Developmental Neuroscience

Early-life sleep disruption increases parvalbumin in primary somatosensory cortex and impairs social bonding in prairie voles

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Across mammals, juveniles sleep more than adults, with rapid eye movement (REM) sleep at a lifetime maximum early in life. One function of REM sleep may be to facilitate brain development of complex behaviors. Here, we applied 1 week of early-life sleep disruption (ELSD) in prairie voles (Microtus ochrogaster), a highly social rodent species that forms lifelong pair bonds. Electroencephalographic recordings from juvenile voles during ELSD revealed decreased REM sleep and reduced $\gamma$ power compared to baseline. ELSD impaired pair bond formation and altered object preference in adulthood. Furthermore, ELSD increased GABAergic parvalbumin immunoreactivity in the primary somatosensory cortex in adulthood, a brain region relevant to both affected behaviors. We propose that, early in life, sleep is crucial for tuning inhibitory neural circuits and the development of species-typical affiliative social behavior.

Introduction

Early in mammalian development, sleep predominates over wakefulness, with both non–rapid eye movement (NREM) and rapid eye movement (REM) sleep at their lifetime maximums. This period of life corresponds to a time of rapid cortical changes and has led to the hypothesis that the endogenous neural activation characteristic of REM sleep in particular may be critical for normal maturation of the central nervous system (1–4).

Sleep deprivation studies in both young felines and juvenile rodents have identified core functions of sleep in the early development of the visual system (3, 5–7), motor systems (8–10), refinement of sensorimotor integration (11), and organization of spinal reflexes (12). Early-life sleep may also be necessary for the maturation of the neurobiological systems that underlie complex social behaviors (13): Previous works in both Drosophila (13, 14) and rats (15–17) suggest that early-life sleep disruption (ELSD) results in long-lasting changes in species-specific socioeconomic behavior (e.g., courting and mating). However, the role of early-life sleep in the development of specific brain circuits that underlie complex social behaviors such as pair bond formation and expression remains largely unexplored.

In mice and rats, inhibitory GABAergic synapses within the barrel fields of the primary somatosensory (SI) cortex undergo marked remodeling in the second and third postnatal weeks (18, 19), with normal whisking behavior emerging between postnatal days (P) 12 and 15 (20). The somatosensory system is crucial for the expression of rodent social behaviors (21). Both neonatal damage to the somatosensory cortex (22) and the deprivation of sensory stimuli to the whiskers alter the development of play behavior (23), which can influence the adult expression of social behavior (24, 25).

Proper synchronization of excitatory and inhibitory processes, essential to normal neural functioning throughout the neocortex (26), is dependent on fast-spiking parvalbumin (PV)–expressing inhibitory interneurons (27). These interneurons are involved in generating electroencephalographic (EEG) oscillations within the $\gamma$ frequency band (20 to 100 Hz) (28, 29) associated with cortical activation present during wake and REM sleep (30). Direct activation of PV interneurons in the barrel cortex of mice selectively amplifies EEG oscillations within the $\gamma$ frequency band (28), and aberrant EEG $\gamma$ band oscillations are a feature of many neuropsychiatric disorders (31).

PV interneuron development is especially vulnerable to atypical experience during early development because of its activity-dependent postnatal maturation (32) and has been shown to be sensitive to REM sleep deprivation in kittens (5). In the rat and mouse, PV immunoreactivity (PV-ir) in the cerebral cortex develops rapidly between P12 and P21 (33, 34) and may represent a time period in rodents whereby social neural networks are sensitive to environmental insults such as ELSD. Notably, PV disruption in the cortex has been linked to abnormal social behavior in mice (35).

To investigate how sleep shapes the neural system’s underlying social development, we disrupted sleep early in life in the highly social prairie vole (Microtus ochrogaster). Prairie voles are socially monogamous rodents that form lifelong pair bonds with opposite sex individuals. In the wild, prairie voles engage in a number of affiliative social behaviors common to humans, including biparental care (36) and extended opposite sex cohabitation (assessed in the laboratory using the partner preference test) (37). We hypothesized that REM ELSD that occurs within a sensitive period of PV development in the cortex of rodents would have long-lasting effects on PV-ir and social bonding in the prairie vole.

In this series of studies, we first validated a method of ELSD in juvenile prairie voles using a laboratory orbital shaker while undergoing chronic in vivo sleep EEG/EMG recordings. EEG/EMG signals were used to determine sleep measures during ELSD compared to baseline, as well as relative EEG power during sleep stages. Prairie vole pups underwent ELSD for 1 week during their third postnatal week in development (P14 to P21), when...
social behaviors with littersmates are starting to emerge (38) and when PV-ir is maturing in the neocortex. Brain tissue was collected from adult animals and processed for PV-ir in the S1 cortex as a first probe into the neocortical excitation/inhibition tuning necessary for appropriate social development. Behaviorally, adult prairie voles were tested for pair bond formation, novel object recognition, and anxiety-related behavior to examine the role of early-life sleep on the development of complex behaviors known to involve the somatosensory system (i.e., sensory integration of environmental cues).

RESULTS
ELSD was accomplished with gentle and automated agitation of the home cage placed on a standard laboratory orbital shaker (39, 40) set to continuously rotate at 110 rpm for 10 s every 109 s (10 s on, 99 s off) (40). We first validated this method of sleep disruption in juvenile prairie voles by examining continuous EEG/EMG signals both on and off the shaker, explored parental care behavior in litters of prairie voles housed on the orbital shaker for seven continuous days from P14 to P21, and measured plasma corticosterone levels shortly after ELSD. In separate experiments, prairie voles were either early-life sleep disrupted using the orbital shaker method for seven continuous days from P14 to P21 (ELSD group) or left undisturbed (control group), and PV-ir, social behavior, novel object recognition, and light/dark anxiety-related behaviors were collected in adult animals (see Fig. 1 for experimental design).

Housing on an orbital shaker decreases REM sleep, fragments NREM sleep, and reduces EEG γ power during REM in juvenile prairie voles compared to baseline
The effects of the orbital shaker on sleep in juvenile prairie voles were investigated using sleep EEG recordings. These recordings provided a snapshot of objective sleep measures both on and off the orbital shaker in prairie voles (see Fig. 2A for a hypnogram of an undisturbed prairie vole and Fig. 2B for a representative hypnogram on the shaker) during the juvenile developmental period. Sleep recordings lasted for 6 days—three successive days with the shaker off, referred to as “baseline” days, and three successive days with the shaker on (Fig. 2C). Cohorts were alternated to start with the shaker on or off. Twenty-four hours of 4-s EEG epochs was classified as either sleep (REM or NREM) or wake and compared within shaker and baseline conditions. Juvenile voles spent less time asleep (REM and NREM) when housed on the shaker than during their baseline recording (paired t test: \( t = 2.484, P = 0.038 \)) (Fig. 2D). We calculated the relative effect of the shaker on each vigilance state as a percentage of change compared to baseline, with zero indicating no change. After Bonferroni correction (P < 0.017 required for significance), voles experienced a nonsignificant increase in time spent in wake (one sample t test, test value = 0; \( t = 2.492, P = 0.037 \)), no significant change in NREM sleep (\( t = 1.206, P = 0.262 \)), and a significant decrease in REM sleep (\( t = 3.645, P = 0.007 \)) (Fig. 2E). We summed the total number of transitions between sleep and wake states over the 24-hour periods. Housing on the shaker resulted in fragmented sleep with significantly more sleep/wake transitions when compared to baseline (paired t test: \( t = 3.325, P = 0.010 \)) (Fig. 2F). We further divided these transitions to wake by NREM and REM sleep. After Bonferroni correction (P < 0.025 is required for significance), there was a trend toward a significant increase in transitions between NREM sleep and wake states compared to baseline values (paired t test: \( t = 2.709, P = 0.027 \)) (Fig. 2F, inset). Average sleep bout length was reduced on the shaker compared to baseline for both NREM (paired t test: \( t = 3.718, P = 0.006 \)) and REM (paired t test: \( t = 9.706, P < 0.001 \)) sleep stages (Fig. 2G).

We conducted a power spectral analysis of EEG signals from 4 hours of recordings (1200 to 1600, lights on) on baseline and shaker days (see fig. S1A for representative baseline hypnograms from three randomly selected prairie voles). Fast Fourier transforms (FFTs; Hanning window) were conducted for each frequency band, averaged across the 4-hour span (see fig. S1C for visual representation of REM and NREM EEG power during both baseline and shaker recordings), and normalized to the animal’s total power (1 to 100 Hz) for the corresponding sleep state (REM or NREM).

Percentage of change in each band was calculated using normalized power values for each sleep stage on the shaker compared to baseline values for each animal for visualization. Power spectral analysis of EEG signals was obtained for δ, θ, α, β, slow γ, and fast γ frequencies and compared using repeated measures multivariate analysis of variance (MANOVA) on each sleep stage. Of the dependent variables, γ power was decreased on the shaker [within subjects: \( F_{1,8} = 5.510, P = 0.047 \) (slow γ) and \( F_{1,8} = 6.066, P = 0.039 \) (fast γ); fig. S1D] (see table S1 for full statistics and Supplementary Methods for exact binning frequencies).

Parental care, pup weight, and corticosterone are not altered when housed for 1 week (P14 to P21) on the orbital shaker
The use of an orbital shaker to disrupt sleep in rodents has been previously validated in mice (39, 40); however, it is a novel approach in both developing rodents and prairie voles. In addition to social
monogamy, prairie voles are biparental, and both males and females rear their young. In this ELSD protocol, sleep was disrupted by housing litters of prairie voles (along with both parents) on an orbital shaker for 1 week before weaning. We examined the possibility that altered parental care toward pups could alter the developmental trajectory of ELSD animals. Parental care was quantified for the duration of the ELSD or control housing conditions by sampling behavior of the male and female parents twice a day (41, 42).

Huddling, nursing, and pup-directed grooming in prairie voles are key components of the maternal bond with pups (43). We averaged the duration of time engaged in each behavior by male and female parents for each recording collected (mean number of recordings = 10 per group). There were no differences in aggregate quantity of either paternal or maternal care on the shaker (Fig. 3B, checkerboard bars) compared to duration of care in control litters [Fig. 3B, solid bars; two-way MANOVA (between group factors: sex and group), all P values > 0.13]. In addition, housing on the shaker did not influence the nursing style of the dam (nursing while ambulatory, stationary, or dismissing pups; fig. S2).

Consistent with studies of chronic sleep disruption with an orbital shaker in adult mice (40), we did not find significant differences in weight at time of weaning [two-way ANOVA: F_{1,74} = 1.661, P = 0.202 (main effect of group) and F_{1,74} = 2.269, P = 0.136 (main effect of sex)] (Fig. 3D) or circulating corticosterone levels [two-way ANOVA: F_{1,25} = 0.537, P = 0.471 (main effect of group), F_{1,25} = 0.158, P = 0.694 (main effect of sex), and F_{1,25} = 0.022, P = 0.883 (sex × group interaction)] between ELSD and controls. Combined, these results suggest that this method is minimally stressful, preserves fundamental parenting behaviors, and is thus relatively selective for sleep disruption in juvenile prairie voles.

**ELSD increases PV-ir in S1 cortices**

GABAergic interneurons in the neocortex are especially vulnerable to environmental insult (44) because of their postnatal laminar circuit integration (32). We examined a subpopulation of GABAergic cells in the neocortex expressing PV in a brain region necessary for sensory processing from the whiskers: the S1 cortex corresponding to the barrel fields. These same cell types are responsible for the production of high-frequency EEG γ oscillations in the cortex. We
counted PV-immunoreactive cells in the S1 barrel cortices, as well as the medial prefrontal cortex (mPFC) in brains harvested from male and female adult voles (~P100), from ELSD and control groups (Fig. 4A).

ELSD significantly increased PV-ir in the barrel fields of the S1 cortex compared to controls [two-way ANOVA: $F_{1,36} = 6.011$, $P = 0.019$ (main effect of group), $F_{1,36} = 0.004$, $P = 0.950$ (main effect of sex), and $F_{1,36} = 0.292$, $P = 0.592$ (sex × group interaction)] (Fig. 4B). The significant main effect of group was followed up with independent sample $t$ tests and revealed that this effect was driven by increased PV-ir in the S1 cortex in males ($t_{20} = 3.646$, $P = 0.002$) and not in females ($t_{16} = 0.959$, $P = 0.352$) (Fig. 4B, inset).

This increase was specific to the S1 cortex, as there were neither main effects of sex [two-way ANOVA, main effect of sex: $F_{1,29} = 0.015$, $P = 0.903$ (infralimbic cortex, IL) and $F_{1,30} = 0.223$, $P = 0.640$ (prelimbic cortex, PrL)] nor group [two-way ANOVA, main effect of group: $F_{1,29} = 3.034$, $P = 0.092$ (IL) and $F_{1,30} = 2.452$, $P = 0.128$ (PrL)] on PV-ir within the mPFC (fig. S3). To further explore the effect of ELSD on PV-ir within S1 cortex, we conducted laminar analysis by measuring 0.1-mm bins from the pial surface (fig. S4A). After Bonferroni correction, there were significantly more PV-positive cells 0.4 to 0.5 mm beneath the pial surface (bin 5; independent sample $t$ tests: $t = 4.514$, $P = 0.001$), at the peak density of PV-ir cells in S1 cortex just superficial to cortical layer IV, in ELSD males compared to controls (fig. S4B; see table S3 for full statistics).

ELSD reduces novelty preference for objects but does not affect baseline anxiety

We hypothesized that ELSD-induced alterations in PV-ir in the S1 cortex could lead to impairments in specific behaviors subserved by S1 cortex, such as sensory integration of environmental cues. To investigate this association, we tested short-term novel object recognition memory using the novel object recognition test (NORT; see Fig. 5A for experimental design). Rodents have a natural tendency to explore unfamiliar items over familiar ones. During the acquisition phase of the NORT, animals were presented with two identical objects that they had never encountered. In the testing phase of the NORT, we tested the animals for novelty preference by quantifying time spent investigating a novel object compared to time spent investigating a familiar object from 10 min earlier. Object recognition was considered intact with the expected preference for novelty if a novelty preference ratio (time interacting with novel object/total time interacting with both objects) was significantly higher than 0.5.

ELSD reduced novelty preference for objects [two way ANOVA: $F_{1,41} = 4.526$, $P = 0.039$ (main effect of group) and $F_{1,41} = 1.258$, $P = 0.269$ (main effect of sex)]. We determined a novelty preference with one sample $t$ test (test value = 0.50) on each group and sex. Both control males and females showed a significant preference to interact with the novel object (males: $t_{12} = 2.934$, $P = 0.013$ and females: $t_{12} = 3.797$, $P = 0.003$), and neither ELSD males ($t_{11} = 0.716$, $P = 0.489$) nor ELSD females ($t_{6} = 1.275$, $P = 0.249$) showed a novelty preference (Fig. 5B).

Fig. 3. No change in nonsleep measures during ELSD. Prairie vole litters were either housed on the shaker (A) or left undisturbed for seven consecutive days from P14 to P21. P14 and P21 were partial shaker days (indicated by angled text). (B) Duration of parental care during ELSD protocol (checkerboard bars) was not different from controls (solid bars). (C) Weight at time of weaning was similar for both conditions ($n = 13$ to 22 per group) as were (D) circulating corticosterone levels ($n = 5$ to 9 per group). Symbols are individual animals. Fill colors indicate breeder pairs as an example of genetic heterogeneity and litter counterbalancing across groups within the prairie vole colony. Bar height is mean; error bars ± SEM.

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Despite no differences in total time spent interacting with the objects during the acquisition phase [two-way ANOVA: $F_{1,41} = 0.352, P = 0.556$ (main effect of group) and $F_{1,41} = 2.622, P = 0.113$ (main effect of sex)] (fig. S5A), ELSD animals spent less time interacting with the objects during the test session (two-way ANOVA, main effect of group: $F_{1,41} = 5.393, P = 0.025$), and females interacted with the objects more than males (two-way ANOVA, main effect of sex: $F_{1,41} = 4.761, P = 0.035$). Follow-up independent samples $t$ tests revealed that ELSD males spent less time with the objects overall ($t_{23} = 3.766, P = 0.001$), whereas time spent with the objects was similar in control versus ELSD females (Fig. 5C).

To examine whether these effects could be influenced by either anxiety or locomotor deficits, voles underwent a 5-min anxiety test in a light/dark box. There were no main effects of sex (two-way ANOVA: $F_{1,82} = 0.118, P = 0.733$) or group (two-way ANOVA: $F_{1,82} = 0.371, P = 0.544$) on time spent in the light portion of the light/dark box (Fig. 5D), suggesting no group differences in baseline anxiety. With the exception of ELSD females, all groups showed a preference for the dark portion of the light/dark box [paired $t$ tests: $t_{28} = 2.422, P = 0.022$ (male controls), $t_{21} = 2.268, P = 0.003$ (male ELSD), $t_{22} = 4.382, P < 0.001$ (female controls), and $t_{11} = 1.10, P = 0.335$ (female ELSD)]. Locomotor behavior was sampled by measuring the total distance traveled in the open-field chamber regardless of zone during the light/dark test (distance light side + distance dark side). Males were more active in the light/dark box apparatus (two-way ANOVA, main effect of sex: $F_{1,82} = 4.310, P = 0.041$), and there were no group effects on the total distance traveled in both sides (light + dark; main effect of group: $F_{1,82} = 0.917, P = 0.341$) and no interaction (sex × group: $F_{1,82} = 1.297, P = 0.258$) (fig. S5B).

**Fig. 4.** ELSD increased PV-ir in adult male S1 barrel cortex. (A) Experimental design: Brain tissue from control and ELSD adults was collected and processed for PV-ir in the barrel region of the S1 cortex. (B) ELSD animals showed increased PV-ir, (left: collapsed across sex; inset: data points for each sex). (C) Representative image of S1 cortex in an adult male control and ELSD prairie vole. Error bars ± SEM ($n = 8$ to 13 per group); *$P < 0.05$; **$P < 0.01$.

**Fig. 5.** NORT and light/dark box test in adults. (A) Experimental design: Control and ELSD prairie voles underwent NORT and light/dark box testing as adults. (B) ELSD animals did not show a preference to interact with the novel object during the test phase (one sample $t$ test, test value = 0.5; *$P < 0.05$), dashed line indicates no preference, and (C) males spent less time interacting with objects (novel + familiar) overall during test ($n = 7$ to 13). (D) There were no significant differences in time spent in the dark portion of a light/dark box, one possible indicator of anxiety in rodents. Bar height is mean; error bars ± SEM ($n = 12$ to 29 per group). *$P < 0.05$, **$P < 0.01$. 

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ELSD reduces affiliative huddling and prevents partner preference in adult males

We next investigated the effect of ELSD on social bonding in adulthood (see Fig. 6A for experimental timeline) by measuring affiliative social huddling with potential mates and selective aggression toward intruders in a partner preference test. ELSD decreased total huddling (time spent huddling with “partner” + “stranger”) [two-way ANOVA: $F_{1,56} = 4.322, P = 0.042$ (main effect of group), $F_{1,56} = 1.727, P = 0.194$ (main effect of sex), and $F_{1,56} = 0.185, P = 0.669$ (no interaction)] (see Fig. 6B, inset, for individual data points by sex and group).

As anticipated for a socially monogamous species, both control males and control females (Fig. 6C) formed partner preferences, evidenced by spending more time huddling with their partner over the stranger (Wilcoxon signed-rank test: $P = 0.003$, for both males and females). ELSD had no adverse effect on huddling in female prairie voles (Wilcoxon rank sum test: $P = 0.013$). However, ELSD impaired pair bond formation in males, as evidenced by a lack of huddling preference for the partner female (Wilcoxon rank sum test: $P = 0.917$) (Fig. 6C).

There was no main effect of ELSD on total aggressive bouts displayed toward stimulus animals (Mann-Whitney $U$ test: $P = 0.676$), and females were less aggressive than males ($P = 0.048$) (Fig. 6D). Males of both groups displayed selectively increased aggression toward stranger females [Wilcoxon signed-rank test: $P = 0.005$ (male controls), $P = 0.003$ (male ELSD), $P = 0.195$ (female controls), and $P = 0.386$ (female ELSD)]. These results suggest that ELSD impairs the expression of affiliative behavior only (e.g., huddling) but does not influence aggressive behaviors related to pair bonding (e.g., mate guarding).

One possible explanation for the lack of partner preference in males who underwent ELSD is that animals may lack the ability to recognize familiar versus unfamiliar animals. To test this possibility, we conducted an olfactory social recognition test on a separate cohort of animals with odor cues from opposite sex prairie voles (fig. S6A). The olfactory social recognition test showed intact habituation to a familiar odor across all groups. Specifically, all groups showed sequentially decreased sniffing time over four trials of bedding exposure from the same animal (repeated measures ANOVA, within-subject effect of trials 1 to 4: $F_{3,108} = 30.871, P < 0.001$). There

![Fig. 6. Partner preference test for pair bond formation.](http://advances.sciencemag.org/)

(A) Experimental design: ELSD and control prairie voles were tested for partner preference after 24 hours of cohabitation with an opposite sex animal. (B) ELSD reduced total huddling time (partner + stranger; inset: individual data points by sex). (C) ELSD males did not show a huddling partner preference. (D) Total aggression was lower in females, and (E) both ELSD and control males displayed selective aggression toward the stranger. Bar height is mean; error bars ± SEM ($n = 13$ to 20 per group). *$P < 0.05$, **$P < 0.01$.
were both group (repeated measures ANOVA, between-subject effect of sleep group: $F_{1,36} = 8.244, P = 0.007$) and sex effects (repeated measures ANOVA, between-subject effect of sex: $F_{1,36} = 5.184, P = 0.029$) during trials 1 to 4 (no sex x group interaction: $F_{1,36} = 2.550, P = 0.119$). There was increased time sniffing during trial 5 (bedding from a new animal) compared to trial 4 (repeated measures ANOVA, within-subject effect of trials 4 and 5: $F_{1,36} = 52.608, P < 0.001$), when bedding from a new animal was introduced (fig. 56B) with no between-subject effects of sex ($F_{1,36} = 0.405, P = 0.529$) or sleep group ($F_{1,36} = 3.041, P = 0.09$) nor was there an interaction ($F_{1,36} = 2.406, P = 0.130$).

Together, ELSD resulted in sexually dimorphic changes to affiliative social behavior in prairie voles. ELSD abolished partner huddling preference in males, an effect not explained by deficits in olfactory social recognition, and ESLD also decreased total huddling time in both sexes.

**DISCUSSION**

The “ontogenetic hypothesis of REM sleep,” first proposed 50 years ago, posited that one of the functions of early-life REM sleep is to provide the developing brain with “endogenous stimulation” to strengthen developing neural circuits. We experimentally disrupted sleep during a postnatal window of rapid neural development of the neocortex and the emergence of social behaviors in rodents. Using an altricial rodent species well known for their complex social behavior, we observed that REM early-life sleep disruption caused long-lasting impairments on affiliative social huddling in adult prairie voles.

In this study, young prairie voles underwent ELSD for 1 week during postnatal development (P14 to P21) using an automated sleep disruption paradigm (39, 40) that caused gentle arousals at timed intervals throughout the day. In rodents, the third and fourth postnatal weeks of life represent a potentially sensitive period of GABAergic maturation for functional integration of multisensory information (45). Chronic in vivo sleep EEG/EMG recordings showed this method fragmented sleep and reduced REM sleep by ~25%. The REM sleep that did occur in ELSD animals was marked by decreased power in the EEG $\gamma$ frequency band. Thus, this pattern of sleep disruption significantly disturbed sleep patterns in juvenile prairie voles without altering aggregate quantity of parental care behavior, pup weight, or circulating corticosterone.

EEG $\gamma$ oscillations are prevalent during information-processing events, such as during cognitive challenges (46, 47), sensory stimulation, and exploration (48), and in REM sleep in particular (46, 49). These $\gamma$ band oscillations are produced by GABAergic PV interneurons (28, 29) whose maturation is dependent on developmental experiences (32, 50). Thus, an experimentally induced reduction in $\gamma$ power may induce long-lasting compensatory changes in PV that outlast the period of sleep disruption.

In our studies, behavioral tests for novel object recognition, anxiety in a light/dark box, and partner preference formation were conducted in adult prairie voles that experienced ELSD or control early-life conditions. We found that ELSD males did not show a novelty preference for objects and did not show a partner preference for a female partner as adults. ELSD males also interacted less with objects overall during the test phase of the novel object recognition task, when animals were returned to the testing chamber with a new object. There were no effects of ELSD on anxiety-related behavior or locomotor activity in the light/dark box, suggesting that the reduced object interaction and reduced partner huddling are not due to impaired activity levels or heightened anxiety in new situations but instead could be due to impaired sensory perception of objects and conspecifics resulting in reduced affiliative social huddling.

Although deficits in short-term memory are also possible, we saw no short-term memory impairment in an olfactory object recognition task for social memory despite similar patterns of decreased interaction times overall in ELSD animals. However, ELSD did result in lower total olfactory investigation of opposite sex social cues despite a pattern of habituation-dishabituation that was similar to controls. Additional studies are necessary to disentangle the influence of ELSD on the development of somatosensation from other sensory modalities (e.g., olfaction) during the third postnatal week and the role of sex in the timing of sensitive periods of cortical PV development (44).

Consistent with our findings in prairie voles, Kayser et al. (13) found that sleep restriction in early development of *Drosophila* resulted in impaired adult courtship behavior and reduced copulation. In rats, nonspecific pharmacological suppression of REM sleep with clomipramine in the first month of life also alters later sexual behavior (15–17). Together, our results support the hypothesis that one of the conserved functions of early-life sleep is to shape the developing brain. When sleep is disrupted during sensitive periods of somatosensation and social development, long-lasting changes in species-specific social behavior may result.

The use of prairie voles as an animal model allows us to examine the role of early-life sleep and the development of cortical brain regions that contribute to social bonding between mates. Expansion of this ELSD model to nonmonogamous rodent species, such as the closely related montane or meadow vole, would provide insight into how ELSD specifically targets social affiliation circuits or somatosensation in general.

**ELSD and brain development: Tuning excitation/inhibition via expression of PV in somatosensory circuits**

PV-ir was examined in the S1 cortex corresponding to the barrel fields of the whiskers, as well as in the mPFC of adult prairie voles that had undergone ELSD or control conditions. We found that ELSD resulted in an adult increase in PV-ir specific to the S1 cortex. In rodents, normal functioning of somatosensory neurons during development is essential for later expression of species-typical social behaviors (51) and for environmental interactions. The altered developmental trajectory of the PV system within the somatosensory cortex observed after ELSD in voles could potentially imbalance the ratio of excitation/inhibition. Resulting behavioral effects could include poor sensory detection or perception and altered approach behavior toward salient stimuli (novel objects and opposite sex cues) and social deficits (35). ELSD may also alter development of PV in other cortical brain regions, including sensory processing areas from other modalities. This could result in behavioral impairments consistent with those observed here and in alternative behaviors not tested in this set of experiments. In addition, targeting different windows of development may differentially influence the developmental trajectory of PV within other brain regions. It is possible that ELSD after weaning, during early adolescence, may lead to a significant increase in PV-ir within the mPFC because of the later maturation of this brain region.

Approximately 40 to 60% of inhibitory GABAergic interneurons express PV in the neocortex (5, 52), with immunoreactivity in rodents emerging around P12 and developing into layers by P21 (34).
The developmental window targeted with the ELSD protocol (P14 to P21) falls squarely within this window of PV development in the neocortex. In both the somatosensory and visual cortices, PV is responsible for timing critical windows of plasticity, where sensory experience is especially crucial in shaping neural development. Environmental experience, such as that provided endogenously by REM sleep, may provide a feedback mechanism that shapes the functional maturation of GABA (γ-aminobutyric acid) signaling systems in early postnatal development (including the third postnatal week tested here), serving to maintain balanced networks of excitation and inhibition (53). Research has found that sensory deprivation of the whiskers early in life also results in increased PV interneurons within the barrel cortex of mice (54).

Consistent with our findings, other methods of ELSD have shown alterations in PV-ir in cortical brain regions across a variety of species. One week of REM sleep deprivation in developing felines significantly decreases PV-ir in the visual cortex (5), and fragmentation of NREM sleep has been linked to abnormal PV functioning within prefrontal circuits in a rat model of neurodevelopmental disease (55). Consolidated NREM sleep may be critical to balance excitation/inhibition within the somatosensory cortex by downscaling excitatory synaptic inputs (56). It remains unclear whether our observed results are driven by REM sleep reduction/γ power reduction, fragmented NREM sleep patterns, or a combination of the two.

Alternative sleep disruption paradigms may offer insight into the developmental distinction between sufficient quantities of REM sleep versus quality of NREM sleep. Notably, most methods of sleep disruption during development in rodents require separation from parents, significantly increasing stress. This automated method provides a unique opportunity to examine naturalistic social behavior in a socially monogamous species after developmental sleep manipulations. Unlike mice and rats, prairie voles have ultradian sleep-wake cycles lasting only 1 to 2 hours throughout the light and dark phases of the day, thus requiring continuous sleep disruption. However, with advances in automation, future work could make use of a video or EEG-synched control groups where shaking only occurs during times when pups are awake.

ELSD in prairie voles may inform models of social development

In rodents, the whiskers are an essential tool for environmental exploration and map onto the somatosensory S1 barrel cortex. Normal functioning of somatosensory neurons during development is essential for later expression of typical cognitive and social behaviors (51). Sleep-dependent processes within the S1 barrel fields are sensitive to sensory experience during the first month of life (57), and altered PV in the S1 cortex may underlie the behavioral impairments that we observed after ELSD, possibly via deficits in tactile processing.

Tangential to the “ontogenetic hypothesis of REM sleep” (4), our results provide empirical support of a theory proposed by McNamara and colleagues (58, 59), suggesting that early-life REM sleep promotes and shapes social attachment between infants and mothers, as well as between sexual partners, by activating social bonding circuits (perhaps through reactivation of circuits activated during awake social interactions). Decreased time in REM sleep could hypothetically decrease such endogenous strengthening of neural circuits, including those involved in social behavior. Our unique animal model provides an avenue by which sleep can be experimentally manipulated in preweaning rodents with minimal disruption to parental care and avoidance of stress as a confounding variable. Results from these studies may ultimately inform our understanding of modifiable factors that shape social development through sensory processing and affect the pathogenesis of neurodevelopmental disorders including autism spectrum disorder.

MATERIALS AND METHODS

Animals

Subjects were laboratory-reared male and female prairie voles (see Supplementary Methods for additional colony details) that were housed at the Veterans Affairs (VA) Portland Health Care System Veterinary Medical Unit and maintained on a 14-hour light/10-hour dark cycle (lights on at 0700 hours) in clear polycarbonate cages (27 cm by 27 cm by 13 cm). Litters were weaned at 21 days of age and housed in same-sex sibling groups (n = 2 to 4 per cage). All procedures were approved by Institutional Animal Care and Use Committee at the Portland VA and adhered to guidelines set forth by the National Institutes of Health (NIH) Guide for Care and Use of Laboratory Animals.

Early-life sleep disruption (ELSD)

On P14 (approximately ZT3-ZT6), home cages containing a litter and both parents were moved from the colony to a separate housing room and placed on either a standard orbital shaker for 7 days of ELSD (ELSD group) or moved onto shelving in the same room as the shakers (control group). All litters were provided hydrogel daily as a supplement for water. Litters that were housed on the shaker had water bottles removed to prevent leakage. Cage card holders were removed to limit noise. The orbital shakers were connected to an automatic timer (5058 Traceable Controller, Fisher Scientific) that was set to turn on at 110 rpm for 10 s every 109 s (99 s off, 10 s on) continuously throughout the day for 7 days. This speed does not agitate bedding and allows for normal ambulation in the cage.

EEG measurements

Surgical implantation of EEG electrodes

Electrode implantation was performed following similar methods in mice with custom-made electrodes (see Supplementary Methods for additional details). In a stand-alone experiment (n = 9), juvenile male and female prairie voles (P20) were anesthetized with inhaled isoflurane (3 to 5% for induction and 1 to 2% for maintenance), two frontal and two parietal EEG leads were implanted into the skull, and EMG leads were threaded through the dorsal neck muscles (see Supplementary Methods).

EEG/EMG recordings

Animals were connected to lightweight recording cables (Cooner Wire) via male header sockets and given enough slack to move freely. Data were collected from a Grass amplifier via AcqKnowledge software (BIOPAC). The second day of both baseline and shaker periods (days 2 and 5) was used for analysis to provide a full 24 hours of signal data.

Sleep scoring and EEG spectral analysis

EEG/EMG records were converted to European Data Format before being scored offline for NREM and REM sleep and wakefulness in 4-s epochs across a 24-hour period (SleepSign software, Kissei Comtec; see Supplementary Methods for additional details). The
total epochs and minutes spent in each stage were aggregated by animal and study condition (baseline/shaker), as were the number of sleep stage transitions.

Spectral analysis was performed on each 4-s epoch by applying an FFT (Hanning window) to generate a power spectrum (at a resolution of 0.98 Hz). REM and NREM spectral power on the shaker (24 hours) was normalized to total power per state, meaning that each animal’s data were expressed relative to the total power density in the relevant sleep state (see Supplementary Methods for additional details).

Behavioral tests

Parental care observations

To observe parental care during ELSD or control conditions, overhead videos were recorded twice a day at 0800 and 1400 hours (lights on at 0700 hours) for 5 to 7 days (mean number of recordings for each group = 10). Each scoring session used continuous focal animal sampling, focusing on one parent at a time and scoring for duration and counts of huddling, nursing, grooming, retrieval, aggression, no pup interaction, and stereotypy (see table S2 for additional details).

Partner preference test

The partner preference test was used as a proxy measure for the strength of the pair bond after 24 hours of cohabitation with an opposite sex animal. Prairie voles are socially monogamous and will display a preference to remain in close social contact (side by side “huddle”) with a mate if a pair bond has formed between the two animals. Around P100, approximately 80 days after sleep disruption ended, subject animals were allowed to cohabitate with a stimulus partner animal of the opposite sex for 24 hours. After 24 hours of cohabitation, the stimulus partner animal was removed from the home cage and placed into one chamber of a custom-built, three-chambered apparatus (Omnitech Electronics). A stranger stimulus animal (either another ovariectomized female primed with estradiol or another stimulus age-matched male, depending on the sex of the test subject) was placed into the chamber on the opposite end. The partner and stranger were loosely tethered to their respective chambers using an adjustable cable tie attached to a flexible chain that allowed the full breadth of horizontal and vertical rear movement within their chambers. The sides where partners and strangers were placed were counterbalanced across groups. The subject was placed in the middle and allowed to interact with either stimulus animal for a duration of 3 hours. Over the course of this test, a pair bond was inferred if the subject spent significantly more time huddling with the partner compared to the stranger (see Supplementary Methods for additional details). Interactions were videotaped and scored by observers blind to sex, sleep group, and partner preference status (C.E.J. and A.A.C.) for time spent huddling with each stimulus animal, as well as aggressive bouts directed toward stimulus animals. Huddling was defined as side by side body contact, and aggression included lunging, biting, or rough and tumble behavior that was not mating.

Improper setup and recording of animals during one cohort of testing required exclusion of two ELSD males, two control females, and two ELSD females from the partner preference data. These females were excluded from analysis because of accidental pairing with a stimulus animal that was not properly age-matched. Final group numbers were as follows: $n = 20$ (male controls), $n = 13$ (male ELSD), $n = 14$ (female controls), and $n = 13$ (female ELSD).

Novel object recognition test

The NORT consisted of two phases (9 min each) separated by a 10-min delay: Phase 1 is the acquisition phase where two identical objects are presented in a testing chamber, and phase 2 is the test phase where one of the objects is replaced by a novel object (see Supplementary Methods for additional details). Objects included a Lego object (4.7 cm by 1.5 cm by 1.9 cm) and a metal bolt (4.5 cm by 1.5 cm by 1.7 cm). Preliminary tests indicated that both objects evoked equal investigation from prairie voles (e.g., no single object was inherently preferred by prairie voles).

Videos were collected and watched by a trained observer blind to experimental condition and novelty status of objects (A.A.C.). The time spent exploring each object was manually recorded with a stopwatch. Exploring an object was counted if the snout was directed toward the object and came within 1 cm of the object or if the subject was actively interacting with the object. Accidental body contact, as well as climbing or sitting on or near the objects, was not counted.

Animals were excluded from analysis if they detached an object from the chamber floor during either session ($n = 3$). Two animals were not included because of video failure. Final sample sizes for NORT were as follows: $n = 13$ (male controls), $n = 13$ (male ELSD), $n = 12$ (female controls), and $n = 7$ (female ELSD).

Olfactory social recognition

Olfactory detection, habituation, and dishabituation to social odors were measured in a subset of adult voles ($n = 7$ to 13 per group) after ELSD, as previously described. Soiled bedding was collected from two single-housed males and two single-housed females and used to fill histology cassettes as an odorant cue for all animals. Subjects were tested with cassettes from opposite sex animals. The task was divided into five odor presentations, each lasting 2 min with a 10-min intertrial interval. The first four odor cues were from one animal, and the fifth odor cue was from a second animal. The animal that provided bedding for cues 1 to 4 was alternated in a manner that counterbalanced groups (see Supplementary Methods for additional details).

Light/dark box

Anxiety-related behavior was measured with a 5-min test inside a light/dark box consisting of an open-field chamber (60 cm by 60 cm by 30 cm; Omnitech Electronics) partitioned with a darkened area consisting of a black insert (30 cm by 30 cm by 20 cm) and a light-enanced area with a lux of 3000. Infrared beams on all sides measured locomotor activity. A cutout door (10 cm by 5 cm) allowed the animal to freely move between zones. Prairie voles were placed in the light portion facing the wall furthest from the door, and time and activity were measured with the infrared beams for each zone (light or dark).

PV immunohistochemistry

Tissue collection

Brains were harvested for PV immunohistochemistry (IHC) as adults (P100). Animals were ELSD or controls from P14 to 21 and, as adults, were euthanized by an overdose of isoflurane gas and immediately decapitated. Brains were rapidly extracted and sagitally dissected, and one hemisphere was drop-fixed into 4% paraformaldehyde for 24 hours and then transferred to phosphate-buffered saline (PBS) and 0.1% sodium azide until IHC.

PV IHC

After fixation, brains were cryoprotected with 30% sucrose in PBS. Hemispheres were sectioned in the coronal plane at 40 μm on
a sliding microtome in six series. Sections were stored in a cryoprotectant at −20°C until immunostaining (see Supplementary Methods for additional details). The primary antibody was used at a dilution of 1:500 (mouse anti-PV, clone PARV-19, P3088, Sigma-Aldrich), and the secondary antibody was used at a concentration of 1:1000 (Biotin-SP anti-mouse, Jackson ImmunoResearch). Sections were developed with 3,3’-diaminobenzidine and 0.015% hydrogen peroxide in PBS for 4 min for visualization.

**Microscopy and cell counting**

Microscopic images were obtained with a digital camera (Optronics MicroFire) attached to a Leica DMRB microscope by an experi- menter blinded to the treatment group (J.R.Q.). Images obtained at 2.5× from the S1 neocortex were rotated before cropping, such that the pial surface aligned with the top of the frame of the image. These images were cropped to a counting frame (1.1 mm by 1.15 mm). Frontal cortex images were obtained at 2.5×, with the medial surface aligned to the lateral side of two counting frames (0.75 mm by 0.89 mm) stacked vertically to count from the PrL and IL regions. Using ImageJ (NIH, Bethesda, MD, USA), images were converted to 16-bit gray scale. Images were thresholded to count cells. The watershed tool was used to distinguish closely spaced cells. Cells were automatically counted on the basis of predefined size and circularity criteria, which were applied equally to all images. Counts were averaged from multiple sections per individual. Cell counts were reported as average counts per square millimeter defined by the counting frame.

**Corticosterone radioimmunoassay**

**Plasma collection**

At P21, a subset of ELSD and control litters were removed from the shaker and shelving, respectively, and weaned into a clean cage with littermates. Animals were transported to a procedure room and left undisturbed for 90 to 120 min. Between 1230 and 1330 hours (lights off), plasma (5 μl) was collected into heparinized tubes and stored on ice. Samples were diluted before running the assay to ensure that values fit within the range designated by the standard curve (25 to 1000 ng/ml or 2.5 to 100 μg/dl). Then, the diluted plasma samples were single-determined in the assay, and corticosterone values were interpolated from the standard curve. Final concentrations were calculated on the basis of the interpolated value and the dilution factor.

**Statistical analyses**

Results were considered significant at α < 0.05. Analyses were conducted with IBM SPSS version 24.0, and figures were generated with Prism GraphPad software version 7.0. All tests were two tailed. Non-parametric tests (Wilcoxon rank sum test for paired data or Mann-Whitney U test for independent comparisons) were conducted when data sets did not meet normality or homogeneity of variance assump- tions. When assumptions for parametric testing were met, two-way ANOVAs with sex and sleep group were used for initial analysis, and repeated measures ANOVAs were used for within-subject comparisons if the same animals were tested twice. Significant main effects and/or significant interactions were explored with post hoc t tests. If multiple t tests were conducted on binned data, then α values were adjusted using Bonferroni correction for multiple comparisons unless comparisons were determined a priori (see Supplementary Methods for full statistical details for each experiment).

**SUPPLEMENTARY MATERIALS**

Supplementary material for this article is available at http://advances.sciencemag.org/cgi/content/full/5/1/eaav5188/DC1

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