The Behavioral Effects of Endocrine-Disrupting Chemicals and Sexual Aggression in Female Adolescent Rats

Ximena De La Cruz

Honors Thesis

Department of Psychology, The University of Texas at Austin

Faculty Advisor: Andrea C. Gore, Ph.D.

Graduate Student Mentor: M. Nicole Kunkel

May 2020

Dedication

My thesis is dedicated to the De La Cruz-Atao family whose sacrifices have made my education and achievements possible.

Acknowledgements

I want to thank Nicole Kunkel for working with me one-on-one for the past year, I am so grateful for your mentorship in research. Thank you to Dr. Andrea Gore and fellow Gore Lab members for welcoming me into your projects. This community has been very supportive of my academic endeavors such as acceptance into my top choice research conference. Lastly, I want to give a big thanks to Dr. Theresa Jones who has provided helpful feedback at every stage of the writing process and served as a reliable thesis advisor.

Abstract

Trauma from unwanted sexual experiences often elicits the development of psychological symptoms including anxiety, PTSD, and depression in women. These responses are governed by biological systems (e.g., the autonomic nervous and endocrine systems) that are susceptible to influence by other environmental challenges such as exposure to ubiquitous endocrine-disrupting chemicals (EDCs). Despite commonalities in mechanisms of environmental and socio-sexual stress, this area has been unexplored to my knowledge. In this study, I used a model of sexual aggression in rodents (SCAR; Shors et al., 2016) combined with pre and postnatal exposure to EDCs, to analyze behavioral changes from socio-sexual stress in female rats. Adolescent females were either unexposed or repeatedly exposed to sexually experienced adult males and assessed for anxiety and mate preference for male aggressors. Higher anxiety and lower preference for male aggressors were predicted in females exposed to SCAR while EDC exposure was expected to exacerbate these behaviors. Results revealed no influence from SCAR exposure, but significant implications from EDC exposure in mate preference. Females exposed to EDCs also exhibited altered social behaviors regardless of sexual experience in adolescence. These findings elucidate influence of external stressors across a lifespan and help advance our understanding of neuroendocrine disruption as it affects behavior.

The Department of Justice (2019) reports that sexual assault affects an American every seventy-three seconds with women ages 16-19 at a risk four times higher than others. The stress or trauma brought on by sexual assault has consequences seen in humans and now animal models like the sexual conspecific aggressive response (SCAR) model developed by Shors and colleagues (2016). Changes in stress hormones and learning abilities have been explored but further investigation is appropriate in order to determine the scope of SCAR as a sexual assault model. Behaviors that may be influenced by sociosexual stress such as sexually aggressive experiences are elucidated using this tool.

Endocrine disrupting chemicals (EDCs) are man-made compounds ubiquitous in our environment that interfere with the body's natural endocrine system. They do so by disrupting hormonal mechanisms, metabolism, or degradation (Zoeller et al., 2012). Consequences from exposure to these chemicals depend on quantity relative to the developmental stage at time of exposure. High exposure to EDCs during more vulnerable periods of development, such as those earlier in life, see longer lasting repercussions (Braun, 2017). Adolescence, for example, brings upon hormonal changes that prompt sexual behaviors ahead of reproduction (Sisk and Foster, 2004). A study by Bell and colleagues (2016) found gestational EDC exposure influenced anxiety and social behaviors exhibited in adolescence. This same particular class of EDCs, or polychlorinated biphenyls (PCBs), were also responsible for decreasing sexual behaviors in adult rats in a study by Chung and Clemens (1999). These findings prompt further interest into the interaction between EDCs, like PCBs, and sociosexual stress experienced later in life.

One goal of this study was to examine how environmental and sociosexual stressors interact and if changes are observed in behaviors of interest. Anxiety and mate preference were compared between virgin female rats and those exposed to SCAR as well as EDCs. It was

hypothesized that SCAR exposure would elicit the higher anxiety and lowest preference for male aggressors while EDC exposure would intensify anxiety.

EDC Exposure

EDCs challenge normal production and regulation of hormones by the endocrine system through stimulation, inhibition, synthesis, and clearance of certain hormones (Dickerson and Gore, 2007). These chemicals have the capacity to mimic hormonal action or block hormones at any magnitude of exposure. Additionally, the body's inability to break down EDCs leads to accumulation in our tissues as well as an unsettling prevalence in our environment.

The pervasiveness and damage potential of these chemicals has ultimately led to the ongoing production ban of polychlorinated biphenyls (PCBs), and the one used in my study (Tabb and Blumberg, 2006). PCBs, in particular, were notorious for their presence in products including industrial coolants and lubricants. Today, these chemicals have contaminated bodies of water affecting the wildlife that inhabit it, as well as consumers through biomagnification (Street et al., 2018). PCBs are one of many examples of EDCs that pose a direct threat to vital functions and responses in all species exposed.

The consequences of EDCs are contingent on the time of exposure. For example, a child or adolescent still in crucial developmental stages will experience more profound hormone disruptions than a fully developed adult at first exposure (Gore, 2010). Animal studies that have focused on in-utero EDC exposure have linked it to a higher likelihood of developing diseases in adulthood and DNA methylation, reducing expression of proteins created by the affected genome (Horan et al., 2017; Crews et al., 2007). Toxicity, improper motor development, and various

cancers have also been observed at high levels of EDC exposure, including to PCBs (Damstra, 2002; Zoeller et al., 2012)

Prenatal development is particularly vulnerable to EDC exposure because the fetus is still developing vital systems such as their endocrine or immune system. It has been predicted that effects from exposure at this stage could last an entire lifespan (Damstra, 2002). Although EDCs are not the only variables of interest in my study, it is important to note how early exposure can predispose those affected to worsened harm.

Social Stress

Social stress is seen in all social animals, such as humans and rodents. It is brought on by negative interactions with peers in a natural environment and can be present as single or repeating events. For rats, this looks like acts of dominance, isolation, instability, and more. Learning and memory processes are often hurt or sometimes enhanced following a stressful experience, depending on the stress severity and information needed to be recalled (Bangasser and Shors, 2010).

Changes in response to stressors can be observed in neuronal excitability, hormone production, and morphology. For example, social stress has been found to be responsible for greater action potentials of neurons in the hippocampus (Weiss et al., 2005). For humans, those who have experienced childhood sexual trauma were found to have a hippocampal region 5% smaller than those who had not (Stein et al., 1997).

Sexual Conspecific Aggressive Response (SCAR) Model

Sexual assault in humans is defined by lack of consent, undesired aggression, and other factors. The ambition to isolate this experience and study its effects requires a strong model for

nonhuman animals. Shors and colleagues (2016) developed SCAR to model sexual assault in rats. This model pairs a sexually inexperienced female rat in early puberty with a sexually experienced adult male. The success of this model's ability to mimic sexual assault was based off higher stress hormone levels found in females following SCAR. Additionally, females exposed to SCAR failed to learn maternal behaviors necessary for offspring care and showed decreased production of neurons in the hippocampus (Shors et al., 2016).

EDC and Social Stress Interaction

Despite persistent investigation of the interactions EDCs have with other variables, there is a lack in research regarding how EDCs interact with social stress. Limited literature that considered the interactions of EDCs and socio-sexual behavior were expected. Few studies have pursued interest in stress paired with EDCs. The transgenerational effects found by Crews and colleagues (2012) when EDCs were paired with social stress will be valuable to extrapolate from, despite its indirect cause-and-effect relationship. Social behavioral differences and higher levels of anxiety have been found in adolescent females exposed to EDCs (Bell, Thompson, Rodriguez, & Gore, 2016). Results of this last study inspired investigation of behavioral effects to be investigated through open-field and conditioned mate preference.

Behavioral Testing

Higher levels of anxiety and depression may follow a sexually traumatic experience in humans (Stein et al., 2004). Animal models have also shown support of higher anxiety following EDC exposure as seen by Bell and colleagues (2016). An open-field test is one of several methods of measuring anxiety in animal models through comparison of time spent along an outer

edge versus in the center of a chamber (Ramos et al., 1997). This paradigm is supported in studies looking at social stress (Rygula et al., 2005) but seemingly new in EDC research.

Another behavior of interest is the potential difference of mate preference in SCAR and No SCAR females. Mate preference is a female rat's desire of a certain male stimulus when presented with two or more stimuli. With past male aggressors marked by the same lemon scent used in SCAR, my study hopes to answer the following: Will the females actively choose to spend more time near a familiar smell or are they averted to it? Crews and colleagues (2007) investigated transgenerational EDC exposure and found no difference in preference, however, this particular study observed the preference of male rats for female stimuli, rather than a female's preference.

Conclusion

Endocrine disruptors are widely researched, providing solid support for claims of its potential harm to a developing brain. The ability of EDCs to interfere in necessary hormone action, paired with its environmental prevalence, prompts investigation of how these chemicals interact with other variables we may encounter. Acute stress, in particular, is also capable of influencing neuronal function resulting in anxiety-like behaviors. The trauma following sexual aggression in particular has well-known detrimental effects when studied alone. Potential interactions between EDCs and stress, such as sexual aggression, in a developing brain require further research to understand. Further evaluation of anxiety and mate preference should lead to a more well-rounded analysis about what EDCs, social stress, and interactions may entail.

Design and Methods

Design Overview

I hypothesized that female rats who received EDCs and SCAR would show: 1) greater anxiety and 2) greater preference for non-aggressors used in SCAR. Vehicle/SCAR females were expected to have the second highest levels of anxiety while vehicle/No SCAR females, or control subjects, were expected to show the lowest anxiety levels and greater preference for SCAR aggressors. The independent variables of the study are in-utero administration of either EDCs or a vehicle and subjection to either SCAR or no SCAR in separate chambers. Dependent variables include measured behaviors of anxiety and mate preference.

High anxiety was measured by time spent in corners and the perimeter of chambers used in open-field tests compared to time spent in the center. Preference, or lack thereof, was measured by the time subjects willingly spend in chambers containing a male marked by the same lemon scent used for SCAR aggressors, or unmarked males.

Subjects

A total of 28 female rats (n = 7) exposed to EDCs or vehicle in-utero were used for all behavior analyses. Sprague–Dawley rats were purchased from Harlan Laboratories (Houston, Texas). Females were housed in pairs in cages (43 x 21 x 25 cm) with a reversed light cycle. They were fed and given water ad libitum throughout the experiment. Double-blind administration of either treatment was employed and measured depending on weight on a given treatment day.

Materials and Measures

ANYMAZE Movement trackers. ANYMAZE Movement trackers were used to track rats during open-field (OF) and conditioned mate preference (CMP). These cameras tracked place in space, speed, and time spent in a certain area. For example, the latter was important in monitoring CMP as more time spent near a certain male stimulus would be indicative of preference.

Enclosures. Chambers with three distinct compartments were used for SCAR, OF, and CMP. SCAR and No SCAR chambers were made up by acrylic dividers with dimensions of 75 x 75 x 31 cm. SCAR chambers were kept separate from chambers designated for no SCAR. OF chambers were composed of the same material but larger to with dimensions of about 92 x 92 x 31 cm. CMP chambers were about 92 x 120 x 31 cm but divided lengthwise into 3 chambers. The dividers for CMP chambers had a door-opening allowing entrance and departure for the female only. Cages were also placed in the two outer chambers to house the male stimuli.

Measures

EDC Treatment and Handling. All subjects were bred to allow for in-utero administration of chemical treatments. Throughout pregnancy, the mothers were given a dose one-third of their body weight in microliters of either EDC or vehicle through cookies with absorbed treatments. The EDC used was Aroclor 1221 (AccuStandard, New Haven, CT), a PCB capable of influencing sexual behaviors when exposed prenatally. This took place until pups were born and ceased once weaned from their mothers (E8-E18, P1-22). Only female pups were kept for this study.

SCAR. SCAR sessions are fifteen-minute periods of an adolescent female in the same compartment as a sexually experienced adult male. Prior to beginning SCAR, each male had a

lemon-scented marker rubbed into the back of their necks where they could not reach it. Once a female started her first SCAR session, she completed one every other day until four sessions had been completed per female. This test is done under red light.

Open Field. OF sessions are five-minute periods of a solitary female placed in a chamber under dim white lighting. Subjects were given two-minutes before beginning OF to adjust to the lighting during what is supposed to be dark-cycle. The females were placed in a corner and left to roam in the compartment for the entire period. This test was completed once per female two days after all her SCAR/No SCAR sessions were finished.

Conditioned Mate Preference. CMP sessions are ten-minute periods of the female placed in a three-chamber compartment while male stimuli are housed in cages in the outer chambers. Cages used were small enough to allow the female closer access in order to smell the males. Both males are novel to the female, and only one of which was marked by the same lemon-scent used for SCAR males. This test was completed on the female's first day in either proestrus or estrus following her final SCAR session. This test is also done under red lights.

Procedures

EDCs and vehicles were double-blind administered through treated cookies and fed to dams from days eight through eighteen post-conception and later throughout pup weaning. Once separated from their mothers, females were housed in pairs and checked daily for vaginal openings (VOs). Appearance of VOs are indicative of puberty onset which prompted: 1) cycle tracking through vaginal cytology and 2) SCAR sessions for an individual female. Estrous cycles were tracked to gauge hormonal fluctuations that influence certain behaviors such as sexual receptivity.

On the day of their VO, females were randomly paired with a sexually experienced male for SCAR sessions. Females were placed in the SCAR chamber first while the male aggressor was marked with the lemon-scent in an adjacent room. This occurred every other day until all four SCAR sessions were completed, using a new male aggressor each day. Behavioral testing began as soon as two days after SCAR completion during their dark cycle.

Females were tested in OF two days after her last SCAR session in dim white light. CMP, on the other hand, varied from female to female due to its estrous cycle-dependent nature. Conditioned mate preference testing was performed when females were sexually receptive, or during proestrus or estrus. If a female had mostly cornified or nucleated cells in her vaginal smear that day, she was tested for sexual receptivity. Sexual receptivity testing paired females with an unmarked male stimuli. Females were sexually receptive if she showed lordosis when the male mounted her. If she resisted sexual advances, no CMP took place. Different chambers were used for open-field testing, as well as conditioned mate preference, all of which were cleaned after use.

Statistical Analysis

Rat behaviors were collected by ANYMAZE motion trackers in open field and conditioned mate preference testing. This program recorded data onto excel sheets ready for analysis using R. Data required no further transformations. Behavioral measures were evaluated by T-tests to assess main effects and a one-way analysis of variance (ANOVA) for interactions. A discontinuity model was used to seek patterns between anxiety and preference, however no significant results were yielded.

Results

Anxiety Behaviors

SCAR exposure appeared to have no main effect on the time females spent in the corners of the apparatus, or high anxiety (see Figure 1). This lack of difference ($t = 0.3$, $p = 0.38$) was more clearly observed than a difference in time spent inside, or low anxiety ($t = -1.09$, $p = 0.14$). SCAR females spent more time inside the open field chamber; however the difference was not significant compared to No SCAR females (see Figure 2).

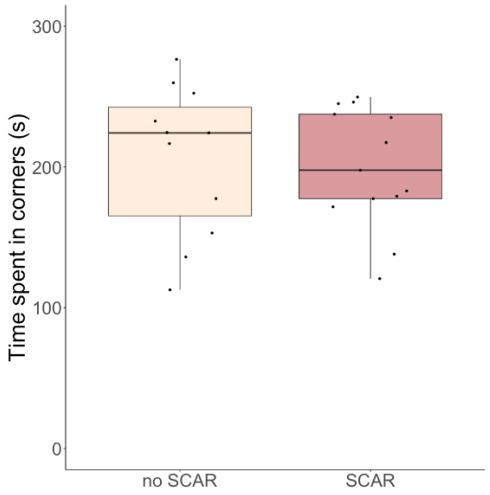

Figure 1. Effect of SCAR on high anxiety behaviors in open field testing. There were no significant differences between SCAR and No SCAR group. Data are $M \pm SE$ ($p > .05$).

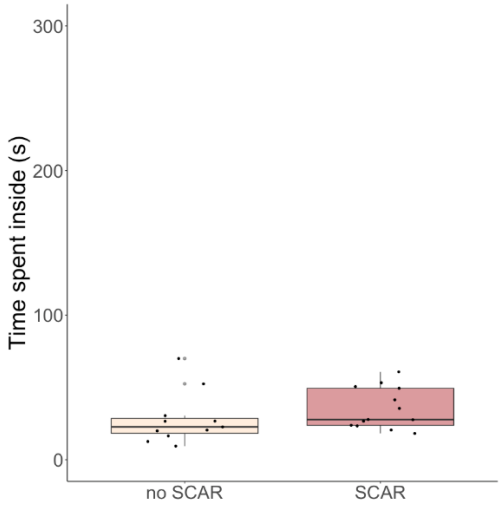

Figure 2. Effect of SCAR on low anxiety behaviors in open field testing. There was no significant difference between SCAR and No SCAR group. Data are $M \pm SE$ ($p > .05$).

EDC exposure alone saw less time spent inside of the open field chamber ($t = -1.48$, $p = .07$) than vehicle females, however this difference did not attain significance (see Figure 3). A similar difference that agreed with this pattern in anxiety behaviors was seen in time spent in the corners of the apparatus (data not shown).

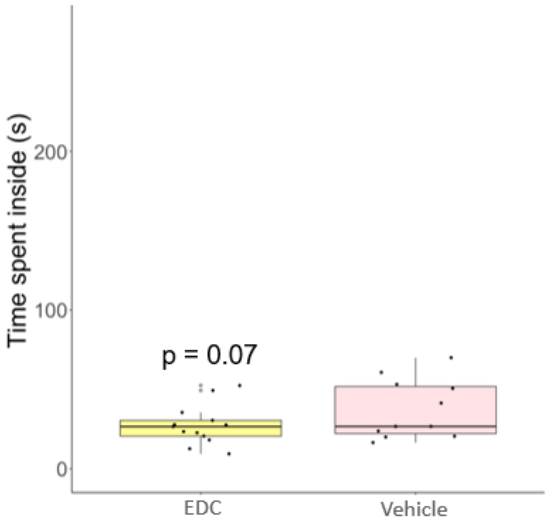

Figure 3. Effect of EDC on low anxiety behaviors in open field testing. Difference between two groups was not significant. Data are $M \pm SE$ ($p > .05$).

The potential for interactions between SCAR and EDC exposure was limited as neither treatment alone yielded statistically significant differences in anxiety. Interactions from one-way analyses of variance (ANOVA) for both behaviors of interest are explored later.

Mate Preference

SCAR exposure had no significant effect on preference for scented or unscented males compared to No SCAR females (data not shown). SCAR also did not influence the time females spent away from either male in the center chamber when analyzed (see Figure 4).

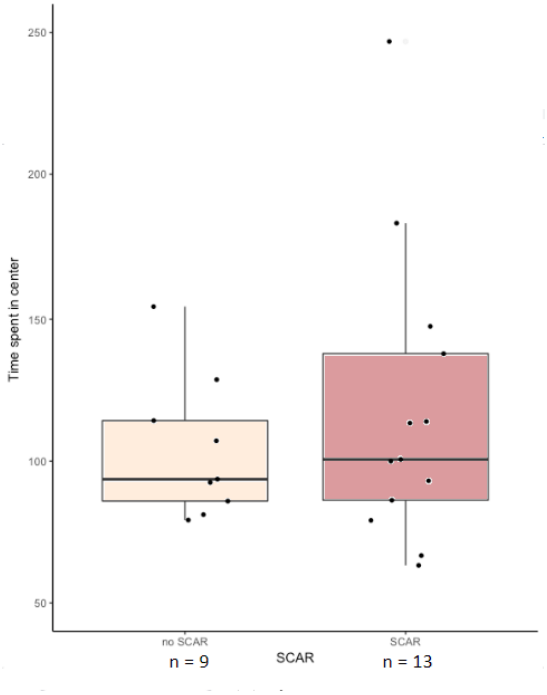

Figure 4. Effect of SCAR on time spent away from males during conditioned mate preference. There was no significant difference between females exposed and unexposed to SCAR. Data are $M \pm SE$ ($p > .05$).

Preference scores were determined by the ratio of time spent exploring males with and without the odor cue. Females exposed to EDCs in early development showed a significantly greater preference for males with the odor cue than vehicle females (see Figure 5).

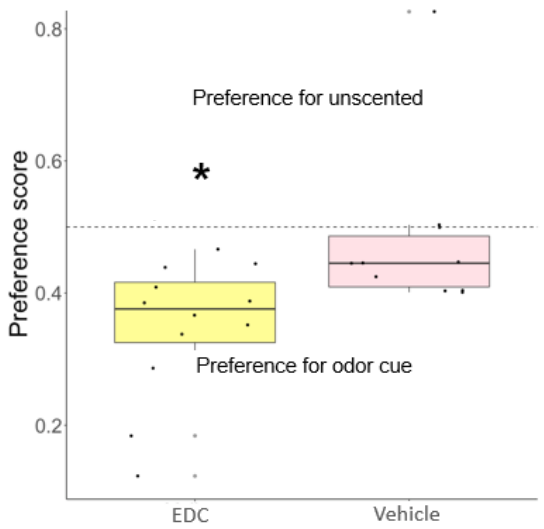

Figure 5. Effects of EDC exposure on preference for unscented or males with odor cue. There was a statistically significant difference between females exposed to EDCs and vehicle (t = -2.62, p = .03). Data are $M \pm SE$ (*p < .05).

EDC exposure also increased time females spent away from either male stimuli (see Figure 6). The amount of time EDC females spent in the center chamber was significantly greater than vehicle females (t = 2.75, p = 0.008).

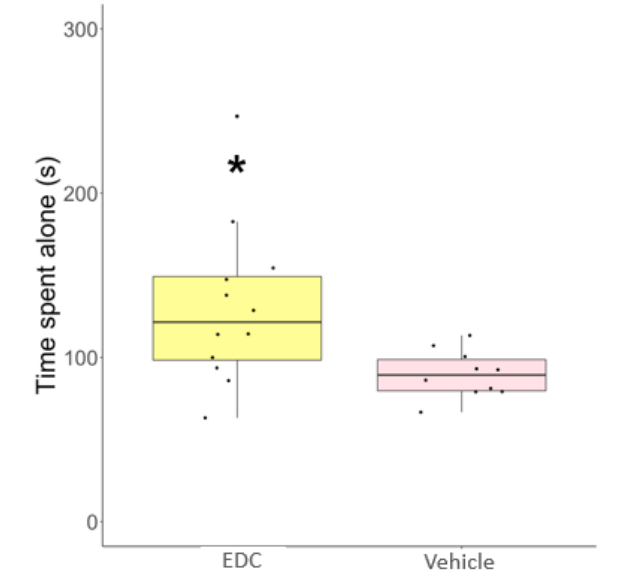

Figure 6. Effects of EDC exposure on antisocial behaviors during conditioned mate preference. A significant difference was observed between EDC and vehicle females. Data are $M \pm SE$ (*p < .05).

EDC and SCAR Interaction

A one-way ANOVA was used to assess interaction between EDC and SCAR exposure in mate preference. There were no interactions observed in anxiety behaviors (data not shown). Females exposed to SCAR and EDC had the highest preference for males with the odor cue while SCAR females unexposed to EDCs had the lowest preference (see Figure 7). This difference, however, did not attain significance ($p = 0.07$).

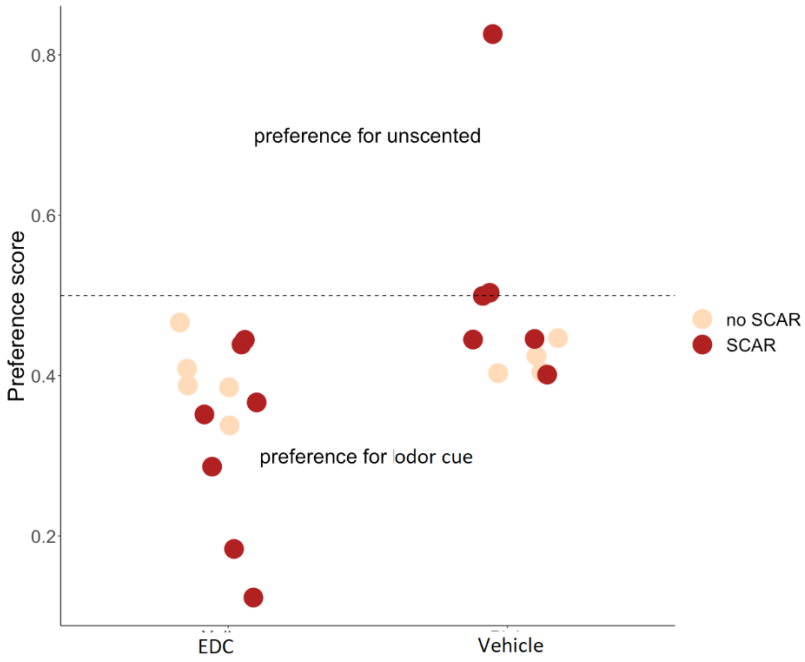

Figure 7. Interaction between EDC and SCAR exposure in conditioned mate preference. Difference between four groups was not significant ($p > .05$).

Discussion

This study applied early exposure to EDCs and sexual aggression in adolescence, or SCAR, to investigate how these stressors influence anxiety and mate preference behaviors. Females who experienced SCAR in adolescence produced no changes in anxiety when compared to virgin females. In conditioned mate preference, these females did not demonstrate a preference or learned aversion to male aggressors marked by odor cues used in SCAR or display antisocial behaviors when compared to unexposed females. Pre and postnatal EDC exposure inhibited exploratory behaviors, indicating higher anxiety, but this effect was not statistically significant. Females who received EDCs significantly prefer males with the odor cue but also exhibited more antisocial behaviors than control females. A greater preference for male aggressors was seen in females exposed to EDCs and SCAR than SCAR females unexposed to EDCs, but this difference did not attain significance. These results suggest environmental and sociosexual stressors influence certain social behaviors later in life.

Effects of Sexual Aggression

It was predicted that SCAR would be the largest driving force in anxiety and mate preference or aversion, but the results did not support this. SCAR females spent roughly the same amount of time in the corners of the open field chamber than control females indicating unvaried anxiety. A similar trend was seen in exploratory behaviors. The SCAR model was developed from hormonal results that increased corticosterone (Shors et al., 2016). It was unclear what other behavioral consequences were a result from SCAR as psychological responses were not immediately assessed. While increased corticosterone would indicate greater stress experienced by SCAR females, the findings of my study could not conclude that increased stress translated to worsened anxiety using this model. This finding would however agree with studies

that have looked at psychological symptoms of human sexual assault victims that claim post-traumatic stress disorder and depression are more common in women than anxiety symptoms (Siegel et al., 1990; Department of Justice, 2019). In the case of SCAR and EDC interaction, SCAR females may have preferred males with the odor cue, or male aggressors, from a learned association of the cue and sexual reward. The potential for significance in this case is limited by the small sample size, but it may be the case that SCAR on its own was not enough to drive a difference since the EDC group saw significant results.

Effects of Endocrine Disruptors

EDCs were expected to worsen anxiety in SCAR females, but results showed it played a larger role in both anxiety and mate preference. Early exposure to EDCs produced a trend in higher anxiety which agrees with previous findings that PCBs, the EDC used in this study, increased anxiety in adolescence (Bell et al., 2016). It should be acknowledged that this trend was shy of significance which may have been a result from the small sample size. One study by Gillette and colleagues (2017) found rodent males experienced reduced anxiety after PCB exposure while females were not affected by low dosage. While my study did not compare sex-specific effects of PCB exposure, it does raise concerns regarding how dosage may have influenced anxiety effects. Effects in mate preference were not as anticipated as they were in anxiety behaviors, but EDC exposure demonstrated significant influence in preference and antisocial behaviors. Males with the odor cue were more greatly preferred by females who received EDCs compared to vehicle. Since this finding includes SCAR and No SCAR females, it cannot be attributed to a preference for male aggressors as only SCAR females would recognize the odor cue. One potential explanation may come from EDCs ability to influence odor discrimination but the literature in regard to this in the context of mate preference is limited.

Results of decreased sociability are comparable to the findings of Chung and Clemens (1999) which saw reduced sexual behaviors in adulthood following early PCB exposure.

This study explored environmental stress from ubiquitous EDCs and sociosexual stress as they influence neuroendocrine systems to produce psychological symptoms and altered mate preference in rodents. SCAR exposure could not produce altered anxiety behaviors or a definitive aversion to male aggressors. In fact, SCAR females had a stronger preference for their male aggressors if they were also exposed to EDCs in early development. Females who received EDCs during pre and postnatal stages preferred males with the odor cue more strongly than control females, but also exhibited more antisocial behaviors. These results suggest behavioral responses to early EDC exposure hold influence worthy of further investigation while sociosexual stress models of rodents may not exhibit expected psychological symptoms.

References

Bangasser, D. A., & Shors, T. J. (2010). Critical brain circuits at the intersection between stress and learning. *Neuroscience & Biobehavioral Reviews*, *34*(8), 1223-1233.

Bell, M. R., Thompson, L. M., Rodriguez, K., & Gore, A. C. (2016). Two-hit exposure to polychlorinated biphenyls at gestational and juvenile life stages: 1. Sexually dimorphic effects on social and anxiety-like behaviors. *Hormones and behavior*, *78*, 168-177.

Braun, J. M. (2017). Early-life exposure to EDCs: role in childhood obesity and neurodevelopment. *Nature Reviews Endocrinology*, *13*(3), 161.

Chung, Y. W., & Clemens, L. G. (1999). Effects of perinatal exposure to polychlorinated biphenyls on development of female sexual behavior. *Bulletin of environmental contamination and toxicology*, *62*(6), 664-670.

Crews, D., Gillette, R., Scarpino, S. V., Manikkam, M., Savenkova, M. I., & Skinner, M. K. (2012). Epigenetic transgenerational inheritance of altered stress responses. *Proceedings of the National Academy of Sciences*, *109*(23), 9143-9148.

Crews, D., Gore, A. C., Hsu, T. S., Dangleben, N. L., Spinetta, M., Schallert, T., ... & Skinner, M. K. (2007). Transgenerational epigenetic imprints on mate preference. *Proceedings of the National Academy of Sciences*, *104*(14), 5942-5946.

Damstra, T. (2002). Potential effects of certain persistent organic pollutants and endocrine disrupting chemicals on the health of children. *Journal of Toxicology: Clinical Toxicology*, *40*(4), 457-465.

Department of Justice, Office of Justice Programs, Bureau of Justice Statistics, National Crime Victimization Survey, 2018 (2019).

Dickerson, S. M., & Gore, A. C. (2007). Estrogenic environmental endocrine-disrupting chemical effects on reproductive neuroendocrine function and dysfunction across the life cycle. *Reviews in Endocrine and Metabolic Disorders*, *8*(2), 143-159.

Gillette, R., Reilly, M. P., Topper, V. Y., Thompson, L. M., Crews, D., & Gore, A. C. (2017). Anxiety-like behaviors in adulthood are altered in male but not female rats exposed to low dosages of polychlorinated biphenyls in utero. *Hormones and behavior*, *87*, 8-15.

Gore, A. C. (2010). Neuroendocrine targets of endocrine disruptors. *Hormones*, *9*(1), 16-27.

Horan, T. S., Marre, A., Hassold, T., Lawson, C., & Hunt, P. A. (2017). Germline and reproductive tract effects intensify in male mice with successive generations of estrogenic exposure. *PLoS genetics*, *13*(7), e1006885.

Ramos, A., Berton, O., Mormède, P., & Chaouloff, F. (1997). A multiple-test study of anxiety-related behaviours in six inbred rat strains. *Behavioural brain research*, *85*(1), 57-69.

Rygula, R., Abumaria, N., Flügge, G., Fuchs, E., Rüther, E., & Havemann-Reinecke, U. (2005). Anhedonia and motivational deficits in rats: impact of chronic social stress. *Behavioural brain research*, *162*(1), 127-134.

Shors, T. J., & Millon, E. M. (2016). Sexual trauma and the female brain. *Frontiers in neuroendocrinology*, *41*, 87-98.

Shors, T. J., Tobón, K., DiFeo, G., Durham, D. M., & Chang, H. Y. M. (2016). Sexual Conspecific Aggressive Response (SCAR): a model of sexual trauma that disrupts maternal learning and plasticity in the female brain. *Scientific reports*, *6*, 18960.

Siegel, J. M., Golding, J. M., Stein, J. A., Burnam, M. A., & Sorenson, S. B. (1990). Reactions to sexual assault: A community study. *Journal of Interpersonal Violence*, *5*(2), 229-246.

Sisk, C. L., & Foster, D. L. (2004). The neural basis of puberty and adolescence. *Nature neuroscience*, *7*(10), 1040-1047.

Stein, M. B., Koverola, C., Hanna, C., Torchia, M. G., & McClarty, B. (1997). Hippocampal volume in women victimized by childhood sexual abuse. *Psychological medicine*, *27*(4), 951-959.

Stein, M. B., Lang, A. J., Laffaye, C., Satz, L. E., Lenox, R. J., & Dresselhaus, T. R. (2004). Relationship of sexual assault history to somatic symptoms and health anxiety in women. *General Hospital Psychiatry*, *26*(3), 178-183.

Street, M. E., Angelini, S., Bernasconi, S., Burgio, E., Cassio, A., Catellani, C., ... & Gargano, G. (2018). Current knowledge on endocrine disrupting chemicals (EDCs) from animal biology to humans, from pregnancy to adulthood: highlights from a national italian meeting. *International journal of molecular sciences*, *19*(6), 1647.

Tabb, M. M., & Blumberg, B. (2006). New modes of action for endocrine-disrupting chemicals. *Molecular endocrinology*, *20*(3), 475-482.

Zoeller, R. T., Brown, T. R., Doan, L. L., Gore, A. C., Skakkebaek, N. E., Soto, A. M., ... & Vom Saal, F. S. (2012). Endocrine-disrupting chemicals and public health protection: a statement of principles from The Endocrine Society. *Endocrinology*, *153*(9), 4097-4110.