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Posttraining Intracranial Self-Stimulation Ameliorates the Detrimental Effects of Parafascicular Thalamic Lesions on Active Avoidance in Young and Aged Rats

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To evaluate whether intracranial self-stimulation (SS) ameliorates conditioning deficits induced by parafascicular nucleus (PF) damage in young and aged rats, the authors gave rats a daily session of 2-way active avoidance until a fixed criterion was achieved. Four experimental groups were established in both young and aged rats: SS treatment after every conditioning session (SS groups), pretraining PF lesions (lesion groups), PF lesions and SS treatment (L + SS groups), and controls. SS treatment not only canceled the detrimental effects of PF lesions, but also improved conditioning in lesioned rats (L + SS groups). This effect was more powerful in aged rats. SS treatment compensated for memory deficits generated by hypofunctionality of arousal systems such as that involving the PF.

Intralaminar thalamic nuclei (ILn) are thought to play an important role in learning and memory, and there are important similarities between the effects of ILn lesions and the pattern of behavioral impairment associated with human amnesia (Mair, Burk, & Porter, 1998). Among ILn, the parafascicular nucleus (PF), located in the posterior region, may constitute a critical thalamic focus for learning. Even though the specific role of PF on learning and memory has not yet been elucidated, it has been shown that lesions of the PF (alone or along with other nuclei) severely disrupt different kinds of conditioning tasks (e.g., several avoidance conditionings, spatial learning in the T or radial maze, place-delayed nonmatching- and matching-to-sample, and object recognition; Burk & Mair, 1998; Guillazo-Blanch et al., 1995; Harrison & Mair, 1996; M'Harzi, Jarrard, Willig, Palacios, & Delacour, 1991; Roberts, 1991; Savage, Sweet, Castillo, & Langlais, 1997; Stokes & Best, 1990; Thompson, 1963, 1981). These results can be interpreted as suggesting that PF could act on some component shared by different learning or memory systems. Because the PF constitutes an important part of the thalamic–cortical arousal system, and memory can be enhanced by posttraining electrical stimulation of the PF (Guillazo-Blanch et al., 1995; Vale-Martínez, Martí-Nicolovius, Guillazo-Blanch, & Morgado-Bernal, 1998), we suggest that PF could act through the generation of an appropriate arousal state during critical periods for information processing.

Intracranial self-stimulation (SS) of the lateral hypothalamus (LH), in the medial forebrain bundle (MFB), facilitates learning and memory processes in a wide variety of paradigms in both young and aged rats (Aldavert-Vera, Segura-Torres, Costa-Miserachs, & Morgado-Bernal, 1996; Aldavert-Vera et al., 1997; Major & White, 1978; Milner, 1991; Redolar-Ripoll, Aldavert-Vera, Soriano-Mas, Segura-Torres, & Morgado-Bernal, 2002; Segura-Torres, Capdevila-Ortís, Martí-Nicolovius, & Morgado-Bernal, 1988; Segura-Torres, Portell-Cortés, & Morgado-Bernal, 1991). Some data support the idea that the LH SS facilitative effect seems to be related to the arousing properties of the MFB reward system. Thus, (a) the rewarding component of the SS does not seem to be necessary to enhance memory (Destrade & Jaffard, 1978); (b) the increase of dopamine resulting from SS in the MFB not only activates the mesolimbic dopaminergic pathways to the accumbens and prefrontal cortex (Shultz, 2000), but also regulates the excitability of basal forebrain cholinergic corticopetal neurons related to different arousal functions (Sarter & Bruno, 2000); (c) LH SS generates cortical and subcortical electrophysiological arousal (Newman & Feldman, 1964) and produces neocortical metabolic activation (Harley, Milway, & Fara-On, 1995); and (d) LH SS increases levels of several excitatory neurotransmitters in some cortical regions (Shankaranarayana Rao, Raju, & Meti, 1998), suggesting that the activatory effects of brain reward systems could affect multiple arousal systems.

Despite the fact that each neurochemical arousal system could play a specific role in brain activation and information processing (Robbins, 1997), some findings indicate that the presence of multiple activating structures may compensate for the loss of certain components (Steriade, 2000). So, it is plausible that the functional lack of one of the arousal systems could be compensated for by the activation of other systems (Kim & Baxter, 2001). Because MFB activation enhances memory and modulates brain arousal, the LH SS could be a way to compensate for memory deficits generated by

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the hypofunctionality of some of the arousal systems, that is, induced by PF damage. In fact, some experiments have shown that it is possible to induce a functional recovery of PF lesion-induced effects after administration of amphetamine (Cardo & Valade, 1965) or ACTH(4–9) analogues (Nyakas, Veldhuis, & De Wied, 1985). Thus, the aim of the present study was to evaluate whether posttraining LH SS can reverse the impairments in two-way active avoidance conditioning that follow PF lesions in both young and aged rats.

Method

Subjects

One hundred forty-two naive male Wistar rats, obtained from our laboratory breeding stock, were used. Sixty-eight of them had a mean age of 91.07 days (SD = 3.16), and the other 74 had a mean age of 507.15 days (SD = 9.55) at the beginning of the experiment. The mean weights at the time of surgery were 441.95 g (SD = 40.82) and 553.81 g (SD = 56.99), respectively.

All the rats were singly housed and kept under conditions of controlled temperature (20–24 °C) and humidity (40–70%), under a 12-hr light–dark cycle (lights on at 0800). Food and water were available ad libitum. The rats were tested during the first half of the light cycle. All the procedures used in this work were performed in compliance with the European Community Council directive for care and use of laboratory animals (European Community Council, 1986) and with the related Directive of the Autonomous Government of Catalonia (DOGC 2073 10/7/1995) and were approved by the ethics committee of the Universitat Autonoma de Barcelona.

Stereotaxic Surgery

Before surgery, both young and aged rats were randomly distributed into the following experimental groups: lesion (rats to receive a bilateral lesion in the PF), SS (rats to receive a SS treatment after each conditioning session), L + SS (rats to receive a PF lesion and SS treatment), and control.

Stereotaxic surgery (Model 1504, David Kopf Instruments, Tujunga, CA) was performed under general anesthesia with intraperitoneal ketamine hydrochloride (Ketolar, 110 mg/kg; Parke-Davis, Alcobendas, Madrid, Spain) and xylazine (Rompun, 8 mg/kg; Bayer, Química Farmacéutica, Barcelona, Spain). Rats in the lesioned groups (lesion and L + SS young and aged groups) were submitted to bilateral electrolytic lesions (using a current of 2 mA for 10 s; Cibertec GL-2) with a bipolar insulated stainless steel electrode (250 μm in diameter) aimed at PF. The incisor bar was set at −2.7 mm below the interaural line, and the following stereotaxic coordinates were used: AP = −4.3 mm from bregma, ML = ±1.2 mm and DV = −6.6 mm, with the cranium surface as dorsal reference (Paxinos & Watson, 1998). Although electrolytic lesions are considered a nonspecific technique, they can be restricted to simple regions with minimal infringement onto neighboring structures (Nader, Majidishad, Amorapanth, & LeDoux, 2001). More specifically, in previous experiments from our laboratory (Guillazo-Blanch et al., 1995; Massanés-Roger, Aldavert-Vera, Segura-Torres, Martí-Nicolovius, & Morgado-Bernal, 1998), electrolytic PF lesions performed with the same current and timing parameters used in the present experiment have been shown to accurately damage the PF region and to preserve the main set of fibers crossing over the PF, the fasciculus retroflexus (fr). Thus, electrolytic lesions could be a useful tool in developing animal models of brain damage (Vale-Martínez et al., 2002). Rats in the SS and L + SS groups were implanted with a monopolar stainless steel electrode (150 μm in diameter) aimed at the LH, into the fibers of the MFB (AP = −2.3 mm from bregma, ML = 1.8 mm right hemisphere, and DV = −8.8 mm, with the cranium surface as dorsal reference and the incisor bar set at −2.7 mm below the interaural line; Paxinos & Watson, 1998). These stimulation electrodes were anchored to the skull with jeweler's screws and dental cement (Vertex self-curing, Dentimex, Zeist, the Netherlands). Finally, rats in control groups received a sham surgery in which neither lesion nor electrode implantation were made. All groups of rats were used for the experiment after a postsurgical recovery period of 13–14 days.

Procedure

Rats in the SS and L + SS groups were taught to self-stimulate by pressing a lever in a conventional Skinner box (25 cm long × 20 cm wide × 25 cm high). Electrical brain stimulation consisted of a 0.3-s train of 50-Hz sinusoidal waves at intensities between 10 and 250 μA. The SS behavior was shaped for each subject to establish the range of current intensities that would support responding on a continuous reinforcement schedule. On 3 consecutive days, rats were trained in SS to establish the individual optimum current intensity of SS (for details see Segura-Torres et al., 1988). The mean of the two current intensities that resulted in the highest response rate in each of the last two sessions was considered the optimum intensity (OI) of SS for each rat.

Three days later, all the rats were submitted to a daily training session (30 trials) of a two-way active avoidance task until they reached a preestablished learning criterion. The learning criterion consisted of performing 25 or more avoidance responses in a single conditioning session. If a rat failed to achieve the criterion, a maximum number of training sessions was established: 10 for the young rats and 15 for the aged rats. We established this demanding criterion (more than 80% of correct responses) because of the high avoidance levels that SS rats can achieve in this paradigm, according to previous experiments performed in our laboratory (Redolar-Ripoll, Aldavert-Vera, Soriano-Mas, Segura-Torres, & Morgado-Bernal, 2002). Active avoidance testing was conducted in a two-way automated shuttle box (50 cm long × 24 cm wide × 25 cm high; Letica LI-916, PANLAB S. A., Barcelona, Spain) enclosed in a sound-attenuating box, which was ventilated by an extractor fan. The conditioning box was illuminated by a fluorescent bulb located on the sound-attenuating box. The two compartment floors (without any physical separation between them) were independently electrifiable and constructed of stainless steel bars (3.9 mm in diameter, 8.8 mm apart) that formed a shock grid. The conditioned stimulus (CS) was a 60-dB, 1-kHz tone of 3 s duration. The grid served to deliver a scrambled footshock unconditioned stimulus (US; 0.5 mA intensity, 15 s duration at maximum) provided by a shock generator. The current supplied by the shocker was a positive semiwave of 100 Hz. The shuttle box was connected to a computer that controlled the training schedule. The trials followed a variable interval schedule of 1 min (± 10 s). Just before each conditioning session, the rats were submitted to one habituation session (10 min) consisting of free ambulation in the shuttle box. Besides the number of avoidance responses (considered as the level of performance of the task), intertrial crossings and crossings during the habituation session (considered as an index of basal locomotor activity level) were also scored. Immediately after each of the conditioning sessions, rats in the SS and L + SS groups were placed in the SS chamber and received an SS treatment session (2,500 trains at the 100% of their OI). To rule out any handling effect, the lesion and control groups were also placed in the SS chamber after each conditioning session for 40 min/day, but without receiving SS treatment.

Histology

At the end of the experiment, histological analyses were performed to verify the location of the SS electrode tip and to quantify the placement and extent of the PF lesions. The rats were killed with an overdose of sodium pentobarbital (150 mg/kg ip) and transcardially perfused with 0.9% (wt/vol) saline. After being fixed with 10% (wt/vol) Formalin (water and formaldehyde 37–40%), the brains were removed and placed in a 30%

(wt/vol) sucrose solution before being cut into 40-μm sections on a freezing stage microtome (Cryocut 1800 with Microtome 2020, JUNG). The tissue sections were stained with Cresyl violet. Lesions were assessed neuroanatomically by examining sections for areas of marked gliosis and neuronal loss. The damaged areas and electrode tip locations were represented by drawing them onto standardized sections of the brain from the atlas of Paxinos and Watson (1998).

Data Analyses

To process the data, the statistical computer package program SPSS 10.0 was used (SPSS, Chicago, IL). The main analyses were performed considering the independent variables as categorical (treatment: four levels, and age: two levels) and the dependent variables as continuous (number of avoidance responses and number of sessions to reach the fixed learning criterion). Thus, one-way analyses of variance (ANOVAs) were performed, followed by their corresponding contrast analyses. In order to compare results in young and aged rats, we performed another analysis considering the eight experimental groups as divided into three categorical factors (lesion, SS treatment, and age). A survival analysis was also done to analyze the cumulative proportion of rats in each conditioning session that did not reach the criterion.

Results

Histology

The histological analyses were done according to a blind strategy; three observers who were not aware of the behavioral data independently examined the brain sections. All SS electrodes were implanted into brain sites corresponding to the LH, between AP −1.40 mm and −2.56 mm AP with reference to bregma. Rats with lesions affecting approximately less than 75% of the PF and/or with damage to adjacent structures were not included in the main analyses ($n = 8$). Figure 1 illustrates the reconstructions of the smallest and largest extent of PF lesions in young and aged rats. Figure 2 shows a photomicrograph of one representative subject in the lesion–aged group. Only 5 rats showed unilateral fr damage in addition to a PF lesion. Because an ANOVA did not detect significant differences in the number of avoidance responses between the lesioned subjects with damage to the fr and lesioned subjects with an intact fr, all 5 of those rats were also included in the experiment.

The final sample consisted of 134 rats. For each age condition, they were distributed into the four groups described in the *Procedure* section: 64 young rats (SS, $n = 15$; L + SS, $n = 17$; lesion, $n = 17$; and control, $n = 15$) and 70 aged rats (SS, $n = 18$; L + SS, $n = 18$; lesion, $n = 14$; and control, $n = 20$).

Two-Way Active Avoidance Conditioning

Young subjects. The present results revealed that PF lesions clearly impaired two-way active avoidance conditioning in young subjects. First, as can be observed in Figure 3A, the lesioned groups (lesion and L + SS) showed a significantly lower number of avoidance responses than the nonlesioned groups (control and SS) on the first conditioning session (when SS treatment had not yet been administered), $F(3, 60) = 4.64$, $p < .04$. Second, the lesion group required a higher number of sessions ($M = 7.47 \pm 2.35$) to reach the learning criterion compared with the control group (5.07 ± 1.67 sessions), $F(1, 60) = 5.76$, $p = .01$ (see Figure 3B). Third, the proportion of subjects that finally were able to reach the criterion in the lesion group (64.7%) was statistically lower than that in control group (93.3%), $\chi^2(1, N = 32) = 3.82$, $p = .05$. Furthermore, these results were confirmed by a survival analysis, which pointed out significant differences between lesion and control groups: Breslow, $\chi^2(1, N = 32) = 9.76$, $p = .01$. As shown in Figure 3C, the control group achieved the learning criterion faster than the lesion group, as shown by the fact that 60% of control rats reached the criterion in a mean of five sessions, whereas the lesioned rats needed nine sessions.

The present results also showed a facilitative effect of SS treatment on the retention of two-way active avoidance conditioning. As observed in Figure 3A, in the second conditioning session (after only one SS treatment session), the SS group performed a significantly higher number of avoidance responses (24.40 ± 5.24) than the control group (16.13 ± 4.52), $F(1, 60) = 16.01$, $p < .01$. Also, the SS group took significantly fewer sessions (2.27 ± 0.59) to reach the learning criterion compared with the control and lesion groups, $F(1, 60) = 37.45$, $p < .01$; $F(1, 60) = 77.79$, $p < .01$, respectively (see Figure 3B). Furthermore, the survival analysis verified that rats in the SS group achieved the learning criterion faster than rats in the control and lesion groups: Breslow, $\chi^2(1, N = 30) = 24.57$, $p < .01$; $\chi^2(1, N = 32) = 31.76$, $p < .01$, respectively (see Figure 3C). In fact, all the subjects in the SS group reached the criterion before the fifth conditioning session (80% rats in the second one, after only one SS treatment session), whereas only 33.3% subjects in the control group did so before this session (none in the second session).

The SS treatment was also capable of facilitating conditioning in lesioned rats. Thus, the L + SS group showed a mean number of avoidance responses in the second conditioning session (20.88 ± 5.21) that was significantly higher than the one observed in the control (16.13 ± 4.52) and lesion (11.18 ± 7.10) groups, $F(1, 60) = 5.61$, $p < .03$; $F(1, 69) = 25.10$, $p < .01$, respectively (see Figure 3A). The L + SS group also needed fewer sessions (3.06 ± 1.09) to reach the criterion than the control (5.07 ± 1.67 sessions) and lesion (7.47 ± 2.35 sessions) groups, $F(1, 60) = 15.76$, $p = .01$; $F(1, 60) = 49.28$, $p < .01$, respectively (see Figure 3B). These results were also verified by survival analyses: L + SS versus control, Breslow, $\chi^2(1, N = 32) = 10.55$, $p < .01$; L + SS versus lesion, Breslow, $\chi^2(1, N = 34) = 23.89$, $p < .01$ (see Figure 3C).

Even though the SS and L + SS groups did not differ in the number of avoidance responses in any conditioning session after the SS treatment was administered, as can be observed in Figures 3B and 3C, the L + SS group needed a higher number of conditioning sessions to achieve the established criterion than the SS group, $F(1, 60) = 6.25$, $p < .02$. The survival analysis verified that acquisition was faster in the SS group than in the L + SS group: Breslow, $\chi^2(1, N = 32) = 6.46$, $p = .01$.

Aged subjects. Lesions in the PF also impaired conditioning in aged subjects. Figure 4A shows that the lesioned groups performed significantly fewer avoidance responses than the nonlesioned groups on the first conditioning session, $F(3, 66) = 17.64$, $p < .01$. The lesion group also required a higher number of sessions (11.71 ± 3.71) to reach the learning criterion compared with the control group (6.55 ± 3.80), $F(1, 66) = 38.02$, $p < .01$ (see Figure 4B). In the same sense, after the complete training (15 sessions), the number of subjects that were able to reach the criterion in the

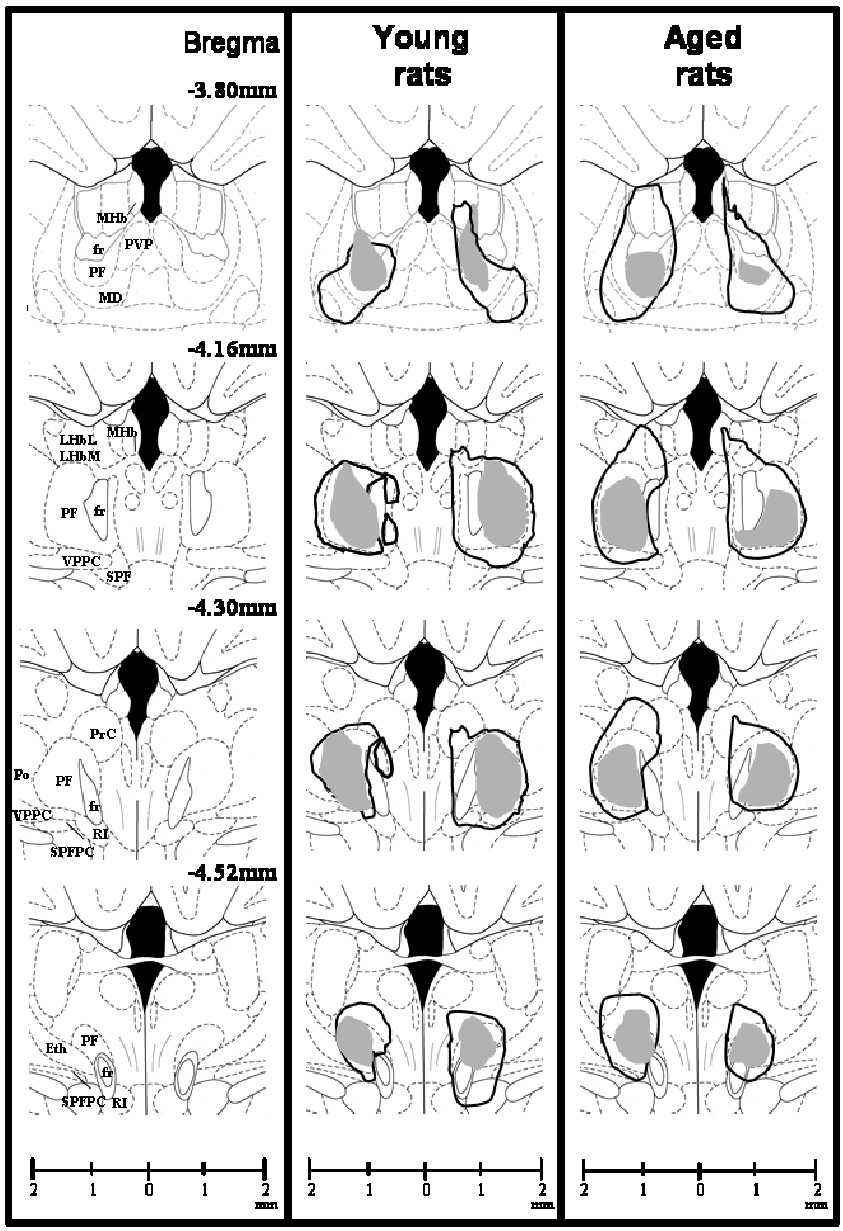

Figure 1. Schematic drawing of the smallest (gray area) and largest (dark line) bilateral parafascicular thalamic nucleus (PF) damage in aged and young lesioned groups, showing the lesion and lesion + self-stimulation goups combined, superimposed on figures modified from Paxinos and Watson's atlas (1998). Reprinted from *The Rat Brain in Stereotaxic Coordinates*, 3rd ed., G. Paxinos and C. Watson, Figures 33–36, Copyright (1997), with permission from Elsevier Science. MHb = Medial habenular nucleus; PVP = paraventricular thalamic nucleus, posterior part; fr = fasciculus retroflexus; MD = mediodorsal thalamic nucleus; LHbL, lateral habenular nucleus, lateral part; LHbM = medial LHb; VPPC = ventral posterior thalamic nucleus, parvicellular part; SPF = sub-PF; PrC = precommissural nucleus; Po = posterior thalamic nuclear group; Eth = ethmoid thalamic nucleus; SPFPC = sub-PF, parvicellular part; RI = rostral interstitial nucleus of medial longitudinal fasciculus.

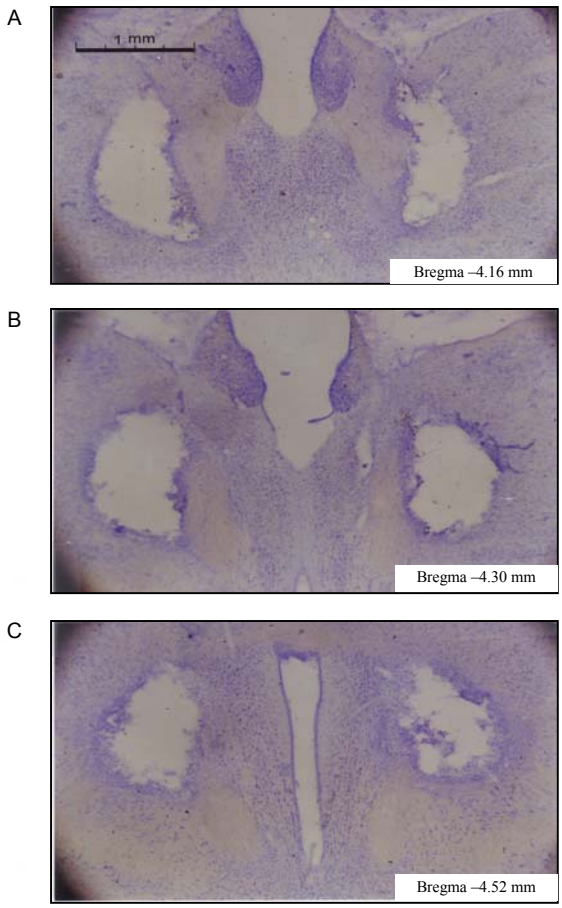

Figure 2. Microphotographs of Cresyl-violet stained brain sections showing the extent of parafascicular thalamic nucleus damage in 1 experimental subject (lesion–aged group) along consecutive anteroposterior coordinates with reference to bregma.

lesion group (61.11%) was statistically lower than the one in the control group (90%), $\chi^2(1, N = 34) = 4.94, p = .02$. Furthermore, these results were confirmed by a survival analysis, which pointed out the existence of significant differences between the lesion and control groups: Breslow, $\chi^2(1, N = 34) = 10.99, p < .01$. As shown in Figure 4C, the control group achieved the learning criterion faster than the lesion group, as shown by the fact that 60% of control rats reached the criterion in a mean of 6 sessions, whereas the lesioned rats needed 13 sessions.

In the present study, SS treatment also facilitated two-way active avoidance conditioning in aged rats. Thus, in the second conditioning session, the SS group performed a significantly higher number of avoidance responses (24.44 ± 3.48) than the control group (10.45 ± 8.12), $F(1, 66) = 16.08, p < .01$ (see Figure 4A). The SS group also required significantly fewer sessions (2.28 ± 0.57) to reach the learning criterion compared with the control (6.55 ± 3.80) and lesion (11.71 ± 3.71) groups, $F(1, 66) = 24.60, p < .01$; $F(1, 66) = 88.92, p < .01$, respectively (see Figure 4B). Furthermore, the survival analysis verified that SS-treated rats achieved the learning criterion faster than control and lesion groups: Breslow, $\chi^2(1, N = 38) = 24.36, p < .01$; $\chi^2(1, N = 32) = 35.25, p < .01$, respectively (see Figure 4C). Thus, all the subjects in the SS group reached the criterion before the fifth conditioning session, whereas only 45% subjects in the control group achieved it.

In lesioned aged rats, SS treatment was also capable of facilitating conditioning. The L + SS group showed a significantly higher number of avoidance responses in the second conditioning session (22.06 ± 3.64) compared with the control (10.45 ± 8.12) and lesion (7.79 ± 3.53) groups, $F(1, 66) = 33.29, p < .01$; $F(1, 66) = 176.89, p < .01$, respectively (see Figure 4A). The L + SS group also needed fewer sessions (3.17 ± 1.34) to reach the criterion than the control and lesion groups, $F(1, 66) = 13.83, p < .01$; $F(1, 66) = 88.92, p < .01$, respectively (see Figure 4B). These results were also verified by survival analyses: L + SS versus control, Breslow, $\chi^2(1, N = 38) = 12.71, p < .01$; L + SS versus lesion, Breslow, $\chi^2(1, N = 32) = 32.41, p < .01$ (see Figure 4C). As we observed in young rats, even though SS and L + SS groups did not differ in the number of avoidance responses in the conditioning session after the SS treatment, the L + SS group needed a higher number of conditioning sessions to achieve the learning criterion than the SS group, $F(1, 66) = 6.25, p = .015$ (see Figure 4B). This result was verified by a survival analysis, showing that all the rats in both groups reached the learning criterion, but SS rats without lesion reached it faster than L + SS aged rats: Breslow, $\chi^2(1, N = 36) = 5.81, p < .02$.

Comparison between young and aged subjects. Variance and survival analyses did not detect significant differences between the performance of young and aged rats in two-way active conditioning under control conditions (the control groups). However, the control–aged rats showed a tendency to acquire conditioning more slowly than young rats: In the sixth session, the proportion of young rats that had already achieved the criterion (93.3%) was significantly higher than the corresponding proportion of aged rats (65%): Breslow, $\chi^2(1, N = 35) = 3.9, p = .05$. Moreover, as can be observed in Figure 5, the control–aged group showed a higher within-group variance than the control–young group: Levene, $df_1 = 1, df_2 = 33; p = .008$. So, even though the control–aged group did not differ from the control–young group, it also did not differ from the lesion–young group. Finally, in a qualitative sense, we can also observe in Figure 5 that there was a considerable subpopulation of control–aged rats that performed as poorly as the lesioned ones, whereas none of the young rats showed such a performance.

Lesions of the PF affected the aged rats more than the young ones. Thus, the lesion–aged group required more conditioning sessions to reach the criterion than the lesion–young group, $F(1, 134) = 13.69, p < .01$. This result was also confirmed with a survival analysis: Breslow, $\chi^2(1, N = 31) = 4.20, p = .04$. The lesion–young group achieved the learning criterion faster (and in a higher proportion of subjects) than the lesion–aged group (see Figures 3C and 4C), as shown by the fact that 50% of young rats reached the criterion in a mean of 7 sessions, whereas aged rats needed 12 sessions.

With reference to the SS treatment, and taking into account the number of sessions to criterion, an ANOVA performed considering three between-groups factors (lesion, SS treatment, and age)

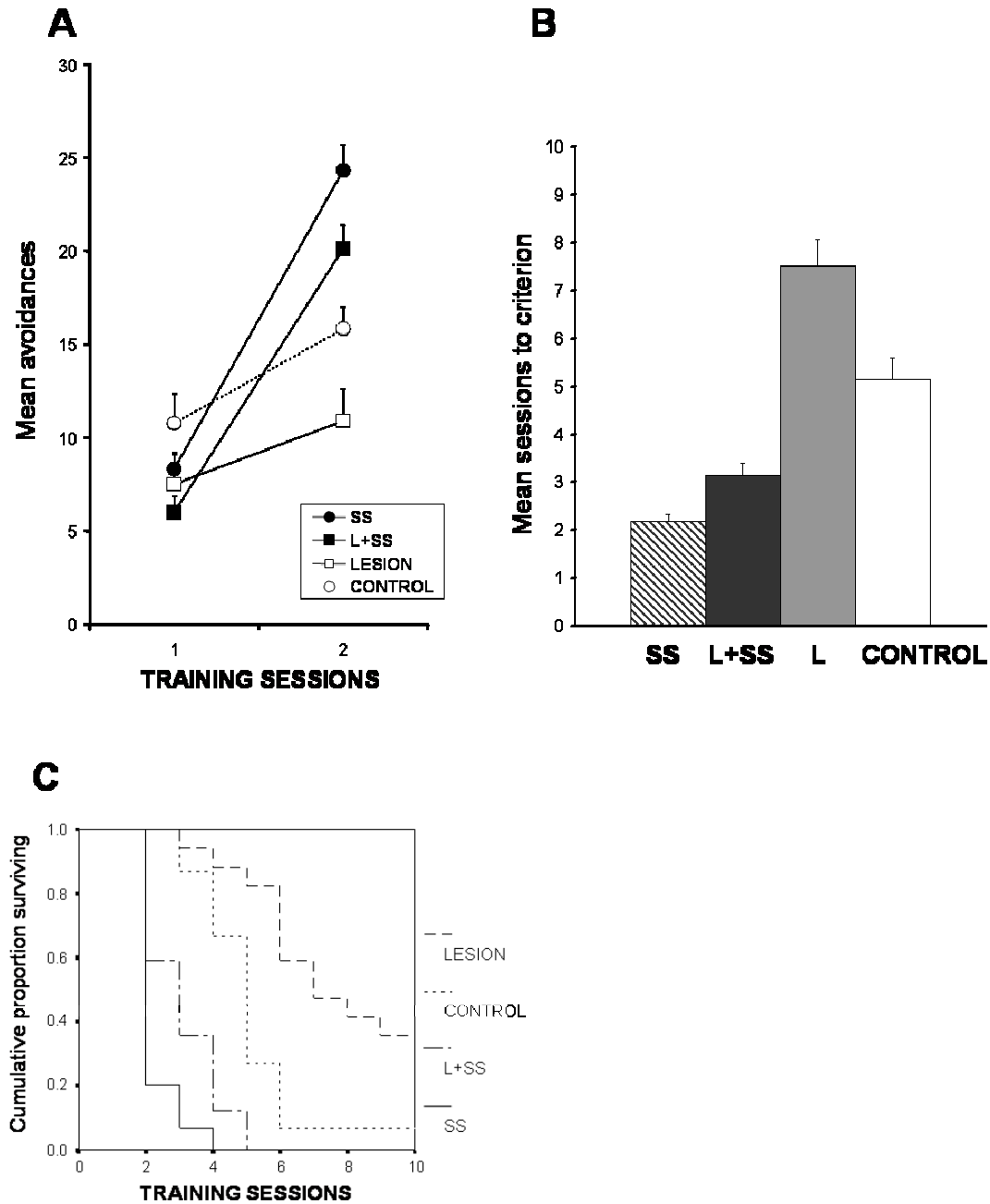

Figure 3. Effects of parafascicular thalamic nucleus lesions (L) and electrical self-stimulation to lateral hypothalamus (SS) treatment on two-way active avoidance conditioning in young rats. A: Mean (±*SEM*) number of avoidances shown by the four experimental groups in the first 2 training sessions. The 7 remaining sessions are not represented because training ended when the rats reached the criterion and, therefore, the number of subjects in each experimental group was progressively decreasing and the corresponding mean did not include the best subjects that had already reached criterion. B: Mean (±*SEM*) number of sessions required by the four experimental groups to reach the learning criterion. C: Survival curve representing the cumulative proportion of subjects that, in each training session, still had not achieved the learning criterion. The percentage of subjects in each experimental group that never (after 10 training sessions) reached criterion can also be observed.

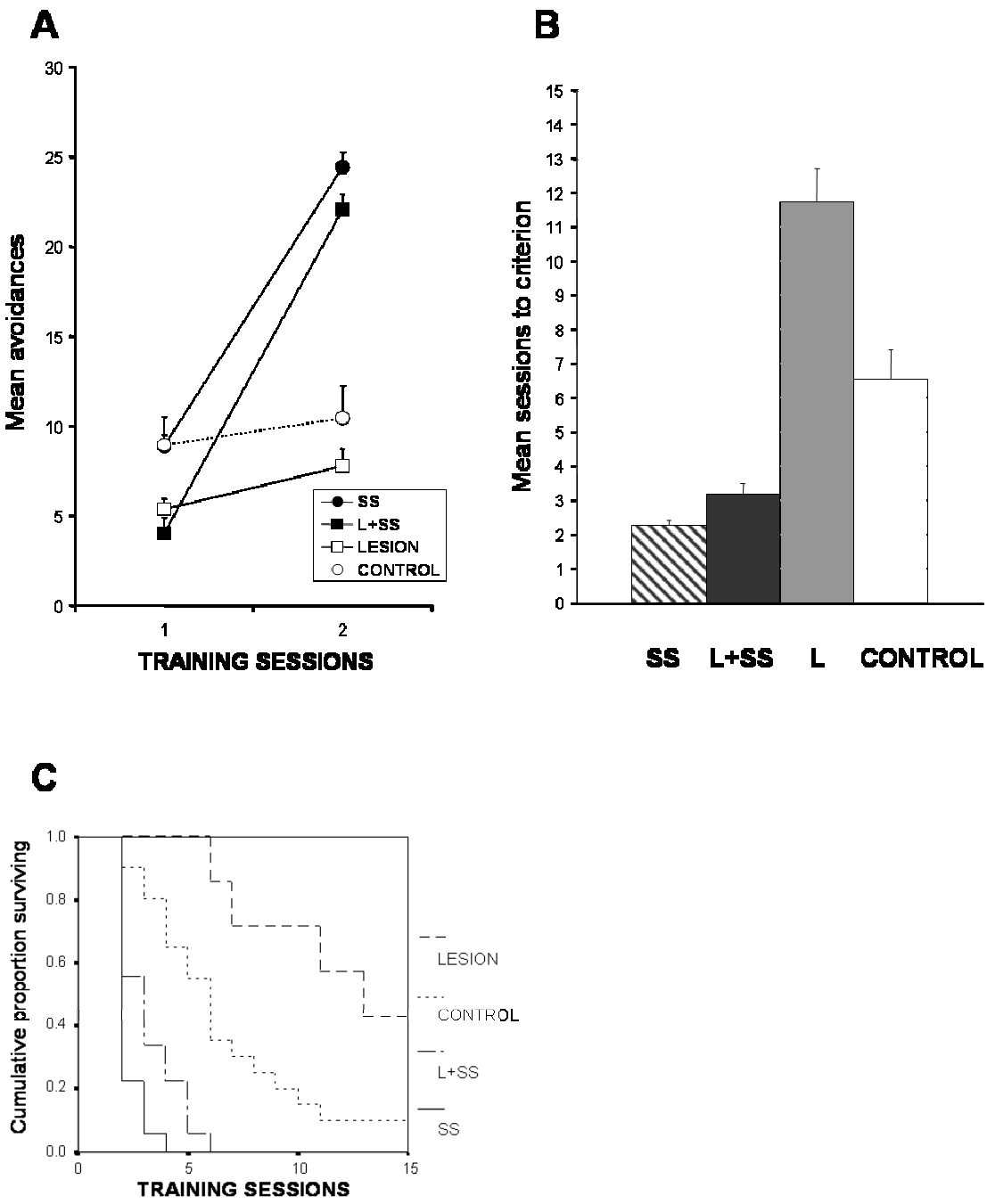

Figure 4. Effects of parafascicular thalamic nucleus lesions (L) and electrical self-stimulation to lateral hypothalamus (SS) treatment on two-way active avoidance conditioning in aged rats. A: Mean (±*SEM*) number of avoidances shown by the four experimental groups in the first 2 training sessions. The 13 remaining sessions are not represented because training ended when the rats reached the criterion and, therefore, the number of subjects in each experimental group was progressively decreasing and the corresponding mean did not include the best subjects that had already reached criterion. B: Mean (±*SEM*) number of sessions required by the four experimental groups to reach the learning criterion. C: Survival curve representing the cumulative proportion of subjects that, in each training session, still had not achieved the learning criterion. The percentage of subjects in each experimental group that never (after 15 training sessions) reached the criterion can also be observed.

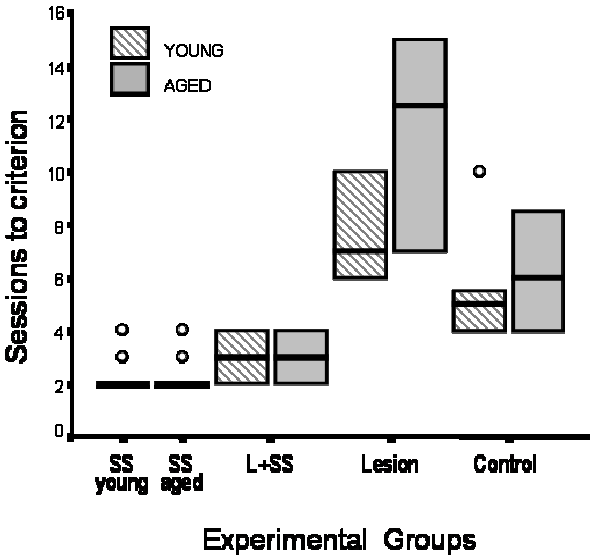

Figure 5. Box-plot of the distribution of the subjects in each experimental group (in both young and aged rats) according to the number of sessions to the learning criterion. The bold horizontal lines indicate the median. The boxes extend to the 25th and 75th percentiles, and the whisker caps indicate the minimum and maximum values of each group included into its normal distribution. Outlier subjects are represented with an open circle. SS = electrical self-stimulation to lateral hypothalamus; L = parafiscicular thalamic nucleus lesion.

showed a statistically significant interaction between age and SS treatment, $F(1, 131) = 10.59$, $p < .01$. That is, the SS treatment was actually more powerful in aged than in young rats, both in lesioned and in nonlesioned rats. However, no differences were observed between young and aged rats in the SS-treated and L + SS groups. Both SS and L + SS groups of aged rats required fewer sessions to reach the learning criterion compared with the control–young group, $F(1, 134) = 7.78$, $p < .01$; $F(1, 134) = 3.64$, $p = .03$, respectively.

Finally, the analyses of response latencies confirmed all the results obtained with avoidance responses in both young and aged subjects. No significant differences were observed between groups in escape latencies.

SS Behavior and Shuttle Box Locomotor Activity

The mean values and standard deviations of SS variables are summarized in Table 1. The lesion of the PF did not affect SS behavior, as no differences were found between SS and L + SS groups in any SS variable (OI, rate, or treatment duration), in both young and aged rats. Aging did not affect the response rate or the treatment duration, but aged rats showed higher OIs than young rats, $F(1, 66) = 13.52$, $p < .01$. Moreover, none of the SS variables correlated with the level of conditioning in any experimental session or with the number of training sessions needed to achieve the learning criterion.

No statistical differences were observed among experimental groups in shuttle box activity levels during the habituation periods or in the number of intertrial crossings made in each conditioning session.

Discussion

Effects of SS Treatment

In the present study, SS treatment clearly facilitated two-way active avoidance conditioning in both young and aged rats, confirming the high power of the posttraining SS at the LH to improve learning and memory in a variety of tasks (Aldavert-Vera et al., 1996, 1997; Coulombe & White, 1980, 1982a, 1982b; Huston & Mueller, 1978; Huston, Mueller, & Mondadori, 1977; Major & White, 1978; Segura-Torres et al., 1988, 1991). How did posttraining SS treatment act on conditioning in the present experiment? Two main effects can be considered. First, SS-treated rats achieved the learning criterion faster than nontreated subjects, supporting the hypothesis that the facilitative effect of posttraining SS lies in an acceleration of memory consolidation processes (Aldavert-Vera et al., 1996; Huston, Mondadori, & Waser, 1974; Landauer, 1969; Major & White, 1978; McGaugh, 2000). Second, the treatment increased the proportion of aged subjects that reach the learning criterion. This result is specially remarkable given that there was a subpopulation of control–aged rats that never reached the learning criterion. Therefore, it can be suggested that SS treatment also seems capable of enhancing memory of the subjects with cognitive impairment caused by aging.

The present results show that SS treatment is even more effective in aged than in young rats. This difference is probably due to the lower conditioning level shown by the nontreated aged rats (specially the lesioned ones), and not to the level of conditioning

Table 1
Mean (± SD) Values of SS Variables

Experimental group	OI (μA)	SS rate (R/min)	Treatment duration
Young rats			
SS	114.60 ± 46.42	168.67 ± 30.39	43.88 ± 3.88
L + SS	130.40 ± 40.62	165.12 ± 21.35	46.58 ± 6.19
Aged rats			
SS	177.70 ± 70.76	151.72 ± 19.56	47.07 ± 11.50
L + SS	168.30 ± 68.10	158.22 ± 26.42	43.74 ± 6.44

Note. Rate of SS (electrical self-stimulation to the lateral hypothalamus) is the maximum achieved 8during the session to establish individual OI (optimum intensity of current). R = repetitions; L = lesion.

achieved by the treated rats. In fact, a ceiling effect can explain the lack of differences between SS–aged and SS–young groups. Both groups reached the learning criterion after only one or two SS treatment sessions, indicating the effectiveness of this treatment. This idea agrees with our previous results showing that the SS treatment was more powerful in rats with low basic conditioning ability (Aldavert-Vera et al., 1996, 1997). Thus, we suggest that posttraining SS could provide learning- and memory-impaired rats with something that unimpaired rats are already endowed with, probably acting through the modulation of one or several brain arousal systems (Destrade & Jaffard, 1978; Massanés-Rotger et al., 1998; Segura-Torres et al., 1991).

Effects of PF Lesions

The deficits found in the acquisition and performance of two-way active avoidance conditioning in bilateral electrolytic PF-lesioned groups agree with the results of previous experiments (Guillazo-Blanch et al., 1995; Massanés-Rotger et al., 1998). Specifically, PF lesions caused both an increase in the number of sessions required by the subjects to reach the established learning criterion, and a decrease in the number of subjects that reached this criterion. The latter effect was specially evident in aged subjects, probably because of an additive effect of the lesion with the aging-related decline shown by some rats. In summary, the present results suggest that PF lesions slow conditioning in such a way that, in some cases, lesioned subjects never reach the criterion. Because we do not know how they would perform with additional training, a more persistent or unrecoverable detrimental lesion effect cannot be ruled out. However, the present results point out that the impairment caused by PF damage can be counteracted by increasing training, suggesting a possible modulatory role of PF on learning and/or memory processes. This idea agrees with the results of other experiments showing that the decrease in performance as a result of brain damage (Yoganarasimha & Meti, 1999) can also be reduced by experience (repetitive testing).

The PF has been related not only to learning and memory, but also to other cognitive processes such as motivation or motor and sensory functions (Burk & Mair, 2001; Dupouy & Zajac, 1997; Vale-Martínez et al., 1998). We suggest that the observed behavioral effects of PF lesions are due to an impairment of learning and memory processes, mainly because (a) posttraining PF lesions also impair the retention of a conditioned response (Thompson, 1963); (b) posttraining PF electrical stimulation improves retention (Guillazo-Blanch et al., 1999; Sos-Hinojosa et al., 2000; Vale-Martínez et al., 1998); (c) in the present experiment, we did not observe any effect of PF lesions on SS behavior, suggesting that such lesions did not affect motivational or motor processes, and (d) PF lesion did not affect the escape response latency, indicating that shock sensitivity also was not affected. However, we cannot reject the possibility suggested by Burk and Mair (2001) that ILn lesions, including PF, could impair motor intention, thus affecting the ability to make a voluntary movement in response to an external stimulus, without producing a general hypokinesia. In any case, PF seems to constitute an important modulatory system that directly or indirectly affects the learning and memory processes.

Effects of SS Treatment in Subjects With Damage to the PF

Surprisingly, the present results show not only that the conditioning deficit induced by PF lesions can be totally reversed by the SS treatment, but also that SS improves conditioning in PF-damaged rats (L + SS groups). These results agree with those of previous experiments showing that the behavioral impairment caused by PF lesions can be reversed by different treatments (see van Rijzingen, Gispen, & Spruijt, 1996), and with reports showing that SS is capable of ameliorating the learning deficits caused by the lesion of other brain structures such as the fornix (Yoganarasimha & Meti, 1999).

Several explanations of the beneficial effects of SS treatment on functional recovery can be considered. One possibility is that SS treatment would accelerate some spontaneous recovery processes of the damaged system (i.e., collateral or axonal sprouting, reactive synaptogenesis), as has been observed with some hormonal treatments (Nyakas et al., 1985). However, the fact that our treatment was administered 2 weeks postlesion and not immediately after, and the large size of the present bilateral lesions, led us to consider that SS does not act on the preserved neurons of the damaged area, and therefore other compensatory mechanisms may be required.

We consider that SS treatment may stimulate, on a short-term basis, other undamaged anatomical systems that may counteract the behavioral deficits induced by the lesion. As a matter of fact, cognitive functions such as learning and memory should be understood as systems with multiple neuroanatomical components that could interact independently, synergistically, or competitively (Kim & Baxter, 2001). Synergistic interactions between memory components would permit compensatory mechanisms when a single structure is lesioned. In the present conditions, both the neuromodulatory systems activated by the LH SS and the thalamo–cortical pathways could be synergistic. Given that SS seems to accelerate memory consolidation and PF lesions seem to slow conditioning, it is possible that the combined effects of both would result in normal performance. In any case, SS treatment seems to have a powerful ability to modulate conditioning, as this treatment was able to improve conditioning even in lesioned rats. The fact that LH SS increases cortical levels of several excitatory neurotransmitters (Shankaranarayana Rao et al., 1998) also supports this hypothesis. SS could functionally compensate for the damage in some PF neurochemical projections, restoring the performance of the rats in tasks such as avoidance, in which those transmitters play an important role. We propose that LH stimulation could improve some cognitive functions, compensating in a synergistic manner for the hypoactivity of the thalamo–cortical system caused by bilateral PF lesions.

The efficacy of this proposed compensatory mechanism could depend on the time elapsed since the lesion was made. In a previous study, we observed that when the SS treatment was administered only 1 week after the lesion, it failed to ameliorate the memory deficits caused by PF lesion (Massanés et al., 1998). This discrepancy with the present results could be explained by the fact that, after brain damage, there are some plastic changes (such as synaptogenesis, increases in the number of postsynaptic receptors, enhanced sensitivity in the projection areas) that start after the injury and reach maximal levels 2 or more weeks later (Cramer & Chopp, 2000; Neve, Koslowski, & Marshall, 1982; Skelton, 1998;

Stroemer, Kent, & Hulsebosch, 1998). Therefore, to compensate for the lack of the arousal induced by the PF and to ameliorate the behavioral deficits, SS could require some postlesion-induced sensitivity in the cortical and/or subcortical projection regions of the lesioned area. That is, the mechanisms underlying the compensatory effects of SS, but not necessarily the facilitative effects, might involve the activation of neural substrates secondarily affected by the PF lesion. Our data suggest that timing of strategies for ameliorating the learning and memory effects of some kinds of brain damage is likely to be critical.

In summary, the present results suggest that posttraining LH SS accelerates memory consolidation in subjects that do not have natural conditioning deficits (neurologically normal young and nonsenile aged rats). It could also enhance memory or reverse memory deficits in subjects showing cognitive impairments, either naturally (aging), artificially (PF lesions), or both. Nevertheless, more experiments are necessary to elucidate the role of PF in learning and memory, the LH SS contribution to such processes, and the possible interaction between both modulatory systems.

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DISCUSIÓN GENERAL Y CONCLUSIONES

REFERENCIAS

ANNEXES

IV. DISCUSIÓN GENERAL Y CONCLUSIONES

Los resultados obtenidos en esta tesis doctoral nos han permitido verificar, una vez más, el potente efecto facilitador de la AEIC post-entrenamiento sobre la retención del condicionamiento de EV2, tanto en ratas jóvenes como en viejas. Además, este trabajo contribuye a avanzar de forma significativa en el conocimiento del efecto modulador de la AEIC sobre la memoria, tanto desde un punto de vista descriptivo como explicativo, proporcionando nuevos datos empíricos en el contexto de nuestra hipótesis general. Según esta hipótesis la AEIC del HL, administrada post-entrenamiento, acelera el proceso de consolidación en curso induciendo un estado de activación generalizado del sistema nervioso central durante el período crítico del procesamiento de la información. Según nuestros resultados, podría hablarse de una interacción entre sistemas moduladores de la memoria, dado que el tratamiento de AEIC es capaz de revertir el deterioro mnésico causado por la lesión bilateral del PF compensando de forma sinérgica la hipoactividad del sistema de arousal tálamo-cortical.

¿Qué estadios de la memoria podrían facilitarse mediante la AEIC?

Partiendo del hecho de que la AEIC del HPM administrada post-entrenamiento parece activar los sistemas de arousal que favorecen de forma generalizada el procesamiento de la información, y considerando que la eficacia del tratamiento depende de su continuidad temporal con el entrenamiento, suponemos que la AEIC puede afectar a varios estadios de la memoria en función de su momento de administración. No obstante, los presentes resultados sugieren que la AEIC facilita la consolidación de la memoria, pero no la recuperación de una información previamente fijada. Considerando que este tratamiento tampoco deterioró la ejecución de los sujetos en la sesión de retención, no podemos pensar que la falta de efectos de la AEIC pre-retención sobre la recuperación se deba a un efecto de dependencia de estado.

Un explicación a esta falta de efecto podría ser que la AEIC tuviera la capacidad de facilitar la recuperación de la información sólo cuando la memoria está activada. De acuerdo con la hipótesis de la reconsolidación de la memoria (veáse, por ejemplo, Kida y col., 2002; Nadel y Land, 2000; Nader y col., 2000a; Sara, 2000a), solamente las memorias reactivadas pueden verse facilitadas por tratamientos que potencian la consolidación de la memoria (Rodríguez y col., 1999). De hecho, existen diversos trabajos que describen una marcada facilitación del recuerdo cuando éste tiene lugar en un estado elevado de arousal, pero sólo si previamente se reactiva la traza de memoria (Dekeyne y col., 1987; Sara, 2000a). En las condiciones de los experimentos que configuran esta tesis doctoral, podría esperarse también que si la

memoria fuera previamente reactivada por un estímulo adecuado, el tratamiento de AEIC pre-retención sería capaz de facilitar el recuerdo. Es por ello que se están llevando a cabo en nuestro laboratorio otros experimentos que intentan analizar los efectos de la AEIC sobre las memorias reactivadas y sobre el proceso subyacente de reconsolidación de la información.

Por otro lado, teniendo en cuenta que la activación cerebral inducida por la AEIC parece persistir durante un período de tiempo prolongado después de la administración del tratamiento, y considerando que cada sesión adicional de entrenamiento implica un proceso de reconsolidación (Sara, 2000a), otra posibilidad sería que el tratamiento de AEIC pre-retención ejerza un efecto anterógrado sobre aquellos procesos de la memoria que están activos después de la sesión de retención facilitando la consolidación (o reconsolidación) de la información, de manera similar a cuando es administrado después del entrenamiento inicial. Si este fuera el caso, se podría esperar que el tratamiento de AEIC no mostrara efectos inmediatos sobre la sesión de retención en curso pero tuviera un efecto sobre la retención en otras sesiones posteriores, tal como se mostró en un experimento previo de nuestro laboratorio donde el tratamiento de AEIC se administraba inmediatamente antes de cada una de las 5 sesiones de entrenamiento (Segura-Torres y col., 1988).

En definitiva, los resultados mostrados en el primer experimento de esta tesis doctoral nos permiten sugerir que el efecto modulador de la AEIC tiene lugar sobre la consolidación, o incluso sobre la reconsolidación, de la memoria, pero no parece afectar al proceso de recuperación de la traza previamente adquirida.

¿Cómo afecta la AEIC post-entrenamiento a la consolidación de la memoria?

Algunos trabajos previos de nuestro laboratorio han sugerido que la AEIC acelera el proceso natural de consolidación de la memoria, permitiendo a los sujetos tratados alcanzar mucho antes que los sujetos controles niveles asintóticos de ejecución en el aprendizaje. Los resultados de esta tesis han puesto de manifiesto que las ratas tratadas con AEIC tardan un número muy inferior de ensayos (primer experimento) o de sesiones (segundo experimento) de condicionamiento en alcanzar un criterio de aprendizaje previamente establecido, en comparación con los sujetos controles. Estos resultados no sólo corroboran el efecto acelerador de la AEIC sobre la consolidación, sino que además han demostrado que la AEIC es también capaz de potenciar la memoria en sujetos con bajo nivel de entrenamiento inicial y en sujetos con deterioro cognitivo asociado a la edad y/o a lesiones cerebrales. De esta forma, en el primer experimento de esta tesis los sujetos tratados con AEIC en la condición de 30 ensayos mostraron un nivel de ejecución durante toda la sesión de retención superior al mostrado por los sujetos controles, mientras que en la condición de 50 ensayos los sujetos controles, a pesar de haber mostrado una respuesta global de aprendizaje muy inferior, igualaron el nivel mostrado por los tratados con AEIC, en los últimos ensayos de dicha sesión. Estos datos confirman que el tratamiento de AEIC es más efectivo en los sujetos con un

bajo nivel de entrenamiento inicial. Además, los sujetos de la condición de 30 ensayos tratados con AEIC mostraron un nivel de retención superior a los sujetos no tratados de la condición de 50 ensayos, sugiriendo que el tratamiento de AEIC post-entrenamiento tiene un efecto más potente sobre la consolidación de la memoria que la adición de entrenamiento. Es decir, a pesar de que la AEIC parece actuar en el mismo sentido que la repetición de la experiencia, probablemente reproduciendo de forma artificial los cambios neurobiológicos que suceden como consecuencia del propio entrenamiento (Coulombe y White, 1980), sus efectos son mucho más potentes.

También a favor de un efecto potenciador, los resultados del segundo experimento han puesto de manifiesto que el tratamiento de AEIC es capaz de incrementar la proporción de ratas viejas que alcanzan el criterio de aprendizaje. Este resultado es especialmente remarcable teniendo en cuenta la existencia de una sub-población de ratas viejas controles que durante todo el procedimiento experimental nunca alcanzaron dicho criterio. De esta forma, el tratamiento de AEIC parece también potenciar la memoria de los sujetos con deterioro cognitivo asociado al envejecimiento.

Considerando que la AEIC es capaz de facilitar una amplia variedad de tareas de aprendizaje (veáse planteamiento), es probable que este tratamiento más que actuar modulando aspectos particulares de un tipo de tarea, lo haga de un modo más general, por ejemplo incrementando la activación del sistema nervioso durante el período crítico del procesamiento de la información. Esta hipótesis está refrendada por diferentes estudios que demuestran la activación de amplias regiones tanto corticales como subcorticales durante el tratamiento de AEIC (Ackermann y col., 2001; Arvanitogiannis y col., 1996a; 1997; Flores y col., 1997; Harley y col., 1995; Hunt y McGregor, 1998; Nakahara y col., 2001; Newman y Feldman, 1964). Por tanto, la AEIC podría acelerar la consolidación de la memoria en condiciones normales y tener efectos potenciadores en condiciones deficitarias, facilitando los mecanismos fisiológicos naturales subyacentes al propio proceso de consolidación a través de la activación de uno o varios de los sistemas de arousal cerebrales.

Efectos del tratamiento de AEIC en sujetos con lesión del PF

Los resultados del segundo experimento de esta tesis doctoral han mostrado que la lesión bilateral del PF genera un déficit importante tanto en la adquisición como en la ejecución del condicionamiento de EV2, concordando con evidencias previas de nuestro laboratorio (Guillazo-Blanch y col., 1995; Massanés-Rotger y col., 1998). Además, este déficit se ha mostrado de forma más evidente en los sujetos viejos, debido, probablemente, a un efecto aditivo de los efectos de la lesión y el deterioro mnésico asociado al envejecimiento. Tal como comentamos en el planteamiento, el PF parece constituir un sistema modulador importante, de afectación directa o indirecta, de los procesos de aprendizaje y memoria. Dado que este núcleo constituye un componente principal del sistema de activación tálamo-cortical, y puesto que su lesión afecta a un amplio conjunto de tareas de aprendizaje y memoria, sugerimos que el PF podría ejercer

estos efectos moduladores contribuyendo a generar los niveles de arousal apropiados para analizar y procesar la información.

En cualquier caso, el efecto más sorprendente que deriva del presente trabajo es que el tratamiento de AEIC post-entrenamiento no sólo revierte totalmente el deterioro mnésico inducido por la lesión del PF, sino que incluso potencia la capacidad de memoria en los sujetos lesionados. Es cierto que cabría la posibilidad de que la AEIC pudiera acelerar algún proceso de recuperación espontánea de la estructura lesionada, reactivando, por ejemplo, la sinaptogénesis y/o el brote de colaterales axónicos, tal como se observa con algunos tratamientos hormonales (Nyakas, 1985). No obstante, es posible desechar esta posibilidad teniendo en cuenta que el tratamiento de AEIC se administró 2 semanas después de la lesión y que las lesiones fueron bilaterales y de una gran extensión (>75% del núcleo). Partiendo del hecho de que diferentes componentes de los sistemas de memoria podrían interactuar independiente, sinérgica y/o competitivamente (Kim y Baxter, 2001), es lógico plantearse la posibilidad de interacciones de tipo activo y concertado entre éstos, de tal modo que cuando uno resulte anatómica o fisiológicamente debilitado pudiera ser compensado funcionalmente por la activación de otro. De este modo, el tratamiento de AEIC podría estimular otros sistemas anatómicos funcionalmente intactos que contrarrestarían el déficit mnésico inducido por la lesión del PF. Además, teniendo en cuenta que la AEIC del HL incrementa los niveles corticales de diversos neurotransmisores excitatorios (Shankaranarayana Rao y col., 1998c), este tratamiento podría compensar funcionalmente la lesión de algunas de las proyecciones neuroquímicas del PF, restaurando, e incluso potenciando, la ejecución de los animales en tareas como la evitación activa, en las cuales estos neurotransmisores desempeñan un papel importante.

En definitiva, la AEIC del HL podría ser un procedimiento útil para recuperar funciones cognitivas compensando de una forma sinérgica la hipoactividad de algún sistema de arousal, como por ejemplo la causada por la lesión bilateral del PF. De este modo, se abre una perspectiva de estudio muy esperanzadora sobre la posible recuperación funcional mediante el tratamiento de AEIC de capacidades mnésicas, o incluso atencionales, mermadas como consecuencia de daños cerebrales específicos o de procesos más globales de senilidad y deterioro cognitivo.

PRINCIPALES RESULTADOS Y CONCLUSIONES:

La tesis doctoral presente supone una continuidad en la línea de investigación de nuestro laboratorio *Potenciación y Recuperación de la Memoria en ratas normales y con daño cerebral.* Los resultados obtenidos confirman el poderoso efecto facilitativo de la autoestimulación eléctrica intracraneal (AEIC) sobre el aprendizaje y la memoria y amplían de manera muy relevante el conocimiento previamente establecido. Los principales resultados y conclusiones de los experimentos que integran la presente tesis son los siguientes:

La AEIC del HL, administrada post-entrenamiento, facilita la retención a las 24 horas del condicionamiento de EV2 (Evitación activa de dos sentidos), pero no muestra facilitación del recuerdo cuando es administrada inmediatamente antes de la sesión de retención. Estos resultados indican que el tratamiento de AEIC facilita específicamente el proceso de consolidación de la memoria.

El tratamiento de AEIC post-entrenamiento fue más efectivo que la repetición de la experiencia (adición de 20 ensayos de entrenamiento) para facilitar la memoria.

Las ratas con lesiones en el PF (núcleo parafascicular del tálamo) necesitan más sesiones de condicionamiento que las normales (control) para alcanzar un determinado criterio de aprendizaje.

El tratamiento de AEIC post-entrenamiento no sólo anuló el efecto disruptor sobre el aprendizaje y la memoria de las lesiones del PF, sino que incluso mejoró el condicionamiento en las ratas lesionadas, jóvenes o viejas.

En contraste con los animales lesionados, muchos de los cuales no alcanzaron el criterio de aprendizaje, todos los sujetos lesionados que recibieron el tratamiento de AEIC post-entrenamiento alcanzaron el criterio. Este efecto facilitativo fue más poderoso en las ratas viejas.

Todos estos resultados apoyan nuestra hipótesis de que la AEIC es capaz de acelerar el proceso de consolidación de la memoria activando sistemas neurales de arousal. Permiten además sugerir que esa facilitación puede beneficiar especialmente a los sujetos con poco entrenamiento inicial o con baja capacidad de aprendizaje debida a factores genéticos, a envejecimiento o a lesiones cerebrales. La AEIC podría activar, o sobreactivar, sistemas neurales de arousal capaces de compensar funcionalmente el déficit en el aprendizaje y/o la memoria debido a causas naturales o patológicas.

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