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The touchscreen operant platform for assessing cognitive functions in a rat model of depression

Thao Phuong Tran [a], Helle Lyng Christensen [a,b], Freja Cecilia Brandt Bertelsen [b,c], Elena Bouzinova [a], Arne Møller [b,c], Ove Wiborg [a,*]

[a] Translational Neuropsychiatry Unit, Department of Clinical Medicine, Aarhus University, Denmark
[b] Center for Functional and Integrative Neuroscience, Department of Clinical Medicine, Aarhus University, Denmark
[c] Department of Nuclear Medicine and PET-Centre, Aarhus University Hospital, Aarhus, Denmark

HIGHLIGHTS

- Cognitive impairments in chronic mild stress rats
- Assessment on the touchscreen operant platform
- Two choice pairwise/visual discrimination reversal paradigm
- Anhedonic-like rats have slower acquisition rates.
- Resilient rats maintain functional plasticity.

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ABSTRACT

In the present study we assessed alterations in cognitive functions in a chronic mild stress (CMS) rat model of depression. Cognitive functions were assessed in two different tasks applying the translational operant platform touchscreen technology; the visual discrimination/acquisition task was used to assess the ability to perceive and distinguish visual stimuli and to assess associative stimulus-reward learning. The visual discrimination/reversal learning task was used to assess functional brain plasticity or reprogramming of previously acquired stimulus-reward associations. These tasks permit the dissociation of multiple cognitive domains. The CMS model is a validated depression model with the useful feature that rats upon stress exposure show a graduated, individual stress response allowing the segregation of rats into different phenotypes including stress-resilient and anhedonic-like subgroups. Anhedonic-like rats are less likely to acquire the pairwise discrimination task, and they have a slower acquisition rate than controls. In the reversal learning task, resilient rats performed significantly better than anhedonic-like rats over time and 50% passed criterion as opposed to 25% for controls and only 14% for anhedonic-like rats. This indicates that resilient rats have higher cognitive flexibility than anhedonic-like rats. Thus they perform better in learning a novel task, which at the same time potentially implies an increased ability to inhibit previously rewarded behavior.

1. Introduction

Major depressive disorder (MDD) is a complex, multifactorial, heterogeneous mental disorder that is highly disabling and affects >120 million people worldwide [21]. MDD consequently represents a major socio-economic burden to society. The clinical symptomatology is heterogeneous and inconsistent among patients and the underlying pathology and etiology is mainly unknown. However, according to current conventions MDD is caused by an interplay between a genetic predisposition and environmental factors, such as ongoing chronic psychosocial stressors, early life stressors or transient traumatic life events [12,19,20]. The Diagnostic and Statistical Manual of Mental Disorders, DSM-5 [2], has included several cognitive symptoms, recognizing that cognitive impairment is a core feature associated with MDD. The main cognitive dysfunctions in MDD relate to executive dysfunctions, attention, processing speed and to some extent also to memory functions. It should be noted that functional impairments might persist in patients even when depressive symptoms have mitigated or disappeared [5,25,28]. Cognitive impairments compromise personal coping abilities and rehabilitation, which in turn impact on functional recovery [16]. Consequently, cognitive functions represent one of the strongest predictors of functional outcome in depressed patients [3] and as such, cognitive impairments are essential to target and assess in pharmaco-

* Corresponding author.
E-mail address: ove.wiborg@clin.au.dk (O. Wiborg).

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and behavioral therapies. Most conventional antidepressants primarily ameliorate depressive symptoms while they improve cognitive functions only to a modest degree, and mainly in an indirect manner [25,26]. However, data are now emerging suggesting a few novel pharmaco-therapies ameliorating cognitive dysfunctions [31].

In the search for novel pro-cognitive antidepressants, valid animal depression models are in demand. First of all the condition in animals should be triggered by the same events that are known to be important for eliciting the human disorder (etiological validity). Application of realistic inducing conditions will ensure the legitimacy of the underlying pathophysiology to be studied. Furthermore it will enhance the likelihood to induce a behavioral phenotype that in several important respects is similar to the human clinical-symptom profile (face validity). Most valid animal models rely on the exposure of rodents to a sequential presentation of unpredictable microstressors [10,30]. Most importantly, these models induce an anhedonic-like behavior in rodents. Anhedonia, which is the cardinal symptom of depression, is a general loss of interest in events that were pleasurable in the premorbid state. The chronic mild stress (CMS) paradigm applied in the present study induces, in addition to an anhedonic-like behavior, several depression-like behavioral abnormalities including cognitive deficits [33,34]. Vulnerable rats will gradually decrease their voluntary intake of a sweet sucrose solution after prolonged stress exposure and become anhedonic-like. However, a fraction of the rats is stress resilient and manages to cope with the applied stressors in order to maintain homeostasis. Cognitive impairments are, however, observed in both stress-exposed groups independent of their hedonic status [14].

Cognitive impairments in humans are assessed by a number of neuropsychological tests. Some are based on questionnaires, but most are based on solving tasks. The Cambridge Neuropsychological Test Automated Battery (CANTAB) is based on the application of touch-sensitive screens for solving tasks addressing different cognitive domains. The tests are simple to administer and show strong correlations to brain constructs and known deficits in various disorders, as well as high sensitivity to interventions and small changes over time. The CANTAB depression battery provides measures of executive function, visual memory, sustained memory, emotional processing bias and subjective mood rating which are often impaired in MDD. Using roughly the same interface as for humans, the technology is applicable to rodents [29], thus facilitating useful preclinical studies of high translational value.

In the present study rats were exposed to the CMS paradigm for five consecutive weeks. Over time rats gradually segregated into different phenotypic subtypes according to their stress coping abilities. Unchallenged control rats, stress susceptible, and stress resilient rats were subsequently assessed for their learning and reversal learning abilities on the touchscreen operant platform. The pairwise discrimination learning requires at least two processes: learning to perceptually discriminate the stimuli and learning which of the two stimuli to associate with reward. It also provides the basis for testing reversal learning, in which the stimulus-reward contingencies acquired during discrimination are reversed [15,23]. Thus these tasks allow for the dissociation of multiple cognitive processes. Importantly, the tasks are computer-automated and carried out in the apparatus using the same types of stimuli, responses and reinforcers. This minimizes the risk of experimenter bias and confounds when comparing data across different tasks and between laboratories. Finally, rats were exposed to the social interaction test to monitor dominant behavior and positive social interaction.

2. Materials and methods

2.1. Animals

Male Wistar rats were purchased from Taconic, Denmark, at an age of 5–6 weeks, weighing 100–120 g. Rats were singly housed except when paired housing was applied as a stressor. A standard diet and water was available ad libitum except when food and/or water deprivation was applied as a stressor or during touchscreen testing when food availability was restricted. The standard 12-h light/dark cycle was only changed in course of the stress regime, e.g. one day/week with intermittent illumination (light on/off every 2nd hour) and one day/week with stroboscopic lighting. The standard cycle was reinstated after each change in light conditions. All animal procedures were approved by the Danish National Committee for Ethics in Animal Experimentation (2013-15-2934-00814).

2.2. The chronic mild stress protocol

The CMS paradigm was applied according to our standard protocol shown below. In short rats were exposed to a number of sequential stressors repeated in a weekly schedule. The microstressors include intermittent illumination, stroboscopic light, paired housing, food and/or water deprivation, damped bedding and cage tilting. All stressors were applied for 6 to 14 h.

	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
Morning	Intermittent illumination On/off every 2nd hour from 10 am to 4 pm	Water deprivation 7 am–5 pm	Stroboscopic lighting 10 am–4 pm	No stress	Sucrose test 8 am–9 am Food or water deprivation 9 am–5 pm	Food or water deprivation 9 am–5 pm	Cage tilting (45°) 9 am–5 pm
Evening	No stress	Cage tilting (45°) 5 pm–7 am	Damped bedding 5 pm–7 am	Food + water deprivation 6 pm–8 am	Paired housing 5 pm–9 am	Cage tilting (45°) 5 pm–9 am	Damped bedding 5 pm–7 am

Reward sensitivity was used as a behavioral readout to assess the hedonic status and was monitored by a weekly sucrose consumption test (SCT). Rats were food and water deprived 14 h ahead of the SCT, which was a one-hour period of free access to a palatable 1.5% sucrose solution. Rats were habituated to the SCT for four weeks prior to the onset of the CMS paradigm. Baseline sucrose consumption was matched for unchallenged controls and for rats exposed to CMS. In the course of the stress paradigm, rats responded individually to stress exposure according to their genetic heterogeneity. Rats that decreased their within-subject sucrose consumption >30% were designated as stress-susceptible or anhedonic-like, while rats