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The effects of oral gestational particulate matter 10 exposure: Insights into neurodevelopmental milestones, inhibitory control, adult sociability, and object recognition

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ABSTRACT

Air pollutants have been associated with various neurodevelopmental disorders, with several studies specifically linking Particulate Matter (PM) exposure to attentional and social deficits. This link is even more pronounced when exposure occurs during the prenatal period, as it can disrupt normal brain development. However, while social deficits have been extensively studied during adolescence, their impact on adult social behaviors remains largely unexplored. To investigate these effects, pregnant Wistar rats were exposed throughout gestation (GD1-GD21) to PM_{10} at a dosage of 200 μg/Kg/day diluted in PBS that was freely drunk. After birth, the pups were evaluated on developmental milestones such as weight progression, ocular opening, and muscular strength. In adulthood, inhibitory control was assessed using the Five Choice Serial Reaction Time Task (5-CSRTT), social behavior using the Three-Chambered Crawley's Test (3-CT), and object recognition using the Novelty Object Recognition test (NOR). The results indicated that prenatal PM10 exposure is associated with higher birth weight and poorer performance in neuromuscular tests. However, no significant differences were observed in inhibitory control (5-CSRTT) or social behavior (3-CT). Interestingly, prenatally exposed rodents showed heightened novelty responses in the NOR test. In conclusion, gestational exposure to PM_{10} is related to differences in neurodevelopmental milestones, including weight and muscular strength. While it does not impact adult inhibitory control or social behavior, it influences novelty recognition in later life.

1. Introduction

Pollution is defined as the introduction of substances into the environment that are harmful to humans and other living organisms (Manisalidis et al., 2020). It is a pressing global issue that many countries are currently facing (Calvillo, 2018). Pollution has been linked to various health concerns, including chronic obstructive pulmonary disease (Park et al., 2021), respiratory diseases in children (Khreis et al., 2017), cardiovascular disorders (Chen and Hoek, 2020), and obesity (Parasin et al., 2021).

Air pollution has recently been identified as contributing to another critical health concern: neurodevelopmental disorders (Costa et al., 2020). The fetal and early life stages are particularly vulnerable periods for neurodevelopment due to their critical role in brain maturation and the formation of neural networks (Block et al., 2012). Particulate Matter (PM) is thought to interfere with normal neurodevelopment through mechanisms involving oxidative stress and neuroinflammation (Rodulfo-Cárdenas et al., 2023; Ruiz-Sobremazas et al., 2023; Shang et al., 2023). Specifically, PM exposure has been linked to alterations in white matter, brain volume, and cortical thickness (Wylie and Short,

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2023), as well as disruptions in the cortico-striato-thalamo-cortical circuit (Peterson et al., 2022). However, the relationship between PM exposure and certain neurodevelopmental disorders, such as Attentional Deficit with/without Hyperactivity Disorder (ADHD), remains unclear (Myhre et al., 2018; Siddique et al., 2011; Min and Min, 2017). ADHD is characterized by deficits in inhibitory control — the ability to regulate or suppress impulsive or compulsive responses (Bari and Robbins, 2013) — and is associated with dysfunctions in cortico-striatal pathways (Dalley et al., 2011). Despite the shared involvement of PM and inhibitory control in the same brain circuit, no studies to date have explored the potential relationship between gestational or early-life exposure to PM and inhibitory control. In rodents, the ADHD phenotype has been studied using several tasks like (Winstanley et al., 2006): the delay discounting task, the rodent gambling task, and the five-choice serial reaction time task (5-CSRTT). We decided to use the 5-CSRTT due to the versatility of the task (allows to assess learning, attention, impulsivity while increasing the task difficulty; Bari et al., 2008).

Another neurodevelopmental disorder recently linked to air pollution is autism spectrum disorder (ASD). ASD is characterized as a neurodevelopmental condition involving increased stereotyped behaviors, impaired social skills, abnormal communication, and heightened repetitive behaviors (American Psychiatric Association, 2013). Previous research has highlighted the potential impact of prenatal PM10 exposure on communication deficits in rat pups, as assessed through ultrasonic vocalizations (Ruiz-Sobremazas et al., 2024a). Additionally, unpublished data from our laboratory revealed reduced social behavior in adolescent rats during the second phase of the three-chambered test after gestational PM10 exposure. Similar findings were reported by Li et al. (2018), who noted impaired social behavior in rodents postnatally exposed to PM2.5. Their study also found disrupted developmental patterns in offspring exposed to PM10 during gestation. Regarding social interaction in adulthood, limited evidence is available. However, Church et al. (2018) observed that 20-week-old offspring exposed to PM2.5 demonstrated reduced social interactions compared to controls. Several models have been proposed in animals to study social behavior (Takumi et al., 2020): ultrasonic vocalizations (USV), social preference tests, operant social behaviors, helping behaviors test among others. We decided to use a social preference test because of the experience that we already have (Morales-Navas et al., 2025; Perez-Fernandez et al., 2022, Perez-Fernandez et al., 2020a) and because we want to see exploratory social behavior.

Nevertheless, most of this evidence has been gathered using the inhaled pathway as the primary absorption route (this can be seen in Ruiz-Sobremazas et al. 2023 systematic review), employing various methods such as intra-tracheal/intranasal instillation, oropharyngeal aspiration, and whole-body inhalation. The importance of atmospheric transport (Lauria et al., 2022) and wet/dry PM deposition are currently considered as important factors (Pramanik et al., 2020). In addition to inhalation, oral exposure to these PM particles may be detrimental to human health as they have been extensively reported to sorb onto dust and aerosols (Faust, 2023), which subsequently deposit on land (Islam and Saikia, 2020; Rathebe and Mosoeu, 2023), dissolve in drinking water (Kaplan et al., 2023; Pramanik et al., 2020; Rathebe and Mosoeu, 2023), and are absorbed by vegetables (Rathebe and Mosoeu, 2023; Noh et al., 2019; Tremlová et al., 2013), fruits (Przybysz et al., 2020; Rathebe and Mosoeu, 2023; Rodríguez-Rodríguez et al., 2023), and various plants (Paull et al., 2020; Heshmatol Vaezin et al., 2021; Sgrigna et al., 2015; Abhijith and Kumar, 2020; Cai et al., 2017). Furthermore, evidence of ingestive absorption has been increasing in recent years, with indoor dust being the most widely studied (Du et al., 2021; Plichta et al., 2022), however, more research is needed to determine the possible neurotoxic effects that this route might develop. Other exposure routes, such as dermal absorption, are also under study (Luo et al., 2020; Bekö et al., 2013). However, oral exposure route remains under-explored, leaving a crucial gap in the relationship of this exposure route and neurodevelopmental disorders.

Additionally, research indicates certain age-related behaviors that change throughout development, including motricity and anxiety (Sudakov et al., 2021), memory (Haider et al., 2014), and social behavior (Ravenel et al., 2024). Specifically, most neurodevelopmental toxicology studies on social behavior have focused on the neonatal or juvenile stage due to their importance in social behavior development (Granata et al., 2022; Achterberg and Vanderschuren, 2023). To our knowledge, there is no evidence linking gestational air pollution exposure and adult sociability behavior.

Given the above, three hypotheses were proposed in this study. First, it was posited that exposure to PM10 during gestation might influence developmental milestones, including weight evolution, ocular opening, and a battery of functional performance measures. Second, it was proposed that gestational exposure to PM10 will lead to an increase of variables linked to ADHD in the 5-CSRTT. Lastly, we wanted to test adult social behavior as most of the research analyzes social behavior in adolescence, creating a gap of knowledge regarding adult sociability; it is worth saying that ASD behaviors continue throughout development. Furthermore, we expected that gestational exposure to PM10 would be related to an altered social interaction in adult rodents. All central behaviors (5-CSRTT and 3-CT) were performed with other control behaviors (anxiety and motricity for the 5-CSRTT and anxiety, motricity, and reaction to novelty for the 3-CT).

2. Methodology

2.1. Experimental animals

Fifteen 3-month-old female Wistar rats (ENVIGO, Barcelona, Spain) served as the F0 generation. These rats were housed in groups of four in clear polycarbonate cages (50 ×35 x 20 cm; total volume of 437.5 cm^2) under controlled environmental conditions (temperature at 22 ± 2 ºC, humidity at 50 ± 10 %, and a 12-hour light cycle starting at 8 pm). To acclimate to their surroundings, rats underwent a 14-day habituation period without human contact. Ad libitum access to food and water was provided throughout this period. Monitoring the estrus cycle of the female rats daily, mating occurred once they reached late diestrus/early proestrus for 24 h. Confirmation of mating was conducted with sperm checking after one day. When sperm plug was confirmed, female rats were individually housed to initiate the gestational period (considered gestational day 0; GD0). In cases where mating was not confirmed, rats remained with the male for an additional 24 h, and sperm analyses were conducted after this extended mating period. Following mating confirmation, rats were exposed to PM10 starting at GD1. Between GD18 and GD20, a cotton swab was placed inside the home cage to allow the F0 rats to construct their nests. Home cages remained undisturbed throughout gestation to minimize stress. The experimental subjects of the F1 generation were born on the expected days, defined as postnatal day 0 (PND0), and cross-foster within the same groups. The F1 generation comprised 104 rats, with 42 were allocated to the 5-CSRTT task (F1–1) and 43 to the 3-CT task in adulthood (F1–2), while 19 were excluded for several reasons (Fig. 1). All pups were included in all the analysis, and all pups performed the same tasks: experiment 1 (developmental tests – five choice serial reaction time task – locomotor activity – anxiety screening), experiment 2 (developmental tests – three chambered task – object recognition - anxiety screening). For the experiment 1 (F1–1), pups were randomly selected from different litters: PBS-Males (12 pups from 2 dams), PBS-Females (10 pups from 3 dams), PM-Males (10 pups from 3 dams), and PM-Females (10 pups from 5 dams). For the experiment 2 (F1–2), pups also were randomly selected: PBS-Males (10 pups from 6 dams), PBS-Females (11 pups from 6 dams), PM-Males (11 pups from 6 dams), and PM-Females (11 pups from 5 dams). Furthermore, to reduce this litter-to-litter effect, we cross-fostered our animals and included the litter in all the analysis as random effect. All F1 generation underwent all the same developmental screening, but behavior depended on the experiment. In experiment 1, the F1–1 started with the

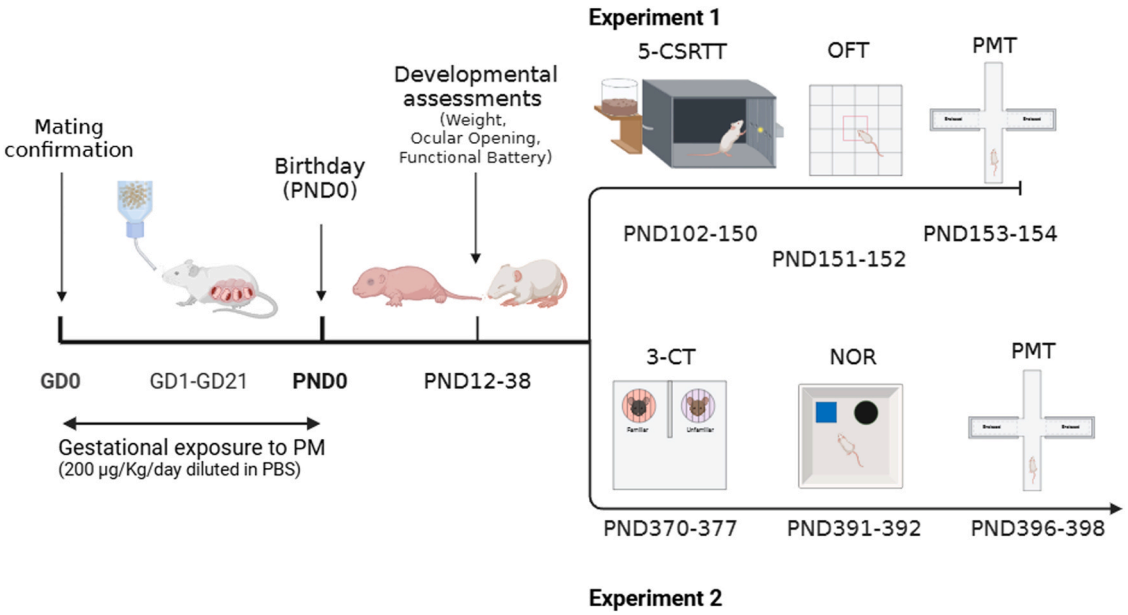

Fig. 1. Graphical representation of the experimental procedure. Two cohorts of animals were grown in our facilities, and once they reached weaning age (PND21), they were allocated to two different experiments. Experiment one analyzed the impact of gestational air pollution on learning, sustained attention, and inhibitory control while controlling motor and anxiety variables in early adulthood. Experiment 2 analyzed the impact of gestational air pollution on late sociability measures, controlling motor variables, reaction to novelty, and anxiety in late adulthood rodents.

operant chamber task, followed by the locomotor activity and the anxiety screening; in experiment 2, the F1–2 started with the sociability behavior, followed by the locomotor activity, by the object recognition and ending with the anxiety screening. This division is depicted in Fig. 1, where F1–1 rodents perform the experiment 1 while F1–2 performed the experiment 2.

All rats were maintained under controlled environmental home-room conditions with a temperature of 22 ± 2 ºC, humidity of 50 ± 10 %, and a 12-hour light/dark cycle starting at 08:00. The diet of F1 rats was restricted in early adulthood to regulate body weight evolution for both experiments (F1–1 started at PND73 to increase motivation; F1–2 started at PND210 to avoid overgrowing). A minimum sample of 10 per group was considered sufficient to detect meaningful differences in behavioral patterns between groups. The current study was conducted under the project PID 2020–113812RB-C32 from the Spanish Ministry of Science and Innovation, adhering to Spanish Royal Decree 53/2013 and the European Community Directive (2010/63/EU) for animal research. Specifically, the Animal Research Committee of the University of Almeria approved the experiment. Moreover, the experiments comply with the ARRIVE guidelines for animal testing.

2.2. Toxic agent exposure

PM10 (Standard Material 2787; NIST, Lot: 110626) was administered oral free at a dosage of 200 µg/Kg/day diluted in 5 mL of PBS (Ph7.4) from GD1 to GD21. Water dispensers equipped with steel balls to prevent dripping were used to expose the animals to the agents. The dispensers were placed daily in their home cages with the specific dosage. All the animals drank the solution within two minutes. As explained previously (Ruiz-Sobremazas et al., 2024a), and in the introduction section, this exposure route is important because PM molecules can be deposited (via wet or dry deposition) into soil and water and absorbed by fruits and vegetables that we drink and eat. Half of the F0 generation was randomly assigned (controlling bodyweight to avoid biases) to the experimental condition (PM10), while the remaining animals were assigned to the control group (PBS) (Experiment 1, n-PBS = 4; n-PM10 = 5; Experiment 2, n-PBS = 8; n-PM10 = 7). There was no blinding between the researchers across the experiments. Exposure took place between 13:00–14:30.

3. Behavioral tasks (Pups and Adults)

3.1. Dam and pup testing

The body weight of dams was recorded daily from GD1 to GD21 and pregnancy outcomes were also recorded (number of pups delivered and sex ratio). Pups' body weights were monitored every two days from PND1 until PND31, with an additional measurement taken on PND38 to assess potential sex differences. Ocular opening assessments were carried out between PND12 and PND15, using direct scores of 0, 1, or 2, which were subsequently transformed into percentages. The scores were based on whether the pup had both eyes closed (0), one eye closed (1), or both eyes open (2). Neuromotor screening took place on PND16 and consisted of three tests: adherence to an inclined plane, climbing ability, and grip capacity. Grip capacity involved placing the pup in a supine position, and the closest part of the tail to the body was gently pushed toward the researcher. Scores were assigned as follows: 0: no resistance, 1: slight resistance, and 2: strong resistance. Adherence to the inclined plane test involved placing the animal in the center of a grid inclined at 60º. Rats that immediately fell received a score of 0, those that remained stable for 10 seconds received a score of 1, and those that remained stable for more than 15 seconds received a score of 2. Climbing capacity was the final test. In this test, the pups were placed on a 60º slope with the grid divided into three sections (bottom, middle, and top). Scoring was based on reaching one of these sections within 10 seconds (0: Unable to climb; 1: reaches the middle within 10 seconds; and 3: reaches the top within 10 seconds). All tests were conducted in the rats' home rooms under dim lighting, maintaining the same environmental conditions described earlier.

4. Experiment 1. Adulthood inhibitory control

4.1. Five-choice serial reaction time task (5-CSRTT)

To assess cognitive functions (mainly inhibitory control, attention and learning), we chose the 5-CSRTT, which is recognized for its

comprehensive approach assessing all the objective variables within the same operant task, making our findings comparable to other studies and contributing to a broader understanding of those mechanisms (Bari et al., 2008; Higgins and Silenieks, 2017). The 5-CSRTT began at PND102 (with training sessions conducted from PND102 to PND107 and testing sessions from PND108 to PND150). The task was performed in six standard sound-attenuated operant conditioning chambers (32 cm long, 25 cm wide, and 34 cm high) equipped with the specific 5-CSRTT panel and steel grid floors (MED Associates, St. Albans, VT). Continuous fan noise was maintained during the sessions. Additional details can be found in (Perez-Fernandez et al., 2020b), Nazari et al. (2020), Mora et al. (2020), and Ruiz-Sobremazas et al. (2024b). Before testing, rats were food restricted (from PND70 to onwards) to maintain their body weight at approximately 85–95 % of their free-feeding body weight following the protocol used by Bari et al. (2008). Furthermore, habituation to the dustless sweet pellets was carried out in their home cages to avoid neophobia. The 5-CSRTT required the rats to monitor five horizontally arranged spatial locations and detect a brief light stimulus to receive a food pellet (Robbins, 2002). Initially, the rats were habituated to the chambers, where pellets were placed in the food magazine and the five holes. Rats were trained to respond to brief flashes of a random light presented in one of the five locations (Carli et al., 1983). Each daily session consisted of 100 discrete trials or lasted for 30 min, whichever occurred first. Once habituated, the rats were trained to meet the following performance criteria: Correct responses ≥ 50; Accuracy ≥ 80 %; and Omissions ≤ 20 %. The initial stimulus duration (SD) was set to 1 s, with a 5 s inter-trial interval (ITI). Each session (100 trials) began with the house and food magazine lights on. At the start of a trial, a food magazine entry turned off the food magazine light, initiating a fixed 5 s ITI. Following the ITI, a light stimulus was presented in one of the five holes for a variable SD, depending on the task phase. If the animal responded to the illuminated hole within the Limited Hold (LH) period specific to that phase, the nose-poke was recorded as a correct response and rewarded with a dustless sweet pellet (TSE Systems). Incorrect and omission responses were also collected. All response errors resulted in 5 s of darkness (time-out period) without reward. Premature behavior was defined as any response performed before the stimulus presentation, while perseverative responses were those made within the LH time after the stimulus presentation. Once the animals reached Phase 5, baseline performance (BL) was calculated using data from three consecutive days meeting Phase 5 criteria (Ph5). Following BL calculation, various manipulations of the 5-CSRTT variables were introduced. First, the ITI was raised from 5 s to 7 s to 10 s to motivate the animals to respond prematurely. Second, the SD was reduced from 1 s to 0.5 and 0.25 to assess attentional differences in the task. Finally, the procedure concluded with an extinction phase, where the food dispenser was disconnected from the food magazine but still full of reward pellets, designed to increase perseverative responses. A two-day washout period using phase 5 parameters was implemented between each manipulation to avoid potential interference. Table 1 summarizes all 5-CSRTT phases and their characteristics. All animals that did not reach Ph5 criteria were excluded from baseline and further 5-CSRTT manipulations.

The following dependent variables were recorded: number of sessions required to reach each phase criteria (n), total number of sessions required to reach baseline performance (n), percentage accuracy $[100x(\frac{Correct\ Response}{Total\ responses})]$ (%), correct responses (n), incorrect responses (n), omission responses (n), percentage of omission responses (%), latency to correct response (sec), latency to reward (sec), total number of responses made (n), total hole entries (n), total premature responses (n), and total perseverative responses (n).

Rats were transported daily to the experimental room 30 min before the start of each session. After each session, the operant boxes were cleaned with 80 % ethanol. Experimental series and boxes were randomly assigned to minimize bias. Behavioral evaluations were conducted between 9:00 and 14:00, with the experimental order counterbalanced across sex and exposure conditions to avoid potential bias.

Table 1
Main phases and characteristics of the 5-CSRTT.

Phase	SD	ITI	LH	Criteria	Remarks
1	8	5	10	CR $\geq$ 50	None
2	6	5	5	CR $\geq$ 50; Acc $\geq$ 80 %	None
3	2.5	5	5	CR $\geq$ 50; Acc $\geq$ 80 %; Om $\leq$ 20 %	None
4	1.25	5	5	CR $\geq$ 50; Acc $\geq$ 80 %; Om $\leq$ 20 %	None
5	1	5	5	CR $\geq$ 50; Acc $\geq$ 80 %; Om $\leq$ 20 %	BL (average of 3 consecutive days)
ITI7	1	7	5	None	
ITI10	1	10	5	None	
SD0.5	0.5	5	5	None	Two WO sessions between manipulations with phase 5 characteristics
SD0.25	0.25	5	5	None	
EXT	1	5	5	None	

ITI (Inter Trial Interval); SD (Stimulus Duration); EXT (Extinction); LH (Limited Hold); CR (Correct Responses); ACC (Accuracy); Om (Omissions); BL (Baseline performance); WO (Wash Out)

5. Locomotor activity

Locomotor activity was assessed using eight plexiglass standard activity cages (39 ×39 x 15 cm) equipped with photocell beams (16x16x16) connected to a PC. The edge is located 7.32 cm from the wall. This procedure allows us to assess locomotor activity and exploratory behavior. This test involves placing the rodents in an enclosed arena and observing their spontaneous movements, such as distance traveled, speed, and frequency of movements. It is particularly useful for evaluating changes in locomotor activity when rodents are exposed to anxiolytic drugs, allowing researchers to compare activity levels before and after treatment (Kraeuter et al., 2019a).

The boxes were controlled using VersaMax®, and data were extracted with VersaData® Software (PLC Control System SL).

The locomotor activity paradigm was conducted at PND151–152. Before starting the experiment, each rat was individually habituated to the experimental room for 1 h, with access to food and water. Following habituation time, the experimental phase began. Each rat was placed in the center of the plexiglass activity chamber (AccuScan Instruments, Inc., USA/Canada), and motor behavior was recorded for 30 min, divided into six 5-minute blocks. After the session, the rats were removed from the open field chamber and returned to their home cages. All F1 from the experiment 1 perform this task under the same food-restriction that was performed for the 5-CSRTT. No animals were excluded from the analysis.

The following dependent variables were analyzed: total distance traveled (cm), movement time (n), vertical activity (n), time spent in the central area (s), time spent in the margins (s), number of movements (n), and number of vertical movements (n). The experimental order was counterbalanced between sex and exposure to avoid any potential bias. Each chamber was cleaned with 80 % ethanol between sessions. The test procedure was conducted between 9:00 and 14:00 under dim-light conditions. Experimental room conditions were maintained at a temperature of 22 ± 2 ºC and a humidity level of 50 ± 10 %.

6. Anxiety (plus maze test; PMT)

The PMT was chosen due to its proven ability to assess anxiety levels in rodents because its design allows for the differentiation between exploratory and avoidance behaviors bases on exposure to open and elevated environments (Kraeuter et al., 2019b). Anxiety was assessed

using an opaque black standard plus maze. The apparatus consisted of a central square platform with two open arms and two closed arms extending outward in a cross shape. This test leverages the natural conflict between the rodent's exploratory instinct and the aversion generated by the lack of physical protection in the open arms compared to the closed arms. The animal's anxiety state was inferred from the time spent in the open arms versus the closed arms: greater time in the open arms indicated lower anxiety levels. Before the test, animals were transferred to a waiting room 1 h prior to testing to acclimate. Room temperature and light conditions matched the home room settings, with dim illumination maintained at 15–25 lux. All F1 from the experiment 1 perform this task under the same food-restriction that was performed for the 5-CSRTT.

The PMT was conducted at PND153. Rats were transferred to an adjacent room with environmental conditions identical to the experimental room and allowed to habituate for 1 h. After the habituation period, each rat was placed at the center of the experimental apparatus, facing the open arm, and their behavior was recorded for 5 min. The experimental order was counterbalanced between sex and exposure to avoid any potential bias. The following dependent variables were analyzed: total distance traveled (cm), Velocity (cm/s), frequency of entries into open and closed arms (n), time spent in open and closed arms (s), and anxiety index [AI $AI = \frac{(CA-OA)}{(CA+OA)}$], where CA refers to time spent in Closed Arms and OA to time spent in Open Arms. No animals were excluded from the analysis. Animal behavior was recorded using OBS Studio (v27.2.3; OBS Project) and analyzed with Ethovision v16 (Noldus). The apparatus was cleaned with 80 % ethanol between each session.

7. Experiment 2. Sociability in late adulthood

7.1. Three chambered test (3-CT)

The 3-chamber test (3-CT), originally developed by Crawley (2004), was chosen for its proven effectiveness in evaluating prosocial behaviors. This paradigm allows the measurement of social interaction and preference, making it a valuable tool for assessing social behavior. Additionally, the 3-CT is widely recognized and validated across numerous studies (Jabarin et al., 2022; Kurahashi et al., 2024; Crawley, 2007), and we have extensive experience applying this method in our research (Perez-Fernandez et al., 2022, 2020; Morales-Navas et al., 2025). Sociability and reaction to social novelty were analyzed using a standard 3-CT. The test apparatus comprises a central chamber and two equally sized chambers (30 ×98 x 50 cm) located at each side (side chambers). Two identical 50 cm plexiglass walls with one gate (10 ×10 cm) separated all chambers. Two identical grid cages (23 ×15 x 23 cm) were used in the side chambers to place the stranger rats during Phases 2 and 3 of the test.

The experiment was conducted between PND370 and PND377. Experimental and stranger rats were habituated to the waiting room for one hour two days before the task. On the test day, rats were brought to the waiting room 30 min before starting. During the first phase (Ph1), each rat was placed in the central chamber with the doors to the side chambers blocked, restricting access to the side chambers. The rat was allowed to explore the central chamber for 10 min. In the second phase (Ph2), the experimental rat was removed, the gates to the side chambers were unblocked, and a stranger rat of similar age, sex, weight, and size was placed inside a grid cage in one of the side chambers, referred to as the social chamber. The experimental rat was then returned to the central chamber, and its exploratory and social interaction behaviors were recorded for 10 min. In the third phase (Ph3), the experimental rat was again removed, and a second stranger rat was introduced into the opposite side chamber, designated the novelty chamber. The experimental rat was then returned to the central chamber, and its exploratory behavior and response to the novel social stimulus were recorded for another 10 min.

Behavior during all phases was recorded using OBS Studio (v27.2.3; OBS Project) and analyzed with Ethovision (v16; Noldus). To avoid bias, the testing order was counterbalanced between exposure and control groups, alternating between groups on different test days. Velocity and total distance traveled were analyzed using body point tracking, while cumulative duration in each chamber and contact zones were calculated using head point tracking. Head point data were corrected for any errors caused by head-tail position changes.

The dependent variables analyzed included total distance traveled (cm), time spent in movement (sec), velocity (cm/S), time spent in each chamber (sec), and time spent in the contact zone (sec). The Social Index ratio was calculated for the second phase [$SI = \frac{(S1-Empty)}{(S1+Empty)}$]. An index close to 1 indicates the rat makes more contact with the Stranger 1 (S1) instead of exploring the empty chamber. The Social Novelty Index was computed for Ph3 [$SNI = \frac{(S2-S1)}{(S2+S1)}$] to assess reaction to novelty. A value close to 1 indicates that the rat spends more time with the Stranger 2 (S2). Rats who did not explore both chambers in Phase 2 and 3 were excluded from analysis, following Bambini-Junior et al. (2014) criteria. After the test, all apparatus was cleaned with 70 % Ethanol. The test procedure was completed under dim-light conditions and between 09:00 and 14:00, maintaining a temperature of 22 ± 2 ºC and a humidity level of 50 ± 10 %.

8. Object recognition (Novelty Object Recognition)

The Novel Object Recognition (NOR) test was chosen to assess recognition memory due to its established efficacy and widespread use in behavioral neuroscience. This test is particularly valuable because it requires minimal training and is sensitive to changes in memory performance (Bevins and Besheer, 2006; Leger et al., 2013). Numerous studies have validated its effectiveness, making it a standard paradigm for assessing cognitive functions. The NOR was conducted to evaluate novelty reactions and complement the third phase of the 3-Chambered Test (3-CT). The test was performed in four open-field arenas, each measuring 75 × 75 × 75 cm, and was divided into three phases. In the first phase, rats were habituated to the open field for 5 min under dim light and environmental conditions matching those described in previous tests. In the second phase, two identical objects (black cylindrical cups) were placed in each open field, and the animals' behavior was recorded for 5 min. In the third phase, one of the identical objects was replaced with a novel object (a blue rectangular prism-shaped cup). The two objects were placed in opposite corners of the open field, with their positions counterbalanced across trials. Both objects and arenas were cleaned with ethanol between tests to maintain hygiene and prevent olfactory interference. Behavior was recorded using OBS Studio (v27.2.3; OBS Project) and analyzed with Ethovision (v16; Noldus). Animals were brought to a waiting room 1 hour before the test. Temperature and light conditions were consistent with the home room, with illumination maintained at 15–25 lux. The paradigm was conducted on Postnatal Day 391 (PND391). Before testing, rats were transferred to an adjacent room and habituated for one hour. Four rats at a time were then moved to the experimental room, with each rat placed individually in an open field to begin the first phase. During this phase, rats freely explored the open field without any objects present, and their behavior was recorded for later analysis. In the second phase, rats were removed from the arenas while two identical objects were placed in opposite corners in a counterbalanced order. The rats were then returned to the open fields and allowed to interact with the objects for 5 min. After this, the third phase began. One of the identical objects was replaced with a novel object (counterbalanced between trials), and the rats were again allowed to explore the open field for 5 min with the novel object present. No animals were excluded from the analysis. The dependent variables analyzed were total distance traveled (cm), velocity (cm/s), discrimination index [DI = (TK-TN)/(TK+TN)], recognition index [RI = TN/(TK

+ TN)], time spent interacting with known object (TK), and time spent interacting with the novelty object (TN) in seconds, and frequency of interactions with both objects (n).

9. Anxiety (PMT)

The PMT used in the second experiment followed the same setup and procedures as described in Experiment 1. Details of the apparatus, paradigm, and experimental procedure can be found in the *Behavioral Tasks* section of Experiment 1.

10. Statistical analysis

Sex (males vs females) and exposure (control vs exposed) were selected as the main factors for analysis. Continuous variables (weight development, ocular opening, total sessions required in each phase in the 5-CSRTT, behavioral manipulations, and variables from the OFT) were analyzed using RM-Bayesian ANOVAs. Discrete variables (birth weight, specific days for ocular opening, functional battery variables, baseline performance in the 5-CSRTT, data from the behavioral manipulations, and PMT variables) were analyzed using Two-Way Bayesian ANOVAs. As we mentioned before, litter was included in all the analyses as random factor to control intralitter likeness, as explained by Golub and Sobin, (2020).The experimental unit is the F1 pups. Evidence supporting the alternative hypothesis was considered significant when BF10 > 1. The interpretation of BF10 values followed the criteria outlined by Lee and Wagenmakers (2013): $1 < BF_{10} < 3$, *anecdotal evidence* for H1; $3 < BF_{10} < 10$, *moderate evidence*; $10 < BF_{10} < 30$, *strong evidence*; $30 < BF_{10} < 100$, *very strong evidence*; $BF_{10} \geq 100$; *extreme evidence*. Due to the lack of sufficient prior evidence, we set a uniform 0.5 prior which reflects unbiased assignment of probabilities between both hypotheses. Anecdotal evidence refers to observed effects in the data that do not reach the threshold that is set in the Bayesian analysis to be considered as moderate evidence. Those anecdotal evidence should be interpreted as illustrative (Quintana and Williams, 2018), offering little support for the alternative hypothesis.

All analyses were conducted using JASP (Amsterdam, Netherlands) software version 0.18.1. Graphs were generated using GraphPad Prism (San Diego, California, USA) version 8.0.0.

11. Results

11.1. Developmental outcomes

In terms of mother pregnancy outcomes, no difference was detected for *exposure* neither for *sex*, in weight development through gestation. In addition, no differences were detected between groups in GD1. Also, no differences were detected for the number of pups delivered, number of males and females neither the ratio between both sexes (data not shown). Regarding birthweight, *exposure* appeared to affect weight with moderate evidence ($BF_{10} = 3.469$), but *sex* had no effect. PM-offspring weighed more than controls (PBS; M = 7.398; 95 % CI = 7.217–7.579; PM; M = 7.781; 95 % CI = 7.534–8.029; Fig. 2b). *Litter* reached extreme evidence ($2.031\ e^{+9}$) towards the alternative hypothesis. As expected, pre-weaning weight analyses revealed extreme evidence for the effect of PNDs ($BF_{10} = \infty$; Fig. 2a), though neither *sex, exposure* or *litter* affected

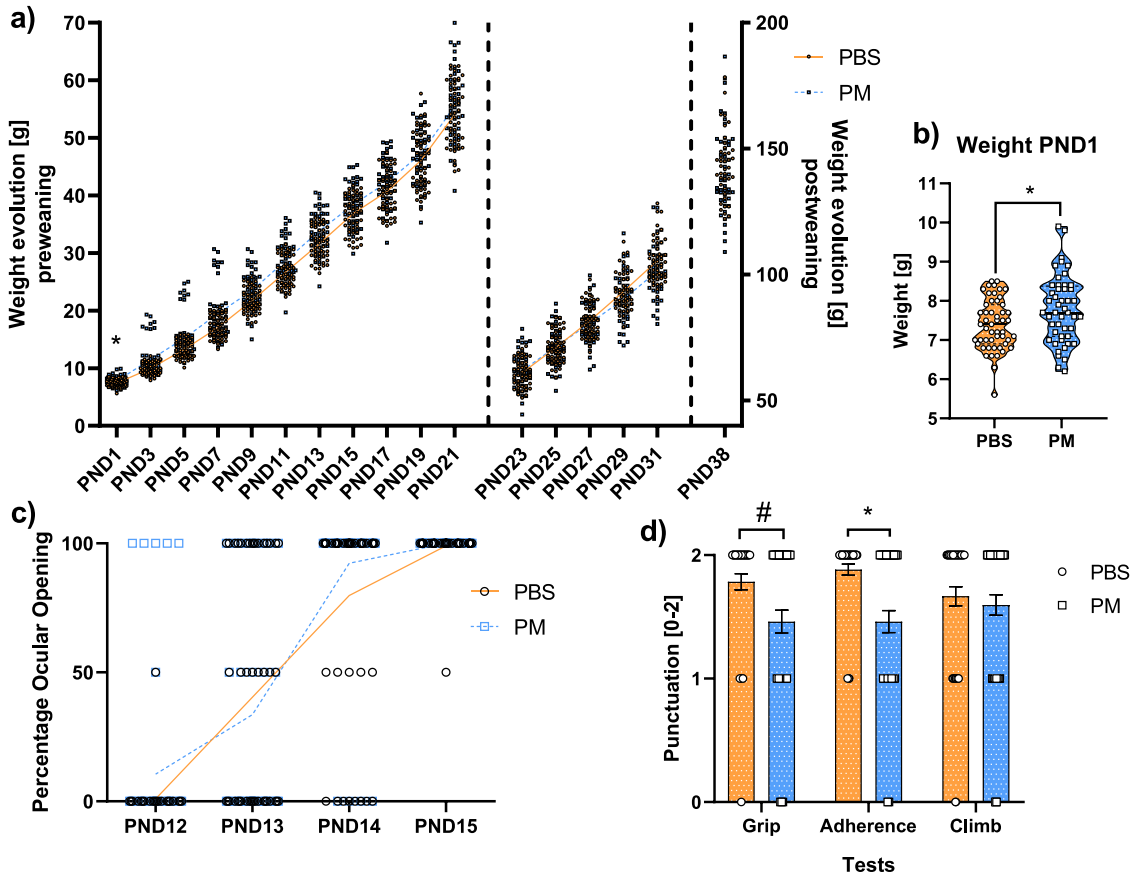

Fig. 2. Graphical representation of developmental outcomes. Part a) depicts weight evolution across three developmental stages: the preweaning stage (PND1-PND21), the post-weaning stage (PND23-PND31), and PND38. Part b) shows birth weight comparisons. Parts c) and d) present the results for ocular opening and the functional battery tests, respectively. The violin plot is represented as median and quartiles; the other graphs show mean values with independent values. # anecdotal evidence; * moderate evidence; * ** * extreme evidence. PBS (n = 51); PM (n = 48) [Weight evolution]; PBS (n = 52); PM (n = 52) [Functional battery]; PBS (n = 52); PM (n = 52) [Ocular opening].

weight development. Similarly, extreme evidence supported H1, with an effect of PNDs in the post-weaning period ($BF_{10} = \infty$). As with the pre-weaning period, neither *sex* nor *exposure* affected post-weaning weight. Sex differences started to be noticed at PND21 ($BF_{10} = 2.400$) and increases alongside PNDs (Fig. 2a).

Expected extreme evidence for the effect of PNDs ($BF_{10} = 3.010\ e^{+89}$) was observed for ocular opening, while neither *sex* nor *exposure* showed evidence to support H_1; nevertheless, *litter* reached moderate evidence ($BF_{10} = 8.676$). No difference was detected for *exposure* nor *sex* when ocular opening is analyzed individually through PND12-PND15 (Fig. 2C). In the neurofunctional battery, *exposure* showed anecdotal evidence on grip strength ($BF_{10} = 1.131$), with PM-offspring possibly scoring lower than controls (PBS; M = 1.783; 95 % CI = 1.594–1.972; PM; M = 1.472; 95 % CI = 1.207–1.738; Fig. 2d). Surprisingly, moderate evidence was found for the effect of *exposure* on adherence ($BF_{10} = 4.108$), while *sex* had no effect. PM-offspring performed worse on this task (PBS; M = 1.882; 95 % CI = 1.747–2.017; PM; M = 1.472; 95 % CI = 1.216–1.729; Fig. 2d). Finally, neither *exposure* nor *sex* affected climbing performance.

12. Experiment 1

12.1. 5-CSRTT learning, baseline performance, and inhibitory control

There was no difference between groups in terms of bodyweight at the start of the 5-CSRTT. Furthermore, no differences were also detected in the percentage of food-restricted weight compared to baseline bodyweight (data not shown).

Most rats successfully learned the task. As expected, extreme evidence was observed for the number of sessions required to reach each criterion in each phase ($BF_{10} = 8.042\ e^{+36}$), though neither *sex, exposure* nor *litter* affected this outcome. In addition, when the phases are analyzed individually, no effect of *exposure* or *sex* were present (Fig. 3a). For baseline performance, no significant effects of *sex, exposure,* or an interaction were detected across most outcomes (Fig. 3b-g).

Behavioral manipulations were conducted, including ITI7, ITI10, and extinction. Nevertheless, several *sex* effects were present in SD0.5: moderate effect was detected for correct responses ($BF_{10} = 7.610$); strong effects were present for incorrect responses ($BF_{10} = 19.448$) and total accuracy ($BF_{10} = 26.751$). Females performed the task under SD0.5 circumstances more accurately than males (Males; M = 73.479; 95 % CI = 69.756–77.202; Females; M = 82.460; 95 % CI = 78.730 – 86.190; Data not shown).

13. Anxiety and locomotor outcomes

For the PMT, moderate evidence was observed for the effect of *exposure* ($BF_{10} = 9.971$) on the total distance moved (Fig. 4a), with PM-offspring moving significantly more than controls (PBS; M = 1279.182; 95 % CI = 1125.424–1382.94; PM; M = 1594.317; 95 % CI = 1376.549–1812.085). A similar result was found for velocity ($BF_{10} = 9.848$; PBS; M = 4.264; 95 % CI = 3.751–4.776; PM; M = 5.314; 95 % CI = 4.588–6.041; Fig. 4b). *Sex* did not affect either variable. Nevertheless, there was no effect of *exposure* or *sex* on latency to enter the closed arm (Fig. 4c). Anecdotal evidence was present for *exposure* (BF10 = 1.497) in frequency to open arm (PM; M = 14.368; 95 % CI = 8.974–19.762; PBS; M = 6.427 – 13.073; Data not shown). No other significant effects of *exposure* or *sex* were detected in latency to enter the first open arm (data

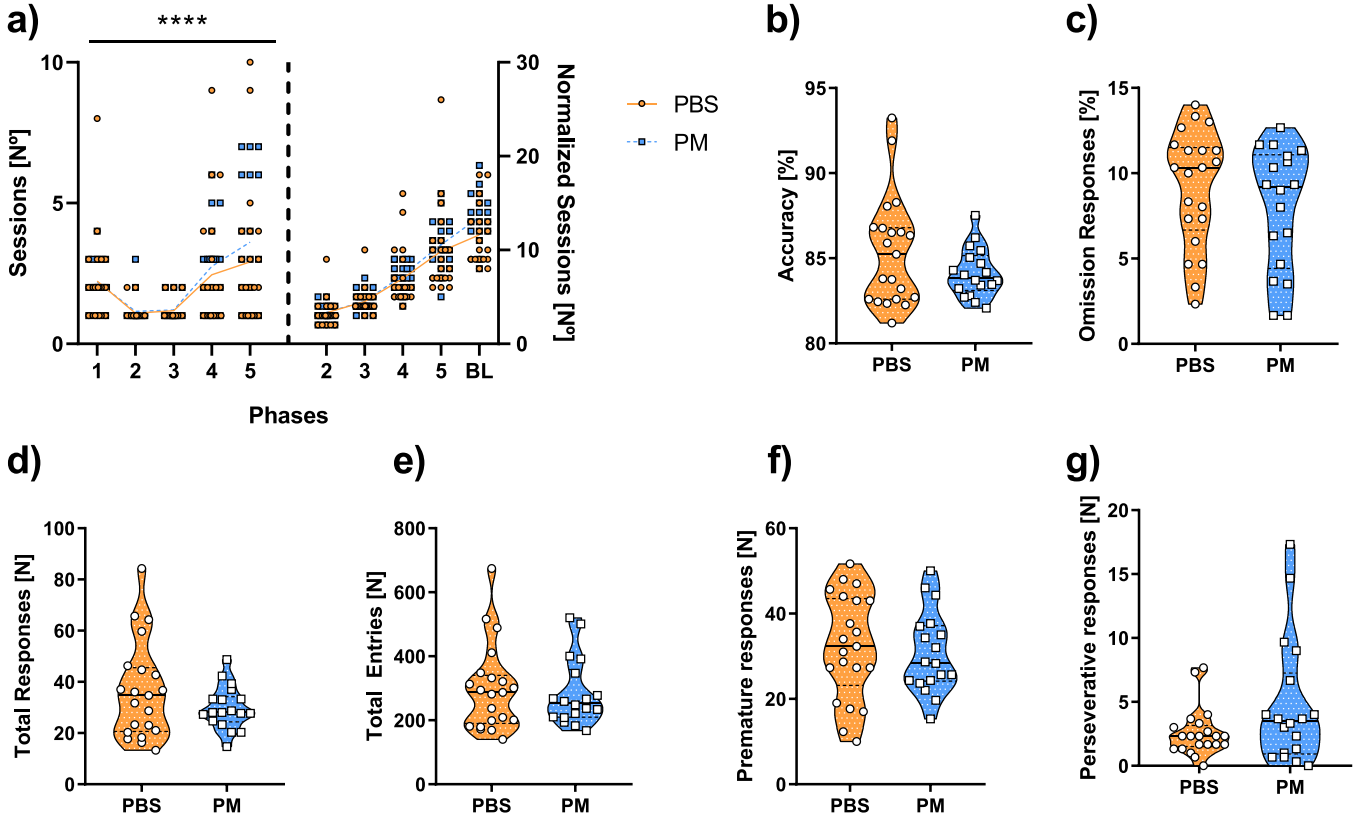

Fig. 3. Graphical representation of 5-CSRTT learning (graph a) and baseline performance (graphs b to g). Graph a) illustrates the total sessions required to achieve each phase criterion displayed in the left y-axis (total n to achieve each criteria requirement), with normalized sessions displayed on the right y-axis (cumulative sessions needed for each animal to move phase; P1 is not depicted because all animals started in that phase); P1 correspond to SD8; P2 to SD6; P3 to SD02.5; P4 to SD1.25 and P5 to SD1. Graphs b) through g) depict percent accuracy, percent omission responses, total responses, total entries, premature responses, and perseverative responses. Each graph includes individual data points, with violin plots representing median and quartile values. # Anecdotal evidence. PBS (n = 21); PM (n = 18).

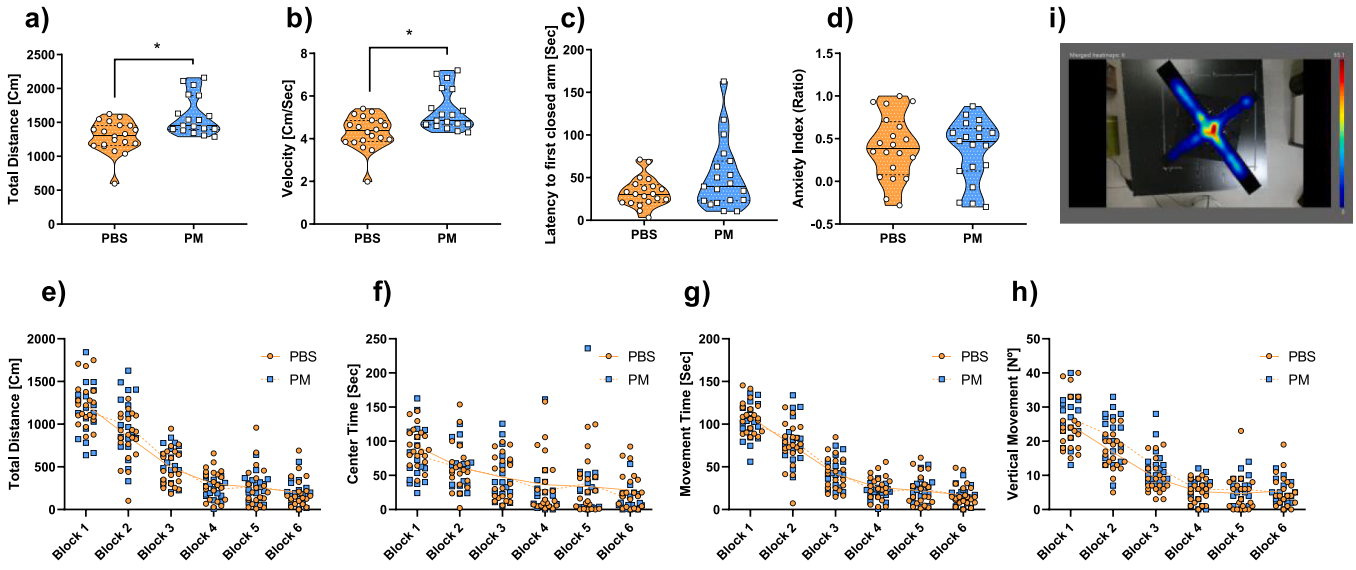

Fig. 4. Graphical representation of selected PMT (a-d) and OFT (e-h) variables. The upper section (a–d) illustrates Plus Maze Test (PMT) outcomes, including total distance traveled (a), velocity (b), latency to the first closed arm (c), and Anxiety Index (d). The lower section (e–h) depicts outcomes from the Open Field Test (OFT), including total distance traveled (e), center time (f), movement time (g), and vertical movement number (h). Panel (i) presents a mean heatmap summarizing the movement patterns of six rodents from the PM group. All graphs display individual data points, with violin plots showing median values and quartiles. Statistical significance is indicated as follows: # for anecdotal evidence and * ** for very strong evidence. Sample sizes: PBS (n = 21), PM (n = 18).

not shown), frequency of entries to the closed arm (data not shown), time spent in the open arm (data not shown), time spent in the closed arm (data not shown), or the AI (Fig. 4d).

Analysis of locomotor activities revealed an expected extreme effect of experimental block (BF_{10} = 7.608 e^{+64}) for total distance, with a gradual decrease in distance traveled across blocks (Fig. 4e). However, neither *sex* nor *exposure* affected this variable. Similarly, extreme evidence was found for the effect of block on movement time (BF_{10} = 1.040 e^{+73}), with no effect of *sex* or *exposure* (Fig. 4g). Extreme evidence was also found for the effect of block on horizontal (BF_{10} = 2.105 e^{+71}) and vertical activity (BF_{10} = 3.179 e^{+48}). However, for vertical activity, the model with the strongest evidence included Block+sex+Block*sex (BF_{10} = 3.917 e^{+54}), primarily driven by the effect of experimental block (BF_{incl} = ∞). In addition, anecdotal evidence for the effect of *sex* was observed for this variable (BF_{10} = 2.140). Extreme evidence for an effect of block was also found for central time (BF_{10} = 3.156 e^{+16}), but the model with the strongest evidence included Block+sex (BF_{10} = 4.306 e^{+16}), primarily driven by the effect of experimental block (BF_{incl} = ∞) (Fig. 4f). A similar pattern was found for margin time, with extreme evidence for the effect of block (BF_{10} = 3.174 e^{+16}) and no evidence for an effect of either *exposure* or *sex*. The model that included Block+sex showed the strongest evidence (BF_{10} = 4.500 e^{+16}). Extreme evidence was also found for the effect of block on the number of movements (BF_{10} = 2.094 e^{+54}) without involving *exposure* or *sex*. Similarly, extreme evidence was found for the effect of block (BF_{10} = 1.035 e^{+57}) without involving *exposure* or *sex*. However, the model with the strongest evidence included Block+sex+Block*sex (BF_{10} = 5.653 e^{+59}), again driven by the effect of block (BF_{incl} = ∞). Finally, no effect was found for the effects of *sex* and *exposure* on the total number of vertical movements (Fig. 4h). Additionally, the model combining exposure+sex yielded the strongest evidence (BF_{10} = 3.575), driven by the effect of *sex* (BF_{incl} = 2.063).

14. Experiment 2

14.1. Social behavior

14.1.1. Motricity in the 3-CT paradigm

The expected effects on motricity were observed during the habituation phase (Ph1).

For total distance moved, the effect of *sex* (combining all control and treated males and females in the experiment) yielded strong evidence favoring H1 (BF_{10} = 5.410), with females covering more distance than males (Males; M = 2306.285; 95 % CI = 2082.274 – 2530.296; Females; M = 2813.879; 95 % CI = 2599.626 – 3028.131; Fig. 5b). As expected, a significant effect of *sex* was found for velocity (BF_{10} = 5.402), with females moving faster than males (Males; M = 3.844; 95 % CI = 3.470 – 4.217; Females; M = 4.690; 95 % CI = 4.332 – 5.047; Fig. 5a). Similar sex-based differences were found in the social phase (Ph2) but with moderate evidence. Females again covered more distance (BF_{10} = 3.384; Males; M = 2755.969; 95 % CI = 2534.301 – 2977.637; Females; M = 3340.454; 95 % CI = 2870.235 – 3810.674; Fig. 5b)) and moved at a higher velocity (BF_{10} = 3.383; Males; M = 4.737; 95 % CI = 3.981 – 5.493; Females; M = 5.249; 95 % CI = 4.753 – 5.746; Fig. 5a). However, neither *sex* nor *exposure* affected total distance traveled or velocity in the novelty phase (Ph3).

14.1.2. Social variables

For cumulative duration in the stranger chamber, moderate evidence was observed for the effect of *sex* (BF_{10} = 5.874) with no effect of *exposure*. Males spent more time in the stranger chamber than females (Males; M = 393.754; 95 % CI = 350.643 – 436.865; Females; M = 303.531; 95 % CI = 250.576 – 356.486). Conversely, for time spent in the empty chamber, a significant effect of *exposure* (BF_{10} = 5.362), but not *sex*, was found. PM-exposed offspring spent more time exploring the empty chamber than PBS (PBS; M = 82.398; 95 % CI = 49.954 – 114.842; PM; M = 142.552; 95 % CI = 111.438 – 173.666; Fig. 5c). Concerning total time spent in contact zones, no effect of *sex* or *exposure* was detected. Finally, in Ph3, a similar pattern was observed for total time spent in both the familiar and novelty chambers. Neither *exposure* nor *sex* affected the cumulative duration of time spent in the familiar or novelty contact zones (Fig. 5d). Finally, no effect of *sex* or *exposure* was observed in the SNI (Fig. 5e).

14.2. Novel Object Recognition (NOR)

14.2.1. Motor variables

In the second phase of the NOR, significant sex differences were

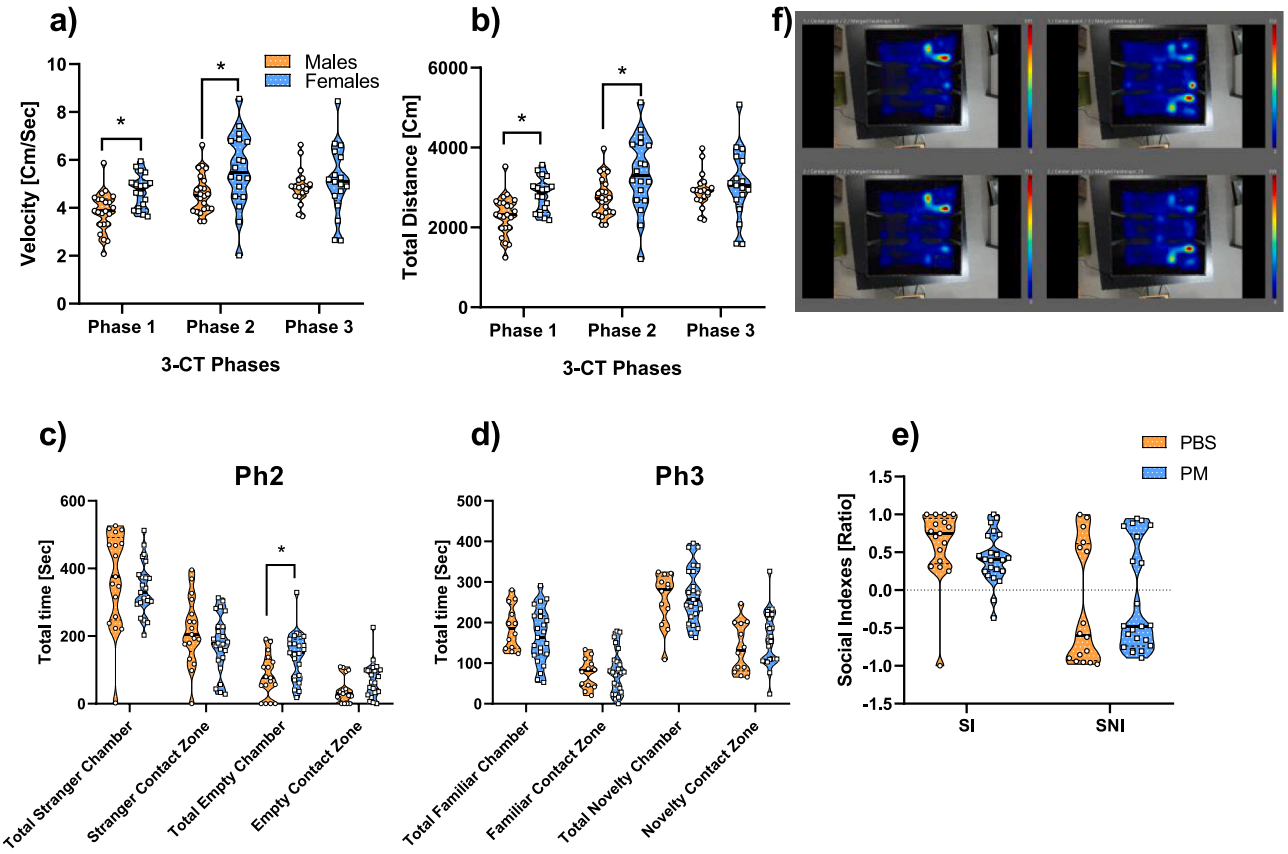

Fig. 5. Graphical representation of the 3-CT. Graphs (a) and (b) depict the velocity and total distance traveled during Phase 1 (habituation) from all the males (PBS+PM) and females (PBS+PM). Graphs (c) and (d) present cumulative duration in both chambers and contact zones during Phases 2 (social phase) and 3 (novelty phase). Graph (e) shows the social indexes calculated for Phase 2 (SI) and Phase 3 (SNI). Panel (f) shows mean behavior visualized through heatmaps. The left heatmaps correspond to Phase 2, while the right heatmaps represent Phase 3. The upper heatmaps display behavior for PBS offspring (n = 17), and the lower heatmaps show PM offspring (n = 23).Total sample sizes are as follows: males (n = 22), females (n = 18), PBS (n = 17), and PM (n = 23). All violin plots show individual data points, including mean and quartile values. Statistical significance is denoted by * for moderate evidence and * * for strong evidence.

observed. Extreme evidence was found for the effect of *sex* on the total distance traveled (BF_{10} = 96.181), while *exposure* did not affect this variable (Fig. 6a). Females covered more distance than males (Males; M = 2107.964; 95 % CI = 1888.295–2327.634; Females; M = 2747.485; 95 % CI = 2500.386–2994.585). Similarly, extreme evidence was found for an effect of *sex* on velocity (BF_{10} = 98.074) without any *exposure* effect (Fig. 6b). Females were faster than males in the second phase of the NOR paradigm (Males; M = 7.026; 95 % CI = 6.294–7.758; Females; M = 9.161; 95 % CI = 8.337–9.985).

14.2.2. Other variables

For frequency, cumulative duration, and latency to make contact with the first known object, no evidence of an effect of *sex* or *exposure* was found (Fig. 6d). However, higher anecdotal evidence (BF_{10} = 2.967) was found for an effect of *sex* on the frequency of interactions with the object that would later be replaced in the third phase. Females interacted with this object more frequently than males (Males; M = 9.238; 95 % CI = 6.588–11.888; Females; M = 11.545; 95 % CI = 9.490–13.601; Fig. 6c). In contrast, no *sex* or *exposure* effects were observed for the cumulative duration or latency to the first contact with this object. Finally, no differences between objects were detected in the second phase when assessed using the Discrimination Index (Fig. 6e).

14.2.3. Motricity measures

In the third phase of the NOR, neither *exposure* nor *sex* reached evidence towards H1 for total distance moved and velocity (Figs. 6a, 6b).

14.2.4. Object interaction variables

No significant effects of *exposure* or *sex* were found for frequency, cumulative duration, or latency to the first known object during the third phase. In the same line as before, no effect of *exposure* or *sex* were detected in frequency of interactions with the novel object (Fig. 6c). For the cumulative duration spent interacting with the novel object, exposure reached anecdotal evidence (BF_{10} = 1.616) and sex reached moderate (BF_{10} = 5.072). PM-exposed offspring might spend more time with the novelty object than controls (PBS; M = 56.470; 95 % CI = 41.458–71.481; PM; M = 92.867; 95 % CI = 73.918–111.815; Fig. 6d). Moderate evidence was also observed for an effect of *Sex* on cumulative duration (BF_{10} = 5.072), with males spending more time interacting with the novel object than females (Males; M = 90.775; 95 % CI = 70.021–111.528; Females; M = 60.121; 95 % CI = 45.554–74.688; Data not shown). No evidence was found for the effects of *exposure* or *sex* on latency to interact with the first novel object. However, moderate evidence was observed for an effect of *exposure* on the Recognition Index, where PM-exposed offspring demonstrated higher novelty recognition than controls (BF_{10} = 3.353; PBS; M = 0.550; 95 %CI = 0.463–0.637; PM; M = 0.690; 95 % CI = 0.620–0.760; Fig. 6f).

15. Anxiety behavior

Strong evidence was found for an effect of *sex* on the total distance traveled (BF_{10} = 21.676; Supplementary Figure 1a) and velocity (BF_{10} = 12.784; Supplementary Figure 1b), where females moved further distances (Male; M = 1560.545; 95 % CI = 1470.454 – 1650.636; Female; M = 1820.816; 95 % CI = 1689.058 – 1952.574) and at higher velocity

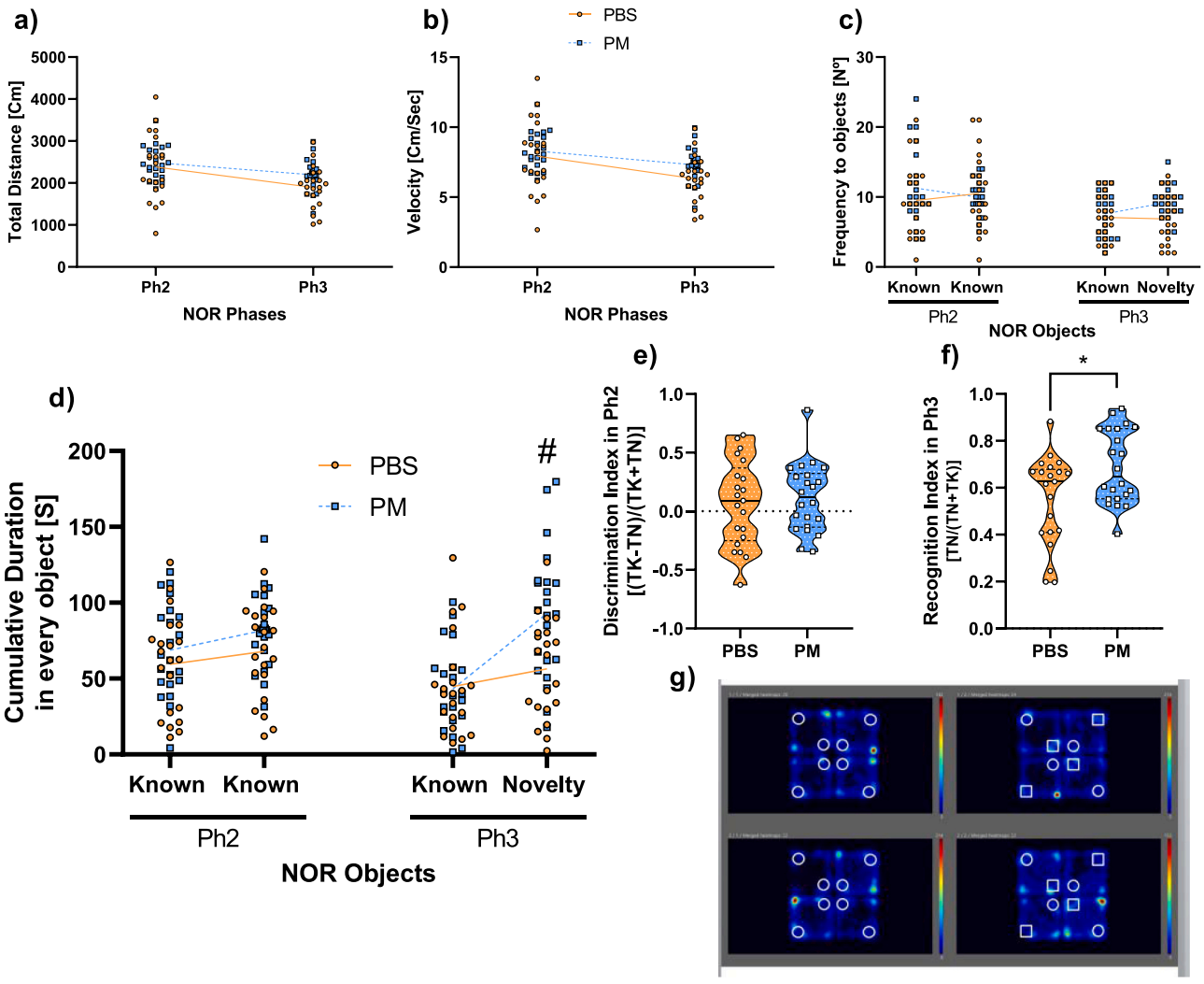

Fig. 6. Graphical representation of key variables in the NOR test. Graph a) illustrates the total distance traveled across all phases of the NOR test. Graphs (b), (c), and (d) display velocity, frequency of interactions with both objects, and cumulative duration of object exploration, respectively. In graph (e), the discrimination index from Phase 2 is shown to assess potential biases toward either object. Graph (f) presents the recognition index from Phase 3, calculated based on the total time spent exploring the novel object. Finally, graph (g) features heatmap representations of exploratory behavior during Phase 2 (left) and Phase 3 (right). The upper row depicts PBS-exposed offspring, while the lower row represents PM-exposed offspring (PBS-Ph2: n = 20; PBS-Ph3: n = 24; PM-Ph2: n = 22; PM-Ph3: n = 22). All graphs show individual data points, with violin plots representing median values and quartiles. Statistical significance is denoted as follows: # for anecdotal evidence, * for moderate evidence, and * * for strong evidence. Sample sizes: PBS (n = 21); PM (n = 22).

(Males; M = 5.250; 95 % CI = 4.950 – 5.551; Females; M = 6.070; 95 % CI = 5.630 – 6.509) than males. No significant effects of *sex* or *exposure* were observed for time spent in closed and open arms (data not shown), frequency of entries into open and closed arms (data not shown), latency to the first entry into either arm (data not shown), or the AI (Supplementary Figure 1c).

16. Discussion

The present study had three primary aims: first, to investigate the potential impact of oral exposure to PM10 through gestation on neurodevelopmental outcomes, particularly physical development; second, to explore whether gestational exposure to PM10 disrupts inhibitory control in early adulthood; and third, to determine if social deficits in adolescence, as reported in previous studies, persist into late adulthood.

We initially hypothesized that gestational exposure to PM10 would be associated with changes across all developmental outcomes. Our findings partially supported this hypothesis, revealing a relationship between air pollution and alterations in physical and neurofunctional strength. Specifically, exposure to PM10 was associated with higher birth weight in the exposed offspring. However, this effect was not sustained throughout subsequent development. Furthermore, no significant differences were observed in ocular opening. Regarding inhibitory control, we hypothesized that PM10-exposed offspring would exhibit higher rates of behaviors indicative of impaired inhibitory control, learning, or attention deficits. Contrary to our expectations, the analyses of 5-CSRTT variables did not reveal significant effects of exposure on these domains. Finally, we expected to find evidence of social deficits in late adulthood, consistent with findings from prior unpublished work in our laboratory. However, no significant alterations in sociability were detected in late adulthood. Despite this, control variables related to social behavior yielded interesting results. PM10-exposed offspring exhibited increased locomotor activity, including greater distances traveled and higher velocity, in an anxiogenic environment such as the PMT during early adulthood. These effects, however, were not observed in late adulthood. Interestingly, the heightened activity observed in the PMT was not reflected in the OFT conducted in the same developmental stage.

Exposure to PM molecules during gestation is increasingly recognized as a significant public concern, but their effects on physical

development remain contentious. Clinical evidence highlights the potential developmental impacts of PM exposure. For instance, Clasen et al. (2022) reported an increased likelihood of low birth weight (<2500 g), though the differences were not statistically significant. Similarly, Younger et al. (2023) found associations with increased spontaneous abortion rates and maternal mortality. However, other studies, such as those by Katz et al. (2020) and Thompson et al. (2011), claim no relationship between PM exposure and abnormal birth weight outcomes. Preclinical research has also produced inconsistent findings. E Silva et al. (2008) and Dang et al. (2018) reported reduced fetal and birth weights in mice and rats exposed to PM during gestation, particularly within the first week. In contrast, studies by Weldy et al. (2014) and Li et al. (2023) found no significant differences in birth weight among exposed animals.

Interestingly, our study yielded the opposite findings. Several methodological differences could explain these discrepancies. First, Weldy et al. (2014) and Li et al. (2023) used diesel exhaust and urban particulate matter, respectively, while we used PM10. Second, Weldy et al. (2014) exposed animals directly to emissions from a Yanmar diesel engine, and Li et al. (2023) used NIST reference material collected in Prague without a specific particle diameter. In contrast, our PM10 was collected in St. Louis and had a defined particle diameter of 10 μm. Lastly, both studies employed whole-body exposure chambers, whereas we exposed animals by diluting PM10 in PBS (Ruiz-Sobremazas et al., 2024a). While we found evidence of abnormal birth weight, the effect was transient. This suggests that prenatal exposure to PM may not consistently lead to sustained birth weight abnormalities. It is also important to consider that the timing of exposure during gestation could significantly influence the outcomes, as different gestational weeks may have varying susceptibilities to air pollutants.

Another critical aspect of developmental outcomes worth discussing is the neurofunctional battery conducted on PND16. While some evidence demonstrates the impact of air pollution on neurodevelopment, the effects of air pollutants on physical development have received less attention. Most research to date has focused on the cardiovascular health implications of air pollution (Zhang et al., 2022), with limited attention given to its impact on muscular function. Emerging evidence suggests an association between air pollutants and muscle strength. For instance, studies have consistently linked air pollutants to an increased risk of sarcopenia (Zhang et al., 2023). Lin et al. (2020) explored this relationship in more depth and demonstrated that higher concentrations of PM2.5 are associated with reduced hand grip strength (HGS), a finding corroborated by Zare Sakhvidi et al. (2022). Similarly, Hagnäs et al. (2016) found that adolescents born to mothers who smoked during pregnancy exhibited lower aerobic fitness in a 19-year follow-up study. Our findings align with this clinical evidence. In our study, PM10-exposed offspring showed poorer performance in grip and adherence tests, but no differences were observed in climbing capacity. These results were consistent across rodents sourced from two different laboratories (Janvier and ENVIGO) using the same exposure procedure. To our knowledge, this study is the first to demonstrate the effects of gestational PM10 exposure on muscular capacity in a preclinical model. Interestingly, the observed deficits were task-specific and most evident in tests requiring strong HGS. This specificity may explain the lack of differences detected in climbing capacity, which relies on a combination of factors beyond HGS, including skeletal muscle growth, muscle endurance, and motor coordination (Assmann et al., 2020). Additionally, the 60º slope used in the climbing task may not have been sufficiently challenging to reveal subtle differences in performance. Although our findings are consistent with clinical evidence showing reduced HGS in individuals exposed to PM10, the mechanisms underlying these effects remain unclear. It is uncertain whether the observed deficits result from abnormal muscular development or impaired innervation. Future research is essential to unravel these mechanisms and provide a more comprehensive understanding of this relationship.

Recent evidence has increasingly established a link between air pollution and Attention Deficit Hyperactivity Disorder (ADHD). As outlined in the introduction, the core symptoms of ADHD include hyperactivity, inattention, and impulsiveness (Thapar and Cooper, 2016). Elevated levels of air pollutants, such as PM10, PM2.5, and NO2 during gestational exposure, have been associated with a higher likelihood of developing impulsive behaviors in childhood, with PM2.5 and PM10 being particularly implicated in this disorder (Liu et al., 2022). However, our findings did not support this association. No significant effect of PM10 exposure was detected on premature responses, while only anecdotal evidence was observed for perseverative responses. Similarly, no effects were observed on attentional variables. Although anecdotal evidence was found in the total number of sessions required to achieve baseline (BL) criteria, this was insufficient to indicate a robust impact of exposure on inhibitory control or attentional performance. This discrepancy between our findings and previous research may be attributed to several factors. First, as discussed in Ruiz-Sobremazas et al. (2024a), the exposure route used in our study might not sufficiently replicate the conditions required to induce an ADHD-like profile detectable in preclinical models. Second, our approach involved exposing pregnant mothers throughout the entire gestational period. However, developmental neurotoxicology emphasizes the critical importance of sensitive periods within the gestational period (1st, 2nd, and 3rd trimesters) and early-life period. Exposure during different stages of development results in distinct neurobehavioral alterations, highlighting the sensitivity of developmental timing to external influences (Oudin et al., 2019; Heyer and Meredith, 2017). Further research is needed to refine our understanding of how timing, exposure routes, and pollutant types influence the development of ADHD-like symptoms in preclinical models.

The present research was performed using a non-common exposure route for analyzing the potential negative effects of PM on neurodevelopment. Most evidence from this link comes from inhalation pathways, leaving the other exposure routes (as explained in the introduction) understudied. Several authors detected that some particles that conform PMs have negative impact when exposed dietary using gavage. Van den Brule et al. (2021) detected (using female APOE -/- and wildtype mice) a dose dependent alteration of the beta diversity of the phyla, families or genera after exposure to diesel exhaust particles (DEP) in APOE -/- mice while in the wildtype, reduced alpha and beta diversity were found in proteobacteria and patescibacteria phyla, and increased campylobacterota phylum. Some evidence points towards an interaction between Microbiota-Microglia (Hallmayer et al., 2011; Cryan et al., 2020). The relationship between maternal microbiota and NDDs in humans is still unclear. However, preclinical evidence found reduced microbiota diversity (Palanivelu et al., 2021), and abnormal immune regulation across several species (Chen Luan et al., 2019). This dysbiosis increases the immune activation, increasing the pro-inflammatory molecules that crosses through the blood brain barrier and impairs normal brain dynamics (Palanivelu et al., 2024). Brain-Gut-Microbiota communication is widely known, but the specific effects on NDDs are still unclear (see Dinan et al., 2015). Another aspect that has been reported in gavage reports is inflammation activity. Kish et al. (2013) detected increased pro-inflammatory cytokines in the colon of mice exposed to PM10; Bosch et al. (2023a, 2023b) also detected an increase interferon and inflammatory pattern in the colon of mice. In addition Mutlu et al., (2011) detected, using mice and Caco-2 cells exposed to Washington's PM10, an increase of epithelial cell death, disruption of tight-junction proteins, inflammation and increased permeability. Lastly, some authors (Miranda et al., 2018) have also detected metabolism alterations after gestational exposure via gavage to PM10 from Benin. Male offspring had higher insulin levels when exposed gestationally to PM10, alongside with pancreatic islets increased. Also, short chain fatty acids were also altered in the stool samples of mice exposed to air pollution (van den Brule et al., 2021; Kish et al., 2013). These articles used gavage to expose their animals. However, we chose oral-free instead of gavage because several reasons. First, several studies

found that the gavage technique increases psychological and physiological stress (Raymond et al., 2022; Warren et al.,2021). Second, we consider this method more ecological when the objective is to analyze oral exposure route. And third, we wanted to follow the exposure route used by Ruiz-Sobremazas et al. (2024a) to be able to conclude more accurately the effects of gestational exposure to PM10.

To our knowledge, no article was found that has analyzed the effects of this exposure on neurodevelopmental outcomes. Miranda et al. (2018) detected an increase of 15 % bodyweight at weaning. However, we did not have the same differences in weaning, but we detected differences in birthweight, that Miranda et al. (2018) did not find. These differences could be explained by some reasons. First, the PM origin is different. Miranda et al. (2018) collected the air from Benin, while we used NIST reference material as PM molecule. Second, the vehicle used are different. Miranda et al. (2018) used corn oil, while we used PBS to dilute the PM sample. And third, the exposure times are different. We exposed our animals through gestation, while Miranda et al. (2018) exposed through gestation and lactation. Both procedures might have altered offspring metabolism, but more data is needed to clarify if metabolism alterations can be created though oral exposure. In terms of behavior, there is no data to compare our findings, but the potential dysbiosis that literature find might be related to behavioral differences in distinct developmental stages. A specific metagenomic study should be performed with stool samples to determine possible relationships.

Finally, the link between air pollutants and sociability is still under debate. However, most research indicates an effect on certain sociability measures (Ruiz-Sobremazas et al., 2023; Rodulfo-Cárdenas et al., 2023). Sensitive phases, such as adolescence, are key to developing social behavior. Social behavior peaks during this phase through social play, which shapes adult sociability (Sachser et al., 2020; Garau et al., 2000). Meaney and Stewart (1981) identified this peak in sociability, reporting increased social behaviors from PND21 to PND55, though they observed no effects in late adolescence or early adulthood. Previous data from our lab shows that adolescent social behavior may be affected in specific ways, though not in total time spent on sniffing behavior. Furthermore, Ruiz-Sobremazas et al. (2024a) detected that offspring exposed gestationally using the same procedure, had higher USV (a widely used ASD-like behavior in pups) emissions than control offspring. Nevertheless, it seems that there are no long-term effects of gestational PM_{10} exposure related to social behaviors. The present findings suggest that the effects observed in the 3-CT might not be related to sociability deficits in adulthood but rather increased motivation to explore. This is evidenced by increased time spent in the empty chamber, while time spent in the social chamber was unaffected by exposure. Varlinskaya and Spear (2008) highlighted the importance of test context in shaping social interactions, with its effects varying depending on the rat's age. Our data support this notion, as PM-exposed offspring demonstrated higher motricity and velocity rates in anxiogenic environments compared to controls. Furthermore, this increased exploratory activity was also observed in Phases 2 and 3 of the NOR, where the offspring explored new objects. Additionally, this effect extended to the main variables in Phase 3 of the NOR. Adult PM-exposed offspring appear more motivated to explore new contexts, such as an empty chamber or a novel object. Although no similar effects were observed in adolescence, this absence might be explained by the typical hypermotricity state and heightened motivation for social behavior characteristic of adolescence, which diminishes in adulthood.

Moreover, we utilized NIST reference material 2787, which consists of a mixture of organic and inorganic molecules (supplementary material 2). Our study involved exposing animals to this material through ingestion. However, the pharmacokinetics of this exposure route remain poorly explored in the literature. Absorption is known to depend on corona proteins, regardless of the exposure route employed. These proteins facilitate the diffusion of microparticles into systemic circulation (Turner and Murphy, 2021). NIST-2787 contains a diverse array of molecules, some of which have been linked to neurotoxic effects, including polycyclic aromatic hydrocarbons (PAHs; Olasehinde and Olaniran, 2022), Nitro-PAHs (Bandowe and Meusel, 2017), dibenzo-p-dioxins (PCDDs; González and Domingo, 2021), aluminum (Skalny et al., 2021), and iron (Chen et al., 2019), among others. The interaction between these molecules is highly complex, and their combined effects on biological systems are still under investigation. Once in systemic circulation, these molecules undergo metabolic processes that may alter their chemical and physical properties. However, limited research has focused on the metabolic pathways associated with PM exposure (Reed et al., 2014). Furthermore, interactions among these molecules may result in the formation of new compounds that could either enhance or mitigate their toxicity. Additionally, these molecules can experience changes in their properties when absorbed by plants or diluted in water, which are primary sources of human exposure through ingestion.

Nonetheless, our study has several limitations. All behaviors performed in experiment 1 were conducted with food-deprived animals. Nevertheless, Claassen (1994) concluded that long fasting periods (16–24 h) severely changes several physiological and biochemical processes, which affects the responsiveness towards the experimental stimuli. Further research is needed to clarify if this fasting strategy is able to modify the control behaviors selected for experiment 1. Therefore, performing the control task with feed-restricted animals might influence control behaviors. Next, the oral exposure route remains under-researched, and there is insufficient information on the toxicokinetic of air pollutants, apart from studies using artificial fluids to explore this dynamic. Second, we mixed PM10 with PBS to expose our rodents. They consumed the solution quickly, but we do not know how the dissolved chemistry of that PM10 is interacting with the animals. Further research should address this issue to determine whether the original PM10 exposure is maintained. The percentage range of food-restricted rats in the 5-CSRTT might be too broad to effectively detect any task-specific effects. Principio del formulario

17. Conclusions

Our observations indicate that gestational exposure to PM10 significantly affects developmental milestones, particularly impairing the development of muscular function during adolescence and early adulthood. Surprisingly, no effects were observed on inhibitory control. Additionally, the results found in adult rats point to a potential relationship between air pollution, increased novelty reactivity, and heightened responsiveness to context. Further research is needed to thoroughly examine the effects of air pollutants on normal neurodevelopment throughout all developmental stages.

CRediT authorship contribution statement

Sánchez-Santed Fernando: Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition, Conceptualization. **Ruiz-Sobremazas Diego:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation. **Coca Mario:** Writing – review & editing, Visualization, Methodology, Investigation. **Morales-Navas Miguel:** Writing – review & editing, Supervision, Software, Methodology, Investigation, Formal analysis, Conceptualization. **Rodulfo-Cárdenas Rocío:** Writing – review & editing, Writing – original draft, Visualization, Formal analysis. **López-Granero Caridad:** Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition, Conceptualization. **Colomina Maria-Teresa:** Writing – review & editing, Supervision, Resources, Funding acquisition, Conceptualization. **Perez-Fernandez Cristian:** Writing – review & editing, Visualization, Supervision, Project administration, Methodology, Investigation, Formal analysis, Conceptualization.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the author(s) used ChatGPT3 to improve the text's readability and comprehensibility. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Fernando Sanchez-Santed reports financial support was provided by Spain Ministry of Science and Innovation. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neuro.2025.04.007.

Data availability

Data will be made available on request.

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