THE EFFECTS OF ADOLESCENT OR ADULT ACUTE STRESS ON COCAINE SEEKING IN MALE RATS

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ABSTRACT

INTRODUCTION:
Adolescent or adult traumatic stress, such as violence and physical assault, has emerged as a substantial risk factor for substance use disorder (SUD). Preclinical studies suggest that stressful experiences during adolescence have long-term behavioral outputs and neurophysiological consequences, and altered efficacy of synaptic transmission in adulthood. To identify groups at risk of developing SUD, researchers must first elucidate the neurobiological mechanisms behind the stress/drug-addiction comorbidity. We hypothesized that stressful experiences, either during adolescence, adulthood, or both, will lead to higher cocaine-seeking behavior.
METHODS:
To test this, we used the fear-conditioning (FC) paradigm as a stressful experience in both, adolescent or adult Sprague Dawley rats. In adolescent rats, 30 days after stress induction, rats were exposed to 12 days of short-access cocaine self-administration, followed by 15 days of extinction, and two reinstatement sessions (cue- and cocaine-primed). In adult rats the exact same protocol was used, except it was started five days after FC.
RESULTS:
Contrary to our hypothesis, the stressed adolescent group showed no differences in cocaine consumption, extinction, and cue-primed reinstatement, relative to the controls. Moreover, cocaine-primed reinstatement significantly decreased compared to the non-stressed adolescent group. On the other hand, stressed adult male rats showed seemingly higher cocaine acquisition, no difference in extinction, and statistically significant difference in both, cue- and cocaine-primed reinstatements, compared to non-stressed adult rats.
CONCLUSION:
Our findings show that the effects of acute stress on cocaine seeking behavior are dependent on the timing of the stressful event, with stressed adults showing higher reinstatement than adolescent.

INTRODUCTION

- Substance Abuse and Mental Health Service Administration (SAMHSA) reports that more than two-thirds of children undergo at least 1 traumatic event by age 16.
- In 2022, it was reported that 1.2 million adolescents and 46.5 million adults aged 18 or older in the United States suffered from substance use disorder (SUD), and among these people, 0.9 million adolescents and 21.5 million adults exhibited mental illness (SAMHSA 2022).
- Adolescent traumatic stress is associated with an increase in substance use disorder and recurrent relapse to drug use (Lo Iacono et al., 2016).
- Studies have identified a co-occurrence between cocaine use disorder (CUD) and trauma-related disorders; according to statistics 34% of trauma-exposed individuals meet lifetime CUD criteria (Khoury et al., 2010; Brady et al., 2000; Perkonigg et al., 2000).
- Preclinical studies suggest that stressful/traumatic experiences as an adolescent have long-term consequences on stress, anxiety, and the efficacy of synaptic transmission in adulthood (Avital, A et al., 2005, Ivens, S et al., 2019).

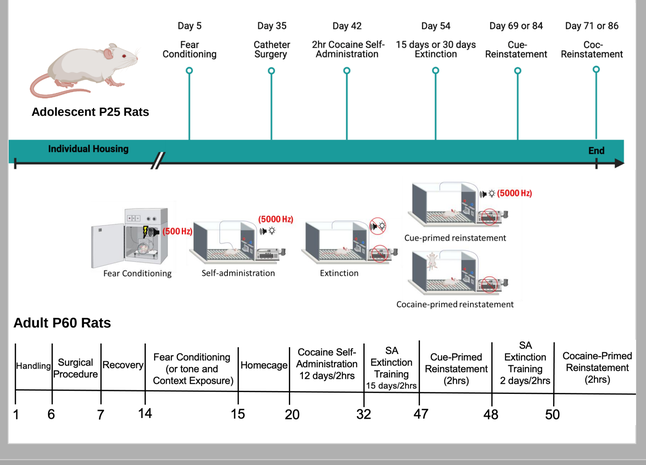
AIM

Determine the effects of adolescent and adult stress on adulthood cocaine-seeking behavior.

HYPOTHESIS

Stressful experiences, either during adolescence or adulthood, lead to an increase in cocaine-seeking behavior.

METHODS



RESULTS

Adolescent Behavioral Results

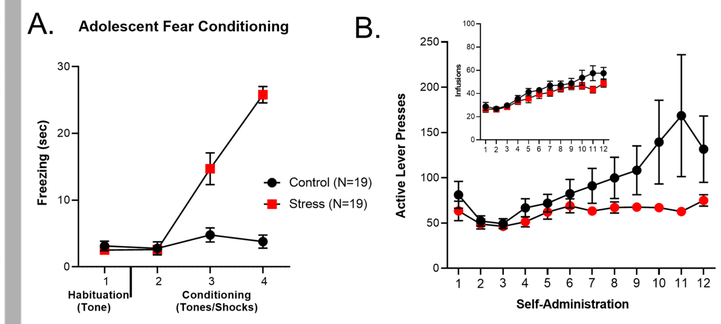
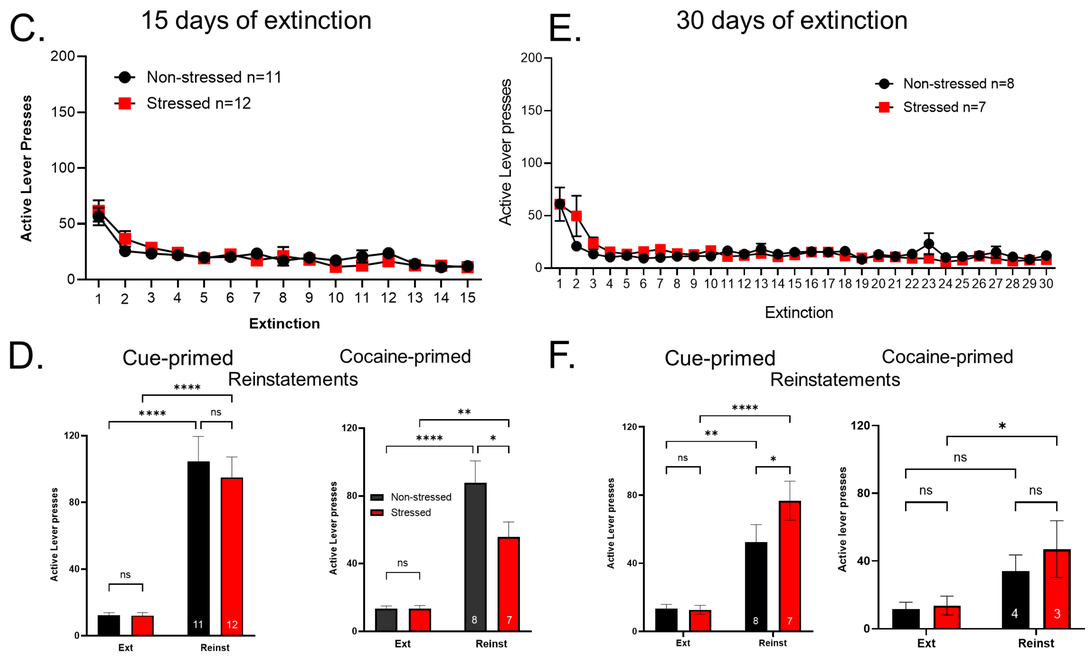


Figure 1. Adolescent traumatic event decreased cocaine-reinstatement after 15 days of extinction, with no changes in cue-reinstatement. Conversely, after 30 days of extinction, cue-reinstatement was increased, with no effect on cocaine-reinstatement. A) Freezing during tone presentation in adolescent rats that received auditory fear conditioning. **B**) Active lever presses of short-access self-administration sessions and cocaine infusions. **C**) Active lever presses on extinction training (15 days) for all rats across groups. **D**) Reinstatement to the presentation of drug-paired cues (left) and cocaine-primed reinstatement (Right; Two-way ANOVA, $F_{(1,34)}$ = 4.175, p = 0.032) measured by active lever presses after 15 days of extinction. E) Active lever presses on extinction training (30 days) for all rats across groups. F) Reinstatement to the presentation of drug-paired cues (Left; Two-way ANOVA: $F_{(1,26)}$ = 2.509, p = 0.038) and cocaine-primed reinstatement measured by active lever presses after 30 days of extinction (right).



Adult Behavioral Results

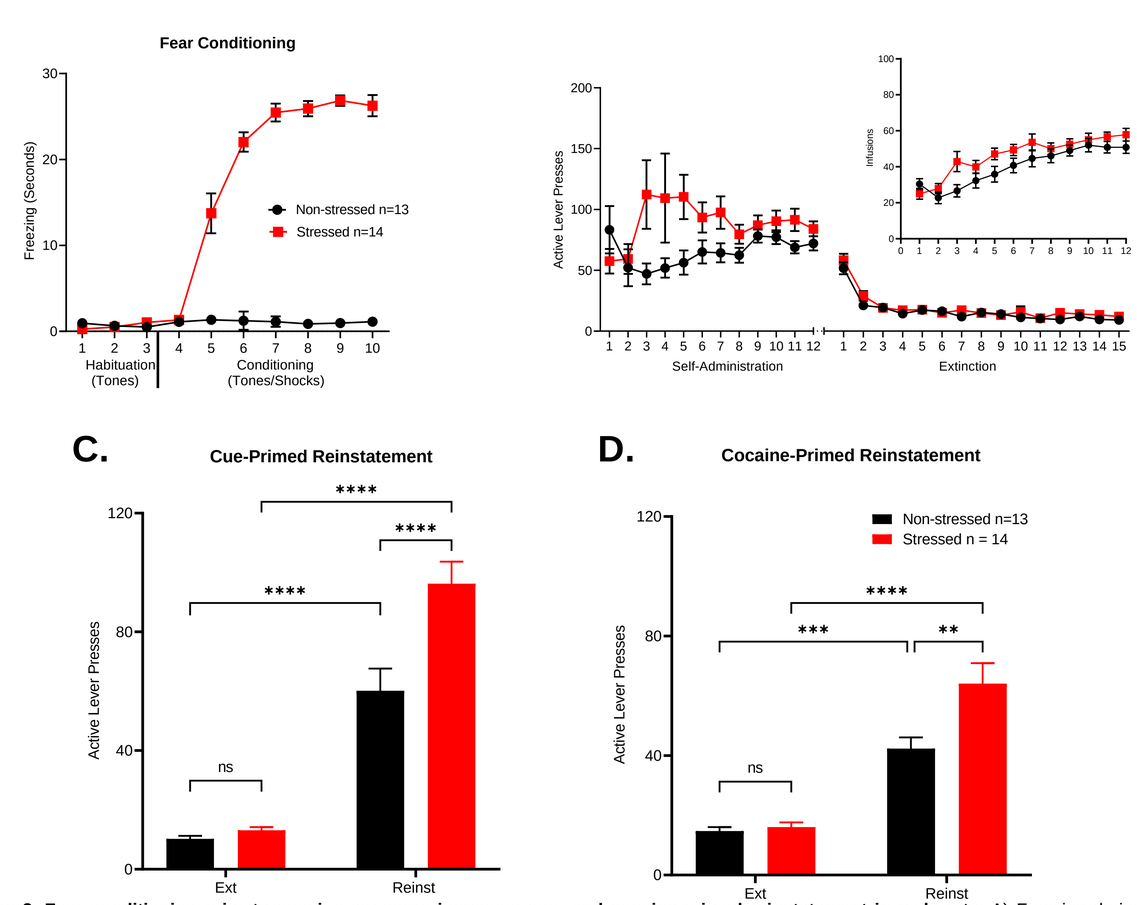


Figure 2. Fear conditioning prior to cocaine exposure increases cue- and cocaine-primed reinstatement in male rats. A) Freezing during tone presentation in adult rats that received auditory fear conditioning. B) Active lever presses on self-administration and extinction training for all rats across groups. Cocaine infusions of rats across groups. C) Reinstatement to the presentation of drug-paired cues measured by active lever presses (right). Average number of lever presses of the last three days of extinction training for each group (left). A Two-way ANOVA with multiple comparison analysis shows a main effect on cue-primed reinstatement of fear conditioned (stressed) vs. context-exposure (non-stressed) groups ($F_{(1,50)}$ = 9.686, p = 0.0031, as fear-conditioned rats had higher cue-primed reinstatement compared to context-exposure rats (p < 0.0001). D) Reinstatement to drug injection measured by active lever presses (right). Average number of lever presses of the last three days of extinction training for each group (left). A Two-way ANOVA with multiple comparison analysis shows a main effect on cocaine-primed reinstatement of stressed vs. non-stressed groups ($F_{(1,50)}$ = 6.129, p = 0.0167), as fear-conditioned rats had higher cocaine-primed reinstatement compared to context-exposure rats (p = 0.0027).

SUMMARY

Adolescent Male rats

- Adolescent stress decreases cocaine-primed reinstatement after 15 days of extinction, with no effect on cue-primed reinstatement from adulthood cocaine exposure.
- After 30 days of extinction from adulthood cocaine exposure, there was an increase in cue-induced reinstatement with no effect on cocaine reinstatement.
- These results suggest that adolescent stress and adulthood cocaine exposure affect cocaine seeking differently depending on the length of the withdrawal.

Adult Male rats

- Stressed rats show increased active lever presses in cue- and cocaine-primed reinstatements compared to non-stressed rats.
- Adult stress prior cocaine exposure increases cocaine-seeking behavior.

An acute traumatic event might influence the transition from recreational use of cocaine to the development of cocaine use disorder (CUD).

REFERENCES

- National Survey on Drug Use and Health. Retrieved from https://www.samhsa.gov/data/report/2022-nhduh-annual-national-report.(2022)
- Perkonigg, A., Kessler, R. C., Storz, S., & Wittchen, H. (2000). Traumatic events and post-traumatic stress disorder in the community: prevalence, risk factors and comorbidity. Acta psychiatrica Scandinavica, 101(1), 46–59. https://doi.org/10.1034/j.1600-0447.2000.101001046.
- Khoury L, Tang YL, Bradley B, Cubells JF, Ressler KJ. Substance use, childhood traumatic experience, and posttraumatic stress disorder in an urban civilian population. Depress anxiety. 2010; 27:1077–86.
- Walker, D. M. et al. Adolescence and Reward: Making Sense of Neural and Behavioral Changes Amid the Chaos. J Neurosci 37, 10855-10866, doi:10.1523/JNEUROSCI.1834-17.2017 (2017)
- Lo Iacono, L. et al. Social threat exposure in juvenile mice promotes cocaine-seeking by altering blood clotting and brain vasculature. Addict Biol 22, 911-922, doi:10.1111/adb.12373 (2017).
- Avital, A. & Richter-Levin, G. Exposure to juvenile stress exacerbates the behavioural consequences of exposure to stress in the adult rat. Int J Neuropsychopharmacol 8, 163-173, doi:10.1017/S1461145704004808 (2005).
- Ivens, S. et al. Persistent increase in ventral hippocampal long-term potentiation by juvenile stress: A role for astrocytic glutamine synthetase. Glia 67, 2279-2293

ACKNOWLEDGEMENTS

Funding sources:
- NIH-G-RISE Program #T32GM144896
- NIH-NIGMS Program #2R25GM082406
- RCMI-Supplement Project NMHHD 3U54MD007579-37S1
- The Hispanic Alliance for Clinical and Translational Research (Alliance) NIGMS–U54GM133807
- PR-INBRE Developmental Research Project Program P20 GM103475-19
- Catalyzer Research Grants Program- CRG-2020-00114

IACUC approval number 2202000755 and 2111000658