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Research report

Evaluating aged mice in three touchscreen tests that differ in visual demands: Impaired cognitive function and impaired visual abilities

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ABSTRACT

Normal aging is often accompanied by reductions in cognitive abilities as well as impairments in visual acuity in men and mice. In preclinical models of human cognition this concomitance can make it difficult to assess the relative contributions of declined vision and cognitive ability on behavioral measures of cognition. To assess the influence of age on cognition and the impact of visual decline on the performance of touchscreen-based behavioral paradigms in mice, aged (11, 12, 16, 17, 19 and 21 months old) male C57BL/6J mice were compared to young (3 or 4 months old) male C57BL/6J mice using three tests of cognition as well as an assessment of visual acuity. Performance of a Visual Discrimination, Spatial Reversal, and an Automated Search Task were all affected by age. However, there was no relationship between reduced visual acuity and the observed performance impairments. Moreover, the visual acuity of animals with profound cognitive impairments overlapped with those showing normal cognitive ability. Despite the potential confound of impaired visual ability, it appears that the touchscreen approach might be particularly effective in studying age-related cognitive decline. This approach will increase the utility of aged mice as a model of decreased cognitive flexibility and may be particularly important for the study of age-related disorders such as Alzheimer's disease.

1. Introduction

Natural aging in humans often results in general health issues such as a decline in vision and decreased motor ability [1,2], and may also cause impairments in cognition ([3–5]; comprehensively reviewed in [6]). These rather minor changes are in sharp contrast to the drastic cognitive decline seen in patients with disorders such as Alzheimer's disease and other dementias [7–10]. As more people continue to live longer, tackling the issue of age-related cognitive decline is becoming an economic and societal necessity. Understanding early signs of age-related disorders, in comparison to normal age-related decline will help in developing treatments to mitigate the impact of these disorders [11]. While not fully understood, one explanation frequently put forward for normal age-related cognitive decline, as well as disease-related cognitive decline is a decrease in synaptic plasticity [12,13]. Abnormal synaptic plasticity occurs in many CNS disorders (reviewed in [14,15]), suggesting that certain cognitive deficits may be associated with a lack of neuronal adaptability. Accordingly, the study of aged animals might allow us to better understand normal human aging and potentially disorders of the central nervous system that are related to reduced synaptic plasticity.

A common problem in assessing cognitive ability in animals, but especially in aged animals, is the confounding factor of poor vision. Most pre-clinical tests of cognition require some visual input. A varied range of tests, including the Morris Water Maze (MWM, [16]), 8-arm radial maze, novel object recognition [17], the 5-choice serial reaction time task, non-spatial touchscreen-based tasks [18], and even contextual fear conditioning [19] have at least some visual element. However, the extent to which any given test might be dependent upon vision can vary depending on the strain of animal used as well as the specific experimental procedure. As such, dissociating the effects of age on vision versus cognition can be difficult. This is further exacerbated when attempting to compare effects across cognitive domains that may require multiple cognitive tests. Last but not least, different strains of rodents inherently display different visual capability [18,20]. For example, C57BL/6N mice (in comparison to the J-strain used here), have innate mutations to the Crb1rd8 gene that result in retinal degeneration [21]. Many transgenic mouse lines are on a C57BL/6N background, making sub-strain differences of visual abilities an issue warranting caution. If, then, compromised vision is expected in test subjects, control measures should be taken to understand the impact on cognitive measures. A cautionary tale that underscores the need for such control

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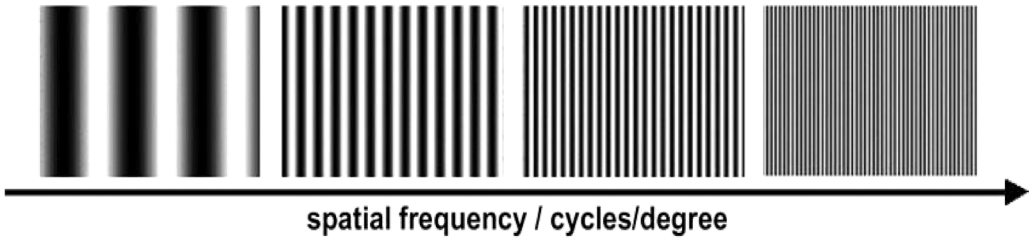

Fig. 1. Increasing levels of cycles per degree illustrating stimuli used in the optomotry test.

was published by Wong and Brown [22,23]. The experimenters used mice displaying an "age-related" cognitive decline which was rescued by treatment with glaucoma-medication in visuospatial learning tasks.

Over the last decade, the use of touch-screen-equipped operant boxes to model human cognition in the rodent has become increasingly popular. The touchscreen approach allows the assessment of numerous aspects of cognition (working memory, perception, cognitive flexibility, attention, etc.) in a highly similar manner which may also have greater relevance for a clinical setting [24]. To study the effects of aging on cognition while taking visual abilities into account, we elected to test male C57BL/6J mice of various ages (3–21 months old) in a series of touchscreen-based tests of learning and memory as well as assessing their visual acuity. We chose the touchscreen approach because it allowed us to examine several cognitive domains, likely dependent upon partially dissociable neurobiology [25–27], in a highly comparable manner (all tasks share the same basic response requirements). This approach increases the likelihood that any differences that are observed are related to changes in cognition as opposed to disparate task response requirements. This facilitates determining which tasks might be impaired because of changes in cognition, instead of visual decline.

To assess cognitive ability we selected a slowly acquired visual discrimination (VD), a spatial reversal task that allows several "reversals" in a single session, and a spatial search and memory task with elements of one trial learning. The first of these tasks, VD, requires that animals learn to distinguish which of two images displayed on the screen (e.g. spider vs plane, [28,29]) is associated with a food reward. This location-independent task takes many sessions to be acquired and requires the ability to direct attention towards a specific stimulus [30].

As indicated above, visual cues are inherently necessary for touchscreen-based tasks; however, changing the nature of the cues from complex images to illuminated locations on the screen might make the task not only more accessible to rodents but also especially attainable by those with declining vision. At least in the rat, location-based tasks seem to not be negatively affected by impaired visual ability [18]. For example, albino rats with limited visual ability were able to perform a touchscreen based spatial search task, despite struggling to complete a visual discrimination. Accordingly, we used two "spatial" tasks which should allow us to assess cognition even in animals with compromised vision; these are Spatial Reversal (SR [31]), as well as the Automated Search Task (AST, [32]).

Similar to VD, SR consists of two stimuli which are simultaneously displayed on the screen. In contrast to VD, however, these two stimuli are identical, white squares and rodents must learn that only one of the locations is associated with a reward. After a criterion (of 9 out of 10 correct trials) is reached, the rewarded side reverses. Perhaps counter-intuitively, SR has been found to be dependent upon the hippocampus under certain conditions [31,33] as well as on pre-frontal cortex-based acquisition of a stimulus-reward-relationship, rule learning, and direction of responses [34]. Additionally, behavioral flexibility [35], is expected to play a key role as this task requires 'fast' reversals. Since the task calls upon intact hippocampal function, it is well suited to assess any changes in the aging hippocampus [36] and their effects on behavior. Additionally, performance of this task was expected to rely less on fully intact visual abilities owing to the simpler nature of the stimuli, potentially making this a more suitable assay to test aging subjects.

The final task selected for use was the Automated Search Task ('AST', [32]). Initially conceived as a 'dry watermaze' [37], the AST requires the rodent to search for a specific, un-cued, rewarded location upon the screen. In AST the rodent is allowed to continue to search until the rewarded location is discovered, earning a pellet every trial. Once ten trials are successfully completed a "new" location is used. As such, every 10 trials results in a new acquisition curve giving rise to a distinct "search" and "recall" phase. The AST has previously been demonstrated to be dependent an intact hippocampus [32] in the rat, and search and recall phases appear to be pharmacologically dissociable [18,32]. Like the SR, we have previously demonstrated that rats with compromised visual ability can perform the AST (although this is the first time this task has been used in the mouse). The relative insensitivity to visual decline and the distinct "learning" and "memory" phase might make the AST an ideal tool to study age-related cognitive decline in animals with compromised visual ability.

To determine visual ability, and better gauge how this might affect task performance, visual acuity was also assessed using an automated procedure. Mice observed a moving sine wave stimuli (black-to-white-to-black bars, [38,39], Fig. 1) and their ability to perceive changes in spatial frequency (as assessed by head movements) was recorded. This was then used to determine a visual acuity threshold. By using this diverse array of tasks we hope to be able to disentangle cognitive deficits from visual impairments and determine the extent to which the aged mouse might be a viable model for human aging, and potentially other cognitive disorders related to impaired synaptic plasticity.

2. Material and methods

2.1. Subjects

All animals were group-housed in accordance with the European Ethics Committee (decree 86/609/CEE), the Animal Welfare Act (1 USC 2131) and the Guidelines for the Care and Use of Animals in Neuroscience and Behavioral Research (National Research Council 2003, August 14, 1986 and subsequent amendments and Royal Decree of May 29, 2013) for the protection of laboratory animals. The study protocol was approved by the local animal experimental ethical committee at Janssen Research & Development (Beerse, Belgium).

Male mice (C57BL/6J, N = 149; Charles River, France) of various ages (3–21 months old, see Table 1) were used for this work. The mice were purchased at the required ages. Animals were housed per age-group in individually ventilated cages (26 × 21 × 14 cm) with 2–4 animals per cage on a normal light/dark cycle (lights on from 6 a.m. to 6 p.m.). Cages had sawdust bedding and were equipped with several enrichment items including a plastic nest box and tissues for nesting. Animals were allowed free access to water but were on a food-restricted diet designed to maintain them at 85% of free-fed body weight. Animals were allowed at least one week to acclimatize to their new setting prior to the beginning of food restriction. Animals were gradually habituated to their feeding regimen over the course of a week. On day one of habituation to the feeding regimen, food was removed from cages in the morning, and mice were weighted in the afternoon. At the end of the day food (3 g per mouse, BioServ, Dustless Precision Pellets, 1 g) was placed in the animal's cage. From day 2 onwards, each mouse received 3 g of food per day (any uneaten food from the previous day was removed), while their weight was monitored daily. During habituation to