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Roman Strains as a Psychogenetic Model for the Study of Working Memory: Behavioral and Biochemical Data

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WILLIG, F., M. M'HARZI, C. BARDELAY, D. VIET AND J. DELACOUR. *Roman strains as a psychogenetic model for the study of working memory: Behavioral and biochemical data.* PHARMACOL BIOCHEM BEHAV **40**(1) 7–16, 1991.—Performances of male rats of the Roman High- (RHA), Roman Control- (RCA) and Roman Low- (RLA) Avoidance strains were compared in two working memory tests, a spatial one, the radial maze, and a nonspatial one, an object recognition test. The same rats were subjected to measures of emotional reactivity and of different forms of motor activity and finally to measures of cholinergic and aminergic activities in the hippocampus, frontal cortex and striatum. Compared to RHA, RLA performed better in the two working memory tests, displayed "anxiety" and had also lower levels of exploratory locomotor activity. Hippocampal ChAT activity was higher in RLA than in RHA. Levels of DA and DOPAC in the striatum were higher in RLA compared to RHA, whereas in the frontal cortex they were lower. For most of these measures, RCA were intermediate between RLA and RHA. These results confirm and extend the finding that the Roman strains are not only a genetic model for two-way avoidance conditioning but also for working memory.

Roman strains of rats Psychogenetic selection Working memory Exploratory behavior Anxiety
Radial maze Object recognition Open field Staircase Test ChAT DA DOPAC NA 5-HT
5-HIAA Hippocampus Frontal cortex Striatum

THE Roman strains have been selected by Broadhurst and Bignami (6,7) from a stock of Wistar rats through performances in an active avoidance conditioning, the two-way shuttle-box test. The Roman High Avoidance strain (RHA) acquires this conditioning quite rapidly and the Roman Low Avoidance strain (RLA), quite slowly or even fails to acquire it; performances of a nonselected control line, issued from the same stock of Wistar rats, the Roman Control Avoidance strain (RCA), are intermediate. It rapidly appeared that RHA and RLA also behave differently in other learning tasks (2, 14, 15, 19, 20, 27, 28, 43, 55, 58); in particular, data from our laboratory showed for the first time that the Roman strains differ in a working memory test, the delayed reinforced alternation (DRA), where RLA are superior to RHA (27, 28, 55). This indication is of special interest for the experimental reproduction of memory disturbances of demented or normal aged people.

Within this scope, the purpose of the experiments reported here was to confirm and extend the finding that the Roman strains differ in working memory and to relate this memory characteristic to other behavioral features and to neurochemical data. RHA, RLA and RCA were compared in two working memory tests: a spatial one, as the DRA: the radial maze which, like the DRA, is based on spatial information (45), and a nonspatial one, a new test based on object recognition (21, 37, 56), similar to the most popular test of working memory used in subhuman primates (38). The same animals were subjected to measures of emotional reactivity and of different forms of motor activity and finally to measures of cholinergic and aminergic activities in the hippocampus, frontal cortex and striatum.

METHOD

Subjects and Housing

Thirty male rats were used, thirteen RLA, six RHA and eleven RCA. The unequal size of the strains and particularly the small size of the RHA strain are due to the difficulty of obtaining rats of a given strain, sex and age (within a week). These animals, born in our laboratory (Roussel-Uclaf, Romainville, France), were the descendants of an initial stock of breeders obtained from the laboratory of Prof. Broadhurst (Birmingham, England). They were three months old at the beginning of the experiments, which covered a three-month period. They were housed in individual cages in a temperature-controlled room ($23 \pm 1°C$) and maintained on a 12:12-h light-dark cycle (7 a.m.–7 p.m.). The animals were handled for five minutes ev-

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ery day before the beginning of the experiments or during their interruption.

Chronology of Experiments

The average amount of time for each experiment is indicated in parentheses and the interval between each experiment in brackets. Subjects were submitted to behavioral experiments in the following order: 1) Nycthemeral motor and locomotor activities (5 days), [1 day]; 2) Spontaneous activity in an automated open field (1 day), [1 day]; 3) Staircase test (1 day), [7 days]; 4) 8-arm radial maze (36 days), [7 days]; 5) Object recognition (10 days), [7 days]; 6) Exploration of a complex environment (1 day). Fifteen days after the end of the behavioral experiments, rats were sacrificed for neurochemical assays.

Data Analysis

Results were expressed as mean (m) ± s.e.m. and median (med). It was not assumed that the scores under analysis were drawn from a normally distributed population, since it was not possible to check this assumption due to the small number of subjects. So, overall comparisons between strains were made with a "distribution-free" test, the Kruskal-Wallis test and post hoc pairwise comparisons, with the two-tailed Mann-Whitney U-test. Within strain comparisons were made with the Wilcoxon matched pairs test. Determination of relationships between the different variables was made with the Kendall rank correlation coefficient τ for the combined data of both strains (49).

Nycthemeral Motor and Locomotor Activities

Activity was measured with an apparatus (Panlab, Apelex) which detects movements by means of high-frequency electromagnetic signals. The sensitivities of the apparatus were adjusted for detecting mainly gross locomotor activity (channel 1, level 2, whose low sensitivity allowed only detection of ample movements of 15–20 cm approximately) and the whole motor activity (channel 2, level 7, whose high sensitivity allowed detection of all head or paws or body movements). Rats were tested singly in their home cage, a clear plastic box (36 × 20 cm; 16 cm high) with sawdust on the floor and a metallic cover. They had free access to water and food (dry biscuits for rats, B.O.4, U.A.R.). The experiment was performed in a sound-attenuated air-conditioned (23 ± 2°C) room, on a 12:12-h (8 a.m.:8 p.m.) light/dark cycle. Measures of nycthemeral activity began for each rat at 8 a.m. and ended at 8 a.m. the day after. Six rats (1 to 3 rats of each strain) were tested simultaneously.

Automated Open Field

The observation area was a plastic box (37 × 40 cm; 30 cm high). Measurements of activity were obtained by means of a sensor, the Optovarimex Activity Monitor (Columbus) which provides an Apple II computer with data on animal position and turning activity that the computer uses to extract the following information: 1) distance travelled; 2) duration of rest; 3) duration of "movement" activity (scratching, grooming, . . .); 4) duration of ambulatory activity; 5) number of movements; 6) number of vertical movements. The experimental room was similar to that used in the preceding experiment. The total duration of the session was 10 min and the data were analyzed by dividing this duration into four periods of 2.5 min each.

Staircase Test

The apparatus and the procedure used were the same as that described by Thiebot et al. (50). The staircase was constructed in grey painted wood (95 × 20 cm, 30 cm high; with five stairs of 20 × 15 cm and 6 cm high). Rats were individually placed onto the bottom step of the staircase for a 3-min observation period during which the number of steps ascended and rears were counted. Steps descended by the rat were not counted. A rear was counted when the rat rose on its hindlegs either on the step or against the wall to sniff the air.

8-Arm Radial Maze

The elevated eight-arm radial maze was made of 0.5 cm black Plexiglas. Each arm (68 × 10 cm) extended from an octagonally shaped central hub (30 cm in diameter). Side walls (1.5 cm high) extended the length of each arm. A small glass cup (4.5 cm in diameter) was placed at the end of each arm. The maze, 78 cm elevated above the floor, was placed in a sound-attenuated room with a masking noise. Several large and quite distinctive objects having a constant location in the room were placed as extramaze cues.

The rats were submitted to ten consecutive habituation sessions (one per day). Rats were put on the central hub and were allowed to explore the entire maze for five to ten minutes. During the habituation stage, rats had ad lib food and water in their home cage. At the end of the habituation stage, they were deprived of water for 48 hours before the first training session, to obtain a reduction in weight to 85% of their initial weight.

Rats were given one session per day. A session lasted until the rat made eight choices or 15 min elapsed. The cups at the end of each arm contained 0.3 ml of water. Choices made by rats were recorded. When a rat entered (engaged its 4 paws in) an already visited arm, an error was counted. Rats were trained for at least 10 sessions and then until they reached the acquisition criterion or for a maximum of 24 sessions. The acquisition criterion used was one error or less per session during five consecutive sessions. When rats did not reach the criterion at the 24th session, their session score was 24 and their error score was the total number of errors made during the 24 sessions.

One hour and a half after the session, rats were given access to water in their home cages. The amount of water was fixed with the intention of maintaining each rat at 85% of its normal weight.

Object Recognition Test

The observation area was a right-angled box (65 × 45 cm; 45 cm high) made out of unpainted wood. Three-dimensional objects to be discriminated were made out of glass, metal or plastic. Before being exposed to the objects, rats were submitted to two habituation sessions (one per day) during which they freely explored the box for 5 min. The experimental procedure was as follows: at each session, the rat was placed near the center of the front wall of the observation area and allowed to explore, for 3 min, a sample (S) object placed against the rear wall in a location equidistant from the rear corners of the box (trial 1). The rat was then returned to its cage for a retention interval (1 or 60 min), during which time the experimenter cleaned the observation area and placed into it the familiar (F) object (a duplicate of the S object, in order to avoid olfactory trails) and a new (N) one. Each object was placed in a rear corner of the observation area. The rat was then put back into the observation area and allowed to explore the two objects for 3 min (trial 2). In order to reduce object and place preference, the position of the F and N objects was pseudorandomly permuted and an object served as a sample for half of the rats and as the new object for the other half. A different pair of objects was used for each

TABLE 1

NYCTHEMERAL MOTOR AND LOCOMOTOR ACTIVITIES

	Locomotor Activity			Motor Activity		
	Whole Nycthemeron	Light Part (8 a.m.–8 p.m.)	Dark Part (8 p.m.–8 a.m.)	Whole Nycthemeron	Light Part (8 a.m.–8 p.m.)	Dark Part (8 p.m.–8 a.m.)
RLA	3990 ± 258 (3930)	791 ± 97 (698)	3199 ± 219 (2909)	58394 ± 1673 (56995)	15106 ± 755 (14383)	43289 ± 1382 (42612)
RCA	4990 ± 513 (4788)	1037 ± 162 (830)	3942 ± 423 (3629)	64331 ± 2287 (62695)	18276 ± 1089 (20286)	46055 ± 1404 (45720)
RHA	4262 ± 213 (4214)	1187 ± 134 (1172)	3075 ± 141 (3041)	68682 ± 2997 (68530)	20374 ± 1792 (19133)	48308 ± 1685 (47431)
Overall Comparison	ns	ns	ns	0.05	0.05	ns
RLA vs. RCA	—	—	—	ns	ns	—
RLA vs. RHA	—	—	—	0.05	0.01	—
RCA vs. RHA	—	—	—	ns	ns	—

Mean group performance ±s.e.m. and median (in parentheses); p values for the overall comparisons (Kruskal-Wallis test) and the post hoc pairwise comparisons (two-tailed Mann-Whitney U-test). Locomotor and motor activities are expressed in arbitrary units.

session. Object exploration was measured by the time spent by the rat in touching the object with its nose or forepaws and/or sniffing it at one cm or less. Three basic measurements were considered: the time spent in exploring the sample during trial 1 = t(S), that spent in exploring the sample during trial 2 = t(F) and that spent in exploring the new object during trial 2 = t(N). Each rat was submitted to 2 sessions (one per day) for a retention interval of 1 min and then to 2 sessions (one per day) for a retention interval of 60 min.

Exploration of a Complex Environment

The observation area was a yellow Plexiglas box (62 × 62 cm; 23 cm high) divided into nine compartments (20.5 × 20.5 cm) communicating by openings (8 cm wide, 9 cm high) and with sawdust on the floor. The center compartment served as a starting box. The session lasted 10 min and was divided in 4 periods of 2.5 min each. The rat was put into the center compartment and allowed to explore the observation area. Number of crossings (going from one compartment to an other) and retracings (returning to the last visited compartment) were recorded.

Neurochemical Assays

Rats were sacrified by decapitation 15 days after the completion of the behavioral experiments. The brain was removed in the cold (+4°C) and the two hippocampi, one striatum and the two frontal cortices were rapidly dissected, weighed and immediately homogenized by sonication. The time from decapitation was always near to 1 min. Choline acetyltransferase (ChAT) activity was measured according to the method described by Fonnum (23). ChAT activity was expressed as pmoles of ACH synthesized/h at 37°C and pH 7.2 per gram tissue wet weight in the presence of choline (10 mM) and (^{14}C) AcCoA (45 μM). Catecholamines, indoleamines and their metabolites were separated on alumina micro-columns by a method based on that of Gauchy et al. (24) and assayed using reversed phase high performance liquid chromatography with electrochemical detection.

RESULTS

Nycthemeral Motor and Locomotor Activities

Table 1 summarizes the main results. Locomotor activity (arbitrary units, sensitivity 2) during the whole nycthemeron was not different ($H = 2.44$, $p > 0.1$) between strains, or during the light part of the cycle ($H = 4.25$, $p > 0.1$) or during the dark part of the cycle ($H = 2$, $p > 0.1$). Motor activity (arbitrary units, sensitivity 7) during the whole nycthemeron was different between the 3 strains ($H = 7.24$, $p < 0.05$). RLA displayed less motor activity than RHA and RCA and this difference was due to their activity during the light part of the cycle ($H = 7.4$, $p < 0.05$), but not during its dark part ($H = 3.7$, $p > 0.1$).

Automated Open Field

Table 2 summarizes the main results. Distance travelled during the whole session was significantly different between the three strains ($H = 22.2$, $p < 0.0001$): RLA travelled significantly ($p < 0.001$) less than RHA, RCA being intermediate between RLA ($p < 0.001$) and RHA ($p < 0.05$). Distance travelled during each period of 2.5 min was also significantly different between the three strains ($p < 0.05$) (see Fig. 1). Results for all other measures also revealed significant ($p < 0.001$) differences between the three strains: except for movement duration, all the measures of exploratory activity were significantly higher in RHA than in RLA, RCA being intermediate (see Table 2). The amount of urination and defecation were comparable between the three strains.

Staircase Test

The number of steps ascended, considered as an index of exploratory locomotor activity, was somewhat lower in RLA ($m = 6.2 \pm 1$; $med = 5$) than in RHA ($m = 9.7 \pm 2$; $med = 8$) and RCA ($m = 8.6 \pm 1$; $med = 9$), but the differences failed to reach statistical significance. The number of rearings, considered as an index of anxiety (50), was somewhat higher in RLA ($m = 5.2 \pm 1$; $med = 5$) than in RHA ($m = 3.5 \pm 1$; $med = 3.5$) and RCA ($m = 3.9 \pm 1$; $med = 4$), but the differences failed to reach statistical significance. However, when the number of rearings was expressed as a percentage of the number of steps ascended [i.e.,

TABLE 2

SPONTANEOUS ACTIVITY IN THE AUTOMATED OPEN FIELD

	Distance	Ambul(t)	Rest(t)	Mov(t)	Mov(n)	Vert(n)
RLA	1575 ± 105	138 ± 10	233 ± 20	221 ± 12	339 ± 16	34 ± 5
	(1546)	(133)	(210)	(224)	(349)	(29)
RCA	2270 ± 47	193 ± 4	162 ± 6	235 ± 4	403 ± 5	51 ± 3
	(2271)	(189)	(165)	(232)	(399)	(48)
RHA	2752 ± 213	231 ± 15	117 ± 13	244 ± 5	425 ± 6	72 ± 7
	(2607)	(221)	(126)	(246)	(426)	(70)
Overall	0.0001	0.0001	0.0001	ns	0.0001	0.001
Comparison						
RLA vs. RCA	0.001	0.001	0.01	—	0.01	0.01
RLA vs. RHA	0.001	0.001	0.001	—	0.001	0.001
RCA vs. RHA	0.05	0.01	0.05	—	0.05	0.01

Mean group performance ± s.e.m. and median (in parentheses) for the ten-minute session; p values for the overall comparisons (Kruskal-Wallis test) and the post hoc pairwise comparisons (two-tailed Mann-Whitney U-test). Distance: distance travelled (in cm); Ambul(t): duration of ambulatory activity(s); Rest(t): duration of rest(s); Mov(t): duration of movements(s). Mov(n): number of movements. Vert(n): number of vertical movements.

(number of rearings divided by the number of steps ascended) × 100], differences between strains became statistically significant, ($H=7.1$, $p<0.05$). RLA ($m=110\pm17\%$; $med=100$) reared relatively more than RHA ($m=47\pm13\%$; $med=39$, $p<0.05$) and RCA ($m=65\pm17\%$; $med=38$, $p<0.05$). As in the automated open field, the amount of urination and defecation were comparable between the three strains.

8-Arm Radial Maze

Only one RLA and one RCA failed to reach the criterion in 24 sessions or less, whereas half of RHA failed. The number of sessions to criterion was significantly different between strains ($H=6.87$, $p<0.05$): it was significantly ($p<0.05$) lower in RLA ($m=3.8\pm2$; $med=2$) than in RHA ($m=16\pm4$; $med=20$), RCA ($m=8.2\pm2$; $med=9$) being not significantly different from the two other strains (see Fig. 2). The number of errors to criterion was also significantly different between strains ($H=7.47$, $p<0.05$): RLA ($m=6.4\pm3$; $med=4$) made significantly ($p<0.05$) fewer errors than RHA ($m=29\pm9$; $med=31$), RCA ($m=13\pm3$; $med=14$) being intermediate between RLA ($p<0.05$) and RHA (ns) (see Fig. 2).

Object Recognition

Table 3 summarizes the main results.

1-Min Retention Interval (1-min RI). Two RLA rats were discarded from the analysis because of freezing which suppressed all object exploration scores. Analyses were performed on the mean performances of the two sessions. The total time spent in exploring objects [$T=t(S)+t(F)+t(N)$] was somewhat higher in RLA than in RHA and RCA but the difference did not reach statistical significance. Further analyses were performed to determine whether or not the subjects were spending more time in exploring S, F or N objects. Strains were not significantly different in either t(S) or t(F): ($H=2.5$, $p>0.1$) and ($H=1.2$, $p>0.1$), respectively. The time spent in exploring the new object [t(N)] was significantly different between strains ($H=7.7$, $p<0.05$): RLA explored the new object significantly ($p<0.05$) more than RHA and RCA which did not differ. Measures of recognition memory disclosed clear-cut differences between the strains. Within strains comparisons showed that the mean values of t(N) and t(F) were significantly different only in RLA ($p<0.01$), this strain spending more time in exploring the new object than the familiar one. RCA ($p<0.06$) and RHA ($p<0.07$) had the

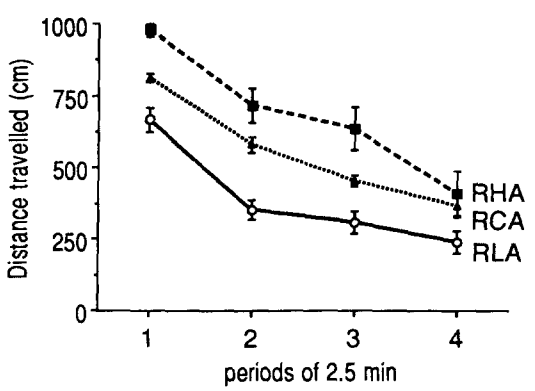

FIG. 1. Exploratory activity in an open field. Mean group performances ± s.e.m. in 4 successive periods of 2.5 min.

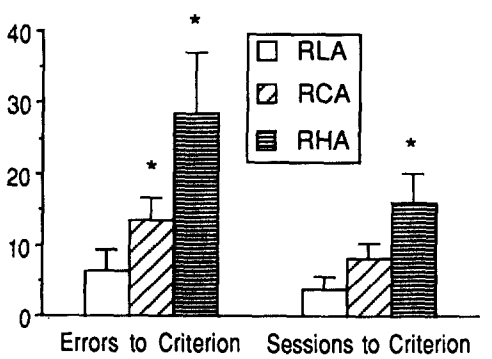

FIG. 2. Learning scores in the 8-arm radial maze. Mean group performances ± s.e.m. Post hoc pairwise comparisons (Mann-Whitney U-test): *$p<0.05$ vs. RLA.

TABLE 3

OBJECT RECOGNITION TEST

	1-Min Retention Interval					60-Min Retention Interval				
	Sample t(S)	Familiar t(F)	New t(N)	Index t(N)-t(F)	Index |t(N)-t(F)|	Sample t(S)	Familiar t(F)	New t(N)	Index t(N)-t(F)	Index |t(N)-t(F)|
RLA	20 ± 2 (21)	12 ± 2 (10)	21 ± 2 (18)	9 ± 2 (9)	11 ± 1 (10)	24 ± 3 (21)	13 ± 2 (14)	26 ± 3 (26)	13 ± 3 (13)	15 ± 3 (13)
RCA	16 ± 2 (15)	10 ± 2 (8)	14 ± 2 (13)	4 ± 2 (5)	8 ± 2 (6)	17 ± 2 (18)	12 ± 2 (12)	18 ± 2 (18)	6 ± 2 (8)	10 ± 2 (9)
RHA	16 ± 2 (15)	12 ± 1 (12)	15 ± 1 (15)	3 ± 1 (3)	5 ± 1 (5)	14 ± 2 (16)	14 ± 2 (13)	15 ± 2 (14)	2 ± 4 (3)	8 ± 2 (8)
Overall Comparison	ns	ns	0.05	0.05	0.05	ns	ns	0.05	0.05	ns
RLA vs. RCA	—	—	0.05	0.05	0.05	—	—	ns	0.05	—
RLA vs. RHA	—	—	0.05	0.05	0.01	—	—	0.05	0.05	—
RCA vs. RHA	—	—	ns	ns	ns	—	—	ns	ns	—

Mean group performance (s) ± s.e.m. and median (in parentheses) of two sessions for each retention interval; p values for the overall comparisons (Kruskal-Wallis test) and the post hoc pairwise comparisons (two-tailed Mann-Whitney U-test). t(N)-t(F): index of preference for the novel object; | t(N)-t(F)| : Index of discrimination between the familiar and the novel object.

same tendency. The variable |t(N)-t(F)| reflects the discrimination between the new and the familiar object and the variable t(N)-t(F), the tendency to prefer the novel object. Their mean values were significantly ($p<0.05$) higher in RLA than in RHA and RCA.

60-Min Retention Interval (60-min RI). One RLA rat was discarded from the analyses because of freezing. Analyses were performed on the mean performances of the two sessions. The total time spent in exploring objects [T = t(S) + t(F) + t(N)] was somewhat higher in RLA than in RHA and RCA but the differences failed to reach statistical significance. Further analyses were performed to determine whether or not the subjects were spending more time in exploring S, F or N objects. Strains were not significantly different in either t(S) or t(F): ($H=3$, $p>0.1$) and ($H=0.2$, $p>0.1$), respectively. The time spent in exploring the new object [t(N)] was significantly different between strains ($H=7.8$, $p<0.05$): RLA explored significantly ($p<0.05$) more the new object than RHA, RCA did not differ from RLA or RHA. Within strains comparisons for t(F) and t(N) showed that RLA ($p<0.01$) and RCA ($p<0.05$), but not RHA ($p>0.1$) explored significantly more the new object. There was a significant difference ($H=7.3$, $p<0.05$) between strains on the basis of the t(N)-t(F) variable: its mean value was significantly ($p<0.05$) higher in RLA than in RHA and RCA. There was no significant differences ($H=3.4$, $p>0.1$) between strains on the basis of the |t(N)-t(F)| variable.

Comparisons between 1-min RI and 60-min RI. Wilcoxon T-test computed on the combined data of the three strains revealed that the total time spent in exploring objects was significantly higher at the 60-min RI than at the 1-min RI ($p<0.05$). This increase was significant in RLA ($p<0.05$); RCA showed the same tendency ($p<0.07$), whereas RHA did not. Further analyses performed on the t(N)-t(F) and |t(N)-t(F)| variables revealed that there were no decay of performances as a function of retention interval (60-min RI/1-min RI).

Exploration of a Complex Environment

For the whole 10-min session, the number of crossings was significantly different between strains ($H=9.9$, $p<0.01$): RLA ($m=61\pm6$; $med=57$) entered significantly ($p<0.01$) fewer compartments than did RHA ($m=94\pm6$; $med=92$, $p<0.01$) and RCA ($m=85\pm7$; $med=83$, $p<0.05$). Figure 3 shows the mean (±s.e.m.) exploratory activity (crossings) in four successive periods of 2.5 min each. Exploratory activity was significantly different between strains during the 2 first and the last one periods ($p<0.05$). The percentage of retracings was also significantly different between strains ($H=6.2$, $p<0.05$): RLA ($m=6\pm1$; $med=6$) retraced significantly ($p<0.05$) less than did RHA ($m=10.3\pm1$; $med=10$); RCA ($m=8\pm1$; $med=1$) did not differ from RLA and RHA. As in the automated open field and as in the staircase tests, the amount of urination and defecation were comparable between the three strains.

Neurochemical Assays

Table 4 shows the results of neurochemical assays. The main results may be summarized as follows: Hippocampal ChAT activity was significantly higher in RLA than in RHA ($p<0.01$) and RCA ($p<0.05$). RLA and RCA had significantly lower cortical dopamine (DA) and 3,4-dihydroxyphenylacetic acid

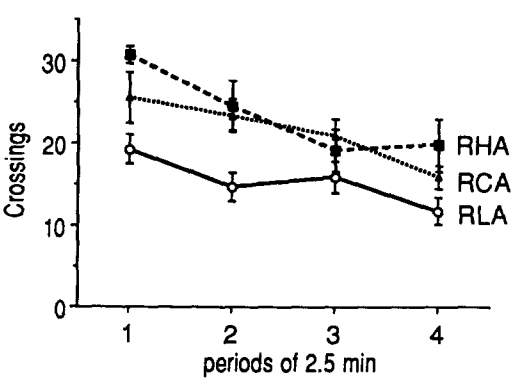

FIG. 3. Exploratory activity in a complex environment. Mean group performances ± s.e.m. in 4 successive periods of 2.5 min.

TABLE 4

NEUROCHEMICAL ASSAYS

	Hippocampus				Frontal Cortex					Striatum		
	ChAT	NA	5-HT	5-HIAA	NA	DA	DOPAC	NA	DA	DOPAC	5-HT	5-HIAA
RLA	9.5±0.2 (9.7)	0.653±0.014 (0.675)	0.486±0.012 (0.495)	0.477±0.014 (0.48)	0.372±0.011 (0.366)	57±3 (60)	11.5±0.6 (11.5)	0.09±0.004 (0.09)	12.7±0.3 (12.5)	1.60±0.06 (1.54)	0.724±0.017 (0.73)	0.816±0.021 (0.8)
RCA	8.7±0.2 (8.8)	0.701±0.021 (0.72)	0.503±0.016 (0.49)	0.469±0.014 (0.47)	0.353±0.012 (0.36)	60±3 (60)	13.9±0.8 (13.6)	0.10±0.005 (0.09)	12.1±0.3 (12.5)	1.43±0.06 (1.44)	0.783±0.015 (0.76)	0.877±0.025 (0.87)
RHA	8.3±0.1 (8.2)	0.708±0.029 (0.71)	0.515±0.016 (0.515)	0.502±0.012 (0.495)	0.352±0.015 (0.344)	71±4 (69)	13.9±0.9 (13.5)	0.13±0.02 (0.13)	11.2±0.1 (11.2)	1.25±0.04 (1.26)	0.807±0.031 (0.81)	0.838±0.024 (0.825)
Overall comparison	0.01	ns	ns	ns	ns	0.05	0.05	0.05	0.05	0.01	0.05	ns
RLA vs. RCA	0.05	—	—	—	—	ns	0.05	ns	ns	0.05	0.05	—
RLA vs. RHA	0.01	—	—	—	—	0.05	0.05	0.05	0.01	0.01	0.05	—
RCA vs. RHA	ns	—	—	—	—	0.05	ns	0.05	ns	0.05	ns	—

Mean group values ±s.e.m. and median (in parentheses); p values for the overall comparisons (Kruskal-Wallis test) and the post hoc pairwise comparisons (two-tailed Mann-Whitney U-test). ChAT: pmoles acetylcholine synthetized/h/g tissue; NA, 5-HT, 5-HIAA: μg/g tissue; DA, DOPAC: ng/g tissue in frontal cortex, μg/g tissue in striatum.

(DOPAC) levels than RHA ($p<0.05$). Striatal norepinephrine (NA) and 5-hydroxytryptamine (5-HT) levels were significantly lower in RLA than in RHA ($p<0.05$), but DA and DOPAC levels were significantly ($p<0.05$) higher in RLA than in RHA. For most of these measures, RCA were intermediate between RLA and RHA.

Correlations Between Variables

Correlation between behavioral variables. Table 5 shows the coefficients of correlation τ between behavioral variables. The main results can be summarized as follows:

Nycthemeral locomotor activity was not correlated with ex-

TABLE 5

COEFFICIENTS OF CORRELATION τ BETWEEN BEHAVIORAL VARIABLES

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Nycthemeral Activity															
Locomotion (1)	—														
Motor activity (2)	.52§	—													
Open Field															
Distance travelled (3)	.09	.31*	—												
Staircase Test															
Rears (%) (4)	−.06	−.05	−.26*	—											
Radial maze															
Sessions to criterion (5)	.06	.17	.31*	−.02	—										
Errors to criterion (6)	.03	.16	.33*	−.05	.95§	—									
Object Recognition															
1-min retention interval															
t(S)+t(F)+t(N) (7)	.05	−.05	−.30*	−.06	−.10	−.14	—								
t(N) (8)	−.16	−.27*	−.47‡	.05	−.08	−.11	.58§	—							
t(N)-t(F) (9)	−.12	−.14	−.38†	.21	−.02	−.04	−.06	.29*	—						
| t(N)-t(F)| (10)	−.08	−.16	−.49‡	.15	−.08	−.09	.16	.33*	.61§	—					
60-min retention interval															
t(S)+t(F)+t(N) (11)	.18	−.04	−.35†	−.05	−.21	−.23	.45‡	.31*	.08	.21	—				
t(N)(12)	.18	−.05	−.39†	.06	−.25	−.27*	.33*	.22	.06	.23	.73§	—			
t(N)−t(F) (13)	−.07	−.16	−.44‡	.23	−.26*	−.28*	.25	.14	−.04	.19	.40†	.60§	—		
| t(N)-t(F)| (14)	−.01	−.06	−.22	.05	−.23	−.20	.20	.01	−.09	.17	.39†	.50§	.59§	—	
Complex Environment															
Crossings(15)	.13	.18	.37†	−.33*	.14	.16	−.11	−.11	−.17	−.30*	−.06	−.12	−.24	−.18	—
Retracings (%)	.09	.22	.27*	−.28*	.06	.07	.10	−.07	−.20	−.11	−.13	−.12	−.06	−.04	.12

Numbers in column heads refer to variables numbers indicated in parentheses in the first column. *$p<0.05$; †$p<0.01$; ‡$p<0.001$; §$p<0.0001$.

TABLE 6

COEFFICIENTS OF CORRELATION τ BETWEEN NEUROCHEMICAL AND BEHAVIORAL VARIABLES

	Hippocampus				Frontal Cortex			Striatum				
	ChAT	NA	5-HT	5-HIAA	NA	DA	DOPAC	NA	DA	DOPAC	5-HT	5-HIAA
Nycthemeral Activity												
Locomotion	.10	.08	.20	.13	−.05	−.27*	.18	.22	.20	.12	−.20	.14
Motor activity	−.10	.20	.25	.08	−.17	−.21	.17	.41†	−.06	−.20	.14	−.03
Open Field												
Distance travelled	−.37†	.26*	.15	.07	−.11	.18	.21	.34*	−.30*	−.45‡	.31†	.14
Staircase Test												
Rears (%)	.36†	−.12	.07	−.09	.18	−.21	−.33*	−.27*	.25	.25	−.46‡	−.10
Radial Maze												
Sessions to Criterion	−.09	.02	.06	−.04	−.07	.20	.20	−.02	−.09	−.14	.10	.03
Errors to Criterion	−.11	.02	.04	−.05	−.08	.23	.21	−.04	−.11	−.16	.13	.04
Object Recognition												
1-min retention interval												
t(S)+t(F)+t(N)	.12	−.08	.25	.01	−.13	.10	−.02	.13	.16	.14	.11	.05
t(N)	.16	−.16	.07	.02	−.06	.10	−.02	−.16	.16	.13	−.13	−.14
t(N)−t(F)	.19	−.12	−.16	−.01	−.08	.01	.02	−.23	.04	.09	−.21	−.21
| t(N)-t(F)|	.11	−.05	.06	.11	.08	.02	.02	−.16	.11	.27*	−.15	.0
60-min retention interval												
t(S)+t(F)+t(N)	.23	−.10	.0	.06	.06	−.14	−.14	−.06	.21	.22	.13	.08
t(N)	.34*	.04	−.02	.02	.16	−.19	−.21	−.03	.32*	.35†	.04	.07
t(N)−t(F)	.33*	.02	−.04	.02	.22	−.17	−.29*	−.14	.22	.31*	−.18	.01
| t(N)-t(F)|	.35†	.09	−.07	−.10	.35†	−.13	−.16	.07	.24	.20	.10	−.01
Complex Environment												
Crossings	−.13	.21	−.04	.01	−.16	.15	.10	.16	−.31*	−.40†	.26*	−.03
Retracings (%)	−.26*	.26*	.35*	.10	−.02	.12	.26*	.39†	−.19	−.30*	.34†	−.03

*$p<0.05$; †$p<0.01$; ‡$p<0.001$.

ploratory locomotor activity in a novel environment (distance travelled in the open field and crossings in the complex environment). The significant ($p<0.05$) negative correlations between the index of anxiety (% rearings in the staircase) and exploratory locomotor activity variables suggest that the differential exploratory locomotor activity in a new environment of the Roman strains depends more on a factor such as emotional reactivity to novelty than on a general activity factor per se (i.e., baseline locomotor activity).

Distance travelled in the open field was negatively correlated with objects exploration variables ($p<0.05$). Exploratory locomotion and objects exploration reflects two differents aspects of exploratory behavior: the last variable provides a measure of a stimulus-oriented exploratory behavior, whereas the first one is an index of a more general, mainly locomotor, exploratory behavior. It suggests that rats which had higher exploratory locomotion had less stimulus-oriented exploratory behavior.

Distance travelled in the open field was positively correlated with learning scores in the radial maze (errors and sessions to criterion) ($p<0.05$). In other words, rats with high exploratory locomotor activity have low performance in a spatial working memory task.

The index of anxiety in the staircase test was negatively correlated with exploratory locomotor variables and with retracings in the complex environment ($p<0.05$). "Anxious" rats explored less novel environments and retraced less.

The only significant ($p<0.05$) correlations between performances in the radial maze and performances in the object recognition test were between the number of errors and sessions to criterion, on one hand, and the mnesic index t(N)-t(F) after a 60-min RI, on the other hand. Rats having low performance in the radial maze explored less the novel object in the object recognition test.

Correlation between behavioral and neurochemical variables. Table 6 shows the coefficients of correlation τ between behavioral and neurochemical variables. The main results can be summarized as follows: Hippocampal ChAT activity was negatively correlated with distance travelled in the open field ($p<0.01$), retracings in the complex environment ($p<0.05$). Hippocampal ChAT activity was also positively correlated with the index of anxiety ($p<0.01$) and with t(N), t(N)-t(F) and |t(N)-t(F)| variables of the object recognition test (60-min RI) ($p<0.05$). In other words, rats which had high hippocampal ChAT activity were more "anxious," had less exploratory locomotor activity and retracings, explored more and preferred the novel object.

Hippocampal NA levels were positively correlated with distance travelled in the open field and retracings in the complex environment ($p<0.05$). Rats which had high hippocampal NA levels, had high exploratory locomotor activity and retraced more. Retracings were also positively correlated with hippocampal 5-HT levels ($p<0.05$).

Frontal DOPAC levels were positively correlated with retracings ($p<0.05$), and were negatively correlated with the t(N)-t(F) variable of the object recognition test (60-min RI) ($p<0.05$). Rats which had high frontal DOPAC levels, retraced more and explored less the novel object.

Striatal NA levels were positively correlated with nycthemeral motor activity ($p<0.01$), distance travelled in the open field ($p<0.05$) and retracings ($p<0.01$) and were negatively correlated with rears in the staircase ($p<0.05$). It means that rats

which had high striatal NA levels had high motor and exploratory locomotor activity, retraced more and were less "anxious."

Striatal DA and DOPAC levels were negatively correlated with distance travelled in the open field and crossings in the complex environment and positively with the novel object exploration of the object recognition test (60-min RI) (correlations with DA = $p<0.05$ and with DOPAC = $p<0.01$). Moreover, striatal DOPAC levels were negatively correlated with retracings ($p<0.05$) and positively correlated with the novelty preference index of the object recognition test (60-min RI) ($p<0.05$). In summary, rats which had high striatal DA and DOPAC levels had low exploratory locomotor activity, retraced less but explored more the novel object.

Striatal 5-HT levels were positively correlated with the distance travelled in the open field ($p<0.01$), with crossings ($p<0.05$) and retracings ($p<0.01$) and were negatively correlated with rears in the staircase ($p<0.001$). In other words, rats which had high striatal 5-HT levels had high exploratory locomotor activity, retraced more and were less "anxious."

DISCUSSION

The research reported here had two main purposes: 1) to confirm and extend previous findings of our laboratory showing that the Roman strains differ in working memory tasks; 2) to relate this mnesic characteristic to other behavioral features and to neurochemical data.

1) Our laboratory was the first to report that the Roman strains not only differ from their performances in the two-way shuttle box, but also in a working memory task based on a positive reinforcement: the delayed reinforced alternation (DRA) (27, 28, 55). The present results confirm and extend this finding by showing that the Roman strains also differ in two other working memory tests: the radial maze (RM) and an object recognition (OR) test. In spite of the small size of the RHA strain, results from the present experiments are clear-cut, illustrating the advantage of genetic models: in the RM and OR tests, RLA are superior to RHA as well as in the DRA. These differences between RHA and RLA in the RM and OR tests were confirmed in another study (57). Other data reported here allow to correlate this memory characteristic to other behavioral features. As already shown, but with different tests, RLA have higher scores of emotional reactivity and lower scores of locomotor activity in an open field (14, 15, 30, 48), as well as in a complex environment (28,55). Differences in locomotor activities are not only quantitative but also qualitative: in the complex environment, the percentage of retracings is lower in RLA, as already observed in our laboratory (28,55).

Some correlations confirm the classical descriptions of the rat's behavior: emotional reactivity is negatively correlated with locomotor activity in the open field or in a complex environment (5, 10, 52, 54); moreover, spatial exploration, as measured by scores of locomotor activity is negatively correlated to object, "stimulus" oriented exploration (5, 22, 34, 41, 42, 44, 52).

In the OR, there is no decay of working memory performances when the RI is increased from 1 min to 60 min. This result may be due to an order effect since rats were first submitted to the 1-min RI then to the 60-min RI. In this respect, it should be mentioned that the total time spent in exploring objects was higher at the 60-min RI than at the 1-min RI. Therefore, one possible explanation is that the familiarization with the task leads to an increase of object exploration and, as a result, to an increase of mnesic scores. Whatever it may be, in another study, Ennaceur and Delacour (21) show that in normal rats, there is no decay of mnesic performances when the retention interval is increased to 4 hours. In this respect, it should be noted that in the radial maze, some studies (3,35) show that working memory performances of normal rats are not impaired by delays of 4 hours.

RM and OR have low and scarcely significant intercorrelations; this confirms other data from our laboratory (37) showing that hippocampal or thalamic lesions have different effects on these tests. A possible explanation is that they measure two different forms of working memory: spatial and nonspatial. However, both tasks have consistent and highly significant negative correlations with locomotor activity in the open field: highly active rats tend to have low memory scores. Retracing during exploratory behavior, that is returning to the last visited place, could be considered as reflecting a defect of spatial working memory. In agreement with this hypothesis, we previously found that retracing was negatively correlated with DRA (28,55); however, retracing is not correlated with performances in the spatial working memory test used in the present experiments, the radial maze, in spite of the fact that RLA, superior to RHA in this task, retraced less.

2) Differences in cholinergic systems between the Roman strains have been already shown: concentrations of ACh are higher in the whole brain, brain stem, cerebellum, hypothalamus, cortex, hippocampus and striatum of RLA (8). Our experiments are in agreement with preliminary data (16) showing that ChAT activity in hippocampus is higher in RLA than in RHA. It should be noted that ChAT activity in the whole brain is comparable in both strains (47), as well as the density and affinity of muscarinic receptors in cortex, striatum and hippocampus (46).

Our results confirm that RLA have higher levels of DA and DOPAC in the striatum (18); it is the reverse in the frontal cortex: this is only in partial agreement with data from d'Angio et al. (12) who found that resting levels of DOPAC in that structure are comparable in both strains but increase more under stress in RHA. In contrast to DA, levels of NA in the striatum are lower in RLA.

Significant differences of Roman strains in 5-HT systems have been already reported: RHA have higher levels of 5-HT in the whole brain and cortex, higher levels of 5-HIAA in the mesencephalon and the medulla (1, 17, 25), and a higher 5-HT turnover rate in the hypothalamus, but not in the hippocampus or striatum (13). Our data are mostly negative; the only significant difference is the lower level of 5-HT in the RLA striatum.

Numerous significant correlations between behavioral and neurochemical data were found. Some are difficult to interpret, such as the very significant ($p<0.001$) negative correlation of rearing activity with 5-HT in the striatum or the several neurochemical correlates, positive or negative, of retracings in the complex environment. On the other hand, our data confirm the importance of the striatum and aminergic neurons in motor activities, especially locomotion (4,26): our measures of these behaviors were mostly correlated with aminergic variables in the striatum; however, the distance travelled in the open field was also correlated with ChAT activity and NA levels in hippocampus.

Probably the most informative data, for the less predictible, concern memory. Surprisingly enough there were no significant correlations between radial maze performances and any of the neurochemical measures. This is especially unexpected in the case of ChAT activity in the hippocampus: lesions of the medial septal area, the main source of cholinergic afferents to hippocampus, impair radial maze performances (11, 29, 32, 39) and, in parallel, decrease ChAT activity in the hippocampus (9,40).

Moreover, our data show that RLA have higher levels of hippocampal ChAT activity and are superior in the radial maze. Possible explanations are that performances in the test are more specifically related to more specific markers of the cholinergic activity, such as sodium-dependent high-affinity choline uptake (31, 33, 51), and/or involve noncholinergic factors. In this respect, it should be noted that temporary decrease in hippocampal ChAT activity has no effect on radial maze performances (53) and that lateral septal lesions, which spare cholinergic activity in the hippocampus, produce significant deficits in this test (36).

In contrast, object recognition had several significant correlations with neurochemical measures, especially after a 60-min RI: the index of recognition | t(N)-t(F)| is positively correlated with ChAT activity in the hippocampus and with NA levels in the frontal cortex; the variable t(N)-t(F) which also measures recognition memory through preference of the new object is also positively correlated with hippocampal ChAT activity, as well as with DOPAC level in striatum; it has a negative correlation with DOPAC in frontal cortex.

In conclusion, we would like to stress the two main results reported here: 1) As regards their different performances in active avoidance but also their different working memory performances and their different hippocampal ChAT activity, the Roman strains are not only a genetic model for two-way avoidance conditioning but also for working memory, which may be of a special interest for the experimental study of amnesic syndromes and cognitive decline with ageing. 2) A new working memory test for rats, object recognition, has significant neurochemical correlates in hippocampus, frontal cortex and striatum.

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