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Effect of food deprivation on a delayed nonmatch-to-place T-maze task

2014년 2월

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Effect of food deprivation on a delayed nonmatch-to-place T-maze task

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A dissertation submitted to the Graduate Faculty of Seoul National University in partial fulfillment of the requirement for the Degree of Master of Science

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Abstract

Effect of food deprivation on a delayed nonmatch-to-place T-maze task

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Motivation can affect performance on difficult cognitive task, such as the delayed nonmatch-to-place T-maze task. The importance of food deprivation on maintaining high motivation for delayed nonmatch-to-place T-
maze task has been emphasized, but not many studies have investigated the optimal conditions for depriving rodents to maximize performance. Establishing appropriate conditions for food deprivation is necessary to maintain motivation required for the delayed nonmatch-to-place T-maze task. We applied different conditions of food deprivation (1-h food restriction vs. 1.5-g food restriction; single caging vs. group caging) and measured body weight and the number of correct choices that 8-week-old C57BL/6J mice made during the delayed nonmatch-to-place T-maze task. The 1.5-g food restriction group maintained 76.0 ± 0.6 % of their initial body weight, but the final body weight of the 1-h food restriction condition group was reduced to 62.2 ± 0.8 % of their initial body weight. These results propose that 1.5-g food restriction condition is effective condition for maintaining both body weight and motivation to complete the delayed nonmatch-to-place T-maze task.

*Key words:* food deprivation, motivation, cognitive ability, delayed nonmatch-to-place T-maze task

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Introduction

Motivation is known to arouse an organism to act toward a desired goal and elicits, controls, and sustains certain goal-directed behaviors. It can be considered a driving force that reinforces an action toward a desired goal. Motivation plays critical role in many behavior tasks, such as morris water maze, delayed nonmatch-to-place T-maze, spontaneous alternation, and reversal learning task (Andersen et al., 2010). Goal-directed behaviors are required to complete these tasks. Task confirming higher cognitive demand consolidated condition to motivate mice to complete the task.

The delayed nonmatch-to-place T-maze task can be used in a variety of ways to assess animals’ cognitive abilities. The natural tendency of mice in a delayed nonmatch-to-place T-maze task, however, is to alternate their choice of goal arm, which requires working memory. Alternation reflects the animal’s motivation to explore its environment and locate the presence of reward. If two trials are performed consequentially, mice tend to choose the arm not explored before, suggesting that they remember their choice on the first trial. This tendency of choosing the correct choice arm can be reinforced by performing the trial while the animal is deprived and rewarding it with a reward if it alternates appropriately between the 2 arms (Nicholls et al., 2008; Shoji et al., 2012).
Motivation plays a critical role in delayed nonmatch-to-place T-maze task performance. In Morris water maze task, mice are motivated to find a hidden platform to escape from water. Motivation of mice sustains at maximum level throughout the experiment due to threatening condition. Unlike Morris water maze, there is no threatening condition in delayed nonmatch-place T-maze task. Food deprivation is directly correlated with motivation level and is used to reinforce performance on tasks that require higher cognitive ability (Dorighello et al., 2013). Different laboratories have their own protocol to deprive mice to maintain a certain body weight. A 15 to 25 % decrease of initial body weight is an ideal percentage that keeps the animal motivated to run the task (Deacon, 2006; Deacon et al., 2006; Roberge et al., 2008). Food deprivation is widely used in rewarding tasks, but few studies have been done on food deprivation to control mouse body weight for optimal delayed nonmatch-to-place T-maze task performance.

To identify the best food deprivation condition for the delayed nonmatch-to-place T-maze task, we employed two paradigms; 8-week-old mice were given 1.5 g of food pellets per mouse per day or given access to food for 1 h per day. To determine if a dominant mouse would control the food, we employed two groups, single and group caging, to assess a possible relationship between social isolation (housing condition) and food deprivation. We found that 1-h food restriction was harsh; two mice in the single caging condition of the 1-h group died of starvation, and the final body weight for the
group caging of 1-h food restriction was reduced by 40%, which is close to starvation. Our findings suggest that the 1.5-g condition is more suitable to maintain motivation level required for the delayed nonmatch-to-place T-maze task performance.

Not only confirming optimal condition for the delayed nonmatch-to-place T-maze task, we conducted water based reversal Y-maze task to identify whether motivation of mice is kept stable during the task. Water based reversal Y-maze is used to provide evidence of a phenotype of perseveration, behavioral inflexibility, and working memory impairments in brain disorder such as obsessive-compulsive disorder and autistic spectrum disorder (Andersen et al., 2010). In this study, we show that mice are strongly motivated during initial training and reversal training of water based reversal Y-maze task to find a hidden platform to escape from water. Since it is demanding to maintain high motivation level in delayed nonmatch-to-place T-maze task, water based reversal Y-maze can be used to provide additional evidence onto the results obtained from delayed nonmatch-to-place T-maze.
Experimental Procedure

Animals

We obtained 8-week-old male C57BL/6J mice from Orient Co. (Gyeonggi, Korea). Animals were housed singly or in group cages and both were maintained on a 12-h light/dark cycle. All behavioral experiments were conducted during the light phases. Food and water were provided ad libitum prior to the experiments. All animal procedures were conducted in accordance with the guidelines of the Institutional Animal Care and Use committee of Seoul National University.

Housing condition

Two different housing conditions were used; single caging and group caging. A mouse was housed in a cage for the single caging group and four mice were housed in a cage for the group caging group. Mice were housed either single or group 1 week prior to the task and these housing conditions were maintained until the last day of the task.
Food deprivation condition

Two different food deprivation conditions were used; 1-h food restriction group and 1.5-g food restriction group. The 1-h food restriction group was allowed to consume food for 1 h per day, and the 1.5-g food restriction group was allowed to consume 1.5 g of food pellets per day per mouse (1.5 g was given for a single cage, and 6.0 g was given for a group cage). The amount of 1.5 g was based on the nutritional needs of an 8-week-old mouse. Each group was subdivided into two group, single and group caging. Food was provided immediately after the last task trial of delayed nonmatch-to-place T-maze. Food deprivation was maintained until the last day of the task to maximize the motivation to run the task.
Delayed nonmatch-to-place T-maze Task

Prior to delayed nonmatch-to-place T-maze task, mice were handled for 4 consecutive days for 3 minutes, habituated for 2 days for 10 min, and trained for 14 days. They were food deprived throughout the experiment. T-maze is a t-shaped maze that composed of left arm, right arm and starting arm. For the delayed nonmatch-to-place T-maze task, condensed milk (70ul, diluted with D.W in 1:1 ratio) was placed at the end of right and left arm of T-maze as a reward. Mice were placed in the starting arm of T-maze to perform a trial. Four trials were given each day for 14 days of training. One trial was composed of two runs, forced run and free run. All mice used in the delayed nonmatch-to-place T-maze task were housed in a holding rack for 30 minutes before the task to exclude increased anxious level affecting the result of task. At the beginning of the trial, food rewards were placed the end of each arm and only one door was open (either left or right). For the forced run, mice were placed in the starting arm and trained to enter the open arm and consume a food reward. Then mice were placed back to the starting arm and the free run was performed 20 sec after the forced run. For the free run, both arms were open. Mice had to remember where they entered for forced run and chose the other arm to obtain a reward. They were allowed to make an arm choice for 90 seconds. Mice entering the new arm were considered as ‘correct choice’ and entering the same arm or refusing to enter either arm were considered as ‘incorrect choice’. Each trial was performed 15 min apart. Mice
learned and formed working memory of new spatial information as the reward location randomly alternated between the 2 arms on every trial. Behavioral flexibility was required for choosing a correct choice (Nicholls et al., 2008; Shoji et al., 2012). Individual mouse body weight was recorded before training trials and food was provided right after the last trial. The number of correct choices was also recorded. Maze was cleaned in an order of diluted water, 70% ethanol solution, and diluted water between each trial while mice waited in a holding cage.
Figure 1. Delayed nonmatch-to-place T-maze task schematic. The reward is placed at the end of each arm. For the forced run, mice are placed in the starting arm of the T-maze and forced to enter open arm. After mice entered the open arm and received the reward, mice were placed back in the starting arm to perform the free run. Entering the arm not visited on the forced run was considered as a correct choice.
**Water based reversal Y-maze Task**

Water based Y-maze is composed of three arms in an angle of 120°; starting arm, left arm, and right arm. Maze is made of gray invisible acryl with dimension of cm height, cm width, cm length. For the task, nontoxic fragrant free white paint was diluted with water to make platform invisible. Water temperature was kept at 21±1°C. All mice used for water based reversal Y-maze task were housed in a holding rack for 30 minutes before task to exclude increased anxious level affecting the result of task. Prior to water based Y-maze task, mice were handled for 4 consecutive days for 3 minutes, habituated for 1 day. For habituation, platform was removed and mice were put in a Y maze for 60 seconds for 3 times. For training, platform was placed in one arm (either left or right) and mice were trained to find the arm with platform while both arms were accessible. Platform was placed 1 cm below water level to keep it invisible. Mice were allowed to make an arm choice for 20 seconds. Mice were removed 5 seconds after they reached the platform during training. If mice made an incorrect choice, they were trapped in incorrect arm for 20 seconds and returned back to their home cage. They were not lead to the correct arm after they made incorrect choice. Twenty trials were conducted in a day and the interval between trials was kept as 15 minutes. A day after training, test was conducted before reversal training. For the test, mice were tested to confirm whether they meet a success criterion of
making 4/5 correct choices and only the mice achieving this success criterion received reversal training. For the reversal training, platform was placed in the opposite arm and the mice were trained to find a new arm with a platform. Thirty trials were given for reversal training. Reversal training procedure was same as training procedure except that the platform was placed in the opposite arm. Reversal training was continued until mice reach success criterion which was 9/10 correct arm choice (Hoeffer et al., 2008; Trinh et al, 2012). Paint stain on inner maze wall was cleaned between each trial while mice were kept in a holding cage.
Figure 2. Water based Y-Maze task schematic. A platform was placed at the end of either arm. For the habituation, mice were placed in the Y-maze to explore the maze. For the training, mice were placed in the starting arm of the Y-maze and trained to find the arm with a platform. On a next day, platform placement was reversed and mice were trained to find a new platform placement. Entering the arm where platform exist was considered as a correct choice.
Results

Many behavior tasks are used to examine whether a mouse model has specific phenotypes. Each behavior task is designed to investigate factors that may underlie certain phenotypes. Delayed nonmatched-to-place task is used to investigate factors that may underlie working memory and behavior flexibility (Fig. 1). Social isolation (single caging/group caging) and food restriction (1-h food restriction or 1.5 g food per day) are two important factors affecting the motivation of mice to perform the delayed nonmatch-to-place T-maze task. In particular, food restriction is a critical variable for successful delayed nonmatch-to-place T-maze task performance because it increases motivation of animal required to run the task. Thus, two conditions of food deprivation were used and compared to maximize motivation; 1-h food restriction and 1.5-g food restriction. Mice were divided into four groups: single caging with 1-h food restriction (n = 4), group caging with 1-h food restriction (n = 4), Single caging with 1.5-g food restriction (n = 4), Group caging with 1.5-g food restriction (n = 33). The goal of both measures was to maintain body weight at approximately 75 - 80% of the initial body weight over time.
Food restriction for 1 h

We found that allowing mice to eat only for 1 h per day was excessively harsh, especially for mice housed singly. In single cages, two mice died due to starvation on the third day of handling, and the other two mice were near death. The average body weight of single-caged mice was reduced to $75.5 \pm 3.7\%$ of their initial average body weight after 3 days of food restriction. Food deprivation could not be continued with this condition. None of the mice in the group cages died, but their final body weights were reduced by nearly 40%. The final average body weight of group-caged mice was reduced to $62.2 \pm 0.7\%$ of their initial average body weight. Moreover, the body weight curve of the group caging group continued to decline (Fig. 3), but they did achieve a stable plateau in behavioral performance throughout the task. All the mice made correct choices during the last 7 days of training (Fig. 4).
Figure 3. Body weight of food restriction to 1 hour. Average body weight (%) of 1-h food restriction-conditioned mice from handling (4 days) to habituation (2 days) to training (14 days) for single caging (n=4) and group caging (n=4).
Figure 4. **Food restriction to 1 hour.** Average number of correct choices (mean ± s.e.m) in the delayed nonmatch-to-place T-maze task following 1-h food restriction for single (n = 4) and group caging (n = 4).
**Food restricted to 1.5 g**

None of the mice died from starvation in the 1.5-g food restriction condition. The final body weight of group caged mice was reduced to 76.0 ± 0.6 % of the initial value, and the singly caged group was reduced down to 69.1 ± 0.8 %. Both groups maintained their final lower body weights. In the single caging group, body weight reduced abruptly during habituation and handling, and their final body weight was reduced to nearly 70% of their initial body weight (Fig. 5). Similar to the 1-h food restriction conditioned group, the 1.5-g group reached a stable plateau in behavioral performance (Fig. 6). Compared to 1 hr food deprivation condition, 1.5-g food deprivation condition came out to be suitable to run delayed nonmatch-to-place T-maze task.
Figure 5. **Body weight of food restriction to 1.5 g.** (A) Average body weight (%) of 1.5-g food restriction-conditioned mice from handling (4 days) to habituation (2 days) to training (14 days) for single (n=4) and group caging (n=33).
Figure 6. Food restriction to 1.5 g. Average number of correct choices (mean \(\pm\) s.e.m) in the delayed nonmatch-to-place T-maze task following 1.5 g-food restriction for single (n = 4) and group caging (n = 33).
Water based reversal Y-maze task

Based on the previous results, we concluded that a group caging with food restriction of 1.5-g condition is an optimal condition to maximize motivation to run successful delayed nonmatch-to-place T-maze task. Despite the result that food restriction of 1.5-g condition is ideal approach to control the body weight of mice, maintaining 75-85 % of initial body weight for long period is challenging. Water based reversal Y-maze task is not a well known behavior task, but used to measure behavior flexibility and perseverative behaviors as delayed nonmatch-to-place T-maze is used to measure behavior flexibility (Fig. 2).

In water based reversal Y-maze task, mice are trained to find a hidden platform to escape from water which is a harsh condition. Falling into the water increased motivation of mice to run the task to go escape from water. Mice were trained to find an arm with an escape platform in Y-maze. After 24 hours, the escape platform was switched to opposite arm and mice were trained to find the new arm. 20 trials were run for the training and 30 trials were run for the reversal training. All of mice achieved a success criterion of making 4/5 correct choices for the test. The number of trials to success criterion of making 9/10 correct arm choice was achieved at trial 30 by all mice (Fig. 7).
Figure 7. Water based reversal Y-Maze task. Percent correct arm choice per trial block number (five trials per trial block) during training, testing and reversal training phase of water based Y-maze task (mean ± s.e.m). n=6
Discussion

Single vs. group caging (relationship between social isolation and food deprivation)

Mice were singly housed to exclude the possibility that dominant mice might monopolize the food supply. Lower final body weight was observed in the single caging groups for both food restriction conditions. This could be due to several reasons. Previous studies on the influence of isolation on behavioral characteristics showed that social isolation induces depression, which can lead to decreased food intake (Fisher et al., 2012; Kwak et al., 2009). Exposure to stressful experiences during early developmental stage can alter cognition, motivation, and emotion of behavioral responses (Ma et al., 2011; Novick et al., 2013; Pechtel et al., 2011). Habituation to novel stimuli is impaired in subjects exposed to social isolation, who show increased excitability response to stressful events. Social deprivation increases the possibility of altered neuronal function and could facilitate the development of neuropsychiatric disorders in adulthood (Kinsey et al., 2007; Ros-Simo et al., 2012). According to previous studies, social interaction is necessary for appropriate behavioral development (Ma et al., 2011; Novick et al., 2013), which supports the hypothesis that group caging is more suitable for mice.
subjected to the delayed nonamatch-to-place T-maze task.

**Condition of maximum motivation**

Even though both types of restriction led to a stable plateau in behavioral performance on the delayed nonmatch-to-place T-maze task, the use of 1-h food restriction should be considered carefully. Compare to the 1.5-g food restriction group, which maintained 75% of the initial body weight of the mice, the 1-h food restriction group was reduced to near 60% of their initial body weight regardless of caging conditions (Fig. 3A, 4A). Although 1-h food restriction succeeded in maintaining high motivation, it failed to keep the mice healthy.

Food deprivation is essential to increase and maintain motivation for mice to perform the delayed nonmatch-to-place T-maze task, but our findings suggest that severe food deprivation can lead to depression and eventually death. We found that the 1-h food restriction condition turned out to be too harsh for mice to maintain healthy condition and that the 1.5-g food restriction condition was more suitable for the delayed nonmatch-to-place T-maze task.

Our goal of this study was to find food deprivation condition which maintains animals’ motivation and learning ability. In the actual study, body weight of single-caging 1-h food restriction and group-caging 1-h food restriction group continuously decreased even to death for starvation. In contrast to 1-h food restriction group, none of mice died from 1.5-g food
restriction group. In our experiment condition final body weight of 1.5-g food deprivation condition maintained 76.0 ± 0.6 % of their initial body weight (Fig. 4A). Keeping animal’s body weight around 75 % is known to be effective condition to maintain learning and memory abilities in the delayed nonmatch-to-place T-maze task (Roberge et al., 2008). Group caged 1.5-g food restriction group successfully performed delayed nonmatch-to-place T-maze task and their motivation was highly maintained throughout the experiment. In our experimental condition, 1.5-g food deprivation condition was found to be suitable to run delayed nonmatch-to-place T-maze task.

From this study, we confirmed the conditions to maintain maximum motivation for mice in delayed nonmatch-to-place T-maze and water based reversal Y-maze task. The most effective food deprivation condition was found for delayed nonmatch-to-place T-maze task. There is no way of measuring motivation but at least we confirmed goal-directed behavior of mice during the delayed nonmatch-to-place T-maze and water based reversal Y-maze task by showing a stable plateau in behavior performance on both tasks.

Successful completion of the delayed nonmatch to place T-maze task requires mice to explore their environment and obtain food, and motivation is known to play a critical role in task completion. The relationship between motivation and fear of the maze is considered important for running the delayed nonmatch-to-place T-maze task. Handling and habituation are useful
for overcoming excessive fear and increasing motivation (Wenk et al., 2001; Zhao et al., 2009). The influence of food deprivation on task performance is less studied. Few investigations have assessed the impact of food deprivation on motivation. Our data suggest that giving 1.5 g of food per 8-week-old mouse in group caging conditions is better for maintaining final body weight to maintain high motivation on the delayed nonmatch-to-place T-maze task. Future studies are needed to identify conditions for other specific behavior tasks that require reward seeking for task performance.
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국문 초록

먹이 제한은 Delayed nonmatch-to-place T-maze에 미치는 영향에 대한 연구

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먹이를 제한하는 것은 높은 인지 능력이 필요한 delayed nonmatch-to-place T-maze task와 같은 행동과학적 과제를 수행하는데 영향을 미친다. Delayed nonmatch-to-place T-maze task에서 먹이 제한을 통한 동기부여를 높게 유지하는 것은 중요하게 여겨져 왔지만 그 중요성에 비해 먹이 제한의 조건을 결정하는 연구
에는 진행된 바가 많지 않다. Delayed nonmatch-to-place T-maze task에서 동기부여를 높게 유지하기 위해선 연구실마다 알맞은 조건을 결정하는 것이 매우 중요하다. 이번 연구는 8 주령 C57BL/6 생쥐를 대상으로 다른 두 가지 먹이제한 조건을 (한 시간 동안 먹이를 먹을 수 있도록 하는 조건과 한 마리당 매일 1.5 g의 먹이만 제공하는 조건) 이용하여 이 두가지 다른 종류의 먹이 제한이 생쥐가 delayed nonmatch-to-place T-maze task를 수행하는 동안 봄무게와 number of correct choices에 어떠한 영향을 미치는지 살펴 보았다. 1.5 g의 먹이를 제공한 그룹은 봄무게가 원래 봄무게의 76 ± 0.6 %까지 감소한 반면 먹이를 매일한 시간만 제공한 그룹은 봄무게가 62.2 ± 0.8 %까지 감소하는 것을 확인할 수 있었다. 이 결과는 delayed nonmatch-to-place T-maze task에서 적정 봄무게와 동기 부여를 유지하는데 매일 1.5 g의 제한된 양의 먹이를 제공하는 것이 효율적임을 보여준다.

핵심어: 먹이제한, 동기부여, 인지 과제, delayed nonmatch-to-place T-maze task,

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