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Research report

Novel images and novel locations of familiar images as sensitive translational cognitive tests in humans

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HIGHLIGHTS

- Object recognition is a sensitive cognitive test across species.
- Novel location recognition is particularly challenging.
- Motivation to explore and lack of neophobia is important.

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ABSTRACT

Object recognition is a sensitive cognitive test to detect effects of genetic and environmental factors on cognition in rodents. There are various versions of object recognition that have been used since the original test was reported by Ennaceur and Delacour in 1988. There are nonhuman primate and human primate versions of object recognition as well, allowing cross-species comparisons. As no language is required for test performance, object recognition is a very valuable test for human research studies in distinct parts of the world, including areas where there might be less years of formal education. The main focus of this review is to illustrate how object recognition can be used to assess cognition in humans under normal physiological and neurological conditions.

1. Introduction

Although since about 1950 it was known that rodents explore novel objects over familiar objects, it took till 1988 before Ennaceur and Delacour reported the first object recognition test in this journal [1]. The test was developed initially for rats and is based on the preferential exploration of novel object and recognition of a familiar one. In a training trial (acquisition), one or two identical objects are presented. In the subsequent testing trial (choice trial), two different objects are presented, a familiar object that was present during the training and a novel object that was not. As pointed out by the authors of the original paper, this test is attractive as: (1) it is based on spontaneous behavior (innate exploratory drive) [2]; (2) it does not involve an aversive stimulus or food restriction; (3) is similar to cognitive tests used in nonhuman primates; (4) it can be used for cross-species comparative research; and (5) it can be used in humans (Baxter [10]). It should be noted that there are other tasks similar to the object recognition tests described in this review that have been used to study recognition processes. For example, the visual paired-comparison test used in nonhuman primates and humans involves selective visual attention to study recognition memory [3,4]. In addition, Aggleton et al. developed a test in which rodents were required to select an arm in a Y-maze containing unfamiliar stimuli [5]. The main focus of this review is to illustrate how object recognition can be used to assess cognition in humans under normal physiological and neurological conditions.

Although in animals the test is based on spontaneous behavior, the novelty can affect behavioral performance, including approach behavior, and elicit a stress response [5]. In addition to memory, attention and anxiety, including neophobia, can be analyzed as well.

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Even if the main interest is to assess learning and memory, these behaviors should be carefully analyzed as well as they could affect learning and memory.

A number of variations of this test have been used to assess object recognition [6]. There are also important species differences to consider. For example, there are species differences comparing the time spent exploring the arena even in the absence of objects and in time to approach objects [7]. For assessment of preferential exploration of novelty, the total time spent exploring all objects is important. Although 2 versus 1 s and 20 versus 10 s would translate in the same preference ratios, assessment of preferential exploration of novelty based on a relatively little amount of time spent exploring all objects would be less robust. A selection criterion based on the minimal amount of time spent exploring all objects during each trial reduces inter-individual variability [8].

As compared to other cognitive tests, tests involving preferential exploration of familiar objects in novel locations and of novel objects are often able to detect effects of genetic and environmental risk factors in rodents [9–20]. For example, object recognition in mice was impaired within weeks following ^{56}Fe irradiation of wild-type mice when there was a 24-h interval between training and testing but there were no significant effects on contextual fear conditioning 1 or 24 h following training [21]. In contrast, in human apoE4 mice, ^{56}Fe irradiation impaired spatial memory retention in the water maze but did not affect novel object recognition [22]. These data indicate that at least under certain conditions object recognition might detect detrimental effects of irradiation when other cognitive tests do not. This in turn might be due to the specific brain regions involved in performance on the object recognition test.

There are a number of versions of the spontaneous object recognition task, which may be used depending on the recognition memory process to be tested. One version involves two objects without an added spatial component. Another version involves three objects with an added spatial component by moving one familiar object to a novel location. In three objects version of the object recognition test, there are typical three training trials with three objects. In preliminary experiments, it is determined that when the animals are exposed to these three objects in a test trial, there is no a priori preference to any of the three objects. This is critical to assess to exclude any potential bias for a particular object not based on previous exposure or novelty but based on general preference. In the fourth trial, one familiar object is moved to a novel location. In the fifth trial, one familiar object is replaced by a novel object. The addition of a spatial component in the fourth trial challenges the animal to recall both the object and its location. Adding a spatial component to the object recognition test often allows detecting effects of genetic or environmental risk factors [5,23–25]. This in turn might be due to the distinct brain areas involved in detecting spatial changes [26–28], as clearly shown in the studies of Norman and Eacott [56] who showed double dissociation between the two tasks [29]. The different versions of object recognition tests in distinct species are described below and their differences are highlighted. In all versions, it is important for the researcher analyzing the data to be blinded to genotype and/or treatment of the animals.

2. Object recognition test involving two objects (Fig. 1)

The version with two objects is often used and based on the method described first by Ennaceur and Delacour [1,2,12,30]. As the amount an object is explored during training might affect performance during the subsequent test trial, it is advantageous to use identical objects during training. Along the same lines, there might be a bias for the object used as the novel one during the test trial. Therefore, counterbalancing the choice of novel and familiar objects would be preferred.

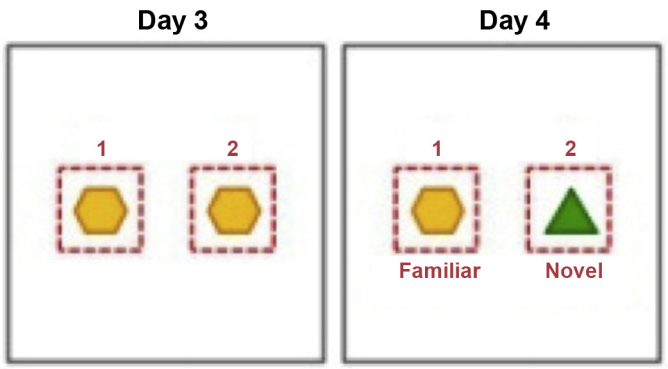

Fig. 1. Object recognition test with two objects in mice. Mice are habituated to an open field. During the training session, two objects are placed in the open field, and the mouse is allowed to explore them freely for 15 min. The following day (24 h later), the mice are re-introduced to the open field, containing a replica of the familiar object and a novel object, and allowed to explore for another 15 min.

Habituation and longer training trials both increase the preference ratio in the test trial [31]. This would be good if impairments in test performance are expected. However, if cognitive enhancement is being studied it would be advantageous to reduce habituation and the length of the training trials. Also, performance during the test trial is impaired when corticosterone is administered after the training trial only in animals that are not habituated to the open field prior to the training trial [32]. Thus, in case the effects of stress on performance during the test trial are being studied it is advantageous to minimize or even eliminate habituation.

In the object recognition test version with two objects, impaired memory during the test trial is seen in female mice expressing apolipoprotein E4, a risk factor for age-related cognitive decline and Alzheimer's disease [33,34], in either neurons or astrocytes [35]. In this version, mice are habituated to an open field. Typically, habituation is for 5 min on 3 subsequent days. However, habituation over less than 3 days can be used if required for a particular experiment. During the subsequent training session, two objects are placed in the open field, and the mouse is allowed to explore them freely for 15 min. On the training day, the two objects are the same. The following day (24 h later), the mice are re-introduced to the open field, containing a replica of the familiar object and a novel object, and allowed to explore for another 15 min. If short-time memory is of interest, shorter delays can be used. The brain areas involved depend on the interval between training and testing. So based on the brain areas of interest, the time between training and testing might be modified. Between trials, the open field and the objects are cleaned with 5% acetic acid to remove potential odors.

The sessions are videotaped, and the time spent with each object is manually recorded or analyzed using video tracking software. Hand scoring of the data is the gold standard. Using automated video tracking might be problematic in analyzing mouse [9] and rat [36] data. For example, sometimes the nose and tail points of the mouse are switched when multiple body point tracking is used. Therefore, it is important to verify whether nose-tail swaps occurred and if so to correct them. Nevertheless, nose-point video tracking software can be reasonably well used to automatically analyze object recognition data in mice [9] and rats [37]. Using center point body tracking only is problematic, as it would not be possible to determine whether the mouse faces a particular object with its nose or tail.