory error – vist to a just-visted, baited hole; *reference* memory error – visit to a hole that had never been baited). Haloperidol treatment had no effect on the poor performance following hippocampal damage, but it impaired that of sham-controls on both measures. Animals with neocortical damage were impaired on the measure of *reference* memory alone, after haloperidol treatment. These measures may reflect two different information processing mechanisms. The hippocampus, the overlying neocortex and the dopaminergic, mesocorticolimbic system seem to be differentially involved. The possibility that these mechanisms could relate to attention or memory and their importance for the study of the associative impairment of psychotic human subjects is briefly discussed.

1. Introduction

A large range of evidence has been taken to indicate that the septo-hippocampal axis of animals plays a role in processing information, perhaps related to time (Solomon, 1979) and/or place (O'Keefe and Nadel, 1978).The mechanisms underlying this process have been interpreted in terms of sensory- (Salafia and Allan, 1980), attention- (Solomon, 1979, 1980; Oades, 1979, 1981a), and memory-related mechanisms (Nakajima, 1975; Iversen, 1976; Jaffard, Destrade, Durkin and Ebel, 1979; Kesner, 1980) and could be interpreted as a combination of aspects of such mechanisms.

From experiments with rats in a radial maze it has been proposed that the deficit after hippocampal damage lay with *working* memory (the ability to choose between a to-be-rewarded alternative from a has-been-rewarded alternative) rather than *reference* memory (the ability to recognise a to-be-rewarded alternative from one that is

* Present address: Max-Planck-Institut für Hirnforschung, Abt. Neurobiologie, Deutschordenstr. 46, 6000 Frankfurt a M 71, German F.R.

never rewarded) (Olton et al., 1979; Olton and Papas, 1979; Jarrard, 1978). These authors were mainly concerned to contrast this finding with the proposal that the hippocampus is exclusively involved with the organization of spatial information (O'Keefe and Nadel, 1978). However Nadel and MacDonald (1980) in a further study of rats with hippocampal lesions in the radial maze, claim that there is a deficit of performance according to both measures in the absence of accessory cues. In the presence of such cues the deficit is transitory. Winocur (1980) also reported that rats with hippocampal damage made many errors in the absence of accessory cues, but improved if such cues were present. But he also found that preoperative training on the 'noncued' condition caused a considerable deterioration of the performance of these rats on the cued task. He suggested that the hippocampus is important for processing not just spatial but stimulus information generally.

To approach the question of stimulus processing, *working* and *reference* memory another task has been used in this report. In this task a rat searches for four pellets of food located consistently in four of 16 holes in an arena (Oades and Isaacson, 1978). In this task similar measures of performance can be made as are reported from the radial-maze experiments. On this task rats with damage to the hippocampus or limbic ventral tegmentum increased the number of errors made according to both *working* and *reference* memory measures (Oades, 1981b, 1981c). Further control rats showed a circadian-dependent performance according to a measure of 'relevance' (better morning than afternoon) but not on the rather similar measures of 'memory'. (Relevance is the ratio of repeated visits to holes that had contained food to the repeated visits to holes that never contained food.) It was suggested that these parts of the limbic system may be involved with stimulus selection mechanisms that would include the ability to decide between relevance and irrelevance (c.f. James, 1890). Indeed a role for the hippocampus in the 'evaluation of errors' (Douglas and Pribram, 1966) or 'the tuning out of irrelevance' has been postulated (Solomon, 1979, 1980).

With regard to the involvement of the ventral tegmentum, it is important to note that the septo-hippocampal complex and the prefrontal cortex receive a dopaminergic innervation from this nucleus (Dahlström and Fuxe, 1964, Simon, Le Moal and Calas, 1979). Disturbance of either pathway, the prefrontal cortex or temporal lobe may affect attention-related mechanisms (Simon, Scatton and Le Moal, 1980, Oades, 1981d; Solomon, Crider, Winkelman, Turim Kamer and Kaplan, 1981) and contribute to the thought disorder of psychotic patients (Stevens, 1973; Oades, 1981a). But it has also been suggested that such patients suffer from problems of interference in short-term memory (Callaway, 1970; Süllwold, 1971). It is therefore of interest to consider whether neuroleptic treatment (the common form of pharmacotherapy for psychotic patients) affects the performance of animals with and without limbic brain damage according to the measures of *working*-memory, a component of which relates to short-term memory, and *reference* memory.

2. Method

Forty-two hooded, Long-Evans rats weighing 250–350 g at the time of surgery were maintained separately, but in visual, auditory and olfactory contact on a 12 hr light/dark cycle at 23 ± 2°C.

There were three experimental groups: 16 animals with bilateral hippocampal (plus overlying neocortical) damage, 14 bilateral neocortical damage (overlying an intact hippocampus) and 12 unoperated controls. All animals were tested after either haloperidol or saline injections from sessions 4–10 of the 11-test sessions. Nine of the hippocampal group received haloperidol (H_D) and seven saline (H_S); seven of the neocortical group received haloperidol (N_D) and seven saline (N_S); six of the controls received haloperidol (C_D) and six saline (C_S).

All animals, including controls, received 50 mg/kg sodium pentobarbital anaesthesia. Lesions were made by aspiration (Isaacson and Woodruff, 1975) in one stage using clean surgical techniques. After operation the animals received 100 000 units of Bicillin. After the experiment the animals were perfused with saline followed by 10% formalin. The brains were frozen and 20 μm sections were cut and stained with thionin. These procedures resulted in bilateral lesions that involved 60 to 90% of the hippocampus and the removal of part of the overlying neocortical surface. The lesions were comparable to those originating in this laboratory (e.g. Woodruff and Isaacson, 1975). After surgery the animals recovered their preoperative weight, were placed on a food deprivation schedule and tested 2–3 weeks later at 80% of their preoperative weight.

The search tests were conducted in an arena measuring 70 × 70 × 50 cm high. In the wooden floor were 16 holes, 3.5 cm dia., below which hung cups, 2 cm deep.

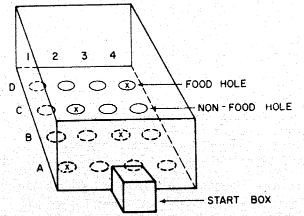

Fig. 1. A schematic drawing of the test apparatus (a 16-hole board) is shown. The numbers and letters designate the rows and columns in the arena (dimensions, see text). The x-symbol in holes A_1, B_3, C_2 and D_4 shows where food pellets were placed during testing.

The holes were 10 cm apart. Peripheral holes were 13 cm from the wall. Entrance was from a start box midway along one wall. The arena was dimly illuminated by a 40 W lamp covered with a red plastic film, 150 cm above the centre of the arena. The rest of the room was dark.

One week before testing animals were exposed to the apparatus for 30 min on each of five consecutive days. On the first two there was no food present, on the next three a 35 mg Noyes food pellet was placed in every hole. All rats learned rapidly to obtain the food pellets. During testing food pellets were placed in holes A_1, B_3, C_2, and D_4 (fig. 1). The floor and food cups were cleaned after every trial. A visit to a hole was scored when the nose of the rat turned to the edge of a hole, moved over or was placed in it. Data were taken manually. Ten consecutive trials were given each morning and afternoon on five successive days. The intertrial inter-

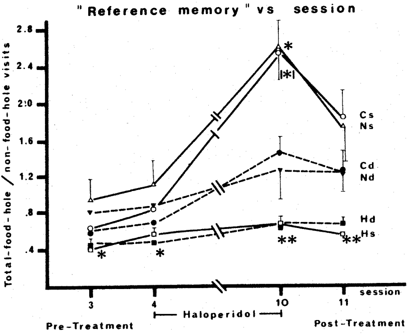

Fig. 2. This diagram shows the development of the mean performance (and SEM) of six groups of rats on the hole board search task according to the measure of reference memory upto test session 11. (Reference memory: total food hole visits/total non-food-hole visits.) Animals were treated with haloperidol or saline solution from session 4 to 10 (details see text). Impairments were recorded for the H group with respect to the C and N groups and for the haloperidol-treated C and N groups with respect to saline-treated C and N groups respectively. The latter effect was not recorded three days after treatment ended (session 11). Animal groups: control group treated with saline (C_S, ○) or with haloperidol (C_D, •); neocortical lesion-group treated with saline (N_S, △) or with haloperidol (N_D, ▾); hippocampal lesion-group treated with saline (H_S, □) or with haloperidol (H_D, ▪); |*| C_D vs. C_S, $0.02 < p < 0.05$ (session 10); * N_D vs. N_S $0.01 < p < 0.02$ (10); * H vs. C, H vs. N $0.01 < p < 0.02$ (session 3, 4); ** H vs. C, H vs. N $p \ll 0.02$ (session 10, 11).

val was 20–30 sec, the intersession interval was never less than 4 h. An eleventh session was performed three days after the tenth. No injections were given on that day. The mean dose of haloperidol was 0.275 mg/kg. Injections were given 15 min before sessions 4–10 inclusive (further details Oades and Isaacson, 1978). The data were tested by the Kruskal–Wallis analysis of variance (Siegel, 1956).

3. Results

Animals with hippocampal damage performed poorly with respect to control groups according to the measures of *working* and *reference* memory (figs. 2 and 3,

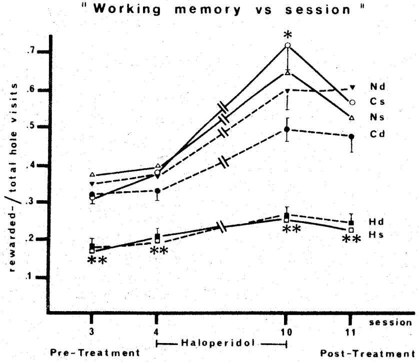

Fig. 3. This diagram shows the development of the mean performance (and SEM) of six groups of rats on the hole-board search task according to the measure of working memory upto session 11. (Working memory: rewarded hole visits/total hole visits.) Animals were treated with haloperidol or saline solution from sessions 4 to 10 (for details see text). Impairments were recorded for the H group with respect to the C and N groups and for the haloperidol-treated C group with respect to the saline-treated C group. The latter effect was not recorded three days after the end of treatment (session 11). No effect of drug treatment was recorded for the N group. Animal groups: control group treated with saline (C_S, ○) or with haloperidol (C_D, ●); neocortical lesion-group treated with saline (N_S, △) or with haloperidol (N_D, ▼); hippocampal lesion group treated with saline (H_S, □) or with haloperidol (H_D, ■); * C_D vs. C_S, $0.02 < p < 0.05$ (session 10); ** H vs. C, H vs. N, $p \leqslant 0.02$ (sessions 3, 4, 10, 11).

$p < 0.01$). The performance of haloperidol- and saline-treated animals with hippocampal damage was similar. By contrast the saline-treated control and neocortical groups showed considerable improvement on both measures during the course of testing ($C_S > H$, $N_S > H$, session 10, $0.001 < p < 0.01$, $H = 9–9.7$).

On the measure of *reference* memory the performance of haloperidol-treated control and neocortical animals was impaired by comparison with their saline-treated counterparts (Session 10, C_D, $0.02 < p < 0.05$, $H = 5$; N_D, $0.01 < p < 0.02$, $H = 6$). However on the measure of *working* memory the control but not the neocortical group was impaired after haloperidol treatment (Session 10, C_D, $0.02 < p < 0.05$, $H = 4.7$). On session 11, three days after the last treatment with haloperidol or saline solutions, there were no significant differences between the performances of either of the control or neocortical groups.

4. Discussion

Olton and his colleagues (Olton et al., 1979; Olton and Papas, 1979) found that fimbria-fornix and hippocampal lesions impaired the performance of rats in an eight-arm radial maze on measures of *working* and *reference* memory at first. With further testing performance according to *reference* memory but not *working* memory improved.

From the present data the following conclusions may be drawn. The different effects of drug treatment show that the two measures used may reflect the operation of separate mechanisms. Haloperidol treatment impaired *reference* memory for both the sham-controls and animals with neocortical lesions, but it impaired the *working* memory for sham-controls alone. In contrast to the work of Olton et al. (1979), Olton and Papas (1979) and Jarrard (1978) and in agreement with that of Nadel and MacDonald (1980) and Oades (1981c) both mechanisms appear to be similarly affected by extensive (60–90%) hippocampal damage. The absence of an effect of haloperidol on the performance of animals with hippocampal lesions suggests that there was no contribution from the potential hypersensitivity of dopaminergic systems that could have resulted from denervation.

There is support for the unexpected, separate effect of haloperidol on the performance of animals with neocortical damage from an earlier analysis of the data (Oades and Isaacson, 1978). It was reported that this group (N_D) changed the normally conservative sequence of food-hole visits more often from session to session than the other lesioned, control or drug-treated groups.

It has been shown that two theoretically distinguishable, cognitive mechanisms, namely *reference* and *working* memory, can be separated on the basis of mesocorticolimbic lesion and drug treatments of rats on a hole-board search task. However the identification of and the difference between these two mechanisms still needs to be clearly drawn. Nadel and MacDonald (1980) wish to retain a distinction between mechanisms for handling spatial and nonspatial information, but Winocur

(1980) prefers to emphasise that both sorts of information can be affected by hippocampal lesions. The present experiment did not address this distinction. The data were analysed in order to see if a distinction exists between *reference* and *working* memory. The question remains whether these terms are adequate.

Olton et al. (1979) drew a parallel between the concepts of working/reference memory and episodic/semantic memory respectively (Tulving, 1972). In this context *reference* memory is understood to store the distinction between correct and incorrect choices (or 'sets') as a 'rule'. Reference memory was measured by means of a comparison between the number of right and wrong hole or arm choices. One must ask if there is a quantitative or a qualitative difference between this measure and one of the repeated (false) visits to holes or arms of the right and wrong set. This latter measure of 'relevance' can be distinguished by its sensitivity to the time of day that the test is made (Oades, 1981b), unlike reference memory, and thus may be more closely related to the arousal-sensitive operation of selective (attention-related) mechanisms (c.f. the Introduction to this paper).

The concept of *working* memory or episodic memory, in terms of Tulving, has a strong autobiographical component. In practice, in the radial maze or hole-board, it has a strong short-term memory component. It is difficult in *these* experiments to draw the distinction between short-term memory, in the conventional sense, and the need, between choices, to hold information for recognition or the operation of match/mismatch operations essential for the operation of selective (attention-related) mechanisms. The existence of these latter mechanisms in the septo-hippocampal axis has been argued by Vinogradova (1975). Although Tulving (1972) drew a logical distinction between episodic and semantic memory, that can also be applied to *working* and *reference* memory, he added that he did this '. . . for the convenience of communication, rather than as an expression of any profound belief about the structual or functional separation of the two'.

In conclusion two cognitive mechanisms appear to be involved in the search behaviour of rats on a hole-board. They are differentially affected by experimentally induced changes of the activity in the mesolimbic and mesocortical systems of the brain. A comparison of the results obtained from the hole-board and radial maze suggests that a separation of these mechanisms into *working* vs. *reference* memory or spatial vs. nonspatial information processing is oversimplified. Further experiment and analysis is necessary to identify what these mechanisms are. Such study should not overlook reports that many schizophrenic subjects suffer from problems of information processing and interference and that there is evidence that mesocorticolimbic dysfunction could be related to such symptoms. Comparisons between these two fields of study should prove helpful in resolving these questions.

Acknowledgments

I am grateful to Professor R.L. Isaacson for facilities to conduct the original research and to the Ludwig-Vogelstein Foundation and the Max-Planck Gesellschaft for financial support. I thank Fr. G. Heiss and Fr. E. Kannonbrock for the preparation of the diagrams.

References

Callaway, E. (1970). Schizophrenia and interference. Archives of General Psychology, 22, 193–208.

Dahlström, A. and Fuxe, K. (1964). Evidence for the existence of monoamine containing neurons in the central nervous system. 1. Demonstration of monoamines in the cell bodies of brain stem neurons. Acta Physiologica Scandinavica, Supplement 232, 1–55.

Douglas, R.J. and Pribram, K.H. (1966). Learning and limbic lesions. Neuropsychologia, 4, 197–220.

Isaacson, R.L. and Woodruff, M.L. (1975). Spontaneous alternation and passive avoidance behavior in rats after hippocampal lesions. In: Hart, B.L. (Ed.). Experimental Psychobiology. W.H. Freeman: San Francisco, 102–109.

Iversen, S.D. (1976). Do hippocampal lesions produce amnesia in animals? International Review of Neurobiology, 19, 1–49.

Jaffard, R., Destrade, C., Durkin, T. and Ebel, E. (1979). Memory formation as related to genotypic or experimental variations of hippocampal cholinergic activity in mice. Physiology and Behavior, 22, 1093–1096.

James, W. (1890). Principles of Psychology. Holt: New York.

Jarrard, L.E. (1978). Selective hippocampal lesions and spatial discrimination in the rat. Society for Neuroscience Abstracts, 4, 222.

Kesner, R.P. (1980). An attribute analysis of memory: the role of the hippocampus. Physiological Psychology, 8, 189–197.

Nadel, L. and MacDonald, L. (1980). Hippocampus: cognitive map or working memory? Behavioral and Neural Biology, 29, 405–409.

Nakajima, S. (1975). Hippocampal protein synthesis and spike discharges in relation to memory. In: Isaacson, R.L. and Pribram, K.H. (Eds.). The Hippocampus. Plenum Press: New York, 393–413.

Oades, R.D. (1979). Search and attention: interactions of the hippocampal–septal axis, adrenocortical and gonadal hormones. Neuroscience and Biobehavioral Reviews, 3, 31–48.

Oades, R.D. (1981a). Attention and schizophrenia: neurobiological bases. Pitman: London.

Oades, R.D. (1981b). Search strategies on a hole-board are impaired in rats with ventral tegmental damage. Biological Psychiatry, 17, 243-258.

Oades, R.D. (1981c). Types of memory or attention: impairments after lesions of the hippocampus and limbic ventral tegmentum. Brain Research Bulletin, 7, 221-226.

Oades, R.D. (1981d). A mesolimbic modulation of attention-related and learning processes: effects of spiroperidol and apomorphine in the ventral tegmentum of rats. Naunyn Schmiedeberg's Archives of Pharmacology, 316, Supplement, 71.

Oades, R.D. and Isaacson, R.L. (1978). The development of food search behavior by rats: effects of hippocampal damage and haloperidol treatment. Bheavioral Biology, 24, 327–338.

O'Keefe, J. and Nadel, L. (1978). The Hippocampus as a Cognitive Map. Clarendon Press: Oxford.

Olton, D.S. and Papas, B. (1979). Spatial memory and hippocampal function. Neuropsychologia, 17, 669–682.

Olton, D.S., Becker, J.T. and Handelman, G.E. (1979). Hippocampus, space and memory. Behavioural Brain Sciences, 2, 313–322.

Salafia, W.R. and Allan, A.M. (1980). Conditioning and latent inhibition with electrical stimulation of hippocampus. Physiological Psychology, 8, 247–253.

Siegel, S. (1956). Non-parametric Statistics for the Behavioural Sciences. McGraw Hill: New York.

Simon, H., Le Moal, M. and Calas, A. (1979). Efferents and afferents of the ventral tegmental-A10 region studied after local injection of (^{3}H) leucine and horseradish peroxidase. Brain Research, 178, 17–40.

Simon, H., Scatton, B. and Le Moal, M. (1980). Dopaminergic A10 neurones are involved in cognitive functions. Nature, 286, 150–151.

Solomon, P.R. (1979). Temporal versus spatial information processing theories of hippocampal function. Psychology Bulletin, 86, 1272–1279.

Solomon, P.R. (1980). A time and a place for everything? Temporal processing views of hippocampal function with special reference to attention. Physiological Psychology, 8, 254–261.

Solomon, P.R., Crider, A., Winkelman, J.W., Turi, A., Kamer, R.M. and Kaplan, L.J. (1981). Disrupted latent inhibition in the rat with chronic amphetamine or haloperidol-induced supersensitivity: relationship to schizophrenic attention disorder. Biological Psychiatry (in press).

Stevens, J.R. (1973). An anatomy of schizophrenia. Archives of General Psychiatry, 29, 177–189.

Süllwold, L. (1971). Die frühen Symptome der Schizophrenie unter Lernpsychologischem Aspekt. In: Huber, G. (Ed.). Ätiologie der Schizophrenien: Bestandsaufnahme und Zukunftsperspektiven. Schattauer: Stuttgart, 37–52.

Tulving, E. (1972). Episodic and semantic memory. In: Tulving, E. and Donaldson, W.D. (Eds.). Organization of Memory. Academic Press: New York.

Vinogradova, O.S. (1975). Functional organization of the limbic system in the process of registration of information: facts and hypotheses. In: Isaacson, R.L. and Pribram, K.H. (Eds.). The Hippocampus. Plenum Press: New York, 3–69.

Winocur, G. (1980). The hippocampus and cue utilization. Physiological Psychology, 8, 280–288.

Woodruff, M.L. and Isaacson, R.L. (1972). Discrimination learning in animals with lesions of the hippocampus. Behavioral Biology, 7, 484–501.