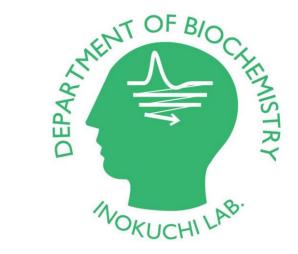# Induction of synaptic protein degradation enhances memory destabilization upon retrieval

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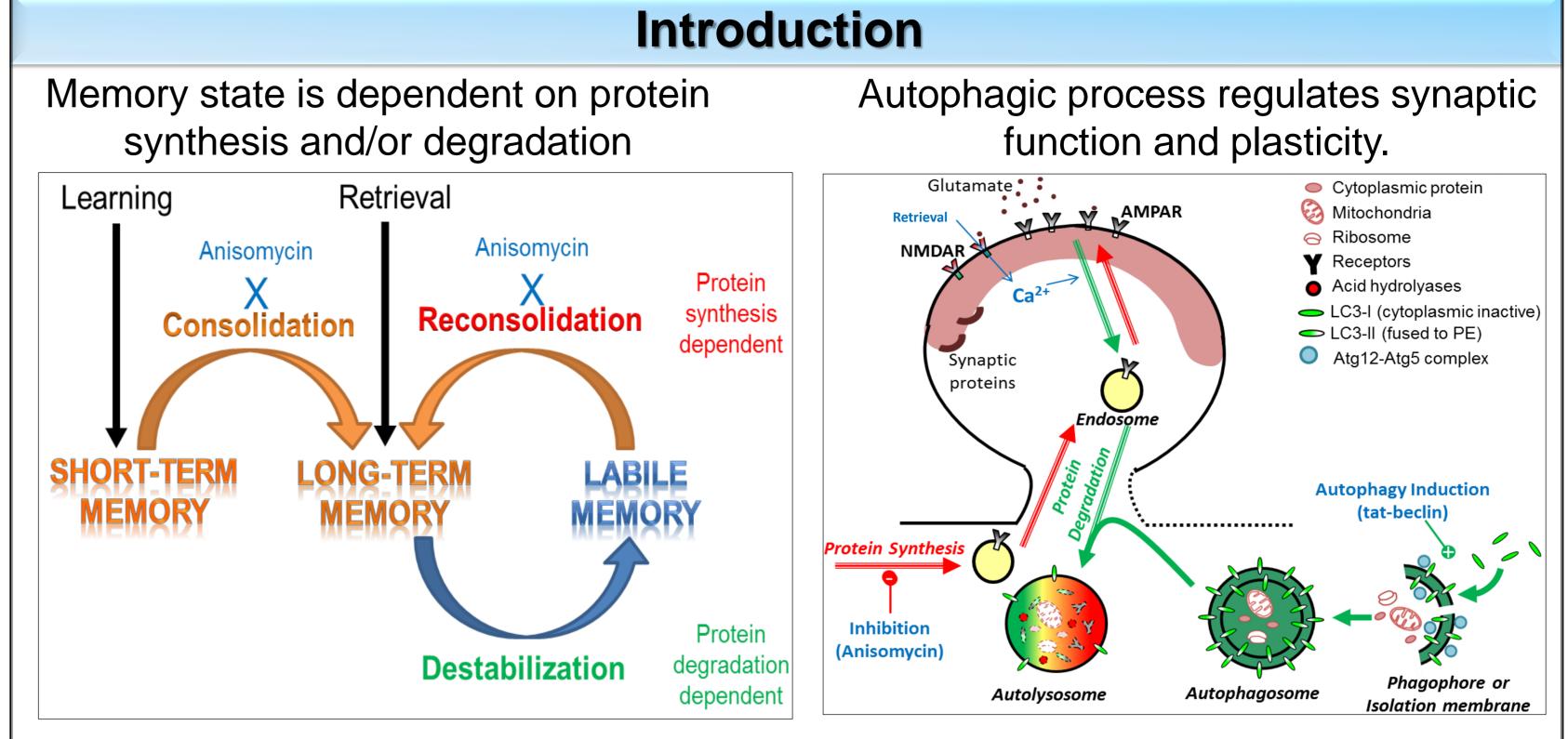2 Japan Science and Technology Agency, CREST, Kawaguchi, Japan
3 Division of Animal Experimental Laboratory, Life Science Research Center, University of Toyama, Toyama, Japan.
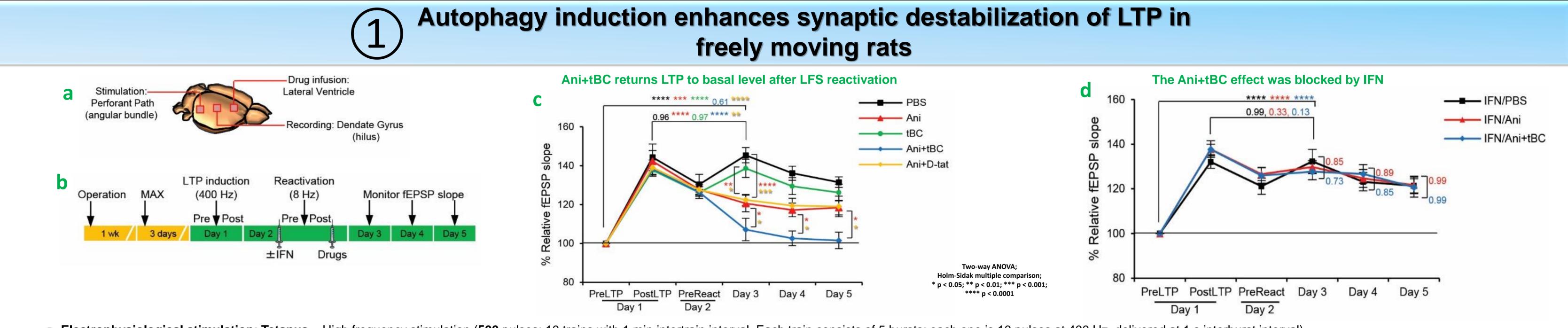
Abstract

Memories, when retrieved, enter in destabilization step which require protein synthesis for re-stabilization. It has been reported that inhibition of synaptic protein degradation prevents memory destabilization; however, whether the reverse relationship is true, is still unknown.

This study demonstrates that induction of autophagic protein degradation enhances synaptic destabilization in a long-term potentiation (LTP)-reconsolidation model in freely moving rats, and enhances fear memory destabilization in a contextual fear reconsolidation paradigm in mice. Furthermore, induction of autophagy overcomes a boundary condition hindering auditory fear memory reconsolidation. The autophagy induction effects are dependent on AMPA receptor endocytosis, and correlate with its degradation in ensemble neurons.
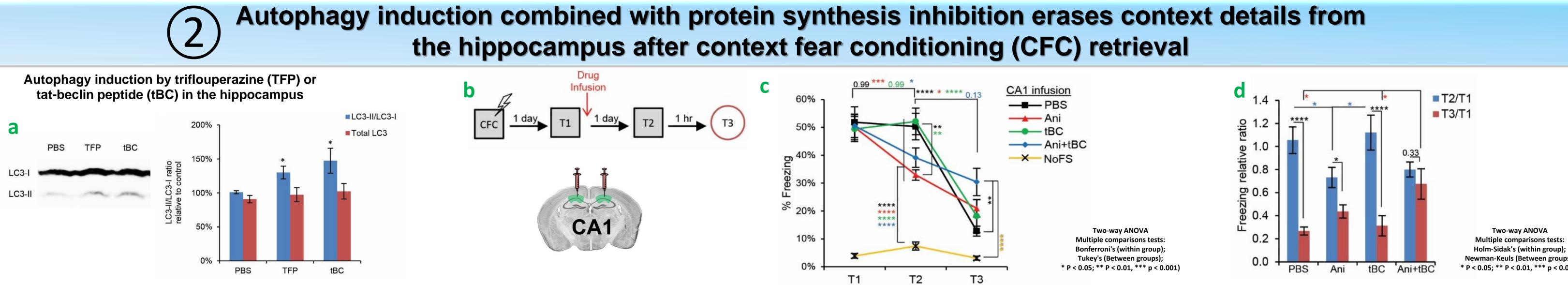
Our results complement the evidence for a causal relationship between protein degradation and memory destabilization, give more insight into the mechanisms controlling memory destabilization and boundary conditions, and suggest autophagy inducers as a useful tool for the treatment of memory-related psychological diseases, such as post-traumatic stress disorder (PTSD).
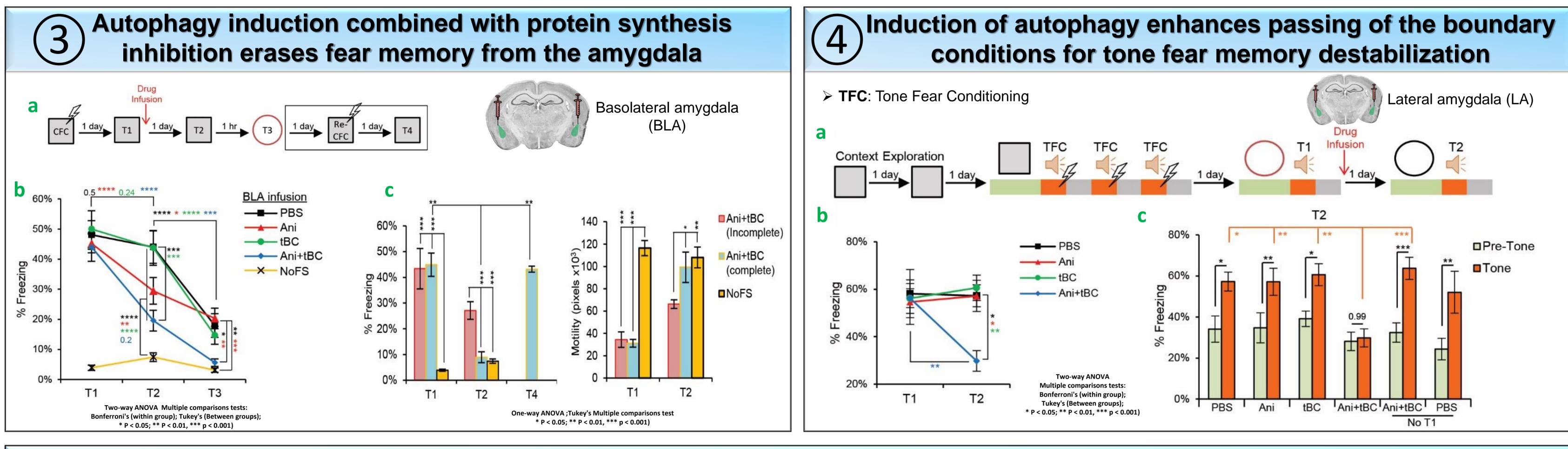
Introduction

Memory state is dependent on protein synthesis and/or degradation

Autophagic process regulates synaptic function and plasticity.

Question: Whether Autophagy induction can enhance memory destabilization, therefore more fear memory erasure will be observed.

① Autophagy induction enhances synaptic destabilization of LTP in freely moving rats

Ani+tBC returns LTP to basal level after LFS reactivation
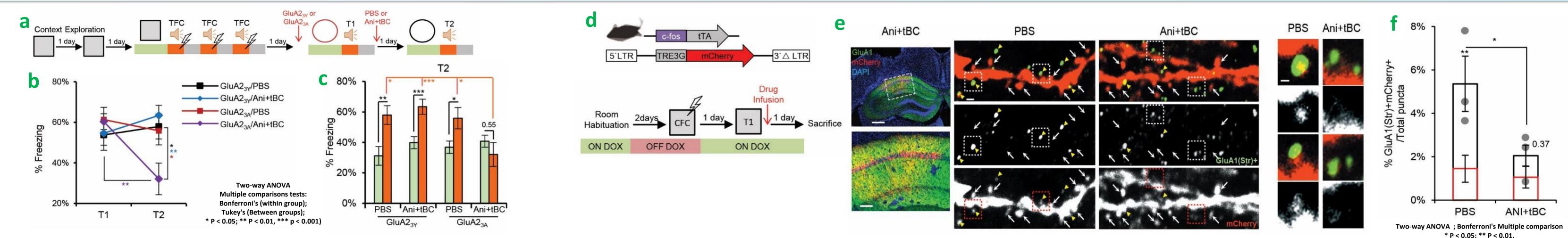
The Ani+tBC effect was blocked by IFN

- **Electrophysiological stimulation: Tetanus** = High frequency stimulation (**500** pulses; 10 trains with 1 min intertrain interval. Each train consists of 5 bursts; each one is 10 pulses at 400 Hz, delivered at 1 s interburst interval).
  Reactivation = Low frequency stimulation (128 pulses at 8 Hz).

② Autophagy induction combined with protein synthesis inhibition erases context details from the hippocampus after context fear conditioning (CFC) retrieval

Autophagy induction by triflouperazine (TFP) or tat-beclin peptide (tBC) in the hippocampus

③ Autophagy induction combined with protein synthesis inhibition erases fear memory from the amygdala

Basolateral amygdala (BLA)

④ Induction of autophagy enhances passing of the boundary conditions for tone fear memory destabilization

➤ **TFC**: Tone Fear Conditioning

Lateral amygdala (LA)

⑤ The Autophagy destabilization effect is mediated by AMPA receptor endocytosis in spines of engram neurons

Conclusion

- Autophagy induction can enhance both synaptic and memory destabilization and it is useful to pass the boundary conditions for memory reconsolidation through the degradation of the endocytosed AMPAR.
- The behavioral outcome of the combined protein degradation induction and synthesis inhibition differs according to the brain area targeted.

a) Proposed molecular mechanism for the effect of autophagy induction on synaptic and memory strength

b) The behavior outcome differ according to the brain area targeted