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Persistent changes in exploration and hyperactivity coexist with cognitive impairment in mice withdrawn from chronic cocaine

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ABSTRACT

Repeated cocaine exposure induces lasting neurobehavioral adaptations such as cognitive decline in animal models. However, persistent changes in spontaneous –unconditioned- motor and exploratory responses are scarcely reported. In this study, mice were administered with cocaine (20 mg/kg/day) or vehicle for 12 consecutive days. After 24 days of drug abstinence, a behavioral assessment was carried out in drug-free conditions and in unfamiliar environments (i.e. no cocaine-associated cues were presented). The cocaine-withdrawn mice showed cognitive deficits in spontaneous alternation behavior and place recognition memory. Importantly, they also displayed hyperlocomotion, increased rearing activity and altered exploratory patterns in different tasks. In the forced swimming test, they were more active (struggled/climbed more) when trying to escape from the water albeit showing normal immobility behavior. In conclusion, in addition to cognitive deficits, chronic cocaine in rodents may induce long-lasting alterations in exploratory activity and psychomotor activation that are triggered even in absence of drug-related stimuli.

1. Introduction

Cocaine is a widely used psychostimulant drug whose dependence-inducing properties may lead to develop a substance use disorder [27]. While acute exposure to cocaine may actually potentiate some cognitive measures [10], chronic cocaine reduces global cognitive functioning, and cognitive deficits are relevant predictors of worse addiction treatment outcome [24]. Considering that researching the impact of cocaine on cognition in clinical populations entails notable methodological caveats, animal models of cocaine-induced neurocognitive impairment provide valuable opportunities for translation [11]. A frequently used paradigm is the 'passive' chronic cocaine administration protocol, where rodents forcibly receive a scheduled daily cocaine dose –usually during 10–14 consecutive days- and they are subsequently tested for behavior after a period of drug abstinence. Albeit its simple methodology, this model has been useful to demonstrate long-lasting neurocognitive impairment and related brain neuroadaptations that persist for several weeks after cocaine abstinence [7, 12, 13, 15–17, 19, 25].

Other significant behavioral consequences of cocaine relate to its psychostimulant properties, which include a heightened alertness, sense of well-being, euphoria, excitement and increases in motor activity [23]. In rodents, the psychomotor activating effects of cocaine are evidenced mainly by an augmented locomotor activity (hyperlocomotion) and have been widely investigated. Cocaine stimulates locomotor activity in a dose-dependent manner [8, 26] and induces lasting neuroadaptations in the mesocorticolimbic circuit responsible for the motor response. This aspect has been extensively studied in both the cocaine sensitization and in the cocaine-induced conditioned locomotion paradigms [4, 5], where an exacerbated motor response is triggered in drug-abstinent rodents either by a cocaine prime –cocaine sensitization- or by a stimulus previously associated with the drug (e.g. re-exposure to the environment where cocaine was previously administered) –cocaine conditioned locomotion-.

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However, it is unclear whether in absence of a cocaine prime or a drug-related stimuli, the spontaneous motor response and/or exploratory patterns in unfamiliar environments could be altered long after cocaine is withdrawn. Studies using the passive chronic cocaine administration paradigm in rodents have generally failed to demonstrate long-term exploratory or motor changes concomitant to cognitive impairment, since the motor/exploratory domain was either not evaluated [7, 16, 17, 19, 25] or found unaltered [12, 13, 15].

This short report describes that mice withdrawn from chronic cocaine for 24 days presented increased motor activity and altered exploratory patterns in unfamiliar testing environments in addition to cognitive deficits. The potential relationship of the motor response with emotional and cognitive variables is discussed.

2. Materials and methods

2.1. Ethical guidelines

Procedures were performed according to the European and Spanish regulations for animal research (Directive 2010/63/UE, Real Decreto 53/20,130 and Ley 32/2007) and received approval from the research ethics committees of the University of Málaga (code: CEUMA 81–2016-A) and Junta de Andalucía (code: 30/03/2017/055).

2.2. Animals

Experiments were performed on sixteen young-adult male C57BL/6 J mice (Janvier Labs; Le Genest-Saint-Isle, France) that were individually housed in standard conditions (temperature: 22 ± 2_C; 12 h light/dark cycle; lights on at 8:00 a.m) with nesting material and ad libitum access to water and food. Administrations started at 13.5 weeks of age.

2.3. Cocaine treatment and experimental conditions

We employed a cocaine administration protocol that reliably induces cognitive impairment in mice [13]. The 'COC' mice ($n = 8$) received a chronic cocaine treatment consisting of a daily intraperitoneal (i.p.) 20 mg/kg dose of cocaine (Alcaliber S.A., Madrid, Spain; diluted in 10 ml/kg volume of saline −0.9% NaCl-) for 12 consecutive days in their home cage; while the 'SAL' mice ($n = 8$) received an equivalent i.p. volume of saline solution. (Fig. 1a). This dose was chosen because it falls within the range of doses (15–30 mg/kg per day) that cause persistent neuroplastic changes in the reward and limbic-related brain regions of rodents after repeated administration [13, 22]. Furthermore, it induces persistent place-conditioned reward [15] and a notable acute locomotor response [3].

2.4. Behavioral assessment

Behavioral testing started 24 days after the last cocaine or saline dose (Fig. 1a); in contrast with the previous study of our group [13] in which mice were evaluated for behavior after 44 days of cocaine abstinence.

Mice were carried to a noise-isolated room at 9:00 a.m. and they were habituated for at least 20 min before starting the assessment. A battery of behavioral tests for exploratory activity, emotional behavior and cognitive performance was performed on the basis of previously published protocols that are detailed elsewhere [13, 15]. Behavioral observations were conducted by a trained experimenter unaware of the mice's treatment.

- Elevated plus maze (Day 36): Mice were placed in the center of the apparatus and allowed to explore for 6 min. Locomotion (cm) and time (s) in each zone of the apparatus –open arms, closed arms, center-, latency to enter an open arm (s) and an anxiety ratio [time in open arms/(time in open arms + time in closed arms)] were calculated.
- Y Maze (Day 37): The mouse was placed in one starting arm and allowed to explore freely for 6 min. Locomotion (cm) and arm entries were analyzed. One spontaneous alternation was defined as three successive entries in different arms [9]. A spontaneous alternation (SAB) score was calculated [(number of spontaneous alternations)/(total the number of arm entries - 2)].
- Open field exploration (Day 38) and place recognition memory (Days 38–39): On Day 38, the mouse was released in a corner of an empty open field and allowed to explore for 5 min (habituation session). One hour later, mice were re-exposed to the open field including two identical copies of an object (sample session) (Fig. 2b). On Day 39, the open field contained two copies of the familiar object, one of them placed in its habitual position but the other displaced to an opposite corner (test session). Sessions were analyzed for 6 min, but the sample session lasted 10 min in order to ensure sufficient object exploration. Locomotion, latency to enter the center and time in zones –center, walls and corners- and time (s) of object exploration (defined as the mouse actively touching an object with its nose or its forepaws; or pointing its nose towards the object at a distance of 0.5 cm or less) were scored. The place memory ratio was calculated in the test session [(time exploring the displaced object−time exploring the static object)/total time exploring both objects]
- Spontaneous behavior: Frequency of rearings (vertical scans supported on the two hindpaws) and risk assessments (stretching its head and forepaws forward, then returning to its initial position) and total time performing grooming (washing itself) and head dipping (peeking into the void –for the elevated plus maze only-) were analyzed in the elevated plus maze, Y maze and open field (habituation) sessions.
- Forced swimming test (Day 40): Mice spent 6 min in a clear cylinder (27 cm high, 10 cm diameter) filled with water (22 ± 1 °C) to a height of 15 cm. Immobility (the mouse floats passively, making only those movements necessary to keep its head above the water), struggling (the mouse is highly active, trying to escape by climbing the cylinder's walls; quick movements of the forelimbs are observed such that the front paws break the surface of the water) and swimming behaviors were scored.

Sessions were recorded and spatio-temporal parameters were analysed with the software Ethovision XT.12. (Noldus, Wageningen, The Netherlands). Observational scorings were carried out by an experimented observer using Ethovision's Manual Score module.

2.5. Statistical analysis

Between-groups comparisons were performed by Student's *t* tests or by analysis of variance (ANOVA) with repeated measures, followed by *post-hoc* Fisher's Least Significant Difference (LSD) analysis only when the F-statistic of the ANOVA was significant. Correlations were Pearson's. Significant comparisons ($p \leq 0.05$) are reported.

3. Results

3.1. Elevated plus maze

Compared to control mice (Fig. 1b-d), the cocaine-withdrawn mice showed increased locomotor activity in the elevated plus maze [$t(14) = 2.904$; $p = 0.012$], which was observed across the whole 6-min session [repeated measures ANOVA ('cocaine x minute'): effect for 'cocaine': $F(1,14) = 8.475$, $p = 0.011$] (Fig. 1c). Hyperlocomotion in the COC mice occurred specifically in the closed arms of the apparatus [repeated measures ANOVA ('cocaine x arm'): 'cocaine': $F(1,14) = 8.432$, $p = 0.012$; 'arm': $F(2,28) = 45.808$, $p = 0.000$; 'cocaine x arm': $F(2,28) = 5.682$, $p = 0.008$] and it was accompanied by increased vertical activity -rearing behavior- in such region ['arm': $F(2,28) = 11.681$, $p = 0.000$; 'cocaine x arm': $F(2,28) = 3717$, $p = 0.037$] (LSD is shown in Fig. 1c). No

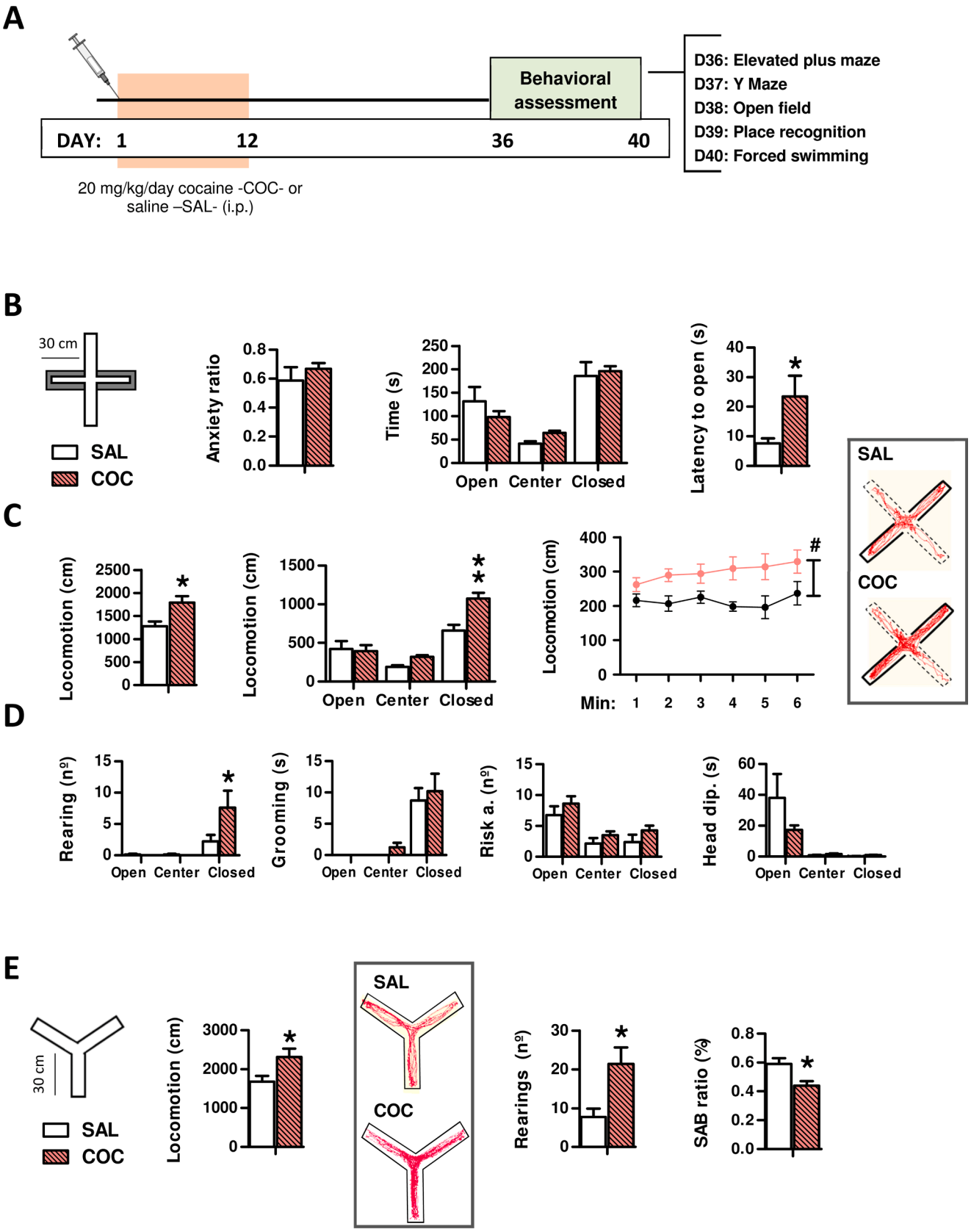

Fig. 1. (A) Experimental protocol. (B, C, D) Performance in the elevated plus maze. (E) Performance in the Y maze. Representative locomotion tracks are shown. The cocaine-withdrawn mice showed hyperlocomotion and increased rearings in both tasks, and they were impaired in the SAB for spatial working memory. ANOVA effect for cocaine: #$p < 0.05$. Difference between groups (Student's *t*-test or post hoc LSD): *$p < 0.05$; **$p < 0.001$. Data are expressed as mean ± SEM. Risk a.: Risk assessment; Head dip.: Head dipping.

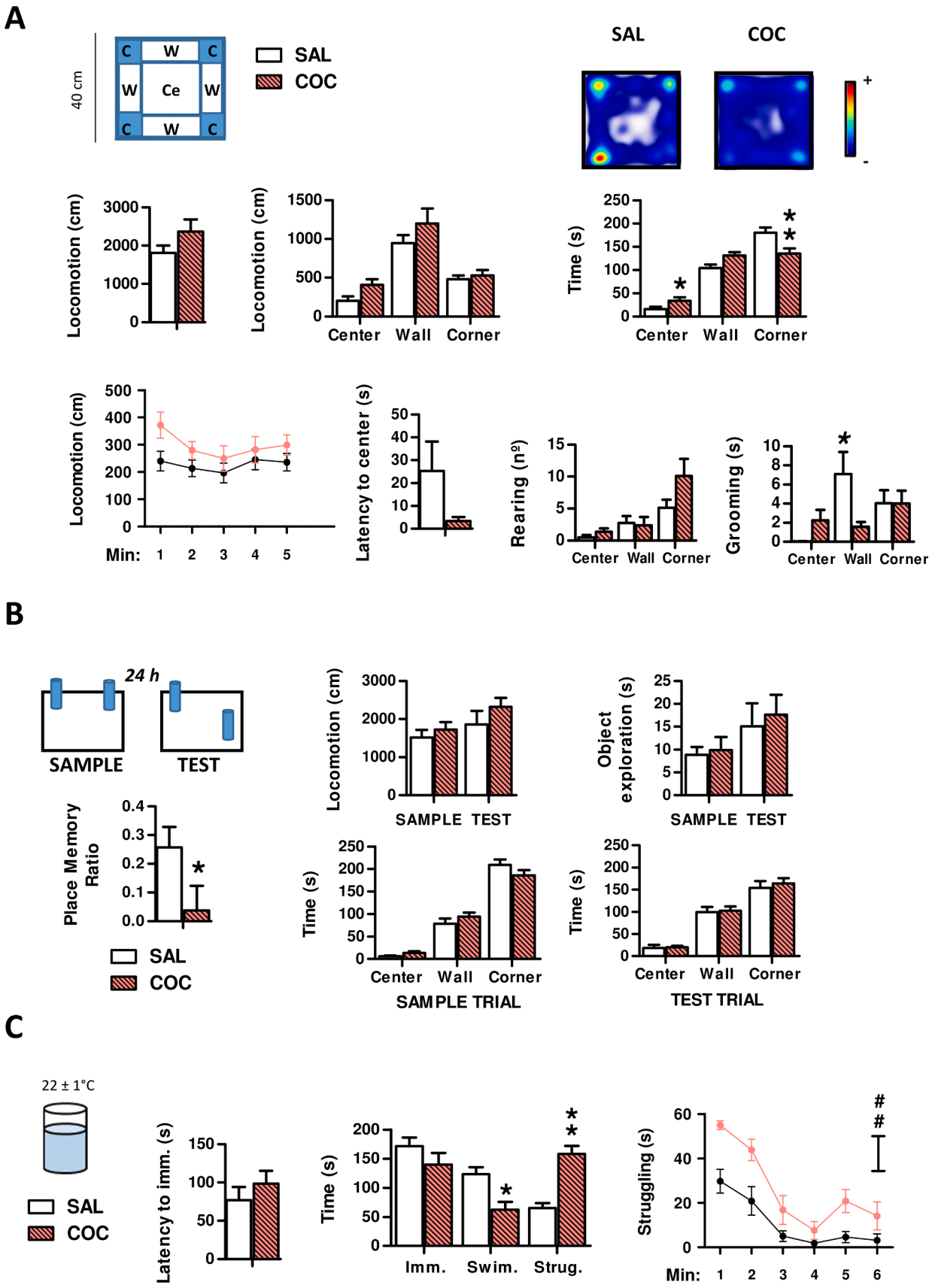

Fig. 2. (A) Cocaine withdraw-mice showed an altered pattern of exploration of a novel open field environment, preferring the unprotected zones. Representative heat-maps are shown. (B) Cocaine impaired place recognition memory in absence of motor or exploratory alterations in the sample and test trials. (C) Increased struggling in the forced swimming test in the COC mice. ANOVA effect for cocaine: $\#\#p < 0.001$. Difference between groups (Student's *t*-test or post hoc LSD): $*p < 0.05$; $**p < 0.001$. Data are expressed as mean ± SEM. C: Corner; W: Wall; Ce: Center; imm.: immobility., swim.: swimming, strug.; struggling.

between-groups differences were found in other exploratory or anxiety-like measures, with exception of an increased latency to enter the open arm in the COC group [$t(14) = 2.192$; $p = 0.046$] (Fig. 1d).

3.2. SAB in the Y maze

The COC mice were impaired in spatial working memory -SAB ratio- [$t(14) = -3.229$; $p = 0.006$] and augmented both locomotor activity [$t(14) = 2.387$; $p = 0.032$] and rearings [$t(14) = 2.684$; $p = 0.018$] in the Y maze (Fig. 1e). Noteworthy, the SAB ratio was negatively correlated with locomotion in the whole sample of mice ($r = -0.595$, $p = 0.015$). The comparison of the number of arm entries, grooming and risk assessment did not result statistically significant (data not shown).

3.3. Open field habituation

In the open field exploration session, the COC mice showed a tendency to increase exploratory activity -locomotion and rearings- and to enter the center zone faster than the SAL animals (Fig. 2a); but statistical signification was not reached for these measures in this task. Nevertheless, the COC mice expend more time in the center zone of the apparatus but less time protected by the corners [repeated measures ANOVA ('cocaine x zone'): 'zone': $F(2,28) = 81.474$, $p = 0.000$; 'cocaine x zone': $F(2,28) = 6.750$, $p = 0.004$], and they reduced grooming behavior compared to the SAL mice ['zone': $F(2,28) = 3.555$, $p = 0.042$; 'cocaine x zone': $F(2,28) = 4.490$, $p = 0.020$] (LSD is shown in Fig. 2a). Risk assessment behavior was practically non-existent during this task.

3.4. Place recognition memory

The COC mice were impaired in discriminating the displaced object from the static one [$t(14) = -2.148$; $p = 0.049$]. Importantly, both groups were similar in locomotion, zone exploration pattern and total time of object exploration across the sample and test trials (Fig. 2b), so they only differed in their cognitive performance.

3.5. Forced swimming test

The COC and SAL mice did not differ in immobility-related measures, an indicator of despair-like behavior. However, the COC mice struggled more to escape from the water [$t(14) = 5.667$, $p = 0.000$] during the whole session [repeated measures ANOVA (treatment x minute'): 'cocaine': $F(1,14) = 32.127$, $p = 0.000$; 'minute': $F(5,70) = 22.804$, $p = 0.000$]. Accordingly, the COC mice engaged in less swimming behavior [$t(14) = -3.367$, $p = 0.004$] (Fig. 2c).

4. Discussion

It is well known that rodents under cocaine abstinence for several days, would show increased locomotor activity in drug-free conditions as long as they are presented with a cocaine prime or with contextual stimuli previously associated with cocaine (e.g. when they are re-exposed to the same apparatus where cocaine was previously administered) [2, 4, 5]. The cocaine-associated stimuli are reminiscent of the drug's psychostimulant and rewarding effects and they remain ingrained in memory, even in presence of anterograde memory impairments to acquire new information [15]. This study shows that a long-lasting hyperactivity under cocaine abstinence may also be manifested in non-drug related conditions, as when animals are tested for spontaneous exploration in unfamiliar, drug-free environments.

Previous studies by our laboratory and others have not found increased spontaneous locomotor activity following abstinence from cocaine exposure [12–15]. One possible explanation relates to differences in cocaine dosage and abstinence periods, considering that the magnitude of neuroplastic brain changes induced by cocaine depends on the amount and duration of drug use and they progressively ameliorate by protracted drug abstinence [reviewed in [24]]. Accordingly, studies not finding this hyperlocomotion effect used either a longer cocaine abstinence period (29 or 44 days) [13, 15] or a shorter cocaine administration protocol (20 mg/kg/day for 5 days) [14] compared to the present experiment. Nevertheless, finding a non-significant tendency of the cocaine-abstinent mice to be more active than controls was not uncommon [14, 15]. The exacerbated exploratory activity during cocaine abstinence may also be influenced by the experimental settings. For example, the study of [12] administered a high cocaine dose (30 mg/kg/day for 14 days; 14 days of abstinence) but they assessed locomotion during 1 h of testing; an extended trial duration that may be sufficient for mice to reduce exploration due to habituation to the new environment.

Furthermore, hyperlocomotion in the cocaine-abstinent mice may be task-dependent. In this study, the COC mice showed increased spontaneous motor activity and vertical exploration -rearing behavior- more notably in the closed arms of the elevated plus maze and in the Y maze. Interestingly, these two paradigms have in common the presence of corridor-like areas enclosed by walls. Enclosed corridors could favor the manifestation of exacerbated exploration since they may be perceived either as a 'safer' or as a 'more suitable' zone to perform both horizontal and vertical activity -since rearings are usually supported against walls. Considering that the elevated plus maze and the Y maze were the first two tasks scheduled in the behavioral testing battery, they could also entail greater novelty or risk incentive to stimulate exploration in the COC mice. Novelty seeking and willingness to take risks are vulnerability factors that predict drug use, but these behavioral traits may also be intensified as a consequence of drug exposure and thus they could be more prominent in the cocaine-treated animals [18, 29].

The increased motor and exploratory activity coexisted with symptoms of cognitive impairment, because the COC mice showed both reduced spatial working –SAB and reference –novel place– memories, according with previous observations [7, 13, 15]. The COC mice did not show exploratory alterations when performing the place recognition task (sample and test sessions), but their disinhibited exploratory behavior in the Y maze may explain impaired SAB performance in this study. Our previous report [13] dissociated exploration from cognition in mice under this same cocaine administration schedule, because they were cognitively impaired –in SAB, novel object and novel place memories- but performed as controls in all measures of motor and exploratory activity. As discussed before, a key difference is that those mice were tested for behavior after 44 days of cocaine abstinence (vs 24 cocaine abstinence days in this study). This suggests that the recovery provided by drug abstinence is faster for the motor/exploratory domain than for the cognitive disturbances, which seem to persist over time.

Similarly, increased anxiety-like behavior is usually found at early phases of cocaine abstinence (e.g. 24–48 h) but not after longer drug abstinence periods (e.g. 10–44 days) in rodents [6, 13, 15]. Accordingly, data in the present study seem insufficient to demonstrate emotional alterations in the cocaine-withdrawn animals. The COC mice took more time than controls to enter the unprotected open arms in the elevated plus maze, tough the total time spent in the open arms was similar. On the contrary, in the open field exploration session the COC mice showed a 'riskier' behavior, consisting of more time in the unprotected center zone and less time in the corners, combined with a reduced self-grooming. This open-field exploration pattern may be attributed to a number of non-exclusive causes, including emotional (i.e. anxiolysis [21]), motivational (i.e. willingness to take risks) and other factors (i.e. disorganized exploratory patterns in relation to salient landmarks –corners-, impulsivity,…)-. It is possible that such 'anxyolitic' tendency was not evident in the elevated plus maze because this task was contaminated by a notable hyperlocomotion in the COC mice, which was preferentially expressed in the closed arms. In fact, the elevated plus maze and the open field are likely to assess different components of anxiety, so experimental manipulations frequently affect behavior in one test but not in the other [20].

Finally, the COC mice struggled notably more than controls in the forced swimming test, but they were unaltered in the immobility-related measures of behavioral despair [1]. Taking into account that the COC mice showed hyperlocomotion in several of the dry mazes, their augmented climbing or struggling could possibly be another sign of their increased motor activation and resistance to exhaustion [28]. In fact, increased struggling/climbing in the forced swimming test is not triggered only by antidepressants but also by psychostimulants [28].

In conclusion, the main finding of this short report is that chronic cocaine administration may induce persistent changes –mainly increases- in motor/exploratory activity of mice long abstinent from the drug. Future studies may further unveil the neurobiological and behavioral correlates of this effect. On the contrary, studies focused on the cognitive domain may be benefited by selecting drug abstinence periods or behavioral tasks with minimal motor confounds.

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Declaration of Competing Interests

The authors declare no potential conflicts of interests.

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