

Effects of Aducanumab on Behavior and MRI Findings in EC-APP770+/App^{NL-G-F} Mice

Hidehiro Ishikawa, MD, PhD¹, Takaya Utsunomiya, MD¹, Shotaro Horie, MD¹, Takuru Kobayashi², Shinobu Kitazume, PhD² and Akihiro Shindo, MD, PhD¹

1. Mie University, Tsu, Mie, Japan, 2. Fukushima Medical University, Fukushima, Fukushima, Japan

Background: Cerebral amyloid angiopathy (CAA) is associated with both dementia and stroke. A mouse model expressing human amyloid precursor protein 770 specifically in endothelial cells (EC- APP770 mice) was developed. When crossed with App^{NL-G-F} knock-in mice, this model shows prominent vascular amyloid deposition. This study aimed to investigate the effects of aducanumab on behavior and MRI findings in the recently developed EC- APP770+/App^{NL-G-F} mice.

Methods: Seven 12-month-old EC- APP770+/App^{NL-G-F/wt} mice (EC- APP770+) and seven EC-APP770–negative App^{NL-G-F/wt} littermates (EC-APP770–) were studied. Behavioral assessments using the Y-maze and novel object recognition test (NORT) were performed once before and once after aducanumab (ADU) treatment, and all behavioral analyses focused on within-subject pre- versus post-ADU comparisons. Aducanumab was administered intraperitoneally once weekly for four consecutive weeks. MRI was performed using a 3T micro-MRI system at baseline and after each weekly ADU injection (five scans total). Imaging sequences included DWI, T1WI, T2WI, T2*WI, FLAIR, and MRA. Behavioral parameters were analyzed using an automated video-tracking system. Y-maze outcomes included total arm entries and spontaneous alternation. NORT outcomes included mobility measures and the discrimination index (DI).

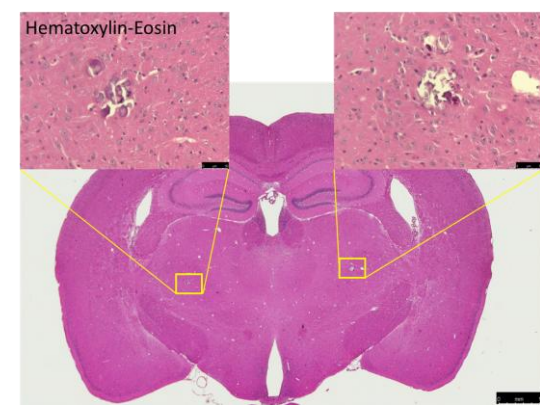
Results: In the Y-maze test, linear mixed-effects models demonstrated a significant reduction in spontaneous alternation after ADU administration (p=0.0030). No significant genotype effect or genotype-by-time interaction was observed, indicating comparable changes between EC-APP 770+ and EC-APP770– mice. In the novel phase of the NORT, the cumulative duration of the highly mobile state was significantly reduced in EC-APP770+ mice compared with EC-APP 770– mice (p=0.035), whereas the DI did not differ between groups (0.53 vs. 0.48, p=0.75). In one ADU-treated EC-APP770+ mouse, T2*-weighted MRI revealed newly emerged hypointense lesions suggestive of amyloid-related imaging abnormalities with hemorrhage (ARIA-H). In another EC-APP770+ mouse, FLAIR images demonstrated newly appeared focal hyperintensities suggestive of ARIA with edema (ARIA-E).

Conclusion: Aducanumab administration induced ARIA-like MRI findings in a limited subset of EC-APP 770+/App^{NL-G-F} mice, suggesting that this model may be useful for investigating mechanisms underlying ARIA.

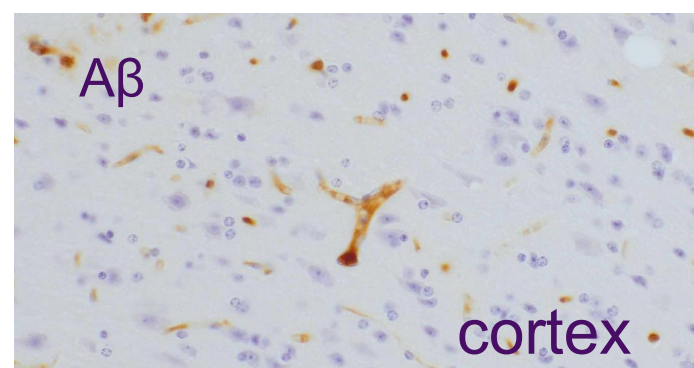
BACKGROUND

Cerebral amyloid angiopathy (CAA) is associated with both dementia and stroke. A mouse model expressing human amyloid precursor protein 770 specifically in endothelial cells (EC- APP770 mice) was developed.

In the brains of 18 Mo EC-APP770+ mice, microbleeds were observed.



When crossed with App^{NL-G-F} knock-in mice, this model shows prominent vascular amyloid deposition.



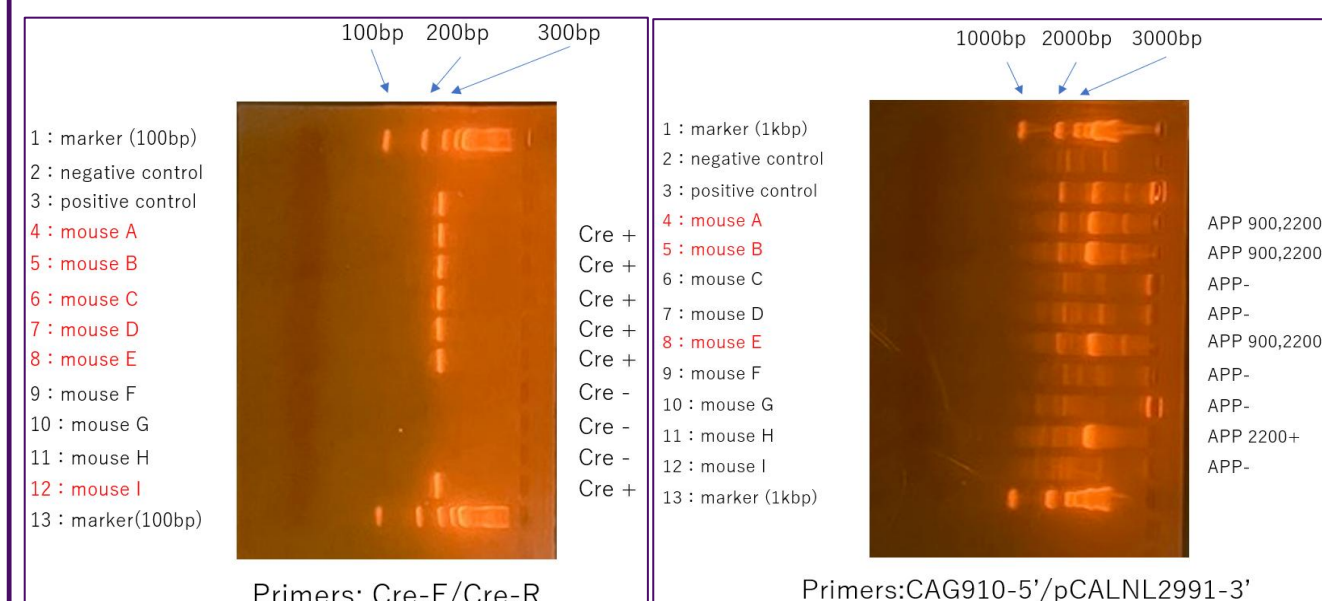
This study aimed to investigate the effects of aducanumab on behavior and MRI findings in the recently developed EC-APP770+/App^{NL-G-F} mice.

METHODS

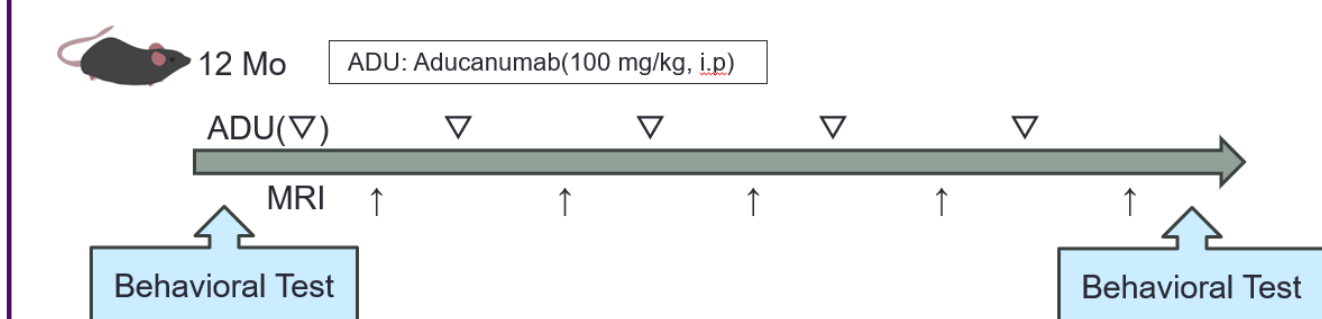
EC-APP770+ mice

Only offspring that were positive for both Cre and APP transgenes were included in the study. High plasma APP levels in EC-APP770+ mice were confirmed by ELISA. EC-APP770+ mice were then crossed with App^{NL-G-F} knock-in mice.

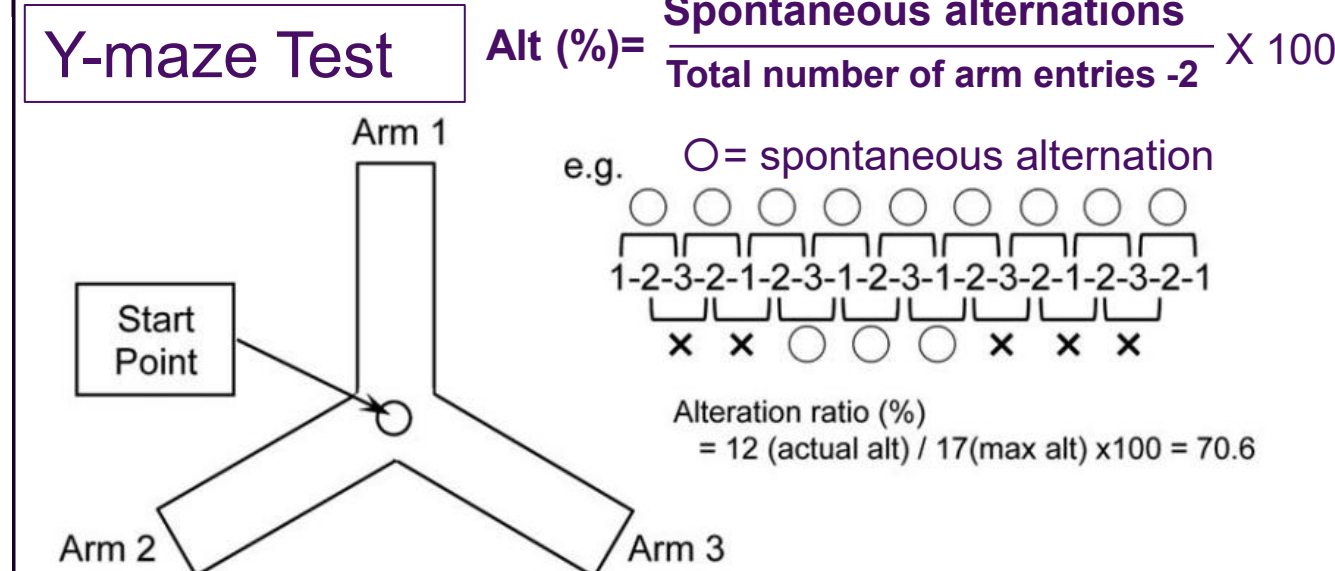
In total, seven 12-month-old EC- APP770+/App^{NL-G-F/wt} mice (EC- APP770+) and seven EC-APP770–negative App^{NL-G-F/wt} littermates (EC-APP770–) were studied. (e.g., mouse A, B, and E can be included as EC-APP770+, F and G can be included as EC-APP770– in the figure).



Aducanumab was administered intraperitoneally once weekly for four consecutive weeks.

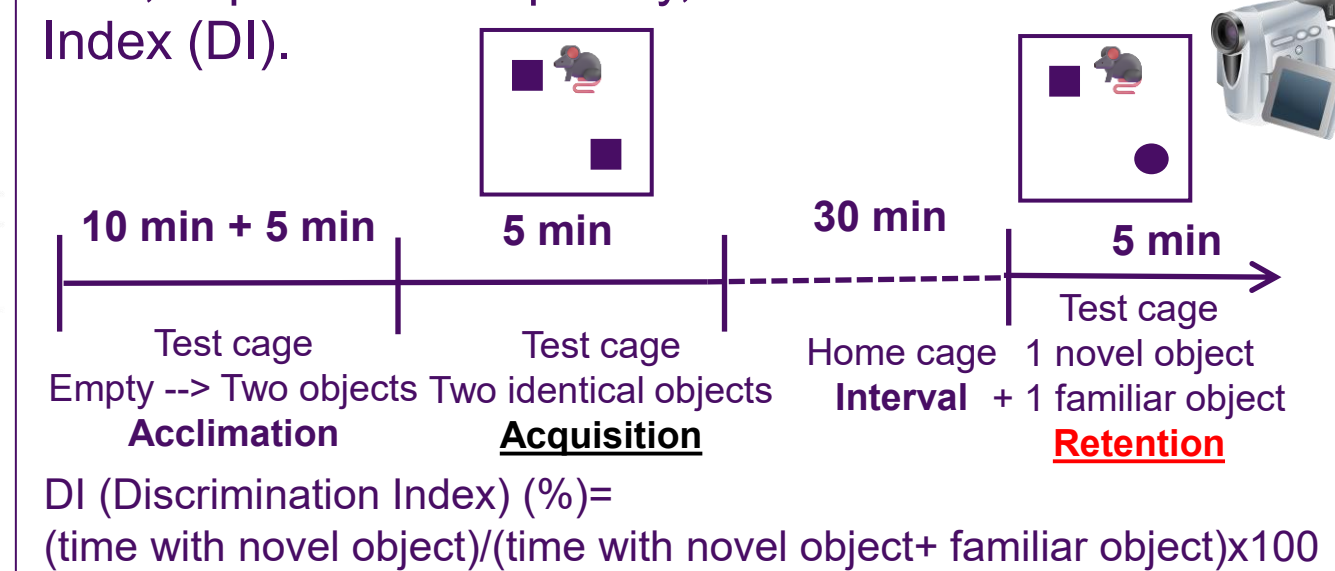


Behavioral data were obtained using the EthoVision XT (version 17) automated video tracking system, with Y-maze assessing parameters such as average speed, travel distance, and spontaneous alternation behavior.



Novel Object Recognition Test (NORT)

In the NORT, we measured total object exploration time, exploration frequency, and the Discrimination Index (DI).

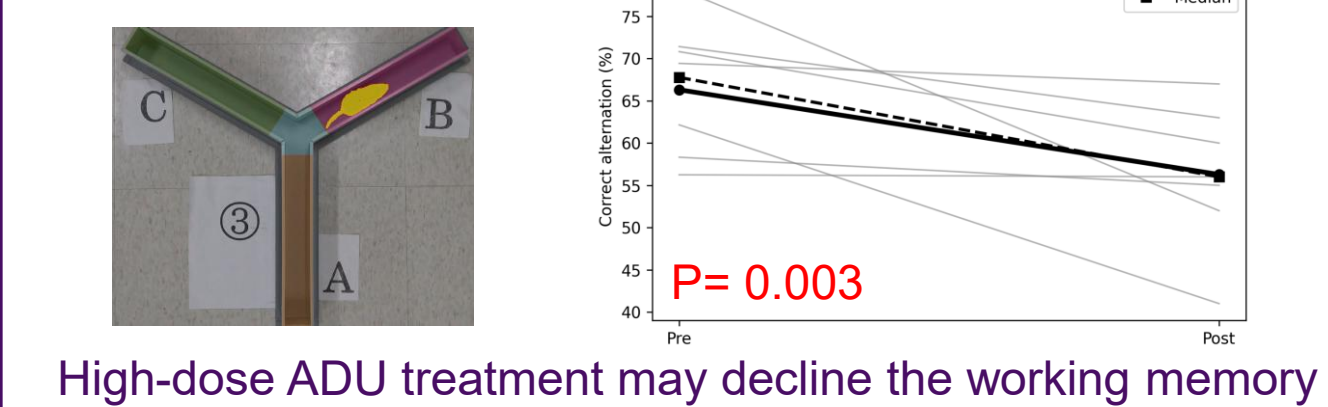


MRI was conducted using a 3T-microMRI system (LabPET/MRI 3016, TriFoil Imaging, Inc., Northridge, CA, USA), including Diffusion-Weighted Imaging, T1-Weighted Imaging (T1WI), T2-Weighted Imaging, T2* imaging, and Magnetic Resonance Angiography (MRA). MRI procedures were conducted with mice under isoflurane anesthesia.

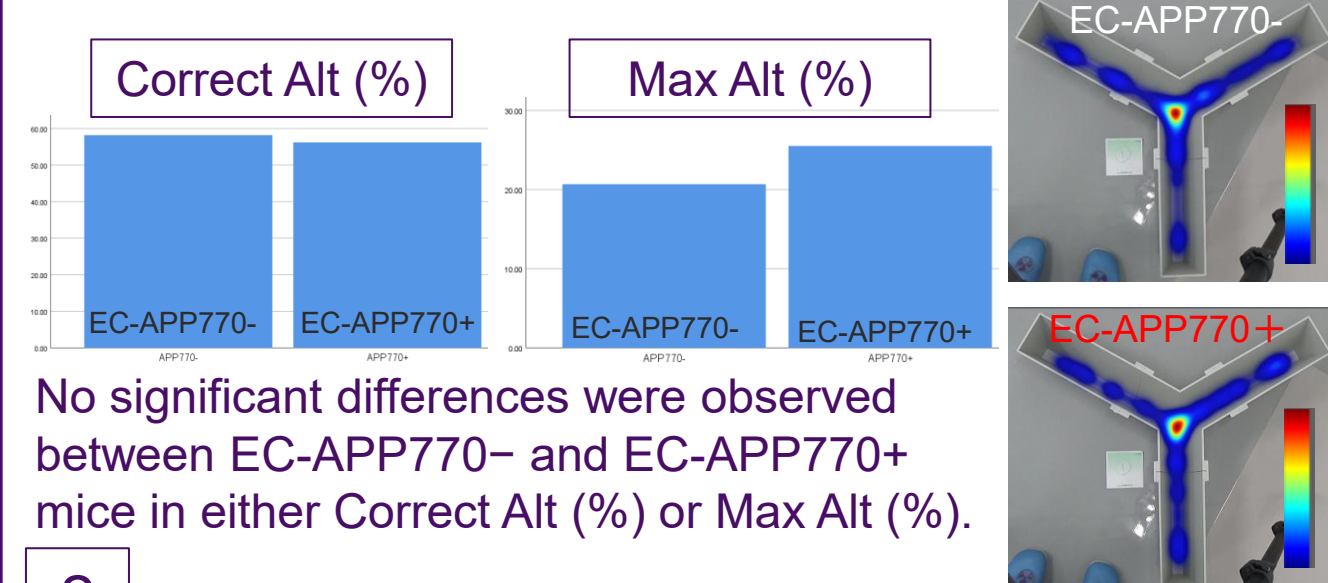


RESULTS

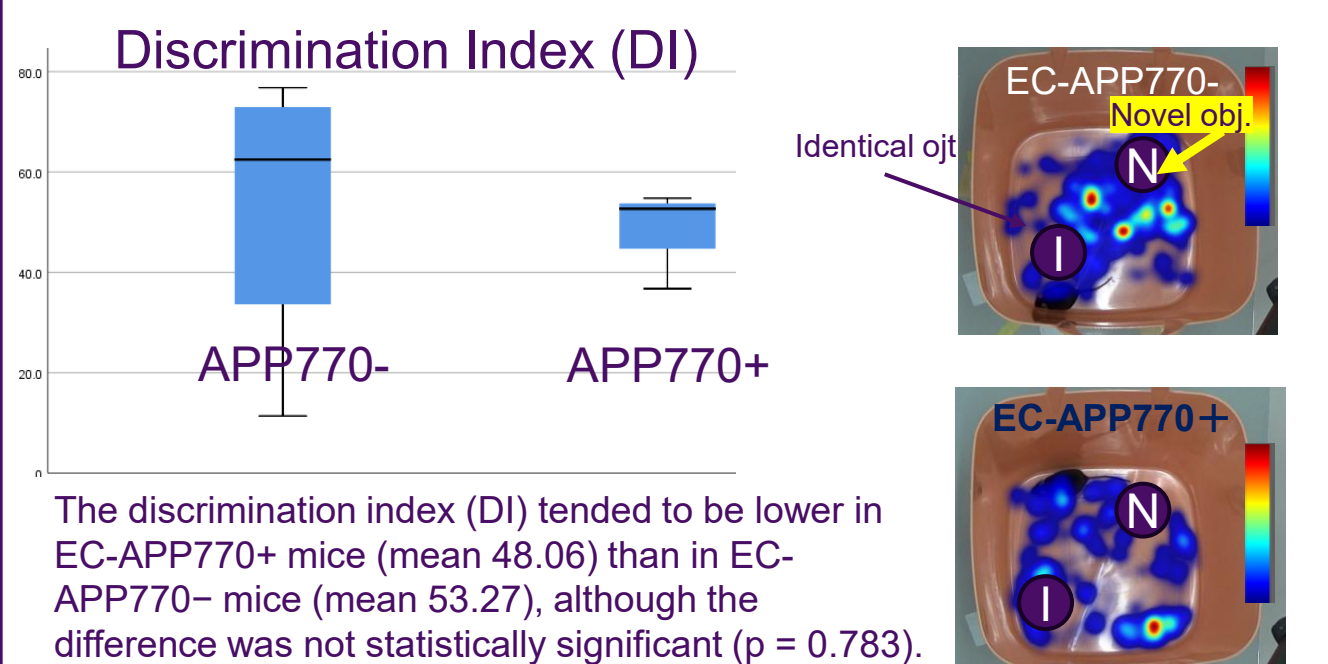
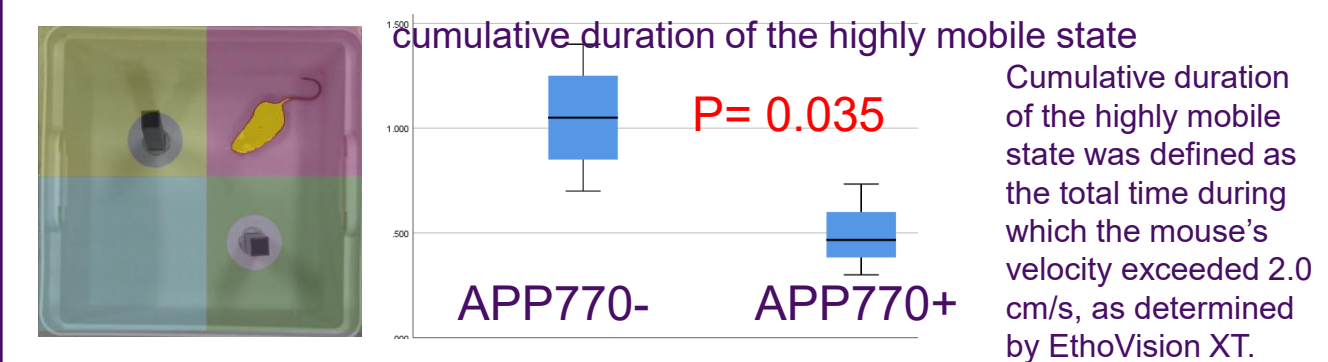
1 Y-maze test



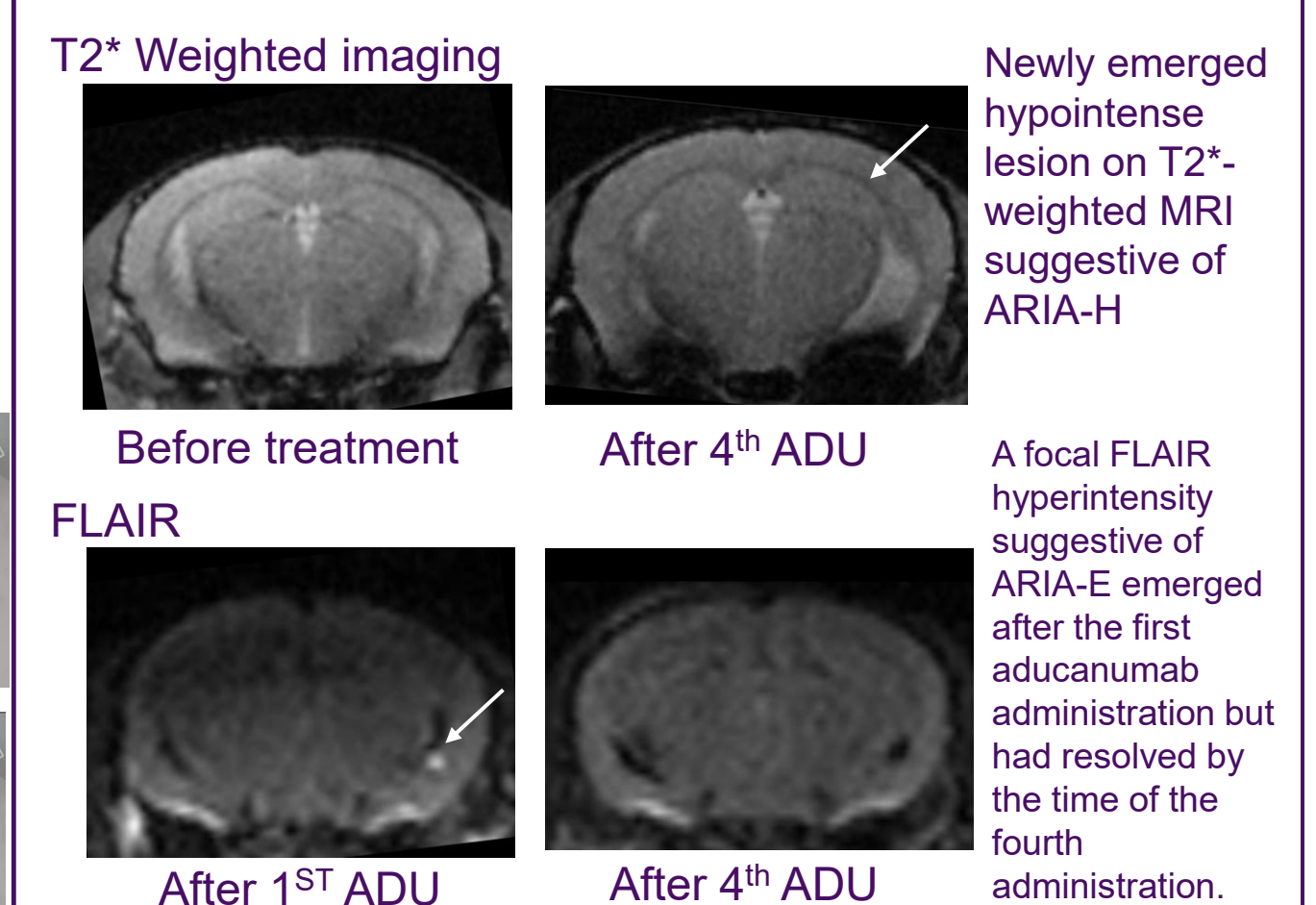
High-dose ADU treatment may decline the working memory



2 Novel object recognition test



3 MRI findings (EC- APP770+)



CONCLUSION

Aducanumab administration induced ARIA-like MRI findings in a limited subset of EC-APP 770+/App^{NL-G-F} mice, suggesting that this model may be useful for investigating mechanisms underlying ARIA.

Further studies, including histopathological analyses, are needed to clarify the pathological basis and relevance of these imaging findings.

FINANCIAL DISCLOSURE:
This study was supported by the TaNeDS program of Daiichi Sankyo Co., Ltd, Japan Society of Promotion of Science KAKENHI (Grant number: 21K15678, 24K02366), and AMED under Grant Number JP25dk0207076.