Circuit mechanisms underlying associative memory impairment in APP-KI

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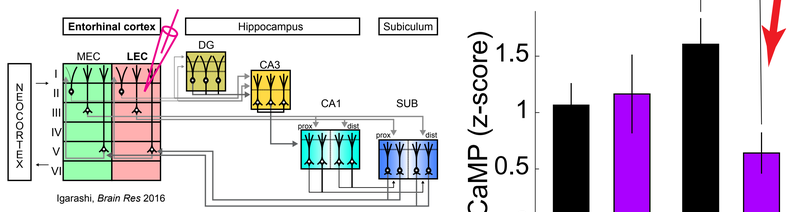
1. Background

Alzheimer's disease (AD) is the most common cause of dementia. Previous fMRI studies show that the lateral entorhinal cortex (LEC) is the primary site of dysfunction in early-stage AD patients (Khan et al., Nat Neurosci 2014).

We previously found LEC Layer 2a fan cells in healthy mice categorized rewarded and unrewarded odor cues when mice were learning a cue-reward associative memory task and dopamine facilitate encoding of associative memory (Lee et al., Nature 2021).

Our preliminary data also showed that dopamine release during novel rewarded odor was significantly diminished in AD mice model.

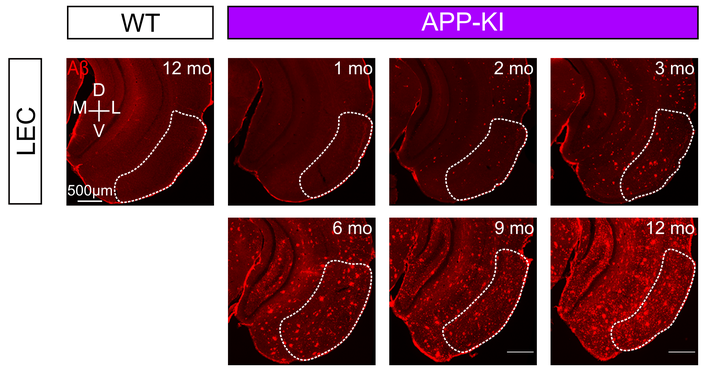


We test whether the stimulation of the LEC dopamine fibers can rescue the associative memory in APP-KI mice.

2. Animal model

Amyloid-β precursor protein knock-in (APP-KI) mice can exhibiting Aβ pathology, producing Aβ 42 plaques which is similar to the Aβ pathology observed in AD brains. (Saito et al., Nat Neurosci 2014)

We recorded LEC cells of APP-KI mice



APP-KI mice show amyloid-β accumulation in the LEC starting at 2 mo.

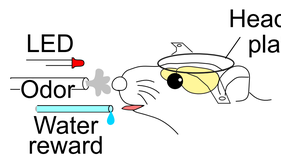
3. General Method

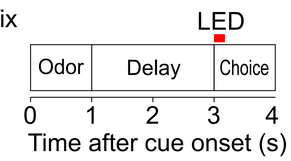
Stimulation of LEC Dopamine Axon

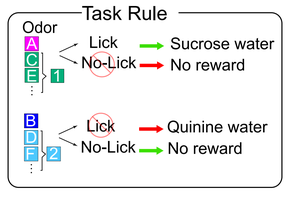
The AAV-DIO-ChR2-eYFP virus injected into the VTA and SNc in APP-KI x DAT-cre mice.
Optic fibers were implanted into the LEC to activate the channelrhodopsin in dopamine fiber of the LEC.

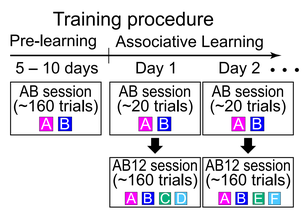
Associative Memory Task Training

Mice will be trained to perform an odor discrimination go/no-go task as previously used in our lab. The heads of the mice will be restrained during this task. Odor A (isoamyl acetate) will be designated as the "go" odor and odor B (alpha-pinene) will be designated as the "no-go" odor. When odor 1 is presented, the mice should lick the water port to get water. When odor 1 is presented, the mice should not lick. The correct rate (licking when odor 1 is presented) and correct rejection rate (not licking when odor 2 is presented) will be calculated.

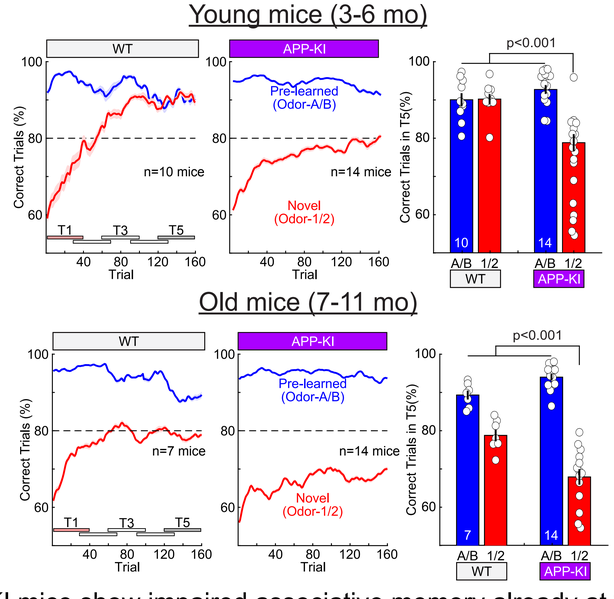






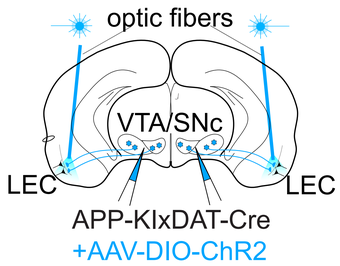


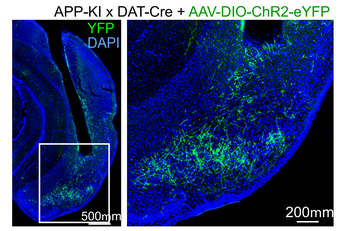
4. Imparied Associative Memory in APP-KI mice

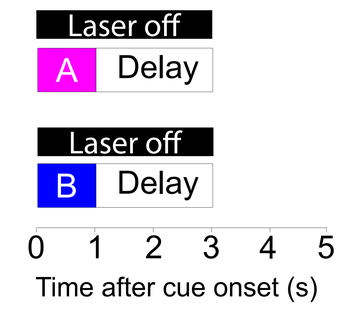


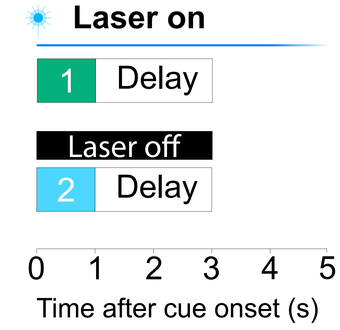
APP-KI mice show impaired associative memory already at 3-6 mo

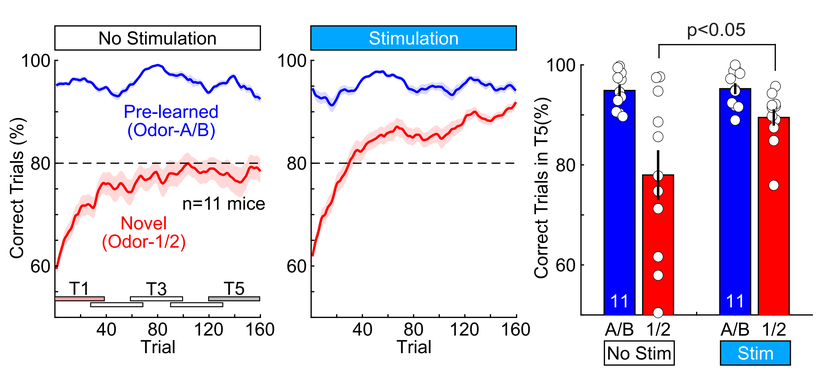
5. Stimulation of LEC dopamine rescued associative memory in young APP-KI mice











LEC dopamine axon stimulation dramatically improved memory task performance in APP-KI mice.

6. Summary and Discussion

1. We found that associative learning was impaired in APP-KI mice.
2. Stimulation of LEC dopamine fibers rescued associative memory in young APP-KI mice.

Our results also suggest that dopamine stimulation may be used as a potential treatment for Alzheimer's disease.

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