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Research report

Repeated cognitive stimulation alleviates memory impairments in an Alzheimer's disease mouse model

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ABSTRACT

Alzheimer's disease is a neurodegenerative disease associated with progressive memory and cognitive decline. Previous studies have identified the benefits of cognitive enrichment on reducing disease pathology. Additionally, epidemiological and clinical data suggest that repeated exercise, and cognitive and social enrichment, can improve and/or delay the cognitive deficiencies associated with aging and neurodegenerative diseases. In the present study, 3xTg-AD mice were exposed to a rigorous training routine beginning at 3 months of age, which consisted of repeated training in the Morris water maze spatial recognition task every 3 months, ending at 18 months of age. At the conclusion of the final Morris water maze training session, animals subsequently underwent testing in another hippocampus-dependent spatial task, the Barnes maze task, and on the more cortical-dependent novel object recognition memory task. Our data show that periodic cognitive enrichment throughout aging, via multiple learning episodes in the Morris water maze task, can improve the memory performance of aged 3xTg-AD mice in a separate spatial recognition task, and in a preference memory task, when compared to naïve aged matched 3xTg-AD mice. Furthermore, we observed that the cognitive enrichment properties of Morris water maze exposer, was detectable in repeatedly trained animals as early as 6 months of age. These findings suggest early repeated cognitive enrichment can mitigate the diverse cognitive deficits observed in Alzheimer's disease.

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1. Introduction

Alzheimer's disease (AD), a neurodegenerative disease that primarily afflicts the elderly population, is associated with progressive memory and cognitive decline. The pathological features of the postmortem AD brain; include extra- and intra-cellular depositions of amyloid-β (Aβ) species, intracellular accumulations of hyperphosphorylated tau protein, neuroinflammation, and irreversible neuronal and synaptic degeneration. These pathological hallmarks are prominently found in brain regions heavily involved in the learning and memory process, including the neocortex, hippocampus and amygdala (Chabrier et al., 2014; DeKosky and Scheff, 1990; Hardy and Revesz, 2012; Querfurth and LaFerla, 2010; Scheff et al., 1990).

Epidemiological and clinical evidence suggests that education, occupation, and an active lifestyle, involving enhanced social, physical, and mental components, can improve cognitive function in healthy older people, and are protective against a general reduction rate of memory decline and the development of AD, in part by an attenuation of disease symptoms, and a slowing of disease progression in patients (Baker et al., 2010; Fratiglioni et al., 2004; Friedland et al., 2001; Mayeux and Stern, 2012; Svensson et al., 2014; Yaffe et al., 2014). Until recently, the most common explanation for the observed beneficial effect of a cognitively and physically active lifestyle, were that such activities enhance cognitive reserve, and enable patients to compensate for cognitive decline without affecting AD-related neuropathology (Le Carret et al., 2005). In this regard, several studies using AD animal models have reported that cognitive and physical stimulation, in the form of repeated learning or environmental enrichment, enhances performance of cognitive

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tasks, prevents AD disease progression, and results in a significant reduction of cerebral Aβ plaques and amyloid angiopathy (Ambree et al., 2006; Billings et al., 2007; Greenough et al., 1972; Herring et al., 2008; Lazarov et al., 2005; Mirochnic et al., 2009). Specifically, our group previously showed that repeated training in the Morris water-maze (MWM) spatial recognition task, produces learning improvements for newly acquired platform locations, and reduces tau and Aβ pathology in 3xTg-AD animals (Billings et al., 2007).

In the present study, we sought to determine whether the beneficial effects observed after multiple MWM training episodes, were specific to that task, or if they could alleviate memory deficits found in other hippocampal-dependent spatial memory task. In addition, we also sought to determine if the beneficial effects of repeated MWM training episodes could extend beyond hippocampal-dependent memory to benefit memory processes that require more involvement of the cortex. Thus, 3xTg-AD mice were trained every three months in the MWM until 18 months of age, and subsequently tested in the Barnes maze spatial memory task, followed by the more cortical-dependent novel object recognition memory task. Our results indicate that our MWM training paradigm not only improved cognitive performance in the Barnes maze spatial task, but importantly, it also ameliorates more cortically-dependent memory deficits found in the novel object recognition task. These findings suggest that the cognitive benefits found after periodic cognitive enrichment throughout aging in one spatial memory task, can also alleviate the deficits found in other spatial memory dependent task, and non-spatial memory task. Thus, our findings support the idea that constant cognitive stimulation could be a part of an integrative treatment to delay memory decline in AD patients (Chapman et al., 2015; Fratiglioni and Wang, 2007; Kelly et al., 2014).

2. Materials and methods

2.1. Transgenic mice

All animal experimental procedures were performed in accordance with protocols approved by the Institutional Animal Care and Use Committee (IACUC) at the University of California, Irvine. All mice were housed with food and water ad libitum under a 12 h dark/light cycle. In this study, we utilized 3, 6, 9, 12, 15, and 18-month old 3xTg-AD mice. The characterization of 3xTg-AD mice has been described previously (Oddo et al., 2003). Briefly, two independent transgenes encoding human APP_{Swe} and human tau_{P301L} (both under the control of the mouse Thy1.2 regulatory element) were co-microinjected into single-cell embryos harvested from homozygous mutant $PS1_{M146V}$ knockin (PS1-KI) mice, all on a mixed 129SvJ/C57BL/6 background, were used for all experiments (Oddo et al., 2003).

2.2. Morris water maze

3xTg-AD mice ($n = 15$ per group) were trained in the Morris water maze (MWM) every three months (3, 6, 9, 12, 15 and 18 months of age) with 4 training trials per day for as many days as needed to reach the training goal of swimming to the submerged platform (escape latency) within 15 s as previously described (Martinez-Coria et al., 2010). The apparatus used for all water maze tasks was a circular aluminum tank (1.5 m diameter) painted white and filled with water maintained at 26–29 °C. Position of the hidden platform MWM was changed for every training episode to avoid bias for the platform location (i.e training 3 months (quadrant 1 Northeast) 6 months (quadrant 2, Northwest), 9 months (quadrant 3 Southeast), 12 months (quadrant 4, Southwest)). Following training at each episode, mice underwent a 24 h probe trial, in which the hidden platform was removed and the latency to cross the location of the hidden platform was measured. We compared the latency to reach the platform between repeatedly trained 3xTg-AD with 10 aged-matched naïve mice (Fig. 1A).

2.3. Barnes maze

At the conclusion of the final MWM probe at 18 months, repeatedly MWM trained 3xTg-AD mice were subsequently trained on the Barnes Maze (BM) along with behaviorally naïve age and sex matched 3xTg-AD mice. The BM was conducted as previously described (Clinton et al., 2007): 4 training trials per day for 5 days and test was performed 24 h after the last training trial.

2.4. Novel object

Following BM training and probe testing, 18 month old repeatedly MWM trained 3xTg-AD mice was trained in a novel object recognition task, as previously described (Martinez-Coria et al., 2010). Briefly, animals were trained by letting them explore two identical objects placed at opposite ends of the arena for 10 min. 24 h later, mice were tested for 3 min with one copy of the familiar object and one novel object of similar dimensions. Recognition index (RI) represents the percentage of time mice spent exploring the novel object. Together with the repeatedly MWM trained group, another two sets of animals were trained on the recognition task: naïve mice, animals trained only on Barnes maze (BM trained).

2.5. Statistical analysis

All data are expressed as mean ± SEM. All the quantitative data were analyzed by Student's *t*-test (two-groups) or repeated-measures ANOVA (multiple groups/multiple training days) with a Bonferroni's post hoc test. Briefly, Morris water maze and barnes maze trainings were analyzed by repeated measure ANOVA followed by pairwise comparisons. Barnes maze test was analyzed by t-test and object recognition RI was analyzed by one-way factorial ANOVA. All significant values were set to $p < 0.05$. All statistical analysis was performed using Prism (GraphPad, La Jolla, CA).

3. Results

3.1. Repeated Morris water-maze training alleviates subsequential spatial learning and memory deficiencies in 3xTg-AD mice

We sought to examine the effects of repeated MWM training on succeeding spatial learning. A group of 3xTg-AD mice was trained in the MWM task every 3 months from age 3 months to 18 months. At each time point, our repeat group of mice was compared with an independent aged and sex-matched naïve 3xTg-AD group (Fig. 1A). Our findings revealed that 3xTg-AD mice subjected to multiple training episodes showed significant learning improvements at 6, 9, 12, 15, and 18 months of age compared to naïve animals. As such, repeat trained mice, from ages 6 to 18, required fewer days to reach performance criterion (<15 s to find the platform) (Fig. 1B). These effects were especially pronounced at 15 and 18 months of age, where repeatedly trained 3xTg-AD showed the greatest learning differences when compared to naïve 3xTg-AD mice (Fig. 1B)

To investigate for potential changes in long-term memory in repeatedly MWM trained 3xTg-AD mice, a probe trial was conducted 24 h following the last training trial at each 3 month episode. During the probe trial, the submerged platform was removed from its training location, and the latency for the animal to cross the former location of the platform was measured. Repeatedly trained 3xTg-AD mice exhibited a significant improvement in long-term

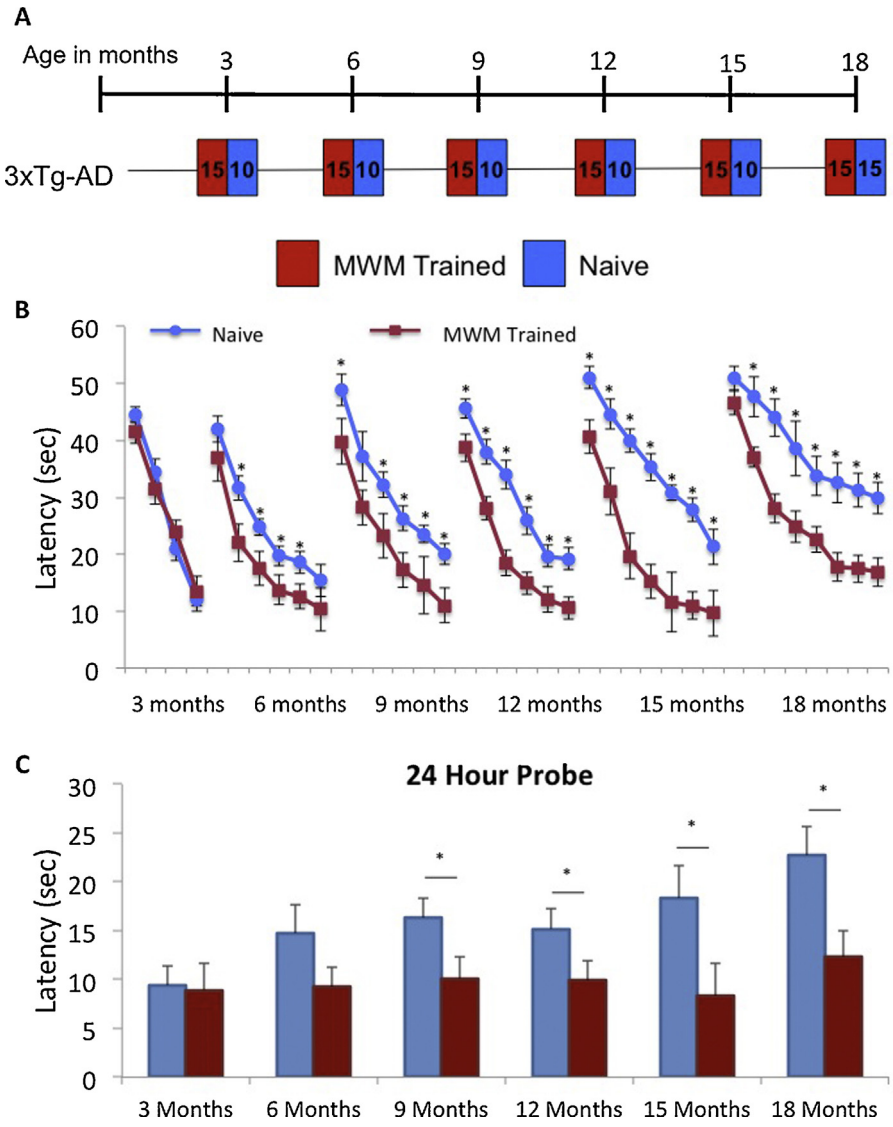

Fig. 1. Repeated Morris water maze training experimental timeline: (A) 3xTg-AD mice were tested in a MWM task for spatial learning beginning at age 3 months and subsequently every 3 months for an additional 15 months. Furthermore, a naïve separate group of age and sexed matched 3xTg-AD mice underwent behavior testing at each time point. (B) Repeat tested 3xTg-AD mice show improved learning vs. aged and sex matched naïve 3xTg-AD mice, as early as 6 months. They continue to show significant latency improvements to find the platform during subsequent training at 9, 12, 15, and 18 months respectively. (C) Following the completion of the final training session, a 24-hour probe test was conducted for each age group. Analysis of repeat trained 3xTg-AD mice versus naïve 3xTg-AD mice found that previous exposer to the MWM resulted in significantly better performance during the probe trial, as measured by latency to find the former platform location, at 9, 12, 15, and 18 months. The values represent the mean ± SEM ($n = 15$). $^*p < 0.05$.

memory performance at 9, 12, 15, and 18 months of age compared to naïve 3xTg-AD mice. (Fig. 1C, p-value < 0.05).

3.2. *Beneficial effects of repeated spatial training are not restricted to one type of memory*

To determine whether recurrent spatial learning in the MWM task could rescue deficits found in other memories apart from MWM, repeatedly trained 3xTg-AD mice were first trained on the hippocampal-dependent Barnes maze spatial task, followed by a more cortically-dependent novel object recognition preference task (Cohen and Stackman, 2015; Maras et al., 2014).

The 3xTg-AD mice that were repeatedly trained in the MWM task showed significantly better Barnes maze learning curve when compared with a group of naïve age and sex-matched 3xTg-AD mice (statistical significances on days 2–5; p-value < 0.05) (Fig. 2B). Furthermore, repeatedly trained 3xTg-AD mice also showed improved memory performance during the probe trial conducted 24 h. after the final training session. We found significant improvements in both the latency to find the target zone, and the number of errors committed, in the repeatedly trained 3xTg-AD group (Fig. 2C and D, p-value < 0.05).

In addition, following BM testing, repeatedly trained 3xTg-AD mice was tested in the novel object recognition task with a new set of naïve 3xTg-AD mice, and the naïve group from the Barnes maze task. In correlation to what was observed in the Barnes maze task, we found that repeatedly trained 3xTg-AD mice performed significantly better compared to naïve 3xTg-AD mice (p-value < 0.001) (Fig. 2D). We also found that a single trained session in the Barnes maze task, is insufficient to produce the degree of memory improvement found in our repeat trained mice (p-value < 0.001) (Fig. 2D). Together, these results suggest that memory improvements upon recurrent MWM training are not task specific, but instead involve a general rescue of memory capabilities likely affecting several brain regions.

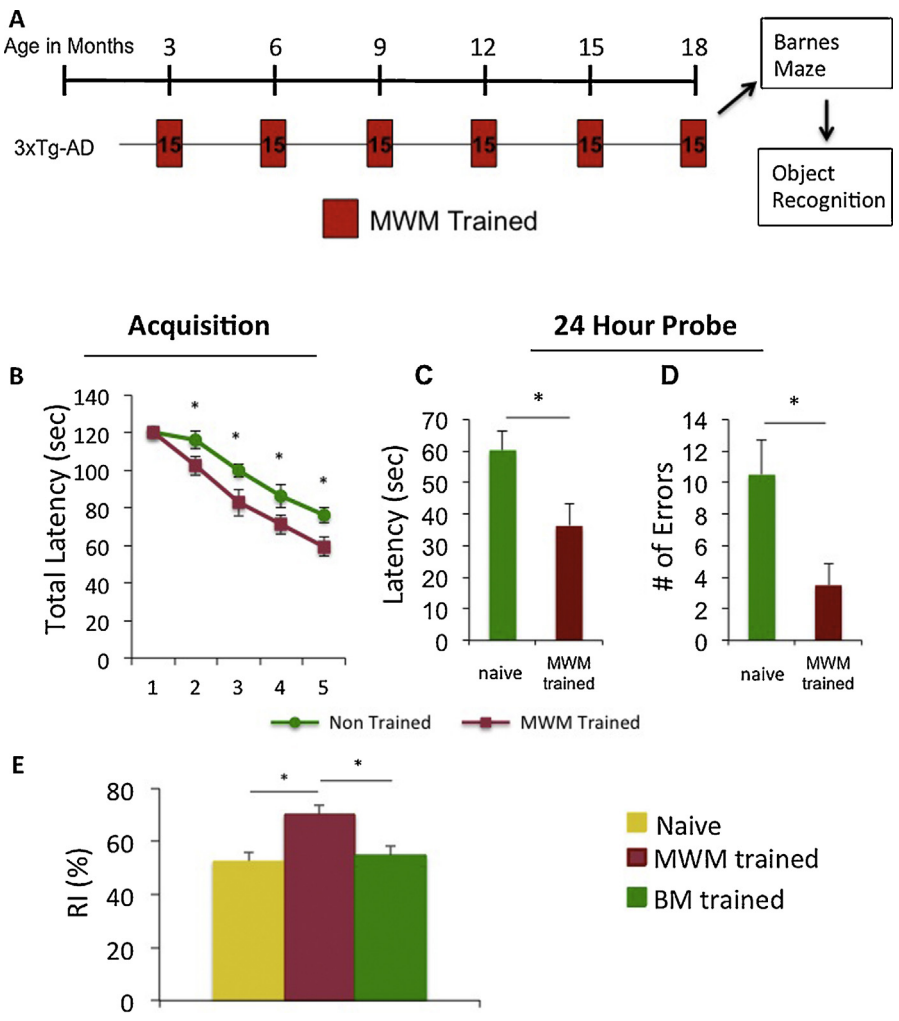

Fig. 2. Repeat spatial trained in the Morris Water Maze task leading to improved cognitive performance in both the Barnes Maze and Object Recognition tasks: (A) 18 month old 3xTg-AD mice repeatedly trained in the MWM were tested in a Barnes maze task followed by novel object recognition. (B) Naïve 3xTg-AD mice had a significantly worse latency to find the target zone (escape box) than repeat MWM trained 3xTg-AD mice on days 2–5. (C and D) During the probe trial, repeat trained mice required significantly less time to find the target zone, and had significantly less error compared to naïve mice. (E) Following Barnes maze testing, 18 month old repeat MWM trained mice, along with the Barnes Maze naïve group, and a new naïve mouse group, were subsequently tested in the novel object recognition task. We find that repeat trained 3xTg-AD mice significantly outperform all other groups. The values represent the mean ± SEM ($n = 15$). $^{*}p < 0.05$.

4. Discussion

In the present study, we corroborated our previous results that spatial MWM training, initiated prior to the development of AD-like pathogenesis, significantly improves subsequent MWM learning in aging 3xTg-AD mice. We also report the novel finding that mice trained in the spatial MWM task present improved performance in a second hippocampal-dependent spatial task, and in an object recognition task, which has an important cortical component. Therefore, our data reveal that continued spatial cognitive stimulation throughout live can mitigate the impairments in spatial and non-spatial dependent memory processes that severely affected aged 3xTg-AD mice.

Epidemiological and clinical studies suggest that exercise, and frequency of cognitive training, enhance learning and memory at later ages (Anguera et al., 2013; Billings et al., 2007; Finn and McDonald, 2015; Greenough et al., 1972; Kelly et al., 2014; Korol et al., 2013; Martinez-Coria et al., 2010; Mayeux and Stern, 2012; Nouchi et al., 2012; Nouchi et al., 2014; Rooney, 2014; Snigdha et al., 2014; Svensson et al., 2014; Woods et al., 2012). The prevalent hypothesis to explain this occurrence is the concept of cognitive reserve. Cognitive reserve proposes that life experience may influence neural processing and synaptic organization by permitting neurological processes to become more efficient, adaptive, and plastic, thus allowing some people to cope with progressing dementia better than others (Xu et al., 2015). Although environments that involve diverse cognitive stimuli may be the most conducive in increasing cognitive reserve, physiological benefits of physical activity have been related to changes in hormone levels, improvement in cerebral blood flow, and an increase in the number of neuronal synapses (Chapman et al., 2015; Coombs, 2014; Jankowsky et al., 2005; Pietropaolo et al., 2014). Social activities may offer a stimulating environment that involves not only navigating social cues, dealing with complex and challenging issues, but also physical movement and information processing that in turn enhance cognitive reserve (Gaillard et al., 2014; Intlekofer and Cotman, 2013; Snigdha et al., 2014). In this regard, previous studies have shown that repeated cognitive enrichment, as a method of environmental enrichment/lifestyle, improves behavioral performance (feeding habits, Morris water maze, new language learning) in healthy and diseased swine, rodents, and humans (Billings et al., 2007; Gilleen et al., 2014; Mayeux and Stern, 2012; Zebunke et al., 2013). Additionally, in a previous study by our group, 3xTg-AD mice experienced significant reduction in Aβ oligomers and tau

pathology and increased learning with new platform locations following repeated MWM training (Billings et al., 2007).

Our results are in agreement with previous reports and show that a repeated spatial learning paradigm started at an early age can mitigate impairments in spatial learning and memory later in life. Additionally, we find that repeated spatial learning can also mitigate impairments in non-spatial dependent behavioral task. Generalization of cognitive recovery is a remarkable finding, and suggests that repeated cognitive stimulation produces global protective effects capable of delaying the cognitive dysfunction found in transgenic AD mice. These effects could be related to the transfer process of spatial information from the hippocampus to the neocortex known as system consolidation (Frankland and Bontempi, 2005). According to the system consolidation theory, memory is reorganized over time shifting its locus, *i.e.*, gradually migrating from the hippocampus to the cortex. The first evidence supporting this idea came from the observation that recent, but not remote, declarative memory is affected by hippocampal damage, suggesting that memory is temporally allocated to the hippocampus but it resides in a broadly distributed cortical network for permanent storage (Rempel-Clower et al., 1996; Scoville and Milner, 1957; Squire and Alvarez, 1995). The process of system consolidation might explain why the repeat learning 3xTg-AD group demonstrated improved performance in the novel object recognition task, while the once tested Barnes maze naïve 3xTg-AD group did not. It is likely that a single exposure of hippocampal spatial learning is not sufficient to improve the performance in a memory task with an important cortical component. Constant cortical reorganization triggered by repeated spatial learning creates favorable conditions for synaptic plasticity and strengthen cortical connections, which may explain, in part, cortical memory recovery. However, the results presented in the current study were not aimed at exploring system consolidation mechanisms and therefore further experiments are needed to address whether system consolidation processes are responsible for alleviating cognitive decline in old 3xTg-AD mice when repeatedly trained on the Morris water maze task.

5. Conclusion

Our study corroborates that recurrent spatial learning and memory training mitigates the negative effects that AD pathology has on the hippocampal-dependent spatial learning and memory impairments found in aged 3xTg-AD mice. Most importantly, our results show that repeated spatial learning could also alleviates the impairments in non-spatial kinds of memory. Therefore, repeated cognitive stimulation could be an effective approach in delaying cognitive decline related to Alzheimer's disease progression.

Conflict of interest

No potential conflicts of interest relevant to this article were reported.

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