News Release

Title

Touchscreen-based location discrimination and paired associate learning tasks detect cognitive impairment at an early stage in an *App* knock-in mouse model of Alzheimer's disease

Key Points

- *The LD and dPAL tasks are useful methods for detecting impairment in pattern separation in App-KI mice at the early stage*
- *The visual discrimination and reversal learning tasks, and Morris water maze test cannot detect impairment in spatial reference memory in App-KI mice at the early stage.*

Summary

Dr. Md. Ali Bin Saifullah (Research Center for Next-Generation Drug Development, Research Institute of Environmental Medicine, Nagoya University), Associate Prof. Hiroyuki Mizoguchi (Department of Neuropsychopharmacology and Hospital Pharmacy, Nagoya University Graduate School of Medicine) and Prof. Koji Yamanaka (Department of Neuroscience and Pathobiology, Research Institute of Environmental Medicine, Nagoya University) showed that using *App*-KI mice, which recapitulate Aβ pathology without overexpression of APP fragments, hippocampus-dependent touchscreen-based tasks can detect Alzheimer's disease (AD)-associated behavioral impairments with high sensitivity at the early stage of the disease when classical tests cannot efficiently assess cognitive impairment. Our findings indicated that touchscreen tests are useful as translational tests for detecting physiological phenomenon at an early stage in *App*-KI mice model. This system could be applied to future translational research.

Research Background

One of the most common age-related neurodegenerative disorders is AD. Early detection of the disease is important for effective intervention, including counseling, cognitive training, and medication. Clinical studies have shown that the benefit of currently available medications is higher when initiated in the early phase of the disease. Basic AD research relies largely on various transgenic mouse models that experience accelerated accumulation of Aβ and tau tangles. We have also demonstrated the mechanism of cognitive impairment in an animal model of AD and provided an effective approach for treatment of AD; however, these mice exhibit artificial phenotypes and pathologies that are not present in human AD. To overcome these undesired phenotypes, we decided to utilize $App^{NL\text{-}G\text{-}F/NL\text{-}G\text{-}F}$ (*App*-KI) mice, a new AD mouse model that overproduces $A\beta_{42}$ without overexpressing amyloid precursor protein (APP). Although *App*-KI mice have been subjected to various classical behavioral tasks to evaluate various cognitive parameters, detection of cognitive impairment at the earliest stage has been a challenge.

Research Results

In this study, we investigated whether hippocampus-dependent touchscreen-based tasks could sensitively detect AD-associated behavioral impairments at the early stage of the disease, at an age when classical tests cannot effectively detect any cognitive impairment. We subjected 4–6-month-old male *App*$^{NL\text{-}G\text{-}F/NL\text{-}G\text{-}F}$ knock-in (*App*-KI) mice to touchscreen-based location discrimination (LD), different object–location paired-associate learning (dPAL), and reversal learning (RL) tests, and compared the results with those of the classical Morris water maze test. These tests are mainly dependent on the brain regions prone to Aß accumulation at the earliest stages of the disease. At 4–6 months, considered to represent the early stage of disease when mice exhibit initial deposition of Aß and slight gliosis, the classical Morris water maze test revealed no difference between groups, whereas touchscreen-based LD and dPAL tasks revealed significant impairments in task performance.

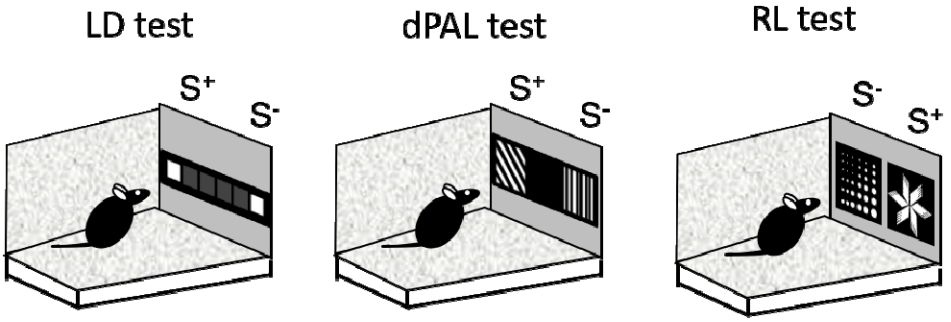

Figure. Diagram represents LD, dPAL and RL tasks

Research Summary and Future Perspective

Our report is the first to confirm that a systematic touchscreen-based behavioral test battery can sensitively detect the early stage of cognitive decline in an AD-linked *App*-KI mouse model. These data suggest that touchscreen-based tasks could be useful for advancing the translational studies by evaluating the efficacy of candidate therapeutics in rodent models of AD from an early stage.

Publication

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Authors: Md. Ali Bin Saifullah[1], Okiru Komine[2], Yutao Dong [1,3], Kazuya Fukumoto[1], Akira Sobue[2], Fumito Endo[2], Takashi Saito[2,4,5], Takaomi C. Saido[4], Koji Yamanaka[2], Hiroyuki Mizoguchi[1,3]

Institutions:

[1,] Research Center for Next-Generation Drug Development, Research Institute of Environmental Medicine, Nagoya University, Nagoya, Aichi 464-8601, Japan.

[2,] Department of Neuroscience and Pathobiology, Research Institute of Environmental Medicine, Nagoya

University, Nagoya, Aichi 464-8601, Japan.
[3,] Department of Neuropsychopharmacology and Hospital Pharmacy, Nagoya University Graduate School of Medicine, Nagoya, Aichi 466-8560, Japan
[4,] Laboratory for Proteolytic Neuroscience, RIKEN Center for Brain Science, Wako, Saitama 351-0198, Japan.
[5,] Department of Neurocognitive Science, Institute of Brain Science, Nagoya City University Graduate School of Medical Sciences, Nagoya, Aichi 467-8601, Japan.
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