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Short communication

Sex and lineage interact to predict behavioral effects of chronic adolescent stress in rats

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HIGHLIGHTS

- We examined the effects of chronic adolescent stress in selectively bred rats.
- Chronic adolescent stress reduced weight gain in all rats in both lineages and sexes.
- Lineage interacted with chronic adolescent stress to dictate activity level.
- Stress-induced anhedonia was dependent on lineage.
- Sex differences in behavior were attenuated by lineage

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ABSTRACT

Neuropsychiatric disorders often derive from environmental influences that occur at important stages of development and interact with genetics. This study examined the effects of stress during adolescence in rats selectively bred for different behavioral responses to stress. The effects of chronic adolescent stress were compared between rats selected for susceptibility to reduced activity following acute stress (Swim-test Susceptible rats) and rats resistant to activity reduction after acute stress (Swim-test Resistant rats). Consistent with lineage, exposure to chronic adolescent stress increased swim-test activity of the Swim-test Resistant rats while tending to reduce activity of the Swim-test Susceptible rats. Consistent with the increased activity demonstrated post-stress in the swim test, chronic adolescent stress increased total activity in the open field for Swim-test Resistant rats. Indicative of anhedonia, chronic adolescent stress exposure decreased sucrose consumption in both male and female Swim-test Resistant rats but only in female Swim-test Susceptible rats. Although chronic stress induced changes in behavior across both breeding lines, the precise manifestation of the behavioral change was dependent on both breeding line and sex. Collectively, these data indicate that selective breeding interacts with chronic stress exposure during adolescence to dictate behavioral outcomes.

Recent advances in the collective understanding of psychopathology indicate that neuropsychiatric disorders are developmental in origin [1], and adolescence in particular is a period of vulnerability to stress and susceptibility to neuropsychiatric disease [2,3]. An adolescent episode of an anxiety or depressive disorder predicts a 2- to 3-fold increased risk for adult affective disorders [4]. Sex also alters the behavioral response to stress. Women experience higher rates of depression and female animal models more frequently develop depressive-like behaviors than males in response to stress exposure [5,6]. Conversely, clinical studies suggest that sex differences in depression are diminished if family history is strong [7]. In an effort to produce better animal models for the study of depression, selective breeding was used to develop rat lines with differences in depression-relevant physiology and behavior [8–11]. To represent different backgrounds for the studies described here, we used two lines of rats selectively bred to be differentially sensitive to the effects of stress – the Swim-test Susceptible (SUS) and Swim-test Resistant (RES) rat lines [10]. This nomenclature reflects different behavioral responses shown by the animals in the forced swim test; the SUS rat, following acute stress,

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responds with reduced activity (depressive-like behavior) in the swim test whereas the RES rat responds to the same stressor with no decrease in swim test activity. Additional studies have characterized responses to antidepressant treatment, substance abuse behaviors, and neurobiology of adult male rats of the RES and SUS lines [12–14]. In sum, these studies have demonstrated distinctly different depression-relevant behavioral and neurochemical phenotypes in adult males of both lines. However, previous studies have not assessed the behavior of adolescents in these lines, effects of chronic stressors, or specific behavior of females. The current study assessed the hypothesis that lineage predicts behavioral consequences of chronic adolescent stress exposure in male and female rats.

Adolescent male and female Sprague-Dawley rats from the RES and SUS lines were housed on a 14:10 reverse light:dark cycle in a facility controlled for humidity (60%) and temperature (20–23 °C). Rodent diet 5001 chow (Purina Mills, Richmond, IN) and water were available ad libitum throughout the study. All experiments were performed in accordance with the Institutional Animal Care and Use Committee of Emory University and the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

The mixed modality chronic stress paradigm used in this study was previously used to elicit sex-specific behavioral changes in adolescent rats [6,15]. Briefly, adolescent stress was defined as individual housing beginning at post-natal day (PND) 36 and continuing throughout the study combined with randomly alternating daily exposure to social defeat or restraint from PND 37–48. The control groups remained pair-housed with a same sex littermate and are referred to as non-stress groups. The following groups were assessed: (1) RES male non-stress ($n = 10$), (2) RES male stress ($n = 10$), (3) RES female non-stress ($n = 10$), (4) RES female stress ($n = 10$), (5) SUS male non-stress ($n = 10$), (6) SUS male stress ($n = 10$), (7) SUS female non-stress ($n = 10$), and (8) SUS female stress ($n = 10$). Social defeat stress (up to 5 min of contact, and an additional 25 min of visual and olfactory stimulation) was performed during the light cycle in the home cage of the resident, a mature Long–Evans rat experienced in territorial fighting. Male residents were adult retired breeders and female residents were ovariectomized adults. Although female rats are commonly viewed as devoid of territorial behavior, Long–Evans female rats housed with a male counterpart will develop territorial behavior and have been shown to defeat adolescent female rats [6], a behavior that persists after ovariectomy [16]. For the restraint portion of the mixed-modality stressor, animals were restrained for 60 min in acrylic rat restraints (BrainTree Scientific, Braintree, MA, USA) that prevented head to tail turns but did not compress the rat. Adolescents received six total exposures to social defeat and six total exposures to restraint over twelve days in a randomly alternating pattern. The study was not designed to assess specific effects of individual housing, restraint, or social defeat but used this combination of established stressors to induce chronic stress during adolescence.

Exposure to chronic mixed modality stress reduced body mass gain for all rats irrespective of line (Fig. 1; $F_{1,68} = 7.887$; $p < 0.05$), reflecting physiological impact of chronic stress exposure. Consistent with well-established sex differences, males weighed more than females for both lines of rats ($F_{1,68} = 161.953$; $p < 0.05$). Rat line also influenced body mass ($F_{1,68} = 29.167$; $p < 0.05$) such that SUS rats weighed more than RES rats ($p < 0.05$). Additionally, a significant interaction existed between sex and chronic stress ($F_{1,68} = 5.829$; < 0.05). Although stress reduced weight gain in both males and females ($p < 0.05$ for both comparisons), stress reduced weight gain among females by only $3.0 \pm 1.0\%$ but among males by $7.8 \pm 1.0\%$.

Behavioral testing commenced 24 h after the final chronic stressor on PND 49, consisting sequentially of a 48-h sucrose consumption test (PND 49–50), open field test (PND 51) and a 10-min

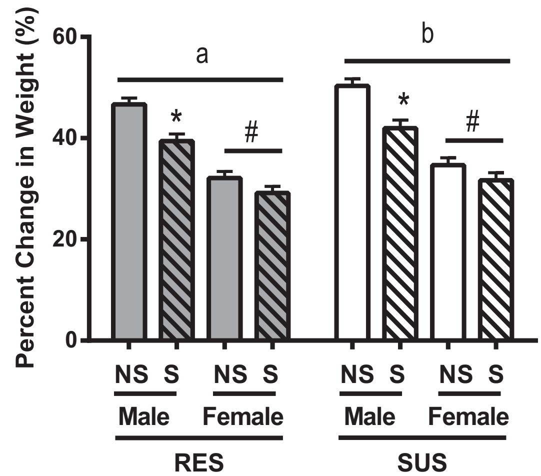

Fig. 1. Body mass. Bars represent percent change in body mass over the duration of the study for rats resistant to showing reduced activity in the forced swim test after stress (RES) and rats susceptible to showing reduced activity in the forced swim test after stress (SUS). Body mass was tracked for both rats that were not exposed to stress (NS) and those exposed to chronic mixed modality stress (S) through adolescence. Data are presented as mean ± SEM. Statistics: significant line differences ($p < 0.05$) are indicated by letters (i.e., "a" and "b"), with different letters indicating significant differences. Also, #$p < 0.05$ compared to males of same line, and *$p < 0.05$ as compared to NS of same line.

Porsolt forced swim test (PND 52). The open field test was conducted 2 h after the onset of the dark cycle and the swim test was conducted during the light cycle. Unlike other studies done with selectively bred lines, this series of experiments did not incorporate the use of an acute stressor immediately prior to testing.

The sucrose consumption test was performed as a measure of hedonic state [17]. Rats were given free access to one bottle of tap water and one bottle of a 0.8% sucrose solution in tap water. Bottles were reversed after 24 h to prevent side bias. Bottles were weighed at the beginning and then after 24 and 48 h to determine sucrose and water consumption. Rats subjected to chronic social defeat typically consume less sucrose than control rats, a behavior described as depressive-like [17]. Chronic adolescent stress decreased sucrose intake compared to non-stressed rats in the second 24 h of exposure (Fig. 2; $F_{1,47} = 4.135$; $p < 0.05$). Rat line also predicted sucrose

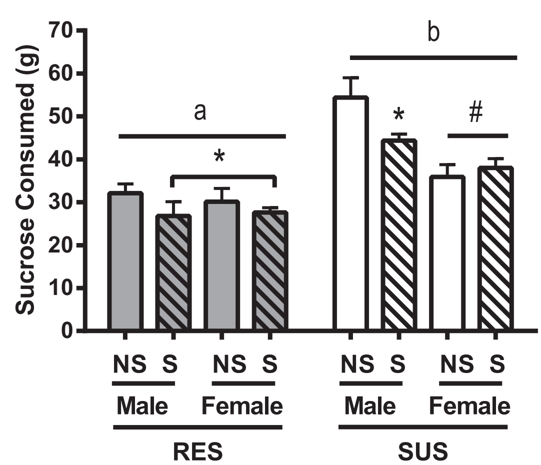

Fig. 2. Sucrose intake. Sucrose and water intake for RES and SUS rats for both non-stressed (NS) and stressed (S) animals. Total sucrose solution consumed on the second day of testing is shown. Data are presented as mean ± SEM. Statistics: significant line differences ($p < 0.05$) are indicated by letters, with different letters indicating significant differences. Also, #$p < 0.05$ compared to males of same line, and *$p < 0.05$ as compared to NS of same line.