European Journal of Neuroscience

WILEY

EJN European Journal of Neuroscience FENS

RESEARCH REPORT OPEN ACCESS

Early-Life Ventral Hippocampal Lesion and Circadian Disruption Result in Altered Behavior in Adult Mice in a Sex-Dependent Manner

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Received: 14 February 2025 | **Revised:** 23 April 2025 | **Accepted:** 26 April 2025

Associate Editor: Gianmaria Maccaferri

Funding: This work was supported by grants from the Canadian Institutes of Health Research (PJT-153299) and the Natural Sciences and Engineering Research Council of Canada (RGPIN-2023-03508).

Keywords: chronic jet lag | circadian rhythms | locomotor activity rhythms | neonatal ventral hippocampal lesion model | schizophrenia

ABSTRACT

Schizophrenia is believed to arise because of the interaction of early abnormal neurodevelopment with environmental insults during key developmental stages later in life. Furthermore, disrupted circadian rhythms are reported in patients, and circadian disruption is associated with increased symptom severity, hinting at its role as a risk factor. Using the neonatal ventral hippocampal lesion mouse model, we aimed to assess the interaction between disrupted ventral hippocampal development with circadian disruption during adolescence in affecting behavior in male and female C57BL/6N mice. After conducting a series of behavioral tests, we found that the neonatal ventral hippocampal lesion and chronic jet lag during adolescence synergistically led to increased anxiety-like behavior in males. In females, the lesion prevented increased social preference caused by chronic jet lag and led to increased anxiety-like behavior. Mice were then moved to running wheel cages to measure their locomotor activity rhythms. We found that the lesioned male mice exposed to chronic jet lag exhibited fragmented rhythms under constant darkness. Moreover, lesioned male and female mice, especially those exposed to chronic jet lag, had reduced activity counts under constant light. These findings highlight that the interaction of abnormal neurodevelopment in areas relevant to schizophrenia with circadian disruption during adolescence results in lasting behavioral changes in a sex-dependent manner in mice.

1 | Introduction

Living organisms have evolved to anticipate daily environmental changes. This adaptation is reflected in endogenous, self-sustaining near-24-h biological rhythms, termed circadian rhythms, driven by intricate molecular mechanisms involving transcriptional–translational negative feedback loops. Although present in most cells, the central clock resides in the hypothalamic suprachiasmatic nucleus (SCN), comprised of a network of coupled neurons (Mieda 2020). Through humoral

Abbreviations: Amg, amygdala; ANOVA, analysis of variance; CJL, chronic jet lag; DA, dopamine; DD, constant dark; EPM, elevated plus maze; HC-PF, hippocampal–prefrontal; IpRGCs, intrinsically photosensitive retinal ganglion cells; LD, light–dark; LL, constant light; Nac, nucleus accumbens; NVHL, neonatal ventral hippocampal lesion; OFT, open field test; PFC, prefrontal cortex; PND, postnatal day; SCN, suprachiasmatic nucleus; SZ, schizophrenia; VHPC, ventral hippocampus; VTA, ventral tegmental area; ZT, zeitgeber time.

and neural signals, this central clock orchestrates peripheral clocks across the brain and body, regulating physiological and behavioral processes such as body temperature, hormone secretion, feeding, and sleep timing (Marcheva et al. 2013; Mohawk et al. 2012).

Although self-sustaining, an essential feature of circadian clocks is their capability to be reset by external environmental cues, including light, temperature, and food intake; however, this feature can have deleterious consequences because of modern lifestyles. Factors such as artificial light at night, irregular work schedules, and transmeridian travel can misalign the body's internal clock with the external environment. Such misalignment has been linked to various health issues, including cardiovascular disease, obesity, and psychiatric disorders (Brainard et al. 2015; Walker et al. 2020). This includes schizophrenia (SZ), a chronic neurodevelopmental disorder and a leading cause of disability worldwide. Furthermore, sleep and circadian rhythm disturbances have been consistently reported in SZ (Bouteldja et al. 2024; Cohrs 2008; Jagannath et al. 2013).

In addition to being symptoms of the disorder, circadian disruptions may also act as risk factors, therefore exacerbating symptom severity, especially during critical developmental periods like adolescence. A previous study has shown that altered circadian function in individuals at risk of psychosis predicts greater symptom severity at the 1-year follow-up (Lunsford-Avery et al. 2017). Adolescence represents a window of heightened neuroplasticity (Fuhrmann et al. 2015), making the brain particularly vulnerable to external perturbations. Given SZ's multifactorial etiology, involving genetic and environmental factors, circadian disruption during this developmental period may exacerbate its onset and symptoms. Supporting this, we previously demonstrated that environmental circadian disruption during adolescence induces sex-dependent deficits in SZ-relevant behavior in *Sandy* mice, which carry a loss-of-function mutation in the SZ risk gene *Dtnbp1* (Cloutier et al. 2022).

SZ is widely understood as a disorder arising from abnormal neurodevelopment, influenced by various genetic and environmental risk factors. Symptoms often emerge in adolescence or early adulthood as affected brain regions mature. Studies have shown progressive changes in gray matter volume in SZ patients during adolescence, particularly in cortical and hippocampal regions, correlating with worsened symptom severity (Ho et al. 2003; Mancini et al. 2020; Mathalon et al. 2001; Nath et al. 2021). Furthermore, meta-analyses have highlighted structural and functional brain connectivity alterations in SZ patients and at-risk individuals (Cai et al. 2022; Pettersson-Yeo et al. 2011).

Atrophy of the hippocampus and cortical thinning, presumably of developmental origin, are consistently reported in SZ (Adriano et al. 2012; van Haren et al. 2011). This is believed to lead to a disruption of the hippocampal–prefrontal (HC-PF) cortex pathway, crucial for many of the cognitive and emotional functions that are impaired in the disorder. Patients exhibit altered HC-PF connectivity both at resting state (Zhou et al. 2008) and when performing a working memory task (Meyer-Lindenberg et al. 2005), leading to the consideration of these alterations as endophenotypes of SZ (Bahner and Meyer-Lindenberg 2017). Altered HC-PF connectivity is also seen in individuals identified as At-Risk Mental State (Benetti et al. 2009), in siblings of patients with SZ (Rasetti et al. 2011), and in animal models of the disorder (Sigurdsson et al. 2010; Dickerson et al. 2010; Phillips et al. 2012).

Although genetic and pharmacological models of SZ capture specific aspects of the disorder, such as the involvement of a single gene or neurotransmitter system (e.g., dopamine [DA]), they often lack the neurodevelopmental component that is critical to understanding SZ. The neonatal ventral hippocampal lesion (NVHL) rodent model, developed by Lipska et al. (1993), addresses this gap and is considered a valid model for studying neurodevelopmental underpinnings of SZ. This model recapitulates SZ-like behavioral deficits (Tseng et al. 2009), as well as neurochemical, anatomical, and electrophysiological changes (Flores et al. 2005; Nath et al. 2023; O'Donnell 2012), in a temporally similar manner. Moreover, when assessing for sleep disturbances, it was observed that NVHL rats show no changes in sleep organization, but present a slowing in electroencephalogram patterns at prepuberty—marked by increases in differences of absolute power at various frequency bands during wake and deep sleep (Ahnaou et al. 2007). Yet, to our knowledge, circadian function remains unexplored in this model. This gap is critical, as addressing it could provide a link between circadian behavior and cortical brain deficits stemming from abnormal neurodevelopment. Moreover, the NVHL model offers the opportunity to study how early abnormal neurodevelopment interacts with environmental circadian disruptions during adolescence, furthering our understanding of SZ's complex origins.

We aimed to address the relationship between circadian function and neurodevelopmental disruptions in the NVHL model. Specifically, we hypothesized that circadian disruption during adolescence would exacerbate the behavioral abnormalities observed in this model. Furthermore, we predicted that NVHL mice would display alterations in circadian function, as measured by daily locomotor activity rhythms. Finally, we tested both males and females, given that there are sex-dependent differences in both circadian regulation and SZ-relevant behaviors (Abel et al. 2010; Duffy et al. 2011).

2 | Materials and Methods

2.1 | Animals and Housing

Six- to eight-week-old male and female C57BL/6N mice from Charles River Laboratories (Saint-Constant, QC, Canada) were used to set up breeding cages. They were placed in ventilated cages under a 12 h:12 h light: dark (LD) cycle with ad libitum access to food and water. All procedures were approved by the Facility Animal Care Committee at the Douglas Research Centre, in accordance with the Canadian Council on Animal Care guidelines.

2.2 | Breeding Protocol

In order to obtain sufficient experimental numbers, mice were bred over a span of 14 months. A total of 24 breeding cages either with a 2:1 or 1:1 female-to-male ratio in each cage were set up

(total litters obtained: 28; average litter size: 9.6). In the case of breeding cages with two females, we cannot exclude that two litters were born on the same day, in which case they were considered as one. Cages were checked each morning to confirm the presence of litter. If a litter was found, the day of birth was marked as postnatal day (PND) 0. The cages were then left undisturbed until the surgery day on PND 14.

2.3 | Stereotaxic Surgeries

NVHL was performed as previously described (Nath et al. 2023). The lesion was performed at PND 14, rather than the conventional PND 7 used in rat NVHL, because of higher mortality associated with earlier surgeries in mice when using ibotenic acid. PND 14 still represents a sensitive period in hippocampal development, characterized by active synaptogenesis and ongoing circuit maturation. We have previously validated the NVHL model in mice, with lesions at P14, with evidence of prefrontal cellular abnormalities (Nath et al. 2023) and impaired behavior (unpublished data). Litters of male and female pups were obtained from the C57BL/6N breeder cages. At PND 14, pups within each litter were randomized to sham or lesion groups and anesthetized with 3% isoflurane (1.5% for maintenance). An incision was made in the skin overlying the skull and 0.20 μL of ibotenic acid (excitotoxic agent) (10 μg/μL, Abcam, Toronto, ON, Canada), or phosphate-buffered saline (1X PBS, pH 7.4) in controls, was stereotaxically injected bilaterally into the ventral hippocampus (vHPC) at a rate of 0.05 μL/min at the following coordinates from bregma: anterior/posterior: −2.8, lateral: ±2.8, and dorsal/ventral: −3.2. Upon the completion of injections, the pups were sutured, identified using an ear punch, and placed in a recovery cage with a heat pad underneath before being returned to their cages. At PND 21, mice were weaned and weighed.

2.4 | Chronic Jetlag Protocol

After weaning, mice were randomly assigned to either the chronic jet lag (CJL) or 12:12 LD condition per cage, with a maximum of 4 mice per cage. They were placed in ventilated light-proof cabinets (Actimetrics, Wilmette, IL, USA), and kept for 2 days under 12:12 LD condition. On the third day, the CJL group was subjected to a 6-h phase advance every 2 days, for a total of 4 weeks (Cloutier et al. 2022). The control group remained at 12:12 LD. Following completion of the 4 weeks, all mice were placed in 12:12 LD for 2 weeks prior to behavioral testing, to ensure that they were tested under the same circadian phase. Males and females were housed in separate cabinets, and cage changes occurred weekly.

2.5 | Behavioral Testing

To maintain consistency in experimental design over the course of the study, behavioral tests were conducted in the same order and at the same ages (±7 days) in all cases, in the following order: elevated plus maze (EPM), open field test (OFT), and three-chamber social preference and social novelty test. They were separated by at least 2 days of rest. All tests were performed during a restricted time slot starting at zeitgeber time (ZT) 1 (i.e., 1 h after lights on) until ZT 7. For all tests, mice were habituated to the testing room 30 min prior to the testing. Tests were performed under dim light conditions (~15 lux) unless indicated otherwise. Experimenters were absent from the room during the testing period for all the tests.

2.6 | Elevated Plus Maze

EPM is one of the most used behavioral tests to measure anxiety-like behavior, based on the rodent's tendency to avoid open spaces and to seek enclosed spaces (Walf and Frye 2007). The apparatus was elevated 75 cm from the floor and consisted of a plus-shaped structure with two open and two closed wooden arms (Length = 50 cm × Width = 5 cm per arm) painted black. The two closed arms were enclosed by 10 cm high walls on three sides. For the test, mice were placed on the center of the structure, while facing an open arm, and left to freely explore for 5 min. Increased time spent in the closed arms indicates increased anxiety-like behavior. One overhead Swann camera was used for recording. Data were analyzed using ezTrack (Pennington et al. 2021). The software uses the center of the mouse's body to track its movement. A mouse is considered to enter a new area (e.g., top open arm) when the center of the body crosses into that zone. Mice that jumped off the structure or spent the entire time frozen on an open arm were excluded from the analysis. The ratio of time spent in open over closed arms was calculated to assess anxiety-like behavior:

$$\text{Time ratio} = \frac{\text{Time spent in open arms} + \frac{\text{Time spent in the center}}{2}}{\text{Time spent in closed arms} + \frac{\text{Time spent in the center}}{2}}.$$

2.7 | Open Field Test

The OFT is a well-established method to measure spontaneous locomotor activity and anxiety-like behavior (Seibenhener and Wooten 2015). The VersaMax Legacy Open Field setup (AccuScan Instruments Inc., Columbus, OH, USA) was used for this test. For a total of 50 min, mice were placed to freely explore in VersaMax acrylic chambers (Length × Width × Height = 17.5 cm × 10 cm × 26 cm) equipped with infrared sensors that record and score locomotion-related variables. Variables included total horizontal activity, total movement time, and total time in the center. A mouse is considered in the margin when it is in proximity (within 1 cm) to the walls, but it is considered in the center when it is outside that range. Data were collected using the VersaMax software (version 4.0, 2004; AccuScan Instruments Inc., Columbus, OH, USA).

2.8 | Three-Chamber Social Preference and Social Novelty Test

The three-chamber test was used to test social preference (preference for a conspecific over an inanimate object) and social novelty (preference for a new mouse over a familiar one) (Yang et al. 2011). The apparatus consisted of a three-chambered plastic structure (Length = 26 cm × Width = 21.6 × Height = 21.6 cm) with small vertical openings between each chamber. Objects and strain-, sex-, and age-matched stranger mice were placed

under wire mesh pen cup containers. Animals used as strangers during the three-chamber social interaction test were all on a C57BL/6N genetic background. On the evening prior to testing, stranger mice were habituated to both the wire mesh pen cup containers they were placed under and the structure itself. The testing component was divided into three consecutive stages, each lasting 10 min: (1) habituation, (2) social preference, and (3) social novelty preference. In the habituation phase, the experimental mouse was placed in the middle chamber to start freely exploring, and the containers had two identical objects (small transparent bottles with rice grains inside) underneath. In the social preference phase, one of the objects was replaced with a stranger mouse. Finally, in the social novelty preference phase, the remaining object was replaced with a novel stranger mouse. Each phase was separated by 5 min of rest, during which the mouse was kept in the middle chamber. Two overhead Swann cameras were used for recording. Data were manually scored while blinded to the mouse group condition by using Chronotate (Philipsberg et al. 2023). Exploration of object/mouse was considered when the mouse's nose was directed toward the cup, around 2–3 cm from it, whereas climbing on top of the cup was excluded from the analysis. Mice that did not have a minimum total exploration time of 20 s for both objects and/or mice were excluded from analyses. The social preference and the social novelty preference ratios were calculated:

$$\text{Social preference ratio} = \frac{\text{Time spent interacting with mouse}}{\text{Time spent interacting with object}},$$

$$\text{Social novelty ratio} = \frac{\text{Time spent interacting with novel mouse}}{\text{Time spent interacting with familiar mouse}}.$$

2.9 | Running Wheel Activity Under Different Lighting Conditions

After the completion of behavioral tests, mice were individually housed in running wheel cages, which were placed in light-proof ventilated cabinets. After 2–3 days of entrainment in 12:12 LD, mice were exposed to constant darkness (DD) and constant light (LL), each for a period of 12–14 days. Light was controlled via ClockLab software, version 6 (Actimetrics, Wilmette, IL, USA). ClockLab software was used to record and analyze wheel-running data. The last 10 days of each lighting condition was included in the analysis. The obtained variables included circadian period (tau; calculated using a chi-square periodogram); active period duration (alpha; refers to numbers of hours between activity onset and offset); total amount of day activity; and total activity counts; an activity bout (specific period of sustained activity) analysis was also performed, which included the total number of bouts and the average bout length. Nonparametric variables were also derived: relative amplitude, which is a measure of rhythm amplitude calculated based on comparing the periods of lowest and highest activity: $RA = (M_{\text{Avg}} - L_{\text{Avg}})/(M_{\text{Avg}} + L_{\text{Avg}})$, where M_{Avg} and L_{Avg} is the average activity during the most active and the least active periods in the activity profile, respectively, and intradaily variability, a measure of rhythm fragmentation, or the frequency of transitions between rest and activity, which ranges from 0 for a perfect sine wave to 2 for random (Gaussian) noise, or higher for highly fragmented patterns. For each mouse, the duration of the subjective night was calculated as the average time of onset of activity plus half of the calculated tau (Delorme et al. 2021), whereas the subjective day was considered the remaining portion of the calculated tau. For mice with a high degree of arrhythmicity in LL, the alpha and day activity were not obtained as the average time of activity onset could not be determined.

2.10 | Lesion Verification

After the completion of the testing period, mice were euthanized. Their brains were collected, snap-frozen in 2-methylbutane (placed in dry ice) and stored at −80°C. A cryostat microtome (Leica) was used to obtain 35-μm-thick coronal sections between Bregma −1.34 and −3.64 mm. The sections were mounted on Fisherbrand Tissue Path Superfrost Plus Gold Slides. The slides were stained using Nissl staining, which allows for the visualization of the nuclei of neurons (Kadar et al. 2009). Slides were cover-slipped using Permount and kept sitting for at least 48 h prior to imaging. Slides were visualized and imaged using an automated brightfield and fluorescent microscope (Olympus BX63). Specifically, all portions of a single brain section imaged at 4X magnification were stitched together using the multiarea images feature on the microscope. Brain section images were blindly assessed and scored for lesion status. Specifically, a lesion (observed as a visible loss of neurons, cavity, or atrophy) was considered successful if (1) the lesion was done bilaterally, (2) the lesion was limited to the vHPC, and (3) nearby regions like the dorsal hippocampus, thalamus, and cortex were spared. Mice that did not meet these criteria were excluded from the analysis.

2.11 | Statistical Analysis

GraphPad Prism (version 10 for Windows, GraphPad Software, San Diego, CA, USA), and ANOVA2 2020 (Dr. Joseph Rochford, McGill University, Montréal, QC, Canada) were used to perform the statistical analyses. The data were graphed using GraphPad Prism. Two-way analysis of variance (ANOVA) for factors of lighting and surgery was performed on normally distributed data sets with equal variance across groups. Simple effects analysis was performed when a significant interaction was found. The Shapiro–Wilks test and Levene's test were used to test for normality and homogeneity of variances, respectively. Square root transformation was applied to resolve normality when it was not met. The ROUT method was used to identify outliers where applicable: A value was considered an outlier if it was significantly different ($Q = 1\%$) from the entire data set. Differences were considered significant when $p < 0.05$ and considered trending when $p < 0.1$. All ANOVA results are available in Tables S1 and S2.

3 | Results

3.1 | Lesion Verification

To ensure consistency between animals and groups, we performed histological verification of the lesions and included in our groups only mice with verified bilateral lesions. The lesion verification was carried out for each mouse, at the end of the

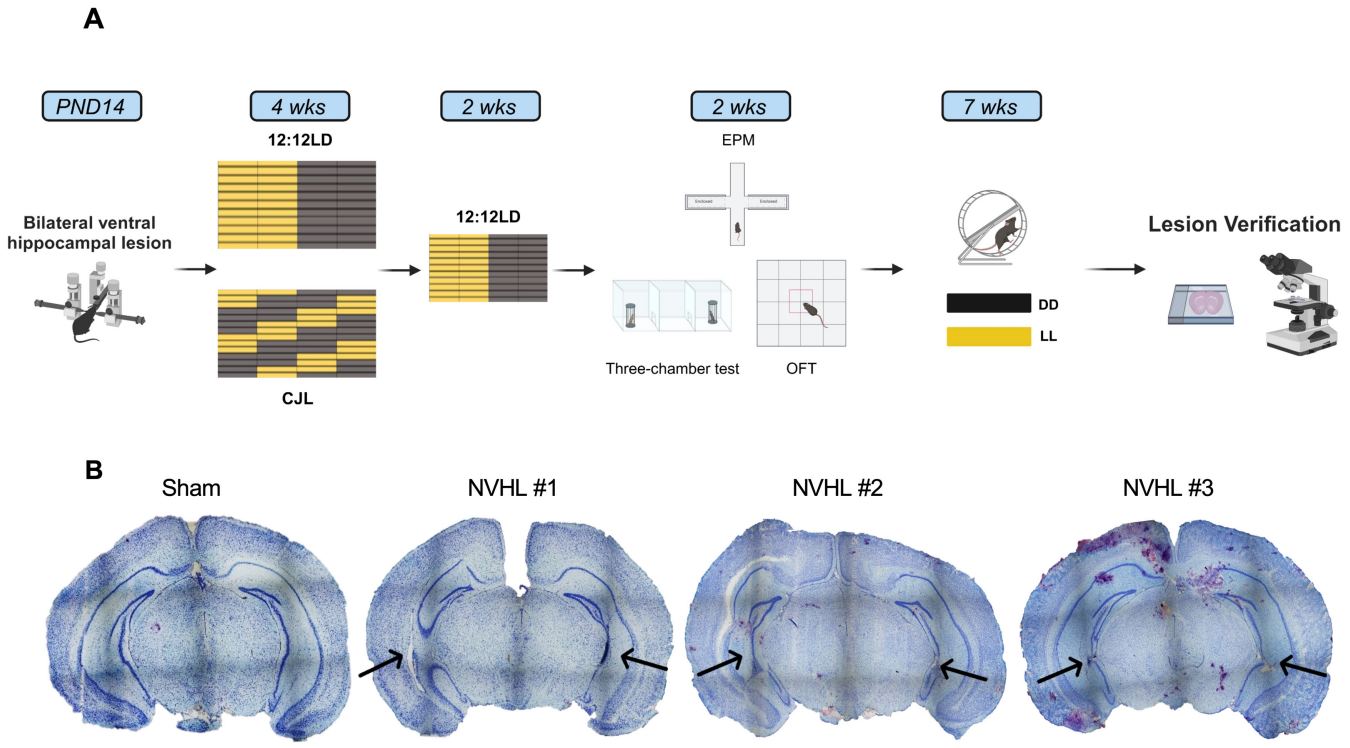

FIGURE 1 | Experimental timeline and lesion status verification. (A) Mice underwent stereotaxic surgery on postnatal day (PND) 14. Control mice were exposed to saline and neonatal ventral hippocampal lesion (NVHL) mice to ibotenic acid. After weaning, they were placed in either 12 h:12 h light–dark (12:12 LD) or chronic jet lag (CJL) conditions for 4 weeks, before being placed in 12:12 LD for 2 weeks. Next, they underwent elevated plus maze (EPM), open field test (OFT), and three-chamber test, before being individually housed in running wheel cages and exposed to constant darkness (DD) and constant light (LL). The brains were then collected, sliced, stained, and imaged to verify lesion status. Schematic created with BioRender.com (B) Images showing an example of a sham brain with no visible changes in the ventral hippocampus and three examples of bilateral lesions of the ventral hippocampus in NVHL mice seen as a visible loss of neurons or cavities. Black arrows are pointing toward the areas where the lesions are present. The grid-like shadow is due to microscopic images being stitched together.

behavioral assessment (Figure 1A). Nissl-stained brain sections were assessed for the presence of a visible loss of neurons, cavities, or atrophy in the vHPC (Chambers and Lipska 2011). Following the lesion status assessment, 27 mice (13 males/14 females) were found to have successful bilateral lesions (Figure 1B). The other mice had either no visible lesions, unilateral lesions, or cavities that extended beyond the vHPC and were therefore excluded from the analyses. Sham mice did not have any visible damage to the vHPC (Figure 1B).

3.2 | Locomotion and Anxiety-Like Behavior

The OFT was used to measure spontaneous locomotor activity and anxiety. In males, no significant changes in total horizontal (Figure 2A) or total movement time (Figure 2B) were found. However, upon analyzing the first 5 min separately, a significant interaction was found in males ($F_{1, 25} = 6.75$, $p = 0.0154$). Of note though, the homogeneity of variances assumption was not met after using Levene's test, despite attempting to correct data. Nevertheless, analysis of simple main effects analyses that the NVHL mice exposed to CJL traveled a greater distance compared to their LD counterparts ($F_{1, 25} = 7.38$, $p = 0.01186$) and that NVHL mice subjected to CJL traveled a greater distance compared to their sham counterparts ($F_{1, 25} = 11.68$, $p = 0.0022$) (Figure 2C). There was a significant interaction in the total time spent in the center ($F_{1, 25} = 7.53$, $p = 0.0111$) (Figure 2D). A simple main effects test revealed that the NVHL mice exposed to CJL spent significantly less time in the center compared to their LD counterparts ($F_{1, 25} = 5.11$, $p = 0.0328$) (Figure 2D), that the NVHL mice subjected to CJL spent significantly less time in the center compared to their sham counterparts ($F_{1, 25} = 4.26$, $p = 0.0495$) (Figure 2D), and a trend showing that the NVHL mice exposed to LD spent more time in the center compared to their sham counterparts ($F_{1, 25} = 3.27$, $p = 0.0827$) (Figure 2D).

In females, the lighting had a trend toward a main effect on total horizontal activity ($F_{1, 23} = 2.96$, $p = 0.0985$) (Figure 2E), and a significant main effect on total movement time ($F_{1, 23} = 7.11$, $p = 0.0138$) (Figure 2F). The analysis of the first 5 min did not reveal significant differences (Figure 2G). There was a main effect of surgery on the total time spent in the center ($F_{1, 23} = 7.66$, $p = 0.0109$) (Figure 2H). In sum, these results demonstrated that the interaction of CJL and NVHL resulted in increased anxiety-like behavior in males, whereas NVHL led to increased anxiety-like behavior and CJL caused overall reduced activity levels in females.

As an additional way to assess anxiety-like behavior, the EPM test was used. No significant differences in the ratio of time spent in open over closed arms in male mice were found, after removing two outliers (1 NVHL-LD/1 Sham-CJL) (Figure 3A). The lack of effects in males may be attributed to low statistical power. A high proportion of male mice jumped from the

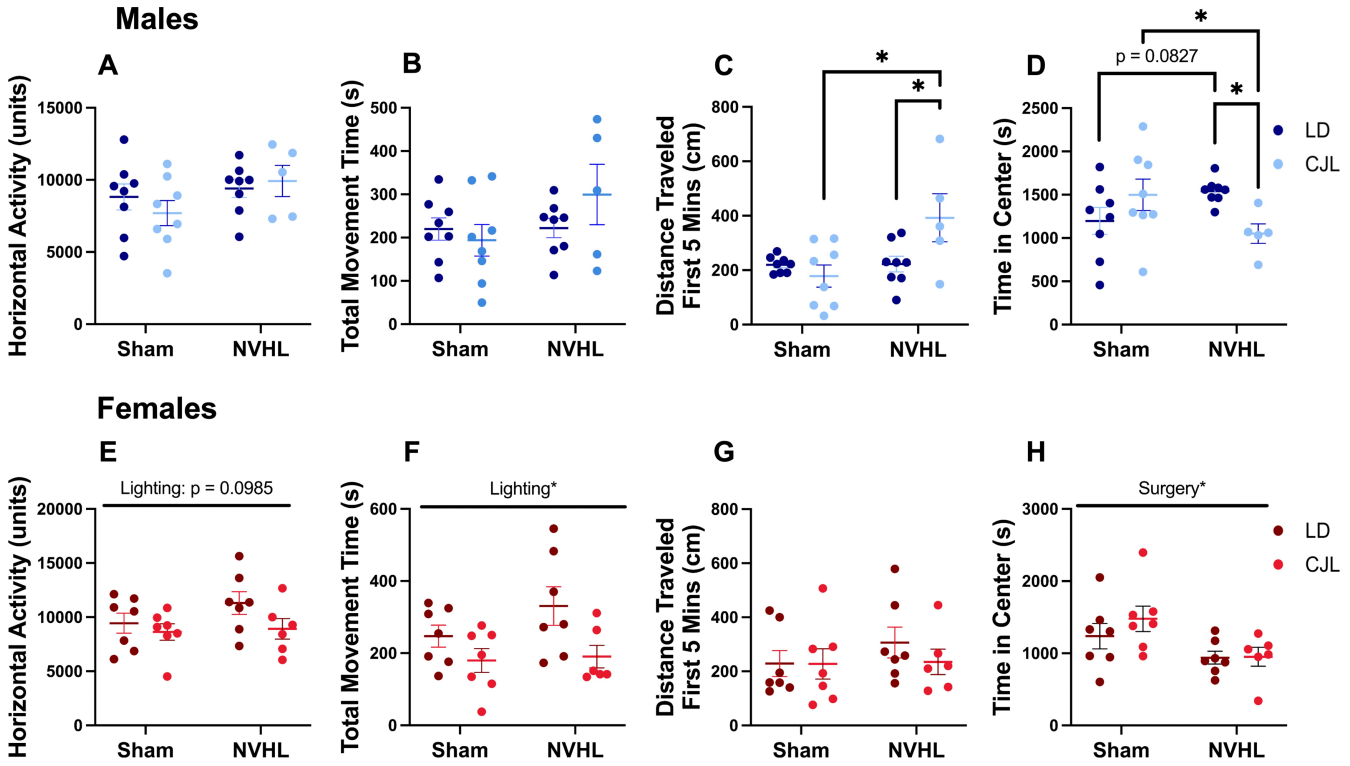

FIGURE 2 | Increased anxiety-like behavior caused by NVHL and CJL in males and increased anxiety-like behavior caused by NVHL in females. Horizontal activity, total movement time, distance traveled in the first 5 min, and time in the center in the open field test were measured in males (A–D) and females (E–H). LD: 12:12 light–dark; CJL: chronic jet lag; NVHL: neonatal ventral hippocampal lesion. Data points represent individual mice and are presented as mean ± SEM. Two-way ANOVAs (Lighting × Surgery) with simple effect test were performed. *$p < 0.05$.

apparatus, either shortly after being placed on the apparatus or a few minutes into the test. Interestingly, NVHL mice exposed to CJL had the highest proportion of jumps compared to other groups (Figure 3B). This extreme behavior might be attributed to fear and the tendency to escape the apparatus. As for females, the ratio of time spent in open over closed arm data did not meet the normality assumption, which was resolved by applying the square root data transformation. Additionally, two mice (1 CJL-PBS/1 CJL-IB) were excluded from analysis after sitting on the open arm for the entire test duration. Analysis of the data revealed a trend toward an interaction in the ratio of time spent in the open over closed arms in females ($F_{1, 21} = 3.43$, $p = 0.0782$), where the NVHL mice exposed to CJL appeared to spend more time in the open arms compared to their LD counterparts (Figure 3C). In addition, females rarely jumped from the EPM structure (Figure 3D). Thus, NVHL male mice exposed to CJL exhibited more anxiety-like behavior, aligning with the OFT data, whereas NVHL females exposed to CJL showed less anxiety-like behavior.

3.3 | Social Preference and Social Novelty

The three-chamber test was used to measure social preference and social novelty. In males, two outliers (1 LD-Sham/1 LD-NVHL) from the social preference phase data were removed. In addition, one mouse (LD-Sham) was removed for not meeting the minimum total exploration time. There was a significant main effect of surgery on social preference ($F_{1, 23} = 4.75$, $p = 0.0398$) (Figure 4A). No significant changes in social novelty were found (Figure 4B). In females, the sociability index data did not meet the normality assumption, which was resolved by applying the square root data transformation. One outlier (LD-Sham) from the social preference phase data and two outliers (1 LD-Sham/1 CJL-Sham) from the social novelty phase data were removed. In addition, one mouse (CJL-Sham) was removed for not meeting the minimum total exploration time. There was a significant interaction on social preference ($F_{1, 22} = 12.19$, $p = 0.0021$) (Figure 4C), and a trend toward a main effect of surgery on social novelty ($F_{1, 21} = 3.86$, $p = 0.0628$). (Figure 4D). Simple main effects analyses showed that the sham mice exposed to CJL had significantly larger social preference compared to their LD counterparts ($F_{1, 22} = 17.96$, $p = 0.0003$) (Figure 4C) and that this effect of CJL was lost in NVHL mice ($F_{1, 22} = 14.15$, $p = 0.0011$) (Figure 4C). Thus, NVHL male mice showed increased social preference but no changes in social novelty, and NVHL prevented increased social preference caused by CJL in females.

3.4 | Running Wheel Behavior Under Constant Darkness

Mice were placed under constant darkness to measure their endogenous rhythms without an influence from photic time cues. The running wheel data are shown for males and females in Figures 5 and 6, respectively. Representative actograms of LD-Sham, LD-NVHL, CJL-Sham, and CJL-NVHL male and female mice under DD are shown in Figures 5A–D and 6A–D, respectively. All actograms for male and female mice under DD are in Figures S1 and

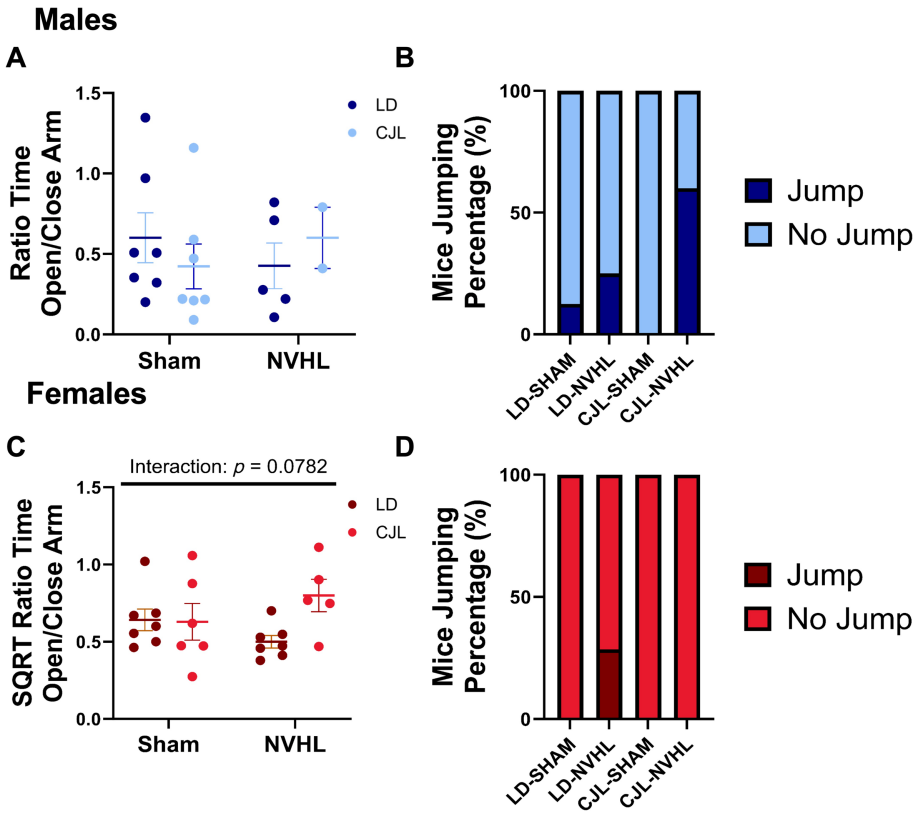

FIGURE 3 | Effect of NVHL and CJL on anxiety-like behavior. The ratio of time spent in open over closed arms was measured in both males (A) and females (C). The proportion of jumps from the elevated plus maze apparatus was calculated in males (B) and females (D). The percentage of jump proportions was measured for each group (group sizes for males: LD-Sham: 8; LD-NVHL: 8; CJL-Sham: 8; CJL-NVHL: 5; for females: LD-Sham: 7; LD-NVHL: 8; CJL-Sham: 7; CJL-NVHL: 6). LD: 12:12 light–dark; CJL: chronic jet lag; NVHL: neonatal ventral hippocampal lesion. Square root data (SQRT) transformation was performed on the ratio time spent in open over closed arms in order to meet all ANOVA assumptions. Data points represent individual mice and are presented as mean ± SEM. Two-way ANOVAs (Lighting × Surgery) were performed.

S2, respectively. In males, there was a trend toward a main effect of surgery on period ($F_{1, 24} = 3.58$, $p = 0.0706$) (Figure 5E) and total activity ($F_{1, 24} = 3.48$, $p = 0.0746$) (Figure 5H). No significant changes in alpha (Figure 5F) or day activity (Figure 5G) were found. In females, there was a trend toward a main effect of lighting on alpha ($F_{1, 22} = 3.30$, $p = 0.0828$) (Figure 6F). Three outliers from the day activity data were removed (1 LD-Sham/1 LD-NVHL/1 CJL-Sham). No significant changes in period (Figure 6E), day activity (Figure 6G), or total activity (Figure 6H) were found.

In males, there was a significant interaction in intradaily variability ($F_{1, 24} = 11.1$, $p = 0.0028$) (Figure 5J). Simple main effects analyses revealed that the NVHL mice exposed to CJL had greater intradaily variability compared to their LD counterparts ($F_{1, 24} = 10.00$, $p = 0.0042$) (Figure 5J) and that the NVHL mice subjected to CJL had greater intradaily variability compared to their sham counterparts ($F_{1, 24} = 13.75$, $p = 0.0011$) (Figure 5J). Additionally, there was a significant interaction in the total number of bouts ($F_{1, 24} = 12.99$, $p = 0.0014$) (Figure 5K). Simple main effects analyses showed that the NVHL mice exposed to CJL had a greater total number of bouts compared to their LD counterparts ($F_{1, 24} = 10.09$, $p = 0.0039$) (Figure 5K) and that the NVHL mice subjected to CJL had a greater total number of bouts compared to their sham counterparts ($F_{1, 24} = 36.16$, $p < 0.001$) (Figure 5K). There was a significant interaction on average bout length ($F_{1, 24} = 5.05$, $p = 0.0341$) (Figure 5L). A simple main effect test revealed that the NVHL mice subjected to CJL had shorter average bout length compared to their sham counterparts ($F_{1, 24} = 15.81$, $p = 0.0004$) (Figure 5L). Five outliers were removed from the RA data (2 LD-Sham/2 LD-NVHL/1 CJL-NVHL). No significant changes in relative amplitude were found (Figure 5I). In females, there was a significant main effect of surgery on the total number of bouts, ($F_{1, 22} = 4.44$, $p = 0.0467$) (Figure 6K) and a trend on average bout length ($F_{1, 22} = 3.35$, $p = 0.0810$) (Figure 6L). Four outliers were removed from the RA data (1 LD-Sham/1 LD-NVHL/1 CJL-Sham/1 CJL-NVHL). No significant changes in relative amplitude (Figure 6I) or intradaily variability (Figure 6J) were found. Altogether, the interaction of CJL and NVHL in males resulted in increased rhythm fragmentation, and NVHL led to less sustained activity in females.

3.5 | Running Wheel Behavior Under Constant Light

Mice were then placed under LL, a condition that can disrupt circadian rhythms. The wheel-running data are shown for males and females in Figures 7 and 8, respectively. Representative actograms of LD-Sham, LD-NVHL, CJL-Sham, and CJL-NVHL male and female mice under LL are shown in Figures 7A–D and 8A–D, respectively. All actograms

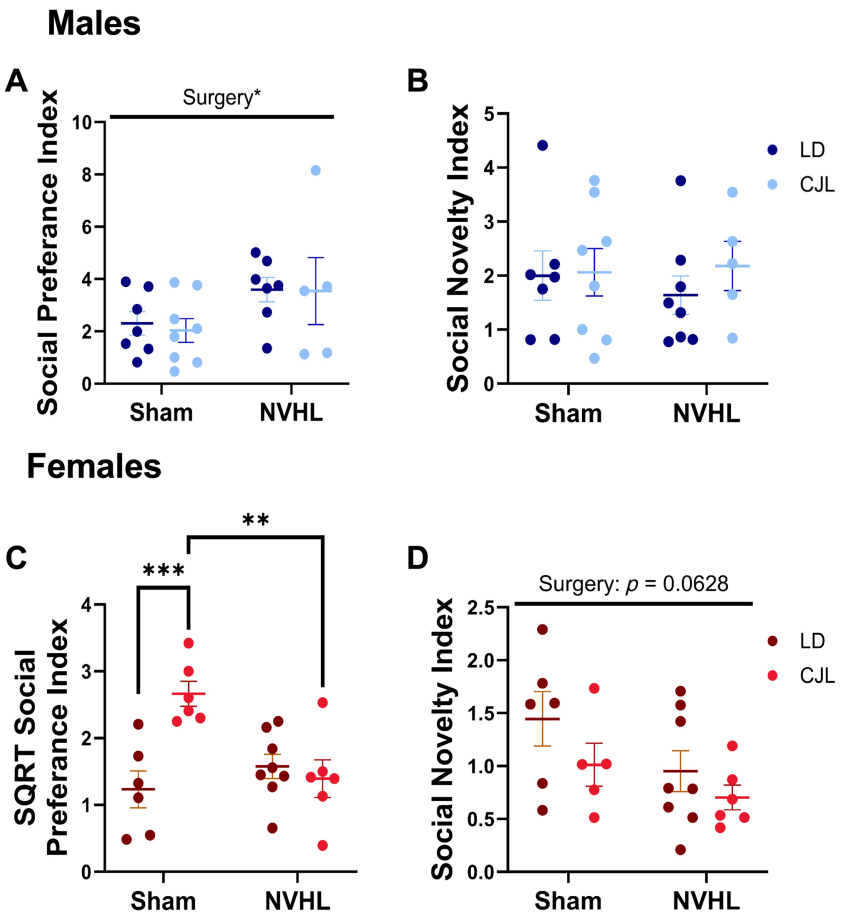

FIGURE 4 | Increased social preference caused by NVHL in males and increased social preference caused by CJL prevented by NVHL in females. Social preference and social novelty were measured in males (A,B) and females (C,D). LD: 12:12 light–dark; CJL: chronic jet lag; NVHL: neonatal ventral hippocampal lesion. Square root data (SQRT) transformation was performed on social preference in females in order to meet all ANOVA assumptions. Data points represent individual mice and are presented as mean ± SEM. Two-way ANOVAs with simple effects test were performed. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

for male and female mice under LL are in Figures S3 and S4, respectively. In males, the total activity data did not meet the normality assumption, which was resolved by applying the square root data transformation. Additionally, three outliers were removed from the period data (1 LD-NVHL/2 CJL-NVHL). There was a main effect of surgery on day activity ($F_{1,\ 23} = 12.3$, $p = 0.0019$) (Figure 7G). Although there was not a significant interaction, a simple main effects test was performed to see whether the main effect of the surgery was significant for both LD and CJL, whose results showed that it was for CJL only ($p = 0.0128$) (Figure 7G). There was a significant main effect of surgery ($F_{1,\ 23} = 15.5$, $p = 0.0007$) and lighting ($F_{1,\ 23} = 6.95$, $p = 0.0148$) on total activity (Figure 7H). Similarly, although there was not a significant interaction, a simple main effects test showed that CJL's effect on NVHL mice was primarily responsible for the main effect of lighting ($p = 0.0545$) (Figure 7H). No significant changes in period (Figure 7E) or alpha (Figure 7F) were found. Alpha and day activity were not obtained for three males (1 LD-IB/2 CJL-IB) because of arrhythmicity. In females, there was a significant main effect of surgery on total activity ($F_{1,\ 23} = 5.31$, $p = 0.0306$) (Figure 8H). No significant changes in period (Figure 8E), alpha (Figure 8F), or day activity (Figure 8G) were found. Alpha and day activity were not obtained for two females (1 LD-Sham/1 CJL-IB) because of arrhythmicity.

In males, the average bout length data did not meet the normality assumption, which was resolved by applying the square root data transformation. Additionally, two outliers were removed from the average bout length data (1 LD-Sham/1 CJL-Sham). There was a significant main effect of surgery on average bout length ($F_{1,\ 21} = 6.26$, $p = 0.0207$) (Figure 7L), and a trend toward a main effect of lighting on the total number of bouts ($F_{1,\ 23} = 3.35$, $p = 0.0803$) (Figure 7K). There was a trend toward a main effect of lighting on relative amplitude ($p = 0.0627$) (Figure 7I), but the data did not meet the normality assumption despite attempts to correct for skewness. No significant changes in intradaily variability (Figure 7J) were found. In females, there was a trend toward a main effect of surgery on intradaily variability ($F_{1,\ 23} = 2.96$, $p = 0.0990$) (Figure 8J), and a significant main effect of surgery on average bout length ($F_{1,\ 23} = 4.96$, $p = 0.0360$) (Figure 8L). No significant changes in relative amplitude (Figure 8I) or total number of bouts were found (Figure 8K). Thus, NVHL male and female mice showed reduced total activity levels under LL, an effect that appeared to be more pronounced in mice exposed to CJL.

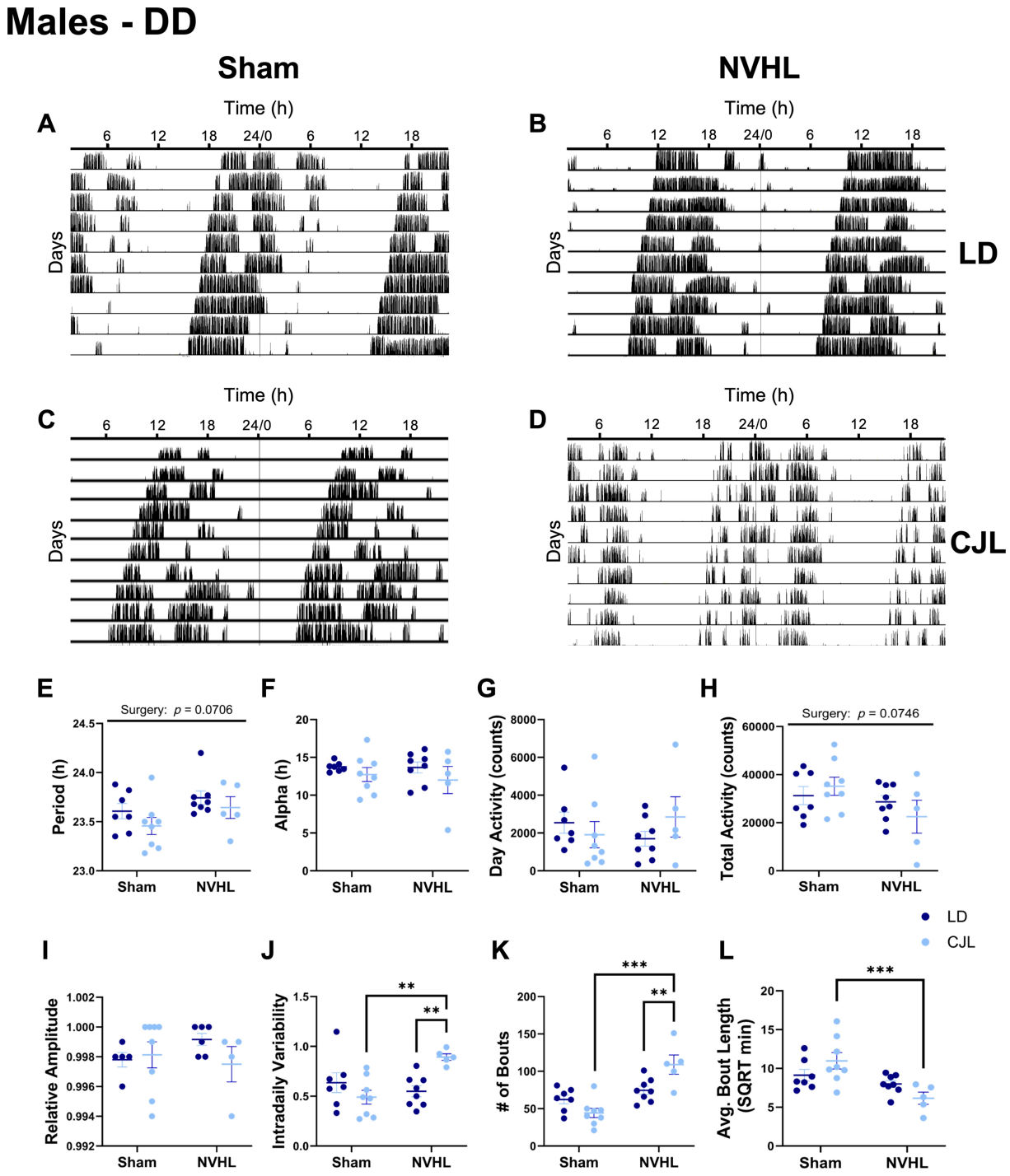

FIGURE 5 | Fragmented rhythms under DD due to interaction of NVHL and CJL in males. Representative actograms demonstrating running wheel activity of LD-Sham (A), LD-NVHL (B), CJL-Sham (C), and CJL-NVHL (D) male mice under DD. General (E–H), nonparametric (I,J), and bout (K,L) variables were analyzed. Days are vertically stacked one on the other, time (in hours) is shown across the *x*-axis, and data are double-plotted to facilitate visualization. LD: light–dark; DD: constant darkness; NVHL: neonatal ventral hippocampal lesion; CJL: chronic jet lag. Square root data (SQRT) transformation was performed on average bout length data in order to meet all ANOVA assumptions. Data points represent individual mice and are presented as mean ± SEM. Two-way ANOVAs with simple effects test were performed. $^{**}p < 0.01$, $^{***}p < 0.001$.

4 | Discussion

In this study, we aimed to assess how neurodevelopmental abnormality in the vHPC interacts with circadian disruption during adolescence to affect adult behavior. We present findings that demonstrate that the interaction of NVHL and CJL during adolescence synergistically leads to behavioral changes that last into adulthood, in a sex-dependent manner. Notably, we show that NVHL and CJL during adolescence lead to increased anxiety-like behavior and fragmented rhythms under DD in males. In addition, we report a striking reduction in total activity under constant light in both NVHL male and

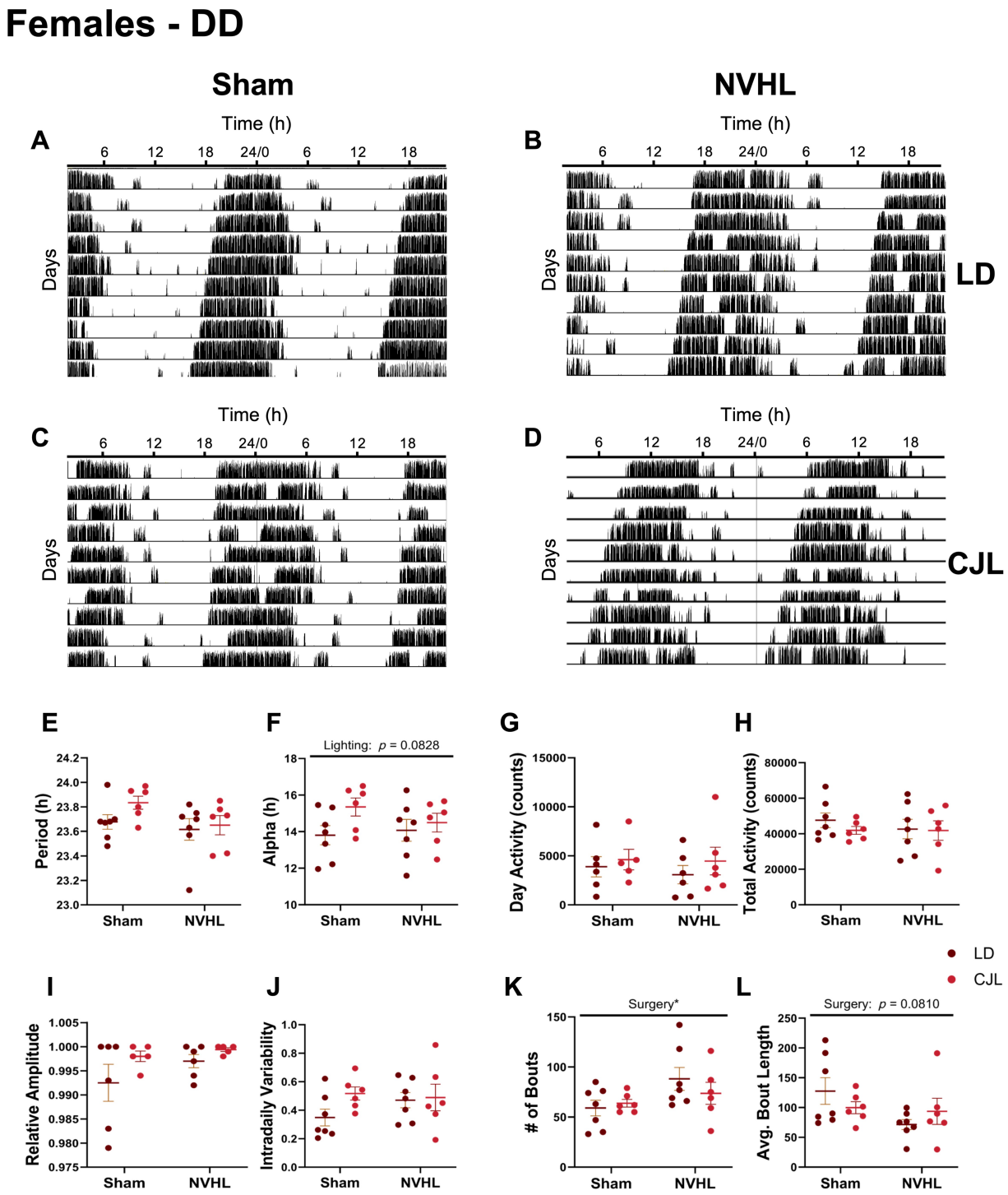

FIGURE 6 | Increased number of bouts due to NVHL in females under DD. Representative Actograms demonstrating running wheel activity of LD-Sham (A), LD-NVHL (B), CJL-Sham (C), and CJL-NVHL (D) female mice under DD. General (E–H), nonparametric (I,J), and bout (K,L) variables were analyzed. Days are vertically stacked one on the other, time (in hours) is shown across the *x*-axis, and data are double-plotted to facilitate visualization. LD: light–dark; DD: constant darkness; NVHL: neonatal ventral hippocampal lesion; CJL: chronic jet lag. Data points represent individual mice and are presented as mean ± SEM. Two-way ANOVAs (Lighting × Surgery) were performed. $^{*}p < 0.05$.

female mice, with those exposed to circadian disruption especially affected.

The NVHL model remains a widely used and well-characterized heuristic model to investigate the neurodevelopmental origins of SZ-related disorders (Tseng et al. 2009). As for the CJL protocol, it was chosen based on previous work demonstrating that it produces desynchronization of the activity–rest rhythms (Casiraghi et al. 2012). Moreover, this schedule was shown to affect hippocampal neurogenesis, behavior, and gene expression in key regions including the hypothalamus and prefrontal cortex (PFC) (Siddique et al. 2022; Acosta et al. 2023; Horsey et al. 2019). Therefore, it provides a useful tool for probing how circadian disruption during a critical period such as adolescence might

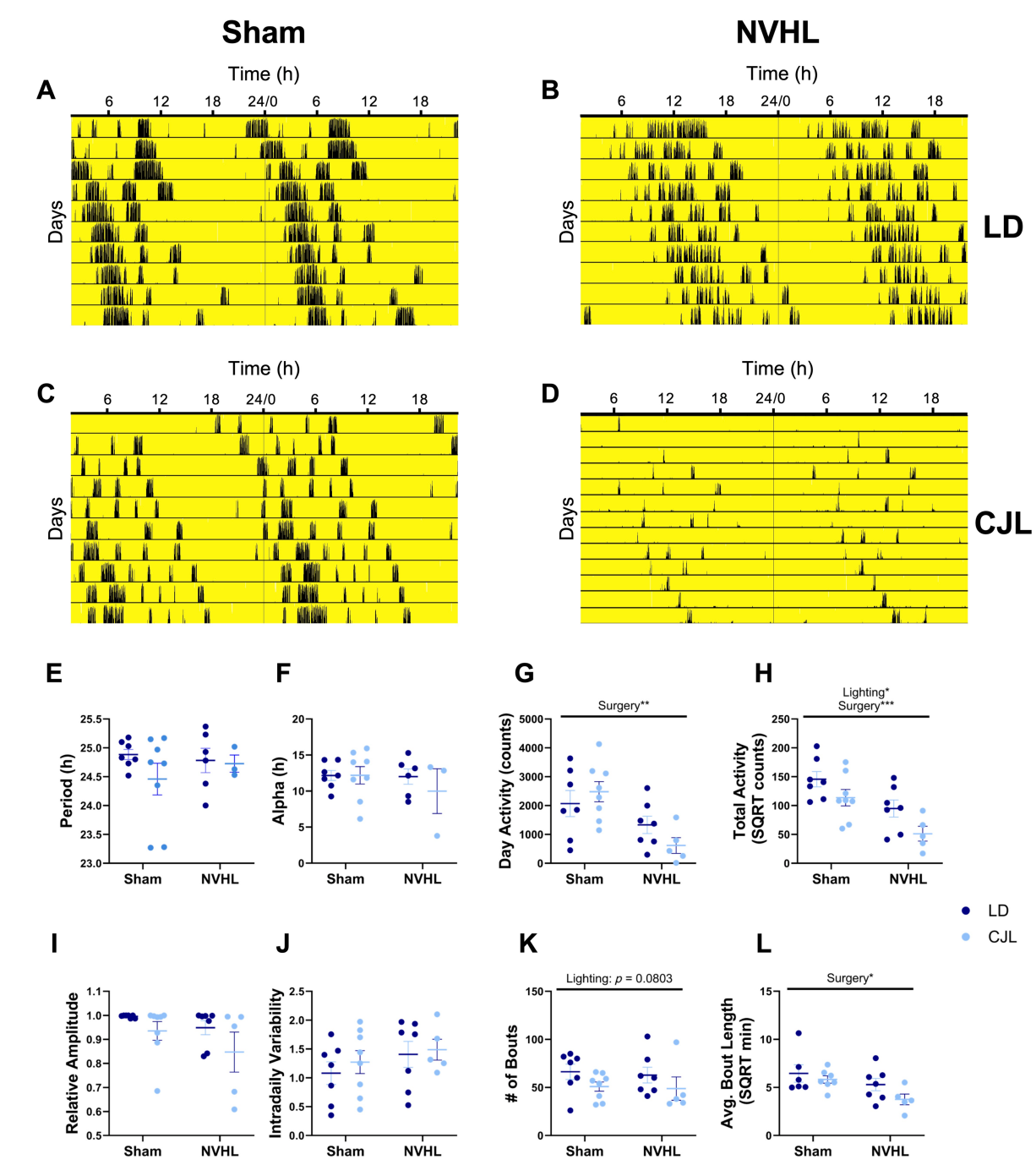

FIGURE 7 | Decreased activity levels due to NVHL in males under LL. Representative Actograms demonstrating running wheel activity of LD-Sham (A), LD-NVHL (B), CJL-Sham (C), and CJL-NVHL (D) male mice under LL. General (E–H), nonparametric (I,J), and bout (K,L) variables were analyzed. Days are vertically stacked one on the other, time (in hours) is shown across the *x*-axis, and data are double-plotted to facilitate visualization. LD: light–dark; LL: constant light; NVHL: neonatal ventral hippocampal lesion; CJL: chronic jet lag. Square root data (SQRT) transformations were performed on total activity and average bout length data in order to meet all ANOVA assumptions. Data points represent individual mice and are presented as mean ± SEM. Two-way ANOVAs (Lighting × Surgery) were performed. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

influence brain and behavioral development and interact with other risk factors.

In our study, mice did not exhibit the hyperactivity and reduced anxiety-like behavior typically found in rat NVHL literature (Lipska et al. 1993; Sams-Dodd et al. 1997; Lecourtier et al. 2012). In addition, we found that NVHL led to increased anxiety-like behavior in females. These differences could be due to the species used and the extent and timing of the lesion, both of which can be modifying factors of the behavioral phenotype produced by NVHL (Tseng et al. 2009). Indeed, in the only published study profiling behavior in NVHL mice to our knowledge

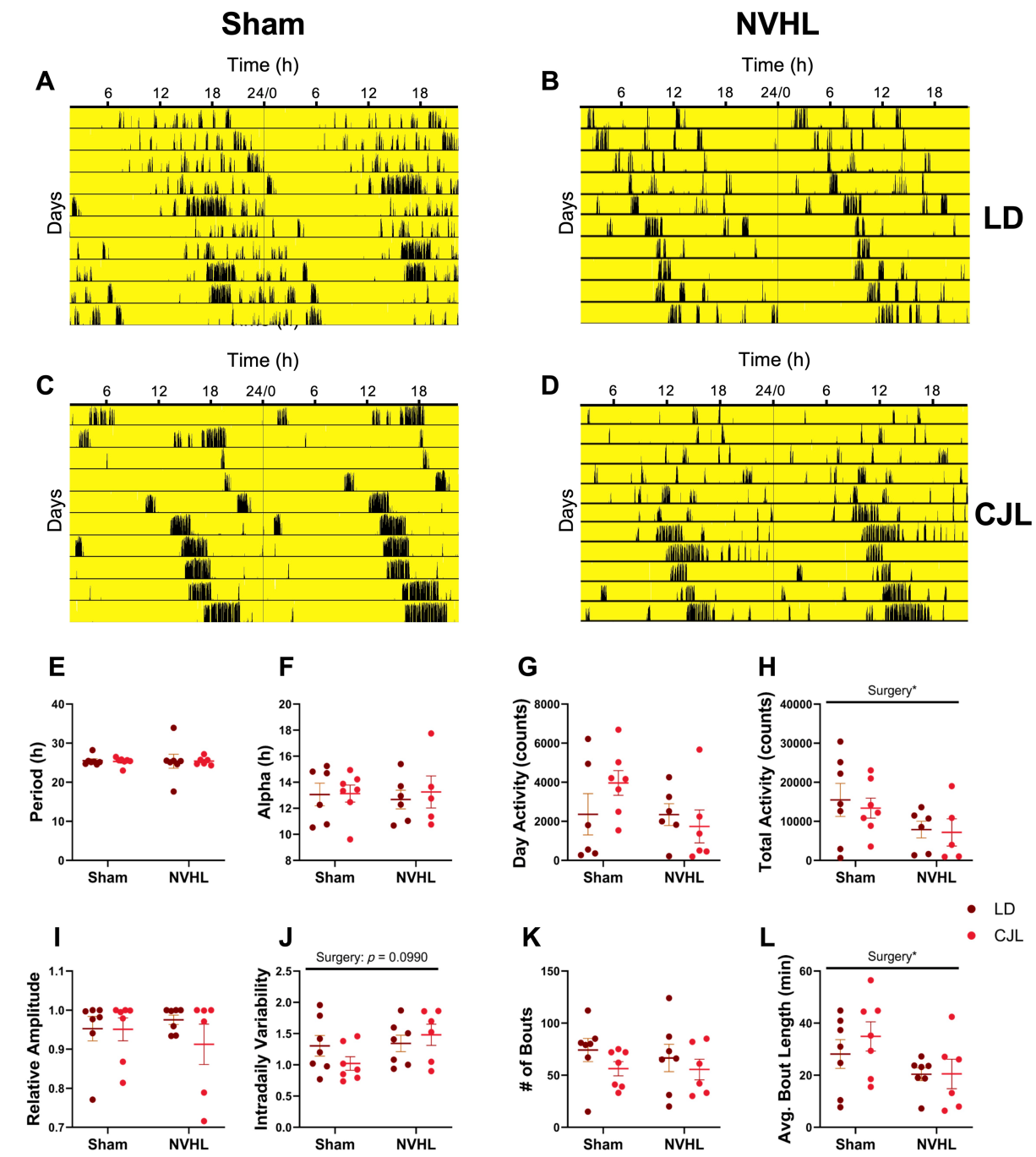

FIGURE 8 | Decreased average bout length and reduced activity levels due to NVHL in females under LL. Representative Actograms demonstrating running wheel activity of LD-Sham (A), LD-NVHL (B), CJL-Sham (C), and CJL-NVHL (D) female mice under LL. General (E–H), nonparametric (I,J), and bout (K,L) variables were analyzed. Days are vertically stacked one on the other, time (in hours) is shown across the *x*-axis, and data are double-plotted to facilitate visualization. LD: light–dark; LL: constant light; NVHL: neonatal ventral hippocampal lesion; CJL: chronic jet lag. Data points represent individual mice and are presented as mean ± SEM. Two-way ANOVAs (Lighting × Surgery) were performed. *$p < 0.05$.

(Naert et al. 2013), mice assigned as having a "small lesion" exhibited neither significant hyperactivity nor decreased anxiety-like behavior compared to controls, unlike those assigned as having a "big lesion," while still showing behavioral deficits in other areas. In our case, the majority of our NVHL mice lesion extent fell in the medium to small range, thus aligning with those findings.

We showed that the interaction of NVHL and CJL during adolescence leads to increased anxiety-like behavior in males. This effect was supported by the observation of an increased proportion of jumps from the EPM by the NVHL mice exposed to CJL. The emergence of anxiety-like behavior due to CJL in adolescence only in NVHL male mice suggests that disrupting ventral hippocampal development at an early age

alters function and structure in areas it projects to, including those involved in affect (e.g., amygdala [Amg])(Hernandez et al. 2015; Vazquez-Roque et al. 2014). This would lead to increased vulnerability to irregular light exposure. This aligns with the dual hit hypothesis of SZ, which suggests that abnormal neurodevelopment due to early risk factors interacts with environmental risk factors during key development periods later in life to synergistically bring about the disorder (Bayer et al. 1999; Guerrin et al. 2021; Maynard et al. 2001; Stepniak et al. 2014).

The effects of CJL during adolescence could be mediated by the intrinsically photosensitive retinal ganglion cells (ipRGCs) (LeGates et al. 2014), which project to downstream pathways involved in sleep regulation, motivation, cognition, and mood either indirectly through the SCN or through direct projection patterns (Fernandez et al. 2018; LeGates et al. 2014). Our findings suggest that NVHL and CJL during adolescence may have an additive effect in disrupting function in areas involved in mood regulation, particularly the Amg and ventral tegmental area (VTA) (LeGates et al. 2014). Previous studies similarly reported increased anxiety-like behavior following chronic CJL exposure (Acosta et al. 2023; Horsey et al. 2019; Kumari et al. 2024); however, these studies measured behavior either directly after or during the CJL protocol. Thus, the increase in anxiety-like behavior might have been due to the acute effects of abnormal light exposure, which can cause dysregulation of the hypothalamic–pituitary–adrenal axis and increased corticosterone levels as reported in one of those studies (Kumari et al. 2024).

In females, we observed that sham mice subjected to circadian disruption during adolescence had increased social preference. Surprisingly, this was not the case for NVHL mice, suggesting a preventative effect of the lesion. Previous literature has shown that exposure to aberrant light schedules leads to morphological and molecular alterations in areas involved in social behavior, including the PFC and Amg. Namely, mice chronically exposed to light at night for 2 weeks showed altered clock protein (PER1 and PER2) rhythms in the basolateral Amg and reduced *brain-derived neurotrophic factor* levels in the basolateral Amg and the medial PFC (Ikeno and Yan 2016). Similarly, mice exposed to abnormal light exposure for 18 days exhibited altered rhythms of clock genes and immediate early genes in the PFC (Otsuka et al. 2020). Considering these findings, it is unclear why CJL would enhance social preference. Because the same regions involved in social behavior (i.e., Amg, medial PFC) are impacted by the NVHL (O'Donnell 2012; Vazquez-Roque et al. 2014), it is possible that the morphological and molecular changes caused by the lesion in those areas prevented CJL from exerting its effects. Furthermore, previous studies employing the dual hit approach do not always show a synergistic effect, with some showing the "first hit" preventing the effect of the second one (Cloutier et al. 2022; Long et al. 2013; Morel et al. 2009; Zamberletti et al. 2012).

To our knowledge, our study is the first to assess the effects of early ventral hippocampal lesion and circadian disruption during adolescence on wheel-running behavior. In mice housed in constant darkness (DD), we showed that only NVHL male mice exposed to CJL during adolescence exhibited more fragmented rhythms. A similar but less pronounced effect was seen in NVHL females. Interestingly, a recent meta-analysis showed that SZ patients in remission exhibit increased intradaily variability of rhythms compared to controls (Meyer et al. 2020). Additionally, individuals identified as at risk for SZ show increased intradaily variability (Castro et al. 2015), which is associated with increased symptom severity (Lunsford-Avery et al. 2017). Similarly, mutant mouse models of SZ show increased intradaily variability and the total number of bouts (Deurveilher et al. 2021; Oliver et al. 2012; Paul et al. 2012; Pritchett et al. 2015).

When placed in constant light (LL), there was a significant reduction in total activity in NVHL male and female mice, which appeared to be greater in mice exposed to CJL during adolescence. As adolescence is characterized by rapid maturation and refinement of several brain regions (Fuhrmann et al. 2015), including the SCN (Hagenauer and Lee 2012), this makes the brain more susceptible to environmental challenges like CJL. In mice, LL reduces the amplitude of locomotor activity rhythms by desynchronizing individual cellular oscillators within the SCN (Ohta et al. 2005). Therefore, our findings suggest that NVHL may disrupt SCN network integrity, increasing its susceptibility to LL exposure, and that CJL during adolescence has an additive effect on that susceptibility. An altered susceptibility of the SCN itself to photic input could be tested by comparing the phase shift and immediate early gene expression in response to light pulses.

However, we cannot exclude that the effects of the two factors on the response to LL are due to mechanisms outside the SCN. One possibility would be that NVHL offspring, including those exposed to CJL, have a higher sensitivity to light at the level of the retina, where DA, whose function is disrupted in the NVHL model, plays a key role in light adaptation (as discussed below). Another possibility is that these mice experience more masking by light (i.e., the suppressive effects of light on locomotor behavior), a process that is independent of the SCN (Redlin and Mrosovsky 1999). Although the intergeniculate leaflet, which contributes to non-SCN light responses (Harrington 1997; Morin 2013), is unlikely to be directly impacted given the lesion location, indirect effects via broader network changes cannot be excluded. Together, these possibilities suggest that the exaggerated suppression of activity under constant light in NVHL mice may result from altered light sensitivity at multiple levels of the circadian system.

A candidate for the potential disruption of SCN network integrity or its response to light cues by NVHL, and its interaction with CJL during adolescence, is the mesocorticolimbic system. This dopaminergic network, which includes the VTA, nucleus accumbens (Nac), and PFC, is known to have altered function in response to NVHL (Tseng et al. 2009). In addition, the mesocorticolimbic DA pathways continue to develop during adolescence, making them particularly vulnerable to irregular light exposure (Reynolds and Flores 2021). DA, the SCN, and the circadian system are closely interlinked, and it was suggested that they may be linked together in SZ pathology because of the mechanisms they share (Ashton and Jagannath 2020). Nearly all aspects of DA signaling, such as receptor expression and transport, exhibit circadian rhythms (Castaneda et al. 2004). In addition, brain

areas part of the mesocorticolimbic system, including the VTA and NAc, are also under circadian control (Becker-Krail et al. 2022). Conversely, DA can modulate SCN function by acting on DA receptors within the SCN, affecting photoentrainment, and the SCN is directly innervated by dopaminergic neurons from the VTA (Grippo et al. 2017). Beyond the SCN, DA plays a role in regulating circadian rhythms in the retina, modulating light responsiveness and its transmission to the SCN (Mendoza and Challet 2014).

Preclinical studies in mice and monkeys show that disrupting DA function in the midbrain leads to increased intradaily variability in DD and LL (Fifel and Cooper 2014; Fifel et al. 2014); in addition, lesioning DA fibers in the medial forebrain results in altered PER2 expression in several motor-related regions, such as the dorsal striatum (Gravotta et al. 2011). Moreover, given that areas involved in DA neurotransmission are under circadian control (Becker-Krail et al. 2022) and that ipRGCs have direct projection patterns to areas involved in DA regulation (LeGates et al. 2014), exposure to abnormal light schedules or exposure to light at inappropriate times may alter DA function. For example, mice exposed to "winter-like" LD cycles (8 h: 16 h) with diminished light exhibit altered clock gene expression in the SCN and changes in DA neurotransmission in the NAc and dorsal striatum (Itzhacki et al. 2018).

With regard to sex-dependent differences, we observed that male mice were generally more impacted by the interaction of NVHL and CJL. In SZ, men tend to have an earlier onset and slightly higher prevalence, whereas women experience more mood disturbances and men exhibit more negative symptoms (Li et al. 2016). Although limited in numbers, studies exploring sex differences in animal studies, including NVHL (Bychkov et al. 2011; Levin and Christopher 2006), report that males exhibit increased vulnerability to genetic and developmental manipulations relevant to the disorder (Hill 2016). Interestingly, this increased vulnerability appears to be present in the mesocorticolimbic system, particularly the PFC (Hill 2016). Sex differences are similarly present in circadian rhythms. Females have shorter circadian periods (Duffy and Wright 2005) and have an earlier phase, although this difference diminishes or disappears with age (Boivin et al. 2016; Duarte et al. 2014; Randler and Engelke 2019).

5 | Conclusion

This study illustrated for the first time that an interaction of abnormal neurodevelopment in areas relevant to SZ with circadian disruption during adolescence results in lasting behavioral changes in mice in a sex-dependent manner. Although the mechanistic links remain undetermined, our findings support the hypothesis that SZ arises because of the interaction of abnormal neurodevelopment with environmental risk factors occurring during critical developmental periods.

Author Contributions

Ahmed A. Bouteldja: conceptualization, data curation, formal analysis, investigation, methodology, validation, visualization, writing – original draft, writing – review and editing. **Lianne A. Marceau:** data curation, formal analysis, investigation, methodology, visualization. **Lalit K. Srivastava:** conceptualization, methodology, resources, supervision, writing – review and editing. **Nicolas Cermakian:** conceptualization, funding acquisition, investigation, methodology, project administration, resources, supervision, writing – review and editing.

Acknowledgments

The authors thank members of the Cermakian and Srivastava laboratories for helpful discussions; Sebastián Boy Waxman, Genavieve Maloney, Victoria Lu, and Sanjeev Bhardwaj for technical help; and Guylaine Gadoury, Tara Thomson, Jessica Balbin, and all the staff at the Douglas Research Centre's animal facility for assistance with the animal work. The graphical abstract was created with BioRender.com.

Ethics Statement

All procedures were approved by the Facility Animal Care Committee at the Douglas Research Centre, in accordance with the Canadian Council on Animal Care guidelines.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

All processed data are available in the figures of the manuscript and Supporting Information. All raw data that support the findings of this study are available from the corresponding authors upon request (e.g., brain images and raw behavioral data).

Peer Review

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/ejn.70134.

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Supporting Information

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