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Effects of prenatal bisphenol S and bisphenol F exposure on behavior of offspring mice

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ABSTRACT

Bisphenol A (BPA) is a representative endocrine-disrupting chemical that exhibits hormonal disturbance reactions. Various alternatives, such as Bisphenol S (BPS) and Bisphenol F (BPF), are being developed. BPS and BPF (which are representative alternatives to BPA) are used in consumer products such as polycarbonate plastics and epoxy resins. They have structures similar to those of BPA and have also been proven to be exogenous endocrine disruptors. However, although there are many studies on BPA, there are few studies on the neurodevelopmental effects of BPS and BPF. Therefore, in this study, we analyzed neurobehavioral changes in offspring mice exposed to BPS and BPF during brain development by administering BPS and BPF to pregnant mice. We found that prenatal exposure to BPS and BPF did not affect anxiety-and depression-like behaviors, locomotion, sociability, memory, or cognition functions in offspring mice. However, exposure to BPS and BPF decreased the preference for social novelty in the offspring mice. Taken together, these findings suggest that perinatal exposure to BPS and BPF affects changes in social behaviors, but not other behavioral changes such as emotion, memory, or cognition in the offspring mice.

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Introduction

Endocrine-disrupting chemicals (EDCs) are exogenous synthetic chemicals that act like hormones in the body, interfering with the normal function of the endocrine system (Diamanti-Kandarakis et al. 2009). Humans are continuously exposed to EDCs as they are used in pesticides, plastics, and drugs, which are essential in modern society. Many studies have suggested that EDCs have anti-estrogenic and anti-androgenic effects, which interfere with normal metabolism and homeostasis regulation and cause developmental, reproductive, neurological, and immunological side effects (Cevasco et al. 2008; Diamanti-Kandarakis et al. 2009; Schug et al. 2011; De Coster and Van Larebeke 2012).

Bisphenol A (2,2-bis-(4-hydroxyphenyl) propane; BPA) is a representative EDC that has estrogen agonist and antagonist properties (Allard and Colaiácovo 2011). BPA is an organic compound and has been used in various production industries owing to its lightness, transparency, outstanding durability, and heat resistance (Allard and Colaiácovo 2011; Ahn et al. 2022; Welch and Mulligan 2022). BPA is used as a major raw material in polycarbonate and epoxy resins. Polycarbonate is mainly used in household goods, such as baby bottles, water bottles, and food storage containers, as well as CDs, DVDs, and sunglasses. In addition, epoxy resins are widely used as coating agents in cans, dental sealants, and industrial paints (Vandenberg et al. 2007; Rubin 2011; Inadera 2015; Rebolledo-Solleiro 2021). However, BPA interacts with estrogen receptors in the body and acts through estrogen receptor-dependent signaling pathways, causing the pathogenesis of several endocrine diseases (Olsson et al. 2015). Furthermore, BPA has a significant adverse effect on reproductive function by interfering with the physiology of the hypothalamus-pituitary-gonad axis, and acts harmful to

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brain development and function by interfering with steroid signaling (Santoro et al. 2019). In particular, as BPA can penetrate the placenta and blood–brain barrier (BBB), its affects fetal neurodevelopment (Kimura et al. 2016; Müller et al. 2018). In rodents, exposure to prenatal BPA reduces neurogenesis in the hippocampal dentate gyrus, thereby affecting long-term memory maintenance (Komada et al. 2020).

The use of BPA has been banned because exposure to it exhibits various adverse effects, including heart and liver diseases, cancer, and obstruction of neurodevelopment. Thus, researchers have developed an alternative to BPA (Garí et al. 2021). Representative BPA alternatives include Bisphenol S (4,4′-Sulfonyldiphenol; BPS) and Bisphenol F (4,4′-Methylenediphenol; BPF), which are structurally similar to BPA but are known to be less toxic (Komarowska et al. 2021). In fact, BPS and BPF are used not only in epoxy resin and plastic manufacturing but also in thermal paper in place of BPA (Inadera 2015; Chen et al. 2016). However, since BPS and BPF have similar chemical structures to BPA, it has been suspected that they may show endocrine disrupting effects (Eladak et al. 2015). A recent study reported that BPS is significantly associated with the incidence of cardiovascular disease and may have harmful effects on the female reproductive system by causing oxidative induction and hormonal changes (Nourian et al. 2020; Wang et al. 2022). In addition, BPS acts as an agonist of estrogen receptor α (ERα), promoting the growth of cancer cells; thereby increasing the incidence of breast cancer (Thoene et al. 2020). Exposure of BPS to *in vitro* bovine oocytes resulted in increased embryonic arrest and apoptosis (Saleh et al. 2021). Moreover, it has been reported that chronic exposure to BPS can lead to infertility in males by inhibiting gonadotropin secretion, inducing structural changes in the testicles, and causing endocrine changes in the male reproductive system to interfere with sperm formation (Ullah H et al. 2021). BPF also showed antagonistic effects on male reproductive hormones and caused changes in testicular morphology when administered to adult male mice (Ullah A et al. 2019). Additionally, exposure of zebrafish to BPF increases the malformation rate of offspring by impairing reproductive function through interference with the balance of steroid hormones (Yang et al. 2017). Moreover, exposure to BPF results in mitochondrial abnormalities, such as reduced oxygen consumption and decreased mitochondrial membrane potential, which severely reduces cell viability (Hyun et al. 2021). In an *in vitro* study, exposure to BPS increased ROS levels and apoptosis rates in hippocampal cells, indicating neurotoxicity (Pang et al. 2019). Many studies have shown that BPS and BPF have negative effects on organisms, but there are significantly fewer studies on neurodevelopment by exposure of BPS and BPF to fetal periods compared to BPA.

The European Food Safety Authority (EFSA) designated the no-observed-adverse-effect-level (NOAEL) of BPA to be 5 mg/kg bw/day and proposed a tolerable daily intake (TDI) value of 0.2 ng/kg bw/day based on the NOAEL value (Lambré et al. 2023). On the other hand, the US Environmental Protection Agency (EPA) proposed the NOAEL of BPS for developmental toxicity as 20 mg/kg bw/day, and the NOAEL of BPF for development has not yet been proposed (Fitzgerald et al. 2020). In this study, the exposure concentrations of BPS and BPF were set to 50 μg/kg bw/day in consideration of the TDI value of BPA because the results of the *in vivo* studies of BPS and BPF are still insufficient in relation to neurodevelopment. In this study, we observed neurobehavioral alterations in offspring mice exposed to BPS and BPF during the experimental period to assess the effect of BPS and BPF on neurodevelopment.

Materials and methods

Animals and treatment

Sexually mature C57BL/6J female and male mice (25–30 g) were purchased from Samtaco (Osan, Gyeonggi, Republic of Korea). Mice were housed under controlled environmental conditions with a constant temperature (24 ± 1°C) and a 12:12 light/dark cycle (lights on from 6:00 to 18:00). After acclimatization, three female mice were mated overnight with one male mouse; the day on which a vaginal plug was observed was considered E0.5. Pregnant mice were housed separately and randomly divided into three groups (two pregnant mice in each group): vehicle (corn oil) and exposure to bisphenol (BPS, BPF). Maternal mice were subcutaneously injected daily with BPS or BPF at a dose of 50 μg/kg bw/day from E9.5–P28. The BPS and BPF were dissolved in corn oil. After weaning (P28), the female and male offspring were separated and housed in group of 4–5 mice under the same conditions until P84 (Figure 1). The Institutional Animal Care and Use Committee of Pusan National University approved all experimental protocols, and all experiments were conducted in accordance with relevant guidelines and regulations.

Behavioral analysis

Experimental design: at the age of 6 weeks, offspring were randomly selected for behavioral tests, as previously described (Jung et al. 2017). All behavioral tests

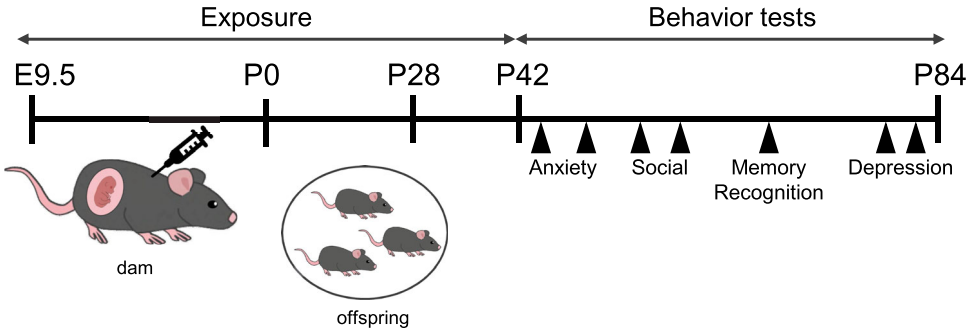

Figure 1. Overview of the experimental process. Pregnant mice were subcutaneously injected daily with corn oil or BPS or BPF from E9.5-P28. After weaning (P28), the female and male offspring were separated and reared under the same conditions, and behavioral experiments were conducted from P42 to P84.

were conducted during the light cycle. On the day of the experiment, the mice were transferred to the testing room for at least 30 min before the start of the experiment, and the test was performed by laboratory technicians who were blinded to the mouse group information. All experiments were conducted between 8:00am and 6:00pm, and a resting period of 2 days per week was provided between two consecutive tests. All experimental areas were cleaned using 70% ethanol before conducting the tests and between each test.

Three-chamber social test

The three-chambered apparatus was composed of three Plexiglas chambers, each measuring $20 \times 40 \times 22$ cm, and a small square opening on the partition wall dividing each chamber. This allows the mouse to enter and exit each chamber freely. Both side chambers had cylindrical plastic cages (17 cm in height, 8 cm in floor diameter, and 1 cm in bar spacing) used to hold strange mice. The three-chambered social test was conducted as follows (Jung et al. 2017). First, the experimental mouse was allowed to freely explore all three chambers during the 5 min adaptation period. For the sociability test, a C57BL/6J mouse (Stranger 1, 'S1') was placed in a cylindrical plastic cage in one side chamber and the cylindrical plastic cage in the other chamber was left empty (Empty 'E'). The subject mouse was then placed in the center chamber and allowed to freely roam all three chambers for 10 min. For the social novelty test, another unfamiliar mouse (Stranger 2, 'S2') was held in an empty plastic cage, and the subject mouse was again allowed to freely roam all the three chambers for 10 min. All stranger mice were of the same strain, gender and age as the subject mice and were habituated to plastic cages separated from the subject mice. The time spent in close proximity, distance traveled, and heat maps were measured using EthoVision® XT16 software. The preference index for each animal was calculated as preference index $= \frac{(S1 - E)}{(S1 + E)}$ or as $\frac{(S2 - S1)}{(S2 + S1)}$; where 'E,' 'S1,' and 'S2' are the time spent in close proximity with the empty cage, the stranger mouse 1, and 2, respectively.

Social interaction test

In the opposite corner of the open-field apparatus, subject mice and unfamiliar wild-type mice were placed and allowed to explore freely for 10 min. The frequency of active social development behaviors (including general sniffing, anogenital sniffing, following) were scored.

Open-field test

The open-field test was performed in an acrylic cube ($50 \times 50 \times 60$ cm) with a white bottom. To assess the degree of anxiety and locomotor activity, mice were individually placed near the wall and allowed to move freely for 5 min. The movement of the mice was recorded and analyzed using the EthoVision® XT16 software (Noldus, Leesburg, VA, USA). The time spent in the central area (15×15 cm virtual square), frequency in the central area, speed, and distance traveled were measured and analyzed.

Elevated plus-maze test

The elevated plus-maze test was performed as previously described (Sur and Lee 2022). The apparatus consists of two open arms (35×5 cm), two enclosed arms ($35 \times 5 \times 15$ cm), and a central platform (5×5 cm). The apparatus was elevated to 45 cm above the floor. A mouse was placed on the central platform facing the open arm and allowed to travel for 5 min. The number of entries and the time spent in the open and closed

arms were recorded and analyzed using EthoVision® XT16 software.

Tail suspension test

Each mouse was suspended from a shelf 50 cm above the table surface. The mice were suspended for 6 min, and a camera was used to record their behavior. The videos were analyzed to record the duration of immobility of the mice in the last 5 min.

Forced swimming test

Each mouse was gently placed in a glass cylinder (20 cm in height and 15 cm in diameter) filled with water (25 ± 2°C) to a depth of 12 cm. For the pre-test, all mice were acclimatized in water for 15 min 24 h prior to the main record. 24 h later, all mice were forced to swim for 5 min and the period of immobility was recorded.

Rotarod test

To evaluate motor coordination and learning in mice, the rotarod test was performed using a Rotamex. This was performed by measuring the time spent on the rod by placing the mice on rotating drums. The rotation speed was increased from 4 to 40 rpm for 5 min. Three trials were performed per day for 6 days: 3 days for the training phase and 3 days for the training phase. A minimum recovery time of 20 min was allowed between trials.

Novel object recognition

To evaluate the memory and cognition functions of the mice, the subject mouse was placed in an open field apparatus with two identical objects (2 × 5 × 9 cm) and allowed to explore freely for 10 min. After 6 h, one of the objects was replaced with another novel object, which was similar size but different color and shape compared to the previous object, and the subject mouse was placed into the apparatus and allowed to explore freely for 10 min. We recorded the time the mouse interacted with novel and familiar objects. The videos were analyzed using the EthoVision® XT16 software.

Statistical analysis

All statistical analyses were conducted using a one-way ANOVA of variance for more than two independent groups (Bonferroni's multiple comparison test for comparing all pairs of columns) or two-tailed, unpaired Student's t tests for two-population comparisons. Data were collected randomly and analyzed using Prism software (GraphPad, USA). The results are presented as mean ± SEM, and the *p*-values for each comparison are described in the figure legends. Each experiment was performed blind and randomized. Animals were randomly assigned to different experimental groups and data were collected and processed randomly. The results of all treatment groups were compared with those of the vehicle group.

Results

BPS and BPF decrease preference for social novelty in offspring mice

To assess each group's discrimination ability of social interaction behavior and social novelty, a three-chamber test was performed. First, to evaluate the sociability of offspring, mice from each group explored the three-chamber apparatus with an unfamiliar mouse in one of the side chambers. In the sociability test, all groups of mice spent significantly more time in the side chamber, in which an unfamiliar mouse (S1) was present, than in the empty chamber (E). For the social novelty test, the empty chamber (E) was replaced with a novel chamber containing a second unfamiliar mouse (S2). In the social novelty test, the vehicle mice spent significantly more time in the novel chamber (S2) than the familiar chamber (S1). However, there was no difference between groups in the preference index for sociability, and in social novelty, the time spent in the novel mouse zone in the BPS and BPF groups was significantly short (Figure 2(A and B)). In addition, in the BPS and BPF groups, there were no differences in the time spent between the novel chamber (S2) and familiar chamber (S1) (Figure 2(A and C)). Next, a social interaction test was performed to evaluate the social interaction behavior of each group. As a result of the social interaction test, the offspring of the BPS and BPF groups had a significantly lower frequency of general sniffing toward the relative mouse than the vehicle group (Figure 2(D)). These results showed that exposure to BPS and BPF decreases the preference for social novelty in the offspring mice and alters social behavior.

BPS and BPF have no effect on anxiety-like behaviors in offspring mice

To assess anxiety-like behavior, an open-field test and an elevated plus maze test were performed. In the open-field test, anxiety was measured using the frequency

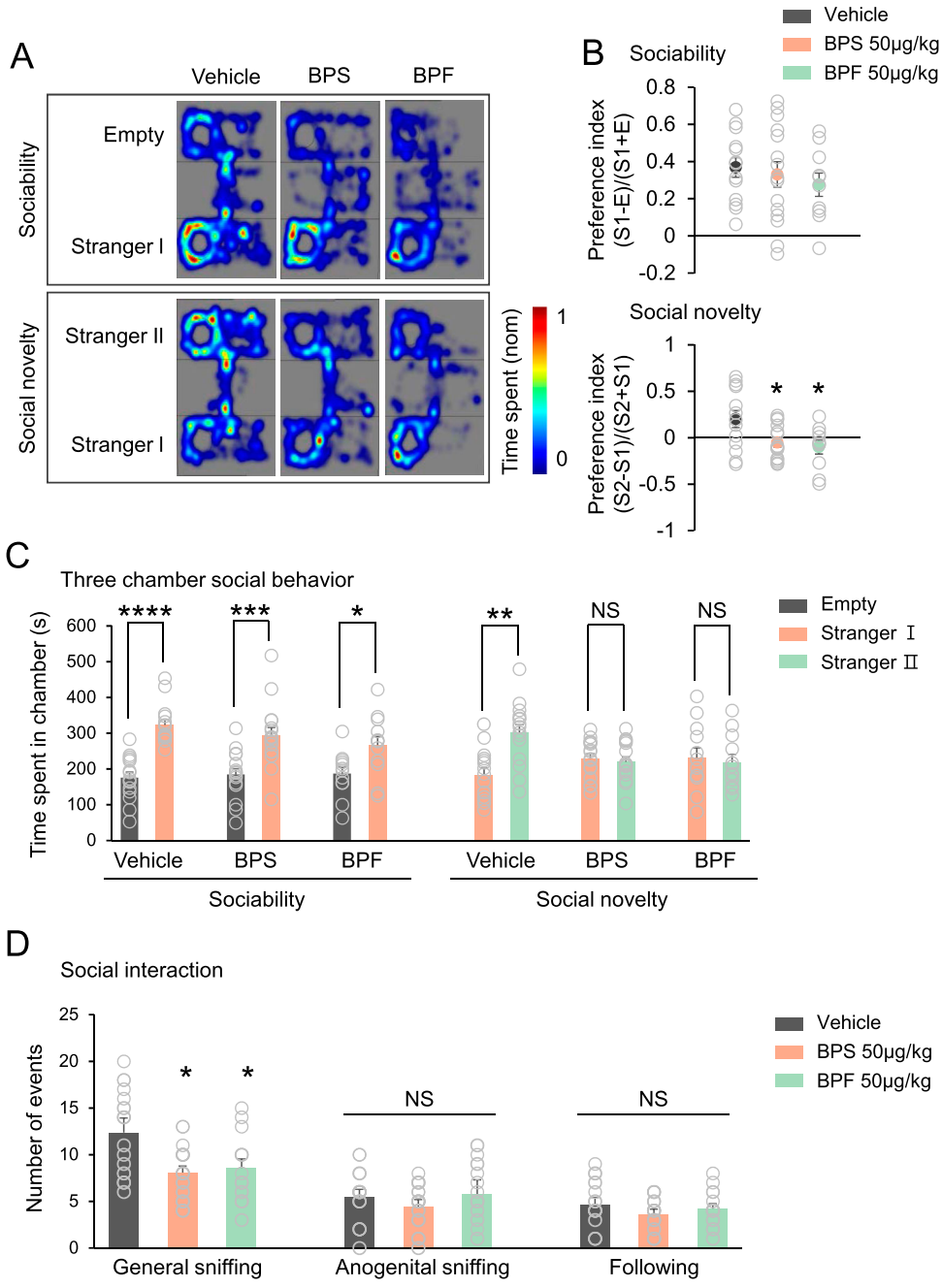

Figure 2. BPS and BPF display alteration of social behavior in offspring mice. (**A**) Representative heat-map images of three-chamber test representing sociability and social novelty for each group. (**B**) The preference index of the BPS- and BPF-treated groups were significantly lower than the vehicle group at the social novelty test but, no change in the sociability (sociability: $F_{2,36} = 0.5033$ and $p = 0.6089$; social novelty: $F_{2,36} = 4.924$ and $^{*}p = 0.013$;) (**C**) In the sociability test, all groups spent more time in the chamber containing the unfamiliar mouse (S1) than in the empty chamber (Vehicle: $t_{15} = 6.893$, $^{****}p < 0.0001$; BPS: $t_{16} = 3.907$, $^{***}p = 0.0005$; BPF: $t_{12} = 2.600$, $^{*}p = 0.0163$). In the social novelty test, while the vehicle group spent more time significantly in a novel chamber (S2) than in the familiar chamber (S1), the BPS and BPF groups have no significant difference in the time spent in the two chambers (Vehicle: $t_{15} = 4.029$, $^{***}p = 0.0004$; BPS: $t_{16} = 0.4670$, $p = 0.6439$; BPF: $t_{12} = 0.3631$, $p = 0.72$). $n = 15$ mice (8 males, 7 females) in the vehicle group, $n = 16$ mice (11 males, 5 females) in the BPS group, and n = 12 mice (10 males, 2 female) in the BPF group; two-tailed student's t-test. Statistical significance was determined between the times spent in the empty chamber and that with stranger 1, or times spent with strangers 1 and 2, for each group and condition. Statistical significance was determined using a two-tailed student's *t*-test. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ vs. opposite chamber. Data are presented as mean ± SEM. NS indicates no significant differences. (**D**) In the open-field apparatus, a social interaction test was performed. There was lower interaction of general sniffing in the BPF groups, as compared to that in the vehicle group and other interaction have no effects. (general sniffing: $F_{2,41} = 5.63$ and $^{**}p = 0.0069$; anogenital sniffing: $F_{2,41} = 1.173$ and $p = 0.3194$; following: $F_{2,41} = 1.148$ and $p = 0.3271$;). $n = 16$ mice (9 males, 7 females) in the vehicle group, $n = 16$ mice (11 males, 5 females) in the BPS group and $n = 12$ mice (10 males, 2 females) in the BPF group; one-way ANOVA, with Bonferroni's correction. $^{**}p < 0.01$ vs. vehicle.

and cumulative time spent in the center area and total movement distance during the test. In the offspring mice exposed to BPS and BPF, there was no significant difference in the vehicle group in frequency and cumulative duration in the central area (Figure 3(A–C)). In addition, the distance moved in the open-field arena and velocity were no significant difference between the groups (Figure 3(D and E)). In the elevated plus maze test, anxiety was evaluated as the frequency of entering the open arms and the time spent in the open arms and total movement distance during the test. In the elevated plus-maze test, the offspring exposed to BPS and BPF showed no significant difference in frequency and time spent in the open arms

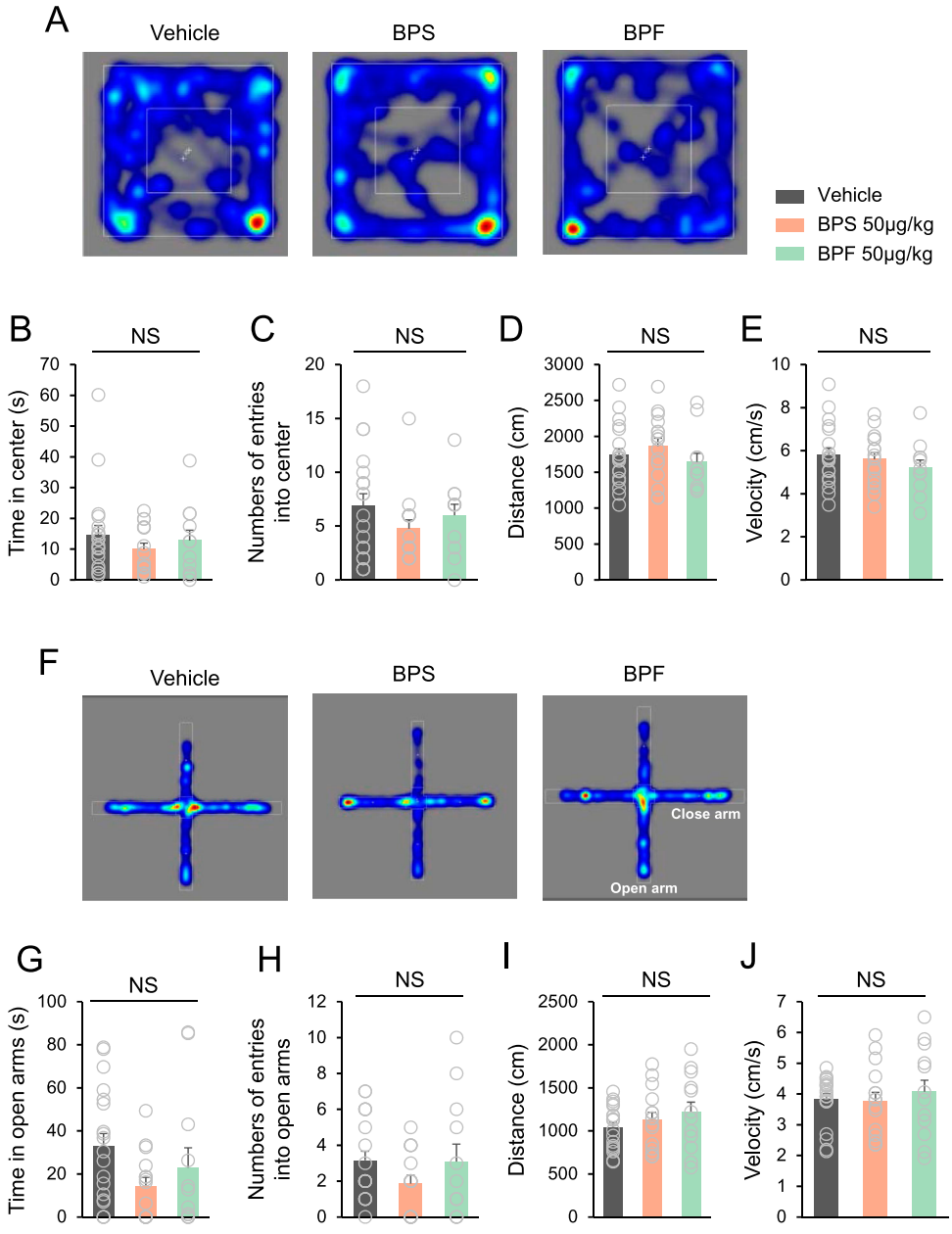

Figure 3. BPS and BPF do not affect anxiety-like behaviors in offspring mice. (**A**) Representative tracing of the mouse's travel in the open field test. (**B**) Time spent in the center ($F_{2,44} = 0.6935$ and $p = 0.5052$). (**C**) Numbers of entries into the center ($F_{2,44} = 1.208$ and $p = 0.3085$). (**D**) Total movement distance in the arena ($F_{2,44} = 0.8915$ and $p = 0.4173$). (**E**) Velocity in the arena ($F_{2,44} = 0.7452$ and $p = 0.4805$). $n = 20$ mice (14 males, 6 females) in the vehicle group, $n = 16$ mice (11 males, 5 females) in the BPS group, and $n = 11$ mice (9 males, 2 females) in the BPF group; one-way ANOVA, with Bonferroni's correction. (**F**) Representative tracing of the mouse's travel in the elevated plus maze. (**G**) Time spent in the open arm ($F_{2,43} = 2.262$ and $p = 0.1164$). (**H**) Numbers of entries into the open arms ($F_{2,43} = 1.3$ and $p = 0.2831$). (**I**) Total movement distance in the arena ($F_{2,43} = 1.013$ and $p = 0.3718$). (**J**) Velocity in the arena ($F_{2,43} = 0.2718$ and $p = 0.7833$). n = 19 mice (12 males, 7 females) for the vehicle group, $n = 15$ mice (11 males, 4 females) for the BPS group, and n = 12 mice (10 males, 2 females) for the BPF group; one-way ANOVA, with Bonferroni's correction. Data are presented as mean ± SEM. NS indicates no significant differences.

compared to the vehicle group (Figure 3(F–H)). Additionally, total movement distance in the arena and velocity were no significant differences between the groups (Figure 3(I and J)). These results show that exposure to BPS and BPF during pregnancy and lactation did not affect anxiety-like behaviors in offspring mice.

BPS and BPF have no effect on depression-like behaviors in offspring mice

Tail suspension and forced swimming tests were performed to evaluate whether depression-like behavior was induced in the offspring mice in the BPs exposure group. In the tail suspension test, the offspring of the BPS and BPF groups showed no significant difference in immobility time compared to the vehicle group (Figure 4(A)). In addition, in the forced swim test, there was no significant difference in the immobility time between the groups (Figure 4(B)). These results indicated that BPS and BPF did not induce depression-like behavior in offspring mice.

BPS and BPF have no effect on locomotion in offspring mice

Rotarod tests was performed to assess locomotion and motor learning of the offspring mice in each group. There was no significant change between the groups in the rotarod test results conducted to evaluate motor learning and motor coordination (Figure 4(C)). These results indicated that offspring mice exposed to BPS and BPF did not exhibit any effect on locomotion or motor learning.

BPS and BPF have no effect on cognition and memory function

The novel object test was performed to assess the memory ability of each group. Initially, each group of mice was allowed to explore two identical objects in an open field. Six hours later, one of the two objects was replaced with a novel object and explored again. All groups showed significantly higher proximity to the novel object than to the familiar object (Figure 4(D)). These results indicate that exposure to BPS and BPF does not affect cognition and memory function in offspring mice.

Discussion

Because BPA, an endocrine disruptor, is toxic to organisms, BPA alternatives such as BPS and BPF have been developed. However, the safety of BPS and BPF is still questionable (Eladak et al. 2015). Exposure to BPS and BPF adversely affects organism development. Studies have shown that BPA adversely affects post-fetal development by interfering with thyroid hormone (TH) signaling in vertebrates. Additionally, its analogues (such as BPS and BPF) also interfere with the TH signaling pathway, affecting vertebrate development (Zhang et al. 2018). Inhibition of the developmental period of TH signaling affects the decline in social behaviors of the offspring (Baek et al. 2014). When rat fetal neural stem cells (rNSCs) were treated with BPF, morphological changes in astrocytes were observed, and an increase in immature neurons and oligodendrocytes was observed (Gill and Kumara 2021).

Since there are not many *in vivo* studies on the neurodevelopment of BPS and BPF, the toxic concentrations of these two substances have not been determined. This study attempted to investigate the behavioral changes in offspring caused by perinatal exposure to BPS and BPF. In a few previous studies that observed behavioral changes following the administration of BPS and BPF, the study was conducted based on the NOAEL value of BPA, 5 mg/kg bw/day (Wang Y et al. 2020; Wang Z et al. 2020). However, there have been studies showing behavioral or molecular changes in the results of exposure to a concentration of less than 5 mg/kg bw/day (Xu et al. 2010; Castro et al. 2015). Therefore, this study used a concentration of 50 μg/kg bw/day, which is lower than the NOAEL value of BPA, based on the TDI value of BPA.

This study showed a deficit of a preference for social novelty in the offspring mice exposed to BPS and BPF, with no effect on sociability. Social behavior is known to be related to psychical disorders such as autism spectrum disorder and schizophrenia, and patients with these diseases have impaired social behavior (Wilson and Koenig 2014; Barak and Feng 2016). Social novelty behavior has been frequently used to evaluate social dysfunction in genetic mouse models of autism spectrum disorders (Silverman et al. 2010; Bicks et al. 2015). A previous study found that chemogenetic inhibition of activated GABAergic neurons in mice disrupted social novelty behavior (Zhao et al. 2022). Similarly, other studies exposing zebrafish larvae to BPS have demonstrated that early exposure to BPS leads to an imbalance of GABA and glutamate, which can lead to decrease in social interactions and neurodevelopmental disorders (Naderi et al. 2022). The offspring were exposed to 0.2 mg/kg bw/day BPS from E8 to P21 decreased social interaction (Kim B et al. 2015). Moreover, estrogen receptors affect social behaviors by acting as transcription factors, and in the previous study, it was observed that the expression of *Esr1* gene was reduced in the offspring mice treated

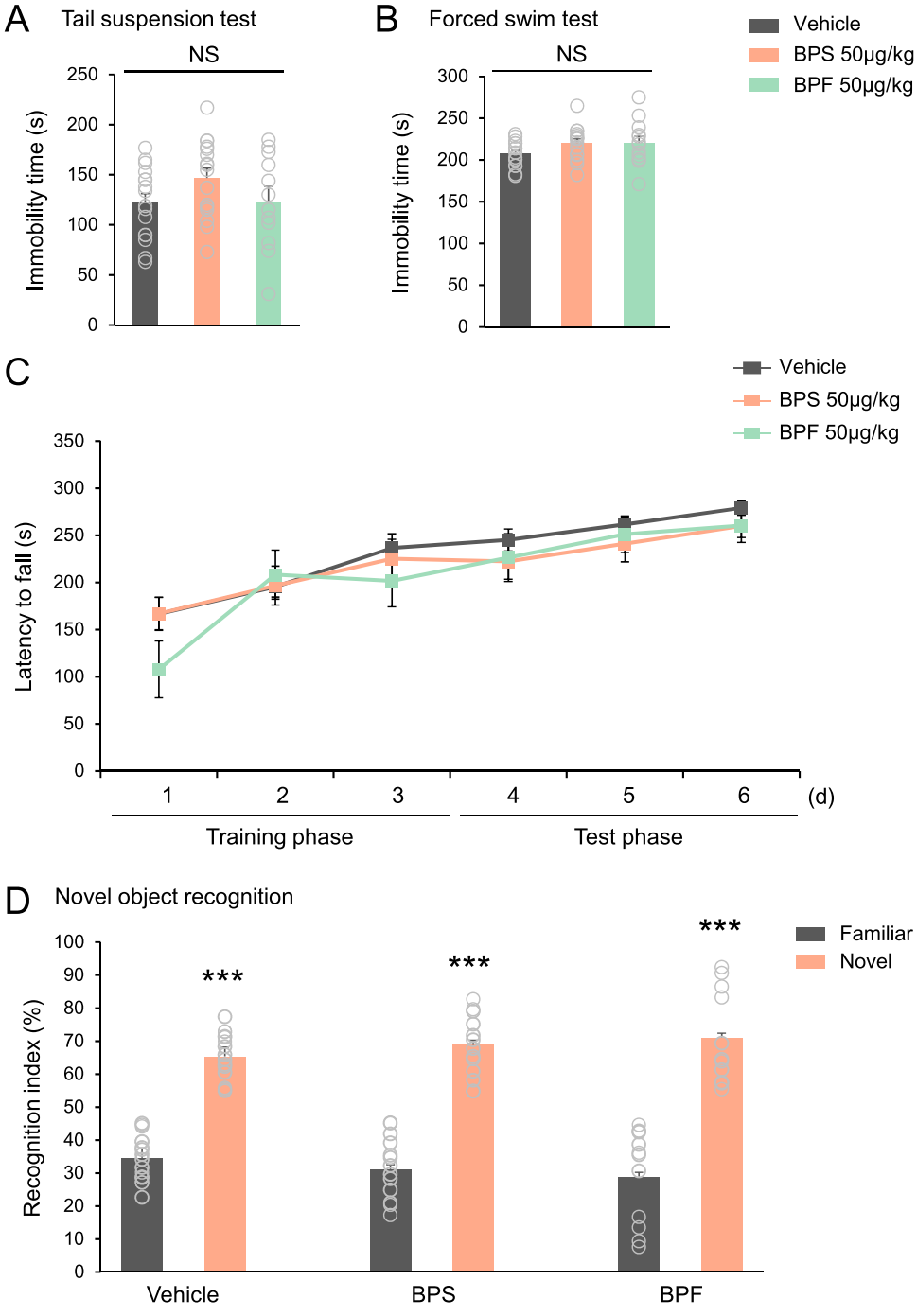

Figure 4. BPS and BPF do not affect depression-like behaviors, motor learning, cognition and memory function in offspring mice. (**A**) In the tail suspension, there was no significant difference between vehicle and bisphenols groups ($F_{2,41} = 1.827$ and $p = 0.17738$). $n =$ 16 mice (9 males, 7 females) in the vehicle group, $n = 16$ mice (11 males, 5 females) in the BPS group, and $n = 12$ mice (10 males, 2 females) in the BPF group; one-way ANOVA, with Bonferroni's correction (**B**) In the forced swim test, there was no significant difference between vehicle and bisphenols groups ($F_{2,40} = 1.936$ and $p = 0.1576$). $n = 15$ mice (8 males, 7 females) in the vehicle group, $n =$ 16 mice (11 males, 5 females) in the BPS group, and $n = 12$ mice (10 males, 2 females) in the BPF group; one-way ANOVA, with Bonferroni's correction. (**C**) In the rotarod test, the latency to fall during test phases was no significant differences in each group. $n = 16$ mice (9 males, 7 females) for the vehicle group, $n = 16$ mice (11 males, 5 females) for the BPS group, and $n = 13$ mice (10, 3 males) for the BPF group; one-way ANOVA, with Bonferroni's correction. (**D**) In the novel object recognition test, vehicle group and BPS- and BPF-treated groups spent significantly more time exploring the novel object than the familiar object (Vehicle: $t_{16} = 12.60$, $^{***}p < 0.0001$; BPS: $t_{16} = 10.44$, $^{***}p < 0.0001$; BPF: $t_{12} = 6.261$, $^{***}p < 0.0001$). $n = 16$ mice (9 males, 7 females) for the vehicle group, $n = 16$ mice (11 males, 5 females) for the BPS group, and $n = 12$ mice (10 males, 2 females) for the BPF group; two-tailed Student's t-test. $^{***}p < 0.001$ familiar vs. novel object. Data are presented as mean ± SEM. NS indicates no significant differences.

with BPA, and social interaction was reduced in these offspring mice (Wolstenholme et al. 2012). In addition, maternal exposure to BPS increases arginine-vasotocin levels in the brains of offspring zebrafish and weakens their social interactions of offspring zebrafish (Salahinejad et al. 2022). Postnatal exposure to BPS disrupts the arginine vasotocin/oxytocin signaling pathway, impairing social interactions in zebrafish (Salahinejad et al. 2020). In this study, a three-chamber social test and social interaction test were conducted to assess whether exposure to BPS and BPF affected the social ability of offspring mice. The results showed that BPS- and BPF-treated offspring mice had no effect on sociability, but had a significant effect on preference of social novelty and reduced the social interaction.

A recent study revealed that exposure to BPS induces a hypoglycemic effect, causing disturbances in the TH signaling pathways (Guo et al. 2021). As studies have shown that hypoglycemia induces depression-like behavior, it could be assumed that exposure to BPS can exhibit depression-like behavior (Park et al. 2012). In rodents, exposure to BPF changes spermatogenesis in the testes and causes a reduction in testosterone secretion (Ullah A et al. 2019). Testosterone is a sex steroid hormone produced in the testicles that reduces anxiety-like behavior and increases exploration of the environment by reducing AVP methylation in the amygdala in rodents (Tong et al. 2019). In an *in vitro* assay, BPS had a function similar to that of estradiol and induced MAPK signaling (Viñas and Watson 2013). Activation of MAPK signaling is involved in the induction of anxiety-like behaviors (Di Benedetto et al. 2009). These results suggest that exposure to BPS and BPF leads to anxiety- and depression-like behaviors. In a recent study using zebrafish, exposure to BPS caused oxidative stress, leading to high levels of anxiety-like behavior (Wei et al. 2020; Salahinejad et al. 2021). A previous study has shown high levels of anxiety-like behaviors in the elevated plus maze of offspring mice exposed to 10 µg/kg bw/day and 50 µg/kg bw/day BPS orally from E9 to P20 (Da Silva et al. 2019). In addition, maternal exposure to 10 mg/kg bw/day BPF by oral gavage from the fetal period to weaning showed increased anxiety- and depression-like behaviors compared to the vehicle group (Ohtani et al. 2017). However, contrary to previous results, offspring treated with BPS and BPF did not show anxiety- or depression-like behaviors in this study. In the open-field test, the movement of the offspring mice treated with BPS and BPF was reduced, and locomotion was evaluated using the rotarod test. There were no differences in locomotion in offspring mice.

Bisphenols have been reported to affect the development of the hippocampus in cell lines and animal studies, and have an adverse effect on memory and cognitive abilities (Kim ME et al. 2011; Kimura et al. 2016; Birla et al. 2019; Pang et al. 2019; Mu et al. 2022). *In vitro* assays have indicated that BPS causes loss of myelin sheaths, decreases the number of synapses in the mouse hippocampus and decreases the expression of BDNF genes (Li et al. 2022). When BPS is administered to HT-22 cells (a mouse hippocampal cell line) ROS levels increase and apoptosis increases, indicating that BPS adversely affects hippocampal cells (Pang et al. 2019). In a zebrafish study, chronic exposure to BPS resulted in the downregulation of genes involved in glutamic acid/ERK/CREB signaling cascades in the brain, leading to a decrease in memory and cognitive function (Naderi et al. 2020). In a population-based pregnancy cohort study, BPF exposure to fetuses showed significant cognitive decline in 7-year-old children, and the study showed that fetal exposure to BPF was associated with cognitive developmental disorders (Bornehag et al. 2021). However, in the present study, there was no effect on memory and cognitive ability in offspring of mice treated with BPS and BPF.

This study was conducted to determine the effects of gestational exposure to BPS and BPF, which are alternatives to BPA, on neurobehavioral changes in mice offspring. In offspring mice treated with 50 µg/kg bw/day BPS and BPF, there was no effect on anxiety-and depression-like behaviors, locomotion, memory and cognitive functions, and sociability. However, they were also found to have reduced social novelty preference and social interaction. Future studies will need to investigate the effects of BPS and BPF on various organs including the brain.

Conclusions

This study observed behavioral changes in mice offspring exposed to BPS and BPF, which are used as alternatives to BPA. Exposure to BPS and BPF did not affect offspring growth. Exposure to BPS and BPF did not affect anxiety-and depression-like behaviors, locomotion, memory and cognition functions, or sociability; however, it was deficient in social novelty in offspring mice. Future studies will be required on mechanisms of social behavioral alterations in offspring mice due to exposure to BPS and BPF.

Data availability statement

The data used to support the findings of this study are available from the corresponding author upon request.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Ethics approval

All experimental protocols were approved by the Institutional Animal Care and Use Committee of Pusan National University Institutional Animal Care (Protocol code: PNU-2023-0331, Approval date: 2023-05-15) and Use Committee (IACUC), and all experiments were carried out in accordance with the relevant guidelines and regulations.

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