

Search Strategies on a Hole-Board are Impaired in Rats with Ventral Tegmental Damage: Animal Model for Tests of Thought Disorder

Robert D. Oades¹

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An ability to distinguish relevance from irrelevance has been attributed to an attention-related mechanism and may be disturbed in thought-disordered schizophrenics. Stimulus choice strategies depend on such mechanisms (ia) and are anomalous in some schizophrenics. An impaired function of the ventral tegmentum (VTA) has been postulated for schizophrenia. The effects of VTA damage on the relevance/irrelevance distinction and strategy formation in rats has been studied. Over a 5 day-period food-deprived rats were given nine sessions of ten trials each on a 16-hole board. They searched for food pellets placed consistently in four holes. During testing the control group (C) reduced the number of empty holes visited more than the group with VTA damage. The proportion of repeated visits to relevant holes (had food) to irrelevant holes (never had food) increased for the C but not for the VTA group. The frequency with which a preferred sequence of food-hole visits was repeated during a session increased over sessions for the C but not the VTA group. The VTA group changed their preference between sessions more often. Animals with VTA damage were capable of simple learning, but were impaired when complexity increased. This may be due in part to a deficit in attention-related mechanisms. This encourages further study of the contribution of the VTA to putative attentional dysfunction and the use of the hole-board search task as a model for the study of cognitive function and dysfunction.

¹ Abteilung Neurobiologie, Max-Planck-Institut für Hirnforschung, Frankfurt, West Germany.

INTRODUCTION

It has been suggested that the dopaminergic mesolimbic pathway originating in the ventral tegmentum (VTA) is overactive in some schizophrenic subjects (Stevens, 1973). Study of postmortem material has not shown that there is an increase of dopamine turnover in the mesolimbic projection areas of the striatum and nucleus accumbens (Bird *et al.*, 1979; Crow *et al.*, 1979; Farley *et al.*, 1980), but that there may be an increased number of dopamine receptors (Cross *et al.*, 1978; Owen *et al.*, 1978; Lee and Seeman, 1980). Neuroleptic drugs that block dopamine receptors can alleviate some symptoms of schizophrenia (Matthyse and Lipinski, 1975; Loyd, 1978; Henn, 1978). Although one of the problems of schizophrenics lies with a dysfunction of attention-related mechanisms (Chapman and Chapman, 1973; Hartwich, 1980; Oades, 1981a), these symptoms often remain when patients are released, "socially cured," after neuroleptic therapy (Serban and Gidynski, 1979; Huber *et al.*, 1979).

In animals VTA damage, like nigrostriatal lesions (Nagy *et al.*, 1978; Reisine *et al.*, 1979), leads to increased receptor binding in projection areas. The mesolimbic pathway projects to the septo-hippocampal axis, cingulate, and entorhinal cortices (Phillipson, 1979; Simon *et al.*, 1979). One of the roles of these areas is related to attention (Oades, 1979; Solomon, 1979). The VTA also projects to the striatum where activity may affect the ordering of behavioral components into stimulus-appropriate sequences (Cools, 1980; Oades, 1981a). Thus it is important to study the role of VTA connections in animals in attention- and strategy-related function in order to better understand the nature of the putative schizophrenic impairment and the role of neuroleptic drugs.

Rats with VTA damage show deficits in the exploration of novel objects (Fink and Smith, 1980a; 1980b), the investigation of holes (Gaffori *et al.*, 1980), the acquisition of an alternation response (Simon *et al.*, 1979; 1980), and reversal learning (Galey *et al.*, 1979). A perseveration of responding during reversal learning and the faster acquisition of an avoidance response seen after VTA lesions (Le Moal *et al.*, 1969) are also characteristic of animals with hippocampal damage (Isaacson, 1974). Largely because rats with VTA damage show much "collateral" behavior (stop, return, rear) during task acquisition these results have been interpreted in terms of attentional deficits (Simon *et al.*, 1980).

However this hypothesis did not emerge from a test of attention-related abilities. In this report I describe how rats with and without VTA damage search over repeated trials for food placed consistently in 4 of 16 holes in an arena. The number of empty-hole visits reflects the progress of learning, the proportion of repeated visits to food-holes and non-food (nf) holes reflects the ability to determine relevance (Oades, 1981b) and the development of a preferred sequence of hole visits (strategy) reflects the extent to which stimuli

control behavior. The latter two measures are indicators of attention-related activity (cf. James, 1890; Mackintosh, 1975).

Discrete effects of hippocampal damage and haloperidol treatment on hole-board search behavior have been shown (Oades and Isaacson, 1978). Haloperidol improved the reduction of errors but not the strategy of lesioned animals. By contrast, haloperidol did not affect the number of errors made but did disrupt the acquisition of a preferred strategy in intact animals. Here I report on the ability to determine relevance and to develop a strategy in animals as a possible parallel for some disturbances reported from subjects with endogenous psychoses, namely, an impairment in "tuning out" irrelevant stimuli (see Oades, 1981a) and the performance of anomalous stimulus-sorting strategies (Dykes and McGhie, 1976; Kay and Singh, 1979). I do not draw a direct parallel between the lesion and human pathology. The component of the VTA responsible for the effects described is the subject of continuing pharmacological study.

METHODS

Preparation of Subjects

Male hooded rats weighing 250-350 g were individually maintained on a 12-hr light/dark cycle at 23 ± 2 C, in visual, auditory, and olfactory contact. Cannulae (outer diam 0.71 mm) were stereotaxically implanted into the VTA of eight rats under 4% chloral hydrate anesthesia (1 ml/100 g) and fixed to the skull with Paladur dental cement (3.5 mm posterior to bregma, 0.55-0.65 mm lateral from midline, 8.5 mm ventral from skull and bite bar at + 0.5 mm). Stylets extending 0.5-1.0 mm beyond the cannula-tips were removed and replaced three times to produce a coagulation (Fig. 1). In seven controls the guide cannulae were implanted to a depth of 6.5 mm and a cannula (0.33 mm) was lowered to the VTA three times. The animals were killed 25 days after operation. The mid-brain was cut, photographed, and fixed in 10% formalin and stained in cresyl violet.

Test Procedure

Animals were operated in Week 1, allowed to recover in Week 2, adapted to the apparatus in Week 3, and tested in Week 4. The test apparatus consisted of an arena (70 X 70 cm) containing 16 holes (3.5 cm wide, 2.5 cm deep). A start box was placed in the middle of one wall (Fig. 2, Oades and Isaacson, 1978). On the first 2 days of Week 3 the animals were placed in the arena and allowed to explore for ½ hr (no food available). On the next 3 days they entered

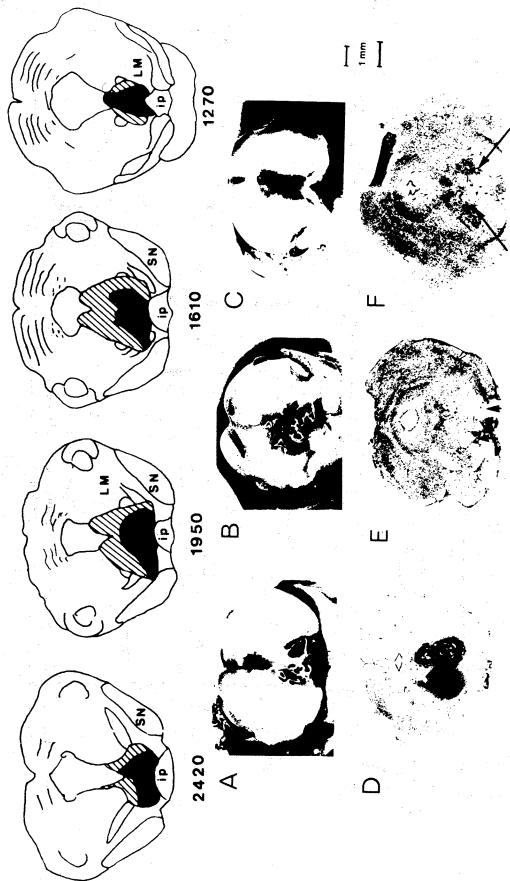


Fig. 1. Above are diagrams of the mesencephalon of the rat in the frontal plane: the anterior plane is presented on the left (Konig and Klippel, 1963). These show the maximum (Hatched) and minimum (shaded) extent of VTA damage.

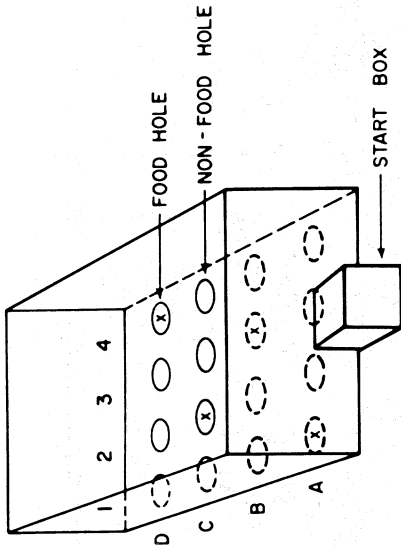


Fig. 2. A schematic drawing of the test apparatus — a 16-hole board — is shown. The numbers and letters designate the rows and columns in the arena. The X-symbol in holes A1, B3, C2, and D4 shows where food pellets were placed.

from the start box and explored for ½ hr (one Noyes precision food pellet, 35 mg, per hole). Food deprivation began on Day 3 of Week 3. Animals were tested in Week 4 at 80.6% (SD 3.1) of their predeprivation body weight.

A test trial consisted of the rat entering the arena, searching for, finding, and eating four food pellets placed consistently in the same four holes. In each session there were ten trials (interval 45 sec). Sessions were conducted at the same time in the morning and afternoon of four successive days (interval 5 hr). Animals were killed after Session 9 on Day 5. During the intertrial interval the gray plastic floor was wiped with a wet and dry cloth to remove olfactory cues. The holes and start box were washed between sessions. The arena was illuminated by a 10-w red bulb 50-cm above the floor. The arena was placed in a sound-attenuation chamber. The sequence of hole visits, rearing, grooming, and the duration of the trial were recorded manually. The data were analyzed with the Kruskal-Wallis analysis of variance and the Mann-Whitney U test (KW and MW, respectively).

RESULTS

Histology

The largest lesion extended dorsally from the border of the interpeduncular nucleus to the ventral extension of the periaqueductal gray: from the nucleus interfascicularis caudally to the nucleus linearis caudalis. Other lesions were more restricted, but extended to the 4 VTA-A10 nuclei (Phillipson, 1979). Damage did not invade the substantia nigra nor the mammillary bodies (Fig. 1). These lesions were larger than those made in other studies (Sessions *et al.*, 1980; Simon *et al.*, 1980). In these studies damage affected the nucleus ruber (like this study) and the interpeduncularis (unlike this study). I draw no parallels between the extent of the VTA lesion and a putative pathology in schizophrenia. I emphasize the effect of VTA damage on performance and cognitive mechanisms. A smaller lesion in animals seems to show the same principal effect. Subsequent to this study two control animals in fact received small lesions (≤ 1 mm) centered ~ 2 mm above the interpeduncularis. On all measures these animals showed a similar deficit to those with larger lesions (e.g., error reduction, 18.7% vs. 21.4%; last session strategy, X 4 vs. X 4.5, respectively). Further the SEM of the VTA group is markedly less than for the controls (see Figs. 5 and 6). These factors suggest that the largest extent of tissue damage was peripheral to the integrity of a more centrally lying system.

General Behavior

Some hyperactivity observed in the VTA group was seldom translated into hyperlocomotion alone. Instead there was a tendency to visit holes more rapidly

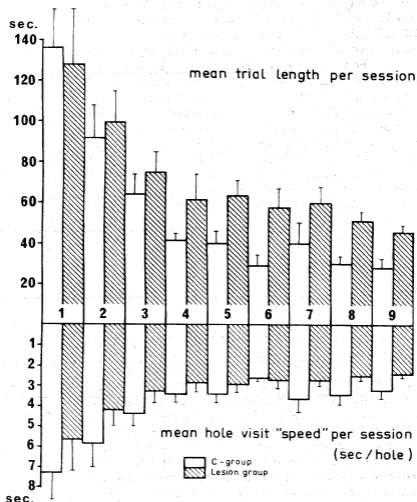


Fig. 3. In this bar diagram the mean length of a trial (sec) on successive test sessions is shown for control and VTA-damaged animals above the abscissa. Below the abscissa the mean rate at which these two groups visited holes (sec/hole) is shown for successive sessions. Standard error bars are given.

than controls (Fig. 3). Despite this the VTA group took longer to find all four food pellets than controls (Fig. 3). The increased trial duration was in part due to the larger number of hole visits and in part due to random locomotion without visits.

Rearing habituated between sessions more rapidly for controls than the VTA group (Session 5: Cs decreased by 2.5/trial, SEM 0.5; VTA by 1.2/trial, SEM 0.4; $p < 0.004$, MW). Rearing often occurred in bouts when the animals

had difficulty in finding the third or fourth food pellet. The frequency of grooming was a tenth of that for rearing and habituated sooner in controls. There were no initial differences on these measures.

Learning

Both groups reduced the number of visits to error/nf holes (Fig. 4A). Percentage reductions are illustrated, for even after prolonged training a control rat will change its strategy on one trial in a session, incurring an unusual number of errors. The VTA group consistently made more errors than the controls ($0.01 < p < 0.05$, $H = 3.8-7.1$, KW). The VTA group visited no more holes than controls in order to find the first pellet (Fig. 4B). But by Session 7 the VTA group performed worse in finding the second pellet (Fig. 4C, $p < 0.05$, $H = 4.3$, KW) and by Session 5 were worse in finding the third pellet (Fig. 4D, $p < 0.05$, $H = 3.9$, KW).

Relevance

The probability of nf-hole visits was high at first. (They had contained food during habituation, Week 3.) On Session 1 both groups revisited many more nf- than f-holes. But by Session 5 controls revisited more f- than nf-holes (ratio > 1). This ratio increased more for the controls than for the VTA group across sessions (Fig. 5, $0.01 < p < 0.05$, $H = 5.2-7.0$, KW). The VTA groups showed no improvement.

Strategy

Rats develop individual preferences for the sequence of holes visited (strategy). In Fig. 6A the increasing frequency with which controls made their first visit on a trial to a given hole (f or nf) is shown. For controls the frequency increased across sessions. The VTA group showed no increase (Session 6-9, $p < 0.02$, $H = 5.2-5.9$, KW). In Fig. 6B the frequency with which animals repeated a given sequence of f-hole visits is shown (e.g., ABC or BCA etc., cf. Fig. 2). The frequency of the preferred strategy increased for controls but not for the VTA group (Session 3-9, $p < 0.02$, $H = 5.6-5.8$, KW).

The strategy that is preferred over ten trials on one session may change on the next session. The proportion of changes of the preferred first hole-visit between sessions showed no differences (C, 25%; VTA, 31%). However the VTA group showed more changes of the preferred f-hole sequence between sessions than the controls (C, 37.5%; VTA, 72.5%; $p < 0.002$, MW).

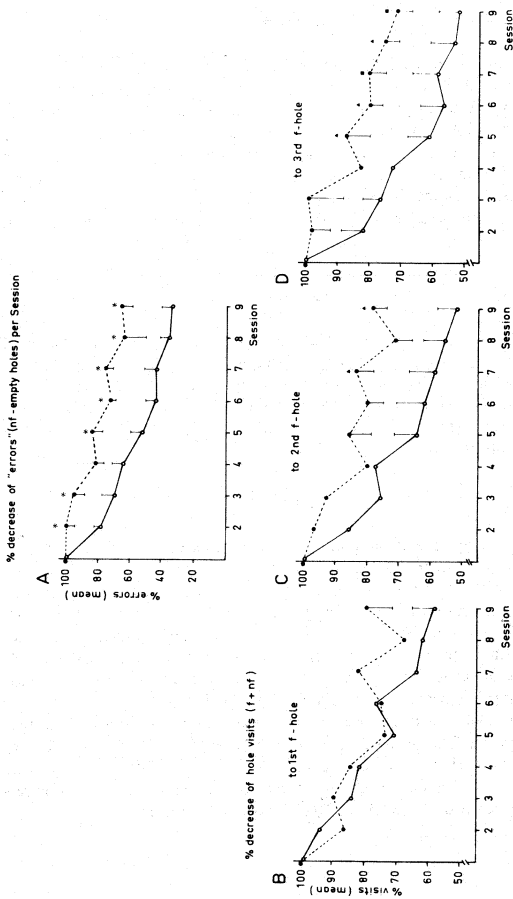


Fig. 4. A shows the mean reduction per trial of the number of nf-holes (errors) visited by the controls (●) and animals with VTA damage (■) over successive sessions as a percentage of the performance on the first session. B, C, and D show, respectively, the reduction of the holes visited (f and nf) on successive sessions in order to find the first, second, and third food pellet as a percentage of the performance on the first session. * = $0.05 > p > 0.01$; H = 3.8-7.1; KW; ▲ = $p < 0.05$; H = 4.3-4.7; KW; ■ = $p < 0.05$; U = 9; MW.

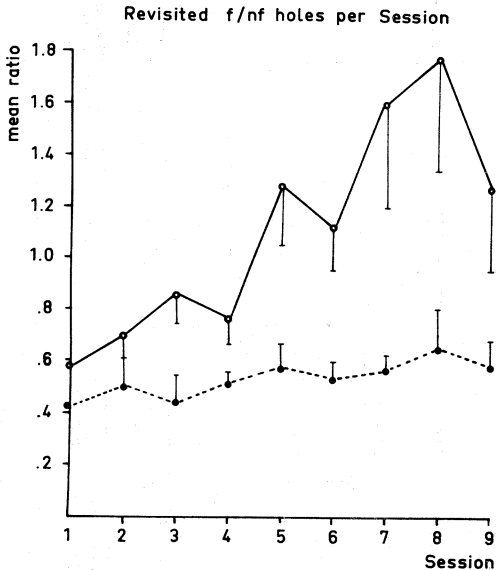


Fig. 5. This figure shows the mean ratio of f- to nf-holes revisited per trial by controls (○) and animals with VTA damage (●) over successive sessions. The standard error bars are large for controls on the last three sessions as individual rats achieved a ratio of infinity on five occasions (zero nf revisits). This was arbitrarily rounded to a value of 3 for these scores. Session 2 on: $0.01 < p < 0.05$; $H = 5.2-7$; KW.

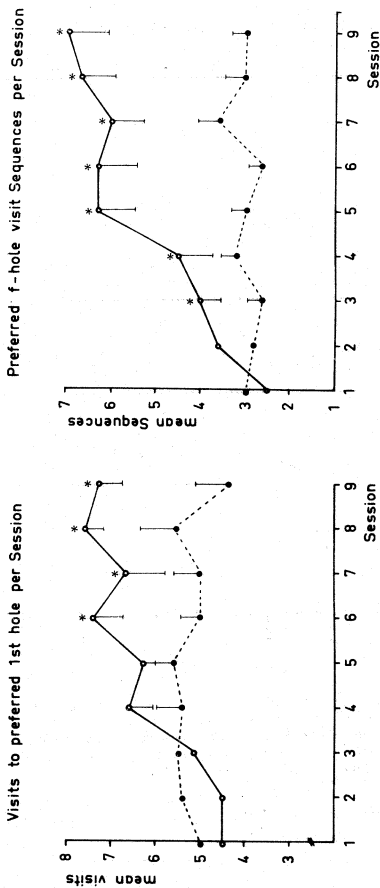


Fig. 6. The left-hand diagram shows the mean frequency per session with which controls (○) and animals with VTA damage (●) revisited the same hole as their first visit on successive trials. The right-hand diagram shows the mean frequency per session with which both groups repeated their preferred f-hole sequence on successive trials. * = $p < 0.02$; $H = 5.2-5.9$; KW.

DISCUSSION

General Behavior

There are several reports of hyperlocomotion in rats with VTA damage (Le Moal *et al.*, 1969; Sessions *et al.*, 1980; Gaffori *et al.*, 1980). In this experiment hyperlocomotion was suppressed in favor of visiting more holes. This agrees with Gaffori *et al.* (1980) who used an arena with four holes in corner alleys. But they reported that the duration of hole visits decreased. This contrasts with an increased frequency of hole visits shown here by rats that were hungry and searching for food. Gaffori *et al.* investigated the nonrewarded exploratory behavior of rats.

Rats with VTA damage did not habituate rearing and grooming as much as controls. An impaired habituation of these collateral behaviors has been reported after 6-hydroxydopamine (Simon *et al.*, 1980) but not after radiofrequency lesions of the VTA (Gaffori *et al.*, 1980). In the latter study, damage was more ventral and included the interpeduncularis. In the present study, damage extended more dorsally and in the rostrocaudal axis. Such damage may have included more dopaminergic cells to which 6-hydroxydopamine diffused in the study of Simon *et al.* (1980). Gaffori *et al.*, (1980) reported that their controls increased rearing over several trials. The rats did not habituate to some aspect of testing in the way that controls of the current study habituated.

Search Behavior

Rats with VTA damage exhibited deficits in learning to find food on a hole-board. They were capable of learning simple tasks, but were impaired in learning complex aspects of the task.

The VTA group reduced the number of errors they made over successive sessions, but not as much as controls. They improved their efficiency in finding the first pellet as much as controls. But their efficiency in finding the remaining pellets decreased successively. Thus VTA damage does not destroy the ability to learn, but rather impairs the ability to learn more complex tasks. Similarly rats with VTA damage can learn a straight alley task or a simple visual discrimination, but are impaired on a spatial Y-maze alternation (Galey *et al.*, 1979; Simon *et al.*, 1980).

Did the learning deficit reflect damage to attention- or memory-related mechanisms (or both)? One aspect of selective attention that has a long history and is applicable to behavioral situations is the ability to distinguish relevance from irrelevance (James, 1890; Mackintosh, 1975; Solomon, 1979; Oades, 1979). A working index of the ability to distinguish relevance is the ratio of the *f*- (relevant) to *nf*-(irrelevant) hole visits (ratio 1:3). When uncertainty is high

over the location of the next food pellet (e.g., third to fourth pellet), the pressure on the decision is greatest and rats start to *revisit* holes. For controls the ratio between *f*- and *nf*-revisits rises over 1.0 by Session 5. This coincides with the significant habituation of rearing. For animals with VTA damage, the ratio showed negligible improvement over the nine sessions.

Could the impairment on a measure of relevance reflect impaired memory mechanisms? *Simple* deficits seem unlikely. First, lesioned animals are capable of reducing their errors in finding the first food pellet. Second, the proportion of changes of the preferred first hole-visit between *sessions* does not differ from control values. But at the same time, the lesioned rats do not return to their preferred first hole on successive *trials* as much as controls. This indicates that the control of behavior by the perceived stimuli (attention-related) may be impaired.

If the control of a response by a stimulus indicates that the animal has attended to the stimulus (Mackintosh, 1975) then the more complex and repeated sequences of *f*-hole visits may reflect the control of response by sensory stimulation. Again controls showed an increase of the number of trials on which they repeated their preferred strategy from session to session. Animals with VTA damage showed no increase. Further the preferred strategy on a given session changed more often between sessions for the lesioned group. Together these deficits suggest that an impairment of stimulus control may be responsible for the poor learning performance of the lesioned animals.

These results may be compared with those from animals with septo-hippocampal damage where a failure of attention-related stimulus control has been demonstrated (Donovick *et al.*, 1978; Rickert *et al.*, 1978). Supersensitivity in the nucleus accumbens disrupts latent inhibition (Solomon, personal communication). Deficits in rats with VTA damage on spatial alternation, passive avoidance, inhibitory, approach-learning tasks, and an improvement on shuttle-box avoidance (Le Moal *et al.*, 1969; 1976) parallel the effects of hippocampal lesions (Isaacson, 1974). This is not unexpected for the VTA sends and receives fibers from the nucleus accumbens, the septum (Lindvall *et al.*, 1974, Phillipson, 1979), and the hippocampus (Simon *et al.*, 1979; Scatton *et al.*, 1980).

The present study demonstrates that rats show an impairment in making decisions between relevant and irrelevant stimuli and in executing normal coherent strategies after VTA damage. These phenomena parallel some of those described following the testing of schizophrenic subjects. Fonseca *et al.* (1978) concluded from an analysis of the responses of schizophrenics on an operant task that they demonstrated an impaired ability to transform decisions. The erroneous interpretation of words with multiple meanings is one example that may reflect the uncertainty of schizophrenics in deciding between relevant and irrelevant stimuli (Frith, 1979), a frequent feature of thought-disordered patients (Oades, 1981a). The increased number of categories selected by schizophrenics on card-sorting tasks (Dykes and McGhie, 1976) shows similarities to the frequent

change of hole-visiting strategy of animals with VTA damage. Further groups of nonmedicated schizophrenics showed only simple and not developed stimulus selection strategies on Piaget's color-form representation task (Kay and Singh, 1976) (cf. first hole-visit strategy). One also notes that an impaired passive avoidance that follows VTA and hippocampal damage in animals has also been reported from a group of schizophrenics (Gruzelier *et al.*, 1980).

This study shows that there are interesting parallels between stimulus selection in animals with VTA damage and schizophrenic subjects for whom impaired VTA function has been postulated (Stevens, 1973). The lesion was not intended to mimic a putative pathology unique to the A10 nuclei but to damage all four of the A10 nuclei irrespective of the transmitter dysfunction so caused. The results do not show that the mesolimbic dopaminergic pathway was necessarily responsible for these effects. But it is instructive that Fink and Smith (1980a; 1980b) in their study of the exploratory behavior of rats found that there were no differences between animals with 6-hydroxydopamine lesions of this pathway with or without protection of the noradrenergic fibers. Indeed, results from studies of the effect of intra-VTA injection of neuroleptic drugs (in progress) show that the syndrome reported here can be elicited by alterations of dopaminergic activity.

The hole-board search task offers opportunities for "dissecting" the psychological and neurobiological components of cognitive and attention-related mechanisms. The parallels discussed between the impaired mechanisms in animals induced by VTA damage and those described from schizophrenic subjects with thought disorder encourage the further testing of hypotheses of schizophrenic dysfunction on animals in this search task.

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