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ORIGINAL ARTICLE

Heterogenous electrophysiological responses of functionally distinct striatal subregions to circadian and sleep-related homeostatic processes

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Abstract

Basal ganglia (BG) are a set of subcortical nuclei that are involved in the control of a wide variety of motor, cognitive, and affective behaviors. Although many behavioral abnormalities associated with BG dysfunction overlap with the clinical picture precipitated by the lack of sleep, the impact of sleep alterations on neuronal activity in BG is unknown. Using wild-type C57BI mice, we investigated the circadian and sleep-related homeostatic modulation of neuronal activity in the three functional subdivisions of the striatum (i.e. sensorimotor, associative, and limbic striatum). We found no circadian modulation of activity in both ventral and dorsomedial striatum while the dorsolateral striatum displayed a significant circadian rhythm with increased firing rates during the subjective dark, active phase. By combining neuronal activity recordings with electroencephalogram (EEG) recordings, we found a strong modulation of neuronal activity by the nature of vigilance states with increased activity during wakefulness and rapid eye movement sleep relative to nonrapid eye movement sleep in all striatal subregions. Depriving animals of sleep for 6 h induced significant, but heterogenous alterations in the neuronal activity across striatal subregions. Notably, these alterations lasted for up to 48 h in the sensorimotor striatum and persisted even after the normalization of cortical EEG power densities. Our results show that vigilance and sleep states as well as their disturbances significantly affect neuronal activity within the striatum. We propose that these changes in neuronal activity underlie both the well-established links between sleep alterations and several disorders involving BG dysfunction as well as the maladaptive changes in behavior induced in healthy participants following sleep loss.

Statement of Significance

The striatum is a subcortical nucleus that regulates motor, cognitive, and mood-related functions, all of which are modulated by sleep/wake behavior. We show that the modulation of neuronal activity by circadian and homeostatic sleep processes within different subdivisions of the striatum is not homogenous. Our results suggest that the diverse physiological functions encoded within the different neuronal networks of the striatum might show different sensitivities towards alterations of both the circadian system and sleep history.

Key words: striatum; sleep; sleep deprivation; circadian system; motivated behavior

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Introduction

Basal ganglia (BG) are a set of subcortical nuclei located in the forebrain. Both neurophysiological and anatomical studies showed that BG receive widespread inputs from different cortical areas [1, 2]. These inputs terminate in topographical well-delineated areas within the input nuclei of the BG (i.e. subthalamic nucleus and the striatum) [1, 2]. As a consequence of this anatomical organization and being the most important input-receiving structure of the BG [1, 2], the striatum can be divided into three broad areas: dorsomedial striatum (DMS; homologous to the caudate in primates), the dorsolateral striatum (DLS; homologous to the putamen in primates), and the ventral striatum (VS; known also as the nucleus accumbens). Based on early lesion studies, and the recognition of striatal dysfunction as a hallmark of Parkinson's disease (PD), BG have been traditionally studied for their role in motor control [3–11]. More recently however, it has been recognized that BG play a causal role in a wide range of cognitive and affective behaviors [12]. These behaviors include action evaluation [13], goal directed behavior, attention and decision making [14], mood regulation [12], reinforcement learning, motivation, and reward [14–16]. Accordingly, the three subdivisions of the striatum (i.e. DMS, DLS, and VS) are now recognized to correspond to, respectively, associative, sensorimotor, and limbic domains [17, 18].

Alterations of sleep/wake cycle are associated with several cognitive and emotional disabilities that are under the control of, and modulation by, BG [19]. Sleep deprivation (SD) is, for example, associated with maladaptive changes in behavior that include: altered cognitive performance [20], impaired judgment and decision making [20], impaired attention and working memory [19], impaired negative emotional processing [19], biased reward evaluation leading to increased emphasis on gain outcomes relative to losses [21–25], and intensified drug abuse and increased likelihood of relapse after drug withdrawal [26–28]. Given the crucial role of BG in controlling several aspects of these behaviors [12–16], the involvement of striatal dysfunctions in the mediation of SD-associated behavioral abnormalities is highly likely.

Indeed, recent imaging studies in humans have shown that SD induces aberrant neuronal activity in multiple nuclei of BG and these alterations were significantly correlated with SD-related behavioral and functional abnormalities [21, 23, 24, 29–34]. However, evidence derived from human SD studies shows that the alterations in neuronal activity, particularly in the striatum, have been inconsistent. Several studies have reported significant alterations [21–24, 29–31, 33, 34], but others revealed a lack of significant difference [32, 34]. These inconsistent findings could result from different experimental conditions (i.e. the use of single or mixed gamble stimuli combining gains and/or losses in the same trial to probe neural responses from reward centers) or inherent genetic differences among tested participants [33].

To circumvent these difficulties, we set out to investigate the impact of sleep loss on striatal neural activity using laboratory animals (i.e. genetically identical mice) housed in homogenous and neutral environment (i.e. no explicit rewarding stimuli except routine bedding, water, and chow). Under these conditions, we aim at examining whether SD per se impacts striatal activity independently from genetic and environmental factors. Characterizing the impact of sleep loss on striatal activity has potential clinical importance, considering that sleep alterations are highly comorbid with numerous psychiatric and neurological conditions associated with striatal dysfunction. These include PD, depression, anxiety, attention hyperactive deficit disorder, and several drug abuse disorders [19, 35]. Motivated by this background evidence, we assessed the acute and long-term effects of a 6-h SD on neuronal multiunit activity (MUA) in the three anatomical and functional subdivisions of the striatum (DMS, DLS, and VS). Additionally, we simultaneously recorded the electroencephalogram (EEG) and electromyogram (EMG) in order to investigate changes in the characteristics of sleep/wake cycle before, during, and after the SD and their correlation with neural activity in the striatum. Because the different subdivisions of the striatum receive inputs from different cortical regions [17, 18] and SD differently affects activity of different cortical areas [19, 29, 30], we hypothesize that SD will differently alter neuronal activity in the different subdivisions of the striatum.

Methods

Animals and locomotor activity recordings

The experiments were performed in constant environment with monitored constant temperature and humidity conditions. Food and water were available ad libitum. A total of 12 adult male C57Bl/6JOlaHsd mice (16–20 weeks age old at the time of experiments, Harlan, The Netherlands) were used for this study. All the experiments were approved by of the Ethics Committee of Leiden University Medical Center and were carried out in accordance with the EU Directive 2010/63/EU on the protection of animals used for scientific purposes. Animal cages were equipped with passive infrared motion sensors to record general locomotor activity.

In vivo MUA, EEG, and EMG recordings

In vivo MUA and EEG and EMG were recorded as described previously [36, 37]. The protocol used corresponds exactly to the protocol used in our previous study [37] with the exception of the targeted neural structures. In our previous study, we recorded from midbrain dopamine structure [37]. In this study, we focused on the striatum. In brief, for the MUA recordings, stainless steel tripolar electrodes (Plastics One, Inc., Roanoke, VA) were implanted in each animal under deep anesthesia. For differential recordings, two electrodes were directed toward the targeted striatal structure with 0.1–0.2 mm space between the electrodes. The third electrode was placed in the cortex as a reference electrode. Measurements were performed from one electrode at a time. The electrodes were placed to record from the VS (relative to Bregma: 0.98 mm posterior and 1 mm lateral; depth: 4.03 mm), DMS (relative to Bregma: 0.5 mm posterior and 1 mm lateral; depth: 2 mm), and DLS (relative to Bregma: 0.5 mm posterior and 2 mm lateral; depth: 1.5 mm). The coordinates were adapted from Paxinos and Franklin (Supplementary Figure S1) [38].

Two miniscrew electrodes (one EEG and a ground) were screwed into the skull, respectively, above the dura over the right cortex (2.0 mm lateral to the midline and 3.5 mm posterior to Bregma) and cerebellum (at the midline and 1.5 mm posterior to lambda). For EMG recordings, two wires with suture patches were inserted in the tissue between the skin and the neck muscle. The animals were connected to the recording system via a flexible cable and counterbalanced swivel system, and

the animals were acclimated to the setup under similar (12:12 L:D, food ad libitum) conditions. Behavioral activity of the animals (drinking and locomotor activity) was recorded continuously in order to obtain an estimate of the circadian rhythm. Neuronal activity in striatal structures was amplified approximately ×40 000, band-pass filtered (500–5000 Hz, –40 dB/decade). Online, a window discriminator converted the action potentials into electronic pulses. A second window discriminator was set at a higher level to detect artifacts caused by the animal's movements. Action potentials and movement-related artifacts were counted in 10-s epochs. The analogue EEG and EMG signals, which were recorded continuously, were amplified approximately ×2000, band-pass filtered (0.5–30 Hz, –40 dB/decade), and digitized at 100 Hz. Action potential counts and EEG/EMG analogue signals were recorded simultaneously and stored on a computer hard disk. The stability of the multiunit signal and EEG recording was evaluated daily by visually inspecting the signals. The circadian rhythm in the signal and the amplitude of the EEG were monitored before baseline data were collected. As soon as the signals were stable, experimental recordings started.

After the experiments, the animals were sacrificed to verify the recording sites. To mark the location of the MUA electrode tip, current was passed through the electrode, and the brain was perfused with a buffered solution containing 4% paraformaldehyde and 8% potassium ferrocyanide. The brains were removed, postfixed overnight in 4% paraformaldehyde, and cryoprotected in 30% sucrose solution. Free-floating coronal sections (40 μm thickness) were cut on a freezing microtome. The sections were stained with cresyl violet, mounted on gelatinized slides, dried, dehydrated in increasing gradients of ethanol, cleared in toluene, and cover slipped with Depex.

Offline, the EEG power density spectra were calculated in 10-s epochs corresponding to the 10-s epochs of the action potentials of the targeted striatal structure using a fast Fourier transform routine within the frequency range of 0–25.0 Hz in 0.1-Hz bins. EMG signals were integrated over 10-s epochs. Three vigilance states (wakefulness, NREM sleep, and REM sleep) were determined visually based on standardized EEG/EMG criteria for rodents [36]. Wakefulness was scored when the EMG showed an irregular, high-amplitude pattern and the EEG signal was low in amplitude with relatively high activity in the theta band (6–9 Hz). NREM sleep was scored when EMG amplitude was low, and the EEG amplitude was higher than during wakefulness, with high values in the slow wave range (1–4 Hz). REM sleep was scored when the amplitude of the EMG and EEG was low, and the EEG showed relatively high values in the theta range. Epochs containing artifacts in the electrical signal or in the EEG signal (observed during the scoring of the vigilance states) were excluded from the analysis of the neuronal activity and EEG spectral analysis. Over the 4 days of recordings, on average 20.5 (±7.8) 10-s epochs per day and per animal were excluded because of electrical artifacts of the signals. This correspond to 0.24% of the entire signal analyzed per animal.

All MUA data and EEG power density data were calculated relative to the respective mean values recorded during NREM sleep over the 24-h baseline L:D period. This enabled us to calculate mean values over all animals. To analyze changes of EEG power density in slow-wave activity (SWA) and changes in neuronal activity at vigilance-state transitions, intervals with a duration of 4 min containing artifacts-free transitions from one vigilance state (VS1) to another (VS2) were selected by the following criteria [36]: (1) In the 2 min preceding the transition, at least 75% had to be scored as VS1, and not more than two epochs of VS2 should occur. (2) In the 2 min after the transition, at least 75% had to be scored as VS2. (3) Furthermore, the three 10-s epochs preceding and following the transition had to belong to the vigilance state corresponding to the transition. Shorter episodes or episodes with more interruptions/contaminations with other states at the transition were excluded because then we cannot be sure the MUA changes we see are really the result of the transition between the corresponding states or the result of interruptions/intrusions by other states and/or artifacts. The mean of the total transitions per day used in our analysis is: NREM/REM: 16 ± 1.3; NREM/wake: 10 ± 1.3; wake/NREM: 9.5 ± 1.5. The description of these analyses is the same as in our previous study [37].

Sleep deprivation

A previously validated method using an enriched, novel environment [39] was used to stimulate spontaneous exploratory wakefulness without inducing stress. The protocol used is the same as in our previous study [37]. SD was performed during the first 6 h of the light–dark (LD) cycle. The duration of 6 h was chosen to avoid potential stress effects that might be precipitated following a longer period of SD. Clean bedding, food, water, toys, and novel nesting materials were used to stimulate exploratory wakefulness. During SD, animals were monitored via their online EEG signal. Whenever the animals appeared to be entering NREM sleep—or if an increase in slow wave amplitude was observed—new material was introduced to the cage of the animal.

Statistical analysis

Data were analyzed using SigmaStat version 12.0. All summary data are reported as the mean ± s.e.m. Statistical significance was determined using ANOVA tests (Figure 1, A, C, and E; Supplementary Figure S2, A–H; Table 1; Supplementary Figure S4, A–L; Figure 2, A–F; Figure 3, A–L; Figure 4, A–E; Supplementary Figure S5, A–F; Supplementary Figure S6, A–F; Supplementary Figure S7, A–F), Wilcoxon paired signed rank test (Figure 1, B, D, and F), Cosinor analysis (Figure 1, A, C, and E; Supplementary Figure S2, A–H), second order polynomial regression (Figure 4; Supplementary Figure S2), or simple linear regression (Supplementary Figure S3, A–F; Figure 5, A–F; Figure 6, A–F). p values are indicated in the text and the figure legends. Differences were considered significant when $p < 0.05$.

Results

Daily and circadian modulation of MUA in striatal subregions

Baseline recording of both sleep/wake cycle and neuronal MUA in the striatum were obtained under LD cycle and constant darkness (DD) condition. As previously reported [40, 41], mice spent 70% and 71% of their time asleep during the light and subjective day phases of LD and DD, respectively (Supplementary Figure S2, A–C). Significant changes of cortical EEG power density (between 0 and 25 Hz) were also observed over time in LD and DD (Supplementary Figure S2, D–H). The EEG SWA (EEG power between 0.1 and 4 Hz) during NREM sleep is the best physiological

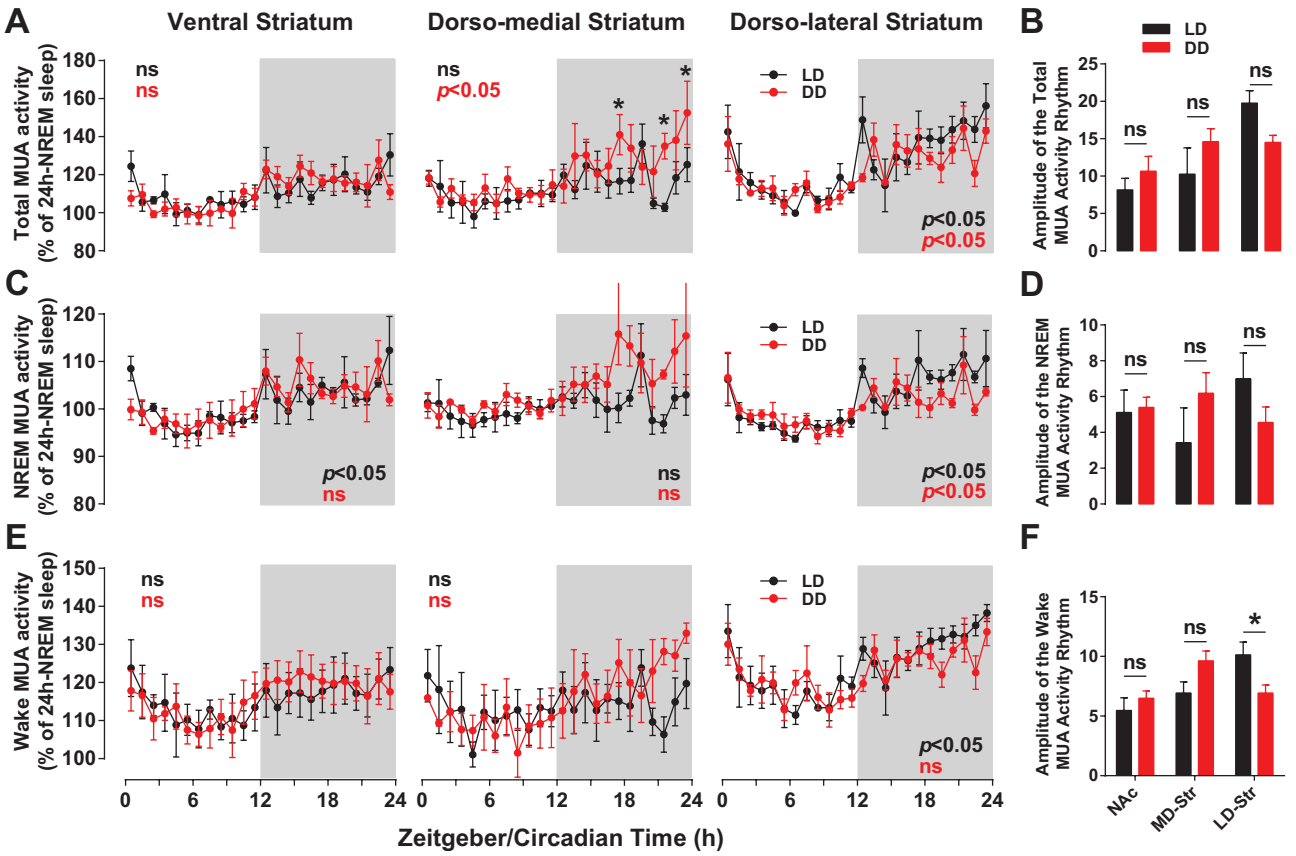

Figure 1. Daily and circadian evolution of MUA in VS, DMS, and DLS over, respectively, LD (black) and DD (red) cycles. Total (A), NREM sleep-related (C), and wakefulness-related (E) MUA are depicted in 1-h bins as a percentage of the mean activity during NREM sleep over LD cycle. The light and dark phases of LD cycles are shown by the white and gray backgrounds, respectively. (B, D, F) Cosinor amplitudes of MUA rhythms. Error bars are s.e.m. ns, not significant (Cosinor analysis in A, C, E and Wilcoxon paired signed rank test in B, D, F). $^{*}p < 0.01$.

Table 1. Modulation of neuronal activity in DLS, DMS, and VS by different vigilance states

Striatal subdivision	Wakefulness	REM sleep
DLS ($n = 4$)	158.2 ± 6.3*	138 ± 5.2*
DMS ($n = 4$)	129.3 ± 8.4*	121.6 ± 6.9*
VS ($n = 4$)	126.98 ± 9.15*	109 ± 4.5*

MUA activity is calculated as a percentage of the mean activity during NREM sleep over 24 h (set as 100). All striatal structures increased their neuronal firing rate during wakefulness and REM sleep.
*$p < 0.001$.

indicator of sleep pressure [40, 42, 43]. It peaked in early sleep phase and progressively decreased to reach low levels in late rest phase. During the active phase, sleep pressure builds up [42], as evidenced by the progressive increase in SWA. In both LD and DD, SWA reached a maximum at the transition to the sleep phase (LD: $r^2 = 0.42$, $p < 0.001$; DD: $r^2 = 0.06$, $p < 0.001$, second order polynomial regression analysis, Supplementary Figure S2, D and E).

Recently, EEG power in the theta (6–9 Hz) and beta (15–35 Hz) were shown to track sleep need during wake [44, 45]. We therefore computed power density from waves in this frequency range from the EEG signal during wakefulness and analyzed their evolution over LD and DD. Consistent with published data in rats [44] and mice [37], the 24 h pattern of the power density of theta waves during waking in both LD and DD showed a decreasing and increasing trends during, respectively, light and dark phases. Power density in the beta range (12.5–25 Hz) showed a weak but significant modulation in both LD and DD conditions (Cosinor analysis, Supplementary Figure S2, H).

MUA recordings were obtained from the three functional subdivisions of the striatum ($n = 12, 4$ for each location). In the DLS, a significant daily (in LD) and circadian (in DD) modulation of MUA was found with high levels during the dark phase and subjective night and low levels during the light phase and subjective day ($p < 0.05$; Cosinor analysis, Figure 1, A) in phase with the behavioral rhythm of the animals (Figure 1, A, Supplementary Figure S2, A). No significant modulation of MUA was found in both VS and DMS except for a slightly significant circadian modulation under DD in DMS (Figure 1, A, Cosinor analysis).

We found that neuronal MUA in all subregions of the striatum was modulated by vigilance states (Table 1, Supplementary Figures S3 and S4). The firing rates were significantly high during wake and REM sleep compared to NREM sleep (Table 1, Supplementary Figure S4). This vigilance states dependent modulation of firing rates, together with the circadian distribution of sleep and waking could be the driver behind the circadian modulation of MUA in the DLS. Alternatively, intrinsic changes in neuronal activity within a vigilance state could also result in a circadian modulation of MUA. To examine the relative contribution of these two factors, we analyzed the patterns of MUA separately for NREM sleep (Figure 1, C) and waking (Figure 1, E). During NREM sleep, VS showed a daily but not a

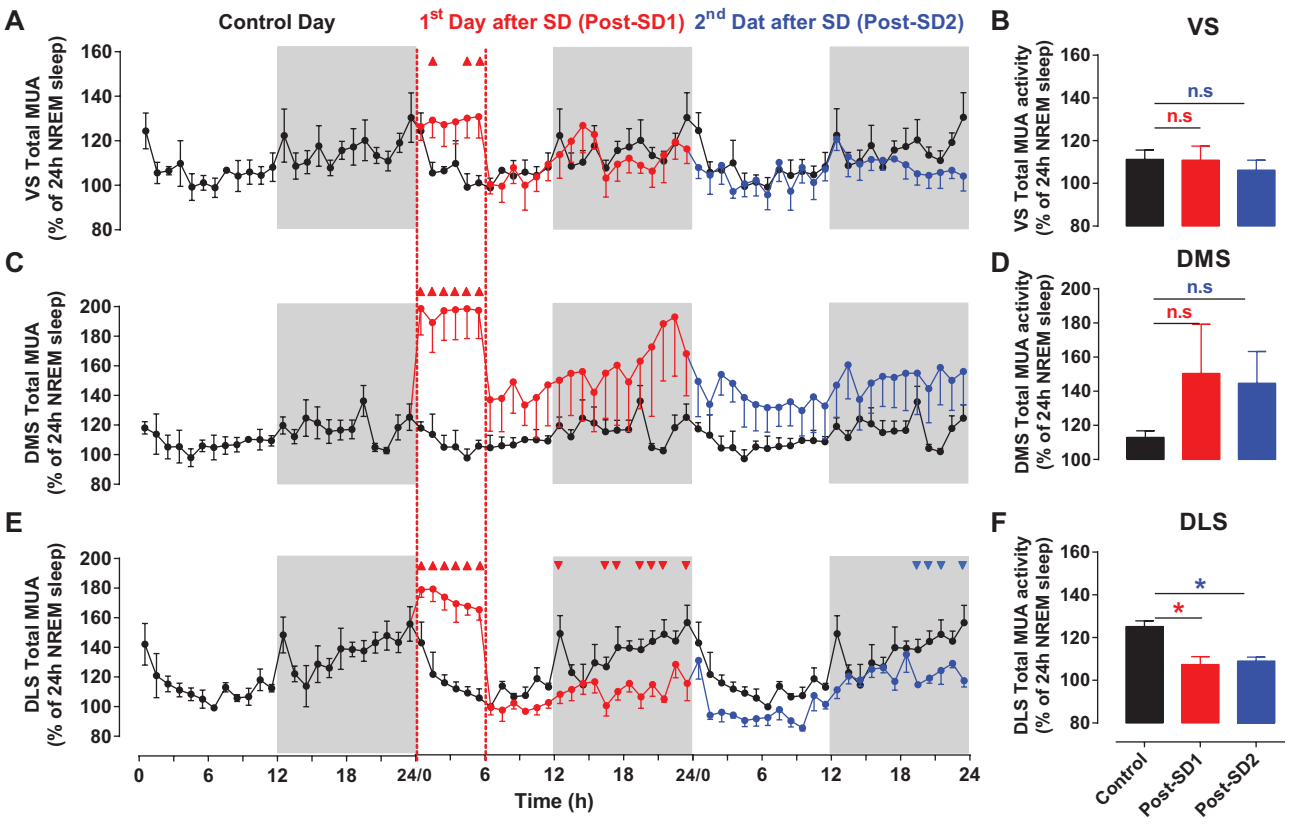

Figure 2. Long-term impact of 6 h of SD on MUA neuronal activity in the striatum. (A, C, E) Time course of mean neuronal activity in the VS ($n = 4$), DMS ($n = 4$), and DLS ($n = 4$) measured over three consecutive days. Activity is shown in 1-h intervals as a percentage of the mean activity measured during NREM sleep during the baseline day. SD was performed during the first 6 h of the first day after baseline, and activity was measured during the first (red) and second (blue) days after SD. The data recorded during the baseline day in (A, C, E) are triple plotted (black lines) for easy comparison. The light and dark phases of LD cycles are depicted by the white and gray backgrounds, respectively. During SD, all striatal regions show significantly increased activity compared to baseline. Triangles indicate significance with $p < 0.05$. Two-way ANOVA (Group and Time as factors: $F_{2,23}$(VS) = 1.121, $p = 0.291$; $F_{2,23}$(DMS) = 0.540, $p = 0.991$; $F_{2,23}$(DLS) = 7.769, $p < 0.001$). (B, D, F) Relative mean neuronal activity measured in 6-h bins in the VS (B), DMS (D), and DLS (F) during control day (black bars), post-SD1 (red bars), and post-SD2 (blue bars). *$p < 0.01$.

circadian modulation of MUA in, respectively, LD and DD conditions (Figure 1, C). In the DMS, no significant modulation was found in both LD and DD (Figure 1, C). In contrast, DLS showed significant circadian rhythms under both LD and DD ($p < 0.05$; Cosinor analysis, Figure 1, C). During wakefulness, none of the striatal subregions showed significant rhythms of their neural MUA with the exception again of the DLS that displayed daily modulation under LD ($p < 0.05$; Cosinor analysis, Figure 1, E).

To compare the strengths of the rhythms between striatal subregions, we extracted the amplitude from the cosinor fits of each individual rhythm (Figure 1, B, D, and F). Compared to the robust rhythms of MUA in the suprachiasmatic nucleus (SCN) [46], the amplitude of MUA rhythms in all striatal subregions was lower (Figure 1, B, D, and F). We found no difference in the robustness of the MUA rhythms between LD and DD under all vigilance-state conditions in all structures with the exception of a slight but significant dampening of MUA rhythm under DD relative to LD condition in DLS ($p < 0.05$, Figure 1, F).

Heterogenous neuronal activity responses of striatal subregions to SD

To assess the consequences of sleep loss on the MUA of striatal subregions, mice were exposed to 6 h of SD. As shown before [40], the animals responded to SD by spending 11.5% more time in sleep (NREM and REM sleep) during the 16 h following SD relative to the corresponding period during LD. In the second day following SD, the animals recovered normal sleep/wake pattern as evidenced by the return of the percentages of all sleep states to baseline levels (Supplementary Figure S5).

During SD, all striatal subregions showed an increase in neuronal activity (Figure 2, A, C, and E). However, after SD, MUA responses diverged, and each striatal subregion showed a unique response. In VS, no significant alterations were precipitated by SD except for a significant decrease of MUA during the last hour of the second day after SD (Figure 2, A). Consequently, the average 24 h neuronal activity in the VS during the first and second day after SD did not differ significantly from baseline day (Figure 2, B). In the DMS, a sustained upregulation of activity was observed throughout the 42 h we recorded following SD. Because of increased response variability, this increase of MUA was however not significant (Figure 2, C). The DLS had the most dramatic SD-induced changes in activity. Following the increment in MUA during SD, neuronal activity dropped to levels far below baseline values (Figure 2, E). This decrease in MUA lasted throughout the entire 42 h we recorded following SD (Figure 2, E). Therefore, and relative to baseline, the average 24 h activity in the DLS was significantly reduced by 22.7% and 20.7%, respectively, during the first and second day post-SD (Figure 2, F). These results show that anatomically and functionally distinct subregions

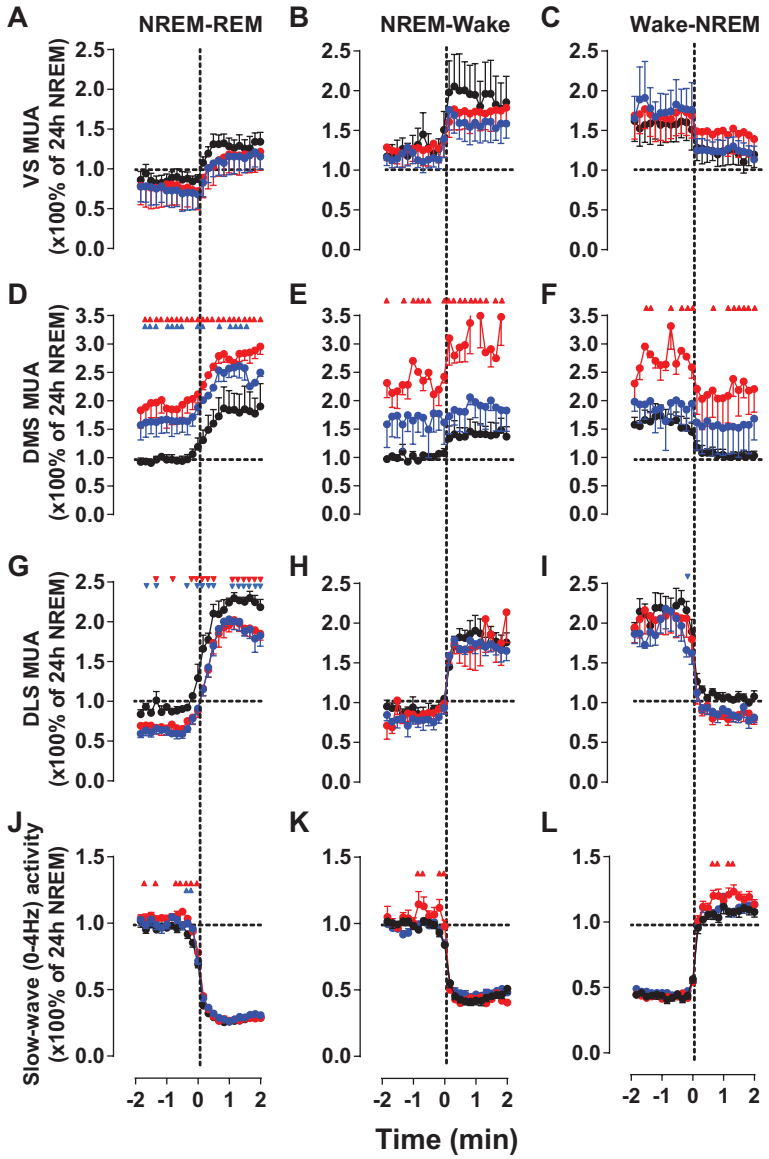

Figure 3. Dynamics of MUA at vigilance-state transitions during baseline (black), SD day (red), and post-SD (blue) day. Time course of the VS (A–C), DMS (D–F), and DLS (G–I) neuronal activity and EEG slow-wave activity (power density 0–4 Hz, J–L) at the transition from NREM to REM sleep (A, D, G, J), NREM to wake (B, E, H, K), and wake to NREM sleep (C, F, I, L) during the 2 min before and after the vigilance-state transition. The data are displayed in 10 s mean values calculated over the entire LD, SD, and post-SD days. All variables are expressed as a percentage of the mean activity during NREM sleep over baseline. All changes at the transition were significant ($p < 0.001$). Red and blue triangles indicate significant changes of neuronal activity during SD and post-SD. Two-way ANOVA (Group and Time as factors: $F_{2,23}(A) = 0.034$, $p = 1$; $F_{2,23}(B) = 0.151$, $p = 1$; $F_{2,23}(C) = 0.135$, $p = 1$; $F_{2,96}(D) = 110.496$, $p < 0.001$; $F_{2,96}(E) = 99.759$, $p < 0.001$; $F_{2,96}(F) = 72.04$, $p < 0.001$; $F_{2,216}(G) = 75.477$, $p < 0.001$; $F_{2,23}(H) = 0.523$, $p = 0.995$; $F_{2,23}(I) = 0.568$, $p = 0.988$; $F_{2,23}(J) = 0.618$, $p = 0.978$; $F_{2,23}(K) = 1.553$, $p = 0.012$; $F_{2,23}(L) = 0.813$, $p = 0.808$).

of the striatum respond differently to SD. Surprisingly, these SD-induced alterations were relatively long-lasting and persisted several hours after SD even after normalization of sleep/wake cycle (Supplementary Figure S5).

Because changes in vigilance states influenced neuronal firing rate (Table 1) and SD-induced changes in sleep architecture (Supplementary Figure S5), the alterations observed in the MUA of striatal subregions could be due to either changes in the pattern of sleep/wake behavior or intrinsic changes in neuronal MUA caused by SD irrespective of vigilance states alterations, or both. To discriminate between these two factors, we analyzed the patterns of neuronal activity separately for wake and NREM sleep (Supplementary Figures S6 and S7). We found that the changes in total MUA induced by SD in all subregions of the striatum (Figure 2) were mirrored both during wakefulness (Supplementary Figure S6) and NREM sleep (Supplementary Figure S7). Notably, the long-term depression of MUA in DLS after SD was also evident during wakefulness (Supplementary Figure S6) and NREM sleep (Supplementary Figure S7) even after the recovery of sleep/wake pattern during the second day following SD (Supplementary Figure S5). These results suggest that SD-induced striatal subregion-specific alterations in neuronal activity during both wakefulness and NREM sleep states.

To further investigate the extent of SD-induced alterations of neuronal activity in relation to sleep/wake states, we analyzed the dynamic of neuronal activity at different vigilance-state transitions (Figure 3). In the VS, no significant alterations were shown in any of the vigilance-state transitions (Figure 3, A–C). In the DMS,

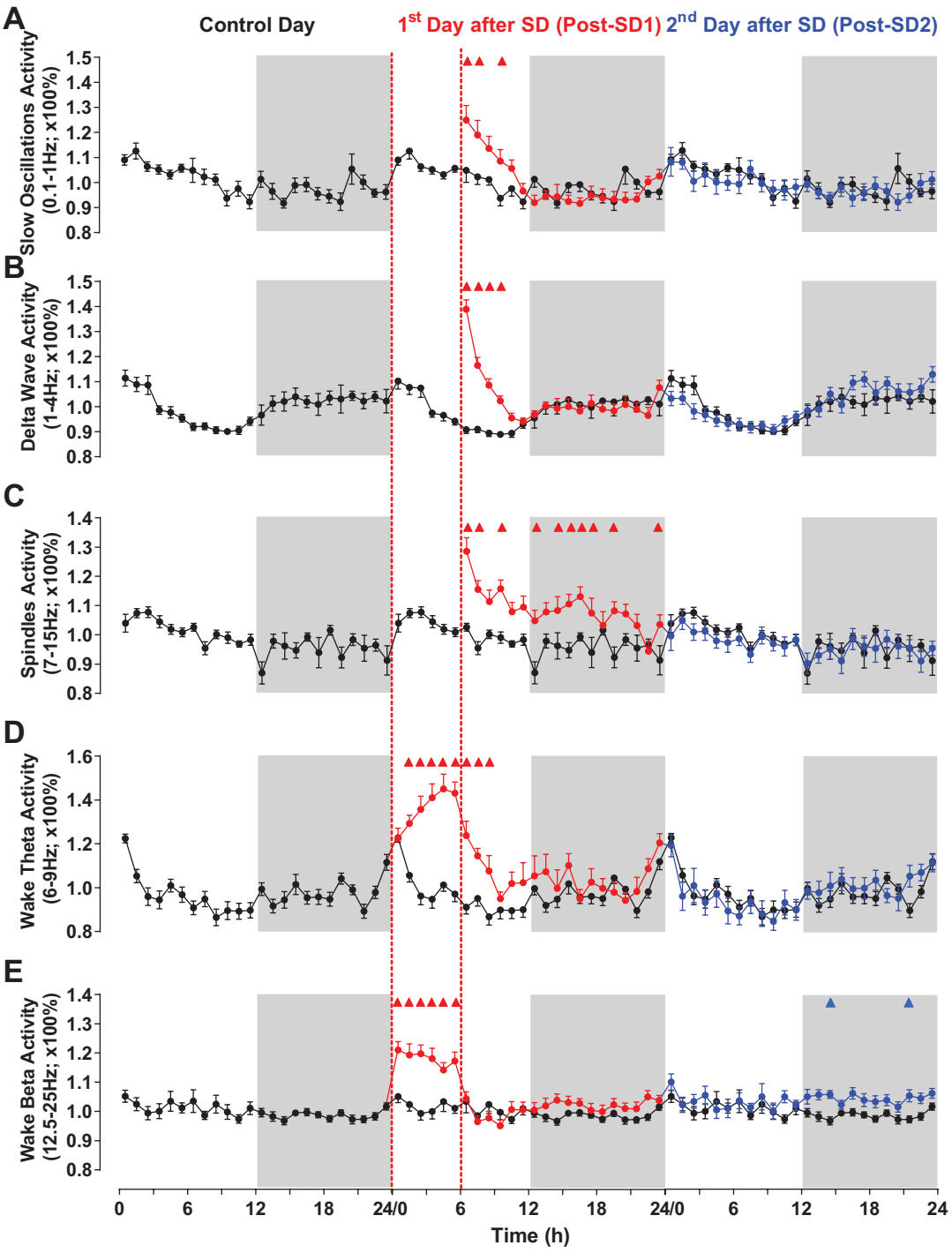

Figure 4. Changes in cortical EEG power density following SD. (A–E) Evolution of mean percentages of EEG slow oscillations activity (A), delta wave activity (B), spindle frequency activity (C) during NREM sleep, and theta activity (D) and beta activity (E) during waking over the entire 72 h experimental protocol. Data are presented as a percentage of the mean activity (±s.e.m.) over the baseline day and averaged in 1 h bins. The traces of the baseline day are triple plotted in black. Values during the 6 h SD in (A–C) are omitted because the remaining ≈10% of NREM sleep during this period are influenced by the SD intervention. The light and dark phases of LD cycles are shown, respectively, by white and black backgrounds. Triangles indicate significance with $p < 0.05$. $F_{2,23}(A) = 2.067$, $p < 0.001$; $F_{2,23}(B) = 6.668$, $p < 0.001$; $F_{2,23}(C) = 3.101$, $p < 0.001$; $F_{2,23}(D) = 3.454$, $p < 0.001$; $F_{2,23}(E) = 3.378$, $p < 0.001$.

a significant increase in MUA was observed in all vigilance-state transitions during the first day following SD (Figure 3, D–F). During the second day post-SD, this increase was significant only for NREM sleep to REM sleep transition (Figure 3, D). Notably, in the DLS, where SD induced the most significant decrease in neural activity (Figure 2, E and F), this effect was restricted to NREM sleep to REM sleep transition (Figure 3, G). No significant alterations were seen at NREM sleep to wake (Figure 3, H) and wake to NREM sleep transitions (Figure 3, I). Collectively, our results show that SD induces heterogenous neuronal responses within anatomically and functionally distinct subdivisions of the striatum with VS and DLS being the least and the most sensitive structure, respectively.

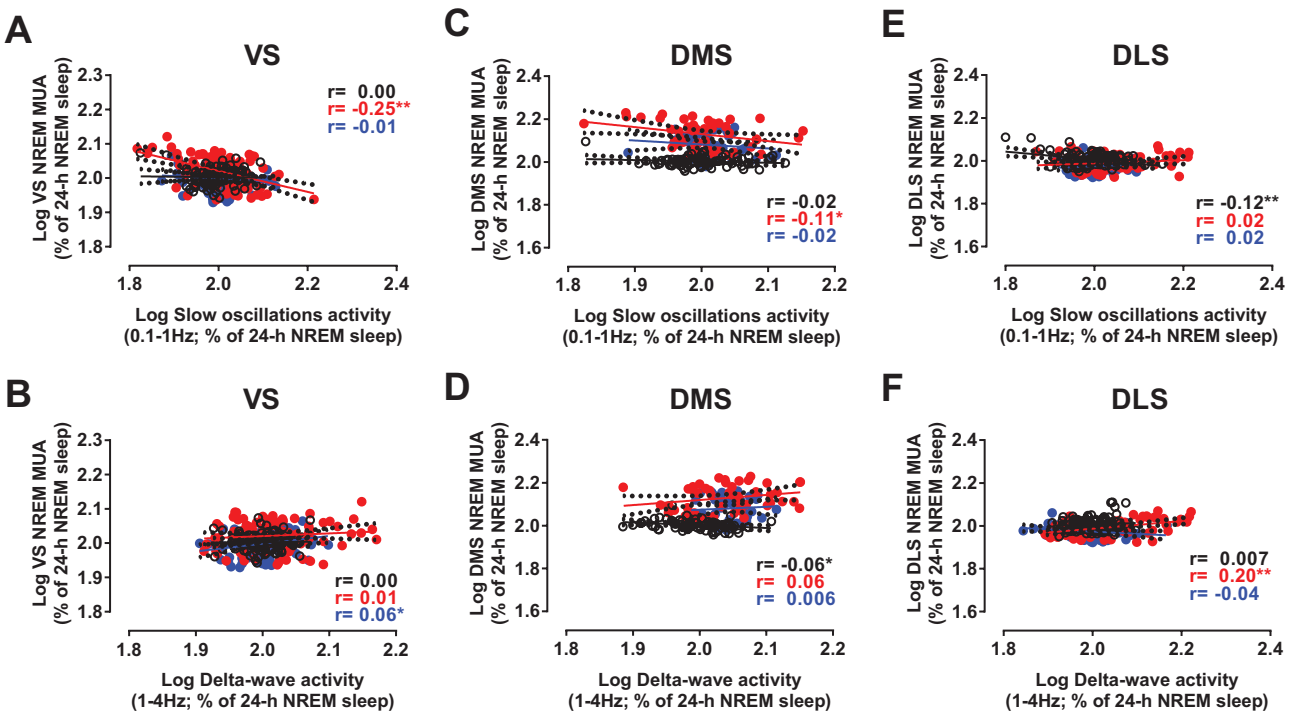

Figure 5. Correlations between neuronal activity in the VS (A, B), DMS (C, D), and DLS (E, F) and slow oscillations and delta wave activities during NREM sleep. Changes in mean firing rates in the VS, DMS, and DLS measured in 1-min bins as a function of the power density of slow oscillations (A, C, E) and delta waves (B, D, F). $^{*}p < 0.05$, $^{**}p < 0.01$ (black circles: control day; red circles: post-SD1; blue circles: post-SD2).

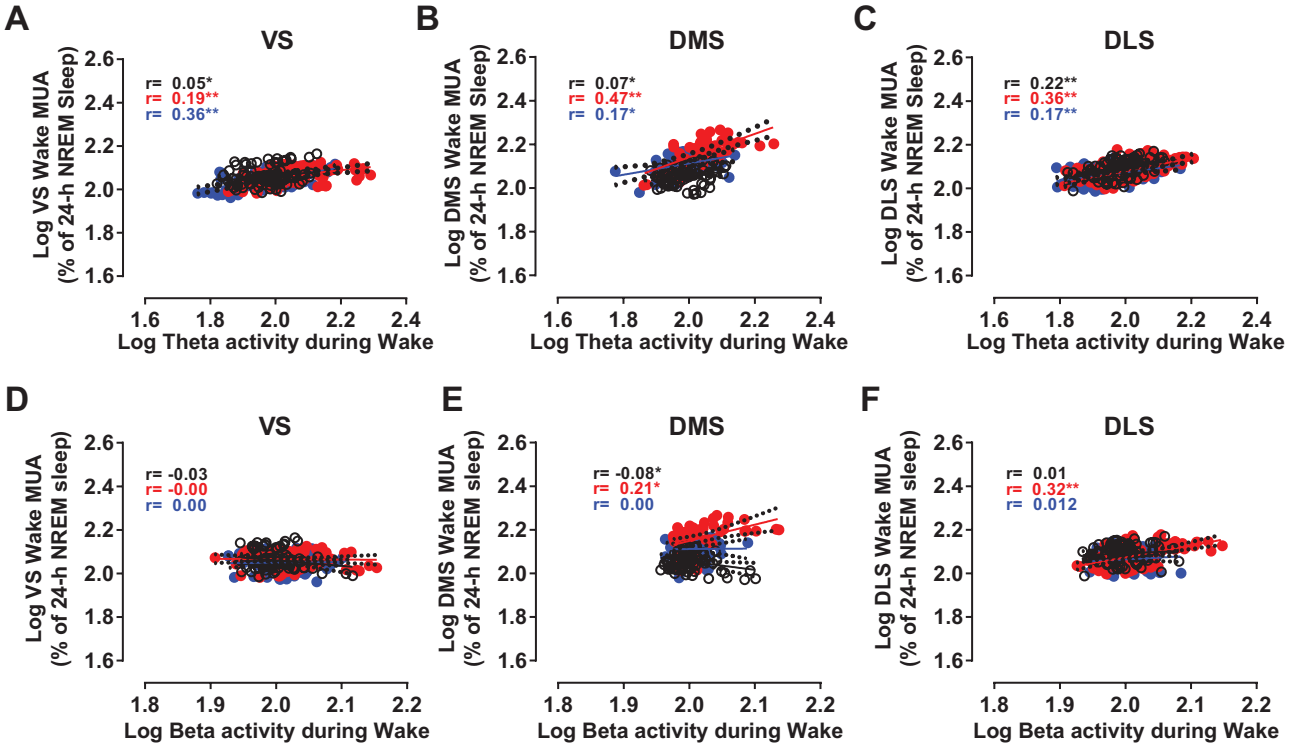

Figure 6. Correlations between neuronal activity in the VS (A, B), DMS (C, D), and DLS (E, F) and theta (A–C) and beta (D–F) activities measured from EEG signals during wakefulness. (A–F) Changes in mean firing rates in the VS (A, D), DMS (B, E), and DLS (C, F) measured in 1-min bins as a function of the power density of theta activity (A–C) and beta activity (D–F). $^{*}p < 0.05$, $^{**}p < 0.01$ (black circles: control day; red circles: post-SD1; blue circles: post-SD2).

Heterogenous modulations of neuronal activity in the different striatal subregions by cortical EEG power densities

In vivo, and across sleep/wake cycles, cortical neurons display robust oscillations in their membrane potential [47, 48]. These oscillations are strongly correlated with the amplitude and frequency of EEG signals [43, 49]. During NREM sleep, cortical activity is dominated by slow waves for which amplitude and incidence are quantified using spectral analysis of the EEG power density of cortical slow (0.1–1 Hz) and delta wave (1–4 Hz) oscillations [42]. This measurement (SWA) is considered the most reliable index of sleep homeostasis [42] and has been successfully used to predict the effects of various SD paradigms and shift-work schedules on alertness and fatigue [42, 50]. Homeostatic changes in cortical SWA following SD have been shown to reflect dynamic changes in neuronal activity in the cortex [43, 51, 52]. This also applies to the striatum under baseline LD conditions [53, 54]. We therefore set to examine the extent of MUA modulation in different striatal subregions by SWA. During baseline day, and consistent with previous studies [36, 37, 43, 51], both slow wave (0.1–1 Hz, $r^2 = 0.42$, $p < 0.001$, polynomial regression analysis, Figure 4, A) and delta wave (1–4 Hz, $r^2 = 0.22$, $p < 0.001$, polynomial regression analysis, Figure 4, B) activities decreased during the day (i.e. the rest phase) and increased during the night (i.e. the active phase). A similar pattern was observed for the spindle frequency activity (7–15 Hz, $r^2 = 0.32$, $p < 0.001$, polynomial regression analysis, Figure 4, C). After SD, both slow oscillations and delta wave activities were significantly higher than baseline for 4 h (Figure 4, A and B) while spindle activity remained higher than baseline for 18 h after SD (Figure 4, C). During the second day after SD, SWA and spindle frequency activity returned to baseline values (Figure 4, A–C). These results show that changes in the dynamic of SWA do not reflect the electrophysiological alterations induced in striatal subdivisions after SD. For example, VS showed no significant alterations of neuronal activity during the few hours following SD (Figure 2, A) during which sleep pressure in high (as evidenced by increased SWA and sleep). Inversely, MUA decrease in the DLS persisted even after SWA returned to baseline (compare Figure 2, E with Figure 4, A and B).

The heterogenous sensitivity of the different striatal subregions to sleep pressure is also evident from correlational analysis between the changes in delta wave (1–4 Hz) activity and MUA during NREM sleep (Figure 5). Under baseline day, this correlation was either not significant in the case of VS and DLS (Figure 5, B and F) or weakly negative in the case of DMS ($r^2 = 0.0036$, $p < 0.05$, regression analysis, Figure 5, D). The first day after SD, DLS was the only structure that showed a positive correlation between delta wave activity and MUA during NREM sleep ($r^2 = 0.04$, $p < 0.01$, regression analysis, Figure 5, B, D, and F). The correlations with slow oscillations (0.1–1 Hz) activity were not significant under baseline day for VS and DMS (Figure 5, A and C) but was negative for DLS ($r^2 = 0.0144$, $p < 0.01$, regression analysis, Figure 5, E). This correlation was negative for both VS ($r^2 = 0.0625$, $p < 0.01$, regression analysis, Figure 5, A) and DMS ($r^2 = 0.0121$, $p < 0.05$, regression analysis, Figure 5, C) and not significant for DLS (Figure 5, E). Although these correlations are sometimes very small, the overall results reveal a regional difference in the sensitivity of striatal subregions to sleep pressure and that the modulation of neuronal activity by SWA is modest in the entire striatum.

Alternatively, power density of other frequencies in the EEG may better represent the dynamic of MUA changes in the striatum [44, 45], Theta (6–9 Hz) power density during wakefulness showed a progressive increase during SD (Figure 4, D). After SD, it remained higher compared to baseline during the first 3 h following SD (Figure 4, D). The power density of beta oscillations (12.5–25 Hz) during wakefulness showed also a significant increase during SD but rapidly decreased to baseline values immediately after SD (Figure 4, E). The correlations between changes in theta power density with changes in MUA during wake were positive for all striatal subregions during both baseline and SD days (Figure 6, A–C). Neuronal activity in all striatal subregions was not sensitive to changes in beta power density except during SD day for both DLS (Figure 6, E) and DMS (Figure 6, F) that showed a significant positive correlation (Figure 6, D–F). Collectively, these results provide functional correlate of the anatomical heterogeneity within the striatum regarding its sensitivity and responses to different behavioral sleep/wake states.

Discussion

In this study, we investigated the circadian and sleep-related homeostatic modulation of neuronal activity in the different subdivisions of the striatum. A significant daily and circadian modulation of MUA was mainly found in DLS while in VS and DMS, no significant daily oscillations were found. Additionally, changes in the vigilance states were associated with significant modulation of MUA in all striatal subregions. The main finding of this study consists of the heterogenous responses of functionally different areas in the striatum to SD; while neuronal activity in VS was immune to sleep pressure following 6 h of SD, a significant increase and decrease was observed, respectively, in the DMS and DLS. Crucially, these alterations persisted several hours after the recovery of cortical EEG power densities. This study shows that the well-established cognitive, affective, and behavioral alterations associated with SD [19] could result from neuronal dysfunction in BG induced by SD.

Circadian and vigilance state-dependent modulation of MUA in the striatum

The LD cycle exerts powerful synchronizing and modulating effects on several physiological and behavioral rhythms [55] including many that are under the control of BG [55, 56]. To investigate the influence of LD on the rhythm of MUA as well as the potential circadian modulation of neuronal activity in different subdivision of the striatum, we recorded under both LD and constant DD conditions. We found a significant daily and circadian modulation of MUA firing rates in the DLS while VS and DMS had, respectively, no or very modest (under DD conditions) modulation. Even in the DLS however, the amplitude of MUA rhythms was about sixfold lower compared to the robust rhythms reported in the SCN [46, 57].

Our recordings consist of MUA from the population of neurons surrounding the tip of the electrode regardless of the neurochemical identity of neurons. In the entire striatum, GABAergic medium spiny projection neurons (MSNs) form most of striatal neurons (95%) while both GABAergic and cholinergic interneurons count for the remaining 5% [58–60]. Because these neurons are homogenously intermingled within the striatum, the rhythms of neuronal activity we recorded in different

compartments of the striatum should be regarded as an estimation of the average activity of all types of neurons. Recent in vivo single-unit recordings in the striatum have shown that MSNs do not significantly alter firing rate across vigilance states [53, 61, 62]. In contrast, tonically active putative cholinergic interneurons displayed a modest but significant increase in firing rate during wakefulness relative to NREM sleep. During REM sleep, no significant changes were observed compared to NREM sleep [61]. Vigilance-state changes in firing patterns have been shown for MSNs but not for putative cholinergic interneurons such that MSNs shifted from bursting patterns characteristic of SWS to less regular firing during REM sleep and wakefulness [53, 61, 62]. These results indicate that changes in firing patterns rather than in firing rates characterize the vigilance state-dependent modulation of neuronal activity of the majority of striatal neurons (i.e. MSNs). These electrophysiological characteristics also explain the lack of, or the modest, circadian modulation of MUA we found, respectively, in VS and DMS in one hand and the DLS on the other. The significant circadian modulation of MUA firing rates in the DLS could be driven by cholinergic interneurons that show vigilance states related modulation of their firing rates [61]. Alternatively, circadian signals from the endogenous clock might be driving neuronal activity in the DLS in order to orchestrate the 24 h timing of the physiological and behavioral parameters under the control of the DLS (*discussed below*).

We show that MUA rates in all striatal subdivisions undergo robust arousal-state-dependent changes with higher activity in REM sleep and wake compared to NREM sleep. These results corroborate recent imaging studies of neural activity across vigilance states in both ventral [63] and dorsal striatum [64]. Interestingly, this pattern reflects the pattern of changes in dopamine concentration in VS and the cortex [65] which is the main source of glutamatergic inputs to the striatum [66]. The sharp changes seen in the NREM sleep to wake and wake to NREM sleep transitions are likely to reflect firing rate changes of putative cholinergic interneurons [61]. Since both MSNs and putative cholinergic interneurons do not significantly increase their firing rates during REM compared to NREM sleep [61], the systematic increase of MUA firing rates at the NREM- to REM sleep transition in all striatal subregions likely reflects firing patterns of putative GABAergic striatal interneurons. Currently however, electrophysiological properties of this population of striatal neurons in relation to vigilance-state changes are unknown and future studies are needed to test this hypothesis.

The impact of SD on neuronal striatal activity

To investigate the impact of SD on functionally distinct subdivisions of the striatum, we subjected the animals to 6 h of SD during the first quarter of their subjective day. SD was insured by promoting spontaneous exploration through the introduction of fresh food and novel objects into the cage whenever the animals feel drowsy [39]. Because of our MUA neuronal recording method, we cannot determine the neurochemical identity of neurons (MSNs, GABAergic or cholinergic interneurons) that altered their firing rates after SD both in DMS and DLS. Future studies using spike-sorted single-unit recordings or single cell in vivo calcium imaging are needed to assess the responses of the different striatal neurons to SD as well as the relative contribution of MSN vs striatal interneurons to the altered MUA in the striatum following SD.

In humans, several studies have investigated the impact of sleep loss on the activity of different brain structures [19]. Early PET studies showed general hypometabolism in several brain areas including BG nuclei [29, 30, 67, 68]. Recent fMRI studies however, revealed inconsistent findings for BG. The majority of studies demonstrated significant disruptions [21–24, 31, 33, 69–71] while others indicate a lack of a significant impact [32, 34]. Among studies reporting significant changes, the magnitude as well as the direction of change is also not consistent. In VS, except for two studies that failed to report any changes in the activity of VS [32, 34], all the others consistently reported significant activation of the VS following SD [22, 23, 31, 71].

At least two possible, and yet, not mutually exclusive explanations might account for these conflicting findings. Either differences in the environmental conditions surrounding the studies (i.e. nature of the task used during imaging) or individual (i.e. genetic) differences in the participants tested in the different studies may interact with SD and produce variable outcomes. Indeed, Greer et al. recently reported the contribution of a genetic polymorphism of the human DAT in shaping the impact of SD on VS response to rewards and punishments [33]. By comparing neural responses of the VS between participants carrying a copy of the 9-repeat DAT allele (linked with higher phasic DA activity) and participants homozygote for the 10-repeat DAT allele, the authors found an amplified striatal response during anticipation of monetary gain following SD in the 9R carriers relative to the 10R homozygotes [33]. Alternatively, differences in the experimental conditions between the different studies might also explain the different results. In the thalamus for example, some studies showed greater activity under conditions of sleep loss [72–77], whereas others have reported intermittent periods of reduced thalamic activity [78, 79]. These discrepancies have been linked to the variable attentional engagement during the performance of the behavioral tasks used during fMRI acquisition. Under conditions of SD, when attentional engagement is maintained, thalamic activity is elevated. During lapses of attention, substantial reductions in thalamic activity were observed [20, 29, 78, 79]. In addition, the pattern and magnitude of activation and/or deactivation in several cortical and subcortical areas under conditions of SD were found to change as a function of the presence or absence of visual stimuli [80] and complexity of the task performed [73]. Collectively, these studies have led to a more nuanced interpretation of neuronal activity changes under sleep loss conditions [19, 73]. According to this view, regions showing relatively reduced levels of activation and deactivation would underlie the behavioral impairments precipitated by SD, while areas showing increased activation after SD are regions that might play a compensatory role [73]. The contribution of a particular brain region to either performance impairment or preservation (through compensation) is task related [73]. In our study, while neural activity in VS showed a significant increase during SD, MUA regained its baseline levels immediately after SD with no significant alterations henceforth. A crucial distinction between our study and human studies is the fact that fMRI experiments are typically conducted while the participants are awake and engaged in a behavioral task. This would make the results obtained in the VS from human studies equivalent to our data during the last hours of SD. Interestingly, and consistent with most human studies [21–24, 31, 33, 69, 70], a significant increase in neuronal activity during the last 2 h of SD (and during the entire 6 h SD in DMS and DLS) was observed in the VS. Given the

involvement of the VS in behavioral activation [81], this neuronal activation in the VS could reflect a compensatory mechanism to counteract sleep pressure and maintain wakefulness during the exploration of the novel objects used to sleep deprive the animals. A similar compensatory role of the VS has also been shown in a recent study in humans revealing that increased VS activity may buffer against depressive symptoms associated with poor sleep [71]. After SD, MUA in the VS returned to baseline levels. This finding suggests that SD does not induce intrinsic alterations of neuronal activity in VS if animals are allowed to recover normally from SD. fMRI analyses during recovery sleep following SD will be required to test whether this is also the case in humans. Taken together, our data combined with insights from human studies suggest that SD induces compensatory activation in VS. This activation dissipates and activity returns to baseline values as soon as animals engage in sleep behavior.

Heterogenous neuronal responses to SD in the striatum

In contrast to VS, even under conditions where animals could compensate for the sleep loss accrued during SD, significant alterations in MUA were found in DMS and DLS (Figure 2, C and E). These alterations were independent of changes in vigilance states given that they persist even after the normalization of sleep/wake cycle following SD and that they were observed during both wakefulness (Supplementary Figure S6) and NREM sleep (Supplementary Figure S7). Furthermore, heterogenous responses were observed within the striatum with the DMS and DLS showing, respectively, an upregulation and a downregulation of neural firing rates. These results suggest that SD differentially affects intrinsic neuronal firing properties within the striatum.

Imaging data in humans show conflicting results regarding the impact of SD on caudate/putamen (equivalent of dorsal striatum in mice). Some studies reported a significant decrease in neuronal metabolism [29, 30, 67], others a significant increase in caudate–putamen neural responses [21, 24, 69] while several other studies failed to find significant neural alterations similar to VS [22, 23, 31–34, 70]. Different experimental conditions are likely to contribute to these discrepant findings. In humans, no study so far has examined systematically the response of the different subdivisions of the striatum to SD. Our study revealed a heterogenous response of functionally distinct striatal subregions to SD. This heterogenous response might originate from the distinct connectivity of the different striatal regions [18]. For example, the organization of cortical inputs defines broad divisions of the striatum to associative, sensorimotor and limbic domains both in humans and rodents [17, 18]. Midbrain dopaminergic inputs project also topographically to these functionally striatal domains [82–85]. SD is known to differently impact different cortical regions. Frontoparietal derivations have been shown to exhibit the largest response to changes in sleep pressure in terms of both SWA during NREM sleep and theta activity during waking [30, 70, 86–90]. Given that glutamatergic cortical projections are the main neural inputs to the striatum [17, 18], this mosaic sensitivity of the cortex to SD is likely to influence the response of different striatal domain to SD. Therefore, the most plausible explanation of the heterogenous neuronal responses of the striatum to SD would be a heterogenous perturbation of the excitation/inhibition balance across the striatum as a result of a heterogenous SD-induced alteration of the activity of cortical and subcortical areas projecting to the striatum. As mentioned before, the impact of the environment under SD (i.e. nature of the tasks performed) [73, 80] is also computed by, and channeled through these inputs to, the striatum. Alternatively, although not mutually exclusive, SD might differently impact striatal subregions by differently affecting the expression of several neurotransmitter receptors across the striatum leading therefore to a mosaic map of neuronal excitability within the striatum [91]. Local alteration of the expression of clock genes in the striatum might also constitute intrinsic mechanism through which SD affect the physiology and function of striatal regions. A series of recent studies have revealed anatomical, neurochemical, and functional heterogeneity across both the rostrocaudal and the dorsoventral axes of the striatum [92–97]. Our findings suggest that such heterogeneity is likely to impact also the response of the striatum to SD. Future studies will be required to investigate more in detail the extent of this SD-induced heterogenous responses across the striatum as well as its underlying mechanism.

Relationship between cortical EEG and striatal MUA

Anatomically, the cortex stands as the main source of inputs to the striatum [18]. These afferents are thought to mediate the up and down oscillations of membrane potential of striatal MSNs [53, 54, 98–103]. Several studies have indeed shown that, in anesthetized animals, the slow up and down membrane potential oscillations of MSNs coincide with cortical slow wave oscillations and are disrupted by electric stimulation of the cortex that results in loss of cortical synchronization [53, 54, 100–103]. Based on these studies, we hypothesized that cortical EEG alterations that are precipitated by SD, mainly in the range of SWA (0.1–4 Hz) (Figure 4, A and B) will impact neural activity in the striatum. Contrary to our hypothesis, we found that the MUA firing rate in all striatal subregions does not change significantly as a function of SWA (Figure 5). A crucial distinction between our study and the studies suggesting a causal link between cortical and striatal slow oscillations is the behavioral state of the animals during data acquisition; we recorded from freely moving animals during both normal wake and sleep states while the other studies used anesthetized animals. Under anesthesia, cortical circuits are locked into synchronized states [48, 104, 105] that are homogenous through the neocortex and striatum [103]. This artificial state prevents the normally occurring cross-region neural integration and cortical traveling waves during sleep [106].

Recently, Mizrahi-Kliger et al. reported the first study examining the relationship between slow oscillations of neuronal activity in the cortex and several BG nuclei in freely moving monkeys [61]. Unlike the synchronized dynamics of both corticostriatal and cortical networks reported, respectively, in anesthetized animals [48, 104, 105] and in vivo cortical recording [43, 49, 51], this study showed an intriguing state of complete desynchrony between striatal MUA and both EEG and cortical local field potentials [61]. These results corroborate our findings regarding both the insensitivity of striatal MUA to SWA (Figure 5) and the failure of cortical EEG dynamic to reflect the alterations of striatal neuronal activity induced by SD (Figures 2 and 4). Collectively, both our results and Mizrahi-Kliger et al. study suggest that neuronal computation within BG during normal sleep [61] and following SD (this study) occur independently of EEG slow oscillations. Therefore, attempts to predict changes in neuronal computation (i.e. changes in firing rates) within BG

solely from cortical EEG or even from local BG local field potentials (LFPs) will be extremely complex if not impossible.

Two mechanisms have been advanced to account for the desynchronization of BG slow oscillations; active desynchronization by lateral inhibition or an anatomical organization of parallel segregated neural connections that guarantees that different striatal cells share only a small fraction of their inputs [61]. Given the convergent nature of neuronal inputs from the cortex and thalamus to the striatum [18] as well as the traveling pattern of slow waves across the cortical mantle [106], sparse common inputs to MSNs is likely to account as the most likely mechanism for desynchronized BG activity [61]. As we stated in the previous section, because SD affects differently EEG across the cortex [30, 70, 86–89], the same mechanism may explain the heterogenous electrophysiological responses we report in the striatum after SD.

Clinical implications

BG do not operate in isolation, but act within a broad network of anatomically and functionally connected cortical and subcortical regions [18]. In accord with this anatomical organization, BG have been implicated in a wide range of motor, cognitive, and affective behaviors [11, 12]. Dysfunctional BG are causally associated with several neurological and neuropsychiatric disorders [12]. Patients suffering from these disorders inevitably display circadian and sleep alterations that worsen their symptoms over disease progression [56, 107–111]. As discussed before, several imaging studies in humans have shown aberrant neuronal responses in the BG following SD [21–24, 29–34]. Interestingly, these responses were significantly correlated with behavioral impairments. Recent genomic data have also revealed functional gene networks within the striatum linking sleep, circadian, cognitive, metabolic, and mood regulation-related biological pathways [112–114]. Lack of sleep does not have a uniform impact on brain areas. Rather heterogenous responses are seen in different brain areas with the frontal cortex being the most sensitive at the cortical level [30, 70, 86–90]. Our study reveals that these heterogenous neural responses to SD apply also to the striatum. We suggest that this heterogeneity might be the neuronal correlate of the SD-induced heterogenous disruptions in human behavior across nearly all domains of cognition and affect [19].

Supplementary Material

Supplementary material is available at *SLEEP* online.

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Authors' Contributions

KF and TD designed the experiments. KF performed the experiments. KF analyzed the data and wrote the manuscript. Both authors worked on, revised and improved the manuscript.

Disclosure Statement

The authors declare no explicit conflict of interest related to this study.

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