

Effects of Postnatal Cocaine Exposure and Environmental Enrichment on Rat Behavior in a Forced Swim Test

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ABSTRACT: This study examined the effects of environmental enrichment on rats exposed to cocaine during the first month of life, in several categories of behavior observed in a forced swim test. Wistar rats were divided in four groups. The first included pups that were subjected to injections of cocaine hydrochloride (15 mg/kg body weight/day, subcutaneously, in two daily doses, from postnatal days 1 to 27) and reared in an enriched environment (CocEE); the second, pups that were subjected to injections of cocaine (as previously described) and reared in a standard environment (CocSE); the third, pups that were subjected to saline injections and reared in an enriched environment (SalEE); the fourth, pups that were subjected to saline injections and reared in a standard environment (SalSE). On postnatal days 26 and 27, rats were tested in a swimming pool in two 5-min sessions. The categories of behavior studied in this work were: fast swim, slow swim, struggling, diving, and immobility. Results showed that postnatal cocaine exposure decreased the time spent on fast swim during the two sessions and increased the immobility behavior during the second session in CocSE pups compared with SalSE pups. SalEE pups increased the time spent in fast swim, slow swim, and diving, and decreased the time spent in struggling and immobility during the two sessions compared with SalSE pups. CocEE animals spent more time in fast swim and struggling and less the time in immobility compared with CocSE pups. The present results suggest that postnatal cocaine exposure affects the ability of these animals to cope with stressful situations, and that environmental enrichment seems to enable the rats to adopt a more active strategy, one that allows them to better cope with this particular stress situation.

KEYWORDS: behavior; cocaine; forced swim test; postnatal; rat; environmental enrichment

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INTRODUCTION

The study of behavioral outcomes of cocaine exposure in humans and animals provided evidence that cocaine can affect emotional behaviors.¹⁻⁵ In the rat, cocaine administration was related with the appearance of anxiety-like behaviors,^{1,6} exaggerated defensive and escape behaviors,¹ immobility,¹ hyperresponsiveness to stimuli,⁷ and fear-like behaviors.² These behaviors, moreover, have been described as characterizing depressive states.⁸

The forced swim test (FST)⁹⁻¹¹ is one of the most widely used experimental tests for studying stress or emotionality in animals.^{5,7,12} The FST, an inescapable stressor trial, activates the hypothalamus-pituitary-adrenal axis and has an anxiogenic effect on behavior.¹³ The test includes an assessment of the immobility response, which is indicative of an animal's resignation to an inescapable stressful situation, and which has been interpreted as a sign of a depression-like state or a state of despair.^{10,14} A more complete characterization of behaviors displayed in the FST was made by examining distinctive active behaviors (swimming, climbing/struggling, diving).¹⁵⁻¹⁸ These active behaviors were interpreted either as panic-like reactions, resulting from the fear and anxiety provoked by a stressful situation,¹⁹ or as an active strategy adopted to cope with an adverse situation.^{15,18}

To our knowledge, there are no previous reports on the effects of cocaine exposure on FST during early postnatal ages; there are, however, a few studies using the FST to evaluate the effects of prenatal cocaine exposure. Prenatal cocaine exposure was shown to alter the performance of rats in FST.^{5,7,12} Some studies showed that prenatal cocaine exposure decreased the time spent by offspring in immobility when facing a specific stressful situation, such as forced swim.⁷ In contrast, other reports demonstrated that rats prenatally exposed to cocaine were more immobile in the same stress situation.²⁰

There is evidence that environment enrichment is a factor that influences the development of the organism.²¹⁻²⁶ In rats, the stimulation provided via an enriched environment (EE), applied early in life, was found to be beneficial for behavior development.^{20,26} Environments that supply a great variety of incentives provide a learning space to the animal, with more possibilities of interaction, manipulation, and exploration of the environment. The exploration presupposes the occurrence of learning, and it is probable that the behavioral sequences used in the exploration will undergo changes through the experience. In fact, there is some evidence that supports the idea that animals reared in a rich environment process the information in a different way from the animals that stayed in a poor environment.²⁷ Animals reared in an EE have shown a greater capacity in executing certain tasks and in the resolution of certain problems (see the review by Renner and Rosenzweig²⁰). The EE attenuated or modified some specific deleterious effects of prenatal exposure to alcohol.²⁵ Other works demonstrated that old mice that had the opportunity of living in an EE displayed a greater capacity for resolution of problems than mice maintained in poor environments.¹¹

Studying the influence of an EE in precocious phases of the life cycle of the organism can be very important because during the early periods of development the organism is in maturation, and it is more susceptible to being modified.²⁸ In the rat, the development of the central nervous system during the first month of postnatal life is a period roughly equivalent to the third trimester of human pregnancy.²⁹ There-

fore, it is important to clarify whether prolonged cocaine exposure during this period may differentiate the behavioral performance of the developing rat in FST, as a way to assess the animal's response to a stress situation, and as a way to determine whether an EE can in some way alter the behavioral changes induced by cocaine.

The present study aimed to test whether the postnatal environmental condition (an enriched environment as opposed to a standard environment) affected the expression and the persistence of behavioral alterations in rats exposed to cocaine during the first month of postnatal life.

METHODS

Animals, Housing, and Drug Procedure

The present study was conducted in rat offspring born from nulliparous females of the Wistar strain, purchased from the Colony of the Gulbenkian Institute of Science, Oeiras, Portugal, and bred at the Institute for Molecular and Cellular Biology, Porto, Portugal. The animals were maintained in a colony room under standard conditions of temperature ($22 \pm 1^\circ\text{C}$) and humidity (50–70%) on a 12 h/12 h light–dark schedule, with *ad libitum* access to food and water. On the day of birth, four litters were standardized to eight pups (four males and four females). Pups were weaned on postnatal day 21.

Seventy-four Wistar rats, which included pups from 10 different litters, were tested in four groups. The first group included pups that received subcutaneous injections of cocaine hydrochloride (Sigma Chemical, St. Louis, MO) and were reared in an enriched environment (CocEE). Each day, from postnatal days 1 to 27, these animals received a dose of 15 mg/kg body weight/day in 0.9% saline. Each daily dose was divided into two equal parts, given at 8:30 AM and 6:00 PM. The second group included pups that were injected with cocaine, as described above, and reared in a standard environment (CocSE). The third and fourth groups, the control groups, included pups that received injections of 0.9% saline according to the protocol used for cocaine injections. Some saline-injected control animals were reared in an enriched environment EE (SalEE), and others were reared in a standard environment (SalSE).

The environmental enrichment consisted of a large acrylic cage ($100 \times 70 \times 70$ cm) that included wooden bedding and was equipped with various objects, such as cardboard tubes and plastic tubes, ping-pong balls and paper balls, wood objects, ladders, and toys. All procedures were approved by the Portuguese Agency for Animal Welfare (General Board of Veterinary).

Behavioral Test: Forced Swim Test

The present study used a previously described method⁹ with some modifications. The swim tank consisted of an opaque plastic cylinder 54 cm in height and 47 cm in diameter. The tank was filled with water to a height of 45 cm to prevent animals from touching the bottom with their tails. Water temperature was 24°C . The rats were evaluated in the FST on postnatal days 26 and 27. On postnatal day 26, the rat pups were placed individually into the cylinder of water for 5 min. Twenty-four hours lat-

er, the rats were tested for another 5 min. The swimming sessions were videotaped with a camera (SONY DCR-TRV9E) placed 1 m above the cylinder. Data analysis was made with the assistance of Observer 4.0 software (Noldus Information Technology, Wageningen, the Netherlands). Focal sampling was used to score the durability of the following behavioral categories: *fast swim* (animal displays rapid swimming motions and moves around the cylinder); *slow swim* (animal displays slow swimming motions and moves slowly around the cylinder, making slow movements with its head and/or one paw at a time, motions suggesting the rat was searching for an escape); *struggling* (animal makes active and vigorous movements with the forepaws in and out of the water, usually against the walls^{15,17,18,30}); *immobility* (animal floats on the surface and makes only the necessary movements to keep its head above the water¹⁴); *diving* (animal submerges its entire body³⁰).

Statistical Analysis

A multivariate analysis of variance (MANOVA) (variables: treatment, environment, session, and gender) was performed to determine differences among groups. Because no effects of gender were found, data were collapsed across gender and re-analyzed by a three-way analysis of variance (ANOVA) (variables: treatment, envi-

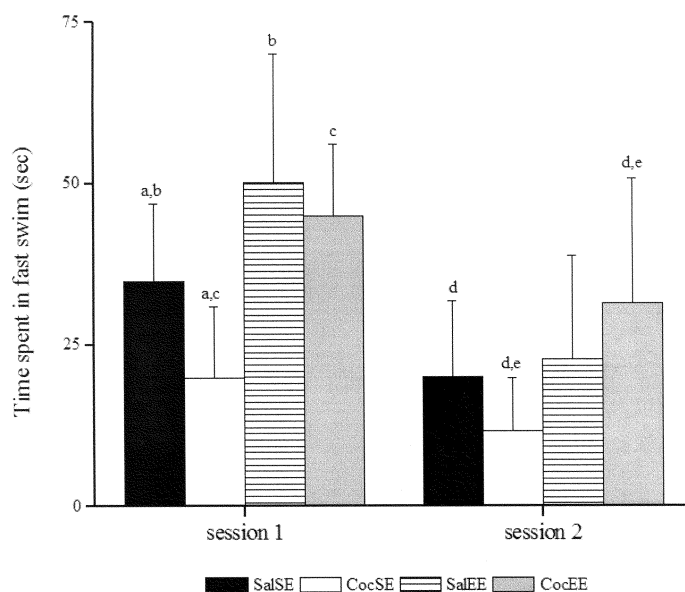


FIGURE 1. Effects of postnatal cocaine and environmental enrichment in fast swim during the FST. Each result represents a mean \pm SD of the time spent in fast swim, in two sessions, expressed in seconds. Columns with the same letter are statistically different (a, c, and e: $P < .001$; b and d: $P < .05$). CocEE: rats subjected to cocaine injections and reared in an enriched environment; CocSE: rats subjected to cocaine injections and reared in a standard environment; SalEE: rats subjected to saline injections and reared in an enriched environment; SalSE: rats subjected to saline injections and reared in a standard environment.

ronment, and session) for each behavioral category. Whenever differences were detected, *t*-test comparisons were performed to assess the significant differences. Results were considered statistically significant at a significance level of $P < .05$.

RESULTS

In the present study, gender had no effect in any of the behavioral categories that were evaluated.

The three-way ANOVA applied to the fast swim data discriminated a significant interaction of postnatal cocaine treatment and environment [$F(1,74) = 6.3, P < .05$]. Postnatal cocaine exposure decreased the time spent on fast swim during the two sessions ($t(24) = -4.47, P < .001$ in the first session; $t(24) = -2.84, P < .05$ in the second) when compared with SalSE rats. The SalEE rats increased the time spent in fast swim ($t(15) = -2.96, P < .05$ in the first session) compared with SalSE rats. CocEE rats spent more time in fast swim ($t(15) = -5.17, P < .001$ in the first session; $t(15) = -4.44, P < .001$ in the second) than CocSE rats (FIG. 1).

The slow swim behavior was affected by the environment paradigm [$F(1,74) = 13.17, P < .001$]. The EE increased the time spent in slow swimming during both ses-

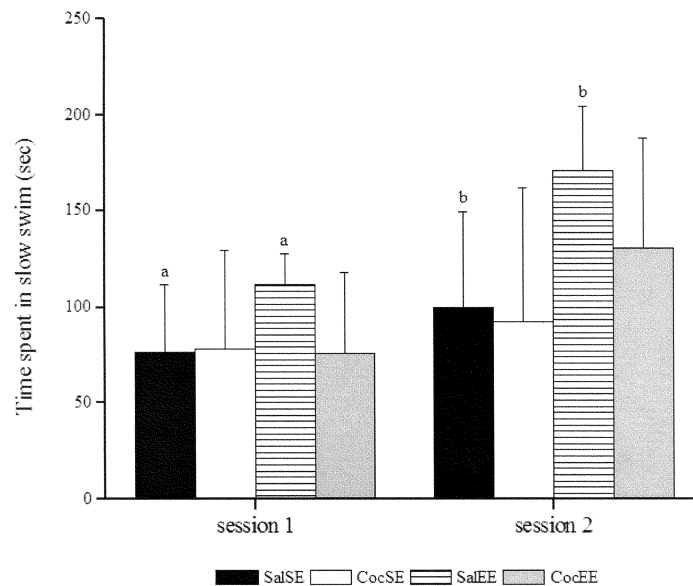


FIGURE 2. Effects of postnatal cocaine and environmental enrichment in slow swim during the FST. Each result represents a mean \pm SD of the time spent in slow swim, in two sessions, expressed in seconds. Columns with the same letter are statistically different (a and b; $P < .001$). CocEE: rats subjected to cocaine injections and reared in an enriched environment; CocSE: rats subjected to cocaine injections and reared in a standard environment; SalEE: rats subjected to saline injections and reared in an enriched environment; SalSE: rats subjected to saline injections and reared in a standard environment.

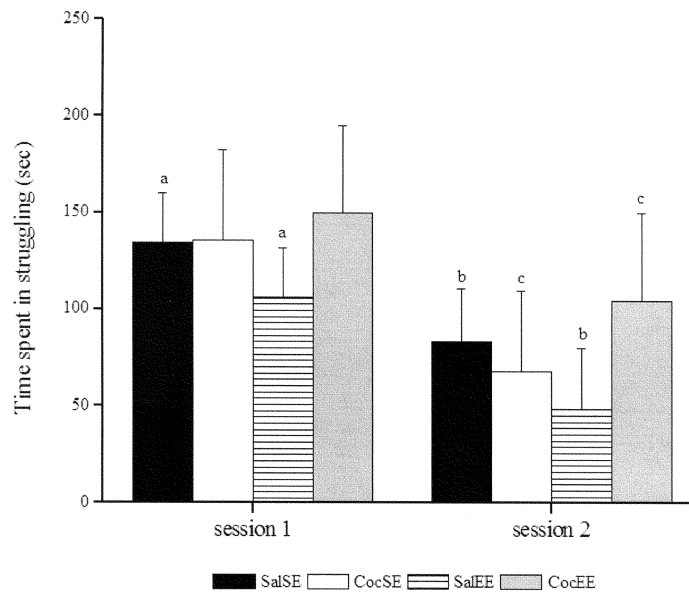


FIGURE 3. Effects of postnatal cocaine and environmental enrichment in struggling during the FST. Each result represents a mean \pm SD of the time spent in struggling, in two sessions, expressed in seconds. Columns with the same letter are statistically different (a and c: $P < .05$; b: $P < .001$). CocEE: rats subjected to cocaine injections and reared in an enriched environment; CocSE: rats subjected to cocaine injections and reared in a standard environment; SalEE: rats subjected to saline injections and reared in an enriched environment; SalSE: rats subjected to saline injections and reared in a standard environment.

sions ($t(15) = -3.64$, $P < .001$ in the first session; $t(15) = -4.44$, $P < .001$ in the second) by SalEE when compared with SalSE rats (FIG. 2).

The analyses of struggling discriminated a significant interaction of postnatal cocaine treatment and environment [$F(1,74) = 14.65$, $P < .001$]. SalEE pups decreased the time spent in struggling during both sessions ($t(15) = 3.36$, $P < .05$ in first session; $t(15) = 3.65$, $P < .001$ in the second) when compared with SalSE pups. However, CocEE rats increased the time spent in this behavior during the second session ($t(15) = -2.57$, $P < .05$) (FIG. 3).

Immobility behavior was significantly altered by the environment paradigm [$F(1,74) = 55.99$, $P < .001$], and there was significant interaction between postnatal cocaine treatment, environment, and session [$F(1,74) = 5.09$, $P < .05$]. CocSE rats spent more time immobile during the second session ($t(24) = 2.05$, $P < .05$) when compared with SalSE rats. In both sessions, EE decreased the time spent immobile in SalEE rats ($t(15) = 2.97$, $P < .05$ in the first session; $t(15) = 3.43$, $P < .05$ in the second) and CocEE rats ($t(15) = -2.97$, $P < .05$ in the first session; $t(15) = 5.14$, $P < .001$ in the second) (FIG. 4).

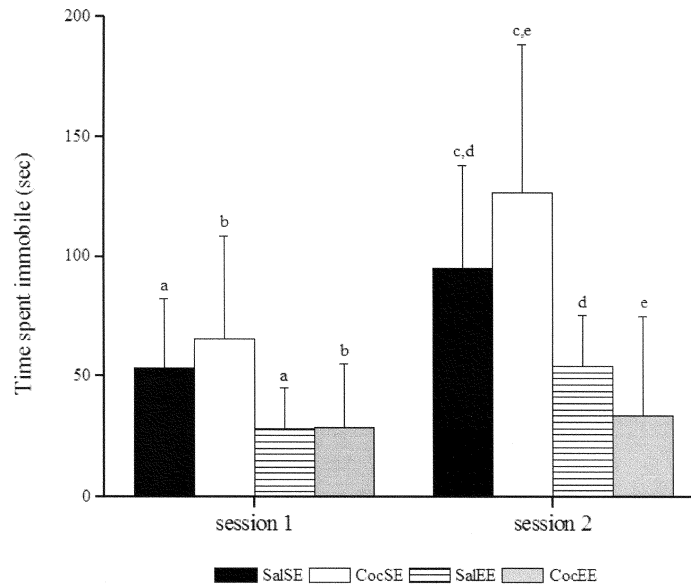


FIGURE 4. Effects of postnatal cocaine and environmental enrichment in immobile behavior during the FST. Each result represents a mean \pm SD of the time spent in immobility, in two sessions, expressed in seconds. Columns with the same letter are statistically different (a, b, c, d, and e: $P < .05$). CocEE: rats subjected to cocaine injections and reared in an enriched environment; CocSE: rats subjected to cocaine injections and reared in a standard environment; SalEE: rats subjected to saline injections and reared in an enriched environment; SalSE: rats subjected to saline injections and reared in a standard environment.

A significant interaction was found between postnatal cocaine treatment and environment in diving [$F(1,74) = 8.64$, $P < .05$]. The SalEE rats spent more time diving than SalSE rats ($t(15) = -2.24$; $P < .05$) (Fig. 5).

DISCUSSION

Postnatal cocaine exposure affected the behavioral response of rats in the FST. Rat pups exposed to cocaine throughout the first weeks of life spent less time on fast swim than did controls, suggesting that postnatal exposure to cocaine decreased the persistence in trying to find an escape. Hypoactivity is one of the indications of depression in animals subjected to an uncontrollable stress situation.⁸ Whether administered saline or cocaine, rats reared in an EE spent more time on fast swim. The present study showed that an EE had beneficial effects in rats postnatally exposed to cocaine, evidenced by increased activity and increased persistence in trying to find an escape. It is established that an EE induces exploratory behavior and diversity of exploratory behavior.²⁰

In the FST, deeper water levels and a larger cylinder allowed the display of a wider range of behaviors.^{15,30} In the present study, we have discriminated one more be-

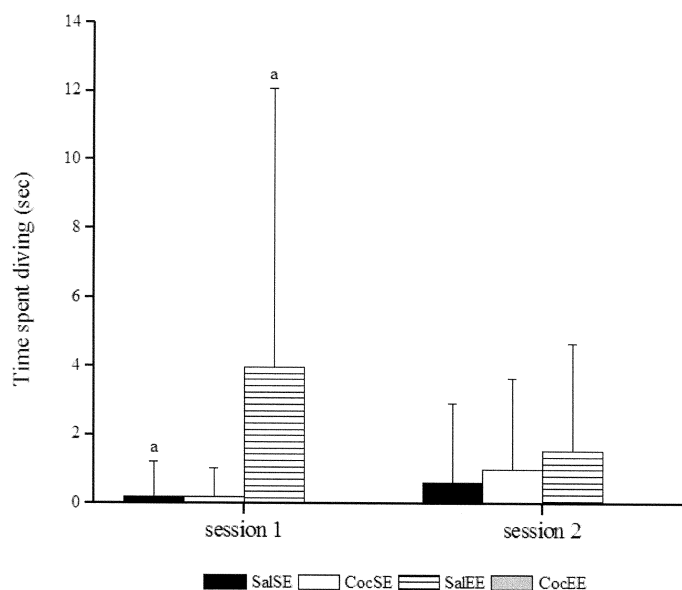


FIGURE 5. Effects of postnatal cocaine and environmental enrichment in diving during the FST. Each result represents a mean \pm SD of the time spent in diving, in two sessions, expressed in seconds. Columns with the same letter are statistically different (a: $P < .05$). CocEE: rats subjected to cocaine injections and reared in an enriched environment; CocSE: rats subjected to cocaine injections and reared in a standard environment; SalEE: rats subjected to saline injections and reared in an enriched environment; SalSE: rats subjected to saline injections and reared in a standard environment.

havioral category, slow swim, because this behavior does not involve vigorous movements like those seen with fast swim, and the slight movements observed could be an attempt to expend less energy. The EE paradigm increased slow swim during both sessions of the FST, and this result may indicate persistence in searching for an escape, with lower energy expenditure. The rat would adopt a less active response without being resigned to the situation. The discrimination of slow swim behavior allowed a more refined evaluation of the response to the FST, and showed that the EE increased the persistence of saline-injected rats in trying to find an escape.

Postnatal cocaine treatment did not affect struggling in rats reared in a standard environment. This result is consistent with previous observations of the effects of prenatal cocaine on rat offspring assessed by the FST.¹² Struggling was shown to be decreased in saline-injected rats that were reared in an EE, and increased during the second sessions in rats exposed to cocaine and reared in an EE. Struggling behavior may be a manifestation of fear and anxiety when animals face stressful situations.³¹ Because cocaine administration to animals and humans may provoke fear and panic-like behaviors,^{2,4} and because struggling has been associated with fear-inducing situations,³¹ it would be expected that rats postnatally exposed to cocaine and reared in a standard environment would struggle more than controls. Also, it would be ex-

pected that struggling would be decreased in rats postnatally exposed to cocaine and reared in an EE. However, this hypothesis was not supported by the present data because the EE failed to decrease the time spent in struggling in rats postnatally exposed to cocaine.

Regarding the display of immobility, a significant increase was observed during the second session in rats postnatally exposed to cocaine. Our results agree with previous reports⁵ that showed that prenatal exposure to cocaine increased immobility in adult offspring. However, other studies have demonstrated that prenatal cocaine exposure decreased the time spent in immobility during the FST.^{7,12} The differences regarding the immobility behavior after prenatal or postnatal cocaine exposure may be related to the period of development in which the drug was administered and/or with the dose of drug administered, as well as with the age of subjects at the moment of FST testing. Another reason for these seemingly contradictory effects of cocaine are the methodological differences in the experiments.

The EE paradigm decreased the time spent in immobility behavior. This result suggests that the EE increased the persistence to find an escape and reduced the animal's resignation in the face of an inescapable, stressful situation. It was hypothesized that the increased immobility behavior in the second session of the FST was observed because the rats were aware that they could not escape. It was suggested that this awareness, which resulted from previous experience, caused a negative motivational state described as behavioral despair.⁹ More recent interpretations have described immobility as a passive strategy.^{15,32}

Rats postnatally exposed to cocaine were more immobile than controls in the FST, and rats reared in an EE were less immobile. Because rats of strains that are considered to be more emotional, such as Wistar-Kyoto, had higher levels of immobility behavior in the FST,^{33,34} it is likely that the animals that spend more time immobile when facing stressful situations are more emotional.

CONCLUSION

Postnatal cocaine exposure affected the ability to cope with stress in the developing rat. The behavioral stimulation provided by an EE improved some aspects of the stress response in rats exposed to cocaine and simultaneously reared in an EE paradigm, by increasing the persistence with which escape was sought and by reducing the level of immobility; however, an EE did not decrease anxiety in rats postnatally exposed to cocaine that faced stressful situations. Nonetheless, the decrease of hypoactivity indicates that an EE may be beneficial in behavioral alterations induced by postnatal cocaine.

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