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

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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.

Keywords

Addiction; Acetylcholine; Complex movement control; Attention

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

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Author contributions

A.K. performed the research. A.K., C.L., and M.S. designed the research and wrote the paper.

Competing financial interests

The authors declare no competing financial interest.

Data accessibility

Raw data generated by these experiments have been stored on a University of Michigan Server. Data and statistical analyses will be made available upon request.

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 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 13GTs 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 × 24.1cm 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 score 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 mounting point for the various cameras, mirrors, and distractor elements.

Rats (30 GT and 37 STs; all males) were first tested using a 14-day battery of progressively demanding MCMCT test conditions (Table 1). Prior to the testing sequence, rats received FrootLoops (Kellogg's; 1.8 cm in diameter, 6 mm height, ~ 230 mg) in their cages daily for one week. Rats also received Froot Loops (3 pieces) daily following completion of MCMCT testing on Test Days 1–9.

As in previous studies, rats performed traversals first on the plank surface, followed by the stationary (non-rotating) rod, and then rotating rods. To add variability and complexity to the rod runs, inclines were increased in later trials (to 25° and 40°) and the direction of the rod was reversed and alternated between clockwise (cw) and counterclockwise (cc) directions. In addition, two distractors were presented during traversals. First, a *passive doorframe distractor*, comprised of a 46.0 × 39.5 cm surface with a door-frame shape cutout of 20 cm × 10 cm made of foam core, was incorporated into the MCMCT test sequence. We previously found that this distractor caused movement disruptions such as freezing of gait and falls [25,28], therefore modeling the effects of such distractor in PD patients [29]. Second, animals were tested with an *active distractor/dual task condition* in which a food reward (Froot Loops) was presented on a platform (4.9 cm diameter) during traversals. The platform was placed midway along the beam, with 2.5 cm separating the rod and the platform. In 6–12 shaping trials over two test days, rats were trained to retrieve Froot Loops from the platform during traversal and carry them (grasped by the teeth) into their home cages. On the first day, rats were given up to 6 chances to retrieve a maximum of 3 Froot Loops (one per run) on the stationary rod. If a rat bypassed the platform without attempting to retrieve a Froot Loop the rat was placed directly on the rod adjacent to the platform in the subsequent trial to encourage retrieval of the Froot Loop. This was repeated until the rat successfully retrieved a Froot Loop or for the remainder of the 6 trials. On the second shaping day the rod was rotated (cc direction) and again the rat was given 6 chances to retrieve 3 Froot Loops. The rats were not placed adjacent to the platform in subsequent runs after bypassing the rewards in these trials. Following shaping, rats were tested with the stationary rod and then rotating rods days (cc and cw direction; 3 trials day). In addition to scoring falls, the number of rewards retrieved, defined as the ability to retrieve and carry the Froot Loop into the home cages without dropping them or falling from the rod, was counted.

Falls, slips, and traversal time were assessed as described previously [25]. A fall was scored in the following instances: when the rat fell completely off the rod onto the netting below the rod or hung from the rod by its paws, when following a slip and stoppage of forward movement the underside of the rat fell on top of the rod requiring active recovery movements to regain posture and continue forward traversal, when a rat ceased forward movement and clung to the rod while it rotated (thus rotating upside down with it), or when a rat ceased forward movement and sat perpendicularly on the rod for longer than 2 s while attempting but failing to resume forward movement. A slip was scored when any of the rats' paws lost contact with the surface of the rod and extended below the lower horizontal border of the rod. Traversal time was defined as the latency to traverse the entire distance of the beam. During trials in which a fall occurred, slips and traversal time were prorated by

multiplying the ratio of the distance of a full traversal to the distance where the hind limbs lost contact with the rod during the fall. Since trials were terminated following falls, the percentage of trials resulting in falls was considered for analyses of fall rates.

All trials were recorded using a system of 4 bullet cameras (KT&C; model KPCS190SH Black/White Bullet Camera with 1/3" SONY Super HAD CCD) with rotatable bases that were fastened to the outer support frame of the outer side of the apparatus by hand clamps. Performance measures were analyzed by video playback by experimenters blind to the lesion status and treatment regimen of the rats.

2.3.2. Apparatus II—A larger MCMCT apparatus was designed for compatibility with additional complex surfaces, including the zig-zag rod. This apparatus was similar in design to the apparatus described above but featured longer (3.0 m) traversable square rods (side length 1.59 cm). The rods were comprised of aluminum tubing covered with gray gaffer's tape for traction. In addition to a 'straight' rod with no bends that was similar to the rod used in the first apparatus, a 'zig-zag' variation was designed to provide additional challenge during traversals. This rod included two zig-zag sections, each 0.6 m in length that began 0.6 m from either end of the rod and separated by 0.6 m of straight rod in the middle (see Fig. 3). Each zig-zag section included three angled sections of varying lengths (two 10.7 cm and one 21.5 cm in length) that bended at 45° angles from the horizontal plane of the rod and which connected two straight sections (each 15 cm in length) that rested 3 cm above or below the plane the vertical plane of the rod.

The rod could be fixed stationary in either a horizontal position, so the zig-zag sections protruded to the sides, requiring rats to turn left or right while traversing, or a vertical position, so the zig-zag sections were angled up and down, or rotated up to 10 RPM so that rats were required to perform sideways and vertical movements while navigating over the zig-zag sections. There was also a plank surface (13.3cm width) that could be placed directly on top of the straight rod and fitted firmly in place inside edges of the support towers. The rods were rotated using a 12 VDC electric motor controlled remotely by a pulse width modulator which was able to adjust the speed of rotation (up to 10 RPM) and switch the direction of rotation. A safety net was suspended 20 cm under the beam to catch the rats during falls. Two identical end stations were situated on top the support towers at opposite ends of the beam. These stations consisted of a 30 × 25 cm platform with a 3-cm diameter copper cup embedded in the floors. Rats were given a banana pellet (45 mg per pellet; BioServ) placed inside the cups following each traversal. Each end station was surrounded by a retractable wall structure (23 cm height in raised position) to allow conversion from an open platform to an end box structure. On the wall facing the beam of each box structure a 9-cm wide opening allowed the rats access to and from the beam. The walls could be raised and lowered mechanically with a 12 VDC electric motor actuated remotely by a toggle switch.

Falls, traversal time, and slips were analyzed in the same manner as previously described, with the exception that the rats' performances over each entire traversal were considered due to the longer lengths of the rods (performance measures were not prorated following falls). If, following a fall, rats were unable to resume forward traversal, the experimenter

immediately assisted the rat in regaining balance on the rod, and no further slips or falls were counted until the rat regained a balanced posture and resumed forward movement. During trials in which falls occurred, the time of stoppage of forward movement during falls (exceeding 0.5 s) was subtracted from the total traversal time. On the straight rod, since multiple falls could occur during a run, *falls per run* were used as a metric for fall rates. Due to the difficulty of assessing multiple falls per zig-zag section, a maximum of one fall per zig-zag section was scored and the *percentages of zig-zag sections that resulted in falls* were quantified as a measure of falls on this surface. Additional analyses of performance details are described in the context of findings in Results. Videos of traversals were recorded with four bullet Marshall 1080-HD-DI model CV500 Series cameras (B-30/25 P frame rate/59.94i) mounted on the net frame parallel to one side of the beam. The videos were converted to a single feed using a quad SDI to HDMI multiviewer (Matrox MicroQuad) and viewed directly on a PC using Elgato Game Capture HD software.

In the second MCMCT experiment, using apparatus II, rats were first habituated with a 5-day traversal sequence (Table 2), including trials on the plank, stationary (straight) rod, and the zig-zag surface (stationary in the vertical and horizontal positions and rotating at 5 and 8 rpm). The rats were trained for 5 consecutive days. These rats also received intracranial infusions of a DREADD vector; data on the effects of DREADD activation are not described in this report.

2.4. Experimental design and statistical analysis

The present experiments were designed to test the hypothesis that STs, when compared with GTs, exhibit impairments in complex movement control and a propensity for falls. For PCA testing, approach responses (response probability, number of contacts, and latency) were analyzed with repeated-measures ANOVAs with phenotype (STs, GTs) as the between groups factor and training day (1–5) as the within- subject factor. One- or two-way ANOVAs were used to compare PCA scores between GTs and STs and sexes. In the first traversal experiment, MCMCT performance measures (falls, traversal time, and slips) were compared between GTs and STs using within-subjects repeated measures ANOVAs. Within-subjects factor incline (0°, 25°, or 40°) was used to assess performances with the plank, stationary rod, and rotating rod surfaces. In rod trials in which the rotation direction was alternated, rotation direction (clockwise or counterclockwise) was also used as a within-subjects factor. The within-subjects factor session number (1–4) was used to compare falls with the door doorframe distractor. Falls and retrievals of FL in the active distractor task were assessed with factors condition (stationary rod, cc rotating rod, or cw rotating rod) and session (1–3). For the zig-zag beam an additional factor of sex was used to assess falls, traversal time, slips, and pauses at the zig-zag sections. Speed of the zig-zig rotating rod (5 or 8 RPM) was also used as a factor when applicable. Assumptions underlying the statistical model were assessed. In cases of violation of the sphericity assumption, Huyhn-Feldt-corrected F values, along with uncorrected degrees of freedom, are given. Post hoc analyses for all within-subjects comparisons and additional analyses were performed using the t test, Least Significant Difference (LSD) test, or χ^2 test when applicable. Statistical analyses were performed using the SPSS for Windows (version 17.0: SPSS). Alpha was set at 0.05. Exact

P values are reported as recommended previously [30,31]. Effect sizes (Cohen's *d*) were computed for major results [32].

3. Results

3.1. PCA-based screening of STs and GTs

A total of 46 STs and 53 GTs were classified and used for subsequent experiments. For the first experiment, on MCMCT performance of STs and GTs, we used 30 GTs and 37 STs. The PCA scores of these STs and GTs differed significantly ($F(1,66) = 3227.84$, $P > 0.001$; PCA scores: GTs: -0.77 ± 0.02 ; STs: $+0.75 \pm 0.02$; Fig. 1a). For the second main experiment, an additional 11 STs and 11 GTs (5 males and 6 females per group) were tested on the expanded MCMCT, including the rotating zig-zag beam. The PCA scores of these STs and GTs again differed significantly ($F(1,16) = 598.03$, $P > 0.001$; GTs: -0.79 ± 0.05 ; STs: $+0.80 \pm 0.04$; Fig. 1b). PCA scores were not affected by sex (main effect sex and phenotype interaction both $F < 2.00$, both $P > 0.18$).

3.2. Higher fall rates in STs

Rats were tested on a 14-day sequence of trials on the MCMCT as detailed in Table 1. This testing sequence was designed to persistently challenge performance by progressively increasing demands on balance and complex movement control [21,25,28,33].

First, rats traversed the plank surface (width: 13.3 cm) at each incline (0° , 25° , or 40°), followed by runs across the rod surface (width: 1.59 cm; stationary, or rotating at 10 RPM). Beginning on test day 5, the doorframe distractor (DF) was introduced, interspersed with non-dis-tractor trials. The Froot Loop (FL) secondary task was presented on the final 5 test days.

3.2.1. Plank traversal—Plank traversal performance served to familiarize rats with beam traversal to reach the opposite, enclosed chamber and retrieve a banana pellet, and to reveal potentially fundamental differences locomotion. As falls and slips were rarely observed during plank traversal, traversal time was the only performance measure. Three successive traversals were performed at each incline on separate test days (see Materials and Methods). Traversal time was assessed using a mixed-factor analysis, with phenotype as a between-subjects factor and rod incline (0° , 25° , or 40°) as a within-subjects factor. Traversal time did not differ between GTs and STs ($F(1,65) = 0.23$, $P = 0.64$). As previously reported [25], rats were slower to traverse the plank at 0° incline relative to the steeper inclines (main effect of incline, $F(2,130) = 19.27$, $P < 0.001$; 0° : 5.32 ± 0.22 s; 25° : 3.86 ± 0.14 s, 40° : 4.11 ± 0.24 s; 0° slower than 25° and 40° , both $P < 0.001$; phenotype $\times$ incline: ($F(2,130) = 0.54$, $P = 0.59$).

3.2.2. Stationary and rotating rod—Following the plank trials, rats traversed the stationary (non-rotating) rod. Traversal time, slips and falls were measured. Falls from the stationary rod were rare ($1.16 \pm 0.42\%$) and did not differ between STs and GTs. Likewise, traversal time and the number of slips did not differ between groups (all main effects of

phenotype $F < 1.36, P > 0.24$) and the effects of phenotype and incline did not interact (both $F < 1.12, P > 0.89$).

Next, the rod was rotated (10 RPM) in the counterclockwise (cc) direction for 3 trials at each incline. Traversing a rotating rod requires precise limb placement and balance control, including for correction of slips, and it is thought to heighten the attentional supervision of forward movement [21,25]. As expected, rotating rod traversal generated more falls than stationary rod traversal ($t(66) = 5.68, P < 0.001$; stationary: $1.16 \pm 0.42\%$ of trials, rotating: $9.14 \pm 1.42\%$); However, both STs and GTs fell at a similar rate ($F(1,65) = 0.93, P = 0.34$; GTs: $7.78 \pm 2.11\%$; STs: $10.51 \pm 1.90\%$). Furthermore, and as observed previously [25], falls were more frequent during flat rotating rod traversal – when traversal time was fastest – when compared to 25° and 40° inclines ($F(2,65) = 9.39, P < 0.001$; 0° : $16.13 \pm 2.40\%$; 25° : $2.46 \pm 1.09\%$; 40° : $8.84 \pm 3.01\%$; *post hoc* pairwise comparisons indicated that more falls occurred at the 0° incline than the 25° ($P = 0.036$) and 40° ($P = 0.050$) inclines; phenotype $\times$ incline: $F(2,130) = 0.34, P = 0.71$). As slips are a major risk factor for falls, the results of the analysis of the number of slips (which includes slips leading to falls) paralleled those of falls (incline: $F(2,130) = 18.25, P < 0.001$; phenotype: $F(1,165) = 2.64, P = 0.11$; interaction: $F(2,130) = 0.29, P > 0.75$).

3.2.3. Reverse rod rotation—We previously demonstrated that reversing the rod's direction of rotation increased the propensity for falls and slips in rats with loss of basal forebrain cholinergic projections to cortex [25]. Given that STs exhibit attenuated levels of cholinergic neuromodulation when performing an attention task [14], we hypothesized that traversing the rod rotating in reversed direction reveals the impact of the relatively poorer attentional control by STs. To test this, the direction of rod was alternated between the familiar (cc) and unfamiliar (cw) direction (one block of cc-cw-cc-cw trials at each of the three inclines; 12 trials total; Table 1). The performance across repeated trials was analyzed to determine the potential efficacy with which rats were able to transfer cc rotating rod traversal skills to the new cw rotation direction. Thus, the within-subjects factors used to analyze the performance measures were direction of rotation (regular or reverse), incline (sessions 5, 6 and 9; Table 1), and trial type repeat for each of the 3 sessions (cc-cc and cw-cw).

As was expected, results from the omnibus ANOVA indicated that reversing the rod's rotation direction almost tripled the number of falls ($F(1,65) = 19.86, P < 0.001$; cc: $5.01 \pm 1.30\%$ of all trials; cw: $14.44 \pm 2.03\%$). Furthermore, the effects of phenotype, rotation direction, and trial type repeat interacted significantly ($F(1,65) = 4.01, P = 0.04$; main effects of group and trial sequence: both $F(1,65) < 3.10$, both $P > 0.07$; Fig. 2).

Post hoc comparisons indicated that this interaction reflected, on the one hand, stable and relatively low fall rates across trials by both STs and GTs while traversing the familiar cc-rotating rod that was contrasted by, on the other hand, higher falls associated with traversal of the rod rotating in the unfamiliar cw-rotating direction. Importantly, the high rate of cw rotation-induced falls in GTs, but not STs, rapidly and significantly decreased with repeated exposure to this rotation direction ($F(1,29) = 10.55, P = 0.003$; Fig. 2a). Falls evoked by reversing the rotation direction were not modified by incline (main effects and interactions:

all $F < 2.85$, all $P > 0.60$), indicating the relatively high efficacy of reversing rotation direction to generate falls across various inclines.

The failure of STs to improve reversed rotation traversal performance was also reflected in their inability to reduce the number of slips across the cw-rotation trial pairs (phenotype x trial sequence: $F(1,65) = 24.34$, $P = 0.007$; GTs: trial 1: 2.25 ± 0.27 slips, trial 2: 1.35 ± 0.22 , $P = 0.006$; STs: trial 1: 2.34 ± 0.24 , trial 2: 2.15 ± 0.20 , $P = 0.56$).

3.2.4. Doorframe distractor- and dual task-induced falls—We tested rotating rod traversal in the presence of a passive doorframe (DF) distractor [29] as well as an active Froot Loops (FL) distractor. While stopping and retrieving the FL, rats were required to maintain balance and continuously reposition their limbs to remain on the rotating rod and re-initiate their forward movement after FL retrieval. Thus, the FL distractor constituted a dual task situation which, in older humans and PD fallers, reliably produces gait errors and falls [34–39]. These dual-tasking deficits have been explained in terms of reduced cognitive control, leading to the prediction that STs should show larger performance declines in this condition.

To indicate the efficacy of the DF distractor, falls occurring in trials in which the doorframe distractor was presented were compared with falls occurring in analogous trials (0° incline; rotating rod alternating directions) in the absence of the distractor. An omnibus ANOVA analyzed the effects of the DF distractor and phenotype based on falls during non-DF trials on day 5 and the DF trials on days 5, 6, 8 and 9 (all runs at 0° incline and rotating in alternating directions; Table 1). The passive DL distractor increased falls (main effect of DL: $F(1,65) = 4.16$, $P = 0.045$) but this increase did not differ by phenotype ($F(1,65) = 2.75$, $P = 0.10$; phenotype x distractor: $F(1,65) = 0.15$, $P = 0.70$; Fig. 2b).

On the final 5 days of this MCMCT sequence, rats were presented with the FL distractor (2 days of practice preceded 3 days of testing, 3 trials per day). Overall, 54 of the total of 67 rats retrieved at least one FL during the test trials (ST: 83%; GT: 78%). In the presence of the FL, STs fell twice as often as GTs ($F(1,65) = 4.12$, $P = 0.046$; Cohen's d : 0.51; Fig. 2c; no main effects of or interactions with the factor rod condition or trial sequence; all $F < 1.98$, all $P > 0.14$). The greater vulnerability of STs for falls was also indicated by the number of rats that experienced at least one fall across all 9 trials involving the FL distractor. While only 9/30 GTs experienced at least one fall, 21/37 STs did ($\chi^2 = 4.80$, $P = 0.029$). Rats retrieved the FL in $64.51 \pm 4.30\%$ of the trials and retrieval rates did not differ between STs and GTs ($F(1,65) = 0.14$, $P = 0.71$), rod condition or session (both $F < 2.93$, $P > 0.06$). Fall rates did not differ between animals that retrieved the FL and those that never did (animals with at least one retrieval: $6.21 \pm 1.20\%$ falls; animals with no retrievals: $6.39 \pm 2.52\%$, $P = 0.95$).

3.3. High falls rates in STs traversing a zig-zag beam

A separate group of STs and GTs of both sexes were familiarized with the 3-m long MCMCT apparatus over 5 days, including runs on the plank and (straight) stationary and followed by 3 days of practice on the zig-zag rod (stationary, in vertical and horizontal

positions, rotating at 5 RPM, and rotating at 8 RPM). Following training, rats' performances were scored on the rotating zig-zag rod with 3 runs at 5 RPM and 3 runs at 8 RPM.

If a fall occurred at one of the 2 zig-zag sections (Fig. 3a–c) rats were placed back on the rod near the straight section separating the two zigzag parts. For this reason, falls were calculated not over runs per day but over the number of zig-zag sections traversed per day (12 sections/ day). Fall rates were significantly higher in STs compared to GTs (main effect of phenotype: $F(1,18) = 5.86$, $P = 0.03$; GTs: $16.05 \pm 4.70\%$ falls, STs: $30.36 \pm 3.55\%$ falls).

There were no effects of rotating speed and sex, and no interactions between the three factors (all $F < 1.82$, all $P > 0.19$ for all). The time required to traverse the entire zig-zag beam did not differ between the phenotypes ($F(1,18) = 0.97$, $P = 0.34$; GTs: 19.57 ± 2.63 s/run, STs: 16.94 ± 2.71 s/run) and rotation speeds ($F(1,18) = 1.45$, $P = 0.24$). However, a significant interaction between the effects of phenotype and rotation speed on traversal time ($F(1,18) = 7.29$, $P = 0.02$) appeared to reflect that GTs traversed the zig-zag rod faster when it rotated at a higher rate (5 RPM: GTs: 21.15 ± 3.09 s, STs: 16.30 ± 2.62 s; 8 RPM: GTs: 18.00 ± 2.26 s, STs: 17.58 ± 2.91 s). *Post hoc* multiple comparisons failed to localize this interaction (both $t < 1.43$, both $P > 0.24$). A main effect of sex on traversal speed indicated that male rats traversed the zig-zag rod more slowly than females ($F(1,18) = 23.37$, $P < 0.001$; males: 24.20 ± 2.76 s/run, females: 12.44 ± 0.62 s/run). This effect of sex did not interact with phenotype or rotation speed (all $F < 1.30$, all $P > 0.27$).

The number of slips did not differ between the phenotypes ($F(1,18) = 2.99$, $P = 0.10$; GTs: 4.88 ± 1.01 slips/run (averaged over 6 runs, 3 per rotation speed), STs: 6.84 ± 1.32 slips/run), and there were no main effect of, or interactions involving, the factors sex and rotation speed on the number of slips (all $F < 1.55$, all $P > 0.22$). Thus, traversing the zig-zag rod produced almost twice the number of falls in STs than in GTs.

3.4. Superior zig-zag entrance control by GTs

As described above, STs fell more frequently than GTs when traversing the rotating zig-zag beam. However, because this phenotype effect was not paralleled by effects on slips and traversal time, falls in STs did not appear to have been associated with lower speed and imprecise limb placements. Thus, when compared with the straight rotating rod traversal, the rotating zig-zag beam appeared to have taxed a different set of risk factors in STs. Therefore, we conducted a detailed analysis of the zig-zag traversal performance, with the goal to determine phenotype-specific characteristics associated with, and potentially contributing to, the greater fall frequency of STs while traversing the zig-zag sections.

The zig-zag rod consisted of two zig-zag sections (Fig. 3a). Each section consisted of 3 angled parts that deviated at 45° from the long axis of the rod and which connect two additional parts that rested above or below but parallel to the axis of the rod when the rod was placed in the vertical position (Figs. 3b,e,f). Because falls predominantly occurred at the first two angled parts of the zig-zag sections (marked in red in the first section in Fig. 3a), we determined: 1) the angle of elevation above or below the horizontal plane (Fig. 3d) at the time when rats approached and entered traversal over them; 2) whether the angled part was facing downwards (Fd; Fig. 3e) or upwards (Fu; Fig. 3f); and 3) whether the angled part was

rotating or upwards (Ru; towards a higher elevation; Fig. 3g) or downwards (Rd; towards a lower elevation (Fig. 3h). For these analyses, we categorized angles of elevation at the time of entrance as flat (F; 0–30° away from the horizontal or flat level shown in Fig. 3d); medium steep (M; 31–60°) or steep (S; 61–90°, with 90° depicting the zig-zag section in vertical position, facing upward or downward as shown in Fig. 3e,f). Thus, the status of an angled part can be completely described as, for example, facing upward while rotating downward, beginning at a 45° (Fu/Rd/M). We also determined the change of angle of the section (or, pause time; 30°/sec at 5rpm) from the first contact of the angled section to entering this section. This analysis was based on 240 approaches total, in 10 STs and GTs each (6 females; 12 angled traversals per rat) from sessions following vehicle treatment.

For the 12 possible states of the angled parts of the zig-zag sections, the sum of entries per state differed between GTs and STs. Compared with an expected equal distribution for each 12 states (10 entries per state and phenotype), the actual distribution of the number of entries differed significantly for GTs ($\chi^2(11) = 30.40$, $n = 120$, $P = 0.001$) but not STs ($\chi^2(11) = 18.00$, $n = 120$, $P = 0.08$; Fig. 3i). Inspection of the data suggested that the angle of elevation at the time of entrance (F,M,S), but not Fu/Fd or Ru/Rd, differed between the phenotypes. Specifically, GTs preferably entered the zig-zag sections at flat (F) angles. Fig. 3i illustrates this finding by showing the ratio between the number of entries by GTs to STs for each of the 12 states of the angled parts of the zig-zag sections. On this graph, the states have been ordered according to these ratios. All 4 states involving a relatively flat starting point (F) were preferably entered by GTs, and all four states involving steep starting angles (S) were preferably entered by STs but, as noted above, the distribution of the number of entries by STs did not differ significantly from an equal distribution of entries across all possible states.

The finding that GTs preferably entered the angled parts of the zigzag sections when these sections are at a relatively flat angle was corroborated by an analysis of the position of the angled part at the very time of a fall. As described above, our analyses were based on 240 entries (120 per phenotype) to the first and second angled part of each zig-zag section. Both GTs and STs fell 1.6–2 times more often on the first when compared with the second angled part for each zig-zag section. In total, STs fell in 16 and GTs in 7 entries ($t(1) = 5.09$, $P = 0.02$). In 14 of the 16 trials in which falls occurred in STs, the rod was at a steep angle (all fall angles; M, SEM: $68.44 \pm 3.92^\circ$) while GTs fell from angled parts that were at flat to medium angles ($45.83 \pm 9.26^\circ$; $t(20) = 7.13$, $P = 0.02$).

These observations prompted an additional analysis to determine strategies that GTs employed to avoid entries onto the angled parts when they were at steep angles or moving towards this riskier state. As already described above, a steep angle at the time of entrance (61°–90°) is a relatively riskier state of the angled part. Moreover, if an angled part, facing up or down, also rotates (30°/s) toward a steeper angle (rotating up or down, respectively; Fu/Ru and Fd/Rd), this was classified as a “difficult approach”. A total of 62 (GTs) and 82 (STs) of such difficult approaches were analyzed (angle location at the time the rats’ forepaws were within 1 cm of the angled part: GTs: $69.60 \pm 2.05^\circ$; STs: $70.12 \pm 1.60^\circ$). However, by the time the rat entered the angled part, defined by all 4 paws being placed on that part, it was at a significantly steeper angle in STs than GTs (STs: $62.50 \pm 2.33^\circ$, GTs: $47.18 \pm 3.24^\circ$; $t(141) = 15.53$, $P < 0.001$). GTs waited significantly longer between approach

and entrance than STs (GTs 1.30 ± 0.12 s; STs: 0.85 ± 0.98 s; $t(141) = 8.50$, $P = 0.004$), equivalent to 39° and 25.5° of rotation, respectively. For example, a GT approached an angled part at 70° , Fu/Ru (from the rat's perspective the facing up angle is at the 11 o'clock position, rotating clockwise). By postponing entry by 1.3 s, the status of that angled part would have shifted over to a less risky Fu/Rd condition (moving toward the 3 o'clock position). By entering the angled part more quickly, a ST would enter it at a nearly vertical, steepest (12 o'clock) position.

4. Discussion

The present experiments tested the hypothesis that compared with GTs, STs exhibit impairments in balance and complex movement control. STs fell more frequently than GTs when traversing a rotating rod, when presented with a secondary task while traversing, or when traversing rotating zig-zag sections. GTs minimized falls from the zig-zag rod by preferably entering angled zig-zag sections when they were at, or rotating toward, a relatively less difficult traversal state.

4.1. Specificity of complex movement control deficits in STs

The present studies used the behavioral apparatus we have previously used to develop and characterize an animal model of enhanced fall propensity in Parkinson's disease. In this prior work, rats with combined losses in basal forebrain cholinergic and nigro-striatal dopaminergic neurons, as seen in Parkinsonian fallers, fell significantly more frequently than control rats. Such rats fall relatively frequently across a wide range of testing conditions and, importantly, fall rates were significantly correlated with impairments in sustained attentional performance [21,24,25,28,33,40]. Thus, these prior findings mirrored the relationship between falls and attention seen in Parkinsonian fallers [22,23,41–47]. We have interpreted these findings as reflecting the cholinergic loss of (compensatory) attentional control in rats with dopaminergic impairments of movement selection and sequencing [21].

Compared with GTs, STs had higher fall rates in three specific testing conditions: a) rod rotating in alternating directions from run to run; b) in the presence of dual task demands; c) rotating zig-zag rod. These testing conditions share exquisite demands on the cognitive control of balance and complex movement, including flexibility in the planning and monitoring of balance and paw placements across changing rotation conditions, maintaining balance and upright position on the rotating rod while retrieving the Froot Loop and, in GTs, awaiting zig-zag entry, and forward planning to select "easy" zig-zag states. The absence of a phenotype effect on falls in the presence of the doorframe distractor - a means to provoke gait disruption in patients with Parkinson's disease [29] - may have been due to high fall rates in both groups of rats and a resulting "ceiling effect". Thus, the deficits seen in STs may have reflected primarily the limited capacity of their basal forebrain-cortical projection system to produce a sustained response to stimulation [15] and the corresponding deficits in executive/top-down control [for review see [48]. STs do not have known dopaminergic deficits, and thus as expected, did not exhibit obvious motor or locomotor deficits as indicated by plank, stationary and rotating rod traversal. However, given that rats with solely cholinergic lesions do not fall more frequently than control rats, even though they exhibit attentional impairments [25], the present results raise the question of whether STs also

harbor cortico-striatal abnormalities, in addition to their documented cholinergic deficits [15]. In particular, the choline transporter dysregulation shown in the cortex of STs [15] likely also limits the signaling capacity of the terminals of other cholinergic systems, including the brain stem cholinergic projections to the basal ganglia and thalamus, and striatal cholinergic interneurons. Together, a limited capacity for cholinergic signaling in these three cholinergic projection systems may be sufficient to cause falls [28,49–51].

4.2. Timing of forward movement as an aspect of superior top-down control in GTs

GTs preferably entered the zig-zag sections at flat angles, and they waited significantly longer than STs to avoid entering the zig-zag when at riskier states. Waiting while on the horizontal, rotating portions *per se* appears to be a challenging task, as paw placements and balance require continuing adjustment. While we previously demonstrated the attentional components of the relatively superior executive control of GTs [14], the present evidence significantly expands the characterization of the cognitive style of GTs by suggesting that GTs are also capable of timing and planning forward movement, including the monitoring of the state of a particularly challenging portion of the beam. Timing has long been considered an essential aspect of cognitive control functions that is mediated by cortico-striatal circuitry [52–54] and depends on cholinergic activity [55,56]. Given the cholinergic capacity limitations of STs [15], and the speculation that cortico-striatal information processing is also relatively impaired in STs (above), relatively poorer timing in STs may constitute an expected finding. However, it not clear whether the relatively poor timing of entrances onto the zig-zag portions by STs primarily reflected timing deficits *per se* or was secondary to limitations in forward planning. Irrespective of the specific cognitive mechanisms underlying the zig-zag performance of STs, the present findings offer a significant broadening of the impact of the opponent cognitive styles utilized by STs versus GTs [57].

5. Conclusion

The present findings establish relationships between two hitherto unrelated fields of research: addiction vulnerability traits and complex movement control. Sign-tracking behavior signals the presence of an endophenotype, or a transdiagnostic risk factor, for a range of neuropsychiatric disorders characterized by a limited capacity for goal-directed, or top-down attentional control and associated executive deficits [58,59]. This view then also predicts the presence of gait and movement abnormalities in patients sharing this endophenotype, such as schizophrenia, as was observed by Bleuler [“...der Gang ist oft auffallend.” Translation: “.the gait is often conspicuous.”; [60], see also [61,62].

Together the present results point to the critical and potentially common contributions of cholinergic function to the control of both cognition and action. Recent evidence from Rinne et al. [63], based on research on stroke patients, also indicates the critical and causal role that top-down attention and executive control play in movement control in humans. Future research on the neuronal mechanisms mediating the opponent cognitive-attentional styles indexed by sign-tracking, and the heuristic opposite, goal-tracking, is likely to advance our understanding of risk factors for a wide range of psychiatric and neurological disorders.

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Fig. 1.

Individual PCA index values across the five PCA training sessions for STs and GTs (data from rats eventually classified as intermediates are not shown). The final classification of the ST or GT phenotype was based on averaging PCA index values from PCA sessions 4 and 5. The pre-determined PCA index score cutoffs for STs and GTs were 0.5 and -0.5 respectively. Rats with PCA scores shown in **a** ($n = 30$ GTs and 37 STs; all males) were used for the assessment of their performance using apparatus I), while those with scores depicted in **b** ($n = 11$ GTs and 11 STs; 5 males and 6 females per group) were assessed on the zig-zag beam (apparatus II).

Fig. 2.

a: Reversing the rotation direction of the rod to the unfamiliar counterclockwise direction significantly increased falls in both GTs and STs ($n = 30$ GTs and 37 STs; all males) but, in contrast to the ability of GTs to rapidly improve reversed rotating rod traversal performance, the fall rate of STs failed to decrease from trial 1 to trial 2 (see Results from omnibus ANOVA; the graph depicts the percent trials per rotation condition that yielded falls). **b:** The passive doorframe (DF) distractor (see inset for illustration) increased fall rates in both phenotypes. In contrast, the Froot Loop (FL) dual task situation (**c**) generated significantly more falls in STs compared with GTs (see Results for ANOVAs; M, SEM; *post hoc* comparisons: *, **, $P < 0.05$, 0.01).

Fig. 3.

a: Dimensions of the 3-m long zig-zag beam. Note that the beam consisted of two zigzag sections; the number of falls was calculated based on the number of sections traversed (one beam run = two sections). Falls occurred primarily from the first two angled parts of each zig-zag section (for illustration, the first two angled parts of the first zig-zag section are marked in red). **b** and **c** show a rat (that was not part of the present experiment) traversing the rotating zig-zag beam. **d-h:** Determination of the state of the angled parts and preferred states of angled parts at the time of entry by GTs and STs. These analyses were limited to the status of the first two angled parts of the two zig-zag sections (**e,f**; see also **a**). The status of an angled part was described by the angle of elevation above or below the horizontal plane (**d**) at the time when rats approached them and entered traversal over them, whether the angled part was facing downwards (Fd; **e**) or upwards (Fu; **f**); and whether the angled part was rotating upwards (Ru; towards a higher elevation; **g**) or downwards (Rd; towards a

lower elevation; h). Furthermore, based on overall fall frequencies, angles of elevation at the time of entrance were categorized as flat (F; 0–30° away from the horizontal or flat level shown in d); medium steep (M; 31–60°) or steep (S; 61–90°, with 90° depicting the zig-zag section in vertical position, facing upward or downward as shown in b). Thus, the status of the angled part can be described by these three dimensions, yielding 12 conditions (see abscissa in i). We analyzed 12 entries per rat (120/phenotype) and expressed preferences by computing the GT/ST ratio of entries for a particular state. For example, GTs entered the angled part when it was at the Fu/Rd/M state 10 times but STs only 3 times, yielding a 3.3 fold preference for this status in GTs (see most left bar in i). In i, the 12 possible states of the angled parts are ordered, left to right, from high to low ratios, with ratios > 1 reflecting the preferences of GTs, and ratios < 1 those of STs. The distribution of entries preferred by GTs, but not STs, differed from the expected random distribution. GTs generally preferred entering the angled parts when they were at a flat (F) angle (see all four bolded F conditions in the left half of i). As described in Results, GTs achieved avoiding entrances on an angled part when it was in a relatively riskier position by waiting longer prior to entry, thereby allowing it to rotate to a more favorable angle. Obviously, this required GTs to maintain balance on the rotating horizontal parts that precede the angled parts for longer periods than STs (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

Table 1

Experiment #1 MCMCT Test Conditions (1.59m length).

Day	Trial type	Rotating (10 rpm)	incline (degrees)	distractor	number of trials
1	plank shaping		0		2
	plank		0		3
2	rod shaping		0		2
	rod		0		3
3	plank		25		3
	rod		25		3
4	rod	cc	0		3
	rod	cc	25		3
5	rod	cc-cw-cc-cw	0		4
	rod	cc-cw	0	doorframe	2
6	rod	cc-cw-cc-cw	25		4
	rod	cc-cw	0	doorframe	2
7	plank		40		3
	rod		40		3
8	rod	cc	40		3
	rod	cc-cw	0	doorframe	2
9	rod	cc-cw-cc-cw	40		4
	rod	cc-cw	0	doorframe	2
10	rod/froot loop distractor shaping		0	froot loop	3
11	rod/froot loop distractor shaping	cc	0	froot loop	3
12	rod		0	froot loop	3
13	rod	cc	0	froot loop	3
14	rod	cw	0	froot loop	3

cc, cw: counterclockwise, clockwise.

Table 2

Experiment #3 MCMCT Test Conditions (3.00m length).

Day	beam	Rotating (speed)	number of trials
1	plank	n/a	6
2	straight rod	no	6
3	horizontal zig-zag	no	3
	vertical zig-zag	no	3
4	zig-zag (training)	5 RPM	6
5	zig-zag (training)	8 RPM	6
6	zig-zag (testing)	5 RPM	3
	zig-zag (testing)	8 RPM	3