The dorsal hippocampus is selectively involved in the processing of spatial information even in mice with a genetic hippocampal dysfunction

MARTINE AMMASSARI-TEULE and ENRICA PASSINO
Consiglio Nazionale delle Ricerche, Rome, Italy

Recent data have shown that, in the rat, the dorsal hippocampus exerts a stronger control on spatial learning performance than does the ventral portion. The present work was aimed at examining the respective function of the dorsal and the ventral hippocampus in two inbred strains of mice, C57BL/6 and DBA/2, providing different models of hippocampal anatomy and of spatial learning abilities. C57 and DBA mice with small dorsal (30%–40%), large ventral (70%–80%), or small ventral (30%–40%) electrolytic lesions of the hippocampus and sham lesions were examined in a nonassociative (reactivity to spatial change) and an associative (radial maze) spatial tasks. The results first confirmed strain differences in nonlesioned mice. C57 reacted more to spatial change and learned the radial maze task better than did DBA. In spite of these behavioral differences, the three hippocampal lesions produced a very similar pattern of effects in the two strains. In each task, the most severe impairment was always related to small dorsal lesions and to a lesser extent to large ventral lesions, whereas the small ventral lesions did not produce any significant effect. It is therefore apparent that, even if DBA mice are considered a genetic model of hippocampal dysfunction, their poor spatial abilities are also controlled by the dorsal subfield. These results confirm, therefore, that the dorsal area is highly specialized in the processing of spatial information, in associative as well as in nonassociative tasks, whatever the genotype considered.

Investigations of spatial learning in different strains of mice have shown that their performance differs, depending on their genetic background. For example, C57BL/6 (C57) mice perform better than DBA/2 (DBA) mice in spatial tasks such as the radial maze (Ammassari-Teule & Caprioli, 1985; Crusio, Schwegler, & Lipp, 1987) or the Morris water maze (Upchurch & Wehner, 1989). In particular, it has been shown that, in the latter task, DBA mice could find the hidden platform when they were released from the same location on each trial but did not succeed when they were released from distinct locations. This has led to the assumption that the DBA mice were able to use extramaze information but failed to elaborate an accurate representation of the environment (Paylor, Bas-kall, & Wehner, 1993; Roulet, Lassalle, & Jegat, 1993).

This hypothesis has been confirmed by the selective impairment shown by DBA mice in situations designed to test reactivity to spatial novelty. Mice of both strains were repeatedly allowed to explore an arena containing five objects at fixed locations. After habituation of object exploration had occurred, the configuration was changed by displacing two objects in the field in order to produce a specific spatial change. Accordingly, any renewal of exploration toward the objects and, in particular, toward the displaced objects should result from a comparison between the current perceived arrangement and a repre-

sentation of the initial one. In that situation, C57 mice were found to react to the new configuration by increasing the time that they spent in contact with the displaced objects, whereas DBA mice did not show any consistent reaction (Ammassari-Teule, Tozzi, Rossi-Arnaud, Save, & Thinus-Blanc, 1995; Roulet & Lassalle, 1990). Conversely, both strains reacted to object novelty—that is, to the substitution of a new object for a familiar one at the same location. Object exploration, however, was generally lower in DBA than in C57 mice independently of the category of objects considered (Ammassari-Teule et al., 1995).

Investigations of the neural basis subserving these different spatial abilities have revealed that these mice possess distinct neurobiological characteristics at the hippocampal level. DBA mice exhibit a lower density of neurons in the dorsal hippocampus (Wimer et al., 1976), less mossy fiber terminals in the hippocampal regio inferior (Barber, Vaughn, Wimer, & Wimer, 1974), and a reduced hippocampal protein kinase C activity (Wehner, Sleight, & Upchurch, 1990) in comparison with C57 mice. Hippocampal lesions were also found to produce less drastic effects on radial maze performance in DBA mice than in C57 mice (Ammassari-Teule, Fagioli, & Rossi-Arnaud, 1992; Rossi-Arnaud, Fagioli, & Ammassari-Teule, 1991), thus suggesting a rather poor functionality of the hippocampal area in the former strain. These lesions, however, were always performed in the dorsal subfield of the hippocampus.

Recently, a number of studies conducted in the rat have shown that the dorsal hippocampal area exerts a stronger control on spatial learning performance than does the ven-

Correspondence should be addressed to M. Ammassari-Teule, Istituto di Psicobiologia e Psicofarmacologia, Via Reno, 1-00198 Rome, Italy (e-mail: teule@vaxiac.iac.rm.cnr.it).

tral area (Chiba, Johnson, & Kesner, 1992; Moser, Moser, & Andersen, 1993). In particular, whereas the degree of performance impairment in the Morris water maze correlates with the magnitude of the dorsal hippocampal lesions, ventral lesions generally spare spatial learning unless the ventral area is almost completely removed (Moser et al., 1993). One line of evidence supporting these data is the observation of a significantly smaller number of place cells in the ventral than in the dorsal subfield (Jung, Wiener, & McNaughton, 1994). Also, in spite of an initial report indicating similar electrophysiological properties for the place cells located in the dorsal or the ventral hippocampus (Poucet, Thinus-Blanc, & Muller, 1994), it appears that the place cells of the ventral area have a reduced spatial selectivity in comparison with those of the dorsal area (Jung et al., 1994).

Clearly, the different involvement of the dorsal and the ventral regions of the hippocampus in spatial learning may also result from the different connections established between each region and the adjacent areas along the septotemporal axis. A variety of sensorial information from cortical association areas and the olfactory bulbs reaches the lateral entorhinal cortex and is conveyed to the dorsal hippocampus either directly or via the perirhinal cortex (Deacon, Eichenbaum, Rosenberg, & Eckmann, 1983; Room & Groenewegen, 1986; Ruth, Collier, & Routtenberg, 1982). Less sensorial information is relayed to the ventral hippocampus by the medial entorhinal cortex afferents (Ruth et al., 1982), but this region projects to the medial prefrontal cortex (Ferino, Thierry, & Glowinski, 1987; Jay, Glowinski, & Thierry, 1989; Jay & Witter, 1991; Swanson, 1981) and is connected to the amygdala (Krettek & Price, 1977; van Groen & Wyss, 1990).

Strain differences in connectivity between the hippocampal regions and their adjacent areas have not yet been reported. Nevertheless, the fact that C57 and DBA mice exhibit, respectively, high and low spatial abilities together with strong anatomical differences more marked in the dorsal than in the ventral hippocampus suggests that the degree of functional differentiation between the two regions may also vary according to the strain. To examine this point, the effect of dorsal hippocampal lesions on detection of spatial novelty and radial maze performance was compared with that of ventral lesions of different magnitudes in C57 and DBA mice.

METHOD

Subjects

The subjects were 64 C57BL/6 and 64 DBA/2 (32 for each strain in each experiment) male mice obtained from Charles River (Calco, Italy). At the beginning of the experiment, they were approximately 3 months old, and their weights ranged from 23 to 28 g. Before surgery, they were housed in groups of five in a room with a 12:12-h light:dark cycle (lights on 0700–1900 h), with food and water freely available.

Surgery

In each experiment, 8 mice were initially assigned to each lesion condition: small dorsal hippocampus lesions (hereafter referred to

as Group SDL), large or small ventral hippocampus lesions (hereafter referred to as Groups LVL and SVL, respectively), or sham lesions performed with both dorsal or ventral hippocampus coordinates.

The mice were anesthetized with chloral hydrate (400 mg/kg) and placed in a Narishige stereotaxic apparatus with a mouse adaptor. The scalp was incised and retracted and holes drilled through the skull at points above the intended sites of the lesions. A stainless steel electrode (0.15 mm in diameter), insulated except at the tip, was inserted bilaterally to produce the following lesions: small dorsal hippocampal lesions ($A = -1.8$ mm posterior to bregma, $L = \pm 2$ mm lateral to the midline, $H = 2.2$ mm ventral from the dura); small ventral hippocampal lesions ($A = -2.9$ mm posterior to bregma, $L = \pm 3.1$ mm lateral to the midline, $H = 4.2$ mm ventral from the dura); large ventral hippocampal lesions ($A = -2.9$ mm posterior to bregma, $L = \pm 3.1$ mm lateral to the midline, $H = 2.9$ and 4.2 mm ventral from the dura). A 2.5-mA anodal current was passed through the electrode for 5 sec at each depth. The circuit was completed by taping the cathode to the tail. Sham operations were performed by inserting the electrode at the coordinates used for lesioning, except that the depth was only 0.5 mm and electrocoagulation was not induced. At the completion of surgery, the scalp was sutured closed. The subjects were then left in their home cages for a recovery period of 1 week. The DBA lesioned groups involved unequal numbers of subjects because of postsurgical animal loss (open field situation, LVL, $n = 7$ and SVL, $n = 6$; radial maze situation, SVL, $n = 6$).

Procedure

Experiment 1: Reactivity to spatial change. Mice were tested in a circular open field, 60 cm in diameter, with 20-cm-high walls made of gray plastic material, and a floor painted white and divided into sectors by drawn black lines (see Figure 1). The open-field was placed into a soundproof cubicle and surrounded by a visually uniform environment except for a conspicuous striped pattern, 20 cm wide and 10 cm high (alternating 1.5-cm-wide vertical white and black bars), attached to the wall of the field. The apparatus was illuminated by a red light (80 W) located on the ceiling. A video camera suspended above the field was connected to a video recorder and a monitor. Five objects, shown in Figure 1, were simultaneously present in the open field: (A) a chromium plated parallelepiped ($7 \times 4 \times 4$ cm) with 10 holes irregularly distributed on the sides and the top; (B) a transparent Plexiglas cylinder (diameter of the section, 8 cm; height, 6 cm); (C) a small ladder made of gray plastic material (height, 16 cm; width, 5 cm; number of steps, 10) inserted on a cylindrical base (height, 2 cm; diameter, 7 cm); (D) a black Plexiglas cylinder (height, 10 cm; diameter, 5 cm) with an edge (height, 2 cm) on the top; (E) a red and white spool (height, 12 cm; diameter of the top and the base, 5 cm), with a small electric light bulb fixed on the top. The initial arrangement was a square with a central object.

The mice were individually submitted to five successive 6-min sessions, which were separated by 3-min delays (during which the subjects were returned to their home cages). During Session 1, each mouse was placed into the empty open field in order to allow the animal to be familiarized with the apparatus and the baseline level of locomotor activity to be measured. During Sessions 2–4, the objects were placed as in Figure 1. For Session 5, the configuration was changed by moving two objects: Object B replaced Object D, which was itself displaced at the periphery of the apparatus so that the initial square arrangement was changed into a polygon-shaped arrangement during the spatial test session (Session 5).

Experiment 2: Radial eight-arm maze acquisition. The mice were tested in a maze made of gray plastic material with eight identical arms radiating from an octagonal starting platform (perimeter, 7×8 cm) without any door. Each arm was 38 cm long and 7 cm wide. A food cup, 1 cm deep and 2 cm in diameter, was inserted in the floor at the distal end of each arm. The maze was elevated 60 cm above the floor and placed in a well-lit room that had several extramaze cues: a

Figure 1. Schematic representation of the apparatus and the object configuration over successive sessions. The open field is initially empty (Session 1), then filled with five objects (Sessions 2–4). In Session 5, Objects B and D are displaced (spatial change).

fluorescent light, a door, two pieces of black cloth on two of the walls, and the experimenter himself. The maze was maintained at a constant orientation during the experiment. Two days before pretraining began, the mice were food deprived in order to bring down their weights gradually to 85% of the initial level. During pretraining, each mouse was placed on the starting platform of the apparatus and allowed to explore and to consume pieces of food scattered in the whole maze for 5 min.

On each training trial, all the arms were baited with a 15-mg piece of Purina chow. The mouse was placed on the central platform and allowed to make runs. Each run consisted in the animal entering an arm and proceeding until half-way down the arm. A trial ended after eight runs. An error was recorded each time the animal entered a previously visited arm and proceeded until half-way down the arm. In order to assess the patterns of choice spontaneously displayed by mice throughout learning—without eliminating a priori the possibility that such patterns might be purely motor based—no between-choice confinement was used. The animals went through one learning trial per day on 10 consecutive days.

Data collection and analyses. In Experiment 1, data were collected on video (for details, see Ammassari-Teule et al., 1995). In Session 1, locomotor activity was assessed by counting the number of sectors crossed by the animal as it moved in the empty open field. In Sessions 2–5, object exploration was evaluated by recording the time spent by the animal in contact with each object. A contact was defined as the subject's snout actually touching an object. In Session 5, the total time spent by each animal in contact with the two displaced objects divided by two and the total time spent in contact with the three nondisplaced objects divided by three were recorded. Prechange interest (Session 4) toward the objects that would be successively displaced or nondisplaced was checked in the same fashion. In each strain, the locomotor activity scores recorded in Session 1 (without objects) were compared in a two-way analysis of variance (ANOVA) with strain (2 levels) and lesion (4 levels) as main factors. In Sessions 2–4, the animals explored the same spa-

tial configuration of objects. *Habituation* of object exploration was assessed by comparing the duration of contacts with all the objects during Sessions 2, 3, and 4. A factorial ANOVA was performed on these data, with Session (3 levels) as within-subjects and strain (2 levels) and lesion (4 levels) as between-subjects factors. In Session 5, the spatial arrangement of the objects was modified. *Response to the spatial change* was assessed by subtracting the mean duration of contacts in Session 4 (the last Session of habituation) from the mean duration of contacts in Session 5 for each category of objects. A factorial ANOVA was performed on these data, with object category (2 levels: displaced vs. nondisplaced) as within-subjects and strain (2 levels) and lesion (4 levels) as between-subjects factors.

In Experiment 2, the following dependent variables were recorded: the rank of occurrence of the first error and maze running time. A three-way ANOVA with trial (10 levels) as within-subjects and strain (2 levels) and lesion (4 levels) as between-subjects factors was performed on the data.

RESULTS

Histology

At the completion of the experiments, lesioned and sham-lesioned mice were sacrificed with an overdose of chloral hydrate. The brains were fixed in formalin (10% solution), sectioned coronally (60 μ m) and stained with toluidine blue according to the Nissl method. Histological results are reported in Figure 2. Examination of the tissue was performed by selecting four coronal sections at fixed anteroposterior levels (from the appearance until the end of the lesion) in all individuals of each lesion group. The extent of the lesion was evaluated by estimating the percentage of damaged area versus the total extent of the area in the four sections with a computerized planimeter (Microcomputer) connected to an Apple computer. Small dorsal lesions destroyed about 30%–40% of the dorsal region, slightly encroached into the corpus callosum, and produced a mild damage to the parietal cortex situated above. Small ventral lesions destroyed about 30%–40% of the ventral region in its medium portion, and large ventral lesions, about 70%–80% of the ventral region. Both small and ventral lesions left the parietal cortex above intact but large ventral lesions included, in some cases, a part of the subiculum area.

Behavior: Experiment 1

Locomotor activity. The locomotor activity scores displayed in Session 1 (without objects) are reported in Figure 3. An ANOVA performed on these data revealed no significant main effect of strain [$F(1,53) = 1.78, p > .05$] but a significant main effect of lesion [$F(3,53) = 10.27, p < .001$]. Post hoc comparisons indicated that only small dorsal ($p < .01$) and large ventral (C57, $p < .01$; DBA, $p < .05$) hippocampal lesions produced an increase of activity in both strains in comparison with controls.

Habituation of object exploration. Object exploration scores during Sessions 2, 3, and 4 are reported in Figure 3. A repeated measures ANOVA revealed significant marginal effects of strain [$F(1,53) = 3.81, p = .056$] and session [$F(2,106) = 20.66, p < .001$]. There was no significant effect of the lesion factor [$F(3,53) = 1.97, p = .129$]. The following interactions were also

Figure 2. Coronal sections depicting the maximal extent of small dorsal (top), large ventral (middle), and small ventral (bottom) hippocampal lesions. Photographs refer to the DBA strain.

significant: strain $\times$ session [$F(2,106) = 15.9, p < .001$] and strain $\times$ lesion $\times$ session [$F(6,106) = 4.11, p < .001$]. Simple effect analyses indicated that habituation of object exploration occurred in the DBA [$F(2,106) = 34.87, p < .001$] but not the C57 [$F(2,106) = .26, p = .768$] mice.

Response to spatial change. Figure 4 reports the mean exploration time for displaced and nondisplaced objects in Session 5 minus the same set of data collected in Session 4. In these histograms, a positive score indicates an increased interest and a negative score a decreased interest for each category of objects. A repeated measures ANOVA revealed a significant effect of lesion [$F(3,53) = 7.79, p < .001$] and of object category [$F(1,53) = 15.81,$

$p < .001$], indicating, respectively, that in each strain the lesions generally reduced object exploration and that the displaced objects were more intensively explored than the nondisplaced ones. Significant strain $\times$ object [$F(1,53) = 5.31, p < .05$] and lesion $\times$ object category [$F(3,53) = 2.99, p < .05$] interactions were also found. Simple effect analyses revealed that there was a different reactivity to each object category in the C57 [$F(1,53) = 20.9, p < .001$] but not the DBA [$F(1,53) = 1.34, p = .252$] strain. In the C57 mice, group comparisons showed that only small dorsal ($p < .05$) and large ventral ($p < .05$) hippocampal lesions reduced object exploration in comparison with that of sham-lesioned mice and that this effect was limited to the displaced objects [$F(3,28) = 4.59, p < .01$]. In the DBA mice, there was no effect of object category [$F(1,25) = 1.75, p > .1$], but there was a significant effect of lesion [$F(3,25) = 4.96, p < .01$]. Group comparisons revealed that, even if the DBA mice did not differentially react to the displaced and the nondisplaced objects, small dorsal ($p < .05$) and large ventral ($p < .05$) hippocampal lesions modified object exploration in Session 5 in comparison with that of sham-lesioned mice.

Behavior: Experiment 2

The data are presented graphically in Figure 5. When the rank of the first error and maze running times were analyzed, the ANOVA revealed that performance improved with training in all groups—that is, that there was a significant main effect of trial [first error, $F(9,486) = 7.49, p < .001$; time, $F(9,486) = 55.19, p < .001$], with no significant strain $\times$ trial and lesion $\times$ trial interactions. The analyses also showed a significant main effect of strain [first error, $F(1,54) = 5.62, p < .05$; time, $F(1,54) = 7.67, p < .01$] and lesion [first error, $F(3,54) = 22.34, p < .001$; time, $F(3,54) = 3.01, p < .05$], indicating, respectively, that in general, C57 performed better than DBA mice and that the performance of the lesioned animals was impaired when compared with that of the controls. Post hoc comparisons revealed that the first error occurred earlier only in mice with small dorsal ($p < .01$) and large ventral ($p < .01$) hippocampal lesions in both strains. Conversely, post hoc comparisons of time revealed that, in the C57 mice, the two ventral lesions reduced significantly ($p < .05$) the time spent in running the maze in comparison with that for sham or small dorsal hippocampal lesioned mice. No significant difference was found between the four groups of DBA mice for this parameter.

DISCUSSION

The present work was carried out to compare the respective involvement of the dorsal and the ventral hippocampus in spatial information processing in two mouse strains, C57 and DBA, presenting neurobiological differences at the hippocampal level associated with well-differentiated spatial abilities. In particular, because these mice exhibit different densities of neurons in the dorsal but not the ventral hippocampus (Wimer et al., 1976), it

Figure 3. Locomotor activity and habituation of object exploration. Locomotor activity (top) is expressed by the mean number of sectors ($\pm$ SE) crossed by mice during 6 min in the empty open field. Only small dorsal and large ventral hippocampal lesions increase locomotor activity in both strains. Habituation of object exploration (bottom) is expressed by the mean duration ($\pm$ SE) of contacts with the five objects in Sessions 2, 3, and 4. Habituation developed more rapidly in DBA/2 than in C57BL/6 mice but was not significantly affected by any hippocampal lesion in either strain.

was expected that the degree of functional differentiation between the dorsal, and the ventral regions of this structure might vary according to the strain. However, in contrast with our working hypothesis, this study shows that small dorsal, large ventral, and small ventral hippocampal lesions produce a rather similar pattern of effects on spatial performance in both strains. That is, for a large majority of the behavioral parameters recorded in these experiments, the larger impairments were always observed following SDL and to a lesser extent following LVL, whereas SVL did not generally produce any effect, regardless of the anatomical properties of the hippocampus and the quality of performance shown by either strain.

Mice were first tested in the empty open field, and no strain difference in baseline performance was found. This observation disagrees with previous data showing higher locomotor activity scores in C57 than in DBA (Rossi-Arnaud & Ammassari-Teule, 1992; van Abeelen & Boersma, 1984), but it could be that the 5-min recording period used in this experiment was too short for strain

differences to be expressed. Interestingly, in both strains, locomotor activity was affected in the same fashion by each type of lesion. In particular, SDL and LVL were found to increase the number of crossed sectors, whereas SVL did not produce any effect. These data confirm that both dorsal and ventral lesions of the hippocampus can produce hyperactivity in a novel environment (Nadel, 1968), even if, for an equivalent amount of brain damage, dorsal lesions are more likely to induce hyperactivity than are ventral lesions.

In Session 2, the five objects were placed in the open field and the striped pattern was attached to the wall of the field. In Sessions 2–4, mice were allowed to explore the five objects left at a fixed location, and the time spent in contact each was recorded. The results show that habituation of object exploration developed more rapidly in the DBA than in the C57 mice but was unaffected by any lesion in either strain.

On the one hand, these results support the finding that C57 mice, contrary to DBA mice, maintain a sustained

Figure 4. Response to spatial change. The histograms represent the differences in mean ($\pm$ SE) time spent exploring the displaced and the nondisplaced objects between Session 5 and Session 4. In C57BL/6 mice, only small dorsal and large ventral hippocampal lesions abolish the peak of reactivity directed selectively toward the displaced objects. In DBA/2 mice, the same lesions induce an aspecific decrease of interest toward the two categories of objects.

level of object exploration across sessions (Ammassari-Teule et al., 1995). It is worth noting that the slow habituation of C57 must not necessarily be viewed as a defect of information encoding but, because of the large number of stimuli present in the situation, may rather reflect an intense exploration of the objects' features (shape contrast, color, etc.) and of their geometrical relationships as well.

On the other hand, the absence of lesion effects in both strains disagrees with a number of reports of modification of habituation following hippocampal damage in the rat (Douglas & Isaacson, 1964; Gray & McNaughton, 1983). These experiments, however, differ from the present ones in several aspects. First, hippocampal lesions were performed through aspiration and generally included large ablations of the overlying cortex, whereas our electrolytic lesions spared cortical areas. Second, habituation was measured in rather poor situations, such as empty open fields or hole boards, whereas we used an open field containing five objects. This point may be of importance in view of previous data indicating that the effect of dorsal and ventral hippocampal lesions on habituation varies according to the degree of novelty provided by the experimental situation (Nadel, 1968). For example, in the low-novelty condition—an open field with white walls—rats with ventral hippocampal lesions were found to habituate more rapidly than rats with dorsal or sham lesions. Conversely, in the high-novelty condition—an open field with striped walls—lesioned and nonlesioned animals habituated in the same fashion. Thus, it could be that the high-novelty condition provided by the present situation prevents the observation of lesion effects on habituation.

Regarding spatial novelty, extensive evidence in rats (Poucet, 1989; Xavier, Stein, & Bueno, 1990) and mice

(Thinus-Blanc, Save, Rossi-Arnaud, Tozzi, & Ammassari-Teule, 1996) shows that hippocampal lesions abolish the capability of reacting to the new object configuration. The fact that DBA mice present neurobiological alterations at the hippocampal level and do not react to the displacement of the objects is therefore consistent with the view that the reaction to spatial novelty is largely mediated by a functional hippocampus.

As before (Ammassari-Teule et al., 1995), C57 mice reacted fairly to spatial novelty and, in that strain, hippocampal lesions were found to affect performance according to the Moser et al. (1993) prediction. SDL abolished the reactivity to spatial novelty, LVL produced less marked effects, and SVL, no effect. Indeed, DBA mice do not show a strong interest in the displaced objects. Nevertheless, careful examination of their behavior in Session 5 indicates that these mice did express a mild reaction to spatial novelty, in that habituation of object exploration, which clearly developed from Sessions 2–4, ceased abruptly when mice were presented with the new configuration. Thus, a possible effect of hippocampal lesions on this limited reactivity might have consisted in a further reduction of the time spent in exploring all the objects in Session 5. The results did support this hypothesis and also show that the lesion effects were basically similar to those observed in C57. That is, in both strains, performance was always more severely affected by SDL, then LVL, and then SVL, even if the lesions decreased the exploration of the displaced objects in C57 selectively and the exploration of both categories of objects in DBA.

Finally, in agreement with previous reports (Ammassari-Teule & Caprioli, 1985), the C57 mice showed higher radial maze scores than did the DBA mice. As for activity and detection of spatial novelty in both strains, SDL and LVL impaired acquisition, whereas the initial deficit pro-

Figure 5. First error and maze running time. Each point corresponds to the mean ($\pm$ SE) recorded on two consecutive daily trials (statistical analysis was performed on single trial values). In both strains, the first error (top) occurred earlier only in mice with small dorsal and large ventral hippocampal lesions. In C57BL/6 mice, both small and large ventral hippocampal lesions decreased maze running time (bottom), whereas dorsal hippocampal lesions did not.

duced by SVL was no longer evident half-way into training. In the C57 mice, however, there was a clear dissociation between the effect of ventral and dorsal lesions on maze-running time. In that strain, both ventral lesions diminished the time spent to run the maze while the dorsal lesions did not. The DBA mice with LVL also ran the maze faster than the other groups but no significant statistical difference in performance between the four lesion conditions was found.

It is therefore apparent that ventral lesions produce a more consistent increase of locomotor activity in the radial maze than in the empty open field. This result is, at present, rather difficult to interpret even if the extensive anatomical connections existing between the ventral hippocampus and the amygdala may suggest a larger involvement of the ventral area in tasks requiring the processing of reward-related information (Lavoie & Mizumori, 1994).

Taken together, these results show a functional differentiation between the dorsal and the ventral hippocampus for a number of parameters such as activity, reactivity to spatial change, and radial maze acquisition in C57 and in DBA mice—that is, even in a strain considered as a ge-

netic model of hippocampal dysfunction (Ammassari-Teule et al., 1995; Paylor et al., 1993).

Regarding the functional properties of the hippocampus in each strain, the reduced density of mossy fiber terminals found in the hippocampal regio inferior of DBA mice suggests that less sensorial information is relayed via the perforant path and the dentate gyrus to the dorsal hippocampus in that strain. These anatomical differences, however, correlate with the ability of each strain to solve spatial learning tasks (Crusio et al., 1987) but do not alter the functional differentiation existing between the two regions of the hippocampus.

Recent electrophysiological studies have shown the existence of hippocampal place cells in the mouse with firing patterns comparable to those observed in the rat (Cho, Tanila, & Eichenbaum, 1996; McHugh & Wilson, 1996; Rotenberg, Mayford, Hawkins, Kandel, & Muller, 1996). It must be noted, however, that no comparison of place cell firing has hitherto been performed between these two mice strains and that only indirect evidence—the lower density of pyramidal neurons in the dorsal but not in the ventral region of the hippocampus—suggests that fewer place cells might be found in the dorsal hippo-

campus of DBA. Thus it could be that, as in the rat, dorsal place cells have a greater spatial specificity than ventral cells do, and, because of their reduced number in DBA mice, they support a less efficient processing of spatial information but a still present functional differentiation between the dorsal and the ventral areas in that strain. This may explain why, for an equivalent amount of brain damage (SDL and SVL), performance in spatial tasks is always more affected by dorsal than by ventral hippocampal lesions, whatever the strain—and the corresponding performance level—considered.

REFERENCES

- AMMASSARI-TEULE, M., & CAPRIOLI, A. (1985). Spatial learning and memory, maze running strategies and cholinergic mechanisms in two inbred strains of mice. *Behavioural Brain Research*, **17**, 9-16.
- AMMASSARI-TEULE, M., FAGIOLI, S., & ROSSI-ARNAUD, C. (1992). Genotype-dependent involvement of limbic areas in spatial learning and postlesion recovery. *Physiology & Behavior*, **52**, 505-510.
- AMMASSARI-TEULE, M., TOZZI, A., ROSSI-ARNAUD, C., SAVE, E., & THINUS-BLANC, C. (1995). Reactions to spatial and nonspatial change in two inbred strains of mice: Further evidence supporting the hippocampal dysfunction hypothesis in the DBA/2 strain. *Psychobiology*, **23**, 284-289.
- BARBER, R. P., VAUGHN, J. E., WIMER, R. E., & WIMER, C. C. (1974). Genetically-associated variations in the distribution of dentate granule cell synapses upon the pyramidal cell dendrites in mouse hippocampus. *Journal of Comparative Neurology*, **156**, 417-434.
- CHIBA, A. A., JOHNSON, D. L., & KESNER, R. P. (1992). The effect of lesions of the dorsal hippocampus or the ventral hippocampus on performance of a spatial location order recognition task. *Society for Neuroscience Abstracts*, **18**, 1422.
- CHO, Y. H., TANILA, H., & EICHENBAUM, H. (1996). Firing patterns of hippocampal cells in mice exploring a cue controlled environment. *Society for Neuroscience Abstracts*, **22**, 912.
- CRUSIO, W. E., SCHWEGLER, H., & LIPP, H.-P. (1987). Radial-maze performance and structural variation of the hippocampus in mice: A correlation with mossy fibre distribution. *Brain Research*, **425**, 182-185.
- DEACON, T. W., EICHENBAUM, H., ROSENBERG, P., & ECKMANN, K. W. (1983). Afferent connections of the perirhinal cortex in the rat. *Journal of Comparative Neurology*, **220**, 168-190.
- DOUGLAS, R. J., & ISAACSON, R. L. (1964). Hippocampal lesions and activity. *Psychonomic Science*, **1**, 187-188.
- FERINO, F., THIERRY, A. M., & GLOWINSKI, J. (1987). Anatomical and electrophysiological evidence for a direct projection from Ammon's horn to the medial prefrontal cortex. *Experimental Brain Research*, **65**, 421-426.
- GRAY, J. A., & MCNAUGHTON, N. (1983). Comparison between the behavioral effects of septal and hippocampal lesions: A review. *Neuroscience & Biobehavioral Reviews*, **7**, 119-188.
- JAY, T. M., GLOWINSKI, J., & THIERRY, A. M. (1989). Selectivity of the hippocampal projection to the prelimbic area of the prefrontal cortex in the rat. *Brain Research*, **505**, 337-340.
- JAY, T. M., & WITTER, M. P. (1991). Distribution of hippocampal CA1 and subicular efferents in the prefrontal cortex of the rat studied by means of anterograde transport of Phaseolus vulgaris-leucoagglutinin. *Journal of Comparative Neurology*, **313**, 574-586.
- JUNG, M. W., WIENER, S. I., & MCNAUGHTON, B. L. (1994). Comparison of spatial firing characteristic of units in dorsal and ventral hippocampus of the rat. *Journal of Neuroscience*, **14**, 7347-7356.
- KRETTEK, J. E., & PRICE, J. L. (1977). Projection from the amygdaloid complex and adjacent olfactory structures to the entorhinal cortex and to the subiculum in the rat and cat. *Journal of Comparative Neurology*, **172**, 723-752.
- LAVOIE, A. M., & MIZUMORI, S. J. (1994). Spatial movement- and reward-sensitive discharge by medial ventral striatum neurons of rats. *Brain Research*, **628**, 157-168.
- McHUGH, T. Y., & WILSON, M. A. (1996). Characterization of place cell activity in the hippocampus of freely behaving mouse. *Society for Neuroscience Abstracts*, **22**, 911.
- MOSER, E., MOSER, M. B., & ANDERSEN, P. (1993). Spatial learning impairment parallels the magnitude of dorsal hippocampal lesions, but is hardly present following ventral lesions. *Journal of Neuroscience*, **13**, 3916-3925.
- NADEL, L. (1968). Dorsal and ventral hippocampal lesions and behavior. *Physiology & Behavior*, **3**, 891-900.
- PAYLOR, R., BASKALL, L., & WEHNER, J. M. (1993). Behavioral dissociations between C57BL/6 and DBA/2 mice on learning and memory tasks: A hippocampal-dysfunction hypothesis. *Psychobiology*, **21**, 11-26.
- POUCET, B. (1989). Object exploration, habituation, and response to a spatial change in rats following septal or medial frontal cortical damage. *Behavioral Neuroscience*, **103**, 1009-1016.
- POUCET, B., THINUS-BLANC, C., & MULLER, R. I. (1994). Place cells in the ventral hippocampus of rats. *NeuroReport*, **5**, 2045-2048.
- ROOM, P., & GROENEWEGEN, H. J. (1986). Connections of the parahippocampal cortex: I. Cortical afferents. *Journal of Comparative Neurology*, **251**, 415-450.
- ROSSI-ARNAUD, C., & AMMASSARI-TEULE, M. (1992). Modifications of open field and novelty behaviours by hippocampal and amygdaloid lesions in two inbred strains of mice: Lack of strain $\times$ lesion interaction. *Behavioural Processes*, **27**, 155-164.
- ROSSI-ARNAUD, C., FAGIOLI, S., & AMMASSARI-TEULE, M. (1991). Spatial learning in two inbred strains of mice: Genotype-dependent effect of amygdaloid and hippocampal lesions. *Behavioural Brain Research*, **45**, 9-16.
- ROTENBERG, A., MAYFORD, M., HAWKINS, R. D., KANDEL, E. R., & MULLER, R. U. (1996). Place cells recorded from freely moving mice: Differences between wild-type and transgenic animals incapable of solving a navigational problem. *Society for Neuroscience Abstracts*, **22**, 912.
- ROULLET, P., & LASSALLE, J. M. (1990). Genetic variation, hippocampal mossy fibres distribution, novelty reactions and spatial representation in mice. *Behavioural Brain Research*, **41**, 61-70.
- ROULLET, P., LASSALLE, J. M., & JEGAT, R. (1993). A study of behavioral and sensorial bases of radial maze learning in mice. *Behavioral & Neural Biology*, **59**, 173-179.
- RUTH, R. E., COLLIER, T. J., & ROUTTENBERG, A. (1982). Topography between the entorhinal cortex and the dentate septotemporal axis in rats: I. Medial and intermediate entorhinal projecting cells. *Journal of Comparative Neurology*, **209**, 69-78.
- SWANSON, L. W. (1981). A direct projection from Ammon's horn to prefrontal cortex in the rat. *Brain Research*, **217**, 150-154.
- THINUS-BLANC, C., SAVE, E., ROSSI-ARNAUD, C., TOZZI, A., & AMMASSARI-TEULE, M. (1996). The differences shown by C57BL/6 and DBA/2 inbred mice in detecting spatial novelty are subserved by a different hippocampal and parietal cortex interplay. *Behavioural Brain Research*, **80**, 33-40.
- UPCHURCH, M., & WEHNER, J. (1989). Inheritance of spatial learning ability in inbred mice: A classical genetic analysis. *Behavioral Neuroscience*, **103**, 1251-1258.
- VAN ABELEN, J. H. F., & BOERSMA, H. J. L. M. (1984). A genetically controlled hippocampal transmitter system regulating exploratory behavior in mice. *Journal of Neurogenetics*, **1**, 153-158.
- VAN GROEN, T., & WYSS, J. M. (1990). Extrinsic projections from area CA1 of the rat hippocampus: Olfactory, cortical, subcortical, and bilateral hippocampal formation projections. *Journal of Comparative Neurology*, **302**, 515-528.
- WEHNER, J. M., SLEIGHT, S., & UPCHURCH, M. (1990). Hippocampal protein kinase C activity is reduced in poor spatial learners. *Brain Research*, **523**, 181-187.
- WIMER, R. E., WIMER, C., VAUGHN, J. E., BARBER, R. P., BALVANZ, B. A., & CHERNOW, C. R. (1976). The genetic organization of neuron number in Ammon's horns of house mouse. *Brain Research*, **118**, 219-243.
- XAVIER, G. F., STEIN, C., & BUENO, O. F. A. (1990). Rats with hippocampal lesions do react to new stimuli but not to spatial change of known stimuli. *Behavioral & Neural Biology*, **54**, 172-183.