ABSTRACT

BACKGROUND: Stress is a prevailing risk factor for mood-related illnesses, wherein women represent the majority of those affected by major depression. Despite the growing literature suggesting that affective disorders can arise after a traumatic event is vicariously experienced, this relationship remains understudied in female subjects at the preclinical level. Thus, the objective of the current investigation was to examine whether exposure to emotional and/or psychological stress (ES) mediates depression-related outcomes in female mice.

METHODS: Female C57BL/6 mice (8 weeks old, null parity) vicariously experienced the defeat bout of a male conspecific, by a male CD1 aggressor, for 10 consecutive days. Twenty-four hours after the last stress exposure, female mice were tested in the social interaction, sucrose preference, tail suspension, or elevated plus maze tests. Furthermore, we examined whether ketamine and chlordiazepoxide, pharmacological agents used to treat mood-related disorders in the clinical population, would reverse the ES-induced social dysfunction.

RESULTS: When compared with control mice, female mice exposed to ES displayed decreased social behavior and preference for sucrose, along with increased immobility in the tail suspension test. Also, they displayed higher levels of blood serum corticosterone, as well as decreased body weight. Lastly, the ES-induced avoidance-like phenotype was ameliorated by both ketamine and chlordiazepoxide.

CONCLUSIONS: Our data indicate that female mice exposed to ES display a behavioral and physiologic profile that mimics symptoms of depression in the clinical population. As such, this experimental model may be adopted to examine vicarious stress-induced mood-related disorders, as well as pharmacological antidepressant response, in a sex-specific manner.

Keywords: Animal model, Chlordiazepoxide, Depression, Ketamine, Psychological stress, Social defeat stress

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According to the World Health Organization, depression will soon become the leading cause of disability across the globe (1). While there have been significant advancements for the treatment of numerous illnesses, such as heart disease and stroke, rapid and effective therapeutic treatments for mood-related disorders continue to fall behind. A likely reason is the complex multifactorial nature of depression, making it difficult to develop preclinical models that recapitulate the etiological factors of the disease.

Exposure to stress is a well-recognized risk factor for the development of mood-related illnesses (2). As such, numerous preclinical models have been developed to assess the deleterious effects of stress and the development of depression-related behaviors in rodents. For example, stressed animals display memory impairment, decreased sensitivity for rewards (i.e., anhedonia), and weight fluctuation, as well as increased social avoidance and despair-like behavior (3). Interestingly, most experimental paradigms rely primarily on exposure to physical stressors. However, a growing body of literature suggests that emotional and/or psychological stress (ES), in particular, may also play a critical role in the etiology of mood-related psychopathology (4–7). As such, there is need for the development of animal models designed to tease apart the specific contributions of individual stress subtypes (i.e., physical vs. psychological) in the mediation of a depressive-like behavioral phenotype. Importantly, such models must recapitulate symptomology of the clinical population, wherein female subjects, when compared with male subjects, represent the majority of those who suffer from mood-related illnesses (8).

To date, most rodent models of depression have been predominantly validated using male subjects. Female subjects, on the other hand, have been primarily incorporated in designs that include social instability (9), isolation (10,11), maternal separation (12–14), and unpredictable stressors (13–18). While these approaches have helped breach the underutilization of female subjects in preclinical stress-related studies, the need for an animal model of female depressive-like behavior that is mediated by a naturalistic stressor, is still much needed.
In recent years, the social defeat stress paradigm has been widely implemented to study the neurobiology of depression, given its high ethological and pharmacological validity, when compared with other preclinical models of stress, in both male (19) and female (20) subjects. Interestingly, the social defeat model has been recently modified to include a vicariously observed stress condition (i.e., ES) incorporating C57BL/6 mice (21). In this paradigm, male mice exhibit depressive-like behaviors after witnessing the defeat bout of a same-sex conspecific, which resembles the behavioral profile of physically stressed (PS) mice (22,23). Surprisingly, whether female mice will exhibit similar outcomes following vicariously experienced stress has not been investigated. As such, the objective of the current investigation is to examine whether the vicarious defeat stress (VDS) paradigm yields depression-like behaviors in female C57BL/6 mice, and if so, whether pharmacological agents used to treat depression and/or anxiety ameliorate the social-related alterations observed.

METHODS AND MATERIALS

Animals

Description of animals (purchased from Charles River, Hollister, CA) and housing conditions are provided in the Supplement.

VDS and Experimental Design

The social defeat stress paradigm was performed as previously described (24), with modifications to incorporate an ES component (21)—where female C57BL/6 mice vicariously experience the defeat of a male C57BL/6 counterpart. We refer to ES as all nonphysical sensory stimuli (visual, olfactory, and chemosensory) associated with indirectly experiencing the defeat of the PS male mouse. To do this, CD1 retired breeders with reliable attack latencies (≤30 seconds on three consecutive screening tests) were housed in cages containing clear perforated acrylic glass separators, which divide the cage into two separate compartments (Supplemental Figure S1A). For each stress session (10 min/day), PS male mice were placed into the same compartment as the CD1 aggressor, while female ES mice were placed in the neighboring compartment, allowing only a vicarious experience (i.e., visual, olfactory, auditory) of the physical bout (Figure 1A). Following each session, ES female mice were housed next to a novel CD1 aggressor for 24 hours until the next stress episode (Figure 1B), while male PS mice were housed for 24 hours in the compartment adjacent to their respective CD1 aggressor (Figure 1C). This procedure ensured that all experimental mice (ES and PS) were exposed to a novel CD1 aggressor each day, for 10 consecutive days (postnatal day [PD] 70–79). In the event that the CD1 aggressor exhibited severe attacks, the defeat bout was immediately interrupted (25). Nonstressed control (CON) female mice were pair-housed in similar cages, but they did not experience stressors associated with the VDS paradigm. (E) Experimental timeline where adult male and female C57BL/6 mice were exposed to the VDS paradigm for 10 consecutive days (i.e., postnatal day [PD] 70–79). Twenty-four hours later (PD80), separate groups of experimental mice were tested on depression-related behavioral tests.

Social Interaction Test

The social interaction test is a two-trial procedure (24), conducted under red light conditions. In the first 2.5-minute session, the experimental C57BL/6 mouse is allowed to freely explore an open-field arena (40 cm × 40 cm × 40 cm) (Supplemental Figure S1C). Along one side of the arena is a single housed. Twenty-four hours later (PD80), separate groups of experimental mice were tested on a battery of mood-related tasks (Figure 1E). This approach was taken to avoid possible testing carryover effects (see Supplemental Table S1 for experimental groups). For the social interaction and elevated plus maze tests, behavior was recorded via an automated video-tracking system (Ethovision XT; Noldus, Leesburg, VA). Behavioral outcomes for the sucrose preference and tail suspension tests were scored by observers unaware of stress conditions.

Figure 1. Schematic of the vicarious defeat stress (VDS) procedure and timeline of experimental design. (A) Diagram of the VDS paradigm where female C57BL/6 mice would witness (emotional and/or psychological stress [ES]) the social defeat (physical stress [PS]) of a male C57BL/6 counterpart by a CD1 male mouse (cage 1). (B) After the 10-minute stress episode, the ES female mouse was moved to the cage of a novel CD1 aggressor (cage 2). (C) While the PS male mouse was moved to the adjacent compartment of the same CD1 aggressor (cage 1). (D) Nonstressed control (CON) female mice were pair-housed in similar cages, but they did not experience stressors associated with the VDS paradigm. (E) Experimental timeline where adult male and female C57BL/6 mice were exposed to the VDS paradigm for 10 consecutive days (i.e., postnatal day [PD] 70–79). Twenty-four hours later (PD80), separate groups of experimental mice were tested on depression-related behavioral tests.
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circular (7-cm diameter) wire cage (Stoelting Co., Wood Dale, IL) that remains empty during the first trial (target-absent condition). The experimental C57BL/6 mouse is then removed from the testing arena for 30 seconds (into a separate holding cage), and a novel CD1 male mouse is placed into the wire cage. In the second 2.5-minute trial (target-present condition), the experimental C57BL/6 mouse is reintroduced into this arena now containing a social target (unfamiliar CD1 male mouse) within the circular wire cage. To determine whether social interaction levels would be influenced by the strain and/or sex of the social target itself, a different group of ES female mice was exposed to an unfamiliar female of the same strain during the social interaction test. Also, to examine the salience of the visual stimuli in mediating ES-induced avoidance, we conducted an experiment where white opaque dividers without holes (Supplemental Figure S1B) were used to prevent female mice from witnessing the resident-intruder interaction—removing visual sensory cues related to the defeat of the male conspecific. In all cases (social target being an unfamiliar male CD1, or an unfamiliar female C57BL/6 mouse), a social interaction ratio was used to evaluate the effects of stress on social behavior—where the time (seconds) spent in the interaction zone (8-cm-wide corridor surrounding the wire cage) in the presence of the social target is divided by the time spent in the interaction zone in the absence of the target (25,27). Lastly, we recorded the distance traveled (in centimeters) during the first 2.5 minutes of the social interaction test (target-absent condition) to examine whether basal locomotor activity or exploratory behavior was influenced by stress exposure.

Corticosterone Immunoassay and Other Behavioral Approaches

See the Supplement for details on the corticosterone immunoassay (28), as well as the sucrose preference, tail suspension, and elevated plus maze behavioral tests (22).

Pharmacological Study

Because social defeat-induced avoidance is reversed by antidepressants in male C57BL/6 mice (19), we conducted an experiment to assess whether pharmacological agents used to treat depression and/or anxiety reduce the decreased social behavior observed in ES female mice. We selected ketamine (Spectrum Chemicals, Gardena, CA) and the benzodiazepine chlordiazepoxide (Toronto Research Chemicals, North York, ON, Canada) because they have been reported to mediate antidepressant-like (29) and anxiolytic-like (30) effects shortly after drug exposure, thus matching our behavioral testing time (i.e., 24 hours after VDS). Ketamine and chlordiazepoxide were diluted in 9% sterile saline and injected at a volume of 2 mg/kg. Specifically, ES female mice received three injections of ketamine (20 mg/kg, intraperitoneally) prior to the social interaction test (immediately and 4 hours after the 10th VDS episode, as well as 30 minutes before the social interaction test); whereas female mice administered with the benzodiazepine received a single injection of chlordiazepoxide (10 mg/kg, intraperitoneally) 30 minutes before the social interaction test. Dose and timing of drug administration were selected based on previous work (29,31).

Statistical Analysis

Description of statistical analyses is provided in the Supplement.

RESULTS

ES Decreases Social Behavior in Female and Male C57BL/6 Mice

As an initial experiment, we examined whether ES exposure decreases social behavior in female C57BL/6 mice, in a similar fashion as in male mice of the same strain (21). The effects of VDS on social behavior, in female and male C57BL/6 mice (n = 11 per group), are shown in Figure 2. A one-way analysis of variance (ANOVA) indicated that the time spent in the interaction test (B) No differences in locomotor activity were evident across the different experimental groups. Data are presented as mean ± SEM (n = 11 per group). *p < .05 when compared with the female CON group. **p < .05 when compared with the male CON group. ***p < .05 when compared with the ES female group.

\[ \text{Distance Traveled (cm)} \]

\[ \text{CON} \quad \text{ES} \quad \text{CON} \quad \text{ES} \quad \text{PS} \]

**Figure 2.** Vicarious social defeat stress decreases social behavior in female and male C57BL/6 mice. (A) Female and male mice exposed to emotional and/or psychological stress (ES) spent significantly less time in the interaction zone, when compared with respective same-sex nonstressed control (CON) mice (p < .05). Similarly, when compared with male CON mice, male mice exposed to physical stress (PS) displayed decreases in social interaction. (B) No differences in locomotor activity were evident across the different experimental groups. Data are presented as mean ± SEM (n = 11 per group). *p < .05 when compared with the female CON group. **p < .05 when compared with the male CON group. ***p < .05 when compared with the ES female group.
interaction zone, with a novel CD1 male aggressor as a social target, was influenced by stress exposure ($F_{4,50} = 11.16, p < .01$). Specifically, Figure 2A demonstrates how ES female mice (left panel) displayed a significantly lower social interaction ratio, when compared with nonstressed CON female mice (Tukey, $p < .05$). Similarly, within the male groups (right panel), both ES and PS mice displayed significantly lower social interactions when compared with male CON mice (Tukey, $p < .05$). Not surprisingly, PS male mice displayed a significantly lower interaction ratio when compared to all other experimental groups (Tukey, $p < .05$, respectively). No differences between the female CON and male CON groups were observed ($p > .05$). Importantly, when assessing distance traveled (in centimeters) during the first 2.5-minute interaction trial (target-absent condition), no differences were noted between the groups ($F_{4,50} = 1.77, p > .05$), thus indicating that stress exposure did not influence general locomotor activity or exploratory behavior (Figure 2B). Furthermore, in a separate group of mice, we examined whether female mice exposed to ES would display altered social interaction levels if they were exposed to the CD1 aggressor for 24 hours, after witnessing the defeat bout of the PS male conspecific (i.e., overnight). Supplemental Figure S2A shows that, when compared with the CON female group, these ES female mice also display decreases in social interaction ($t_{20} = 2.18, p < .05$), indicating that VDS exposure results in lowered sociability regardless of whether the ES female stays overnight with the CD1 aggressor.

### Housing Conditions Do Not Influence Baseline Levels of Social Interaction

To examine whether differences in baseline levels of social interaction would be observed as a function of housing and/or chemosensory conditions, we conducted a separate experiment where CON female mice were exposed to the bedding of PS male mice for 10 consecutive days ($n = 12$). Also, a separate group of CON female mice was pair-housed with CD1 male mice (as in Figure 1D), thus removing the visual aspects of physical defeat stress in the presence of the aggressor ($n = 10$). In Supplemental Figure S2B, a one-way ANOVA indicated that, when compared with the original CON female group (Figure 2A), these housing and/or chemosensory conditions do not influence baseline levels of social interaction ($F_{2,30} = 1.37, p > .05$).

### ES-Induced Avoidance Is Influenced by Visual Cues, but Not Social Target Strain and/or Sex

As additional control conditions for the development of avoidance-like behavior, we examined whether social behavior would be influenced by the strain and/or sex of the social target during the social interaction test, as well as the role that visual cues play during VDS exposure. Figure 3A shows that the ES-induced reduction in social behavior is exhibited even when the social target is an age-matched unfamiliar C57BL/6 female counterpart ($t_{20} = 3.33, p < .05$), indicating generalized avoidance ($n = 11$ per group). However, as depicted in Figure 3B, when an opaque divider is used to block visual cues during the VDS episodes, ES female mice do not develop avoidance-like behavior ($n = 10$ per group), because no

#### Figure 3. Effects of social target sex and strain, as well as visual stimuli, on social behavior in female C57BL/6 mice exposed to the vicarious defeat stress model. (A) When compared with control (CON) mice ($n = 11$), female mice exposed to emotional and/or psychological stress (ES, $n = 11$) spent significantly less time in the interaction zone when exposed to a same sex/strain social target during the target-present condition of the social interaction test ($p < .05$). (B) Using opaque dividers to block visual stimuli during vicarious defeat stress exposure prevented the development of avoidance behavior, because no differences in the time spent in the interaction zone were observed between the groups ($p > .05, n = 10$ per group). (C) Twenty-four hours after vicarious defeat stress exposure, ES female mice ($n = 6$) exhibited higher levels of serum corticosterone when compared with CON mice ($n = 8; p < .05$). Data are presented as mean ± SEM. *$p < .05$ when compared with CON mice.
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Figure 4 shows the effects of 10 days of VDS on body weight.

Figure 5 shows the effects of VDS on the anxiogenic environment of the elevated plus maze. While ES female mice (n = 11), compared with CON mice (n = 12), displayed decreased time in the open arms of the maze, a Student t test indicated that this difference did not reach statistical significance (t(21) = 1.86, p = .07).

Ketamine and Chlordiazepoxide Ameliorate ES-Induced Decreases in Social Behavior

Figure 7 shows the effects of ketamine and chlordiazepoxide on social behavior after exposure to ES in female mice. A one-way ANOVA indicated that social behavior was influenced by drug treatment (F(3,40) = 3.22, p < .05). Specifically, when compared with CON mice (n = 18), the female mice exposed to ES and administered saline (ES-saline; n = 8) displayed significantly lower interaction ratios (Tukey, p < .05). Conversely, no differences between CON and ES female mice receiving either ketamine (n = 8) or chlordiazepoxide (n = 10) were observed (p > .05, respectively), indicating that both drugs ameliorated the ES-induced decrease in social behavior (Figure 7A). No differences in distance traveled (in centimeters), as a function of drug administration, during the target-absent condition of the social interaction test, were detected between the groups (F(3,40) = 1.15, p > .05) (Figure 7B).

DISCUSSION

The purpose of the present investigation was to examine whether depression-related outcomes would be evident in female mice after exposure to VDS (26). To achieve this, we exposed female C57BL/6 mice to ES by witnessing the defeat bout of a male conspecific for 10 consecutive days. Twenty-four hours later, separate groups of female mice were tested on a collection of behavioral tests that are designed to evaluate social functioning (social interaction), anhedonia (sucrose preference), despair (tail suspension test), anxiety (elevated plus maze), and hypothalamic-pituitary-adrenal (HPA) axis activation (corticosterone). Collectively, our data indicate that exposure to ES, in female mice, is a significant stressor that induces behavioral and physiologic responses that recapitulate depression-like symptomology.

Because an association between depression and impaired social functioning is well recognized (32) and social avoidance...
is a behavioral endophenotype recapitulated by preclinical social stress models (19,26), we first examined the impact of ES on the social interaction test. We found that ES female mice spent less time interacting with a novel social target, regardless of the social target’s sex and/or strain (Figures 2A and 3A, Supplemental Figure S2A), when compared with CON mice—demonstrating a generalized decrease in social behavior. This behavioral response is comparable to that of male mice experiencing similar psychosocial stressors (21) or PS itself (Figure 2A). Yet here, we extend these findings to female C57BL/6 mice, which display avoidance as a result of indirectly experiencing the defeat bout of a male conspecific—an effect that is prevented when visual cues are blocked (Figure 3B). Furthermore, because the reduced ability to experience pleasure (i.e., anhedonia) is a core symptom of depression, we also examined whether female mice exposed to ES would display decreased preference for sucrose. We found that, when compared with CON mice, ES female mice displayed significantly lowered preference for sucrose as of the seventh day of the VDS procedure, an effect that remained 24 hours after stress exposure (Figure 5A). This finding appears to be sex dependent, because previous work suggests that ES male C57BL/6 mice do not develop a decrease in preference for sucrose 24 hours after VDS (21). Importantly, although ES-female mice displayed decreases in body weight (Figure 4), no differences in total liquid intake were observed between the groups (Figure 5B), which is indicative of an anhedonia-like state (33)—an effect that extends face validity to the VDS model in female C57BL/6 mice specifically. Hence, our findings indicate that this paradigm induces a negative affect state in female mice, per decreases in social behavior and sucrose preference, that may lend translational significance to the clinical population, where women report depressive symptoms as a result of emotional distress (34).

In addition to social dysfunction and anhedonia-like behavior, ES increased sensitivity to subsequent stressors designed to assess mood-related behavior. Here, when compared with CON mice, ES female mice displayed increased total immobility in the tail suspension test (Figure 6A). Conversely, when examining behavioral responses to the anxiogenic environment of the elevated plus maze, ES female mice did not display a significant reduction in the percentage of time spent in the open arms of the maze. This contrasts with male mice that have experienced PS or ES (21), highlighting sex-dependent differences to escapable versus inescapable stressors (35). It appears that 24 hours after VDS,
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both ES female and ES male C57BL/6 mice display decreases in social behavior, along with increased sensitivity to despair measures. Interestingly, female mice also display an anhedonia-like behavioral profile (decreased sucrose preference), without changes in exploratory behavior in the elevated plus maze. Conversely, ES male mice do not display a decrease in sucrose preference at this time point, yet they display an anxiogenic profile in the elevated plus maze (21). Together, these findings suggest that the VDS paradigm is a powerful tool that may dissect the ES-induced neurobiological factors underlying specific mood-related syndromes (anhedonia vs. anxiety) as a function of sex. This is a critical factor when developing preclinical models of affective disorders, given that men and women exhibit different symptoms and approaches do not mimic the nature of stress in humans, in which social and emotional stressors predominate. Thus, we postulate that the female VDS model better recapitulates critical behavioral (social avoidance, anhedonia, despair) and physiologic (increased corticosterone and weight change) endophenotypes that may allow researchers to uncover the neurobiological factors of ES-induced mood-related illnesses (37,38). Thus, we examined how VDS would influence blood serum levels of corticosterone in ES female mice. Here, we found that witnessing the defeat bout of a male conspecific is salient enough to activate the HPA axis, as indicated by elevated levels of corticosterone when compared with that of female CON mice (Figure 3C). Indeed, previous work in rodents has supported the link between stress and depression-related behaviors, such experimental approaches do not mimic the nature of stress in humans, in which social and emotional stressors predominate. Thus, we postulate that the female VDS model better recapitulates critical behavioral (social avoidance, anhedonia, despair) and physiologic (increased corticosterone and weight change) endophenotypes that may allow researchers to uncover the neurobiological factors of ES-induced mood-related illnesses.

To examine whether pharmacological agents commonly used to treat mood-related disorders ameliorate the depression-related behaviors induced by VDS, we conducted an experiment where separate groups of ES female mice were administered ketamine or chlordiazepoxide prior to the examination of social behavior. We selected the social interaction test given that it is a behavior associated with both depressive-like and mood-related illnesses (37,38). Thus, we examined how VDS would influence blood serum levels of corticosterone in ES female mice. Here, we found that witnessing the defeat bout of a male conspecific is salient enough to activate the HPA axis, as indicated by elevated levels of corticosterone when compared with that of female CON mice (Figure 3C). Indeed, previous work in rodents has supported the link between stress and depression-related behaviors, such experimental approaches do not mimic the nature of stress in humans, in which social and emotional stressors predominate. Thus, we postulate that the female VDS model better recapitulates critical behavioral (social avoidance, anhedonia, despair) and physiologic (increased corticosterone and weight change) endophenotypes that may allow researchers to uncover the neurobiological factors of ES-induced mood-related illnesses.

To examine whether pharmacological agents commonly used to treat mood-related disorders ameliorate the depression-related behaviors induced by VDS, we conducted an experiment where separate groups of ES female mice were administered ketamine or chlordiazepoxide prior to the examination of social behavior. We selected the social interaction test given that it is a behavior associated with both depressive-like and
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anxiogenic-like characteristics with high pharmacological validity (19,40). Specifically, decreases in social behavior, after defeat stress, are reversed by both traditional antidepressants (fluoxetine, a selective serotonin reuptake inhibitor) and novel antidepressants (ketamine, a noncompetitive N-methyl-D-aspartate receptor antagonist), but not by anxiolytic drugs (chlordiazepoxide, a benzodiazepine) in male mice (19,41). Here, we found that both ketamine and chlordiazepoxide ameliorated the ES-induced reductions of social behavior in female mice (Figure 7). The finding that chlordiazepoxide reversed ES-induced social avoidance in female mice, unlike what was previously reported in PS male mice (19), is likely due to experimental differences that include type of stress (ES vs. PS), sex (female vs. male), dose (10 vs. 2.5 mg/kg), and regimen (1 day vs. 28 days) between the studies. This finding suggests that the female VDS paradigm is sensitive to both traditional anxiolytics and antidepressants, providing pharmacological validity to this model.

The neurobiological factors that underlie the female ES-induced behavioral dysfunction and pharmacological reversal of these alterations are unknown. Nevertheless, previous work in ES male mice suggests that adaptations in signaling molecules within reward-related brain regions, such as the nucleus accumbens (NAcc) and ventral tegmental area, may underlie the social avoidance phenotype (21,27). Specifically, ES alters extracellular signal-regulated kinase (ERK)-signaling within these brain regions. ERK is a signaling molecule that has been highly implicated in regulating responses to both affect-related (42–44) and reward-related behaviors (45,46). For example, within the NAcc of male mice, ES increases ERK2 gene expression (27) while decreasing ERK-related signaling transcripts within the ventral tegmental area (21). Whether these molecular alterations within the ventral tegmental area–NAcc circuitry modulate depression-like behavioral responses in ES female mice has yet to be determined. Interestingly, a recent report utilizing subchronic variable stress in female C57BL/6 mice found a similar depressive-like behavioral profile as the ES female mice in our study (i.e., decreased sucrose preference, increased corticosterone, without changes in explorative behavior in the plus maze). Furthermore, they also reported gene alterations within the NAcc of female mice that matched those found in postmortem tissue of female humans with depression (47), thus highlighting this brain circuitry as a potential target to examine the neurobiological factors that underlie psychological stress-induced depression.

It is important to note that we did not determine the phase of the estrus cycle across the female mice utilized in our experiments when behavioral testing was conducted. Thus, it is possible that the normal fluctuations in estradiol and/or progesterone may have affected both the corticosterone and behavioral responses observed—particularly when the social target was a male mouse, versus a female mouse during the social interaction test. As such, future work will be needed to thoroughly examine whether or not the estrus cycle may play a role in the depression-related phenotype induced by VDS.

Given the increased rates of mood-related illnesses across the globe, particularly depression, it is imperative to develop preclinical models that allow researchers to uncover the neurobiological mechanisms that underlie the disorder. Both sex and stress are common risk factors in the development of depression; thus, we propose that the VDS model can be used to experimentally dissect the individual contributions that specific social stressors (i.e., psychological), as a function of sex (i.e., female), can contribute in the expression of depression-related behavior. Collectively, we propose that our data provide face, ethological, and pharmacological validity to the VDS paradigm as a model of ES-induced depression in a sex-specific manner.

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ARTICLE INFORMATION

From the Department of Psychology (SDI, FJF-R, IG-C, MAH, DOS, SAC), The University of Texas at El Paso, El Paso, Texas; Department of Anatomy and Neurobiology (LMR, JBA, MKL), University of Maryland School of Medicine, Baltimore, Maryland; and the Department of Psychology (PAS, SHB), Hunter College, New York, New York.

Address correspondence to Sergio D. Ilizguez, Ph.D., Department of Psychology, The University of Texas at El Paso, 500 W. University Avenue, El Paso, TX 79968; E-mail: sdi1@utep.edu.

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