Experimental Animals
Exp. Anim. 70(3), 398–405, 2021

Original

Female dominance of both spatial cognitive dysfunction and neuropsychiatric symptoms in a mouse model of Alzheimer's disease

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Abstract: Alzheimer's disease (AD) is a prevalent neurological disorder affecting memory function in elderly persons. Indeed, AD exhibits abnormality in cognitive behaviors and higher susceptibility to neuropsychiatric symptoms (NPS). Various factors including aging, sex difference and NPS severity, are implicated during in development of AD. In this study, we evaluated behavioral abnormalities of AD model, PDAPP transgenic mice at young age using the Morris Water Maze test, which was established to assess hippocampal-dependent learning and memory. We found that female AD model mice exhibited spatial learning dysfunction and highly susceptible to NPS such as anxiety and depression, whereas spatial reference memory function was comparable in female PDAPP Tg mice to female wild type (WT) mice. Spatial learning function was comparable in male AD model mice to male WT mice. Multiple regression analysis showed that spatial learning dysfunction was associated with NPS severity such as anxiety and depression. Furthermore, the analysis showed that spatial reference memory function was associated with status of depression, but not anxiety. Thus, these results suggest female dominance of spatial learning dysfunction in the AD model mice accompanying increased NPS severity. The understandings of AD model may be useful for the development of therapeutic agents and methods in human AD.
Key words: Alzheimer's disease model, cognitive function, correlation analysis, neuropsychiatric symptom, PDAPP Tg mice

Introduction

Alzheimer's disease (AD) is one of neurodegenerative disorders. The degree of neural cell loss in hippocampus correlates with the severity of AD [1–3]. Because the emotional behavior and cognitive function relate to hippocampus, AD causes abnormal cognitive functions spatial learning function and spatial reference memory function and neuropsychiatric symptoms (NPS) including anxiety and depression [4–11]. NPS is also called behavioral and psychological symptoms of dementia (BPSD) [12]. Medications on BPSD such as anti-psychotics, anti-depressants, mood stabilizers, and hypnotic drugs are clinically used in patients with AD [13].

The cognitive dysfunction is associated with NPS in AD [14–17]. It is reported that women are susceptible to NPS than men [18]. Sex difference is a risk factor for neurodegenerative disorders [19]. The genetic factor, sex

(Received 12 January 2021 / Accepted 25 March 2021 / Published online in J-STAGE 9 April 2021)
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difference and environmental factors are implicated in the development of AD [20, 21]. In fact, women have a higher risk of developing of AD than men [21].

One of AD model mice, the platelet-derived growth factor promoter-driven amyloid precursor protein (PDAPP) transgenic (Tg) mice, which overexpress mutated form of the human amyloid precursor protein (APP) bearing both the Swedish (K670N/M671L) and Indiana (V717F) mutations [22]. It is reported that middle-aged (4–6 months of age) and old-aged (over 10 months of age) PDAPP Tg mice show impaired cognitive function and motivation to escape the water in Morris water maze (MWM) test with pathological conditions mainly in the hippocampus [23–26]. However, we found that young-aged (10–12 weeks of age) PDAPP Tg mice showed abnormal cognitive functions in MWM test, and the cognitive dysfunctions were ameliorated by neural cell transplantation [27, 28]. These results suggested that we may utilize PDAPP Tg mice at young age for AD research. It can reduce the time and costs required to study.

MWM test has useful procedures to assess spatial cognitive functions and NPS severity, and parameters of MWM test were affected by various factors including sex difference [29–34]. In this study, we analyzed cognitive functions and behavioral symptoms in MWM test using both sexes of PDAPP Tg mice at young age for further understanding of the property of the AD model mice.

Materials and Methods

Ethics Statement

All experiments were approved by the Animal Care and Use Committee in St. Marianna University School of Medicine (SMU) and were conducted according to the institutional ethical guidelines for animal experiments and safety guidelines for gene manipulation experiments.

Mice

AD model, PDAPP Tg mice (strain name: B6.Cg-Tg (PDGFB-APPSwInd) 20Lms/2J), were obtained from The Jackson Laboratory (Bar Harbor, ME, USA, RRID: MMRRC_034836-JAX) [22]. Middle-aged (4–6 months of age) and old-aged (Over 10 months of age) PDAPP Tg mice showed impaired cognitive dysfunction in MWM test [23]. However, the parameters for cognitive function and NPS severity in the young-aged (10–12 weeks of age) PDAPP Tg mice were largely unknown. PDAPP Tg mouse lines were maintained by breeding PDAPP Tg males to littermate control females. Mice were kept in the environmentally controlled clean room at the animal center of SMU.

Morris water maze test

For assessment of spatial cognitive functions and NPS in young PDAPP Tg mice and littermate control mice as WT mice at 10–12 weeks of age, these mice were subjected to MWM test [24, 31, 35]. Mice were tested for 6 consecutive days in each trial as follows: visible test at the first day, hidden test for 4 days, and probe test at the final day. A pool (radius: 50 cm) was filled with opacified water at 26 ± 0.5°C. The water basin was surrounded by a brown curtain. An escape platform (diameter: 15 cm) made of transparent acrylic resin was placed in one of four quadrants in the pool and submerged 1.5 cm below the water surface at visible and hidden test (Fig. 1A).

At the visual test, the platform was visualized by a mark using a black bottle placed on the platform (Fig. 1B). Mice were gently placed into the water basin facing the wall. They were allowed to search for the platform for 90 s; if they did not reach the platform in the defined time, they were manually placed onto the platform. They were left on the platform for 30 s to learn and memories the special position before the next attempt. The visible

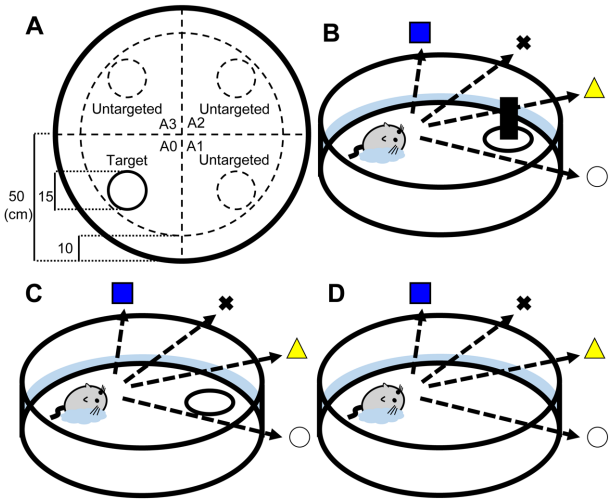

Fig. 1. Schematic representation of Morris water maze test. (A) Mice were subjected to Morris water maze (MWM) test using a pool (radius: 50 cm) with opacified water and a transparent plastic escape platform (diameter: 15 cm) for 6 consecutive days as follow: (B) visible test, (C) hidden test, and (D) probe test. The area of 10-cm-wide banded zone along the wall was defined as the peripheral area for behavioral analysis. (B) At the first day, visible test using the platform, its position being visualized by a black bottle on it with an ample space for the mouse to stay on it. (C) Hidden test for 4 consecutive days using escape platform without a black bottle. (D) At the last day, probe test with the same condition except removal of the escape platform. The swimming trajectory was monitored by a CCD camera and recorded in PC.

test was performed for examination of the visual ability and motivation to escape from water. Mice which did not reach the platform 4 times in 8 attempts were excluded from this study (WT mice (male: n=0 (0/23, 0%), female: n=1 (1/29, 3.4%) and PDAPP Tg mice (male: n=7 (7/102, 6.9%), female: n=4 (4/123, 3.3%).

Following 4 consecutive days, to examine the spatial learning function, mice were trained to find the hidden platform using spatial cues (hidden test: 4 attempts per day, Fig. 1C). They allowed to search for the platform for 90 s; if they did not reach the platform in the defined time, they were manually placed onto the platform. They were left on the platform for 30 s to learn and memorize the special position before the next attempt. We analyzed the data at day 4 in hidden test.

On the final day, to examine spatial reference memory function, mice were placed into the water basin without platform (probe test: 1 attempt, Fig. 1D). Mice were allowed to search for the platform for 90 s; and the time required for the mouse to stay in the quadrant area where the target platform had existed or not was recorded. The time of each performance was summed up and expressed in percent of the total time. The number of crossing over the target platform and untargeted platform ranges was counted.

In this study, we measured various parameters of each test component of MWM test for assessment of cognitive functions and NPS [30–34]. The time to reach the platform was defined as the platform escape latency (max 90 s). At the visible test, we defined escape latency from the water (s) as "the motivation" to escape the water. At the hidden test, we defined escape latency (s) as "the spatial learning function". At the probe test, we defined duration in target or untargeted guardant area as "the spatial reference memory function". At each test, we defined mean swimming speed (s) as "the locomotion activity", thigmotaxis (s) as intensity of "anxiety", and immobility time (s) as intensity of "depression". The exploration in the periphery area (10-cm-wide banded zone along the wall) was defined as thigmotaxis, and suspension time in the water was defined as immobility time (Fig. 1A). The location and moving speed in the water basin were digitally recorded by an automated tracking system (O'hara & Co., Ltd., Tokyo, Japan), which was implemented in the modified software based on the Image J software (NIH, Bethesda, MD, USA).

Experimental design and statistical analysis

The truncated violin plot of each parameter in MWM test were drawn by Prism8 software (GraphPad, San Diego, CA, USA), and red bar indicating the median, and dark dot line indicating the quartiles. All statistical analysis was performed using JASP software (JASP Version 0.14.1, Team (2020), jasp-stat.org). Data were statistically assessed using two-way ANOVA and Tukey-Kramer post-hoc test, with PDAPP genotype and sex as independent variables, and moving speed (cm/s), thigmotaxis (s), immobility time (s), escape latency (s) and duration in target (%) as dependent variable [36, 37]. Multiple regression analysis was assessed using escape latency (s) in visible and hidden tests and duration time in target (%) as dependent variable, thigmotaxis (%) and immobility time (%) as explanatory variables.

Results

The motivation to escape the water negatively associated with status of anxiety and depression

In visible test, we assessed the parameters about escape latency, moving speed, thigmotaxis, and immobility time in both sexes PDAPP Tg mice and WT mice. We found that all parameters were significantly affected by genotype (Escape latency: F (3, 261)=14.3422, $P<0.001$, Moving speed: F (3, 261)=10.8720, $P=0.001$, Thigmotaxis: F (3, 261)=16.2629, $P<0.001$, and Immobility time: F (3, 261)=8.0029, $P=0.005$). However, the effects of sex (Escape latency: F (3, 261)=0.0416, $P=0.839$, Moving speed: F (3, 261)=0.0003, $P=0.986$, Thigmotaxis: F (3, 261)=0.0481, $P=0.827$, and Immobility time: F (3, 261)=0.3504, $P=0.554$) nor interaction between two factors (Escape latency: F (3, 261)=3.7567, $P=0.054$, Moving speed: F (3, 261)=0.4025, $P=0.526$, Thigmotaxis: F (3, 261)=1.7605, $P=0.186$, and Immobility time: F (3, 261)=1.1044, $P=0.294$) were not significant. We found that all parameters except for immobility time in the visible test increased significantly in female PDAPP Tg mice compared with female WT mice (Figs. 2A–D). However, all parameters had no differences between male PDAPP Tg mice and male WT mice (Figs. 2A–D). Multiple regression analysis showed escape latency in the visible test was significantly associated with the status of thigmotaxis and immobility time (Table 1).

The spatial learning function was abnormal in young PDAPP Tg mice and the spatial learning function associated with the status of anxiety and depression

It is well-known that middle and old PDAPP Tg mice have the cognitive dysfunction [23, 38]. In the hidden test using young PDAPP Tg mice, we found that all parameters were significantly affected by genotype (Escape latency: F (3, 261)=14.3, $P<0.001$, Moving speed: F (3, 261)=10.9, $P=0.001$, Thigmotaxis: F (3, 261)=16.2, $P<0.001$, and, Immobility time: F (3, 261)=8.00,

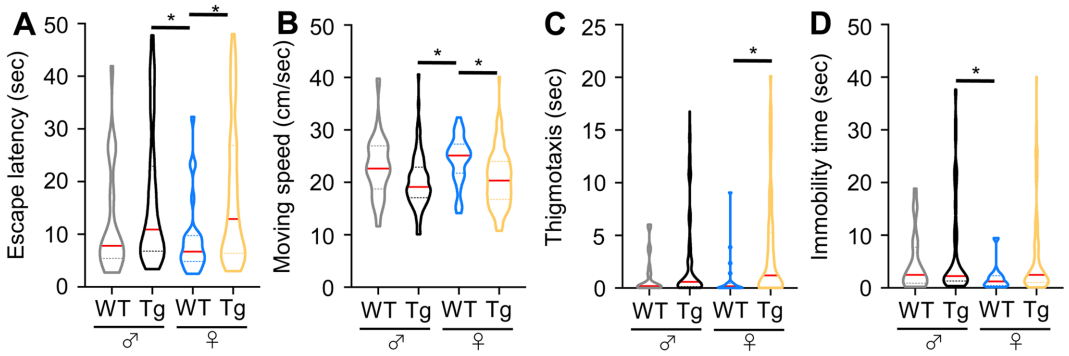

Fig. 2. Female PDAPP Tg mice showed neuropsychiatric symptoms in the visible test. Behavioral and psychological symptoms of WT mice (male: n=23, white, female: n=28, blue) and PDAPP Tg mice (male: n=95, black, female: n=119, yellow) were assessed by the visible test with the following parameters: (A) Escape latency as a motivation to escape the water, (B) Moving speed as a locomotion activity, (C) Thigmotaxis as an intensity of anxiety, and (D) Immobility as an intensity of depression. *P<0.05. P values are derived from Tukey-Kramer post hoc test.

Table 1. Effect of thigmotaxis and immobility time combined genotype on escape latency in the visible test

Variable	Coefficients	Standard error	Lower 95% CI	Upper 95% CI	P value
Intercept	2.985	0.485	2.03	3.941	<0.001
Thigmotaxis (%)	1.025	0.028	0.97	1.081	<0.001
Immobility time (%)	0.093	0.015	0.063	0.123	<0.001

Data are presented as β coefficients and standard error with lower and upper 95% confidence interval (CI) and P value. Multiple R^2=0.874. Adjusted R^2=0.873. VIF=1.000.

P=0.005). However, the effects of sex (Escape latency: F (3, 261)=0.0416, P=0.839, Moving speed: F (3, 261)=0.0003, P=0.986, Thigmotaxis: F (3, 261)=0.0481, P=0.827, and Immobility time: F (3, 261)=0.3504, P=0.554) nor interaction between two factors (Escape latency: F (3, 261)=3.757, P=0.294, Moving speed: F (3, 261)=0.402, P=0.526, Thigmotaxis: F (3, 261)=1.761, P=0.186, and, Immobility time: F (3, 261)=1.104, P=0.294) were not significant. We found that all parameters in the hidden test increased significantly in female PDAPP Tg mice compared with female WT mice. However, these parameters had no differences between male PDAPP Tg mice and male WT mice (Figs. 3A–D). Thus, female, but not male, PDAPP Tg mice at young age showed abnormal spatial reference function. Multiple regression analysis showed escape latency in the hidden test was significantly associated with the status of thigmotaxis and immobility time (Table 2). Thus, these results reveal that NPS severity is implicated in the level of spatial learning function.

The spatial reference memory function was normal in young PDAPP Tg mice and the spatial learning function associated with status of depression

At the probe test, all parameters except for thigmotaxis: F (3, 261)=12.93, P<0.001), were not affected by genotype (Duration in target: F (3, 261)=0.275, P=0.600, Moving speed: F (3, 261)=1.169, P=0.281, and Immobility time: F (3, 261)=1.739, P=0.188). And the effects of sex (Duration in target: F (3, 261)=0.230, P=0.632, Moving speed: F (3, 261)=0.489, P=0.485, Thigmotaxis: F (3, 261)=0.403, P=0.526, and Immobility time: F (3, 261)=1.346, P=0.247) and interaction between two factors (Duration in target: F (3, 261)=0.199, P=0.656, Moving speed: F (3, 261)=0.170, P=0.680, Thigmotaxis: F (3, 261)=1.169, P=0.281, and Immobility time: F (3, 261)=2.938, P=0.088) were not significant. We found that thigmotaxis in the probe test significantly increased in female, but not male PDAPP Tg mice compared with WT mice (Fig. 4C). However, other parameters had no differences the both sexes PDAPP Tg mice and WT mice (Figs. 4A–D). Multiple regression analysis showed that duration time in target was significantly associated with the status of immobility time but not thigmotaxis (Table 3). Thus, these results reveal that status of depression is implicated in the level of spatial reference memory function.

Discussion

In this study, we found that the spatial learning function was associated with NPS severity. Although the interaction between genotype and sex was not significant, young female PDAPP Tg mice definitely exhibited

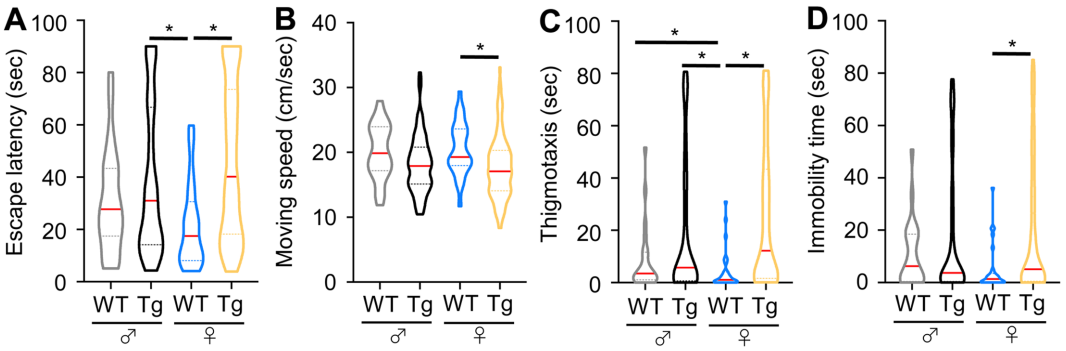

Fig. 3. Abnormal spatial learning function of female PDAPP Tg mice showing its association with neuropsychiatric symptoms in the hidden test. Spatial learning function of WT mice (male: n=23, white, female: n=28, blue) and PDAPP Tg mice (male: n=95, black, female: n=119, yellow) were assessed by the hidden test with the following parameters: (A) Escape latency as a motivation to escape the water, (B) Moving speed as a locomotion activity, (C) Thigmotaxis as an intensity of anxiety, and (D) Immobility as an intensity of depression. **P*<0.05. *P* values are derived from Tukey-Kramer post hoc test.

Table 2. Effect of thigmotaxis and immobility time combined genotype on escape latency in the hidden test

Variable	Coefficients	Standard error	Lower 95% CI	Upper 95% CI	*P* value
Intercept	10.09	0.657	8.793	11.38	<0.001
Thigmotaxis (%)	0.891	0.021	0.85	0.932	<0.001
Immobility time (%)	0.144	0.02	0.104	0.184	<0.001

Data are presented as β coefficients and standard error with lower and upper 95% confidence interval (CI) and *P* value. Multiple R^2=0.936. Adjusted R^2=0.936. VIF=1.705.

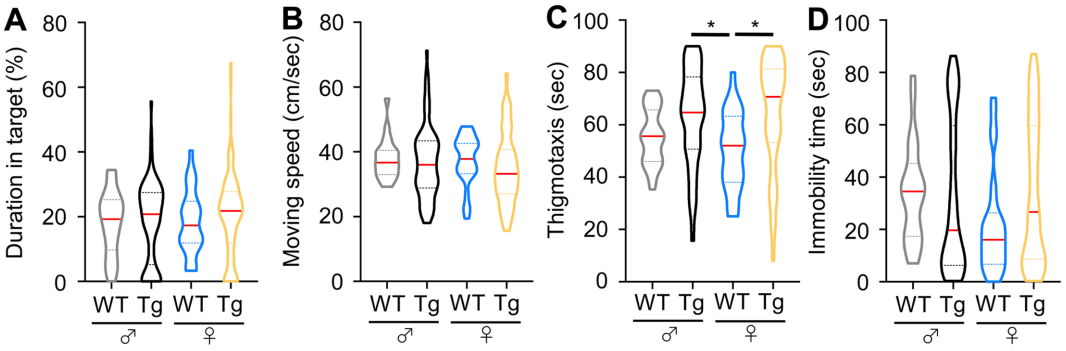

Fig. 4. Spatial reference memory function was normal in both sexes of PDAPP Tg mice and was associate with the status of depression in the probe test. Spatial learning function of WT mice (male: n=23, white, female: n=28, blue) and PDAPP Tg mice (male: n=95, black, female: n=119, yellow) were assessed by the hidden test with following parameters: (A) Duration time in the target and untargeted quadrant areas as a spatial reference memory functions, (B) Moving speed as a locomotion activity, (C) Thigmotaxis as an intensity of anxiety, and (D) Immobility time as an intensity of depression. **P*<0.05. *P* values are derived from Tukey-Kramer post hoc test.

Table 3. Effect of thigmotaxis and immobility time combined genotype on duration time in target in the probe test

Variable	Coefficients	Standard error	Lower 95% CI	Upper 95% CI	*P* value
Intercept	26.96	2.174	22.68	31.24	<0.001
Thigmotaxis (%)	−0.002	0.032	−0.065	0.062	0.955
Immobility time (%)	−0.212	0.023	−0.258	−0.166	<0.001

Data are presented as β coefficients and standard error with lower and upper 95% confidence interval (CI) and *P* value. Multiple R^2=0.276. Adjusted R^2=0.267. VIF=1.140.

spatial learning dysfunction and NPS compared to young female WT mice. Even more surprising was that multiple regression analysis showed that the level of spatial reference memory function was associated with the status of depression, but not anxiety, and spatial reference memory function was similar to WT mice in both sexes of PDAPP Tg mice. Thus, female PDAPP Tg mice at young ages can reduce the time and costs required to the AD research such as the elucidation of AD pathogenesis and the development of AD treatment.

Many reports using AD model did not refer sex of experimental animals. We found that female PDAPP Tg mice showed spatial learning dysfunction and high NPS severity in MWM test and these parameters are significantly associated. It was reported that various factors including sex, age and species influence MWM performance [29]. Notably, male animals have an advantage in spatial cognitive function [39–41]. And development patterns of psychological symptoms is differ in sex [42]. These reports and our findings suggest that a level of the spatial learning function may be caused by the difference in NPS severity at the age recognized between the sexes. NPS such as anxiety and depression is typical features of AD [43–45]. Effect of music therapy on anxiety and depression moderated AD phenotypes [46]. It was well known that females showed more intense NPS than males [18, 42, 47–50]. In fact, women have a higher risk of developing of AD than men [21]. For the treatment of NPS and cognitive dysfunction, anti-NPS drugs such as anti-psychotics, anti-depressants, mood stabilizers, and hypnotic drugs are used for AD patients [13].

Physical activity was associated with a risk for cognitive decline and dementia [51, 52]. In this study, we found that moving speed in water decreased in PDAPP Tg mice. Locomotion activity regulated by theta oscillations in CA1 region of the hippocampus [53]. Neural cell loss at CA1 regions in the hippocampus is a typical pathology in AD patients and the loss in CA1 appeared in the early stage of AD [54, 55]. Neural cell loss appeared from the juvenile aged PDAPP Tg mice and the extent of neuron loss in the CA1 region increased with age [56]. Thus, these reports and our results suggested that loss of neural cells in the CA1 region may contribute the impairment of the locomotion activity in AD patients.

In the current study, PDAPP Tg mice showed abnormal spatial learning function, but spatial reference memory function was normal. Previously, we showed transplantation of neural cells into dentate gyrus improved cognitive dysfunction of PDAPP Tg mice [27, 28]. The therapeutic effect for spatial learning function, but not spatial reference memory function correlated with NPS severity on PDAPP Tg mice, in part [57]. Physical exercise-promoted neurogenesis improved spatial learning dysfunction and anxiety-like behavior but not spatial reference memory dysfunction in mouse models [58, 59]. In addition, the voltage- and calcium-activated potassium channels (BK channels)-deficient mice showed that impaired spatial learning function and normal spatial reference memory function [60]. On the other hand, repulsive axon guidance molecule, FLRT2-deficient mice showed that abnormal spatial reference memory function and normal spatial learning function in MWM test [61]. These reports and our findings suggested that the synaptic mechanism underlying the spatial learning function and spatial reference memory function were different in the models.

The understandings of this AD model will be of benefit for the development of new therapeutic strategies for AD. In general, old AD model animals used for AD research. It needs a considerable time and costs. Our results suggested that spatial learning function associated well with NPS severity such as anxiety and depression, and spatial reference memory function associated with status of depression in young female PDAPP Tg mice. NPS may be frequently accompanied by spatial cognitive dysfunction in human AD. Our findings reveal that female PDAPP Tg mice at young age can be useful experimental AD model to reduce the time and costs.

Author Contributions

MAM, AN and NS designed research. MAM and YI analyzed data, MAM wrote the paper. MAM and NS edited the paper. NF and KT transplanted neural cells. All authors performed the MAM test.

Funding

This work was supported JSPS KAKENHI (Grant No. JP17K01378, JP17K14978, JP19K20681 and JP19K12766); SRF Foundation (No. 2019Y005).

Conflict of Interests

The authors declare no competing financial interest.

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