Behavioural Brain Research 350 (2018) 139–148

Contents lists available at ScienceDirect

Behavioural Brain Research

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

Addiction vulnerability trait impacts complex movement control: Evidence from sign-trackers

Aaron Kucinski, Cindy Lustig, Martin Sarter*

Department of Psychology and Neuroscience Program, University of Michigan, Ann Arbor, MI 48109, USA

ARTICLE INFO

Keywords:
Addiction
Acetylcholine
Complex movement control
Attention

ABSTRACT

Cognitive-motivational vulnerability traits are associated with increased risk for substance addiction and relapse. Sign-tracking (ST) behavior in rats is associated with poor attentional control, mediated by an unresponsive basal forebrain cholinergic system, and an increased risk for substance addiction/relapse. A separate literature links poor attentional control and cholinergic losses to increased fall risk in Parkinson's disease. Here we tested the hypothesis that the relatively inferior attentional control of STs extends to complex movement control and a propensity for falls. STs were found to fall more often than goal-trackers (GTs) while traversing a straight rotating rod and, similar to human fallers, when taxed by a secondary task. Furthermore, STs fell more often while traversing a rotating zig-zag rod. GTs exhibited fewer falls from this rod by avoiding entry to the rotating zig-zag sections when in, or rotating toward, a difficult traversal state. Goal-tracking rats approached risky movement situations using strategies indicative of superior top-down control. These results suggest that the impact of opponent cognitive-cholinergic traits extends to complex movement control, and that impairments in the cognitive-motor interface are likely to be comorbid with addiction vulnerability. Sign-tracking indexes an endophenotype that may increase the risk for a wide range of neurobehavioral disorders.

1. Introduction

Cognitive-motivational traits, such as impulsivity, and underlying cortico-striatal abnormalities have been associated with vulnerability for drug-seeking behavior and relapse [1–5]. Research on the causal role of such traits for addiction vulnerability has greatly benefited from the demonstration of such traits in selectively bred rodents and in rodent outbred populations, including as indexed by sign-tracking behavior. Sign-trackers (STs) were named as such based on their propensity to approach and contact a Pavlovian reward cue, and they have been extensively demonstrated to be more prone than goal-trackers (GTs) to addiction-like behaviors. GTs, in contrast, do not approach Pavlovian reward cues and resist Pavlovian cue-evoked drug seeking [6–12].

Guided by evidence indicating that cognitive, specifically attentional, control deficits are an essential component of addiction vulnerability traits, our research has suggested that sign- and goal-tracking behavior indicate the presence of even broader, opponent cognitive-motivational styles [for a recent review see [13]. GTs exhibit a top-down, relatively "strategic" analysis of the behavioral significance of reward or drug cues, mediated by task-evoked increases in cholinergic neuromodulation in association with the absence of cue-evoked increases in dopaminergic activity. In contrast, STs show a more stimulus-driven, bottom-up, and impulsive behavioral pattern which promotes approaching to Pavlovian reward cues and cue-evoked drug seeking, and which is mediated by greater cue-evoked dopaminergic activity in the absence of increases in cholinergic activation [14–17].

We recently demonstrated more pronounced drug seeking behavior evoked by higher-order contextual cues in GTs relative to STs [17]. This finding indicates the superior ability of GTs to utilize such information and the relatively limited capacity for executive (cognitive) control in STs. This finding, however, does not reject the notion that STs are more vulnerable for developing addiction-like behavior. Indeed, just because STs exhibit relatively poor control of high-order cues, they likely are less able to utilize contextual information to resist the escalation of Pavlovian cue-evoked drug seeking and drug taking. Thus, sign-tracking continues to be considered a behavioral index of a psychological trait that bestows vulnerability for addiction-like behavior [this issue is addressed in more detail in [18].

Perhaps reflecting cortico-striatal abnormalities in addicts, movement control deficits have also been associated with addiction, although the relative contributions of pre-existing vulnerabilities versus the effects of chronic addictive drug taking on cortico-striatal functions remains undefined [19,20]. The present experiments tested the hypothesis that STs, owing to their relatively weak top-down control

* Corresponding author at: Department of Psychology and Neuroscience Program, University of Michigan, 530 Church Street, 4030 East Hall, Ann Arbor, MI, 48109, USA.
E-mail address: msarter@umich.edu (M. Sarter).

https://doi.org/10.1016/j.bbr.2018.04.045
Received 23 March 2018; Received in revised form 25 April 2018; Accepted 25 April 2018
Available online 26 April 2018
0166-4328/

capacity, mediated in part by their unresponsive cortical cholinergic input system, exhibit vulnerabilities in traversing dynamic surfaces, which requires the attentional supervision of balance, limb placement and the rapid detection of movement errors [reviewed in [21]. This hypothesis was derived from evidence indicating that patients with Parkinson's disease who experience falls also exhibit decreases in the cholinergic innervation from basal forebrain to cortex [22] and associated impairments in top-down attentional control [23]. The present experiments utilized the Michigan Complex Motor Control Task (MCMCT) which was previously used to develop a model of Parkinsonian falls [24,25]. Furthermore, the ability of STs and GTs to traverse a newly designed rotating zig-zag beam was assessed. The results indicate a relatively greater propensity of STs for falls and that GTs avoid falls by timing the traversal of the most demanding aspects of beam traversal.

2. Materials and methods

2.1. Subjects

Adult male and female Sprague-Dawley rats (N = 239; 158 males and 81 females) between 2 and 3 months of age were purchased from Envigo (Haslett, MI). All rats underwent Pavlovian Conditioned Approach (PCA) screening to yield 52 GT s and 104 STs (21.76 and 43.51%, respectively). Of the 158 male rats screened there were 39 GT s and 68 STs (24.68 and 43.04%, respectively) and of the 81 females there were 13 GT s and 36 STs (16.05 and 44.44%, respectively). In total, 46 GT s (37 male and 9 female) and 53 STs (45 male and 8 female) were randomly selected from these screenings to be used for the experiments. In the first experiment, 67 male rats (30 GTs and 37 STs) underwent 14 days of behavioral testing on the Michigan Complex Motor Control Task (MCMCT). In the second experiment, 22 rats (11 GT s and 11 STs; 6 females and 5 males per group) were tested on the zig-zag beam. Rats were purchased and introduced into individual housing at approximately 2 months of age. Rats were between 2 and 3 months of age during PCA screening and were between 3 and 5 months of age during MCMCT testing.

Animals were individually housed in opaque single standard cages (27.70 cm × 20.30 cm) in a temperature- and humidity-controlled environment (23 °C, 45%) and maintained under a 12:12 h light/dark schedule (lights on at 7:00 AM). Food (Envigo Teklad rodent diet) and water were available *ad libitum*. PCA testing and MCMCT traversal experiments were conducted during the light phase (7:00A.M. – 7:00P.M.). All procedures were conducted in adherence with protocols approved by the Institutional Animal Care and Use Committee of the University of Michigan and in laboratories accredited by the Association for Assessment and Accreditation of Laboratory Animal Care.

2.2. PCA screening

The purpose of the PCA test was to determine the extent to which behavior was lever or food cup-directed. A PCA index score (below) was generated for each rat. Pavlovian training procedures were similar to those previous described [11,15–17].

2.2.1. Apparatus and procedures

Rats were handled daily for at least 3 days prior to screening in the Pavlovian approach test. Rats were given ~15 banana-flavored sucrose pellets (45 mg; BioServ) in their home cages for 2 days prior to start of testing. Rats were tested in conditioning chambers (MedAssociates; 20.5 × 24.1 cm floor area, 20.2 cm high). A food magazine with an automatic feeder that delivered sucrose pellets was located in the center of one of the walls of the chamber. Infrared photobeam breaks detected magazine entries. On either the left or right side of the magazine was a retractable lever with an LED backlight that was illuminated only when the lever extended into the chamber. Deflections of the lever were used to quantify lever contacts. The beginning of a test session was signaled by the illumination of a red house light located near the ceiling of the side of the chamber opposite to the magazine/lever. On the first day of testing ("pre-training"), rats were placed into the conditioning chambers and the house light was illuminated after a 5-min habituation period. 25 sucrose pellets were then delivered on a VI-30 (0–60 s) schedule. The pre-training session lasted 12.5 min on average and the lever was retracted throughout the session. During this session and all subsequent PCA sessions, rats consumed all the sucrose pellets. In the next five PCA sessions, the house light was turned on after a 1-min period and rats were then presented with 25 lever-pellet pairings delivered on a VI-90 (30-150 s) schedule. The conditioned stimulus (CS) for each trial was the extension of the illuminated lever into the chamber for 8 s. Upon retraction of the lever a sucrose pellet was delivered into the magazine. The PCA test sessions lasted 37.5 min on average.

2.2.2. PCA measures and classification criteria

Lever presses and magazine entries during the CS periods were used to quantify three measures of approach (scores ranging from −1 to 1) to compute the PCA index score. (1) Response bias was defined as the difference between lever presses and magazine entries, expressed as a proportion of the total responses [(lever presses – magazine entries)/(lever presses + magazine entries)]. (2) Latency score was calculated as the difference between the latency to approach the lever and the magazine upon CS presentation; this difference was normalized by dividing the maximum 8 s latency [(magazine latency – lever latency)/8]. (3) The probability difference score was calculated as the difference between the probabilities of pressing the lever during the CS (i.e., the number of trials with a lever presses out of 25 trials) minus the probability of entering the magazine. The PCA index score was the average of the response bias score, latency score, and probability difference score. The values of this score ranged from 1.0 to −1.0, with a score of 1.0 indicating approaches and contacts of the lever on every trial and a sore of −1.0 indicating approaches and contacts of the magazine entry on every trial. A score of 0 indicates that lever contacts and magazines entries following CS presentation were distributed equally across trials. PCA index scores were averaged from testing days 4 and 5 to obtain a single score that classified rats as GTs or STs. Rats were considered STs if they obtained scores ranging from 0.5 to 1.0, with scores greater than 0.4 on both days, indicating that lever-directed behavior was more than twice as frequent as food cup-directed behavior. Rats with scores ranging from −0.5 to −1.0 were classified as GTs [9,11,26,27]. Rats with intermediate scores were not used in these studies.

2.3. Michigan complex motor control task (MCMCT)

2.3.1. Apparatus I

The MCMCT beam traversal apparatus [for details and an illustration see 25] was designed to tax the ability of rats to perform attention-demanding beam traversals and correct for stepping errors while crossing a narrow square rod surface (side length: 1.59 cm). Traversal of the rod, particularly when rotating, reliably caused falls in rats with attentional deficits resulting from losses of cortical cholinergic inputs [25,28].

The apparatus consists of a traversal beam (2.0 m length) with a start platform (23.0 × 31.5 cm area) on one end and a cradle for home cages on the other. The ends of the beam are held in sockets that allowed the rod to be rotated by a gear motor (10 RPM) coupled to one end of the beam element. The lower central section of the U shaped central frame is held in a support saddle that allows the upper section to pivot, thus allowing the rod to be adjusted to any angle from 0° to 45°. A flat plank surface (13.3 cm wide) is also used to assess basic motor capacity and for habituation to the apparatus. When falls occur, animals fall into a safety net (0.7 × 0.2 m) section of a badminton net (generic) placed 20 cm below the beam element. The net frame also serves as a