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The development of a cognitive rehabilitation task for mice

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Abstract

Obesity, neurodegenerative diseases, and injury can all lead to cognitive deficits, which can be improved clinically with the implementation of cognitive rehabilitation. Due to a lack of effective cognitive rehabilitation tools in mice, we re-designed a cognitive task utilized to detect problem-solving deficits, to develop a cognitive rehabilitation paradigm for mice. In this study, we developed a modified version of the Puzzle Box task by exposing B6 mice to a variety of obstacles and assessing the escape latencies. We then combined obstacles in order to create a “complex obstacle” for the problem-solving task. We determined that our task was reproducible in different cohorts of mice. Furthermore, with repetition the mice display an improvement in the performance, evident by a shorter escape latency and the ability to maintain this improvement in performance, indicative of long-term memory. Given that this approach is new, we validated whether this task could successfully detect deficits in a mouse model of cognitive impairment, the high-fat diet mouse. We demonstrate that high-fat diet mice have longer escape latencies when exposed to the complex obstacle compared to standard diet control mice. Taken together, these data suggest that the Puzzle Box is a valid task for cognitive rehabilitation in mice.

Keywords

Behavioral task; cognitive impairment; light-dark box; memory; problem-solving; Puzzle Box

1. Introduction

Cognitive rehabilitation is a therapeutic process designed to improve cognitive function in areas related to attention, memory, comprehension, problem-solving and awareness

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Credit Author Statement

Alexus Williams contributed to the conceptualization, data curation, formal analysis, methodology, writing original draft, and review & editing. Taylor Lowry contributed to data curation, data analysis, writing original draft, and review & editing. Catrina Sims-Robinson contributed to the conceptualization, formal analysis, funding acquisition, methodology, project administration, resources, software, supervision, writing original draft and review & editing.

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(Barman, Chatterjee, and Bhide, 2016; Cicerone, Dahlberg, Kalmar, Langenbahn, Malec, Bergquist, Felicetti, Giacino, Harley, Harrington, Herzog, Kneipp, Laatsch, and Morse, 2000). Cognitive rehabilitation is divided into two components: restorative and compensatory. (Barman et al., 2016; Cicerone et al., 2000). The restorative approach reinforces, strengthens, and reestablishes previously learned patterns. On the other hand, the compensatory approach enables adaptation to the deficit. For example, stroke survivors experiencing a neurological disorder characterized by the inability to explore or respond to external stimuli contralateral to the lesion, known as spatial neglect, undergo cognitive rehabilitation to enhance visual perception to compensate for the spatial deficits (Barrett and Muzaffar, 2014). Cognitive rehabilitation improves cognitive function in older adults (>65 years and older) with cognitive impairment (Willis, Tennstedt, Marsiske, Ball, Elias, Koepke, Morris, Rebok, Unverzagt, Stoddard, Wright, and Group, 2006). Cognitive rehabilitation also improves cognition in disorders such as schizophrenia (Fiszdon, Whelahan, Bryson, Wexler, and Bell, 2005; Twamley, Vella, Burton, Becker, Bell, and Jeste, 2012; Wexler and Bell, 2005; Wykes, Huddy, Cellard, McGurk, and Czobor, 2011), head injuries (Cicerone, Dahlberg, Malec, Langenbahn, Felicetti, Kneipp, Ellmo, Kalmar, Giacino, Harley, Laatsch, Morse, and Catanese, 2005; Cicerone, Langenbahn, Braden, Malec, Kalmar, Fraas, Felicetti, Laatsch, Harley, Bergquist, Azulay, Cantor, and Ashman, 2011), stroke (Lincoln, Gladman, Berman, Noad, and Challen, 2000; Rohling, Faust, Beverly, and Demakis, 2009), and substance abuse (Vocci, 2008). Furthermore, preliminary results suggests that cognitive rehabilitation also improves cognitive deficits associated with Alzheimer's disease and Parkinson's disease (Choi and Twamley, 2013; Sinforiani, Banchieri, Zucchella, Pacchetti, and Sandrini, 2004).

Combining cognitive rehabilitation with a motor task may be useful for elderly to prevent falls, in stroke survivors, and in individuals with traumatic brain injury (Pellecchia, 2005). Tasks that require more cognitive effort are predicted to be more effective for motor learning (Hochstenbach, Mulder, van Limbeek, Donders, and Schoonderwaldt, 1998). Many of the current cognitive tasks for mice are excellent at assessing cognitive function but may not be suitable for cognitive rehabilitation in mice with motor impairments. For example, common cognitive tasks such as the Morris Water Maze and radial arm maze, which assess learning and memory deficits, require normal motor function. Hence, there is a need to develop a cognitive task that can be achieved even with limited motor function.

The Puzzle Box was previously designed as a problem-solving task (Galsworthy, Paya-Cano, Liu, Monleon, Gregoryan, Fernandes, Schalkwyk, and Plomin, 2005). The Puzzle Box has demonstrated consistency and effective for detecting cognitive deficits (Ben Abdallah, Fuss, Trusel, Galsworthy, Bobsin, Colacicco, Deacon, Riva, Kellendonk, Sprengel, Lipp, and Gass, 2011; Galsworthy et al., 2005; Van der Jeugd, Vermaercke, Halliday, Staufienbiel, and Gotz, 2016). The purpose of this study was to modify the Puzzle Box to develop a reliable and valid cognitive rehabilitative task for animals. The development of a cognitive rehabilitation task in mice can be useful to study the benefits of cognitive rehabilitation in preclinical models of stroke, Alzheimer's and Parkinson's disease. A good cognitive rehabilitation task must reveal an enhancement in performance with repetition (Barman et al., 2016). Furthermore, an effective cognitive rehabilitation task will lead to retention of performance from day to day (Cicerone et al., 2000). Thus, in this study

we characterize the development of a cognitive rehabilitation task for mice by modifying the Puzzle Box paradigm. We also validated the ability of this modified Puzzle Box paradigm to detect cognitive impairment in a mouse model of cognitive impairment, the high-fat diet (HFD) mouse.

2. Materials and Methods

2.1 Puzzle Box design

The Puzzle Box is a two-compartment arena consisting of an open field (12×10 inches) and a covered/enclosed compartment (dark box) connected via a 1.5-inch escape door (Fig. 1A). The arena was constructed using three 18×10 inches, three 10×10 inches, and one 6×10 inches acrylic sheets. The dark box compartment was painted black (Rust-Oleum Professional). The acrylic sheets were glued together with 2-part epoxy (Loctite plastic epoxy) and all spaces and cracks were sealed with sealant (Lexel). Five different obstacles were placed in the open door zone (Fig. 1A; red box, 4.25×4.25 inches) used to obstruct the escape door (Fig. 1B): 1) nestlet, which is used by the mice as bedding in their home cages, was placed behind the escape door (Fig. 1C); 2) enviro-dri, which was placed in front of the escape door requiring the mouse to burrow through or remove the enviro-dri (Fig. 1D); 3) LEGO bridge, which was placed in front of the escape door requiring the mouse to either go over or under to enter the dark box (Fig. 1E); 4) LEGO stairs, which required the mouse to walk up and then down the stairs to enter the dark box (Fig. 1F); and 5) the tunnel is a T shaped tunnel giving the mouse three ways to enter the dark box (Fig. 1G).

2.2 Animals

Male and female C57BL6 mice (Jackson Laboratory, Bar Harbor, Maine) 6–24 months of age fed a regular chow diet from Teklad were used for these studies. This age range was used to establish baseline behavior in normal mice at ages typically used in preclinical models with cognitive impairment. Mice were housed in a pathogen-free environment. All protocols were approved by the Medical University of South Carolina Institutional Animal Care and Use Committee, and are in compliance with the university guidelines, state and federal regulations, and the standard of the “Guide for the Care and Use of Laboratory Animals”. The animal welfare assurance number on file with the NIH Office of Laboratory Animal Welfare (OLAW) is A3428–01. The Medical University of South Carolina is accredited by the Association for the Assessment and Accreditation of Laboratory Animal Care International (AAALAC, Intl.).

2.3 Development of problem-solving task

The problem-solving task was performed in the Puzzle Box as described above. A video camera (Besteker HD) was mounted above the open field and Panlab Harvard Apparatus’s SMART video tracking software (Barcelona, Spain) is used to record the movements of the mouse and the escape latency from the open field to the dark box. The mice were allowed to explore the empty Puzzle Box until they escaped to the dark box or for 300 seconds. Following three trials with the open door, the escape latency with the nestlet, enviro-dri, LEGO bridge, LEGO stairs, and tunnel trials were recorded. Three different complex obstacles were designed by combining 2–3 of the aforementioned obstacles: complex (1)

LEGO stairs and nestlet; complex (2) LEGO bridge, enviro-dri, and nestlet; and complex (3) the tunnel, enviro-dri and nestlet. The mice were subjected to three trials for each obstacle. The arena, LEGO and tunnel obstacles were thoroughly cleaned with ethanol between each trial and mouse. Furthermore, fresh enviro-dri and nestlet were used for each trial and mouse.

2.4 Validation in a mouse model of cognitive impairment

To generate a mouse model of cognitive impairment, B6 mice purchased from Jackson Laboratory (Bar Harbor, Maine) were placed on either the standard diet (STD) consisting of 10% kcal from fat (Research Diets Inc.; #D12450B, New Brunswick, NJ) or a HFD with 54% kcal from fat (Research Diets Inc.; D05090701) ad libitum at 4 weeks of age per our previously published protocol (Sims-Robinson, Bakeman, Bruno, Jackson, Glasser, Murphy, and Feldman, 2016; Watson, Stone, Williams, Williams, and Sims-Robinson, 2020a). After 28 weeks of diet, both groups were subjected to the Puzzle Box and performed 3 trials each of open door, nestlet, enviro-dri and tunnel. In addition, the mice were also subjected to 3 trials of the complex obstacle 3. Recording and tracking of the mice was done according to the protocol above.

2.5 Statistical Analysis

Data analyses were performed using Prism v6 (GraphPad Software, Inc.). All sample sizes represent the number of animals. All data were analyzed using either a one-way ANOVA with Tukey's Multiple Comparison Test (Evidence of learning for problem-solving the complex obstacle and long-term memory retention for problem-solving the complex obstacle) or a mixed-effects repeated measures analysis with Bonferroni's multiple comparisons test (Validation of the Puzzle Box: Problem-solving deficits in high-fat diet mice). All analyses significance was determined using an alpha-level of 0.05.

3. Results

3.1 Latency of individual obstacles

The escape latency of the third trial was evaluated, to establish the latency for each individual obstacle (Fig. 1H; n=9). The shortest escape latency occurs with the open door (18.9 ± 12.8 seconds) and the tunnel (21.8 ± 13.8 seconds). The escape latency is approximately 4–5 times longer with the nestlet (87.3 ± 33.5 seconds), enviro-dri (73.1 ± 45.1 seconds), LEGO bridge (69.5 ± 24.9 seconds) compared with the open door. The longest escape latency occurs with LEGO stairs (133.3 ± 41.5 seconds).

3.2 Reproducibility of the Puzzle Box task

To investigate the reproducibility of the problem-solving task, the escape latency for 3 different cohorts of mice following the third trial were evaluated (Fig. 1I; n=9). No significant differences were found in the escape latencies between cohorts 1 (18.9 ± 12.8 seconds), 2 (60.0 ± 18.2 seconds), and 3 (22.2 ± 9.3 seconds) with the open door. Similarly, there were no significant differences in the escape latencies for cohorts 1 (87.3 ± 33.5 seconds), 2 (149.8 ± 31.6 seconds) and 3 (155.2 ± 26.6 seconds) with the nestlet. The escape

latency for the enviro-dri was also similar among cohorts 1 (93.1 ± 45 seconds), 2 (42.5 ± 14.2 seconds), and 3 (64.9 ± 18.2 seconds).

3.3 Correlation of escape latency with age

To investigate the correlation between escape latency and age, simple linear regression analysis was performed (Fig. 1J). There was no correlation between escape latency and age with the open door ($F = 0.04$; $P = 0.836$) and enviro-dri ($F = 3.94$; $P = 0.058$) obstacles. On the other hand, a significant correlation between escape latency and age was observed with the nestlet ($F = 5.03$; $P = 0.034$) obstacle.

3.4 Development of the cognitive rehabilitation task

3.4.1 Evidence of learning with the problem-solving task—To develop a problem-solving task, the escape latency for 3 trials in a subset of mice (cohort 2; $n=9$), were assessed using multiple obstacles combined to create 3 different complex obstacles. For complex 1, the escape latency decreased by 70% from trial 1 (301.0 ± 85.61 seconds) to trial 2 (100.5 ± 30.03 seconds) and decreased 60% from trial 1 to trial 3 (130.0 ± 45.5 seconds) (Fig. 2A). For complex 2 (Fig. 2B), there were no significant differences among trial 1 (44.4 ± 10.3 seconds), trial 2 (41.6 ± 10.0 seconds), and trial 3 (35.2 ± 7.4 seconds). Finally, complex 3 consisting of the tunnel, enviro-dri and nestlet resulted in the most significant improvement in subsequent trials (Fig. 2C), which led us to select complex 3 for subsequent analysis. There was a 90% decrease from trial 1 (1142.1 ± 159.6 seconds) to trial 2 (156.5 ± 33.2 seconds) and from trial 2 to trial 3 (75.1 ± 16.2 seconds).

3.4.2 Evidence of retention with the problem-solving task—To assess retention for performance using complex 3, trials were performed using cohort 2 ($n=9$), 12 and 26 days later. The data reveals no significant differences at day 0 (75.1 ± 16.2 seconds), 12 (82.2 ± 11.6 seconds), and 26 (44.9 ± 13.2 seconds) (Fig. 2D).

3.5 Validation of problem-solving task using HFD mice

To validate that the complex 3 obstacle detects cognitive deficits, the escape latencies were assessed in STD ($n=4$) and HFD mice ($n=11$), a model of cognitive impairment, after three trials. A mixed-effects repeated measures analysis revealed a significant effect of obstacle on escape latency ($F = 17.8$; $P < 0.0001$). Analysis also revealed interaction effect between diet and obstacle on escape latency ($F = 5.4$; $P = 0.0010$). There were no significant differences in the escape latencies between STD versus HFD mice, for the open door (20.9 ± 6.5 versus 9.1 ± 1.4), nestlet (64.7 ± 25.4 versus 56.2 ± 21.8), enviro-dri (31.0 ± 8.0 versus 20.4 ± 3.3), and tunnel (19.7 ± 2.8 versus 12.6 ± 1.6). The escape latency in the HFD (201.6 ± 21.7) mice was increased by 115% compared with the STD (93.7 ± 23.6) mice when completing complex 3. There was a significant interaction with obstacles (individual and complex 3; $F = 15.3$); however, there was no significant interaction with diet (STD and HFD; $F = 0.5$; Fig. 3A). To evaluate the potential impact of HFD on mobility, total distance for mice was assessed in STD and HFD mice. There were no significant differences in total distance between STD versus HFD mice for open door (191.5 ± 117.0 versus 30.9 ± 4.1), nestlet (207.7 ± 95.4 versus 169.6 ± 53.9), enviro-dri (49.0 ± 14.4 versus 52.8 ± 11.9), tunnel (34.9 ± 10.4 versus 30.5 ± 5.6) and complex 3 (99.2 ± 52.6 versus 218.2 ± 36.7 ; Fig. 3B). To evaluate

potential differences in exploratory behavior, we assessed the time in the open door zone, which corresponds to time exploring/ interacting with the obstacles. There were no significant differences between STD versus HFD mice the time spent interacting with, open door (6.2 ± 1.3 versus 4.8 ± 1.3), nestlet (10.2 ± 4.2 versus 17.5 ± 4.6), enviro-dri (15.9 ± 3.8 versus 13.1 ± 2.2), tunnel (12.6 ± 3.3 versus 7.1 ± 1.6) and complex 3 (65.8 ± 45.6 versus 34.4 ± 6.8 ; Fig. 3C).

4. Discussion

Cognitive rehabilitation has been effective for improving attention, memory, and executive function in patients with traumatic brain injury, stroke (Arciniegas, Held, and Wagner, 2002; Barman et al., 2016; Cicerone et al., 2000; Fiszdon et al., 2005). Currently, there are no established cognitive rehabilitation paradigms for preclinical models. We provide for the first-time evidence for the use of the Puzzle Box as a cognitive rehabilitation task. Similar to the initial Puzzle Box design described by Ben Abdallah et al (Ben Abdallah et al., 2011), our arena was made of Plexiglas with an open field and a dark box connected by an escape door. In our study, we used objects to obstruct the door that closely resembled objects used in previous studies (Ben Abdallah et al., 2011; O'Connor, Burton, Leamey, and Sawatari, 2014; Van der Jeugd et al., 2016). On average the escape latency in our study is comparable to those observed in other Puzzle Box studies (Ben Abdallah et al., 2011; O'Connor et al., 2014). Furthermore, similar escape latencies among three different cohorts of mice for the open door, nestlet, and enviro-dri suggests that the escape latencies are consistent among three cohorts of mice.

In order for the Puzzle Box to be a viable cognitive rehabilitation task, there must be evidence of improvement with repetition, indicative of learning (O'Connor et al., 2014) and the ability to retain this improvement long-term. We demonstrated that the escape latency decreases between consecutive trials. This suggests that the animals learn, evident by the enhancement in performance with repetition when completing the problem-solving task. Furthermore, the mice retained this enhancement of performance 12 and 26 days after the initial trial. Overall, this data suggests that this modified version of the Puzzle Box may be a useful paradigm for cognitive rehabilitation in mice.

Finally, in order to validate that this modified version of the Puzzle Box is capable of detecting cognitive deficits, we performed the task in a mouse model of cognitive impairment, the HFD mouse model. We previously demonstrated that cognitive impairment is evident in HFD mice by 28 weeks of age using both novel object recognition test and Morris Water Maze (Sims-Robinson et al., 2016; Watson, Stone, Williams, Williams, and Sims-Robinson, 2020b). While there appears to be no differences in the escape latencies between STD and HFD mice with the open door, HFD mice demonstrate a significant increase in escape latency with the complex obstacle. This data suggests that HFD mice have deficits in problem-solving. Previous tasks such as the novel object recognition task and the Morris water maze detect deficits in recognition and working memory, respectively. On the other hand, the Puzzle Box task detects problem-solving deficits (Galsworthy, Paya-Cano, Monleon, and Plomin, 2002). The advantage of using the Puzzle Box is that it can be potentially used for rehabilitation. Interestingly, a previous study revealed that consumption

of “good fats”, omega-3-polyunsaturated fatty acids-enriched, formula can improve problem-solving abilities in 9 month old babies (Drover, Hoffman, Castaneda, Morale, and Birch, 2009). Our previous studies demonstrates that HFD mice spend similar amounts of time exploring during object recognition tasks (Sims-Robinson et al., 2016; Watson et al., 2020b). Our current data reveals that the distance traveled by the STD and HFD mice are comparable, suggesting that diet does not impact mobility. Furthermore, STD and HFD mice spend similar amounts of time interacting with obstacles and in the open field, which indicates that diet does not affect the motivation to explore. Thus, in addition to memory deficits previously reported (Sims-Robinson et al., 2016; Watson et al., 2020b), our data suggests that HFD also contributes to impairments with problem-solving.

In summary, we have demonstrated that the Puzzle Box can be modified for cognitive rehabilitation training. Our data reveals that the Puzzle Box task is reproducible among various cohorts of mice. Furthermore, we demonstrate that mice display an enhancement in performance evident by the decrease in escape latency with repetition. The enhancement in performance is retained for several days suggesting that the tasks augments long-term memory. We also observed problem-solving deficits in a mouse model of cognitive impairment, the HFD mouse. We conclude that the Puzzle Box is a useful task for assessing cognitive impairment and can be used as a cognitive rehabilitation task in mice.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

HFD	high fat diet
STD	standard diet
ANOVA	analysis of variance
LEGO Brdg	LEGO Bridge

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Highlights

- The Puzzle Box task detects problem solving deficits in a mouse model of cognitive impairment.
- The Puzzle Box may be a useful paradigm for cognitive rehabilitation in mice.
- High-fat diet contributes to problem solving deficits.

Figure 1. Puzzle box design, escape latency for individual obstacles and reproducibility of the Puzzle Box.

(A) The top view of the puzzle box arena. The puzzle box consists of an open field (*) connected by an (B) open door (black arrow) to a dark box (). The open door zone (red box) is obstructed with either (C) the nestlet, (D) enviro-dri, (E) LEGO bridge and (F) LEGO stairs and a (G) tunnel. (H) Escape latency in seconds (sec) with open door, nestlet, enviro-dri, LEGO Bridge (LEGO Brdg), LEGO stairs, and tunnel. (I) Reproducibility of the escape latency in sec for the open door, nestlet, and enviro-dri for 3 different cohorts of mice. White, grey and black bars represent cohort 1, 2, and 3, respectively. (J) Correlation of escape latencies (sec) and age (months) with open door (open circles and solid black line), nestlet (black squares and dashed line) and enviro-dri (grey triangles and black dotted line) in cohort 1, 2, and 3. Data represents mean $\pm$ SEM; $n=9$ per group; * $P < 0.05$.

Figure 2. Evidence of learning for problem-solving the complex obstacle and long-term memory retention for problem-solving the complex obstacle.

Escape latency in seconds (sec) during 3 consecutive trials with (A) complex 1 obstacle, which consists of LEGO stairs and nestlet; (B) complex 2 obstacle, which consists of the LEGO bridge, enviro-dri and nestlet; (C) complex 3 obstacle, which consists of the tunnel, enviro-dri, and the nestlet; Repeated measures one-way ANOVA and Tukey's post-hoc used for multiple comparisons. (D) Escape latency in sec at 0, 12, and 26 days with complex 3 obstacle; Ordinary one-way ANOVA and Tukey's post-hoc used for multiple comparisons. Data represents mean $\pm$ SEM; $n=9$; * $P < 0.05$; *** $P < 0.001$; not significant (NS).

Figure 3. Validation of the Puzzle Box: Problem-solving deficits in high-fat diet mice.

The (A) escape latency (seconds; sec), (B) total distance (centimeters; cm), (C) time (sec) interacting within the open door zone indicative of exploratory behavior in both standard diet (STD; white bars) and high-fat diet (HFD; black bars) mice with individual obstacles and the complex 1 obstacle. Data represents mean $\pm$ SEM; $n=4$ (STD) and $n=11$ (HFD); * $P < 0.05$. A mixed-effects repeated measures analysis with Bonferroni's multiple comparisons test used for analysis.