Learning Deficiencies in Borna Disease Virus-Infected but Clinically Healthy Rats

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Borna disease (BD) virus, a still unclassified neurotropic agent, causes either fatal encephalomyelitis or persistent asymptomatic infection in a variety of animal species. We monitored the neuronal functions of intracerebrally infected but healthy rats with three types of learning experiments. Spatial discrimination learning, using the y maze and the hole board, was significantly less successful in BD virus-infected (I) compared with mock-infected (M) rats. Similarly, I rats tended to show a certain emotional disturbance (reduced resting behavior and less anxiety) as evaluated by open-field and neophobia tests. Furthermore, in two aversive learning experiments (taste aversion and reaction suppression via Skinner box), it appeared that the I rats expressed a significantly diminished ability to learn pain avoidance compared with M rats. In conclusion, we found specific learning deficiencies together with subtle behavioral alterations suggesting that BD virus causes certain modulations of high integrative brain functions which are only detectable under experimental conditions.

Introduction

Borna disease (BD) virus is highly tropic for the central nervous system (Joest and Degen 1911) and the neuron has been identified as the preferential target cell based on viral antigen expression (Gosztonyi and Ludwig 1984a). Natural infections are known in horses and sheep (Nicolau and Galloway 1928; Zwick 1939), and recently published data have demonstrated infection of humans (Bode et al. 1988). Experimental infection is possible in a variety of other animal species (Mayr and Danner 1974; Ludwig et al. 1985). The virus either causes a usually fatal encephalomyelitis or a persistent asymptomatic infection (Hirano et al. 1983; Narayan et al. 1983). Besides its use in conventional neuropathological studies, BD became a special object of interest when pronounced behavioral alterations were demonstrated in experimentally infected tree shrews (*Tupaia glis*) by Sprankel et al. (1978). These animals never became obviously ill, but showed hypersexual activity and unusual social behavior. These changes could be correlated with inflammatory reactions, predominantly in the limbic system, the preferential target site in natural infections

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Table 1. Virological and Serological Data from Borna Disease Virus-Infected (I) and Mock (M)-Treated Rats[a] Randomly Selected After Learning Experiments Were Finished

Group	Learning experiment[b]	Animals selected (n)		Infectivity mean titer (FFU/ml)	Serum antibodies: mean titer (reciprocal) with standard error	
					ELISA	Neutralization
1	y maze	I	8	4.55×10^5	36 ± 4.5	4.4 ± 1.3
	taste aversion reaction suppression	M	3	0	<10 ± 0	<4.0 ± 0
2	y maze	I	6	2.37×10^5	10 ± 0	4.0 ± 0
	taste aversion	M	4	0	<10 ± 0	<4.0 ± 0
3	hole board	I	8	3.15×10^5	10 ± 0	4.0 ± 0
		M	8	0	<10 ± 0	<4.0 ± 0
4	hole board	I	4	8.55×10^5	1496 ± 4.6	15.6 ± 3.2
		M	8	0	<10 ± 0	<4.0 ± 0
5	reaction suppression	I	8	3.10×10^5	73 ± 9.3	5.6 ± 2.0
		M	6	0	<10 ± 0	<4.0 ± 0

[a]Rats from the I and M groups were inoculated i.c. at day 1 and tested 7–10 months later. Infectivity (brain) and antibody titers were assayed as described (Hirano et al. 1983).

[b]In parallel with spatial learning experiments (y maze, hole board), the emotional activity was measured by open field and neophobia tests (groups 1–4).

(Seifried and Spatz 1930; Roggendorf et al. 1983; Gosztonyi and Ludwig 1984a). With successful experimental infection of the rat (Nitzschke 1963; Hirano et al. 1983; Narayan et al. 1983) and the mouse (Kao et al. 1984), appropriate small animal models became available, characterized by a persistent asymptomatic infection. The presence of the virus can only be detected by expression of specific antigens in morphologically unaltered neurons. However, slight effects on neuronal activity are likely (Ludwig et al. 1988). We therefore wondered whether such expected neuronal dysfunctions could be monitored by psychological tests. We now report the detection of learning deficiencies in clinically healthy rats infected by BD virus.

Material and Methods

Animals

For all experiments, Wistar mother rats were purchased from the Bundesgesundheitsamt (Berlin) in approximately the same stage of pregnancy. The litters were inoculated when 1 day old. Prior to the learning experiments, all animals were kept individually in Makrolon type 2 cages for 2 weeks and maintained with standardized dry food (Höveler, FRG), tap water *ad libitum*, and artificial light (7:30 AM–7:30 PM).

Virus Infections

One-day-old Wistar rats were inoculated intracerebrally (i.c.) with the rat-adapted BD virus (I rats, n = 45) or mock-treated (M rats, n = 45) as described previously (Hirano et al. 1983). The virological data from a selected number of animals, confirming successful infection, are summarized in Table 1.

Learning Experiments

Three types of learning experiments were performed to test spatial discrimination (y maze, hole board), taste aversion, and reaction suppression (Skinner box). Emotional reaction patterns were investigated in open-field and neophobia tests, simultaneously with the evaluation of spatial discrimination. The animals (I and M rats) were distributed among five groups according to the learning experiments applied (Table 1). Fifteen I and 15 M rats (groups 1 and 2) were tested in the y maze. Another set of 15 I and 15 M rats was used for the hole board (groups 3 and 4). Forty-eight of these animals (24 I and 24 M rats) were observed in parallel under open-field and neophobia conditions. For the taste aversion experiments, 12 I and 12 M rats were randomly selected from groups 1 and 2. Finally, reaction suppression tasks were conducted, using 15 I and 15 M rats from groups 1 and 5, respectively. Statistical significance for the differences between I and M rats was calculated by the Mann-Whitney U test, based on randomly selected rats (10 I and 10 M) from each learning experiment, as well as 20 I and 20 M rats from the open-field and neophobia tests.

All learning experiments were started at age 15 weeks postinfection (p.i.). The rats had a mean body weight of 210 ± 19 g. Each training session took place between 8 AM and 11 AM, and between 4 PM and 7 PM. Prior to each experiment involving food reward, the rats were food-deprived to 80% of their body weight (y maze, hole board, reaction suppression). Food reward was a 45 mg precision pellet (Noyes Comp., Lancaster NH, USA). In case of negative reinforcement (Skinner box training), an 0.8 mA electroshock was given for 0.2 sec. Five days prior to the taste aversion experiments the animals were trained to drink twice a day (morning and afternoon) for 20, 15, and 10 min in their home cages.

Results

The evaluation of spatial discrimination learning (Olton 1982) was based on performance in the y maze (Figure 1a, and b) and the hole board (c and d). In the simpler y maze, the rats were trained to distinguish between two symmetrical arms of a y maze where food is placed only at the end of the right arm. The infected rats made a significantly higher number of incorrect choices (Figure 1a) compared with mock-infected rats. The unexpected shorter running time of infected rats (Figure 1b) could be explained by the altered resting behavior as shown later (open field test). For the hole board, which is designed to give precise data on the processing of spatial information (Oades and Isaacson 1978; Oades 1982), the rats were trained to search for four food pellets placed diagonally in 4 of 16 holes. After three learning sessions, the mean number of errors in I rats was significantly higher than that in M rats (Figure 1c), with I rats requiring considerably more time (except for the first trial) to find the fourth baited hole (Figure 1d). These results were confirmed by the reverse task, namely, baiting the other diagonal (Figure 1c and d). In addition, I rats showed a slower decrease in number of errors than M rats.

In parallel with spatial discrimination learning, we measured the emotional activity and exploratory behavior of both groups by an open field and neophobia test (Denenberg 1969; Archer 1973; Walsh and Cummnins 1976). The open field is a well-lighted rectangular box (100 cm square × 40 cm high), with a white bottom divided into 25 equal shares (20 cm × 20 cm) by a painted black grid. Each rat was placed in the middle of

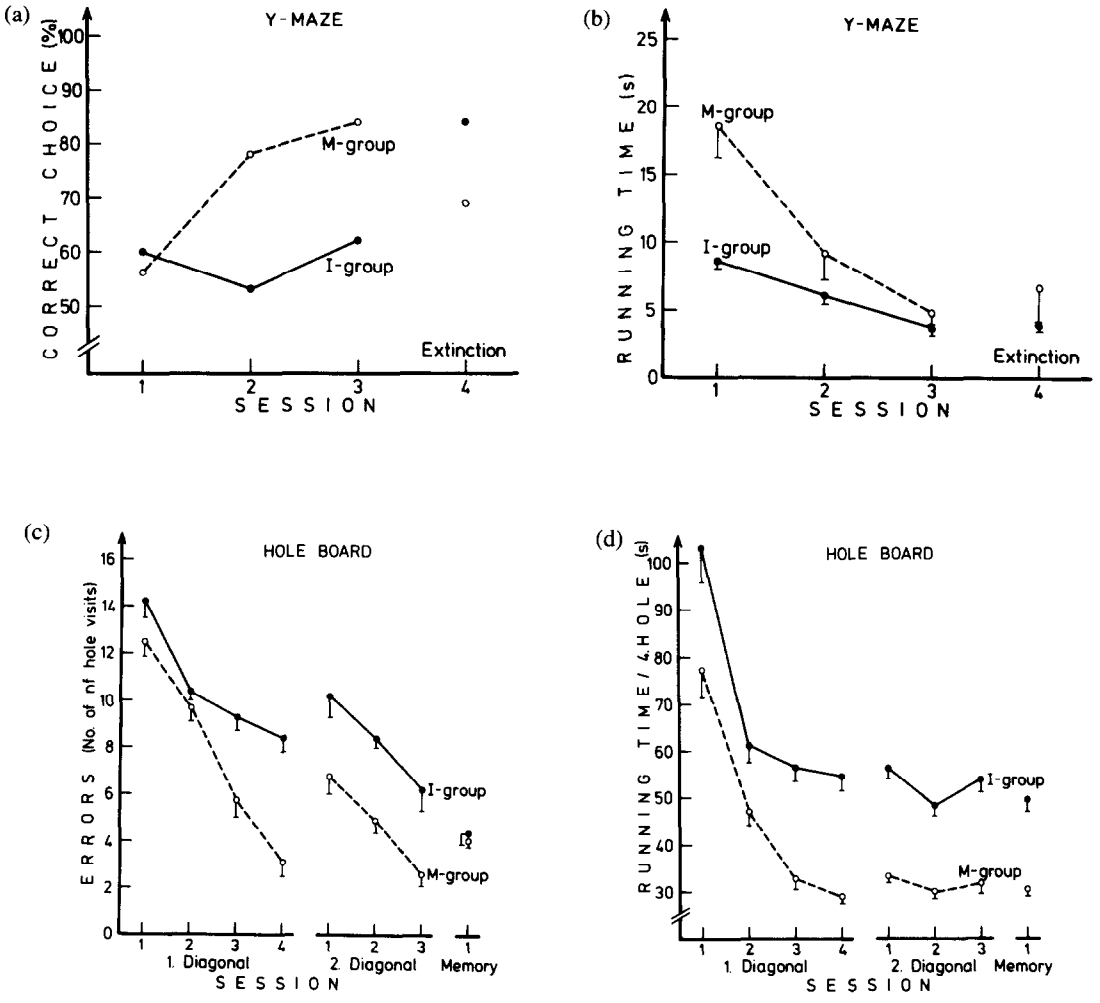

Figure 1. Spatial discrimination abilities in BD virus-infected (I) and mock-infected (M) rats. Mean number of trials to reach criterion (13 of 15 correct choices) (a) (I = 45.5/M = 28.9/$p < 0.05$) and mean time (b) with standard error (SE) (1 trial: I = 8.59 s/M = 18.58s/$p < 0.0001$) to reach goal box in a y maze during acquisition (sessions 1–3) and extinction (session 4). Each session consisted of 10 trials. Mean number of visits to holes without food (nf) (c) with SE (1 diagonal/3 session: I = 8.4/M = 3.1/$p < 0.001$; 2 diagonal: I = 8.2/M = 4.8/$p < 0.001$) in a hole board arena with learning to find four pellets of food consistently located in 4 of 16 holes and running time (d) with SE (1 diagonal/2 and 3 session: I = 68.8s/M = 46.5s/$p < 0.001$. 2 diagonal: I = 52.8s/M = 31.9s/$p < 0.001$) from start to the fourth hole with food for M and I rats during acquisition (sessions 1–4, 1 diagonal), reversal learning (sessions 1–3, 2 diagonal), and memory session (4 weeks later).

the box and observed for 2.5 min for the parameters change of direction, crossing the box, and rearing (measured in number of responses) and for the parameters freezing, remaining in the inner sector, and grooming (measured in time duration). In the first of three trials, the infected rats showed significantly more crossing (Figure 2a), less freezing, and a prolonged stay in the inner field (Figure 2b) compared with M rats. Although the next two trials confirmed differences only in the change of direction (I = more often;

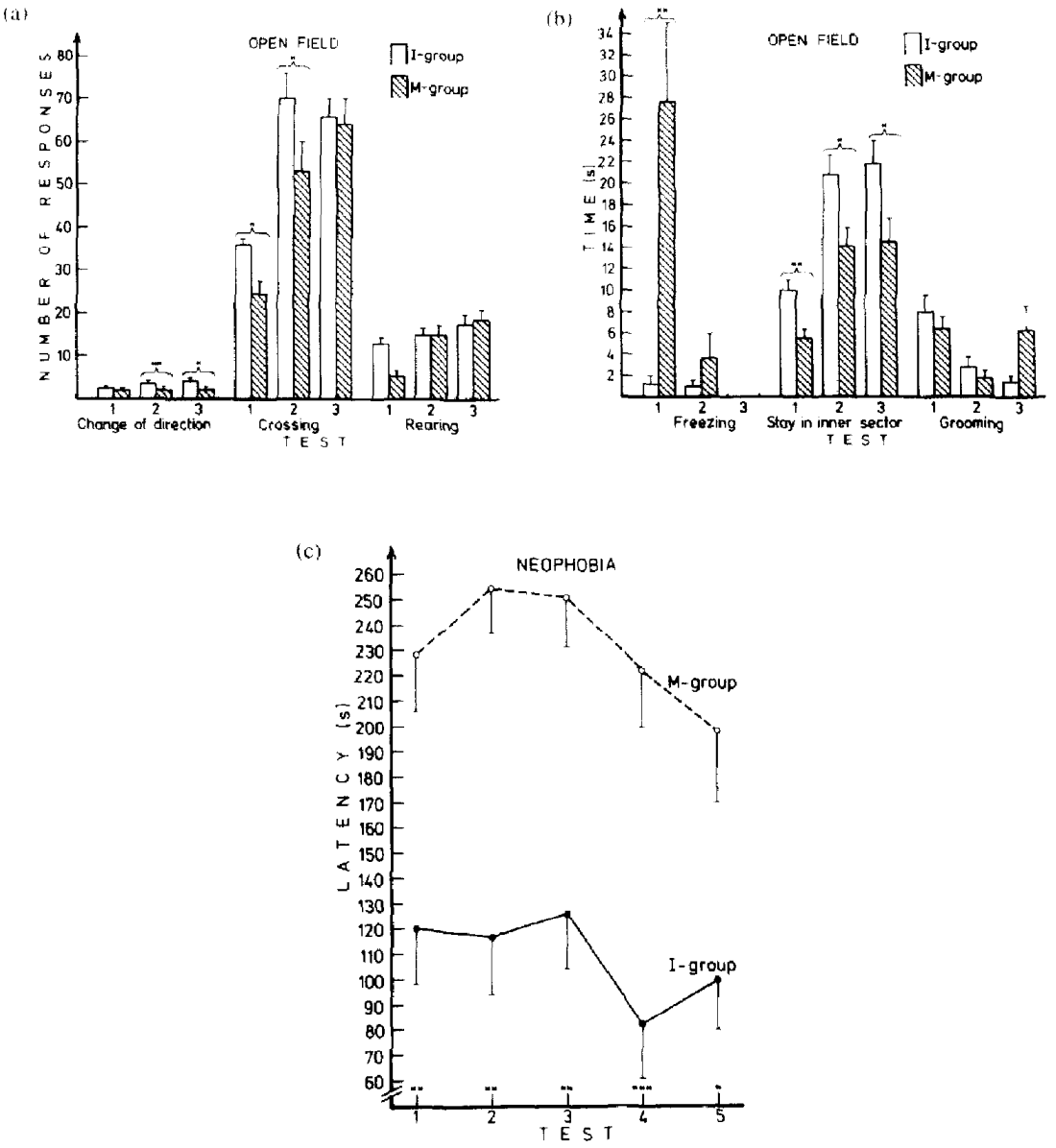

Figure 2. Emotional reactivity in BD virus-infected (I) and mock-infected (M) rats. Mean number of responses (a) with SE for the open-field parameters change of direction (2 and 3 session: I/M more often, $p < 0.05$), crossing (1 session: I = 36.0/M = 24.4/$p < 0.05$), rearing, and mean duration (b) with SE of freezing (1 session: I = 1.1s/M = 27.6s/$p < 0.01$), stay in inner sector (1 session: I = 10.0s/M = 5.7s/$p < 0.01$; 2 and 3 session: I/M longer, $p < 0.05$), grooming, throughout 3 sessions for M and I rats. $*p < 0.05$, $**p < 0.01$. Latency (c) with SE: (I = 109.9s/M = 231.4s/$p < 0.001$) in running out of a dark box to lighted arena in a neophobia test for M and I rats during sessions 1–5 (5 consecutive days, 10 trials each). n = 40. $*p < 0.05$, $**p < 0.01$. $***p < 0.001$.

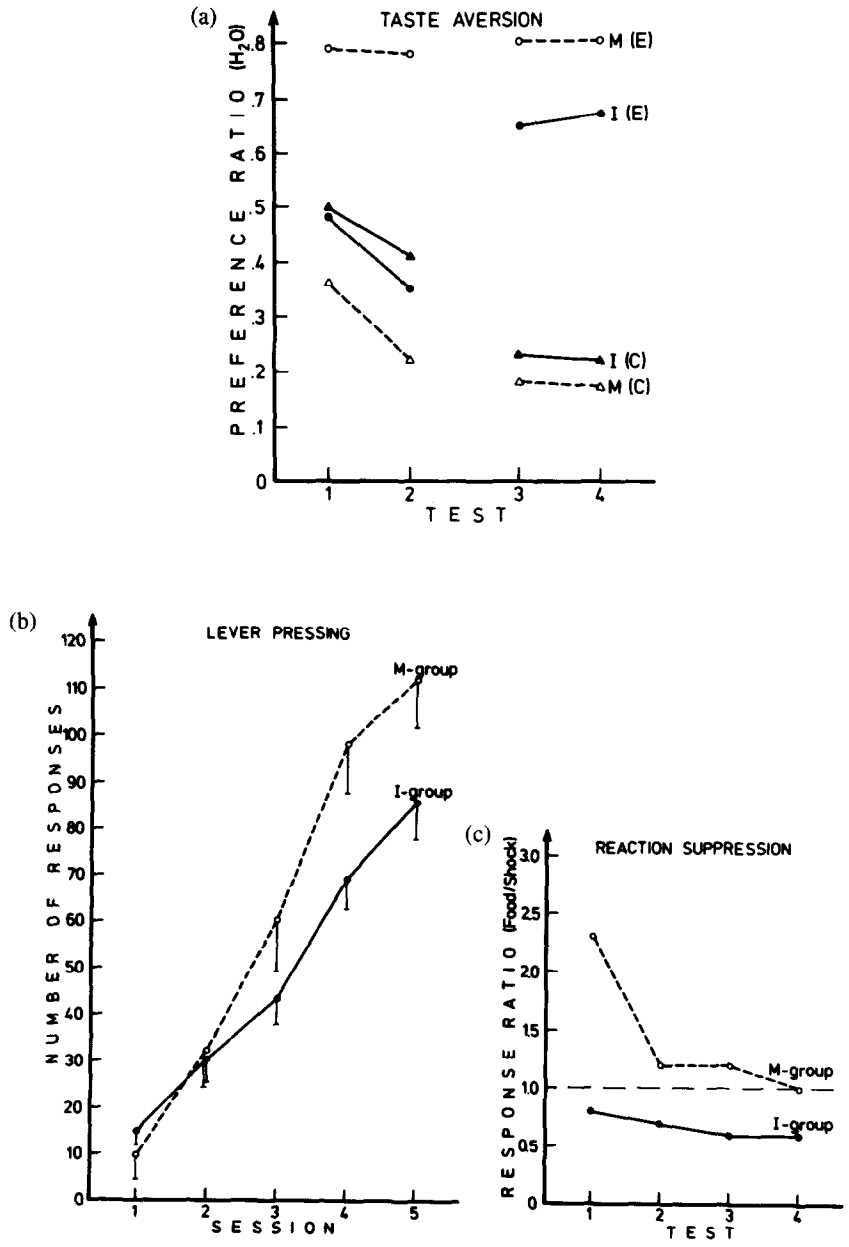

Figure 3. Avoidance learning in BD virus-infected (I) and mock-infected (M) rats. (a) Relative preferences of water versus saccharine for M and I rats after first LiCl injection (sessions 1 and 2) and second LiCl injection (sessions 3 and 4). Experimental animals (E group) received LiCl treatment 5 min after drinking saccharine, and control animals (C group) after 20 hr (E group, water preference, 3. session: I = 63.7%/M = 80.1%/$p < 0.001$; 4. session: I = 67.2%/M = 80.8%/$p < 0.05$). (b) Mean number of lever pressing responses (I = 86.1/M = 112.3/$p < 0.019$) during five acquisition sessions (note: initial phase, number of trials: I = 99.6/M = 61.4/$p < 0.001$, data not shown) for M and I rats. (c) Response ratio relating lever pressing under food condition (I = 28.8/M = 39.3/$p < 0.05$) to lever pressing under shock condition (I = 45.8/M = 37.5/$p < 0.05$) for M and I rats during four test sessions. During acquisition, shock, and test phase, 20 trials make up one session. One acquisition trial consists of a 20-sec stimulus wherein each lever press results in a food reinforcement and a 10-sec interstimulus interval. During the other phases, an identical time schedule was used.

Figure 2a) and length of stay (I = longer; Figure 2b), the results gave clear evidence that virus-infected rats tended to have reduced resting behavior and less anxiety. This tendency was confirmed in the neophobia test in which the time interval required to run from a dark box into a well-lighted area (40 cm × 40 cm) was determined on 5 consecutive days (Figure 2c); the I rats ran from the dark into the light significantly faster than the M rats.

Two additional sets of experiments were designed to evaluate learning by avoidance (Kamin 1969). First, a taste aversion task was used (Garcia et al. 1976; Schneider and Wothe 1979). Water-deprived rats of both groups (I and M = E; Figure 3a) were given a 0.1% saccharine solution for 10 min. The experimental group (E) was injected with 0.05 M LiCl solution (2% of body weight) 5 min after drinking (conditioning stimulus; CS), whereas a control group (I and M = C; Figure 3a) was injected 20 hr later (unconditioning stimulus; UCS). Two acquisition trials were done, and after the second trial (tests 3 and 4), I and M rats of the E group had both learned to avoid the saccharine, unlike the C-group rats, which still preferred saccharine (Figure 3a). However, comparison of infected and uninfected rats within the E group indicated that the I rats required more trials and showed much weaker avoidance as measured by the preference ratio for water.

The reduced responsiveness of the BD virus-infected rats to avoid pain was confirmed in the final experiment done in a reaction suppression task (Skinner box; Garcia et al. 1976). The test program followed three consecutive phases: an initial training phase with positive reinforcement (food) caused by lever pressing by the rat in the presence of a left-sided light; a second phase with negative reinforcement (electroshock) caused by lever pressing in the presence of a right-sided light combined with a 20-sec tone (1000 Hz, 80 dB); and the test phase (extinction) where the conditions of phase 1 or 2 were presented randomly, predicting either food or shock. During the initial phase, the infected rats required significantly more trials and pressed the lever less often (Figure 3b), leading to less food reinforcement, compared with the M rats. During the test phase, the choices of the rats for either conditions of phase 1 (food) or phase 2 (shock) were analyzed with a response ratio (food/shock; Figure 3c). Under the shock condition, I rats showed more responses than the M ones (which became nearly immobilized), whereas under the food condition, I rats showed fewer responses.

Discussion

We did three types of learning experiments to trace slight neuronal dysfunctions suspected to be due to the presence of BD virus in the brain of persistently infected but clinically healthy rats. The first set of experiments, based on spatial learning tasks with the y maze and the hole board, resulted in significantly less successful spatial and temporal information processing of BD virus-infected rats compared with the mock infected. The suggestion that these diminished learning abilities are caused by the presence of virus in the brain is supported by similar results obtained by McFarland and Hotchin (1983) who used the persistence of HSV-1 in mice as a model. Spatial discrimination studies with those mice infected at the age of 8 weeks and tested 3 weeks later in a y maze resulted in a significantly higher number of errors during acquisition and reversal task compared with uninfected controls.

The second set of our experiments evaluated learning by avoidance of pain (negative taste or shock), and showed a significantly reduced ability of the BD virus-infected rats compared with the mock-infected. There is no report on comparable experiments with other virus models, but Hotchin and Seeg (1977) showed clear evidence for altered

sensitivity to electroshock in mice infected with lymphocytic choriomeningitis (LCM) virus compared with controls. In contrast to the BD virus-infected rats, the LCM mice exhibited enhanced reactivity.

In the third set of experiments, in parallel with the learning tasks, behavioral observation studies based on open-field and neophobia tests indicated emotional alterations in the BD virus-infected rats (reduced resting behavior, less anxiety, and diminished neophobic reactions). In contrast to our findings, especially in terms of reduced anxiety, LCM virus-infected mice observed in an open-field arrangement similar to ours showed reduced explorative activity (Hotchin and Seeg 1977).

From recent neuropathological studies we know that persistently BD virus-infected rats neither display inflammatory infiltrates in their brains nor any obvious neuronal damage (Hirano et al. 1983). The most prominent alteration is the presence of virus-specific antigens in central nervous system (CNS) cells which can be detected only indirectly by immunohistological staining methods. Kinetic experiments using these techniques indicate that the virus infection spreads along neuronal chains, and thus a transsynaptic passage of the agent seems likely (Ludwig et al. 1988). In the hippocampus, this spreading pattern is most conspicuous, where a chain of four neurons (perforant path, dendate gyrus neurons, CA 4/3 neurons, and CA 1 neurons) becomes sequentially involved. Additionally, the hippocampus shows BD virus-specific antigen distribution particularly in synaptic fields controlled by aspartate and glutamate neurotransmitters (Gosztonyi and Ludwig 1984b). There is clear evidence that hippocampal structures especially are preferential targets of BD virus, because of the concentration of virus-specific proteins there (Hirano et al. 1983; Roggendorf et al. 1983; Gosztonyi and Ludwig 1984a; Kao et al. 1984; Carbone et al. 1987).

The present study reveals that sensitive cognitive functions such as spatial and recognition memory, which are assumed to be commonly associated with hippocampus (O'Keefe and Nadel 1978; Solomon 1979; Zola-Morgan et al. 1982; Olton 1983; Kesner 1985) and amygdala activity (Gallagher et al. 1977; Morris et al. 1982; Saunders et al. 1984; Squire and Zola-Morgan 1985; Bachevalier and Mishkin 1986), are diminished in persistently BD virus-infected but apparently healthy animals. The reduced learning process of the infected rats in avoiding pain suggests some malfunction in the nucleus amygdalae (Pellegrino 1968; Ellis and Kesner 1983). In addition, we also observed subtle behavioral alterations that could be correlated with certain disorders of the whole limbic system (a preferred site for BD virus infection) which is known to derive information in terms of emotional feelings (Mishkin et al. 1984; MacLean 1985). In contrast to the striking global behavioral disturbances previously found in Tupaias or rats infected as adults (Sprankel et al. 1978; Narayan et al. 1983), the behavioral changes reported here in rats infected at day 1 could only be detected under defined experimental conditions (open-field), but not in their normal environment.

This interest in appropriate animal models to study subtle virus-induced alterations in the brain has recently been aroused by the recognition of potential BD virus infections in humans. These antibodies have been found not only in patients with mental disorders (Amsterdam et al. 1985; Rott et al. 1985), but also in immunocompromised persons (HIV infection) and to some extent in controls (Bode et al. 1988). The present model system serves to demonstrate that this virus interferes with complex cognitive activity. The HSV-1/mouse model investigated by McFarland and Hotchin (1983) showed that other viruses infecting the brain could induce effects on learning abilities similar to those of the BD virus. Those data, however, were based only on simple spatial discrimination tests (y maze) and did not reflect other highly integrative brain functions. Nevertheless, the HSV study together with our own report provide evidence that infections with different viruses

can function as modulatory inputs to neurons, thus influencing the efficiency and modulation of learning functions (Singer 1987). Although we have shown that persistent infection of rats leads to accumulation of antigen in limbic structures (Ludwig et al. 1988, Plate I), we cannot at present rule out the possibility that virus in other brain areas may also somehow influence the learning deficiency phenomenon described here. In terms of behavioral observation studies, the specificity of the alterations caused by BD virus (less anxiety, reduced resting behavior) is supported by the previously reported LCM study (Hotchin and Seeg 1977) showing LCM virus-specific but opposite effects (more reluctant behavior, less locomotor activity).

In conclusion, we found that the BD virus model of the persistently infected apparently healthy rat was a particularly useful tool for the study of subtle brain dysfunctions that can impair learning and memory processing without disturbing normal behavior.

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