Handedness Leads to Interhemispheric EEG Asymmetry During Sleep in the Rat

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Abstract: Sleep electroencephalographic (EEG) slow-wave activity is increased after wakefulness and decreases during sleep. Regional sleep EEG differences are thought to be a consequence of activation of specific cortical neuronal circuits during waking. We investigated the relationship between handedness and interhemispheric brain asymmetry. Bilateral EEG recordings were obtained from the frontal and occipital cortex in rats with a clear paw preference in a food-reaching task (right, n = 5; left, n = 5). While still naïve to the task, no waking or sleep EEG asymmetry was present. During the food-reaching task, the waking EEG showed significant, substantial power increases in the frontal hemisphere contralateral to the dominant paw in the low theta range (4.5-6.0 Hz). Moreover, the non-REM sleep EEG following feeding bouts was markedly asymmetric, with significantly higher power in the hemisphere contralateral to the preferred paw in frequencies >1.5 Hz. No asymmetry was evident in the occipital EEG. Correlation analyses revealed a positive association between the hemispheric asymmetry during sleep and the degree of preferred use of the contralateral paw during waking in frequencies <9.0 Hz. Our findings show that handedness is reflected in specific, regional EEG asymmetry during sleep. Neuronal activity induced by preferential use of a particular forelimb led to a local enhancement of EEG power in frequencies within the delta and sigma ranges, supporting the hypothesis of use-dependent local sleep regulation. We conclude that inherent laterality is manifested when animals are exposed to complex behavioral tasks, and sleep plays a role in consolidating the hemispheric dominance of the brain.

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Handedness Leads to Interhemispheric EEG Asymmetry During Sleep in the Rat

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Vyazovskiy VV, Tobler I. Handedness leads to interhemispheric EEG asymmetry during sleep in the rat. *J Neurophysiol* 99: 969–975, 2008. First published December 12, 2007; doi:10.1152/jn.01154.2007. Sleep electroencephalographic (EEG) slow-wave activity is increased after wakefulness and decreases during sleep. Regional sleep EEG differences are thought to be a consequence of activation of specific cortical neuronal circuits during waking. We investigated the relationship between handedness and interhemispheric brain asymmetry. Bilateral EEG recordings were obtained from the frontal and occipital cortex in rats with a clear paw preference in a food-reaching task (right, $n = 5$; left, $n = 5$). While still naïve to the task, no waking or sleep EEG asymmetry was present. During the food-reaching task, the waking EEG showed significant, substantial power increases in the frontal hemisphere contralateral to the dominant paw in the low theta range (4.5–6.0 Hz). Moreover, the non-REM sleep EEG following feeding bouts was markedly asymmetric, with significantly higher power in the hemisphere contralateral to the preferred paw in frequencies >1.5 Hz. No asymmetry was evident in the occipital EEG. Correlation analyses revealed a positive association between the hemispheric asymmetry during sleep and the degree of preferred use of the contralateral paw during waking in frequencies <9.0 Hz. Our findings show that handedness is reflected in specific, regional EEG asymmetry during sleep. Neuronal activity induced by preferential use of a particular forelimb led to a local enhancement of EEG power in frequencies within the delta and sigma ranges, supporting the hypothesis of use-dependent local sleep regulation. We conclude that inherent laterality is manifested when animals are exposed to complex behavioral tasks, and sleep plays a role in consolidating the hemispheric dominance of the brain.

INTRODUCTION

The diversity of behaviors with a lateral preference in the animal kingdom suggests that laterality is favored by natural selection. Inherent lateralities (Ross et al. 1981) become apparent when an animal is faced with complex tasks (Collins 1975). Throughout the life span, execution of such tasks may shape local brain circuits and strengthen unilaterally organized neuronal pathways. It is well known that rodents exhibit an individual tendency toward preferential use of either the right or the left paw (Biddle and Eales 1996; Biddle et al. 1993; Collins 1975; Pence 2002; Tang and Verstynen 2002; Tsai and Maurer 1930; Waters and Denenberg 1994, 1991). Rats belonging to two strains preferentially used the right or left paw when exposed to a food-reaching task (Long–Evans: Tang and Verstynen 2002; Sprague–Dawley: Pence 2002). Such peripheral asymmetries might be a result of, or lead to, interhemispheric asymmetries of the brain.

Sleep-state–related interhemispheric EEG asymmetries were found in humans, cats, and rabbits (Goldstein et al. 1972; Roth et al. 1999). Interestingly, a left-hemispheric predominance of low electroencephalographic (EEG) frequencies during non-rapid eye movement (NREM) sleep in Sprague–Dawley rats was enhanced during recovery after increased physiological sleep pressure attained by 6 h sleep deprivation (SD) (Vyazovskiy et al. 2002). Such asymmetries are likely to arise from the pronounced morphological asymmetries of the rat brain (Dowling et al. 1982; Kolb et al. 1982; Sherman and Galaburda 1984). Alternatively, we hypothesize that they may be related to the lateralized behavior during preceding waking. In Sprague–Dawley rats distinct aspects of spatial learning in a spatial-learning task were associated with use of the left or right whiskers and involvement of the corresponding contralateral hemisphere (LaMendola and Bever 1997). These data suggest a relationship between hemispheric dominance and peripheral sensorimotor lateralization. Several experiments entailing unilateral peripheral sensorimotor stimulation during waking induced predictable unihemispheric and regional gradients in EEG activity (Huber et al. 2004; Vyazovskiy et al. 2000, 2004b). Striking evidence for "unihemispheric sleep" was found in aquatic mammals belonging to the orders Cetacea, Pinnipedia, and Sirenia. Dolphins, sea cows, and several species of seals can engage in deep slow-wave sleep only with one hemisphere at a time, whereas the other hemisphere exhibits either a waking EEG pattern or one that is intermediate between waking and "light" sleep (Lyamin et al. 2002a,b, 2004; Mukhametov et al. 1977, 1985, 1992; Oleksenko et al. 1992). It is still unclear, however, whether behavioral asymmetries contribute to this remarkable feature of sleep in these animals.

It is well established that EEG slow-wave activity (SWA; EEG power between 0.5 and 4.0 Hz) during NREM sleep increases in proportion to the duration of preceding waking and declines exponentially during subsequent sleep (Deboer and Tobler 2003; Franken et al. 2001; Huber et al. 2000; Larkin et al. 2004; Strijkstra and Daan 1998; Tobler and Borbély 1986; Vyazovskiy et al. 2006; reviewed in Borbély and Achermann 2005 for humans; Tobler 2005 for animals) and is thus considered a measure of sleep intensity. It was recently proposed that SWA is a result of the local increase of synaptic strength occurring during wakefulness, and the slow waves typical for sleep enable synaptic downscaling (Tononi and Cirelli 2006).

Here we address the relationship between behavioral laterality and brain asymmetry in the rat. We hypothesized that sleep epochs following spontaneous unilateral paw use would be characterized by interhemispheric EEG asymmetry with higher sleep intensity in the hemisphere corresponding to the activated region.

METHODS

Animals and paw preference assessment

The experiments were performed in accordance with the European Communities' Council Directive of November 24, 1986 (86/609/ EEC) and were approved by the Cantonal Veterinary Office of Zurich. Adult male rats of the Sprague–Dawley strain ($n = 15$) with a mean body weight 301 ± 18.1 g (SE) at surgery were used. Prior to the beginning of the protocol the animals were kept individually in Macrolon cages with food and water available without restriction, and maintained on a 12-h light/12-h dark cycle (light from 10:00 to 22:00 h; 7-W Osram Dulux EL energy saving lamp, ~30 lux). Ambient temperature was maintained at 21–22°C. To assess the direction of paw preference, we used a modified food-reaching task (Collins 1975; Tang and Verstynen 2002). The animals were kept in individual cages where food pellets (length 1.2 cm, diameter 0.5 cm; Kliba NAFAG, Kaiseraugst, Switzerland) were provided via two dispensers placed left and right outside the front wall of the cage (angle 45°), spilling pellets onto a tray connected to a grid. The grid had two rectangular openings (2.2 cm horizontal × 0.9 cm vertical, 3.0 cm from the cage floor) separated by one square of the remaining grid (1.2 × 0.9 cm). The rats could retrieve food pellets with quick reaches through the grid with only one paw at a time or with the snout. Video recordings were obtained by an infrared-sensitive camera (TVCCD-30M) mounted in front of the grid. The number of reaches with each paw or with the snout was determined by scoring the tapes of those days when the rats were exposed to the food-reaching task (see following text). Feeding behavior usually occurred in "bouts," defined as periods during which the rat retrieved a food pellet and ate it, usually close to the grid, facing the camera.

EEG data acquisition and analysis

Under deep pentobarbital anesthesia (Nembutal sodium, 80 mg/kg, administered intraperitoneally, volume ~0.5 ml) the rats were implanted with gold-plated miniature screws (diameter 0.9 mm) inserted into the skull that served as EEG electrodes. The frontal electrodes were implanted above the primary motor representation of the forelimb, 1 mm anterior to bregma, 3 mm lateral to the midline; the occipital electrodes 4 mm posterior to bregma, 3 mm lateral to midline; both EEGs were referenced to the electrode above the cerebellum (on midline). Two gold wires (diameter 0.2 mm) inserted into the neck muscles served to record the electromyogram (EMG). The electrodes were connected to stainless steel wires fixed to the skull with dental cement. At least 8 days were allowed for recovery. EEG acquisition and analysis and scoring of the three vigilance states—NREM sleep, REM sleep, and waking—were performed for 4-s epochs as previously (Vyazovskiy et al. 2002). The EEG and the EMG signals were amplified (amplification factor ~2,000), conditioned by analog filters (high-pass filter: −3 dB at 0.016 Hz; low-pass filter: −3 dB at 40 Hz, less than −35 dB at 128 Hz) sampled with 512 Hz, digitally filtered [EEG: low-pass finite impulse response (FIR) filter 25 Hz; EMG: band-pass FIR filter 20–50 Hz] and stored with a resolution of 128 Hz. EEG records for consecutive 4-s epochs were subjected to a fast Fourier transform routine to obtain EEG power spectra. Adjacent 0.25-Hz bins were added to yield 0.5-Hz (0.25–5.0 Hz) and 1.0-Hz (5.25–25.0 Hz) bins, and those >25.0 Hz were omitted. Epochs containing EEG artifacts recognized during visual scoring were excluded from spectral analysis of all the EEGs ($16.8 \pm$

1.7%). Most artifacts occurred during waking. The EEG of the 2-h waking interval before light onset and the first 3 h of sleep during "recovery" in the light period was analyzed (see following text). One rat was excluded from the analysis of the 2-h waking interval before light onset due to numerous artifacts in one of the four derivations precluding interhemispheric comparisons. Vigilance states could always be determined.

Experimental design

EEG recordings consisted of an undisturbed baseline (day 1) with unrestricted access to food followed by two experimental days (days 2 and 5) separated by two intervening days. Experimental days always started at dark onset. On day 2 the rats were kept awake for the last 2 h of the dark period (see following text) while food was still available ad libitum ("food ad lib"), followed by undisturbed sleep. Prior to day 5 the rats were habituated to the food-reaching task (day 4; see earlier text and Fig. 1) for 24 h beginning at onset of the dark period. On day 5 food was removed at dark onset for 10 h to induce frequent feeding bouts during the following 2 h when the food-reaching task was expected to induce intense unilateral paw use. During the 2-h food-reaching task the rats were kept awake as during "food ad lib." Since sleep intensity depends on the preceding sleep–wake history (Borbély 1982; Vyazovskiy et al. 2007), it was important to monitor sleep in animals under the same level of sleep pressure. Therefore the rats were kept awake during the last 2 h of the dark period of the two experimental days. This procedure required only a minimal amount of interventions to maintain wakefulness because the dark period is the preferential wake time for rats, and the animals spent most of the time feeding. Nevertheless, when necessary, fresh nesting material was provided to stimulate wakefulness.

Statistical analysis

Data analysis and statistics were performed with MATLAB (The MathWorks, Natick, MA) and SAS (SAS Institute, Cary, NC), respectively.

Contrasts were tested with two-tailed paired t-test. The relationship between EEG power and the laterality index was assessed by Pearson linear correlation.

RESULTS

Paw preference

To confirm stability and consistency of paw preference, in $n = 15$ rats behavior was scored and analyzed for 4 days within
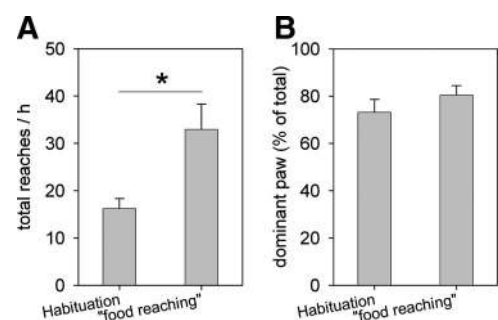

FIG. 1. *A*: total number of reaching attempts per hour during the habituation day, when the animals were exposed to the task for the first time, and during the 2-h induced waking during exposure to the reaching task ("food reaching") on the following day. *B*: number of reaches with the dominant paw as percentage of total reaching attempts on the habituation and food-reaching days. Mean values $\pm$ SE ($n = 10$). The asterisk denotes the significant increase in the total number of reaches per 1 h during the "food reaching" day ($P < 0.05$; paired t-test).

1 wk [habituation day (day 4; see earlier text), entering the mean value of the laterality index, day 5 ("food reaching"), day 7, and day 9]. We continued to record behavior on videotapes for several additional days after collecting the EEG data to clarify whether the direction of paw reference remained stable across a longer time period. Therefore starting from the last 2 h of the dark period of experimental day 5 food was continuously provided only via the grid. Rats were considered to have a paw preference if they used one specific paw in >70% of total reaches (mean of the 4 days mentioned earlier) and did not change paw preference throughout the experiment. Ten rats met the 70% criterion of paw preference and were used for further analysis. Some individuals performed <70% reaches with the dominant paw on the habituation or on the "food reaching" days, but consistently increased unilateral paw use during the experiment reaching the 70% criterion in the mean 4-day value. During the 2-h food-reaching task the rats made significantly more attempts to retrieve food pellets compared with the habituation day (Fig. 1A). In the 10 rats that met the laterality criterion, 73.2% of total paw reaches were executed with one specific paw on the habituation day (range 65–97%) and 80.4% (range 63–100%) during the "food reaching" task (Fig. 1B; comparison between the 2 days: $P = 0.25$, paired t-test). Rats using predominantly the left paw ($n = 5$) and right paw ($n = 5$) showed a similar paw preference index (not shown).

Unilateral paw preference was associated with waking EEG asymmetry

To investigate whether the intense unilateral paw use was reflected in the waking EEG, we compared the EEG power spectra of the 2 h "food ad lib" with the 2-h "food reaching" interval (Fig. 2). During "food ad lib" no interhemispheric asymmetry occurred in either derivation. In contrast, an inter-

hemispheric asymmetry favoring the hemisphere contralateral to the preferred paw was observed during "food reaching" in the low theta band (4.5–6.0 Hz) that was restricted to the frontal EEG (i.e., the motor cortex). The asymmetry within the theta band was evident in both animals exhibiting either a right- or a left-paw preference. (Only $n = 9$ animals were included in this analysis due to numerous artifacts in one individual. Therefore the small number of animals, $n = 4$ and 5, precluded statistical comparisons within the groups.) In the occipital derivation a prominent theta peak was apparent on both days. It was neither related to the direction of paw preference nor affected by the paw use (Fig. 2). The occipital EEG power in low frequencies showed high variability between the animals during wakefulness and was not different between the ipsilateral and contralateral side on either of the 2 days, and did not differ between the days.

Unilateral paw use led to hemispheric EEG power asymmetry during sleep

We hypothesized that the preferential paw use would induce an EEG asymmetry during the first intervals of sleep following the task, and expected it to be specific for the frontal derivation over the frontal motor representation of the forepaw. In rats still naïve to the task a significant, but minor asymmetry clustered in the 3.5- to 6.0-Hz band occurred in the frontal hemisphere in the first 3 h after light onset (Fig. 3, *left*). After the 2-h "food reaching" task the asymmetry was more pronounced, encompassing almost the entire frequency band >1.5 Hz. This asymmetry favored the hemisphere contralateral to paw use and was limited to the frontal derivation (Fig. 3, *right*). No asymmetry was encountered in the occipital derivation, except in one frequency bin between 17.0 and 18.0 Hz. Mean EEG power at 1.0 Hz was higher on the contralateral side compared with the ipsilateral derivation but, due to the large
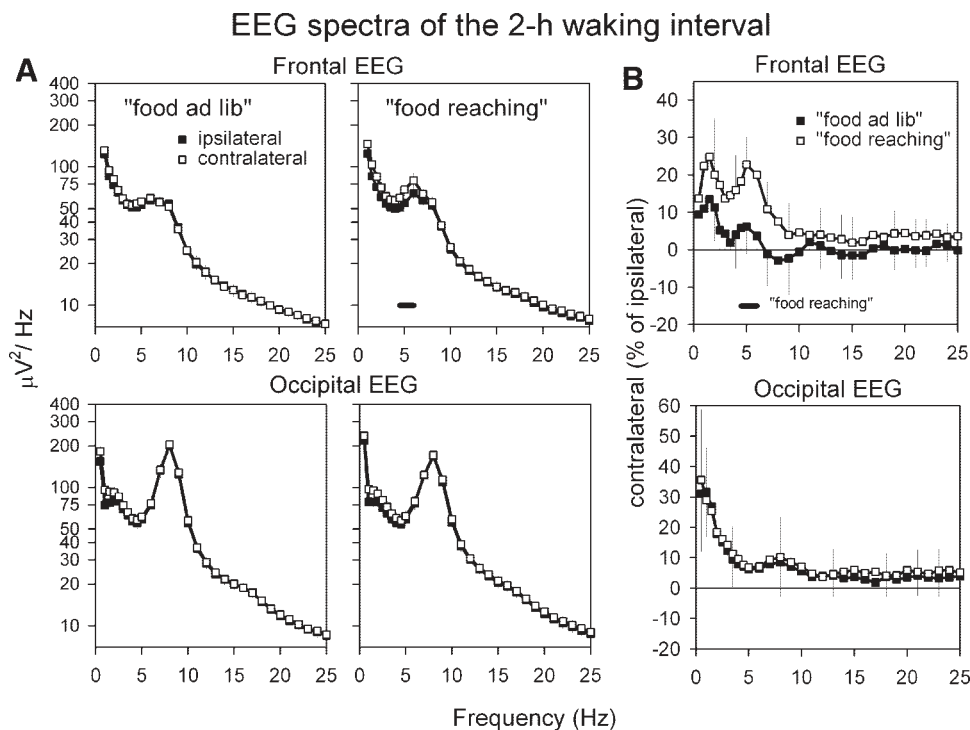
EEG spectra of the 2-h waking interval

FIG. 2. Electroencephalographic (EEG) power density of the 2-h interval of induced wakefulness in the rats still naïve to the task ("food ad lib") and of the 2 h of wakefulness with unilateral paw use ("food reaching"). *A*: mean values ($n = 9$ rats) in μV^2/Hz are plotted at the upper limit of each bin on a logarithmic scale for the frontal (*top*) and occipital derivation (*bottom*). *B*: EEG power density of the hemisphere contralateral to the dominant paw expressed as a percentage of power in the ipsilateral hemisphere. The horizontal line below the curves indicates frequency bins that differed significantly between the 2 hemispheres ($P < 0.05$; paired t-test on log-transformed values).

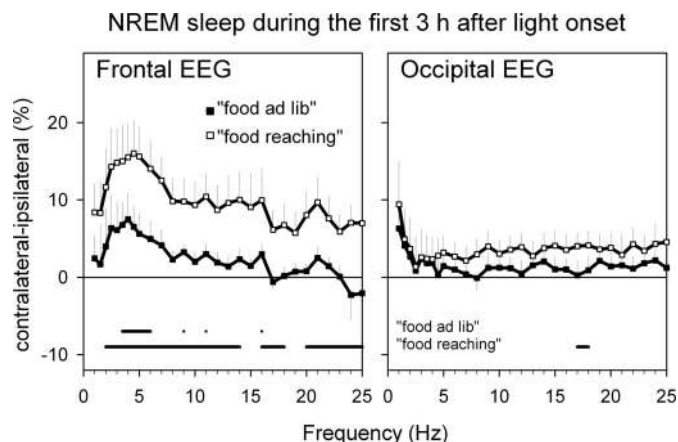NREM sleep during the first 3 h after light onset

FIG. 3. EEG power density in nonrapid eye movement (NREM) sleep of the hemisphere contralateral to the dominant paw expressed as a percentage of power in the ipsilateral hemisphere during the first 3-h interval after light onset on the 2 experimental days (one with food ad lib and one with the food-reaching task). Power in each frequency bin is normalized to the mean 12-h baseline light period value of the corresponding bin. The curves connect mean values ± SE ($n = 10$ rats). Horizontal lines designate those bins that differed significantly between the ipsilateral and the contralateral derivations on the "food ad lib" and "food reaching" days ($P < 0.05$; 2-tailed t-test).

variability between animals, did not reach significance. Both the animals exhibiting a right- or a left-paw preference contributed to this result. A significant asymmetry occurred between 2.5 and 7.0 Hz in the animals with left-paw preference, and either significance or a statistical tendency ($P < 0.1$) was attained in frequencies >4.5 Hz in the rats with right-paw preference (not shown). The asymmetry was specific for NREM sleep. The EEG in REM sleep during the first 3 h after "food ad lib" showed no evident asymmetry in either derivation. After "food reaching" no REM sleep asymmetry was apparent in the frontal derivation and a slight, but significant asymmetry occurred in frequencies between 1.0–1.5 and 2.5–3.0 Hz in the occipital derivation (not shown). The amount of NREM and REM sleep during the 3-h interval after light onset was similar between the 3 days: NREM sleep: undisturbed baseline: $105.7 ± 3.6$ min; "food ad lib": $98.1 ± 5.4$ min; "food reaching": $102.4 ± 5.9$ min ($P > 0.3$ for any of the three comparisons, paired t-test; REM sleep: undisturbed baseline: $22.1 ± 1.4$ min; "food ad lib": $21.1 ± 1.9$ min; "food reaching": $21.3 ± 2.0$ min ($P > 0.6$ for any of the three comparisons, paired t-test).

Hemispheric dominance of EEG power during waking and sleep correlated with the paw-use laterality index

Next we investigated whether the EEG asymmetry during waking and the larger increase of EEG power in the hemisphere contralateral to the dominant paw after the food-pellet–reaching task during sleep is indeed related to the preferential use of the corresponding paw. The analysis was based on the laterality index (defined as the number of reaches: [dominant − nondominant paw]/[dominant + nondominant paw]) determined for the 2-h "food reaching" task. The index was computed for each individual rat and correlated with waking EEG power during the corresponding 2-h interval of "food reaching" and with NREM sleep EEG power during the subsequent 3 h for all frequency bins between 0.25 and 25.0 Hz (Fig. 4). During waking, a positive correlation attained a tendency ($P <$

0.1) for one frequency bin within the theta band (7.0 Hz). Interestingly, a negative correlation reached a tendency level at about 1.0 Hz, which might indicate a redistribution of EEG power from the slow to theta frequencies as a function of unilateral paw use. No correlation reached significance or a tendency level for the occipital derivation (not shown).

During subsequent sleep, a significant positive correlation or a tendency ($P < 0.1$) was found for several EEG frequency bins encompassing the high SWA range (2.0–4.0 Hz) and frequencies ≤9.0 Hz. Based on this result we computed the correlation for the entire 2.0- to 9.0-Hz band. This analysis revealed that those individuals with a stronger preference toward unilateral paw use, had higher EEG power between 2.0 and 9.0 Hz in the hemisphere contralateral to the preferred paw (Pearson product-moment correlation coefficient $r = 0.69$, $P < 0.05$; no correlation reached significance on the ipsilateral side). Based on this correlation, we compared EEG power in NREM sleep in the 2.0- to 9.0-Hz frequency band between baseline and after "food reaching." As expected, a significant asymmetry specific to the frontal motor cortex was found after food reaching ($12.5 ± 3.4\%$, $P < 0.05$; Fig. 5).

Reaching with the snout

The rats sometimes used their snout to reach for food pellets behind the grid ($13.1 ± 3.2\%$ of total reaches). Intriguingly, these reaches appeared to have a lateral bias. Most of the snout reaches ($77.1 ± 5.8\%$) were performed through the opening in the grid ipsilateral to the dominant paw and contralateral to the dominant hemisphere (Fig. 6).

DISCUSSION

This study is the first demonstration of EEG laterality in relation to paw use in rodents. The main finding was a clear relationship between the direction and strength of spontaneous paw preference and interhemispheric EEG asymmetry during sleep. The data provide evidence that sleep intensity may be the consequence of the activation of specific brain regions during wakefulness.
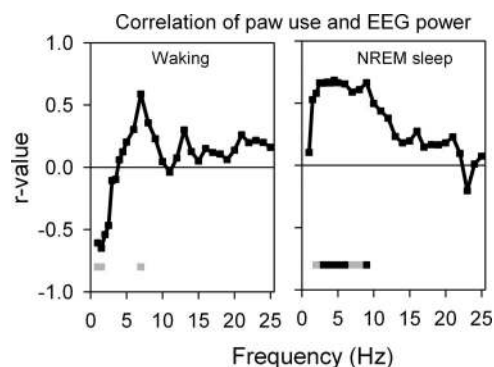
Correlation of paw use and EEG power

FIG. 4. Linear correlation analysis between EEG power density in the hemisphere contralateral to the dominant paw in the 2-h waking during the "food reaching" day (*left*, computed as the difference between the contralateral and the ipsilateral power, expressed as percentage of the corresponding 2-h waking during "food ad lib"; $n = 9$) and for NREM sleep during the first 3-h interval after light onset on the "food reaching" day (*right*, expressed as percentage of the 12-h baseline light period; $n = 10$) and the behavioral laterality index of the 2-h "food reaching" (paw use). R-values are shown for each frequency bin. Horizontal lines: bins where the correlation was significant (black, $P < 0.05$) or reached a tendency (gray, $P < 0.1$).
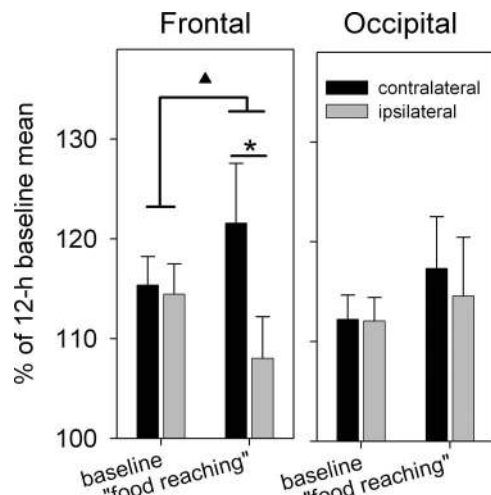
Frontal Occipital

FIG. 5. EEG power in the frequency band between 2.0 and 9.0 Hz in NREM sleep during the first 3 h of the light period after a night with food ad lib in the cage (baseline) and following a 2-h waking interval with food pellets available only through 2 horizontal slots in a grid ("food reaching"). Mean values ($n = 10$ rats) are shown for the frontal (motor cortex) and for the occipital area of the hemisphere contralateral and ipsilateral to the dominant paw. The data are represented as percentage of mean EEG power in the 2.0- to 9.0-Hz band during the 12-h baseline light period. The asterisk denotes the significant difference between the hemispheres after food reaching; the triangle indicates a significant difference between the ratio contralateral vs. ipsilateral power on the baseline day and the day after exposure to the food-reaching task ($P < 0.05$, paired t-test).

The task to which the rats were exposed unmasked an inherent behavioral laterality (preference of the left or the right paw) that led to local interhemispheric EEG asymmetries. These asymmetries were manifested to some extent in the waking EEG, and to a larger degree during subsequent sleep. Separation of the data based on right- and left-paw preference confirmed our findings. EEG power was higher in the left hemisphere of the rats, which preferentially used their right paw, whereas the opposite was evident in the rats preferentially using their left paw. Moreover, those individuals that preferentially used the left paw showed higher EEG power in the right hemisphere than in the left hemisphere, whereas the opposite relationship occurred in the animals preferentially using the right paw.

The interest of our findings is that interhemispheric EEG asymmetry occurred not only while the rats were performing the task (i.e., during wakefulness), but also in subsequent sleep. It is well established that sleep is a regulated process. Its main electrographic hallmark—slow-wave activity (EEG power between 0.5 and 4.0 Hz)—increases as a function of preceding waking duration and decreases during sleep (Borbély and Achermann 2005; Deboer and Tobler 2003; Franken et al. 2001; Huber et al. 2000; Larkin et al. 2004; Strijkstra and Daan 1998; Tobler 2005; Tobler and Borbély 1986; Vyazovskiy et al. 2006). Moreover, it is now widely accepted that sleep is not only a global process but has a local use-dependent component manifested in regional differences in SWA (Kattler et al. 1994; Krueger and Obál 1993; Krueger et al. 1999). However, the mechanisms underlying both the global and local time course of SWA are unknown. It was recently proposed that SWA is a result of the local increase of synaptic strength occurring during wakefulness, and the slow waves typical for sleep enable synaptic downscaling (Tononi and Cirelli 2006). Evi-

dence for this hypothesis was provided by high-density EEG recordings in humans. Local, topographically distinct enhancement of slow waves was associated with learning of a motor task (Huber et al. 2004). In contrast, unilateral arm immobilization led to a local decrease in slow waves (Huber et al. 2006). Our results are consistent with the notion that local sleep regulation is a consequence of neuronal activity resulting from spontaneous use or experimentally induced stimulation during wakefulness (Kattler et al. 1994; Vyazovskiy et al. 2000, 2004b).

However, it should be noted that the asymmetry was not restricted to the low EEG frequencies but was also evident in higher frequencies, ≤25.0 Hz. It will be important to investigate in detail the origin and physiological significance of the use-dependent changes occurring at different EEG frequencies. It was proposed that increased neuronal synchronization due to stronger cortico-cortical connections might lead to increased EEG power not only in the SWA range but also in higher frequencies (Tononi and Cirelli 2006). Moreover, delta and sigma (0.5–4.0 and 10.0–15.0 Hz, respectively) rhythms, the two most characteristic EEG oscillations during NREM sleep, are not mutually exclusive but they rather reflect different aspects of the same phenomenon—cortical bistability—inasmuch as they refer to the down- and up-states of the "classical" slow oscillation, respectively (Steriade et al. 1993, 2001). We recently showed in mice that after sleep onset, SWA and the number of spindle events increase concurrently and the occurrence of spindle events is accompanied with an overall increase in EEG power ≳7 Hz (Vyazovskiy et al. 2004a). Moreover, in our previous studies addressing regional use-dependent aspects of sleep regulation in a whisker stimulation model in rats and mice (Vyazovskiy et al. 2000, 2004b) we observed that the EEG asymmetry during sleep following the peripheral stimulation also occurred in higher frequencies.

Despite this overall increase in EEG power, correlation analyses revealed that those animals with a stronger preference toward unilateral paw use had significantly higher EEG power in the range encompassing the high SWA range (2.0–4.0 Hz) and the frequencies ≤9.0 Hz in the contralateral frontal cortex.
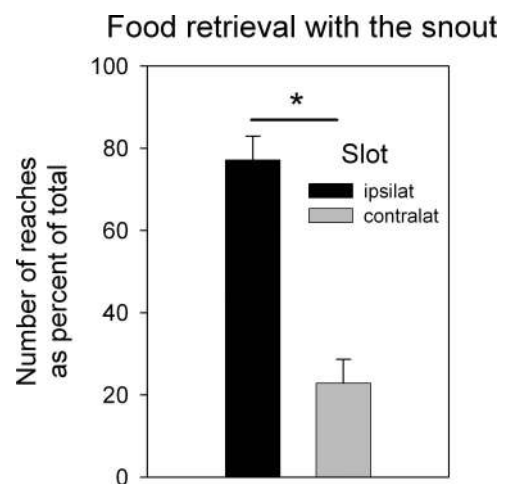
Food retrieval with the snout

FIG. 6. Number of reaches with the snout toward the slot in the grid ipsilateral or contralateral to the dominant paw as percentage of total attempts to retrieve food pellets with the snout, averaged over 4 days. Mean values ± SE ($n = 10$ rats). Asterisk denotes a significant bias of reaching with the snout toward the slot ipsilateral to the dominant paw ($P < 0.05$, paired t-test).

This result suggested that behavioral laterality is primarily related to the EEG asymmetry in low frequencies in subsequent sleep. Interestingly, when compared with baseline, the asymmetry in the 2.0- to 9.0-Hz band appeared to be a result of the shift of EEG power toward the contralateral side (Fig. 5). Such a redistribution might be the consequence of a decreased use of the nondominant paw at the expense of more intense use of the dominant paw after exposure to the task.

The waking EEG asymmetry that we encountered during the food-reaching task and its restriction to the frontal derivation support the notion that cortical activation was elicited by the intense unilateral paw use. This asymmetry occurred within the lower theta band (4.5–6.0 Hz). Theta activity in rodents is believed to originate from the hippocampus, although prominent theta activity has also been recorded locally from several extra-hippocampal regions, including cortical areas (reviewed in Kahana et al. 2001). Thus the enhancement of theta power over the frontal derivation may be an indication of local neuronal activation. It was recently shown that theta activity (5.0–8.0 Hz) in the waking EEG also increased as a function of preceding waking duration in both humans (Aeschbach et al. 2001; Cajochen et al. 1995) and rats (Vyazovskiy and Tobler 2005). Taken together these data suggest that theta activity might represent a waking counterpart of the homeostatic process at both the global and the local levels. The occipital EEG power in low frequencies around 1.0 Hz was asymmetric both in sleep and in waking, but this asymmetry did not reach significance due to the large variability between the animals (Figs. 2 and 3). Low EEG frequencies are susceptible to artifacts, especially due to movements in waking (Vyazovskiy and Tobler 2005), and therefore should be interpreted with caution.

An additional interesting finding was the laterality in the reaching attempts with the snout that was related to the paw dominance. Since food retrieval with the snout also entails the use of whiskers, especially those on the side facing the preferred grid slot, the snout laterality suggests that asymmetry may be present in several brain areas, not only in the motor cortex but also in the sensorimotor area within the same hemisphere. Indeed, we previously showed that unilateral whisker use leads to a selective increase in SWA in the contralateral hemisphere during subsequent NREM sleep (Vyazovskiy et al. 2000). The data suggest the intriguing possibility that the hemispheric dominance of the brain, reflected in selective strengthening of unilateral neural pathways and local cortical circuits, is established during sleep and manifested in the NREM sleep EEG.

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