Behavioural Brain Research 317 (2017) 424–433

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Research report

Selective amotivation deficits following chronic psychosocial stress in mice

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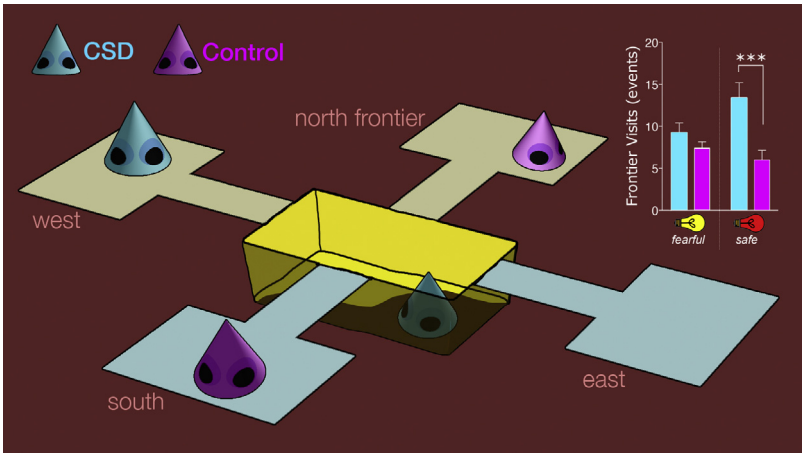
HIGHLIGHTS

- We find psychosocial stress in mice affects amotivation non-uniformly.
- Our chronic social defeat manipulation blunts novelty-driven exploration.
- Fear-driven exploration is comparatively resistant to psychosocial stress.
- Anxiety and short-term memory are also unaffected by the CSD manipulation used here.
- Fostering exploration could be a novel treatment for depression.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 22 August 2016
Received in revised form
22 September 2016
Accepted 24 September 2016
Available online 28 September 2016

Keywords:
Curiosity
Major depressive disorder (MDD)

ABSTRACT

Amotivation is a major symptom of several psychiatric disorders. However, which specific motivations are most affected in various illnesses is not well understood. In major depressive disorder (MDD), anecdotal evidence suggests the motivation to explore may be especially affected, but direct evidence from either patients or animal models is lacking. To investigate the potential for, and nature of, exploratory drive deficits in MDD, we subjected mice to a chronic social defeat (CSD) manipulation that gives rise to a MDD-like behavioural ensemble, and performed a behavioural battery to examine bodyweight homeostasis, ambulation, anxiety, exploratory behaviour motivated by either novelty or fear, and short-term memory. Consistent with previous reports, we found a disruption of bodyweight homeostasis and reduced ambulation following CSD treatment, but we found no evidence for anxiogenic effects or impairments

Abbreviations: CSD, chronic social defeat; MDD, major depressive disorder; EPM, elevated plus maze; NFT, new frontier task.

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http://dx.doi.org/10.1016/j.bbr.2016.09.055

New frontier task (NFT)
Spatial memory
Exploration
Mice

in short-term memory. Surprisingly, we also observed profoundly delayed and diminished exploration of novel, safe space following CSD, while exploration motivated by fear remained intact. These results extend our knowledge of the behavioural phenotypes in mice resulting from CSD by homing in on specific motivational drives. In MDD patients, reduced exploration could compound disease symptomatology by preventing engagement in what could be rewarding exploration experiences, and targeting deficits in the motivation to explore may represent a novel avenue for treatment.

1. Introduction

Amotivation is a symptom of many mental illnesses, and a core symptom of major depressive disorder (MDD) [8,13]. While amotivation is often considered as a single phenotype, it can probably be more accurately described as a composite of motivational deficits, all of which may not be uniformly affected in a given mental illness. The specific loss of motivation to explore, for example, has been reported in some mental illnesses that exhibit cognitive dysfunction, such as autism [55,22] and schizophrenia [48,46]. In MDD, deficits in exploratory excitability (a measure of novelty-seeking) are prominent, despite no change in overall impulsivity (another measure of novelty-seeking) [4,57], suggesting patients with MDD experience less reward when presented with novel stimuli. In addition, patients with MDD are less engaged by, and are less engaging in, their environments [11,8]. Together, these findings hint towards the potential for exploratory drive deficits in MDD. However, little clinical or preclinical research has directly examined exploratory drive in MDD or in experimental animals exposed to MDD-phenotype-inducing manipulations. Understanding if deficits in exploratory drive are present in MDD is important because exploration can yield rewarding information from the environment and facilitate the efficiency of learning [38], indicating that restoring the motivation to explore could be a potent new treatment strategy in psychiatry, or at least be a marker for treatment response.

Despite the clear importance of an active exploratory drive in maintaining mental health, exploratory drive deficits have received surprisingly little attention from the clinical and research communities. There is therefore only a limited theoretical framework and narrow selection of tools currently available to probe the mechanisms underlying loss of exploratory drive in mental illness [11,8,25]. Given this minimal examination, and since better understanding exploration deficits could yield novel targets and strategies for treating mental illness, we examined exploratory behaviours in mice following chronic social defeat (CSD), a social manipulation that induces pathophysiology reminiscent of MDD [33,56,3,18,20,5].

To distinguish between different drives to explore, we made use of the new frontier task (NFT), a paradigm that provides experimental animals with the opportunity to climb out from their homecage and explore four dimly lit novel platforms positioned along the cardinal axes [49,44]. Classically, the NFT is performed with the homecage either dimly or brightly lit. The dimly lit or dark version of the NFT is proposed to measure volitional exploration motivated by the inherently rewarding nature of novel stimuli, while the brightly lit version is proposed to assess fear-driven exploration, since bright light is a fear-inducing stimulus for small nocturnal prey, like mice. In both types of illumination, the unfamiliar environments (or "frontiers") remain dim. In addition, scents of other mice are eliminated and subjects always have free access to food and water, thereby minimizing potential interference from socio-sexual-satiation drives.

In this study, the NFT was one component of a behavioural battery that also assessed bodyweight homeostasis, ambulation, anxiety and short-term memory. We find strong effects on bodyweight homeostasis and exploration, but no effect on anxiety and short-term memory. With respect to exploration, CSD-treated mice exhibited impairment exclusively under dim illumination, suggesting a surprising specificity with their amotivation phenotype.

The results highlight exploration deficits in a social stress manipulation that induces some important behaviours resembling MDD core symptomatology. The data thereby provide an important starting point for careful interrogation of circuits and molecules involved in the pathogenesis of diminished exploration affecting patients with MDD and other mental illnesses, and highlight exploratory drive as a potential new target for novel treatment strategies in MDD.

2. Materials and methods

2.1. Experimental subjects and ethical standards

All experiments and manipulations conformed to the guidelines set by the Animal Care Commission of Switzerland and were covered under the authority of animal permit ZH170/2012. All possible measures were taken to ensure minimal pain and discomfort.

Experimental subjects were 24 young adult (8 wks of age at study onset) B6/J-Rj male mice obtained from Janvier (France). Prior to engaging in any experimental paradigms, the mice were provided with one week to acclimatise to the facility, followed by 10 min/day of handling for 4 days (Fig. 1A). Mice were maintained on a reverse light cycle (lights off at 7:00 am; lights on at 7:00 pm) with access to Purina mouse chow and sterile water ad libitum throughout the study. Internally ventilated cages containing tissue for nest building, pinewood bedding and a transparent plastic red house were used. The subjects were divided equally into 2 groups: 12 CSD, 12 controls.

Aggressor subjects required to induce CSD consisted of 12 adult (8 mth of age) male CD-1 ex-breeder mice, pre-selected for demonstrating aggressive behaviour as previously reported [3].

2.2. Chronic social defeat (CSD)

The two groups, each consisting of 12 mice (CSD or control) were formed by counter-balancing motor activity measured for 15 min as horizontal and vertical beam breaks in a TSE Multi-conditioning system arena (50 lx) one day prior to the CSD manipulation. CSD procedures were then carried out as previously reported [3] in a dimly lit room (20 lx) adjacent to the vivarium. For 15 days, CSD mice were introduced daily into the cage of a different aggressive CD-1 mouse for a total of 10 min, or 60 s of one-to-one attack (cumulative), whichever came first. Subject weights were determined immediately prior to the attack session. The control group was caged in pairs and transferred to new cages on the same days the CD-1 mice received new cages. Bedding was changed by the experimenter on day 7 and 15 during CSD, and at the same time of day for both groups. The incisor teeth of CSD mice were trimmed