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Research report

The impact of social stress during adolescence or adulthood and coping strategy on cognitive function of female rats

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HIGHLIGHTS

- We compared social stress effects on cognition in adolescent and adult female rats.
- Stress-coping strategy determined the impact of adolescent stress on cognition.
- Consequences of female adolescent social stress do not endure into adulthood.
- Female adolescent cognitive flexibility correlates to prefrontal cortex activity.

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ABSTRACT

The age of stressor exposure can determine its neurobehavioral impact. For example, exposure of adolescent male rats to resident-intruder stress impairs cognitive flexibility in adulthood. The current study examined the impact of this stressor in female rats. Rats were exposed to resident-intruder stress during early adolescence (EA), mid-adolescence (MA) or adulthood (Adult). They were tested in an operant strategy-shifting task for side discrimination (SD), reversal learning (REV) and strategy set-shifting (SHIFT) the following week. Performance varied with age, stress and coping style. MA and EA rats performed SD and SHIFT better than other ages, respectively. Social stress impaired performance in rats depending on their coping strategy as determined by a short (SL) or long (LL) latency to become subordinate. SL rats were impaired in SD and REV, whereas EA-LL rats were impaired in SHIFT. These impairing effects of female adolescent stress did not endure into adulthood. Strategy set-shifting performance for female adolescents was positively correlated with medial prefrontal cortex (mPFC) activation as indicated by c-fos expression suggesting that this region is engaged during task performance. This contrasts with the inverse relationship between these indices reported for male adolescent rats. Together, the results demonstrate that social stress produces cognitive impairments for female rats that depend on age and coping style but unlike males, the impairing effects of female adolescent social stress are immediate and do not endure into adulthood. Sex differences in the impact of adolescent social stress on cognition may reflect differences in mPFC engagement during the task.

1. Introduction

Stress has been implicated in diverse psychiatric disorders including depression, anxiety, post-traumatic stress disorder and substance abuse [1–3]. In an effort to understand these links, research has focused on stress-induced alterations of affective processes. More recently, impairments in cognitive functions have become recognized as core features of stress-related psychiatric diseases that contribute to their debilitating nature. Although it is adaptive for stressors to alter cognitive processes such as arousal state, attention biases, decision-making and working memory to promote survival, chronic or repeated stress can impair these

Abbreviations: EA, early adolescent; LL, long latency; mPEC, edial prefrontal cortex (mPFC); MA, mid adolescent; OSST, operant strategy set-shifting task; PND, post natal day; REV, reversal learning; SL, short latency; SD, side discrimination; SHIFT, strategy shifting.

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processes and contribute to cognitive symptoms of psychiatric disorders [4–6].

Substantial individual variability exists in the pathological consequences of stress, giving rise to the concepts of stress vulnerability and resilience [7,8]. Various factors contribute to individual variability including the sex of the subject, genetic factors, environmental or social modulating factors and the developmental stage at which the stress occurs. Given the prevalence of social stress in humans and its negative impact on mental and physical health [9,10], our laboratory has investigated individual differences in the consequences of the rat resident-intruder model of social stress [11,12]. We determined that exposure of male rats to repeated resident-intruder stress results in the emergence of two subpopulations based on their coping strategy to exhibit a subordinate defeat posture with either a short latency (SL) vs. long latency (LL) [11]. SL male rats show certain behavioral, endocrine and physiological endpoints of depression, including increased immobility in the Porsolt swim test, decreased sucrose preference, decreased heart rate variability and dysregulation of the hypothalamic–pituitary–adrenal axis [11,13,14]. Recently, the effects of resident-intruder stress presented at different ages on cognitive function were investigated in male rats [15]. This social stress presented during early or late adolescence or adulthood had no immediate effects but adolescent social stress impaired strategy shifting, a form of cognitive flexibility, when tested in adulthood and rats with the SL coping strategy were more vulnerable. This study revealed that social stress in male rats has distinct effects on cognitive processes that are dependent on the age at which it occurs, the age at which the endpoint is tested and the coping style of the subject. Notably, strategy-shifting performance in adult male rats was positively correlated to activation of medial prefrontal cortical (mPFC) neurons as indicated by c-fos expression, whereas in adolescent males this correlation was negative, suggesting that different circuits are engaged in adolescent and adult male rats during task performance.

Although social stress is also relevant for females, this has been primarily modeled in the laboratory using social isolation or social instability because neither male nor female rats are typically aggressive to female rats [16–18]. However, lactating females exhibit aggression towards female rats and this has been used as a female resident-intruder social stress model [19–21]. The present study used this model of female resident-intruder stress to investigate the effects of social stress occurring in early and mid-adolescence or adulthood on cognitive function tested shortly after the last stressor or later for adolescent rats, in adulthood. The modifying influence of coping style determined by the latency to become subordinate on stress effects was assessed. Finally, because the mPFC mediates cognitive flexibility and is exquisitely stress-sensitive [22–24], measures of mPFC activity were related to behavioral effects.

2. Materials and methods

2.1. Animals

Female Sprague-Dawley rats (Charles River, Wilmington, Massachusetts) served as social stress “intruder” rats or matched controls. Rats had free access to food and water and were allowed to acclimate to a 12-h light:12-h dark cycle (lights on at 06:00 AM), temperature-controlled room for 4 days prior to the study. Sprague-Dawley lactating adult rats that were housed separately were used as resident rats in the resident-intruder test. The care and use of animals was approved by the Institutional Animal Care and Use Committee of the Children's Hospital of Philadelphia.

2.2. Experimental design

Stress or control manipulations occurred during early adolescence (PND 28–32, EA), mid-adolescence (PND 42–46, MA), or adulthood (PND 70–74, Adult). These ages were selected to span the social and physical stages of early and mid-adolescence as designated previously [25–27]. In addition a group of EA stressed rats were tested as adults (PND 70–74; EA-Adults) and a group of MA stressed rats were tested as adults (PND 70–74; MA-Adults). Rats were exposed to 5 consecutive days of social stress or control manipulation. On the last day of social stress or control manipulation EA, MA, and Adult rats began food restriction to maintain 85% free-feeding weight. Training in the operant strategy set-shifting task (OSST) began 3 days after the last experimental manipulation and testing occurred after 3 days of training, 6 days after the final experimental manipulation. EA-Adult and MA-Adult animals were food restricted, trained, and tested in the operant chamber at the same age as Adult animals. These rats were group housed after the last experimental or control manipulation until training and testing as adults.

2.3. Social stress

The social stress and matched control methods were a modification of the resident-intruder model [28] and identical to that previously described [15] except that lactating female rats were used as resident rats. Intruders were individually placed in the home-cage of a novel lactating female (resident) whose pups had been removed immediately prior. The resident and intruder were allowed to interact until either the intruder exhibited a submissive defeat posture (>2 s frozen in a supine position) or 15 min elapsed. Upon reaching one of these criteria, the animals were separated by a wire barrier, allowing only auditory, olfactory and visual contact for the remainder of the 30-min test period. Intruders were then returned to their home-cages and lactating mothers were reunited with their pups. This was repeated for 5 consecutive days with the intruder being randomly placed into the cage of a different lactating female each day. Control rats were placed into a novel cage for 30 min/day with the last 15 min spent behind the wire mesh cage for 5 consecutive days. For all rats subjected to resident-intruder stress the latency to assume the defeat posture was recorded for each session and averaged across all 5 sessions for an individual intruder. If the defeat posture was not assumed during the 15 min period, the latency was given the value of 900 s. The mean latencies for all intruder rats of each age group (EA, MA and Adult) were subjected to a K-means cluster analysis (JMP 9.0; SAS, Cary, NC) to define the subpopulations of rats as short latency (SL) or long latency (LL).

2.4. Operant training and testing

Training and testing were carried out in two-lever operant chambers (Med-Associates, St. Albans, VT, USA), each within a sound-attenuating box. A stimulus light was positioned above each lever, and a house light was positioned top-center on the wall opposite the levers. Data were recorded and stored onto a PC computer via an interface module.

The operant strategy-shifting task (OSST) was adapted from Floresco et al. [29]. On Day 1, rats were shaped to lever press on a fixed-ratio 1 schedule on one lever (randomly chosen left/right) to a criterion of 50 presses within 30 min. On Day 2, rats were trained to the same criterion with a fixed-ratio 1 schedule on the opposite lever. On Day 3, rats were introduced to the trial structure of the task, under conditions with no discernable “rule”. On each trial, the house light and both stimulus lights were illuminated for 15-s during which rats could press one of the two levers