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Disruptions of Sleep/Wake Patterns in the Stable Tubule Only Polypeptide (STOP) Null Mouse Model of Schizophrenia

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Disruption of sleep/wake cycles is common in patients with schizophrenia and correlates with cognitive and affective abnormalities. Mice deficient in stable tubule only polypeptide (STOP) show cognitive, behavioral, and neurobiological deficits that resemble those seen in patients with schizophrenia, but little is known about their sleep phenotype. We characterized baseline sleep/wake patterns and recovery sleep following sleep deprivation in STOP null mice. Polysomnography was conducted in adult male STOP null and wild-type (WT) mice under a 12:12 hours light:dark cycle before, during, and after 6 hours of sleep deprivation during the light phase. At baseline, STOP null mice spent more time awake and less time in non-rapid eye movement sleep (NREMS) over a 24-hour period, with more frequent transitions between wake and NREMS, compared to WT mice, especially during the dark phase. The distributions of wake, NREMS and REMS across the light and the dark phases differed by genotype, and so did features of the electroencephalogram (EEG). Following sleep deprivation, both genotypes showed homeostatic increases in sleep duration, with no significant genotype differences in the initial compensatory increase in sleep intensity (EEG delta power). These results indicate that STOP null mice sleep less overall, and their sleep and wake periods are more fragmented than those of WT mice. These features in STOP null mice are consistent with the sleep patterns observed in patients with schizophrenia.

Key words: polysomnography/sleep and wake states/sleep homeostasis/rodent model/microtubule-associated protein

Introduction

Disruption of sleep and circadian rhythms are common in many psychiatric conditions, including schizophrenia, and can be sufficiently severe to warrant clinical attention.[1–4] Sleep disturbances occur in 40%–90% of patients with schizophrenia,[5] and include reduced sleep duration and efficiency, sleep fragmentation, and increased sleep onset latency. Furthermore, there are reports that sleep abnormalities correlate with positive or negative symptoms and with cognitive deficits in patients with schizophrenia.[5–8] It is unclear whether patients' sleep abnormalities are secondary to other symptoms of the illness or contribute to them. Animal models provide opportunities to address these questions.

The cytoskeletal-associated protein, stable tubule only polypeptide (STOP; also known as MAP6) plays a key role in the stability of neuronal microtubules and in synaptic plasticity.[9] Transgenic mice deficient in STOP display anatomical, physiological, and neurochemical abnormalities that resemble certain features of psychosis.[9–16] Notably, STOP null mice display cognitive and behavioral impairments observed in schizophrenia, including fragmentation and abnormal sequences of behaviors, nurturing deficits, social withdrawal, and impaired object recognition memory.[9,13,17,18] In addition, many of these behavioral and cognitive deficits in STOP null mice are alleviated by administration of antipsychotic drugs used to treat symptoms of schizophrenia,[9–11,19,20] further validating this model.

Only 1 study has examined any aspect of sleep/wake behavior in STOP null mice.[9] Using behavioral observation for a 3-hour period in the dark phase, Andrieux et al[9] reported that STOP null mice spent less time asleep, and shifted more frequently between behaviors, compared to wild-type (WT) mice. While the number of sleep episodes was unchanged, STOP null mice spent less total time sleeping relative to WT mice, indicating a shortening of individual sleep episodes. However, without electroencephalogram (EEG) and electromyogram

(EMG) recordings, these results remain preliminary. Furthermore, it is unclear whether these sleep alterations observed during one short time period during the dark phase can be generalized to a full day. To address these issues, we used EEG and EMG recordings and EEG power spectral analyses to characterize sleep/wake patterns and the associated EEG in STOP null mice.

Sleep is regulated homeostatically, and sleep loss leads to compensatory increases in sleep duration and/or intensity.[21,22] The reported sleep fragmentation in patients with schizophrenia,[5] therefore, could impede such homeostatic responses. Thus, we also used a brief period of sleep deprivation (SD) to examine the capacity of STOP null mice to compensate for acute sleep loss.

Methods

Animals

Adult male STOP null mice (n = 7) and WT littermates (n = 8), 3–4 months of age and weighing 26.3 ± 0.8 g and 27.8 ± 1.6 g, respectively, at the time of surgery were used. Animals were bred in-house from heterozygous breeding trios (C57Bl/6 background) in an animal colony room. All animals were kept under a standard 12:12 hours light:dark cycle (lights on [Zeitgeber Time (ZT) 0] at 07:00) at 23 ± 1°C, with ad libitum access to food and water. Animal handling procedures followed the guidelines of the Canadian Council on Animal Care, and were approved by the Dalhousie University Committee on Laboratory Animals.

Surgery

For EEG/EMG electrode implantation procedures, see supplementary methods.

Experimental Design

One week following surgery, each mouse was placed in a clear Plexiglas cage (38 cm × 30 cm × 30 cm) inside an individual recording chamber, equipped with an incandescent light controlled by a timer to produce the same 12:12 hours light:dark cycle as in the animal colony room. Food and water were available ad libitum. The next day, each mouse was briefly anesthetized (2%–4% isofluorane) and connected to a light-weight, flexible recording cable. The other end of the cable was connected to a swivel that allowed the mouse to move freely in its cage. After 5 additional days of habituation, EEG and EMG were recorded during a 24-hour baseline period (starting at ZT6), followed by a 6-hour SD during the second half of the light phase (ZT6-12), and a 24-hour recovery period. SD was done by introducing novel objects, gentle cage tapping, or slightly moving the bedding tray whenever signs of sleep were evident in the animal's behavior or EEG (ie, slow waves).

Data Acquisition and Analyses

EEG and EMG signals were amplified (×5000), band-pass filtered (EEG, 0.1–100 Hz; EMG, 10–100 Hz), digitized (sampling rate at 256 Hz), and stored using SleepSign software (Kissei Comtec). Recordings were automatically scored offline (SleepSign) in 10-second epochs, with each epoch classified as wake, non-rapid eye movement sleep (NREMS), or rapid eye movement sleep (REMS). For sleep/wake parameters and EEG analyses, see supplementary methods.

Statistical Analyses

P values < .05 were considered statistically significant. Data in all figures are shown as means ± SEM, see supplementary methods.

Results

Significant group differences and interactions are reported in supplementary tables S1 and S2.

Sleep Amount is Reduced in STOP Null Mice

Over the 24-hour baseline recording, STOP null mice spent more time awake (+65 min; P = .023; figure 1A, *left*) and less time in NREMS (−53 min; P = .044; figure 1B, *left*) than WT littermates. There was also a trend toward less REMS in STOP null mice (−11 min; P = .089; figure 1C, *left*). STOP null mice showed substantial light:dark differences in sleep and wake amounts, as in WT mice (figures 1A–C, *right*; supplementary figures S1A–C). The proportions of each state shown in the light and dark phases were similar between genotypes (supplementary figure S1).

The temporal distribution of sleep and wake within each daily phase was altered in STOP null mice. While WT mice showed a gradual decrease in wake amount during the dark phase (figure 1A, *right*) in parallel with a gradual increase in NREMS (figure 1B, *right*) and REMS (figure 1C, *right*) amounts, STOP null mice showed relatively flat distributions across the dark phase for all 3 behavioral states. Similarly, during the light phase, the early peak in sleep amounts seen in WT mice, followed by a gradual decrease, was absent in STOP null mice, which again showed a flattened distribution of states (figures 1A–C, *right*).

Both Sleep and Wake are Fragmented in STOP Null Mice

STOP null mice showed severely fragmented sleep and wake during the baseline dark phase. Specifically, compared to WT mice, they had more episodes of wake (+54%; P = .045; figure 2A) and NREMS (+53%; P = .001; figure 2C), and shorter individual episodes of NREMS (−56%; P = .032; figure 2D) and REMS

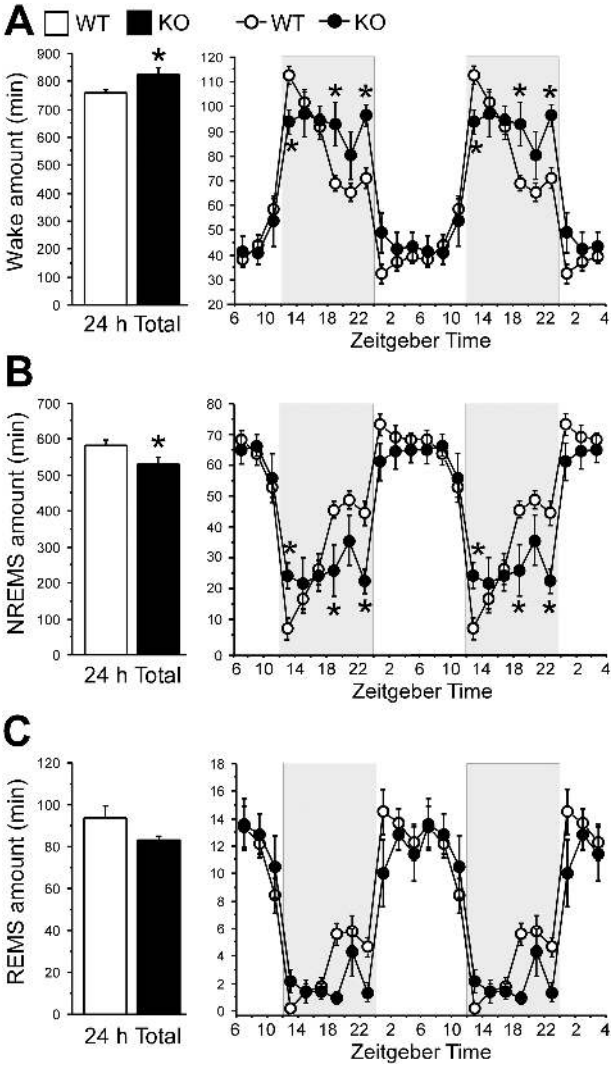

Fig. 1. Baseline sleep/wake amounts in wild-type (WT; $n = 8$) and stable tubule only polypeptide (STOP) null or knockout (KO; $n = 7$) mice. Amounts (min) of wake (A), non-rapid eye movement sleep (NREMS) (B), and rapid eye movement sleep (REMS) (C) during baseline recordings over a 24 h period (*left*) and in 2 h intervals across the 12 h light and 12 h dark phases (*right*). Time of day is indicated as Zeitgeber Time (ZT), with ZT12 corresponding to onset of the dark phase (shaded areas). Time points are double-plotted to facilitate visual detection of rhythmicity. *$P < .05$ vs WT.

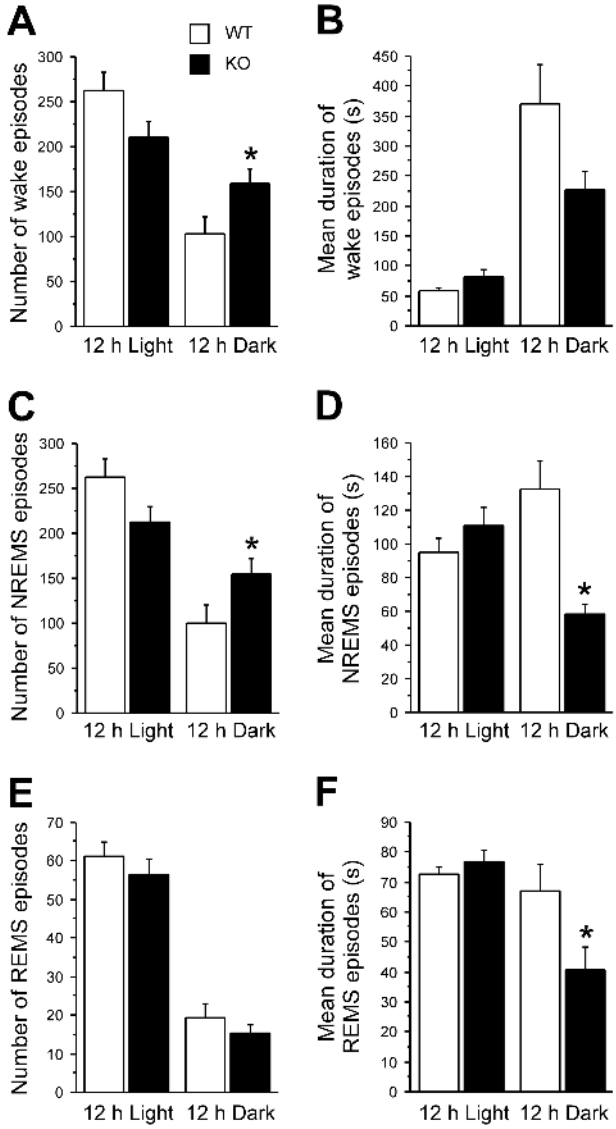

Fig. 2. Numbers and mean durations of episodes of wake (A, B), non-rapid eye movement sleep (NREMS) (C, D), and REMS (E, F) during the 12 h light and 12 h dark phases of the baseline recording day in wild-type (WT; $n = 8$) and stable tubule only polypeptide (STOP) null or knockout (KO; $n = 7$) mice. *$P < .05$ vs WT.

(−39%; $P = .039$; figure 2F); the duration of individual wake episodes also tended to be shorter in these mice (−39%; $P = .084$; figure 2B). Consequently, STOP null mice switched more often from wake to NREMS (+55%; $P = .049$) and from NREMS to wake (+74%; $P = .018$) during the dark phase, compared to WT mice (figure 3A). These genotype differences were not observed during the light phase (figure 2; state transition data not shown).

To further examine the ability of STOP null mice to maintain sleep and wake during the dark phase, we calculated the frequency distribution of episode durations. STOP null mice generated more mid-length wake episodes (80–1270 s) and fewer long wake episodes (>2560 s) than WT mice (figure 3B). These long wake episodes accounted for only 18% of the time spent awake in STOP null mice vs 62% in WT mice ($P = .0013$; *insert* in figure 3B). Similarly, STOP null mice generated more short (10–30 s) and fewer long NREM sleep episodes (160–630 s) than WT mice (figure 3C). No genotype differences were found for REMS episodes of any duration (data not shown).

Changes in Baseline EEG Activity in STOP Null Mice

We next examined relative EEG power values (% of total power) in each sleep and wake state. During wake, especially in the dark phase, STOP null mice showed

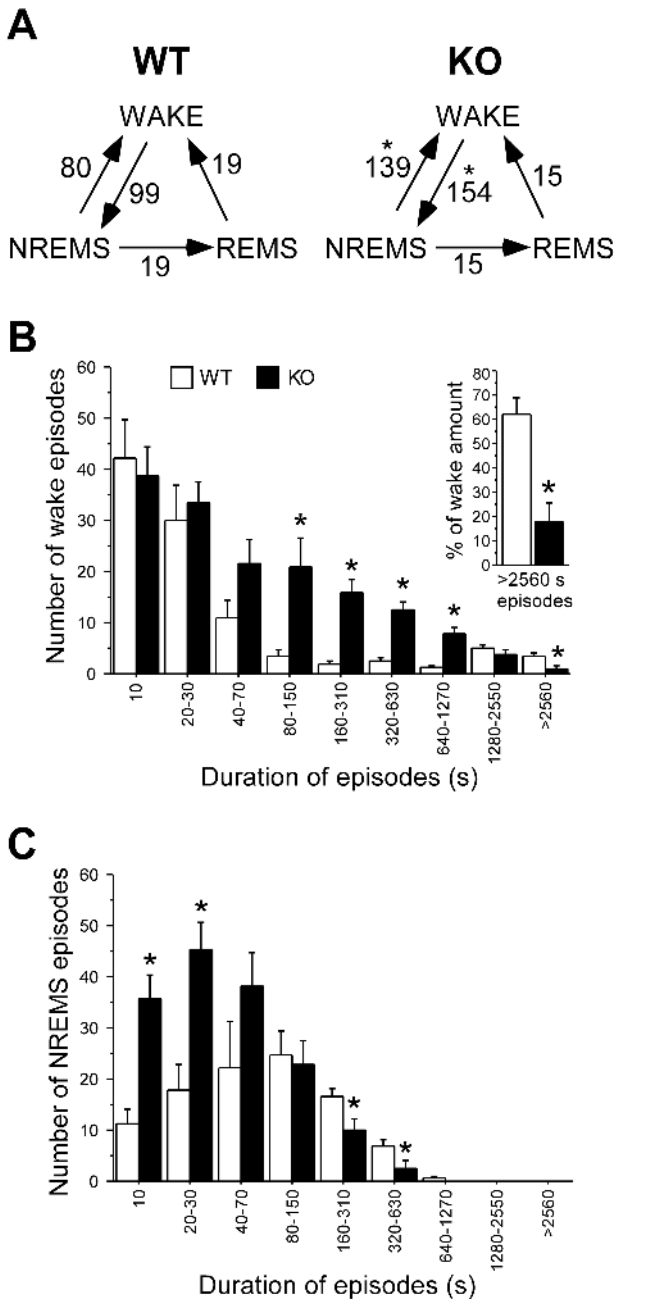

Fig. 3. Behavioral state transitions and frequency histograms of the durations of sleep/wake episodes in wild-type (WT; $n = 8$) and stable tubule only polypeptide (STOP) null or knockout (KO, $n = 7$) mice during the baseline 12 h dark phase. (A) Mean number of transitions between wake, non-rapid eye movement sleep (NREMS), and REMS. *$P < .05$ vs WT. Arrows show the direction of transitions, and numbers show the average frequency of such transitions. (B, C) Frequency histograms of wake (B) and NREMS (C) episodes are shown as a function of episode duration. *$P < .05$ vs WT. The insert in (B) shows the duration of the longest wake episodes (>2560 s) as a percentage of the total amount of wake during the 12 h dark phase. *$P < .05$ vs WT.

higher relative EEG power in the low theta range (5–7 Hz), but lower power in the high theta range (7–9 Hz), compared to WT mice (figure 4A, *right*). Thus, the ratio of high-to-low theta activity, which is indicative of cortical activation,[23,24] was reduced (by 25%) in STOP null mice during the dark phase ($P = .025$ vs WT; figure 4A, *right*, *insert*), suggesting reduced arousal levels during the active phase.

During NREMS in the light (inactive) phase, STOP null mice showed an increase (+20%) in relative power in the delta band (0.5–4 Hz), which is a measure of sleep intensity or sleep need[25] ($P = .044$ vs WT; figure 4B, *left*). By contrast, these mice showed a reduction (−20%) in relative power in the sigma band (10–12 Hz), which corresponds to the frequency of sleep spindles in mice[26] ($P = .044$ vs WT; figure 4B, *left*).

We also examined the daily patterns of relative values of delta and sigma power in the NREMS EEG (figure 5D and supplementary figure S2, *baseline*). For NREMS delta power, while WT mice typically showed a peak during the dark phase with a trough during the light phase, STOP null mice showed a relatively flat distribution across both phases, except for a peak at the beginning of the light phase (figure 5D). NREMS sigma power was higher in the STOP null mice during the second half of the dark phase and lower during the second half of the light phase, compared to WT mice (supplementary figure S2).

The relative REMS EEG spectra of STOP null mice were shifted toward lower frequencies during both the light and dark phases (figure 4C). The peak theta frequency was slightly, but significantly, lower (−0.5 Hz [light phase] and −1 Hz [dark phase]) in STOP mice ($P = .021$ and 0.017 vs WT, respectively). In addition, power at several frequency bins in the alpha (9.5–12 Hz) and beta (12.5–30 Hz) bands was reduced in the light phase for STOP null mice.

Homeostatic Responses to SD are Intact in STOP Null Mice

To determine the capacity of STOP null mice to respond to sleep loss with homeostatic increases in sleep duration and/or intensity, both WT and STOP null mice were sleep deprived for 6 hours, and then allowed to sleep ad libitum for 24 hours. During SD, both genotypes lost similar amounts of NREMS (~72%) relative to corresponding baseline levels; REMS was abolished (supplementary table S3). The number of interventions required to keep the mice awake did not differ significantly between genotypes (supplementary table S3).

After SD, STOP null mice showed shorter latencies than WT mice to enter NREMS (1.9 ± 0.7 vs 16.6 ± 2.3 min; $P < .001$; figure 5A) and REMS (15.9 ± 6.7 vs 97.0 ± 26.9 min; $P = .017$; supplementary figure S4A). However, the compensatory increase in NREMS during the first 12 hours (dark phase) following SD relative to the time-matched baseline period was similar between STOP null and WT mice (STOP: $P = .0088$; WT: $P = .0013$; figure 5B). This

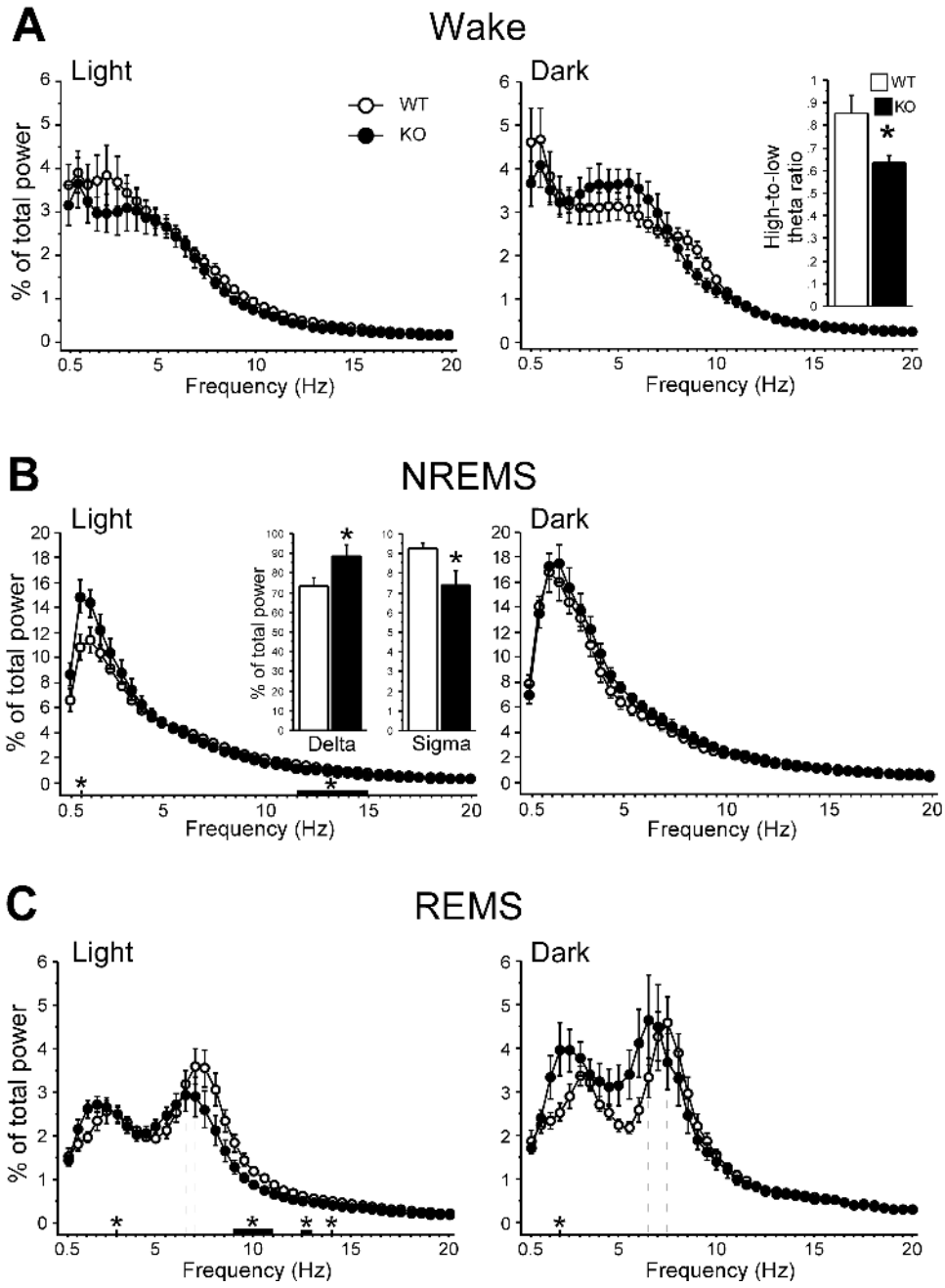

Fig. 4. Average electroencephalogram (EEG) power spectra in wake (A), non-rapid eye movement sleep (NREMS) (B), and REMS (C) during the baseline 12 h light (*left*) and 12 h dark (*right*) phases in wild-type (WT; $n = 7$) and stable tubule only polypeptide (STOP) null or knockout (KO; $n = 7$) mice. EEG power was normalized to total EEG power (0.5–50 Hz) over all 3 behavioral states in each animal, and the mean values (±SEM) were plotted in 0.5 Hz bins. The relative contribution of each behavioral state to total power was weighted in each animal. (A, *insert*) The ratio of high-to-low theta power (7–9 Hz/5–7 Hz). (B, *insert*) Normalized sigma (10–12 Hz) and delta (0.5–4 Hz) power. In (C), peak theta frequency is indicated by vertical dashed lines. Black bars at the bottom indicate intervals in which EEG power differed significantly between the 2 groups (*$P < .05$ vs WT).

NREMS rebound was due to an increase in the number, not the duration, of NREMS episodes (supplementary figure S3).

To examine the time course of recovery NREMS, we calculated the cumulative gains in NREMS from corresponding baseline values in 2-hour intervals (figure 5C). STOP null mice tended to show a greater initial increase in NREMS (first 2 hours of recovery; +29 ± 4 vs +17 ± 4 min; $P = .051$) and, by the end of the 24-hour period, tended to gain more NREMS (+108 ± 17 vs +56 ± 22 min; $P = .089$), with greater recovery of lost NREMS (91 ± 22% vs 38 ± 15%; $P = .068$) than WT mice.

The relative NREMS delta power (% of 24-hour baseline mean) increased during the first 4 hours of

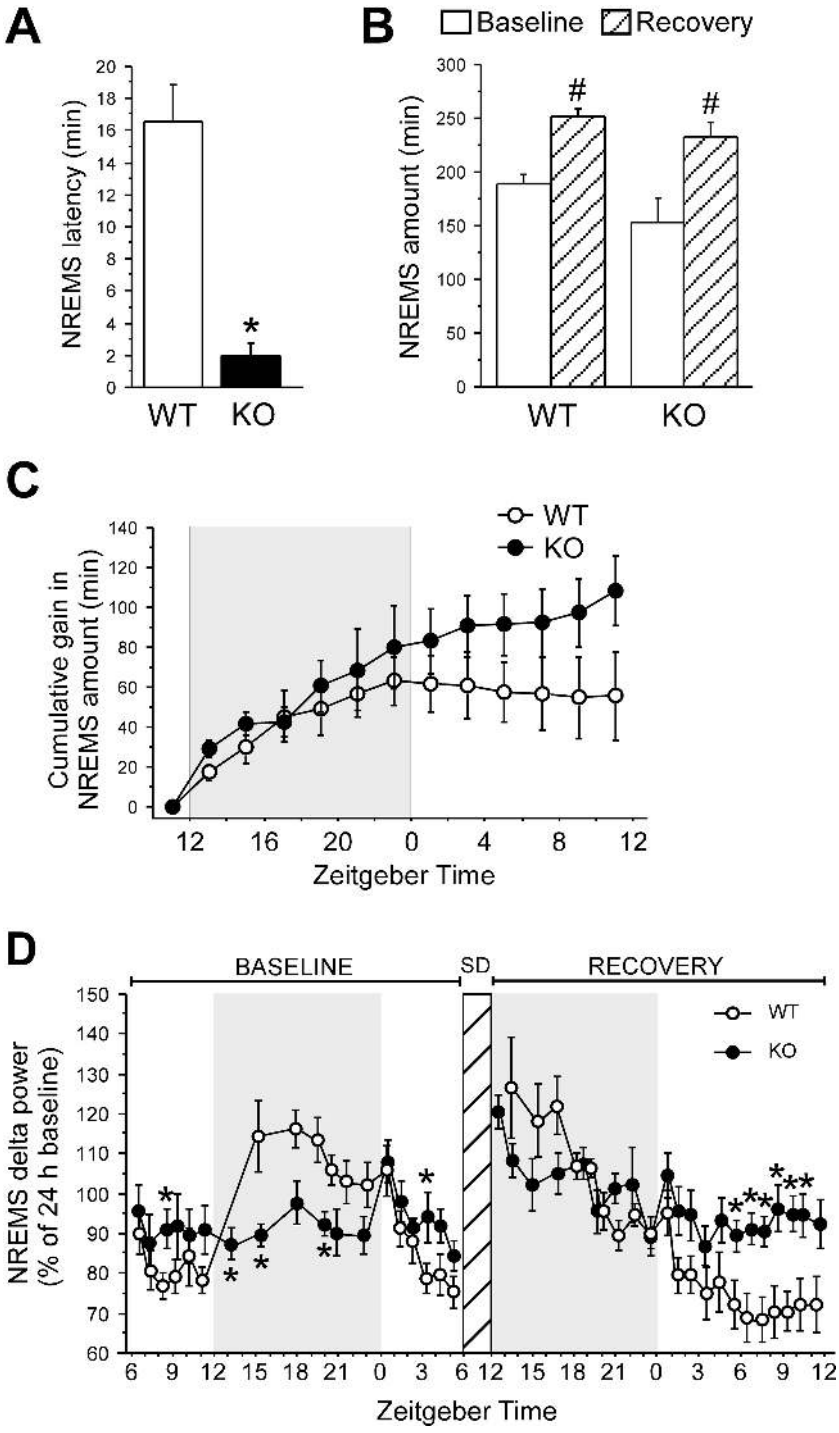

Fig. 5. Recovery non-rapid eye movement sleep (NREMS) and EEG following sleep deprivation (SD) in wild-type (WT; $n = 8$) and stable tubule only polypeptide (STOP) null or knockout (KO, $n = 7$) mice. (A) Sleep onset latency (min). $^{*}P < .05$ vs WT. (B) Amount (min) of NREMS during the first 12 h period (dark phase) of recovery (dashed bars) and time-matched baseline period (open bars). $^{\#}P < .05$ vs baseline. (C) Time course of cumulative gain in NREMS in 2 h intervals across the 24 h recovery period. The Genotype × Time interaction did not reach statistical significance ($P = .13$). The shaded area indicates the dark period. (D) Time course of normalized delta (0.5–4 Hz) EEG power (% of 24 h baseline mean) in NREMS across the 24 h baseline recording and the 24 h recovery recording in WT ($n = 7$) and STOP null (KO; $n = 7$) mice (see the supplementary methods for details). Shaded areas indicate dark phases, and dashed boxes indicate 6 h SD period. $^{*}P < .05$ vs WT during the corresponding interval.

the recovery dark phase, relative to the first 4 hours of the baseline dark phase, in both STOP null (from 85.5 ± 2.8% to 102.6 ± 4.7%; $P = .0001$) and WT mice (from 105.2 ± 6.2% to 120.8 ± 8.2%; $P = .026$), with no significant genotype differences ($P = .82$). This increase was followed by a gradual decline during the remainder

of the dark phase (figure 5D). During the recovery light phase, STOP null mice had significantly greater relative NREMS delta power than WT mice, as was the case at baseline (figure 5D). Normalized NREMS sigma power showed no change following SD in either genotype (supplementary figure S2).

The increase in REMS amount above baseline during the first 12 hours of recovery was similar between genotypes (supplementary figure S4B), being due mainly to more frequent, rather than longer, REMS episodes (supplementary figure S4C and S4D). The amount of cumulative gain in REMS over the 24 hours recovery period did not differ between genotypes (supplementary figure S4E).

Discussion

STOP null mice slept less overall. The temporal pattern of sleep during both the light and dark phases also differed by genotype, as did features of the EEG during sleep and wake. In particular, STOP null mice had more fragmented sleep and wake than WT mice during the dark phase. In response to acute SD, both groups showed a rebound increase in NREMS delta power, a measure of sleep intensity, with no significant difference between genotypes, although there was a trend toward a larger increase in the STOP null mice.

Altered Sleep Architecture in STOP Null Mice

STOP null mice slept less than WT mice over 24 hours. In addition, both sleep and wake were markedly fragmented in STOP null mice during the dark phase. They transitioned more often between wake and sleep than did WT mice, and did not sustain long episodes of either sleep or wake in the dark phase. These results are consistent with the behavioral observations of reduced sleep in STOP null mice by Andrieux et al.[9] Deficits in sleep/wake patterns and locomotor activity rhythms have also been reported for other rodent models of schizophrenia.[9,27,28]

Slow waves and sleep spindles in NREMS EEG have been identified as playing important roles in the recovery function of sleep[25] and in the beneficial cognitive effects of sleep.[29] In baseline EEG recordings during the light phase, NREMS delta power was increased while sigma power (representing the frequency range of spindles) was reduced in STOP null mice. Increased NREMS delta power suggests an increase in sleep intensity. Although spindles were not counted individually, reduced sigma power might reflect reduced numbers of spindles, which is characteristic of patients with schizophrenia.[8,30] Given that sleep spindles have been associated with elevated arousal threshold,[31,32] STOP null mice may have lowered arousal thresholds, resulting in sleep fragmentation, despite increased sleep intensity. Additionally, sleep spindles are thought to play a role in memory consolidation,[29] and reductions in sleep spindle density have been correlated with impairments in memory, attention and executive function in patients with schizophrenia.[8,30] The decrease in sigma power observed in STOP deficient mice is consistent with cognitive and memory deficits documented previously in these mice.[13,14,17–19,33]

While our findings of reduced sleep time, fragmented sleep/wake patterns, and reduced sigma power (the frequency band corresponding to sleep spindles) are consistent with a number of studies of patients with schizophrenia,[2,3,30] schizophrenic patients have also been reported to show reduced slow wave (delta) activity during sleep,[34–36] although there is little consistency in the specific sleep abnormalities reported in these studies. These inconsistent findings probably relate to small sample sizes, lack of control for medication status (eg, drug-naive vs undergoing neuroleptic withdrawal), and heterogeneity in features such as symptom severity, illness subtype, and duration of illness.

The neural mechanisms underlying sleep abnormalities in STOP null mice may reflect a variety of neurochemical abnormalities[10–12,14,15,17] that are also found in patients with schizophrenia.[37,38] Of particular interest are imbalances in dopaminergic,[10] noradrenergic and serotonergic neurotransmission,[17] as well as elevated basal cerebral glucose metabolism[12] in STOP null mice, which may contribute to the observed increase in wake amount and in sleep fragmentation. For example, the findings by Hanaya et al[12] suggest that elevated dopaminergic neurotransmission and deficits in the hypothalamus and olfactory cortex of STOP null mice contribute to sleep disturbances observed in the present study and those seen previously in schizophrenic patients.[1–4] In addition, STOP null mice show synaptic plasticity dysfunction, reflected, eg, in deficits in long-term potentiation in the hippocampus.[9,20] Abnormal synaptic function may affect interactions among sleep/wake regulatory neurons, and may alter the synaptic regulatory function that has been attributed to sleep.[39] It remains to be determined whether these neurochemical and synaptic plasticity abnormalities are directly responsible for, or are secondary to, their sleep abnormalities.

Several aspects of the effects of STOP gene deletion on sleep were related to time of day: (1) sleep and wake fragmentation occurred predominantly in the dark phase (figure 2); (2) the distributions of wake, NREMS and REMS amounts were flattened during both light and dark phases (figure 1); and (3) NREMS delta power showed little variation across the 24-hour day (figure 5D). There are several possible explanations for these time-of-day effects. One possibility is that circadian regulation of sleep-wake cyclicity, which helps to consolidate sleep patterns,[40] is altered in STOP null mice, thereby contributing to sleep fragmentation. Another possibility is that STOP null mice respond abnormally to the entraining effects of

light-dark cycles (as do Bdr mice[27]), since STOP null mice were studied only in lighting cycles. Further studies are needed to identify the mechanisms underlying these sleep abnormalities.

Intact Ability of STOP Null Mice to Recover Sleep After Acute SD

STOP null mice show apparent difficulty in generating normal durations of sleep episodes under baseline conditions. It was, therefore, of interest to assess whether these animals also showed deficits in compensatory responses to sleep loss, which normally involve lengthening sleep durations. Acute SD was timed to end at the start of the daily dark phase, during which STOP null mice normally showed greatest sleep fragmentation. Nevertheless, STOP null mice had shorter sleep onset latencies than WT mice, and tended to show greater recovery of lost NREMS and REMS amounts, when SD ended. Although this could be explained by the fact that STOP null mice typically had more NREMS than WT controls at that time of day (figure 1B), STOP null mice showed initial rebound increases in NREMS delta power that were similar to those observed in WT littermates, relative to their 24-hour baseline NREMS delta power.

Unlike our results, patients with schizophrenia have been reported to show reduced recovery sleep following SD for 40 hours[41] or 85 hours.[42] As our animals were not fully sleep deprived for 6 hours, it remains to be determined whether more complete SD or longer periods of SD might reveal deficits in sleep homeostasis in STOP null mice.

Methodological Issues

Obviously, animal models cannot reproduce all features of complex human illnesses. The utility of using animal models to study psychiatric illnesses, however, resides in their ability to identify neural substrates for specific psychotic symptoms and to test novel therapeutic agents for pre-clinical efficacy. Consistent with these goals, STOP null mice show many neurobehavioral deficits[13,17,18] and features of impaired sleep architecture reminiscent of those seen in schizophrenia.

One issue particular to animal models of psychiatric or mood disturbances is the degree to which gene deletions, vs differences in maternal care secondary to such deletions, alter adult physiology and behavior. It is unclear whether STOP null pups are treated differently from WT pups by their heterozygous mothers[9,18]; such maternal care differences could affect sleep/wake regulation of pups in adulthood. Finally, genetic/developmental compensation may occur, and caution is required in attributing phenotypic differences exclusively to direct effects of the gene deletion.

Conclusions

This study provides the first EEG characterization of sleep abnormalities in STOP null mice. Although direct comparisons are difficult, especially because mice, unlike humans, are polycyclic sleepers, many sleep abnormalities observed in STOP null mice were consistent with those seen in patients with schizophrenia, including reduced sleep time, fragmented sleep/wake patterns and reduced sigma band activity. STOP null mice might therefore be a useful animal model in which to evaluate the pre-clinical efficacy of novel therapeutic treatments for improving sleep abnormalities in patients; eg, normalizing sleep amounts and reducing sleep fragmentation.

Supplementary Material

Supplementary material is available at http://schizophreniabulletin.oxfordjournals.org.

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