Electroconvulsive shock impairs retrieval of long-term memory and disrupts engram reactivation during recall

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Introduction

- Electroconvulsive therapy (ECT) is a non-invasive stimulation intervention highly effective for relieving severe symptoms of major depressive disorder, especially in antidepressant-resistant patients[1]
- However, the wide use is limited by concerns on memory side-effects[2]
- Evidence from human clinical studies and animal studies, which employs electroconvulsive shocks (ECS), the analog of ECT in animal model, reports anterograde amnesia being transient even with potential improvement afterwards[2,3]; but the extent and persistence of retrograde amnesia remains unclear[3]
- A group of neurons simultaneously activated by an experience creates an engram, the neural representation of a memory and reactivation of an engram executes the memory retrieval[4]
- Yet, neural mechanisms underlying side-effect retrograde amnesia remains under-researched and engram reactivation have not been examined

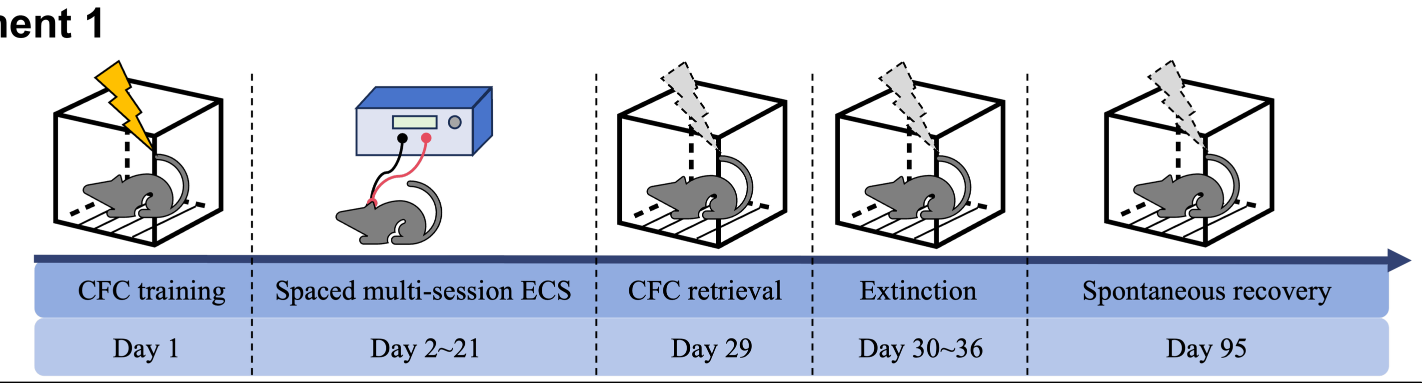
Aim 1. Establish the behavioral phenotype of ECS-induced retrograde amnesia
Does spaced multi-session ECS treatment impair memory retrieval?
Would ECS-impaired memory extinct with time, and recover at further time?

Aim 2. Examine the neural basis of ECS-induced retrograde amnesia
Does ECS-induced retrograde amnesia reflect on engram reactivation?

Method

Experiment 1

- Timeline



Contextual Fear Conditioning (CFC)

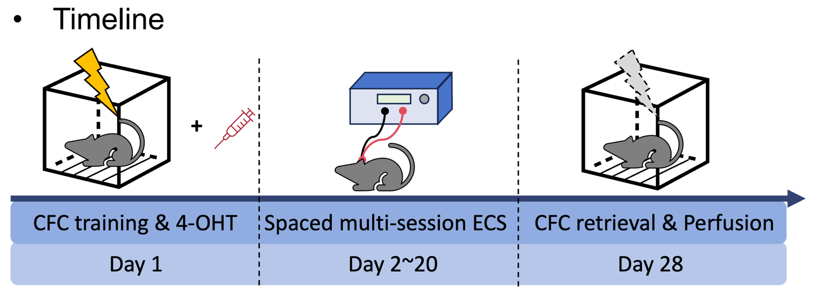
- Operant chambers were scented with diluted octanal for 30 minutes
- In training session, each animal received 3 or 8 electrical foot shocks at the amplitude of 0.5mA and duration of 2 seconds each, within 5 or 10 minutes respectively
- In testing sessions, mice were returned to the same context for 5 minutes without foot shocks
- Freezing behaviors were recorded to assess memory retrieval, extinction, and spontaneous recovery of fear memory

Electroconvulsive Shocks (ECS)

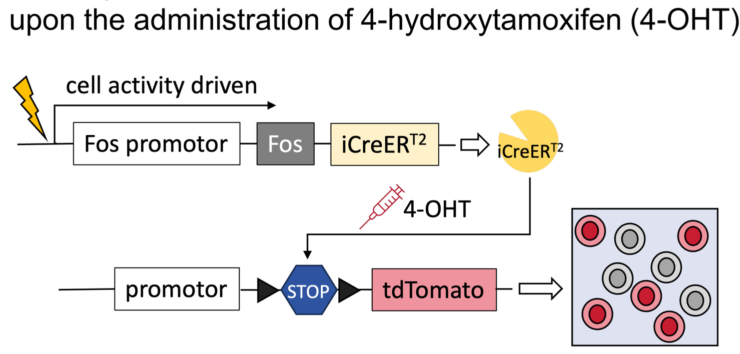
- Animals received 10 ECS sessions every other day over 20 days under anesthesia
- A shock was delivered at 30mA, 100Hz, with 0.5ms square pulse width and a duration of 1-1.5s, adapting for habituation, to generate a seizure for each session (Ugo Basil ECS machine)

Experiment 2

- Timeline

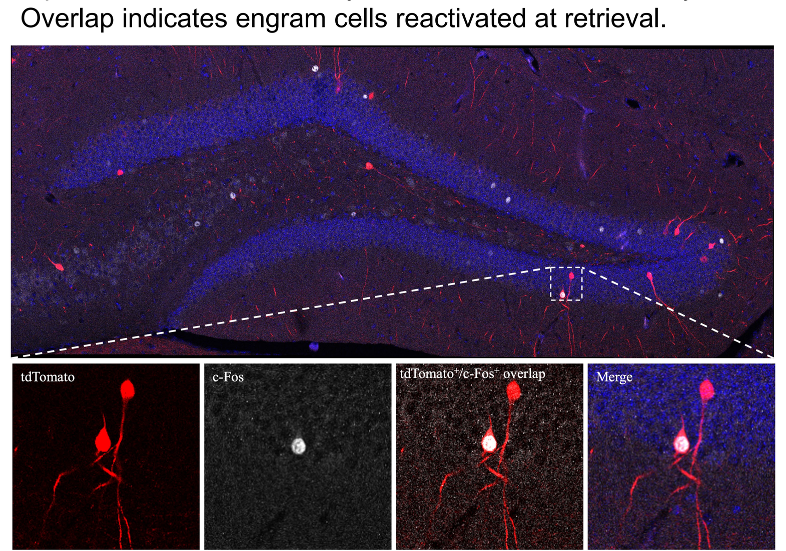


- **FosTrap2A:tdTomato transgenic mice model** labels learning-activated neurons with red fluorescent protein upon the administration of 4-hydroxytamoxifen (4-OHT)



Immunohistology

Brain slices were stained for tdTomato and c-Fos expression in dorsal dentate gyrus. tdTomato+ and c-Fos+ cells were quantified manually. tdTomato expression represents engram cells activated by the learning of fear memory and c-Fos represents cells activated by the retrieval of fear memory. Overlap indicates engram cells reactivated at retrieval.



Result 1: ECS-induced retrograde amnesia

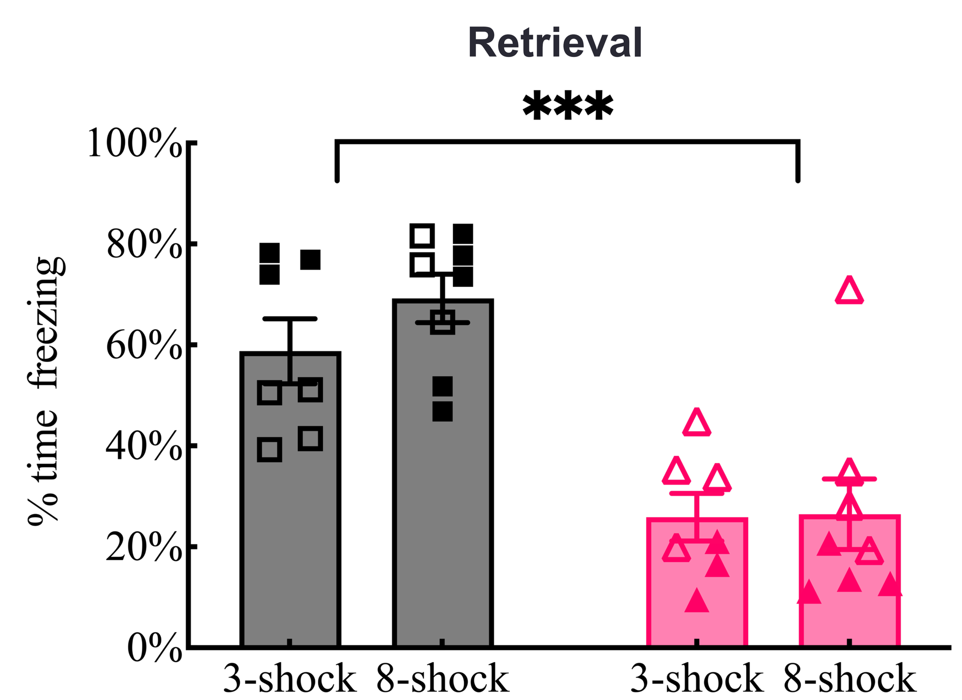
ECS impaired memory retrieval

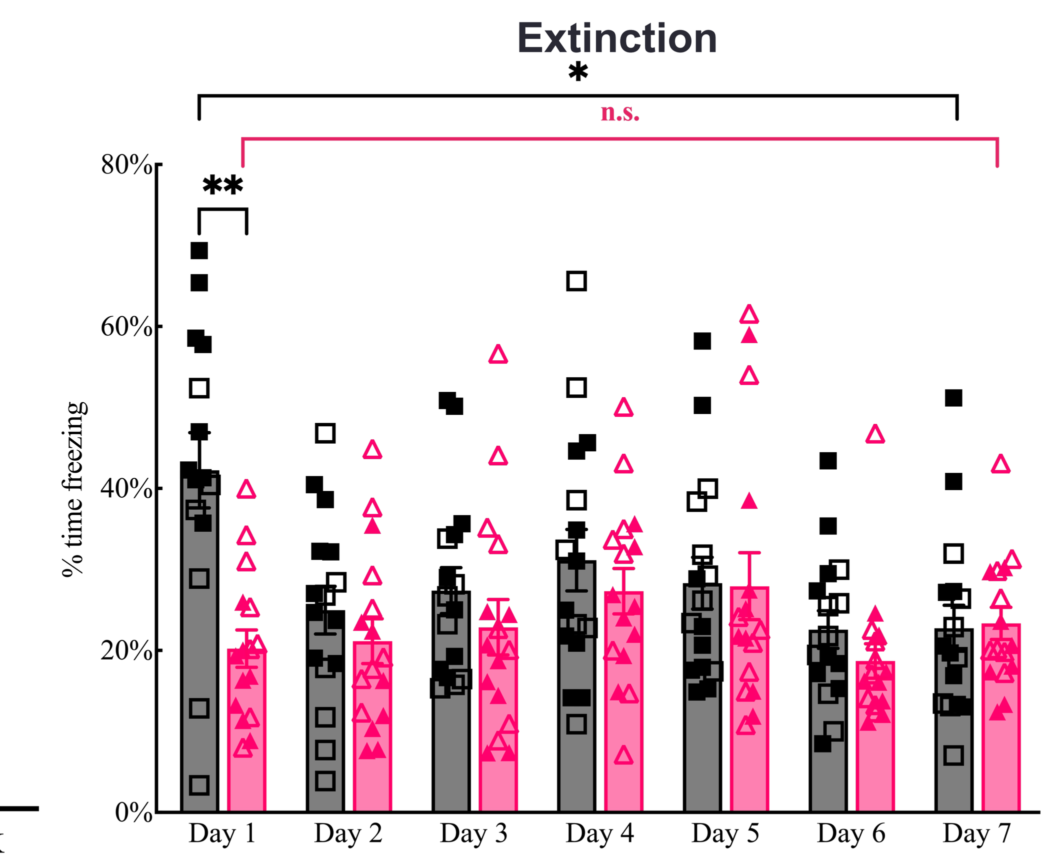
- ECS-treated mice showed significantly less freezing than sham controls in the 5-minute memory retrieval testing session

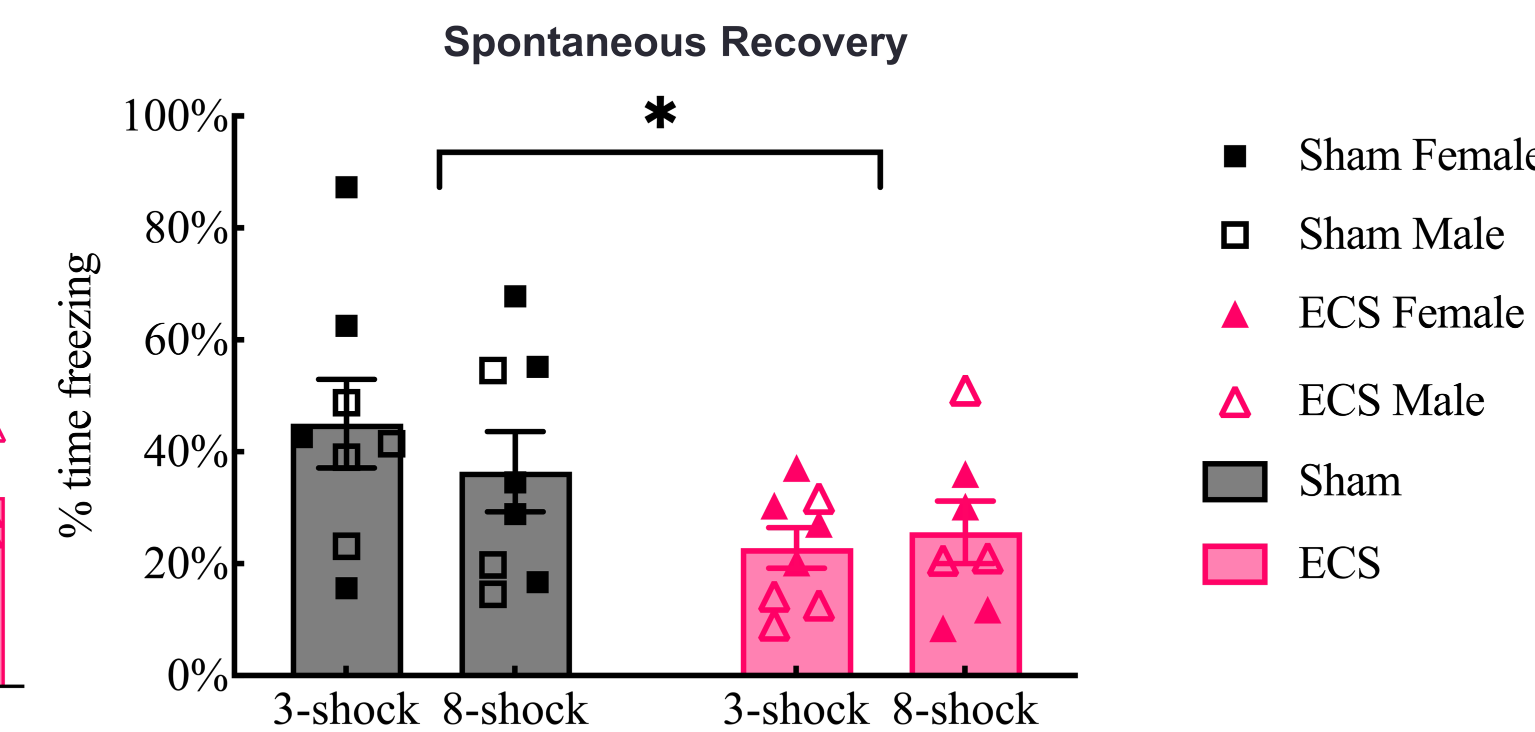
Extinction and spontaneous recovery were absent in ECS-induced retrograde amnesia

- ECS-treated mice showed no decline in freezing over the 7-day extinction
- ECS-impaired memory did not spontaneously recover after 2-month delay

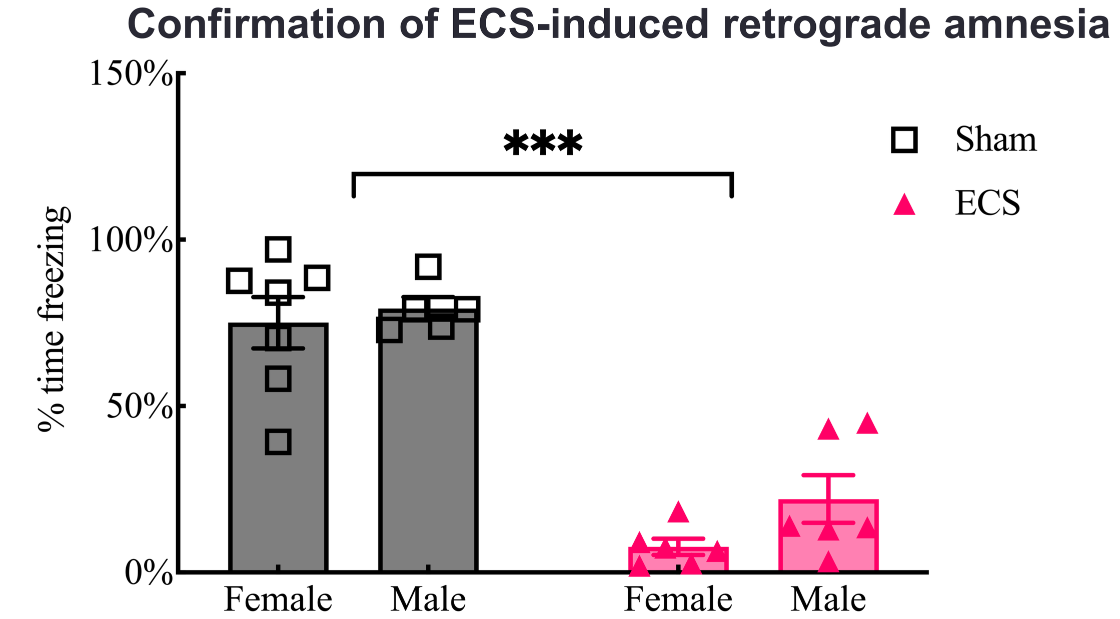
	Sham	ECS
3-shock	n = 8 F = M = 4	n = 8 F = M = 4
8-shock	n = 8 F = 5, M = 3	n = 8 F = M = 4
AsclCre mice; aged 4-5 months		







Result 2: ECS disrupted engram reactivation



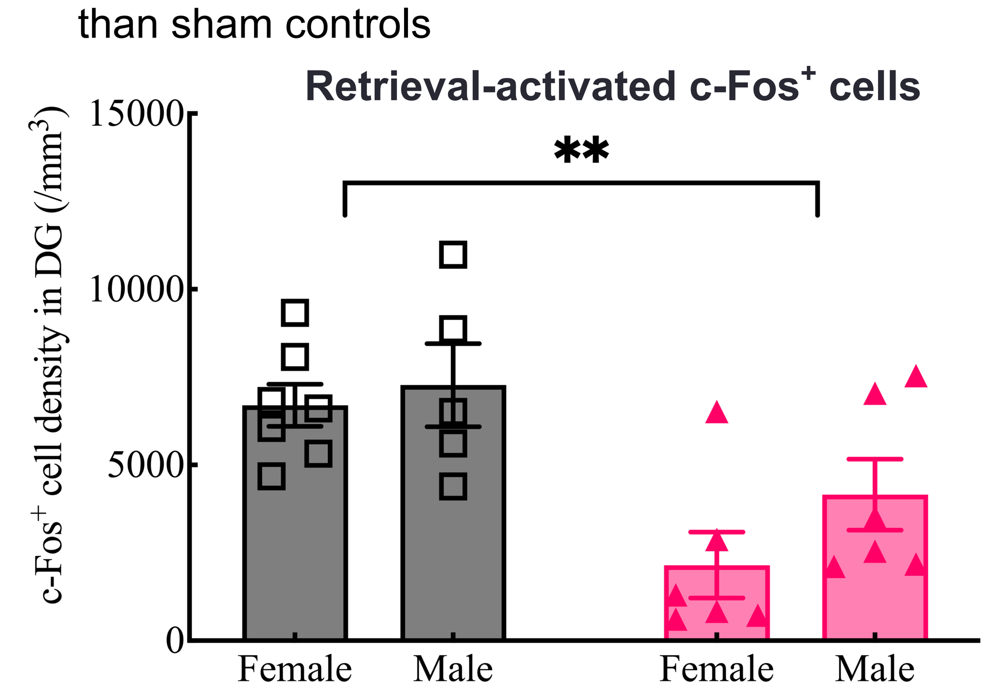
	Sham	ECS
Female	n = 7	n = 6
Male	n = 5	n = 6
FosTrap2A:tdTomato mice; aged 2-5 months		

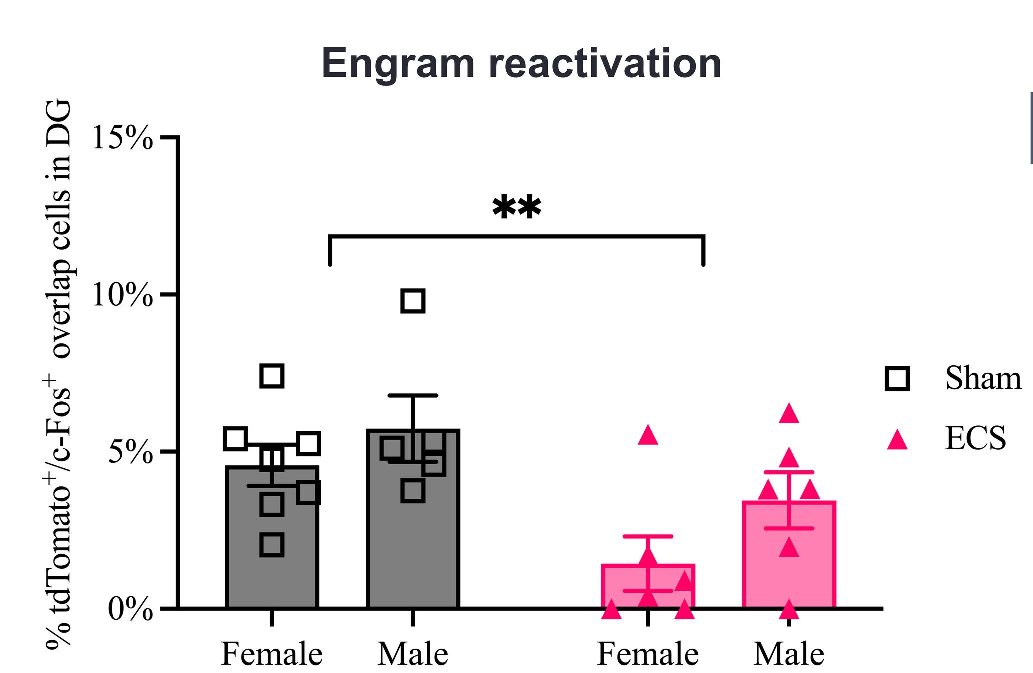
ECS reduced cell activation at retrieval

- ECS-treated mice showed significantly lower c-Fos+ cell density in superior blade of DG

ECS disrupted engram reactivation

- tdTomato+/c-Fos+ overlap were normalized by dividing the number of overlapping cells by the total number of tdTomato+ cells
- The percentage of engram cells reactivated by retrieval was significantly lower in ECS-treated mice than sham controls





Discussion

Experiment 1 established the behavioral phenotype of retrograde amnesia induced by repeated ECS

- Multiple sessions of ECS were delivered on a spaced schedule , mimicking the schedule of clinical ECT in human
- Retrograde amnesia was validated with long-term context fear memory, with well-known hippocampus-dependence
- Extinction effect was absent; however, current study is subject to the floor effect of an impaired memory
- The absence of spontaneous recovery in ECS-impaired memory suggested prolonged impairment; however, whether it can be attributed to the persistence of ECS-induced amnesia[6], or the reinforced learning of extinction sessions[3], requires further investigations

Experiment 2 revealed the disrupted neural representation of ECS-impaired memory

- Reduced engram reactivation provided neural basis for the observed ECS-induced retrograde amnesia
- ECS-treated animals showed reduced cell activation level during memory retrieval, which may explain the reduced reactivation
- Future studies will investigate whether engram of impaired memory is not retained or become inaccessible after ECS treatment[5]

Reference

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