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Strain-dependent effects on acquisition and reversal of visual and spatial tasks in a rat touchscreen battery of cognition

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HIGHLIGHTS

- Albino animals were impaired on a visual discrimination task.
- No impairment was observed in the visually less demanding spatial task.
- MK-801 and scopolamine showed a distinct impairment profiles in spatial task.
- Selecting appropriate strain for use in touchscreen cognition tasks is important.

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ABSTRACT

Aim: The use of touch-screen equipped operant boxes is an increasingly popular method for modeling human cognition in the rodent. A concern of this approach is that the dependence upon vision may limit the strains of rats that can be tested in the apparatus. This is of particular concern because of the increased availability of genetically modified rats that are disproportionately on an albino background and may have compromised vision. Here we test pigmented and albino strains of rats on three touch-screen tasks of learning and memory that may require different levels of visual ability. In tests where albino animals have similar levels of performance as the pigmented rats we also tested common pharmacological models of cognitive impairment to determine the generalizability of these challenges across strains. By doing this work we hope to determine the robustness of common models of pharmacological impairment in albino rats.

Methods: We tested four strains of rats (albino: Wistar and Sprague Dawley, pigmented: Long Evans and Lister Hooded) in three touchscreen-based tasks of cognition with differing visual requirements: visual discrimination (VD) acquisition and reversal learning, and the more spatial and less visually demanding, automated spatial search task (AST). Furthermore, we tested the effects of the muscarinic antagonist scopolamine and the non-competitive NMDAR antagonist MK801 on performance of the four strains in AST. Finally, visual acuity was also assessed via a movement detection test.

Results: The rate of acquisition (% correct) in albino rats was significantly slower than in pigmented rats. Wistar rats were significantly slower to acquire the task, and showed differences in reversal learning when compared to the pigmented strains. Moreover, SD rats performed so badly during the acquisition phase of the VD that they failed to reach inclusion criteria (80% correct responses over 3-sessions) for the reversal phase. In contrast, no effect of strain was found in AST. Some of these differences can likely be attributed to differences in visual acuity as albino animals appeared to have reduced visual acuity when compared to the pigmented animals as previously reported in the literature. Pharmacological challenge with scopolamine or MK801 induced dissociable effects between compounds, but generally comparable impairments in all four strains.

Conclusions: Albino animals showed a clear impairment on tasks that are dependent upon intact vision, while no impairment was observed in the visually less demanding spatial task. Despite a published report to the contrary, these results demonstrate that albino strains may not be appropriate for use in touchscreen tasks that are dependent upon a visual discrimination. Furthermore, the spatial search task showed distinct impairment profiles as a result of treatment with either MK-801 or scopolamine. While an interaction did exist between strain and treatment, the dissociation between MK-801 and scopolamine was consistent across 3 of 4 strains. These results highlight the importance of selecting the appropriate strain for use in tasks of visual learning and memory and also demonstrate the potential robustness of pharmacological models of cognitive impairment across strains.

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1. Introduction

Over the last decade the use of touchscreen-based cognitive tasks for rodent battery has become increasingly popular as a means to model human cognition in a preclinical setting. The advantages and benefits of using the touchscreen approach for rodents in research and drug discovery programs are numerous and include protocol consistency, minimal experimenter contact, and a less stressful experimental environment with a positive reward-based reinforcement (see review by [7,28]). Possibly the largest benefit of a rodent touchscreen platform is that it may facilitate a translational approach from animal to human by allowing cognition in the rodent to be measured in a similar fashion as to how it is measured in human. Rodent touchscreens have already been used to study the effects of genetic [3,25], pharmacological and region specific manipulations on cognitive performance using rats and mice [19,24,26,31]. Despite this, surprisingly little is known about the influence of background strain on task performance or on common challenge models within a touchscreen setting, despite it being well established that strain can substantially influence performance on cognitive tasks [6,10,11,15,18,36].

Frequently reported strain differences may be due to disparities in cognitive abilities, but could also be due to other factors, for example, differences in sensory function. Effects driven by visual differences are of special concern for the touchscreen approach being that it relies on intact vision (this has never been formally evaluated). In fact, the touchscreen approach is frequently criticized for requiring rodents to use vision which is not thought to be their preferred modality for exploring their environment. This problem may be aggravated in albino strains that are well known to have poor vision relative to many pigmented rat strains [22,33,36]. However, a sole study in the rat has reported that an albino rat strain (Sprague Dawley) was able to acquire a simple visual discrimination with complex stimuli as efficiently as a pigmented strain (Lister-Hooded rat). On the contrary in mice albinism did influence acquisition rate (BALB/cJ or FVB/NJ mice vs C57BL/6J) [8,14].

Until recently, the effect of rat strain, as well as the potential confound of albinism in particular, has been of little importance as the vast majority of work using touchscreen equipped operant boxes with rats has been published using LH rats. However, LH rats are not the preferred strain of all labs and can be difficult to obtain in North America. Moreover, transgenic rats are becoming increasingly available and at present, overwhelmingly use a Sprague–Dawley background, potentially limiting the ability to use these models in touchscreen cognition tasks and likely other vision dependent behavioral test. Moreover, the ability to replicate work in multiple strains is necessary to confirm that the effects are not caused by strain specific genetic differences. Thus, a better understanding of the performance of rats of various backgrounds in touchscreen tasks will be necessary to further facilitate the adaptation of this technology. Overwhelming evidence suggests that the influence of visual acuity on performance in tests of cognitive function can account for a significant proportion of the variance in a variety of learning and memory tasks [5,27,34,36]. These studies suggest that some touchscreen tasks may unintentionally serve as better measures of visual acuity than cognitive ability. To specifically address this we have tested four common strains of rats, Wistar (WI), Sprague Dawley (SD), Lister-Hooded (LH), and Long Evans (LE) on their performance in three touchscreen tasks. These strains were selected because they are commonly used to study cognition and represent both pigmented and albino strains. The tasks were selected in part because of their likely different visual requirements.

While many touchscreen tasks require a visual discrimination (e.g., visual discrimination (VD) acquisition and reversal, and paired associate learning (PAL)), there are a number of tasks that are more dependent upon a spatial element (e.g., the automated spatial search task (AST) or trial-unique non-matching to location (TUNL)). It is possible that rats with impaired vision may still be able to perform these "spatial" tasks at a level commensurate with pigmented rats. If so, these "spatial" tasks may provide a powerful tool that could allow a reproducible method for studying spatial cognition in visually compromised animals across laboratories. Accordingly we employed tasks from each group, namely VD acquisition and reversal learning, and AST. In VD, animals are required to learn that a response at one of two images displayed on the screen will result in a reward, whereas the other will not. Accordingly, the rodent is encouraged to learn which image is associated with reinforcement to maximize rewards earned. Numerous studies using touchscreen VD have been published, investigating the effects of pharmacological or genetic manipulations, or lesions, on acquisition and reversal (for example, see [2,4,7,31,35]). Usually, touchscreen VD requires discrimination between complex visual stimuli displayed on a monitor. Subjects are required to learn that a response at one stimuli, regardless of location, results in a reward whereas a response at the other stimuli will not. Given the complex nature of the visual stimuli, a VD likely requires that the visual abilities of a rodent be fully intact. In contrast, the AST requires distinct 'search' strategies where the visual component is probably limited to navigation and the formation of a spatial "map" of the operant box. Here, rats need to find a "hidden" location that is not specifically marked on the illuminated touchscreen; a response at this hidden location will result in the delivery of a food reward. The hidden location remains in the same location for 10 trials before it is moved to another position on the screen. Responses at incorrect locations are not punished, but are recorded and are used as the primary measure of performance. Accordingly, the AST allows several learning curves to be generated for each day of testing. Based on the fact that the AST is devoid of complex stimuli, it is conceivable that animals with compromised vision but intact cognitive abilities may still perform normal on this test if the environment contains enough information for areas on the screen to be experienced as distinct.

Contrary to what has previously been reported in rat VD tasks, we anticipate that albino strains will not be able to effectively complete a visual discrimination, but will be able to perform the spatial search task. To date no data has been generated on the pharmacological sensitivity of the AST. Accordingly, if normal behavior is observed we will determine the sensitivity of the task to basic pharmacological manipulations as strain has also been reported to influence the response of rats to pharmacological challenges [10,23]. Of specific interest are the muscarinic antagonist scopolamine and the NMDA antagonist MK-801. Previous work has illustrated that scopolamine is not appropriate for use in a rat based VD or PAL when LH rats are used [29,31]. The search task is likely less dependent upon visual ability and therefore may be more amenable to use with pharmacological manipulations that can disrupt visual ability. Based on previous research, we expect that strain will interact with the pharmacological manipulations used here. However if albino animals perform the search task at a similar level to their pigmented counterparts then it would suggest that deficits induced by scopolamine are not primarily the result of visual impairments unlike what has previously been reported in PAL and VD.

2. Material and methods

2.1. Subjects

All animals were treated 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 Wistar (WI), Sprague Dawley (SD), Lister-Hooded (LH), and Long Evans (LE) rats were used for this work (n = 12 per strain). All