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# Does fast-acting antidepressant action of ketamine reverse psychosocial stress-induced hippocampal-dependent cognitive deficits in the mouse?

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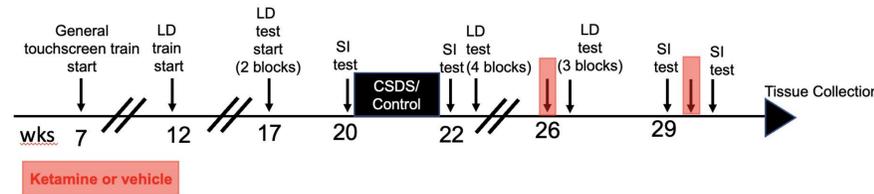
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## QUESTIONS

- Does psychosocial stress decrease hippocampal-dependent pattern separation and cognitive flexibility in mice?
- Can fast-acting ketamine antidepressant reverse stress-induced cognitive deficits?

## APPROACH



## RESULTS

- Psychosocial stress induces:**
- Increased social avoidance in susceptible mice
  - Cognitive inflexibility in the Large separation paradigm → Decreased reversal # and percent correct to reach to the 2nd reversal
  - Longer session length to 1st reversal in the spatial discrimination learning
- Fast-acting ketamine Antidepressant:**
- Significantly improve cognitive flexibility in susceptible mice → Increased reversal # in CSDS/ketamine mice vs CSDS mice in Small separation → Increased reversal # after ketamine injection vs. before injection in CSDS/ketamine group in Large separation
  - Shortened session length to reach to 1st reversal in Small separation in CSDS mice

## IMPLICATION

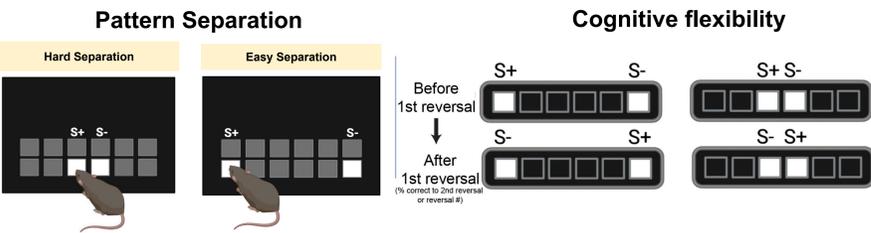
- Our study adds to limited TS LDR literature on both psychosocial stress and fast-acting ketamine.
- Allows for further study of the cellular implications of stress and fast-acting ketamine.

## ABSTRACT

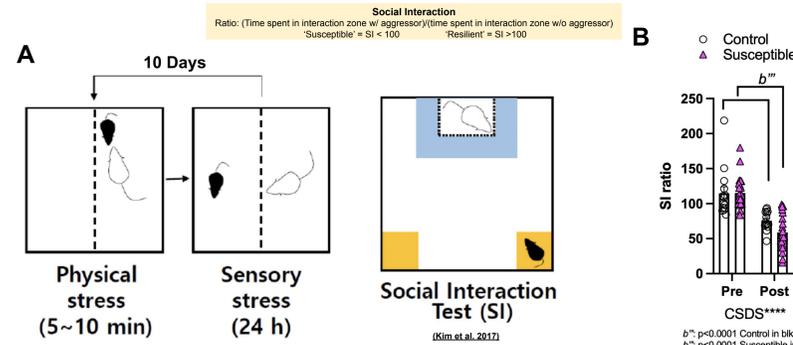
Major depressive disorder (MDD) is extremely prevalent, affecting more than 248 million people worldwide in 2017. Long-term deficits in executive function, attention, and memory are associated with MDD, alongside daily occupational and social impediment. Crucially, suicide attempts (SA) are prevalent amongst over a third of MDD patients, with higher risks for patients currently undergoing an episode opposed to MDD patients fully readmitted to hospitals. Chronic social defeat stress is a relevant psychosocial paradigm that can cause depression-like behavior, alongside long-lasting effects on episodic memory and hippocampal gene expression when left untreated. MDD is commonly treated with antidepressants, however currently approved antidepressants targeting neurotransmitters have delayed response times and are ineffective in approximately a third of MDD patients. Fast-acting ketamine, a N-Methyl-D-Aspartate (NMDA) receptor antagonist, has been found effective against MDD symptoms in the resistant groups, and to reduce the prevalence of suicidal ideation. While there is limited literature stating ketamine reduces reversal learning performance, there is also evidence ketamine can reverse the social deficit caused by depressive-like behavior. Further, the chronic social defeat stress (CSDS) effect on touch screen test (a translational test to the DG) is unknown, along with whether ketamine can improve CSDS related cognitive-deficits. Henceforth we investigated whether psychosocial stress decreases pattern separation and cognitive flexibility in mice, and can fast-acting ketamine antidepressants reverse or improve pattern separation and cognitive flexibility? Location discrimination reversal (LDR) is a touch screen (TS) pattern separation test reliant on the DG. Performance (%correct and session length to 1st reversal) in large vs small separation can indicate discrimination learning (i.e. pattern separation abilities or spatial learning), whereas total reversal numbers and %correct to 2nd reversal in LDR indicate cognitive flexibility. 7-week-old male mice were trained for five weeks to use a TS operant chamber, then underwent LDR testing (2 blocks). A social interaction (SI) test was performed on all mice before and after CSDS which lasted 10 days (animals that interacted with CD-1 mice for 5 minutes each day- "Stress" and animals that did not- "Control"). The 2nd SI ratio was used to determine if the animals were susceptible or resilient to the CSDS effect. LDR testing continued for 4 blocks before half of the mice were injected with ketamine or saline. To test the effect of ketamine on social interaction, the mice were injected with ketamine (15 mg/kg i.p.) or saline underwent a SI test. Results in the large separation paradigm indicate that psychosocial stress leads to impaired cognitive flexibility (higher reversal # and % correct to 2nd reversal in susceptible mice vs. control mice). Further, in the large separation paradigm, psychosocially stressed mice take longer to reach reversal criteria in spatial discrimination learning (longer session length to the 1st reversal in susceptible mice vs control). Fast-acting ketamine antidepressant significantly improves cognitive flexibility in susceptible mice and reversed deficit in cognitive flexibility caused by psychosocial stress. Our study added to the limited TS LDR literature surround psychosocial stress and/or fast-acting ketamine. Follow up studies should include tissue collection to investigate the molecular and cellular implications of psychosocial stress and fast-acting ketamine on the brain.

- MDD is associated with impaired pattern separation and cognitive flexibility (Cambridge et al. 2018).
- Chronic social defeat stress, an ethologically-relevant psychosocial paradigm, can cause depression-like behavior, alongside long-lasting effects on episodic memory (Martin et al. 2017).
- Current antidepressant has delayed response times and are ineffective in approximately a third of MDD patients (Schwartz et al. 2016).
- Fast-acting ketamine, a NMDA receptor antagonist, has been found effective against MDD symptoms in the resistant groups, and to reduce the prevalence of suicidal ideation (Schwartz et al. 2016).

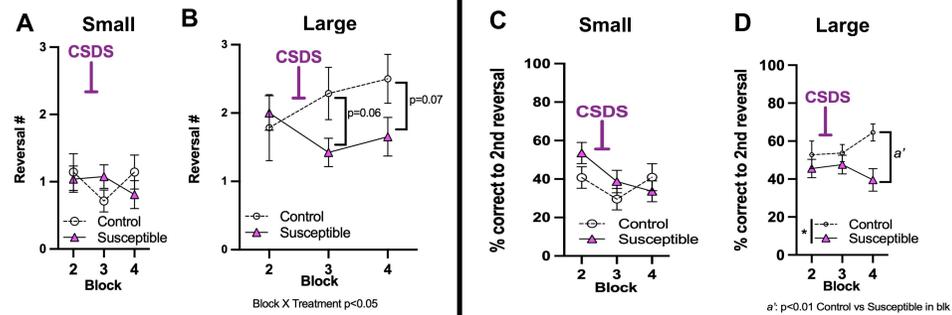
- Pattern Separation:** The ability to distinguish similar stimuli (i.e. pattern, place or time changes) to different outputs
- Cognitive Flexibility:** The ability to appropriately adapt to changes in the environment
- The operant touch screen (TS) allows for the investigation of pattern separation and cognitive flexibility in rodents.



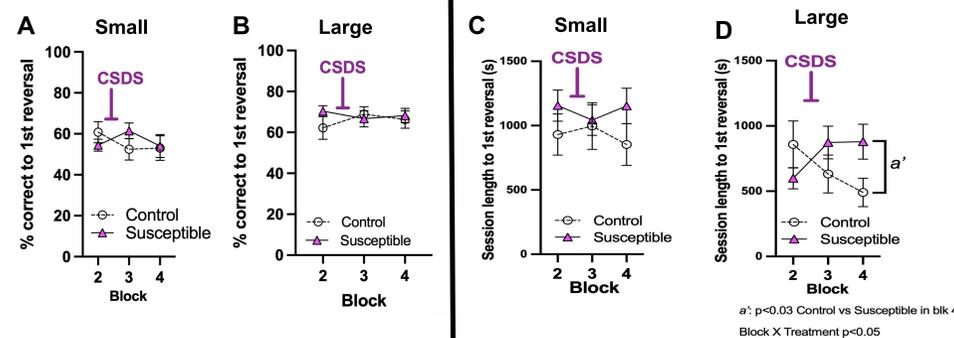
## Stress-susceptible mice were selected after chronic social defeat stress based on social avoidance performance.



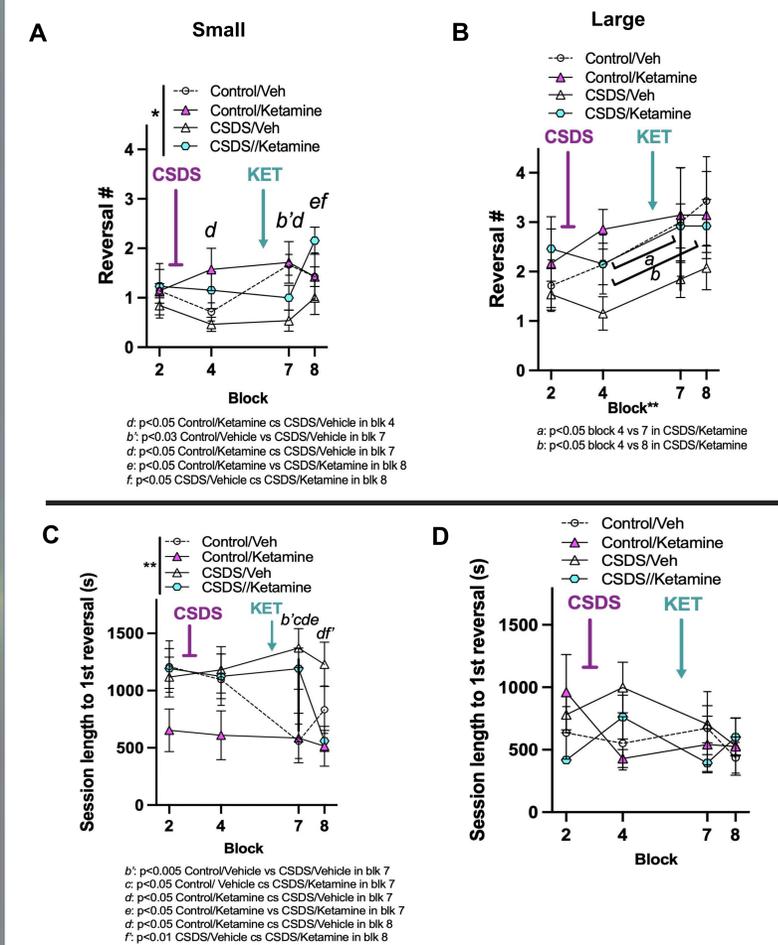
## Psychosocial stress leads to impaired cognitive flexibility in Large separation paradigm.



## Psychosocial stress mice takes longer to reach criteria in discrimination learning with large separation.



## Ketamine reverses stress-induced cognitive deficits.



## Ongoing/Future Directions

- Does fast-acting ketamine improve performance in other "classical" behavioral tests?
- How do acute vs chronic administration of fast-acting ketamine affect cognitive flexibility and pattern separation in mice?
- What are the molecular and cellular implications of psychosocial stress and fast-acting ketamine?

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