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Research report

Assessment of disease-related cognitive impairments using the novel object recognition (NOR) task in rodents

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HIGHLIGHTS

- NOR deficits are demonstrated in animal models of human disorders and conditions.
- The NOR test is cost and time effective, non-rewarded and ethologically relevant.
- The NOR test is invaluable in identifying the neural basis of cognitive deficits.
- The NOR test is useful in evaluating the efficacy of novel therapeutic targets.

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ABSTRACT

The novel object recognition test (NOR) test is a two trial cognitive paradigm that assesses recognition memory. Recognition memory is disturbed in a range of human disorders and NOR is widely used in rodents for investigating deficits in a variety of animal models of human conditions where cognition is impaired. It possesses several advantages over more complex tasks that involve lengthy training procedures and/or food or water deprivation. It is quick to administer, non-rewarded, provides data quickly, cost effective and most importantly, ethologically relevant as it relies on the animal's natural preference for novelty. A PubMed search revealed over 900 publications in rats and mice using this task over the past 3 years with 34 reviews in the past 10 years, demonstrating its increasing popularity with neuroscientists. Although it is widely used in many disparate areas of research, no articles have systematically examined this to date, which is the subject of our review. We reveal that NOR may be used to study recognition memory deficits that occur in Alzheimer's disease and schizophrenia, where research is extensive, in Parkinson's disease and Autism Spectrum Disorders (ASD) where we observed markedly reduced numbers of publications. In addition, we review the use of NOR to study cognitive deficits induced by traumatic brain injury and cancer chemotherapy, not disorders per se, but situations in which cognitive deficits dramatically reduce the quality of life for those affected, see Fig. 1 for a summary. Our review reveals that, in all these animal models, the NOR test is extremely useful for identification of the cognitive deficits observed, their neural basis, and for testing the efficacy of novel therapeutic agents. Our conclusion is that NOR is of considerable value for cognitive researchers of all disciplines and we anticipate that its use will continue to increase due to its versatility and several other advantages, as detailed in this review.

Introduction

As early as 1950, Berlyne observed that rats spend more time exploring a novel compared with a familiar stimulus [1]. Ennaceur and Delacour subsequently utilised this innate behaviour and developed the novel object recognition (NOR) test based on the natural propensity of rats to explore novel objects [2]. The NOR test is a non-rewarded, ethologically relevant paradigm based on the spontaneous exploratory behaviour of rodents that measures recognition memory. In most commonly used forms of the test, each test session consists of two trials. In the first trial (acquisition), animals are exposed to two identical objects in an open field or chamber of varying dimensions. During the second trial (retention), rats are exposed to two dissimilar objects, one familiar object from the first trial and one new object. Object recognition can be

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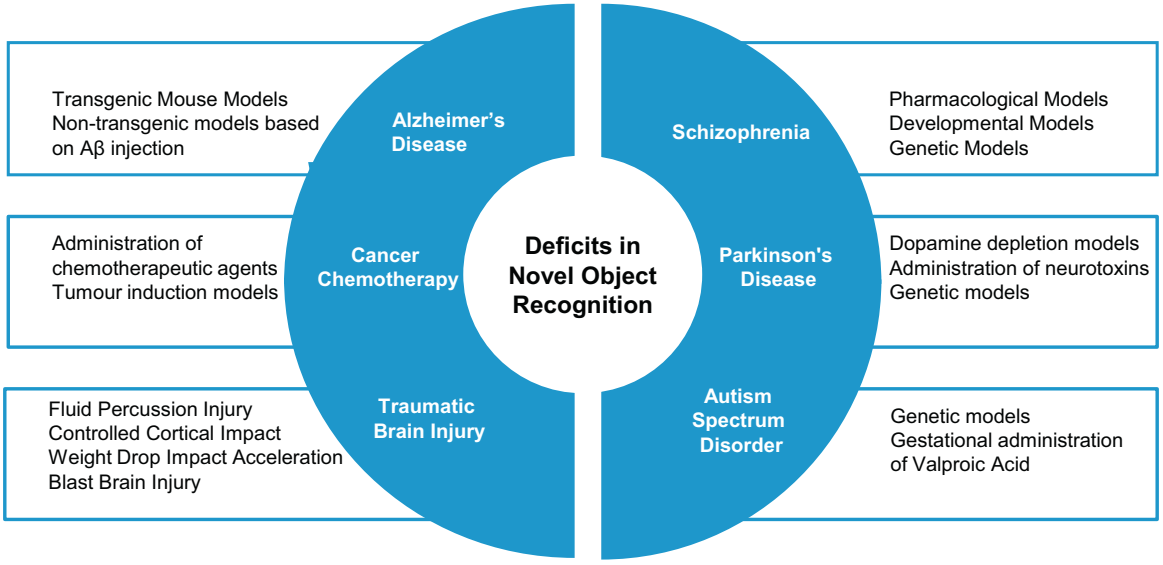

Fig. 1. Novel object recognition is used to study cognition of relevance to a variety of human disorders and their associated preclinical models.

measured as the difference in time spent exploring the familiar and the new, or novel, object. Rodents (and other species) have been shown to spend more time exploring the novel compared with the familiar object. Rats in our laboratory are able to discriminate between the familiar and the novel object when the inter-trial interval (ITI) is between 1 min and 1–6 h, but not when it is greater than 6–8 h (Mclean, personal communication). The duration of each trial is important as a preference for the novel object only lasts during the first 1 or 2 min, after which time preference diminishes as both objects become familiar and are explored equally.

A PubMed search of the literature covering the last three years (01.07.2011–01.07.2014) using *object recognition* and *rat* as keywords generated 444 publications while the keywords *object recognition* and *mouse* generated 479 publications. PubMed also revealed a total of 34 reviews published on object recognition in rats and mice over the last 10 years demonstrating its growing use in neuroscience research. Recent reviews have focused on anatomy, genetics and neurotransmitter involvement [3], task parameters and procedures [4], pharmacology [5] and neuropsychology [6]. Very few have focused on the utility of the NOR test for studying cognitive impairment in specific disorders, the exception being schizophrenia [6]. There are several features of NOR that make it the test of choice for researchers studying cognitive disturbances in a variety of human disorders. It is quick (a two trial test), cost effective (does not require complex or expensive equipment), ethologically relevant (relying on animals' preference for novel stimuli), has no stressful elements such as food or water deprivation and does not require any training, relying on innate behaviour. It is also robust, replicable and versatile, and it may be used for studying cognitive deficits in a range of disorders and conditions, the focus of our review. Recently in our laboratory, we have used NOR to assess cognitive deficits in a wide range of conditions in rats, including streptozocin-induced diabetes, cross-fostering, hydrocephalus and in the offspring of fasted mothers. Most other cognitive tests available (e.g. Morris water maze, radial maze, operant tasks including the touch screen) require training schedules and the rats are often food restricted while the NOR test confers the advantages of being ethologically relevant, and not requiring training or food restriction. Furthermore, lengthy training procedures preclude their use at specific time points in development e.g. to compare cognitive function in juvenile and adult animals. This led us to prepare this review article describing studies where NOR is used to study cognition of relevance to a variety of human disorders and situations where cognitive deficits are particularly debilitating: Alzheimer's disease, Parkinson's disease, Autism Spectrum Disorder, traumatic brain injury and cancer chemotherapy including an update on schizophrenia which was the subject of two recent reviews [7,8]. See Fig. 1 for a summary of the disorders and models covered. Our review, together with the large number of recent original research publications and review articles in this area, demonstrates just how valuable a resource this test has become in the field of cognition research, and how it may be used to assess cognitive deficits in a range of animal models and to identify novel targets for drug therapy.

1. Alzheimer's disease and NOR

Alzheimer's disease (AD) is a neurodegenerative disorder characterised by a progressive dementia related to the severity of brain lesions. The most common form of AD is sporadic, characterised by a late onset and resulting from a complex interaction between various environmental risk factors and susceptibility genes [9]. The familial form of AD occurs in less than 10% of all AD cases and is characterised by an early onset induced by an autosomal dominant mutation in one of three genes involved in amyloid signalling, leading to abnormal brain lesions of beta peptide amyloid deposits: the amyloid precursor protein (APP), presenilin 1 (PS1) or presenilin 2 (PS2) [10].

The most pervasive symptom of early AD is progressive cognitive impairment leading to a dementia syndrome. Among the early cognitive symptoms of AD, short-term episodic memory impairment associated with attention and spatial orientation disturbances have been mainly described [11]. Recently, impaired visual recognition memory reflecting dysfunction of the anterior subhippocampal cortex (transentorhinal, entorhinal and perirhinal cortices) [12], has been proposed as an early marker for AD diagnosis [13]. Assessed through the NOR test in animals, visual recognition memory, i.e. recognition of the features of different objects, is mainly supported by interactions between the neocortex and the perirhinal and entorhinal cortices, while the hippocampus is recruited more in the spatial and temporal context of object recognition [14]. The NOR task is thus dependent on the integrity of the temporal regions in both rodents and primates [14–17], that are similar to the medial temporal cortex progressively affected during AD in humans [18,19]. The NOR test is particularly relevant in the field of AD research as it allows assessment of visual recognition