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Short communication

Pre-training blocks the improving effect of tetrahydroaminoacridine and D-cycloserine on spatial navigation performance in aged rats

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Abstract

We investigated the effect of pre-training on the improvement of spatial navigation performance provided by a cholinesterase inhibitor, tetrahydroaminoacridine (3 mg/kg, i.p.), and a positive modulator of NMDA receptor, D-cycloserine (10 mg/kg, i.p.), or their combination in aged rats. Pre-training consisted of spatial or non-spatial conditions and took place in either the same or a separate room. We found that any kind of pre-training was able to eliminate the enhancing effect of tetrahydroaminoacridine and D-cycloserine on spatial navigation. However, none of these pre-training conditions was able to block the age-related deficit in spatial navigation. These results indicate that tetrahydroaminoacridine and D-cycloserine, separately or in combination, do not themselves alleviate the age-related spatial memory deficit, but may enhance procedural aspects of water maze learning in aged rats.

Keywords: Acetylcholine; Cholinergic; Glutamate; Interaction; Motivation; Behaviour

1. Introduction

Pharmacological studies support the involvement of acetylcholine and NMDA receptor dysfunction in age-related cognitive decline (Nuettner, 1991; Sirviö et al., 1992; Aigner, 1995). For example, a combined daily administration of D-cycloserine (3 mg/kg), a partial agonist on the glycine B-site on the NMDA receptor, and tetrahydroaminoacridine (1 mg/kg), a cholinesterase inhibitor, at subthreshold doses improved water maze spatial navigation as effectively as did optimal doses of either of the compounds alone (Aura et al., 1998). Administration of tetrahydroaminoacridine, 3 mg/kg, or nicotine, 0.3 mg/kg, and D-cycloserine, 10 mg/kg, daily before the training trials dose dependently alleviated the failure to escape to a hidden water maze platform induced by ageing in rats (Baxter et al., 1994; Riekkinen et al., 1996). Furthermore, a combination of subthreshold doses of nicotine, 0.1 mg/kg, and D-cycloserine, 3 mg/kg (Riekkinen and Riekkinen, 1997b) or tetrahydroaminoacridine, 1 mg/kg, and D-cycloserine, 3 mg/kg (Aura et al., 1998) markedly improved spatial navigation in aged rats. The hippocampus is one possible site of action for cholinesterase inhibitors, nicotine and D-cycloserine, to improve water maze spatial navigation accuracy. Indeed, we found that daily infusion of scopolamine (10 μg), a muscarinic receptor antagonist, or ((+)-3-(2-carboxypiperazin-4-yl)-propyl-l-phosphonic acid (CPP) (0.03 μg), a NMDA receptor antagonist, before the daily training sessions directly into the dorsal hippocampus impaired water maze spatial navigation (Riekkinen and Riekkinen, 1997a). However, NMDA and acetylcholine receptors not only synergistically modulate hippocampal behavioural functions and long term potentiation (Hirotsu et al., 1989), but can also jointly modulate the electrophysiological functioning of cortical cells (Greuel et al., 1988). Therefore, it is possible that the positive modulation of muscarinic and NMDA receptors jointly enhances the spatial navigation performance of aged rats in the water maze task, and that this effect may be mediated via hippocampal or cortical areas.

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In this study, we wanted to examine in detail the nature of the enhancement of water maze spatial navigation of aged rats that is induced by tetrahydroaminoacridine and D-cycloserine. It has been shown earlier that non-spatial pre-training in the water maze alleviates the learning deficit caused by the NMDA receptor antagonist, (±)-2-amino-5-phosphonopentanoic acid (AP-5), and that the AP-5-induced learning deficit can be almost completely prevented if the rats are pre-trained in a different water maze (Bannerman et al., 1995; Saucier and Cain, 1995). Thus it seems that pre-training affects the performance in subsequent water maze tests, and may alter the drug-induced spatial navigation performance. Since it is possible that tetrahydroaminoacridine and D-cycloserine enhance spatial navigation performance of aged rats by improving non-spatial components of learning, such as procedural learning, sensorimotor skills or motivation, we examined the influence of pre-training on the effects of tetrahydroaminoacridine and D-cycloserine on spatial navigation in the water maze. The expectation was that, if a drug acts primarily to improve spatial memory and learning, its effects should still be significant after pre-training to a non-spatial cue strategy, spatial training in a different environment or reversal of the relationship between the extra maze cues and the escape platform. On the other hand, to learn how to complete a water maze task successfully, a rat must also acquire non-spatial components of learning such as swimming, searching for and climbing onto a hidden platform and ''appreciating'' that the platform represents rescue from the tank. Consequently, if a drug facilitates acquisition of non-spatial components of learning, then these already acquired abilities are not likely to be further improved in the new environment. A previous study showed that spatial pre-training in a different water maze did not protect from the spatial navigation deficit induced by subsequent hippocampal lesioning (Bannerman et al., 1995). Furthermore, a similar design was used in a second study which revealed that the spatial navigation deficit induced by medial septal-lesioning in rats was not blocked by spatial pre-training (Riekkinen et al., 1997). These findings suggest that septohippocampal dysfunction may contribute to the age-related spatial navigation deficit. Therefore, we also wanted to compare whether aged rats are still impaired for spatial navigation after they have undergone different pre-training schedules. This would indicate that the age-related spatial navigation deficit might at least to some extent be due to septohippocampal dysfunction.

In our study, pre-training was conducted with or without drug administration, in the same or a different water maze or using a spatial (hidden platform) or non-spatial (visible platform) navigation strategy. In addition to the placebo group, a group of young rats was used as a second control group to analyse whether any of these pre-training conditions could block the spatial navigation deficit present in aged rats.

2. Materials and methods

2.1. Animals

Young (4 months old, $n = 44$) and aged (22–26 months old, $n = 192$) male Han:Wistar rats were used in the present study. The rats were obtained from the National Laboratory Animal Centre, Kuopio, Finland. The rats were housed in a controlled environment with food and water available ad lib (temperature 22 ± 2°C, lights on: 0700–1900 h, humidity 60%). The study was approved by the provincial government of Kuopio.

2.2. Drugs

Tetrahydroaminoacridine (3 mg/kg, i.p., 2 ml/kg, 40 min before daily testing) and D-cycloserine (10 mg/kg, i.p., 2 ml/kg, 30 min before daily testing) doses were selected based on previous experience (Riekkinen and Riekkinen, 1997b; Aura et al., 1998). For control purposes, NaCl 0.9% injections of equal volume (vehicle) were used.

2.3. Water maze

The swimming patterns of the rats to the hidden platform were monitored with a computerised video tracking system. The computer calculated the means of daily escape distance (cm) to the hidden platform. The daily escape distance values were stored for statistical analysis of the effects of drug treatment on water maze acquisition.

The starting locations (labelled north, south, east, and west) were located arbitrarily on the pool rim. The pool was divided into four quadrants (Southwest (SW), Southeast (SE), Northwest (NW), and Northeast (NE)) and three annuli of equal surface area. The temperature of the water was 22 ± 1.5°C. The rats were placed in the water with their nose pointing towards the wall, at one of the starting points. In every experiment, there were three trials per day, with a 30-s inter-trial interval between trials.

In experiments 1 and 2 (Fig. 1, parts A and B, respectively), the initial training consisted of 5 consecutive days of training (three trials per day, maximum duration 70 s). The hidden platform was located in the SW quadrant. To make any re-learning possible and to assess possible drug effects on re-learning we used a 30-day period to allow some forgetting of the familiar environment after pre-training. In experiment 1, another training period of 5 days was assessed identically to that performed during the initial training period. In experiment 2, another training period of 5 days was assessed, but in this case the location of the hidden escape platform was reversed to the NE quadrant.

In experiment 3 (Fig. 1, part C), initial training consisted of 3 consecutive days of training to a visible platform located in the SW quadrant. Then, a break of 30 days was allowed before the next stage of testing. Subsequent

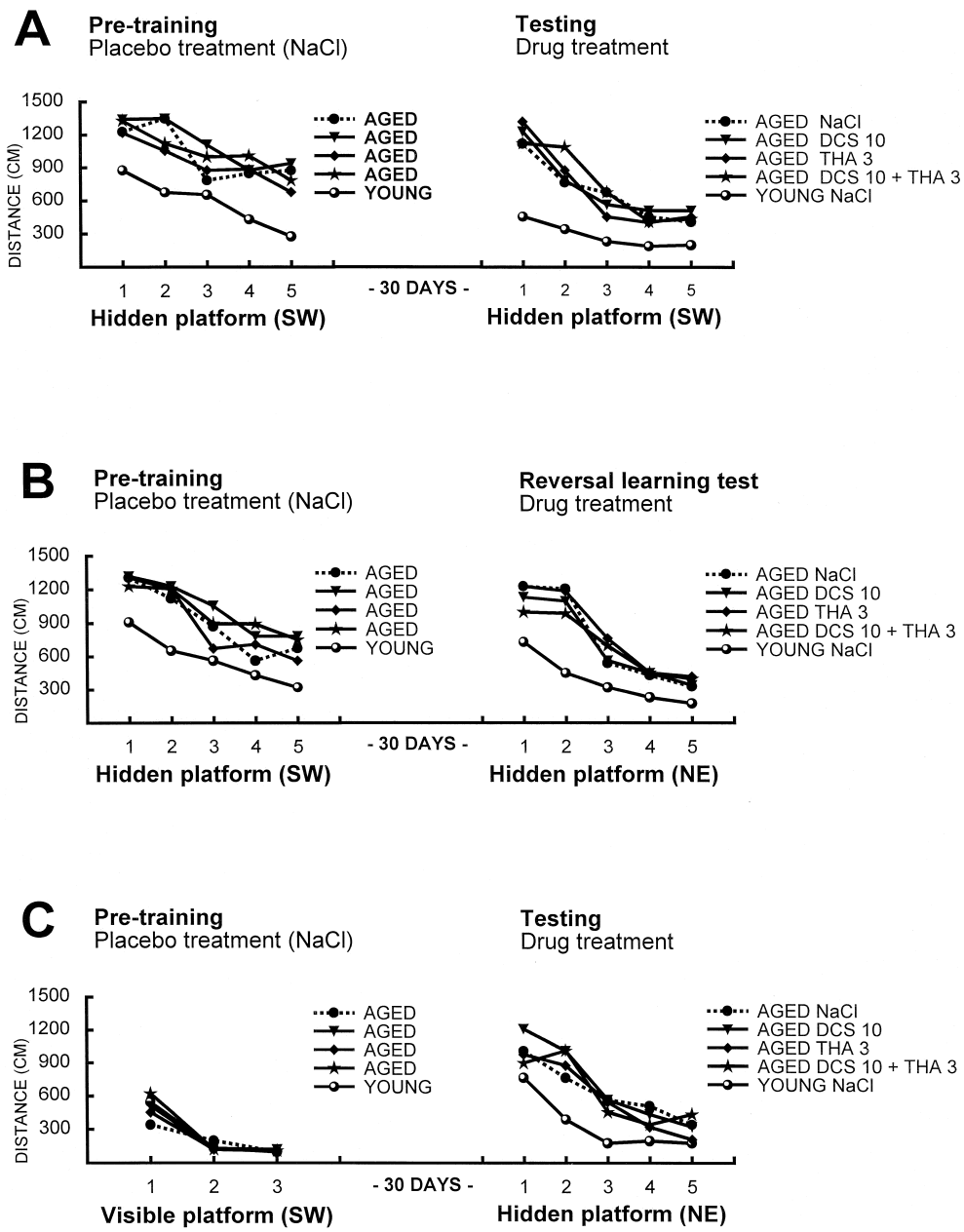

Fig. 1. Spatial pre-training, with placebo treatment, to finding a hidden platform blocked the improving effect of single or combined tetrahydroaminoacridine (3 mg/kg i.p.) and D-cycloserine (10 mg/kg i.p.) doses, but did not have an effect on the age-related deficit of spatial navigation performance (Part A). There was no effect of single or combined tetrahydroaminoacridine (3 mg/kg i.p.) and D-cycloserine (10 mg/kg i.p.) doses on reversal learning of aged rats after spatial pre-training to finding a hidden platform (Part B). Single or combined tetrahydroaminoacridine (3 mg/kg i.p.) and D-cycloserine (10 mg/kg i.p.) doses did not affect hidden platform learning of aged rats after non-spatial pre-training to finding a visible platform (Part C). Aged rats were as accurate as young rats in non-spatial navigation (Part C), but after spatial or non-spatial pre-training the aged rats remained impaired in spatial navigation when compared to the young rats (Parts A, B and C, right plots). Pre-training (left plot in each part) was conducted 30 days before the testing (right plot in each part) in the same water maze as the pre-training. Abbreviations: AGED = aged rats, DCS 10 = D-cycloserine 10 mg/kg i.p., NaCl = 0.9% sodium chloride, NE = north-east (position of the platform), SW = south-west (position of the platform), THA 3 = tetrahydroaminoacridine 3 mg/kg i.p., YOUNG = young rats. *X*-axis: training days 1–5, *Y*-axis: escape distance in cm, group mean of daily training trials.

training consisted of 5 consecutive days of training, and the hidden platform was located at the NE quadrant.

In experiment 4 (Fig. 2, part A), training was conducted in two separate rooms that had clearly different appearances (maze A and maze B). The initial training consisted of 8 consecutive days (old rats) of training in maze A to a hidden platform located in the SW quadrant (young rats were trained for 5 days). A break of 2 days was allowed between the two training stages. During the second stage in maze B, the training consisted of 6 consecutive days of

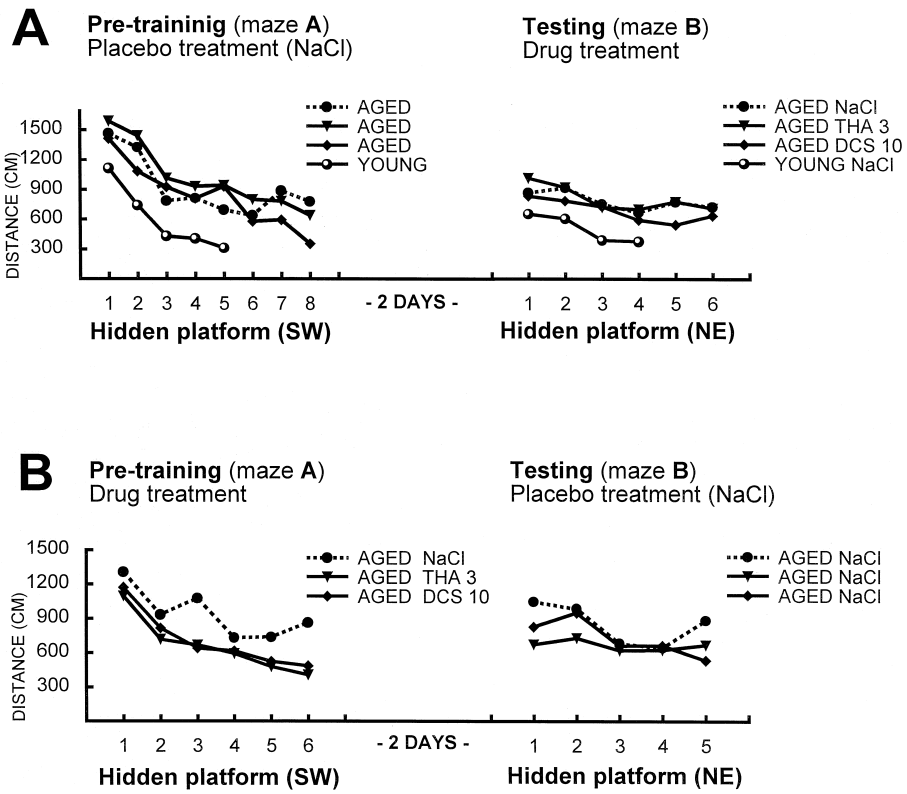

Fig. 2. Spatial pre-training with placebo treatment in one maze (part A, left plot) blocked the improving effect of single or combined tetrahydroaminoacridine (3 mg/kg i.p.) and D-cycloserine (10 mg/kg i.p.) doses on spatial navigation performance of aged rats, when tested in a second water maze in a different environment (part A, right plot). Pre-training had no have effect on the age-related deficit of spatial navigation performance (part A, right plot). Tetrahydroaminoacridine (3 mg/kg i.p.) and D-cycloserine (10 mg/kg i.p.) improved the spatial navigation performance of aged rats in one maze (part B, left plot), but the aged groups did not have significant differences in spatial navigation learning when tested with placebo treatment in a second maze in a different environment (part B, right plot). Abbreviations: AGED = aged rats, DCS 10 = D-cycloserine 10 mg/kg i.p., NaCl = 0.9% sodium chloride, NE = north-east (position of the platform), SW = south-west (position of the platform), THA 3 = tetrahydroaminoacridine 3 mg/kg i.p., YOUNG = young rats. *X*-axis: training days, *Y*-axis: escape distance in cm, group mean of daily training trials.

training (old rats), and the hidden platform was located in the NE quadrant (young rats were trained for four days).

In experiment 5 (Fig. 2, part B), the first stage training consisted of 6 consecutive days of training in maze A. The hidden platform was located in the SW quadrant. A break of 2 days was allowed between the two training stages. During the second stage, the training consisted of 5 consecutive days of training in maze B and the hidden platform was located in the NE quadrant.

The first daily trial was always started from the location furthest away from the hidden or visible platform. The starting point of second and third trials was selected in a semi-random manner (never from the same place as during the second and third daily trial). Those rats that did not find the platform during the maximum duration of a trial (70 s) were placed on the platform by the experimenter. The rats were allowed to stay on the platform for 5 s.

2.4. Statistics

A one-way-analysis of variance (ANOVA) followed by Duncan's post hoc multiple group comparison was used to measure the effects of drug treatments on water maze acquisition (escape distance).

3. Results

In experiment 1 (Fig. 1, Part A), five groups of 10 rats were used: young and aged + vehicle, aged + tetrahydroaminoacridine 3 mg/kg, aged + D-cycloserine 10 mg/kg and aged + tetrahydroaminoacridine 3 mg/kg + D-cycloserine 10 mg/kg. During the first training period, no drug treatments were given and all the groups of aged rats were impaired for finding the hidden platform in the SW quadrant ($F(4,45) = 6.1$, $P < 0.01$) when compared to the young controls ($P < 0.05$, young vs. aged groups). During the second training period assessed after a break of 1 month, drug treatments failed to alleviate the age-related impairment of performance ($F(4,45) = 0.2$, $P > 0.1$), as none of the single or combined treatments improved the performance of aged rats in locating the hidden platform in the SW quadrant ($P > 0.05$ vs. aged vehicle treated).

In experiment 2 (Fig. 1, Part B), five groups of 10 rats were used: young and aged + vehicle, aged + tetrahydroaminoacridine 3 mg/kg, D-cycloserine 10 mg/kg and tetrahydroaminoacridine 3 mg/kg + D-cycloserine 10 mg/kg. Again, during the first training period, no drug treatments were given and all groups of aged rats were impaired for finding the hidden platform from the SW quadrant ($F(4,45) = 5.0$, $P < 0.01$) when compared to the young controls ($P < 0.05$, young vs. aged). During the second training period, drug treatments failed to alleviate the age-related impairment of reversal learning performance ($F(4,45) = 0.3$, $P > 0.05$), as none of the single or combined treatments improved the performance of aged rats to find the hidden platform in the NE quadrant ($P > 0.05$ vs. aged vehicle treated).

In experiment 3 (Fig. 1, Part C), five groups of 10 rats were used: young and aged + vehicle, aged + tetrahydroaminoacridine 3 mg/kg, aged + D-cycloserine 10 mg/kg and aged + tetrahydroaminoacridine 3 mg/kg + D-cycloserine 10 mg/kg. During the first period, rats were trained to find a visible platform and no age-related defect was found ($F(4,45) = 0.1$, $P > 0.05$). During the second stage of training, the rats were searching for a hidden platform and the aged rats were impaired at this stage of training ($F(4,45) = 6.3$, $P < 0.01$) when compared to the young controls ($P < 0.05$, young vs. aged). None of the single or combined drug treatments alleviated this failure of the aged rats ($P > 0.05$ vs. vehicle-treated aged rats).

In experiment 4 (Fig. 2, Part A), four groups of 12 rats were used: young and aged + vehicle, aged + tetrahydroaminoacridine 3 mg/kg or aged + D-cycloserine 10 mg/kg. During the first stage (hidden platform), the aged rats were impaired ($F(3, 43) = 6.46$, $P < 0.01$) when compared to the young controls ($P < 0.05$, young vs. aged). At this stage, no drug treatments were given and there was no difference in the escape distance values of the different groups of aged rats ($P > 0.05$ vs. aged vehicle-treated). The second stage was conducted in a novel testing room after a break of 2 days (hidden platform). Again, aged rats were impaired ($F(3,43) = 6.8$, $P < 0.01$) when compared to the young controls ($P < 0.05$, young vs. aged). The drug treatments failed to alleviate the age-related impairment of performance as the single treatments did not improve the escape performance of the aged rats ($P > 0.05$ vs. aged vehicle-treated).

In experiment 5 (Fig. 2, Part B), three groups of 12 rats were used: aged + vehicle, aged + tetrahydroaminoacridine 3 mg/kg and D-cycloserine 10 mg/kg. During the first stage of training, the tetrahydroaminoacridine- and D-cycloserine-treated groups had shorter escape distance values to the hidden escape platform ($F(2,33) = 5.53$, $P < 0.05$; $P < 0.05$ vs. vehicle-treated aged rats). During the second stage conducted in a novel testing room, no drug injections were given (hidden platform). Those groups that had been treated with tetrahydroaminoacridine and D-cycloserine during the first stage did not perform any better than those previously treated with vehicle ($F(2,33) = 1.76$, $P > 0.05$).

4. Discussion

The present study showed that aged rats remained impaired for water maze navigation even though they had different non-spatial and spatial pre-training schedules. This may be further support for the concept that the age-related water maze deficit is, at least to some extent, due to impaired functioning of the septohippocampal system (Nuettner, 1991; Sirviö et al., 1992; Aigner, 1995). However, we did observe that non-spatial and spatial pre-training in the same or different environment blocked the improvement in water maze spatial navigation performance induced by tetrahydroaminoacridine and D-cycloserine.

Several studies have shown that hippocampal function may be compromised during ageing. Barnes (1994) has reviewed evidence indicating that during normal ageing there are regionally specific deficits in hippocampal synaptic transmission. For example, the number of synapses from the medial entorhinal cortex to the middle third of the granule cell dendritic tree is reduced by approximately one-third in aged rats (Geinisman et al., 1986) and this is paralleled by a reduction in the size of the presynaptic fibre potential at stimulus intensities above threshold (Barnes and McNaughton, 1980b). The aged brain appears to have a mechanism to compensate for this loss of synapses by making the synapses functionally more powerfully (Barnes and McNaughton, 1980b). The maintenance of synaptic plasticity, as assessed by long-term potentiation analysis, is also impaired in the dentate gyrus of aged rats (Barnes and McNaughton, 1980a). Furthermore, the rate of decay of hippocampal long-term potentiation in aged and young rats was inversely correlated with their learning rates in a spatial memory test (Squire, 1992).

We found that none of the pre-training conditions was able to block the impairment of spatial navigation in aged rats. After repeated spatial navigation training periods conducted in the same or different environments, aged rats remained impaired for learning the spatial navigation task, and were still deficient in their ability to relearn the location of the escape platform. Furthermore, aged rats were as accurate as young rats for non-spatial navigation (visible platform), but were still grossly impaired for learning the location of the hidden platform when they were trained after non-spatial pre-training in a familiar testing environment. These results indicate that learning the basic skills of water maze performance during the different pre-training conditions did not help the aged rats to learn the spatial relationships between the hidden escape plat-

form and the cues in the testing environment. Interestingly, previous behavioural studies have found that lesions of the septohippocampal system can also impair spatial navigation accuracy irrespective of the pre-training protocol (Bannerman et al., 1995; Riekkinen et al., 1997). Therefore, behavioural and electrophysiological studies suggest that hippocampal dysfunction contributes to the impairment of spatial navigation in aged rats.

Our results also revealed that all the pre-training conditions blocked the beneficial effects of tetrahydroaminoacridine and D-cycloserine on spatial navigation accuracy in aged rats. The failure to detect any beneficial drug effects on spatial navigation after the different pre-training schemes is difficult to explain in terms of a floor effect, since the aged rats were still clearly impaired. Consistent with results of earlier studies (Miyagawa et al., 1998), the performance of individual aged rats varied a lot, which may have obscured some group differences. However, the risk of a type II error is minimal because the group averages practically overlapped among the aged animals (Fig. 2A, right plot). On the other hand, tetrahydroaminoacridine and D-cycloserine highly significantly improved performance when the rats were trained for the first time (Fig. 2, left plot). In addition, this finding is replicable (Aura et al., 1998). Furthermore, the age-related impairment was still present after pre-training. Therefore, it is likely that tetrahydroaminoacridine and D-cycloserine alleviate the spatial navigation defect in aged rats by modulating some processes required for spatial navigation other than spatial memory per se. It is possible that the drugs improved non-spatial procedural learning, sensorimotor processes necessary for the task or motivation. Therefore, if a drug (tetrahydroaminoacridine or D-cycloserine) acts to facilitate acquisition of non-spatial components of water maze learning and memory, it will not be able to further improve the navigation performance of those rats that have already learned these skills during the pre-training sessions.

In conclusion, we observed that pre-training blocked the beneficial effect of D-cycloserine and tetrahydroaminoacridine on spatial navigation in aged rats. This suggests that a cholinesterase inhibitor and a positive allosteric modulator of NMDA receptors do not alleviate the age-related deficit of spatial memory per se, but facilitate the acquisition of some skills important for spatial navigation. In addition, various pre-training schedules did not block spatial navigation deficit present in aged rats. Previous behavioural studies have shown that lesions restricted to the septohippocampal system produce spatial navigation deficits that are not blocked by pre-training (Bannerman et al., 1995; Riekkinen et al., 1997). Our results are consistent with previous evidence that the age-related impairment in water maze learning reflects a true spatial memory deficit in these animals.

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