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## **The Rat Lux Actuating Search Task (LAST) and Effects of Sleep Deprivation on Task Reversal Performance**

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## **Abstract**

Sleep deprivation (SD) causes significant deficits in multiple aspects of cognition, including sustained attention and working memory. Investigating the neural processes underpinning these cognitive losses has proven challenging due to the confounds of current animal tasks; many employ appetitive or aversive stimuli to motivate behavior, while others lack task complexity that translates to human studies of executive function. We established the Lux Actuating Search Task (LAST) to circumvent these issues. The LAST is performed in a circular, open-field arena that requires rats to find an unmarked, quasi-randomly positioned target. Constant low-level floor vibrations motivate ambulation, while light intensity (determined by the rodent's proximity to the target destination) provides continuous visual feedback. The task has two paradigms that differ based on the relationship between the light intensity and target proximity: the Low Lux Target (LLT) paradigm and the High Lux Target paradigm (HLT). In this study, on days 1 to 6, the rats completed nine trials per day on one of the two paradigms. On day 7, the rats were either sleep deprived by gentle handling or were left undisturbed before undertaking the opposite (reversal) paradigm on days 7 to 9. Our results showed that SD significantly impeded the ability of Long Evans rats to learn the reversal paradigm, as indicated by increased times to target and increased failure percentages compared to rats whose sleep was undisturbed. Rats also showed reduced learning with the HLT paradigm, as the initial task or as the reversal task, likely due to the rodents' photophobia limiting their motivation to navigate toward a bright light, which is required to succeed.

## 1. Introduction

High-pressure decision-making scenarios, requiring sustained attention and executive functions, are common to demanding occupations (e.g., military, emergency services, and healthcare). To adequately attend to the demands of these scenarios, individuals must partner knowledge acquired from previous decisions with new information presented in the context of a dynamic environment. Thus, successful decision-making requires cognitive flexibility — the ability to adjust behavior in response to changing contingencies. Unfortunately, many cognitively demanding occupations require long work hours and shift work, which is associated with poor sleep, errors in decision-making, and reduced cognitive flexibility capabilities (James et al., 2017; Ganeson et al., 2019; McHill and Wright., 2019).

Reversal learning paradigms have been integral to identifying the neural correlates of cognitive flexibility. Several studies suggest that reversal learning is mediated by cortico-striatal networks (Remijne et al., 2005; Ghahremani et al., 2010). Although lesions in these regions have led to reversal learning deficits (Fellows and Farah, 2003, Hornak et al., 2004), modulating cortico-striatal neurotransmitter activity has had limited success in clinical settings (Marinova, Chuang, & Fineberg, 2017; Robbins, Vaghi, & Banca, 2019). The specific mechanisms underpinning reversal learning are still under investigation; however, the detrimental impact of sleep deprivation (SD) on reversal learning is consistent across human (Ghahremani et al., 2010; Pilcher & Huffcutt, 1996; Rahman, et al., 1999), primate (Chau et al., 2015; Dias et al., 1996) and rodent models (Palchykova S et al., 2006; Marti et al., 2020).

Elucidating the neurobiological basis of SD-induced deficits in cognitive flexibility requires a robust animal paradigm that yields SD-mediated declines in performance that

are comparable to the complexities of human decision making. Studies in humans have demonstrated that sleep loss and fatigue critically impact sustained attention (Gunzelmann et al., 2011; Chua et al., 2014); thus, to be an accurate translational model, a rodent paradigm must be capable of demonstrating and quantifying this key aspect of cognition. Such a paradigm should also be simple enough to allow for rapid task acquisition – thereby reducing resource and time requirements – while maintaining sufficient complexity to accurately model the dynamic and continuous performance feedback that is crucial to many applications of empirical and real-world human tasks.

Current rodent reversal-learning paradigms use appetitive or aversive incentives to reinforce task-related behavioral responses. Appetitive rewards, such as food pellets and water given in response to successful performance, can be confounded by satiation, which reduces reward salience (Bissonette et al., 2014; Goltstein, et al., 2018). To overcome this, rodents are typically food- or water-restricted prior to task initiation — though this naturally leads to a gradual decrease in motivation as the hunger or thirst is reduced, which introduces changes to the animals' physiological state (Iivonen et al., 2003; Oonk et al. 2015). Meanwhile, aversive stimuli, such as forced swim and foot shock, induce physiological and psychological confounds, such as fatigue and stress induction, which can impede a clear interpretation of results (Agterberg & Versnel; 2014 Armario, 2021; Hurtubise & Howland, 2017).

The Lux Actuating Search Task (LAST) is a novel, open-field spatial navigation paradigm described herein. It replaces traditional motivational stimuli with gradient visual feedback used to guide rats to an unmarked target destination (Fig. 1). Our group introduced an earlier iteration of this task as a mouse paradigm (Bushana et al., 2020)

and later as a rat paradigm (Lawrence-Sidebottom et al., 2021), called the Vibration Actuating Search Task (VAST), which used floor vibration as continuous haptic and audio feedback for guidance. Here, we have successfully implemented the LAST to examine how SD affects cognitive flexibility, as evidenced by performance decrements in a cued reversal spatial navigation task. In these experiments, the rat's proximity to the target destination determined the light intensity, providing continuous feedback. With movement toward the target, the lights either diminished or increased in intensity, corresponding with the Low Lux Target (LLT; Fig. 2A and B) paradigm and the High Lux Target (HLT; Fig. 2C and D) paradigm, respectively. Floor vibrations were delivered continuously, and without change in intensity, throughout the task. Once the rat reached the unmarked target destination, the lights and vibration ceased, and the rat was removed from the apparatus. Thus, the rat's distance from the target destination modulated the visual feedback intensity in a smooth, graded fashion (Fig. 2B and D). The instantaneous rodent spatial position-based continuous feedback on the LAST and earlier VAST (Bushana et al., 2020; Lawrence-Sidebottom et al., 2021) is unprecedented compared to contemporary rodent goal-oriented navigational tasks.

## **2. Methods**

### **2.1 Animals**

56 male Long Evans rats aged 9–12 weeks were used for these studies. The rats were progeny from our onsite colony generated from breeder stock (Envigo). Rats were housed two to a cage at  $23 \pm 1$  °C and placed on a 12:12hr light:dark cycle with access to food and water *ad libitum*. Cages were also enriched with nesting materials and a Nylabone chew. All LAST-related experimentation (including handling) was performed during the final 2 hours of the light cycle, zeitgeber time (ZT) 10–12, except for the 10-

hour SD which occurred from ZT0-10 in some cohorts. Rats completed the experiment in serial cohorts of four. Cohorts were randomly assigned to SD or control (CONT) groups. All animal procedures were approved by the Washington State University Institutional Animal Care and Use Committee and were compliant with National Institutes of Health guidelines. At the end of the study, rats were euthanized by CO<sub>2</sub> inhalation in a manner consistent with the Panel on Euthanasia of the American Veterinary Medical Association.

## 2.2 Apparatus

The LAST was delivered on a circular open-field arena (122 cm diameter), which was encircled by a 45 cm wall of white acrylic (Fig. 1A). The open-field arena was painted flat tan to reduce glare. Attached to the top of the wall were two LED strips: one white (850 nm, type 5050) and one infrared. Four support legs elevated the arena, with vibration motors mounted at the base of each leg. This elevation also served to obscure any extra-maze visual cues from the rats.

### 2.2.1 Position and motion tracking

A downward-angled strip of infrared LEDs mounted around the top of the wall provided platform coverage adequate for tracking throughout the surface area of the arena. A Manta Vision camera video, mounted above the open-field arena, recorded each trial through an infrared filter, allowing the rat's position to be determined and recorded for data analysis of trial performance. The camera recorded position at ten frames per second, and image acquisition was implemented in LabVIEW using NI-IMAQdx 4.0 driver software (National Instruments, Austin, TX). The video feed was filtered based on a predetermined pixel intensity threshold, enabling us to distinguish the rat from the platform. A center mass algorithm was used to define the rat's centroid to estimate and

track the rat's position from the resulting image. A criterion of at least 1 pixel (approximately 1 mm) change in position was used to determine whether the rat moved between frames (Dielenberg, Halasz & Day, 2006). The data were saved using the LIVE HDF5 software package (UPVI LLC, Hancock, MI).

### 2.2.2 Visual LED feedback

The DC output was governed by a pulse width modulator that controlled the duty cycle of the second downward-angled LED strip of white lights via the LINX vi package (LabVIEW, MakerHub). A LabVIEW software subroutine calculated the distance between the centroid position and the target destination. These values drove the microcontroller to govern the intensity of the lights (range: 35–350 lux). Figure 2 shows the relationship between distance to target and light intensity across the entire field, as measured with a lux meter (sampled in triplicate for each X, Y coordinate and averaged).

## 2.3 Experimental Design

### 2.3.1 Handling/habituation protocol

The rats were habituated over ten days (H1-H10). On the first five days (H1-H5), each rat received 5 minutes of gentle handling to acclimate them to the experimenters. The handling consisted of gentle stroking, holding, and repeatedly removing and replacing the rats in their home cages to acclimate them to the LAST process. On H6, the entire cohort was placed in the LAST arena for 300 s in the absence of lights and vibration. Then, each individual rat was placed in the LAST arena for 300 s without lights or vibration. On H7, the rats were individually exposed to the arena for 150 s with no lights or vibration, then for 150 s with only lights and no vibration. On H8, the rats were exposed to the arena for 300 s without lights but with continuous, low-level vibration



delivered whenever they were on the arena's perimeter (defined as 15 cm from the edge of the arena) to encourage movement toward the center. On H9 and H10, the rats were exposed to the arena for 300 s in the presence of ambient white light ( $63 \pm 3$  lux) and constant, low-level vibration when they were on the arena's perimeter.

### 2.3.2 LAST sessions and sleep deprivation

Prior to LAST performance testing, the rats' home cages were moved from the colony room to the experiment room. For each trial, each rat was positioned to face the apparatus wall at one of four predetermined entry locations: A, B, C, or D. Each entry point had three potential target destinations (depicted as A1-3, B1-3, C1-3, D1-3; Fig. 1B), all of which were 25 cm in diameter and equidistant from their corresponding entry point. Target destination borders were at least 15 cm from the wall to prevent unintentional discovery from thigmotaxis. Entry points and target destinations were quasi-randomly selected for each performance testing day using a Latin square. Once a rat entered the apparatus, the motors began vibrating at a constant 2500 RPM (41.6 Hz) and the LED strips illuminated at an intensity determined by the rat's proximity to the target destination (Fig. 2). In the LLT paradigm, the illumination intensity diminished as the rat approached the target (Fig. 2A and B). In the HLT paradigm, the illumination intensity increased as the rat approached the target (Fig. 2C and D). The vibration and lights shut off immediately once the rat entered the target, or after 90 s of searching without locating the target. The latter was classified as a "failed" trial. Rats were tested with nine trials each on either the LLT or HLT paradigm on each of the first six days (54 trials total). On day 7, at light onset (ZT0), the rats either remained in their home cage for spontaneous sleep (CONT group) or were subjected to total SD by gentle handling for 10 hours (SD group). At ZT10, immediately following spontaneous sleep or 10-hours SD, rats were tested on the reversed paradigm for the remaining three days.

Rats alternated trials with their cage mate, and the second pair from a cohort began trials immediately after the first pair completed all nine trials. The arena was cleaned with 10% ethanol between each trial. After completing all nine trials, two Froot Loops were given to each rat as a reward. After each cohort completed their nine trials for the day, the rats were returned to the colony room in their home cages. Sessions occurred once per day, beginning at ZT10, on five successive days before a two-day weekend break, with the remaining four sessions carried out the following week.

## 2.4 Statistical analyses

Data were analyzed using SAS 9.4. All type I error thresholds were set to  $\alpha = 0.05$ . Group trends are reported as mean  $\pm$  standard error of the mean (SEM), as calculated using estimates within each analysis of variance (ANOVA). Rats with more than two failures (<78% success) on day 6 were eliminated from the analysis. 23 rats did not successfully complete >78% of the trials on day 6, indicating inadequate task acquisition and retention (HLT  $n=16$  vs. LLT  $n=3$ ), and were therefore excluded from the data analyses. Thus, 32 rats were included in the data analyses, of which, 18 were in the CONT group (LLT reversal  $n=10$ ; HLT reversal  $n=8$ ), and 14 were in the SD group (LLT reversal  $n=7$ ; HLT reversal  $n=7$ ).

### 2.4.1 Dependent variables

For each trial, "failure" in task performance was based on whether the rat located the target within 90 s. Time to target was the time it took for the rat to end the trial, which is the time from the entry to the target destination for successful trials or 90 seconds for failed trials. Path distance was the cumulative movement of a rat's centroid from the trial start to finish. Time still was operationally defined as the total amount of time the rat spent immobile or moving a negligible amount (e.g., a position change due to a non-

ambulatory head movement), operationalized as any 0.1 s interval during which the change in position was less than 15 pixels (approximately 1.5 cm).

#### 2.4.2 Between-session analyses

Data acquired from the nine trials per day were averaged for each rat on each dependent variable (*viz.* failure percentage, time to target, path distance, and time still) and used for the between-session data analyses. Data were analyzed using mixed-effects ANOVA with fixed effects of day, group (SD and CONT), task paradigm (HLT – LLT or LLT – HLT), and a random effect of the subject on the intercept. For each task paradigm, planned contrasts were performed between consecutive days – i.e., day 1 was compared to day 2, day 2 was compared to day 3, etc. – to assess for changes in performance over days. All rats were analyzed as a single group for comparisons between day 1 and day 6. For comparisons between days 6 to 9 the rats were differentiated into SD and CONT groups. Also, for each task paradigm, between-groups planned contrasts were performed for days 7 to 9 to determine the effect of SD on post-reversal performance.

#### 2.4.3 Within-session analyses

For the within-session data analyses, time to target and path distance results from each block of three trials (i.e., trials 1-3, 4-6, and 7-9) were averaged per day for each subject over days 1 to 6 to assess within-session daily performance. Data were analyzed using mixed-effects ANOVA with fixed effects of day, trial block, task paradigm, and a random effect of the subject on the intercept. For each task paradigm, planned contrasts were performed between the first trial block (trials 1-3) and the last trial block (trials 7-9) on each day.

### 3. Results

### 3.1 Between-session data analyses

For percent failures, significant main effects of day ( $F_{8,224}=9.48$ ,  $p<0.001$ ), group ( $F_{1,224}=7.93$ ,  $p=0.005$ ), and a significant interaction between day and group ( $F_{8,224}=2.80$ ,  $p=0.006$ ) indicate that SD impedes task completion in reversal learning (Figs. 3A and E). Task paradigm (LLT vs. HLT) also affected trial failures per significant interactions with day ( $F_{8,224}=13.22$ ,  $p<0.001$ ) and with group ( $F_{1,224}=8.46$ ,  $p=0.004$ ). A main effect of day ( $F_{8,224}=7.00$ ,  $p<0.001$ ) and a day by task paradigm interaction ( $F_{8,224}=13.45$ ,  $p<0.001$ ) were detected for time to target (Fig. 3B and F). Significant interactions between day and group ( $F_{1,224}=3.88$ ,  $p<0.001$ ) and group and task paradigm ( $F_{1,224}=4.11$ ,  $p=0.044$ ) suggest that SD delayed task completion times. Task performance efficiency changed over sessions as demonstrated by a significant main effect of day ( $F_{8,224}=4.60$ ,  $p<0.001$ ) and significant interactions of day with task paradigm ( $F_{8,224}=9.62$ ,  $p<0.001$ ) and with group ( $F_{8,224}=3.06$ ,  $p=0.003$ ) on path distance (Fig. 3C and G). Finally, time still was different across days ( $F_{8,224}=6.54$ ,  $p<0.001$ ), groups ( $F_{1,224}=7.07$ ,  $p=0.008$ ) and this effect was also reflected by a day and group interaction ( $F_{8,224}=2.41$ ,  $p=0.017$ ; Fig. 3D and H). Other significant interactions on time still occurred between task paradigm and day ( $F_{8,224}=9.39$ ,  $p<0.001$ ) and group ( $F_{1,224}=7.78$ ,  $p=0.006$ ).

#### 3.1.1 HLT– LLT reversal paradigm

For rats subjected to the HLT paradigm during the pre-reversal phase, the incremental decreases from day 1 to day 6 on percent failures were not statistically significant (between-day comparisons  $p>0.05$ ; Fig. 3A). Time to target and time still changes across days were also not detected (Fig. 3B and D, solid gray bars). However, we did observe a 1.5 m decrease in path distance from day 4 to day 5 ( $F_{1,224}=5.07$ ,  $p=0.025$ ) (Fig. 3C, solid gray bars).

Failure percentage, time to target, path distance, and time still following reversal to LLT were unchanged (day 6 vs. day 7) (Fig. 3A-D gray striped bars) in the CONT group. These results indicate that well-rested rats rapidly adapt to the more ethologically relevant behavior of low lux preference when approximating the target in the LLT reversal paradigm following the HLT pre-reversal paradigm. Furthermore, the performance of well-rested rats was not affected by reversal to the LLT paradigm from the HLT counter-preferent paradigm.

SD group performance was significantly impaired on the first day of reversal to the LLT paradigm. From day 6 to day 7, the percentage of failures increased by about three-fold ( $F_{1,224}=12.93$ ,  $p<0.001$ ), time to target increased by 25.3 s ( $F_{1,224}=52.97$ ,  $p<0.001$ ), path distance increased by 2.2 m ( $F_{1,224}=4.82$ ,  $p=0.029$ ), and in time still increased by 11.9 s ( $F_{1,224}=7.44$ ,  $p=0.007$ ; Fig. 3A-D black striped bars). While the failure percentage, time to target, path distance, and time still decreased over the reversal days (day 7 to day 9) for the SD group, the only statistically significant change observed was a decrease in the percentage of failures from day 7 to day 8 ( $F_{1,224}=6.60$ ,  $p=0.011$ ). Despite moving to a much easier LLT paradigm, the lack of sleep disrupted cognitive flexibility on all performance measures.

Between-groups comparisons confirmed that the SD group performed worse than the CONT group on the first day of reversal (day 7), with the SD group failing the task more than the CONT group (46.0% vs. 8.3%;  $F_{1,224}=15.64$ ,  $p<0.001$ ), spending 31.4 s more time finding the target ( $F_{1,224}=10.57$ ,  $p=0.001$ ), and staying still for 15.1 s longer ( $F_{1,224}=9.69$ ,  $p=0.002$ ) than the CONT group. Path distance did not differ between-groups on the first day of reversal. The percentage of failures, time to target, and path

distance also did not differ between groups on the subsequent reversal days (days 8 and 9) (Fig. 3A-C). However, time still was greater for the SD group than the CONT group on day 8 ( $F_{1,224}=4.18$ ,  $p=0.042$ ) and day 9 (comparison approached statistical significance;  $F_{1,224}=3.02$ ,  $p=0.084$ ). These results indicate that SD impaired the rats' ability to perform the LLT paradigm after being subjected to the HLT paradigm. There appear to be improvements in LLT paradigm performance over the reversal days for the SD group, suggesting a recovery in the performance impairments induced by SD, but these changes were not statistically significant.

### 3.1.2 LLT – HLT reversal paradigm

Increased response efficiencies in rats initially performing the LLT paradigm were more subtle but evident from day 5 to day 6, based on a 13.7 point decrease in percentage of failures ( $F_{1,224}=4.69$ ,  $p=0.031$ ), a 10.5 s decrease in time to target ( $F_{1,224}=5.22$ ,  $p=0.023$ ) and a 5.6 s decrease in time still ( $F_{1,224}=4.52$ ,  $p=0.035$ ; solid gray bars on Fig. 3E, F and H, respectively).

Following reversal to the HLT paradigm, the well-rested CONT group exhibited impairments in performance. From day 6 to day 7, the percentage of failures increased by about four-fold ( $F_{1,224}=18.47$ ,  $p<0.001$ ), time to target increased by 18.0 s ( $F_{1,224}=8.91$ ,  $p=0.003$ ), path distance increased by 3.1 m ( $F_{1,224}=13.66$ ,  $p<0.001$ ), and time still increased by 6.6 s (comparison approached statistical significance;  $F_{1,224}=3.21$ ,  $p=0.075$ ; Fig 3E-H, gray striped bars). For the CONT group, the percentage of failures was stable from day 7 to 8 but decreased from day 8 to day 9 (comparison approached statistical significance;  $F_{1,224}=2.96$ ,  $p=0.087$ ). Time to target increased from day 7 to 8 (comparison approached statistical significance;  $F_{1,224}=3.25$ ,  $p=0.073$ ), as did time still

( $F_{1,224}=10.35$ ,  $p=0.002$ ), then both variables were stable from day 8 to 9. Path distance was stable over the post-reversal days (days 8 and 9).

For the SD group, performance was significantly impaired on the first reversal day. Most notably, from day 6 to day 7, the percentage of failures increased by approximately fourteen-fold ( $F_{1,224}=51.71$ ,  $p<0.001$ ). Additionally, time to target increased by 52.4 s ( $F_{1,261}=52.97$ ,  $p<0.001$ ), path distance increased by 5.7 m ( $F_{1,261}=31.58$ ,  $p<0.001$ ), and time still increased by 25.5 s ( $F_{1,261}=33.91$ ,  $p<0.001$ ; Fig. 3E-H, black striped bars). The percentage of failures observed for the SD group decreased from day 7 to day 8 ( $F_{1,224}=4.22$ ,  $p=0.041$ ), but remained stable from day 8 to day 9. Time to target, path distance, and time still were stable from day 7 to day 9 for the SD group, though the comparison between day 7 and 8 approached statistical significance for time to target ( $F_{1,224}=2.85$ ,  $p=0.093$ ).

Between-groups comparisons revealed that the SD group performed worse than the CONT group on the first day of reversal (day 7). Indeed, the SD group failed the task more than the CONT group (71.4% vs. 42.2%;  $F_{1,224}=10.36$ ,  $p=0.002$ ), spent 32.1 s more time reaching the target ( $F_{1,224}=8.96$ ,  $p=0.003$ ), and spent 14.3 s more time still ( $F_{1,224}=9.51$ ,  $p=0.002$ ). However, no difference in path distance was observed between SD and CONT on day 7. On days 8 and 9, the CONT and SD groups did not differ in failure percentage, time to target, or time still, but the SD group did have a significantly greater path distance than the CONT group on day 9 ( $F_{1,224}=4.12$ ,  $p=0.044$ ). These results indicate that when compared to the well-rested CONT group, SD impaired the rats' ability to perform the HLT paradigm after reversal.

### 3.2 Within-session data analyses

In the analysis of trial blocks for time to target, there were statistically significant effects of group ( $F_{1,510}=5.93$ ,  $p=0.015$ ), day ( $F_{5,510}=6.00$ ,  $p<0.001$ ), and trial block ( $F_{2,510}=40.97$ ,  $p<0.001$ ). The interaction of group and day was also significant ( $F_{5,510}=2.44$ ,  $p=0.034$ ). For path distance, there were significant effects of group ( $F_{1,510}=4.89$ ,  $p=0.027$ ), day ( $F_{5,510}=3.68$ ,  $p=0.003$ ), and trial block ( $F_{2,510}=21.82$ ,  $p<0.001$ ). These data suggest that rat response efficiency increases across trials. Within-session data for time to target and trial block separated by task paradigm are reported in Table 1.

### 3.2.1 HLT paradigm

Rats completing the HLT paradigm in the initial phase, on average, lowered their time to target from the first to the third trial block by 16.1 s ( $F_{1,510}=5.77$ ,  $p=0.017$ ), 25.4 s ( $F_{1,510}=14.22$ ,  $p<0.001$ ) and 22.4 s ( $F_{1,510}=11.19$ ,  $p<0.001$ ) on days 4, 5 and 6, respectively. In addition, path distance was shortened from the first the third block by 2.1 m ( $F_{1,510}=4.13$ ,  $p=0.043$ ), 2.2 m ( $F_{1,510}=4.72$ ,  $p=0.030$ ) and 3.1 m ( $F_{1,510}=8.81$ ,  $p=0.003$ ), respectively. These results demonstrate that, especially as the number of days increased, the rats learned to perform the HLT paradigm more efficiently from the start to the end of each day.

### 3.2.2 LLT paradigm

Likewise, rats completing the LLT paradigm in the initial phase, time to target decreased on days 2 ( $F_{1,510}=6.61$ ,  $p=0.010$ ), 3 ( $F_{1,510}=4.78$ ,  $p=0.029$ ), and 6 ( $F_{1,510}=17.32$ ,  $p<0.001$ ) from the first and the third block by 16.2 s, 13.8 s, and 21.2 s, respectively. Path distance was shorter in the third block compared to the first block on days 1 ( $F_{1,510}=5.75$ ,  $p=0.017$ ), 2 ( $F_{1,510}=4.57$ ,  $p=0.033$ ), 3 ( $F_{1,510}=7.10$ ,  $p=0.008$ ), and 6 ( $F_{1,510}=11.90$ ,  $p<0.001$ ) by 2.3 m, 2.1 m, 2.6 m and 3.4 m, respectively. As with the HLT



paradigm, these results indicate that the rats learned to perform the LLT paradigm more efficiently from the start to the end of each day.

#### **4. Discussion**

This study introduces a rapidly learned, ambient light-cued navigational task that demonstrates significant performance deficits incurred due to SD. We used the LAST to assess cognitive flexibility in rats, while avoiding confounds that are common to reversal learning paradigms. Indeed, the implementation of lights and vibration in lieu of foot shock, forced swim, and other aversive stimuli are extremely favorable given the impact of stress (LeBlanc, 2009; Yaribeygi et al., 2017) and fatigue (Van Dongen & Dinges, 2005; Chen et al., 2021) on behavior and performance. Other paradigms have also been designed to circumvent the common confounds of rodent paradigms. For example, similar to the LAST, the Barnes maze utilizes bright lights and open spaces to encourage rodents to locate an unmarked escape box. However, this task has faced criticism due to the high light intensity, ranging between 600–1000 lux. Long-term exposure to white LEDs with intensities of as little as 500 lux can induce retinal damage in albino rats and pigmented rats (Krigel et al., 2016). Furthermore, our previous study showed that exposure to 900 lux incurred corticosteroid levels comparable to both foot shock and forced swim (Lawrence-Sidebottom et al., 2021).

In contrast, in the LAST, the rats averaged only 6.83 mins per session, with the maximum light intensity in the HLT paradigm approaching 350 lux. This upper lux range is lower than the recommended lux for domestic lighting in a vivarium. We also recently demonstrated that rats exposed to vibration and bright light had lower corticosterone levels than those exposed to forced swimming in water, and that rats exhibited place preference for vibration over foot shock, water, and bright light environments

(Lawrence-Sidebottom et al., 2021). Although the rats selected to spend more time in an environment with floor vibrations over bright light, the number of entrances to bright light vs. vibration were similar. Additionally, the place preference observed for the floor vibration environment was more pronounced for comparisons between vibration vs. foot shock and water. Notably, in the previous study of place preference, we used more than double the brightest light intensity than was used in the LAST (900 lux vs. 350 lux). Within the context of these previous findings, our present application of bright light in the LAST uses light that is likely to be much less aversive and is below the threshold for retinal damage (Krigel et al., 2016).

Another criticism of the Barnes maze is that there is little incentive to attempt to complete the trial, due to the lack of a strong motivational stimulus. The LAST addresses this criticism because it pairs visual cues with haptic motivation delivered via continuous low-level floor vibrations. It has been demonstrated that rodents are sensitive to vibrations (Norton et al., 2011), resulting in effects on breeding efficacy (Atanasov et al., 2015, Rasmussen et al., 2009) and digestion (Toraason et al., 1980). Furthermore, long-term, whole-body vibrations (240 mins) produce increases in circulating glucocorticoid levels and nominal changes in brain serotonin and noradrenaline levels in rats (Ariizumi & Okada 1983 & 1985). However, the LAST uses a low intensity of vibration (41.6 Hz), which is safely outside the 70–100 Hz range that consistently induces behavioral responses in rats (Garner et al., 2018). This low intensity, paired with the relatively short duration of exposure and intensive habituation protocol, sufficiently motivates behavior while minimizing anxiety/stress-related neurochemical responses. In support of this, the rats exhibited reduced thigmotaxis (a proxy for rodent stress) from the second habituation day relative to the third and fourth habituation day. This was evidenced by 25 s longer dwell time in the center (the inner

92 cm) from the arena edge (the outer 15 cm;  $p < 0.001$ ) and on average 4 more entries ( $p = 0.002$ ) into the arena center on the third and fourth habituation days compared with the second habituation day.

While the floor vibration provided a motivational stimulus with only modest stress induction, the ambient light cues in the LAST also confer moment-to-moment visual feedback on performance to aid the rat in locating the target destination. Commonly used rodent task paradigms that incorporate motivational stimuli lack real-time directional feedback. Thus, the LAST more accurately models real-world settings and traditional human paradigms measuring sustained attention, attentional control, and cognitive flexibility (Whitney et al., 2015; 2017). As a relatively complex and more nuanced search task, the LAST is poised to be a powerful tool used for assessing the underlying neurological processes required for more elaborate assessment of decision-making and the impact of SD on these functions. The added benefit of the LAST is that it can accurately measure many behavioral metrics beyond trial success. For example, the moment-to-moment measurement of position and speed allows for in-depth analysis of specific search strategies and path directions available in path trace outputs. Time spent moving toward and away from the target, time still, path distance, and average speed are also candidate metrics. Furthermore, the LAST can accommodate electrophysiological monitoring and optogenetic manipulation to delve into the biochemical correlates that underpin the behavior.

While the LAST was quickly acquired and revealed performance deficits induced by SD, the LAST reversal paradigm also has limitations that must be addressed. The HLT paradigm is a naturally 'more aversive' paradigm, as successful performance requires rats to navigate in a direction that increases ambient light and goes against their innate

aversion to exploring brightly lit and open areas (Crawley et al., 1985). This results in a greater disparity between- and within-groups, with individual differences in bright light tolerance leading to more variable pre-reversal task performance. Hence, a high number of rats were excluded with the day 6 failure criterion (HLT  $n=16$  vs. LLT  $n=3$ ). The HLT – LLT reversal paradigm showed rapid adaptation to the less adverse directional cue via successful navigation that dimmed ambient lighting such that post-reversal performance outcomes in well rested rats mirrored day 6 values – as if a reversal had not taken place. Several metrics also demonstrated that the HLT– LLT paradigm switch blunted reversal learning following sleep loss, and significantly worsened performance on each parameter measured. Taken together, these effects indicate that LLT – HLT reversal may be a more robust paradigm that allows for better between-group comparisons, although multiple day 7 performance outcomes achieved statistical significance, regardless of the reversal paradigm. Comparing the two paradigms also suggests that the application of more noxious stimuli may blunt task acquisition, regardless of vigilance state, and that such effects are exaggerated by insufficient sleep.

In summary, the LAST is a novel, goal-oriented, rodent spatial navigation task. It is rapidly learned and easily modified to become a reversal-learning task, which is advantageous compared with other rodent paradigms. Utilizing the LAST, we have demonstrated that cognitive flexibility is impeded by SD and that more noxious stimuli disrupt cognitive flexibility to a greater degree, regardless of vigilance state. Moreover, due to the task complexity and continuous feedback, the LAST parallels human tasks of sustained attention and decision making. Finally, the experimental apparatus and system can accommodate multi-sensory detection, sustained cognitive evaluation, and motor response efficiency in an associative spatial task. Indeed, the LAST is a

promising behavioral assay to investigate the underlying neurobiological mechanisms of information processing and how these mechanisms are impacted by sleep.

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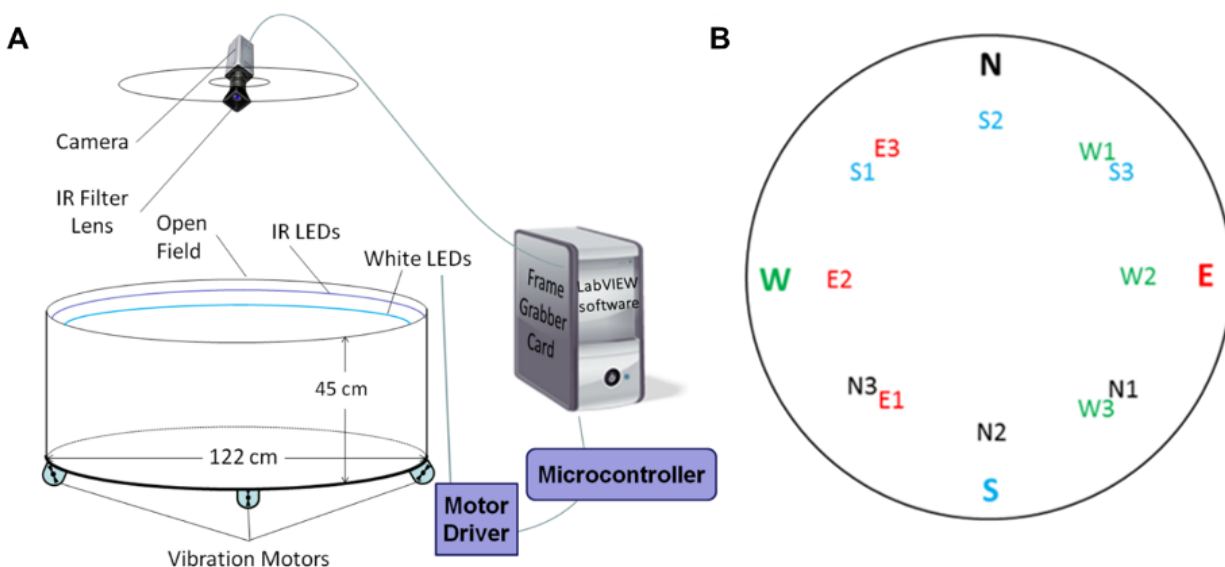
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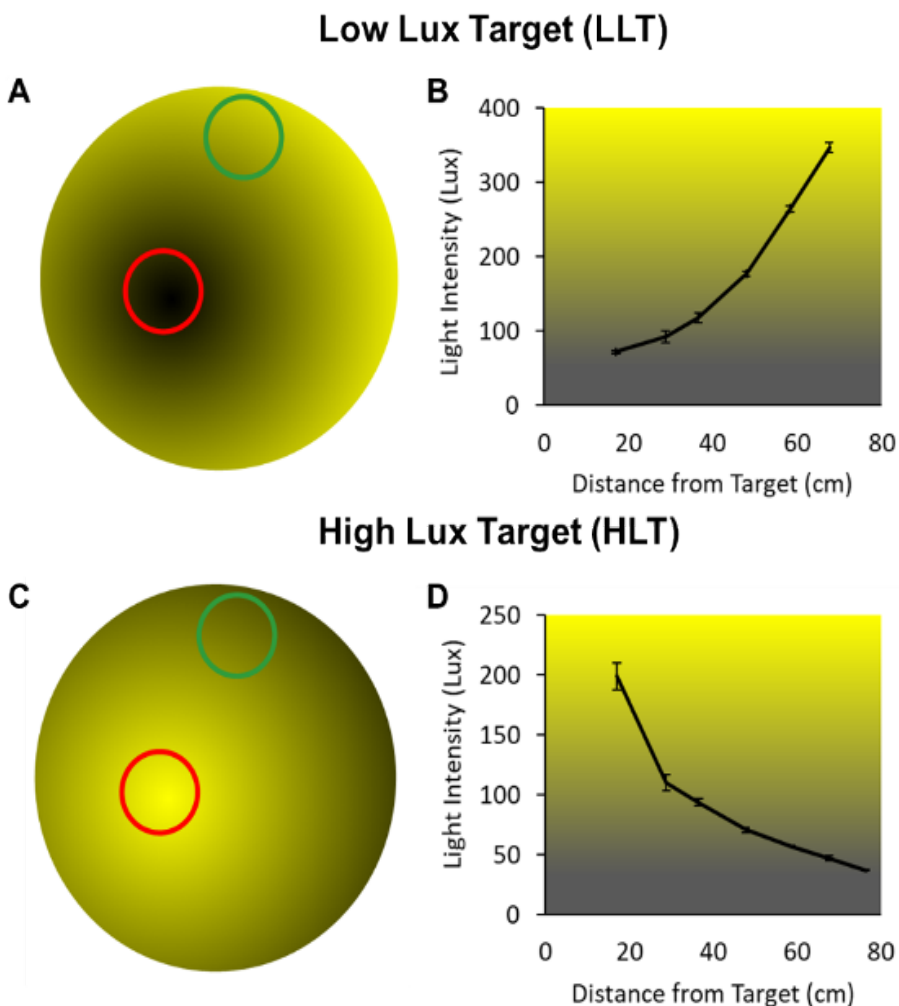
**Table 1. LAST pre-reversal performance over trial blocks for the HLT and LLT paradigms.** Data are reported as mean  $\pm$  SEM for each trial block over the six pre-reversal days for each task paradigm. A statistically detected difference between trial block 1 and trial block 3 is indicated after the trial block 3 data. \*  $p < 0.05$ . \*\* $p < 0.01$ . \*\*\* $p < 0.001$ .

Day	Trial block	HLT		LLT	
		Time to target (s)	Path distance (m)	Time to target (s)	Path distance (m)
1	1	58.3 $\pm$ 5.3	7.9 $\pm$ 0.8	44.2 $\pm$ 5.0	8.3 $\pm$ 0.7
	2	42.6 $\pm$ 5.3	7.2 $\pm$ 0.8	35.2 $\pm$ 5.0	6.3 $\pm$ 0.7
	3	45.3 $\pm$ 5.3	7.3 $\pm$ 0.8	35.6 $\pm$ 5.0	6.0 $\pm$ 0.7 *
2	1	58.9 $\pm$ 5.3	8.8 $\pm$ 0.8	49.2 $\pm$ 5.0	8.5 $\pm$ 0.7
	2	48.7 $\pm$ 5.3	8.7 $\pm$ 0.8	36.3 $\pm$ 5.0	6.5 $\pm$ 0.7
	3	47.1 $\pm$ 5.3	7.6 $\pm$ 0.8	33.0 $\pm$ 5.0 *	6.4 $\pm$ 0.7 *
3	1	59.0 $\pm$ 5.3	9.7 $\pm$ 0.8	44.9 $\pm$ 5.0	8.5 $\pm$ 0.7
	2	48.4 $\pm$ 5.3	8.9 $\pm$ 0.8	38.8 $\pm$ 5.0	7.3 $\pm$ 0.7
	3	46.2 $\pm$ 5.3	7.6 $\pm$ 0.8 *	31.1 $\pm$ 5.0 *	5.9 $\pm$ 0.7 **
4	1	59.9 $\pm$ 5.3	10.5 $\pm$ 0.8	41.5 $\pm$ 5.0	7.7 $\pm$ 0.7
	2	44.3 $\pm$ 5.3	8.2 $\pm$ 0.8	31.9 $\pm$ 5.0	6.4 $\pm$ 0.7
	3	43.8 $\pm$ 5.3 *	8.2 $\pm$ 0.8 *	31.2 $\pm$ 5.0	6.7 $\pm$ 0.7
5	1	58.9 $\pm$ 5.3	9.7 $\pm$ 0.8	46.0 $\pm$ 5.0	6.8 $\pm$ 0.7
	2	29.5 $\pm$ 5.3	6.0 $\pm$ 0.8	35.8 $\pm$ 5.0	6.7 $\pm$ 0.7
	3	33.5 $\pm$ 5.3 ***	6.6 $\pm$ 0.8 **	41.9 $\pm$ 5.0	7.9 $\pm$ 0.7
6	1	48.9 $\pm$ 5.3	7.8 $\pm$ 0.8	47.5 $\pm$ 5.0	8.3 $\pm$ 0.7
	2	29.5 $\pm$ 5.3	6.8 $\pm$ 0.8	23.7 $\pm$ 5.0	5.4 $\pm$ 0.7
	3	26.5 $\pm$ 5.3 ***	6.1 $\pm$ 0.8	21.2 $\pm$ 5.0 ***	4.9 $\pm$ 0.7 ***



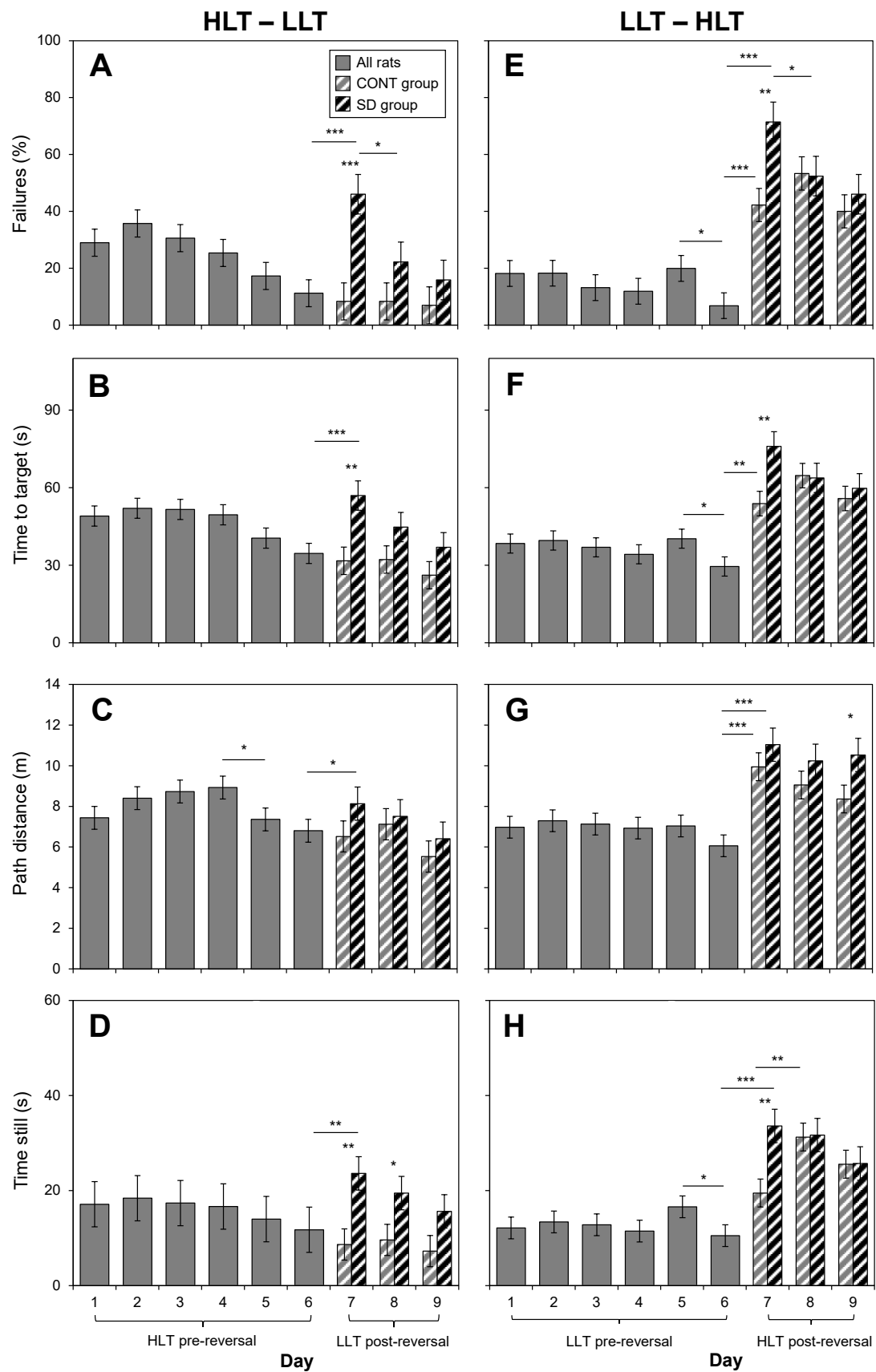
**Figure 1. Schematic of the LAST arena and insertion/target map.**

The open field arena is encircled by an acrylic wall, with two LED SMD 5050-300-IR infrared Tri-Chip flexible LED strips (LEDLightsWorld) mounted around the arena perimeter (**B**). There are also four, 45 mm electric rotary motors (model 345-400; Precision Microdrives) located at the base of each leg of the arena platform. The apparatus also includes a Manta G-201 digital camera with an infrared filter (Allied Vision), two TB6612FNG dual motor driver carriers (Pololu), a chipKIT WF32 microcontroller (Digilent), and a computer with LabVIEW 2012 software and a PCIe-6341 multifunction I/O card (National Instruments). (**B**) The LAST arena insertion points (N=North, W=West, E=East, and S=South) are shown with their associated, equidistant target destinations (N1-3 for entry point N, W1-3 for entry point W, S1-3 for entry point S, E1-3 for entry point E).



**Figure 2. Light intensity gradients for the LLT and HLT paradigms.**

A schematic of the ambient light intensity produced for any given XY coordinate of rat position in the open field arena with light intensity either decreasing (**A**; LLT) or increasing (**C**; HLT) as the rat approaches the target (red circle). The green circle identifies the pre-determined entry location. The LAST light intensities are shown as mean ( $\pm$  SEM) functions of the distances from the target for the LLT (**B**) and HLT (**D**) paradigms. Lux was measured with a luminometer (sampled in triplicate), while a stationary object was incrementally moved from the outer edge of a target destination.



**Figure 3. LAST performance for rats in the LLT – HLT reversal and HLT – LLT reversal groups.** Data are plotted as group means  $\pm$  SEM for all rats (solid gray) on days 1 to 6 (pre-reversal days), and for the CONT (gray stripes) and SD (black stripes) groups on days 7 to 9 (post-reversal days). Between-day comparisons between days 1 to 6 included all rats (not differentiated by group) and between-day comparisons between days 6 to 9 were made within-group (CONT and SD differentiated). Statistically significant between-day differences are indicated by lines and asterisks. Between-group comparisons were performed for days 7 to 9. Statistically significant within-day differences between the CONT and SD groups are indicated by asterisks alone. \* $p < 0.05$ , \*\* $p < 0.01$ . \*\*\* $p < 0.001$ .



## **The Rat Lux Actuating Search Task (LAST) and Effects of Sleep Deprivation on Task Reversal Performance**

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Declarations of interest: none

Keywords: Light, cognition, rodent models, attention, sleep loss, cognitive flexibility

Abbreviations:

CONT= undisturbed sleep control animal

HLT=High Lux Target paradigm

LAST=Lux Actuating Search Task

LLT=Low Lux Target paradigm

SD=Sleep deprivation

VAST=Vibration Actuating Search Task