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CHAPTER 15

Evoked electrical and cerebral vascular responses during sleep and following sleep deprivation

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Abstract: Neuronal activity elicits vascular dilation, delivering additional blood and metabolites to the activated region. With increasing neural activity, vessels stretch and may become less compliant. Most functional imaging studies assume that limits to vascular expansion are not normally reached except under pathological conditions, with the possibility that metabolism could outpace supply. However, we previously demonstrated that evoked hemodynamic responses were larger during quiet sleep when compared to both waking and rapid eye movement (REM) sleep, suggesting that high basal activity during wake may elicit blunted evoked hemodynamic responses due to vascular expansion limits. We hypothesized that extended brain activity through sleep deprivation will further dilate blood vessels and exacerbate the blunted evoked hemodynamic responses observed during wake, and dampen responses in subsequent sleep. We measured evoked electrical and hemodynamic responses from rats using auditory clicks (0.5 s, 10 Hz, 2–13 s random ISIs) for 1 h following 2, 4, or 6 h of sleep deprivation. Time-of-day matched controls were recorded continuously for 7 h. Within quiet sleep periods following deprivation, evoked response potential (ERP) amplitude did not differ; however, the evoked vascular response was smaller with longer sleep deprivation periods. These results suggest that prolonged neural activity periods through sleep deprivation may diminish vascular compliance as indicated by the blunted vascular response. Subsequent sleep may allow vessels to relax, restoring their ability to deliver blood. These results also suggest that severe sleep deprivation or chronic sleep disturbances could push the vasculature to critical limits, leading to metabolic deficit and the potential for tissue trauma.

Keywords: auditory cortex; blood volume; evoked response potential; hemoglobin; optical; NIRS; quiet sleep.

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Introduction

Neural activation initiates vascular dilation that delivers oxygen and glucose to the activated region; a phenomenon that forms the basis for a variety of functional imaging techniques including positron emission tomography (PET), functional magnetic resonance imaging (fMRI), and near infrared spectroscopy (NIRS; Belliveau et al., 1991; Franceschini et al., 2008; Logothetis et al., 2001; Martin et al., 2006; Oakes et al., 2004; Roy and Sherrington, 1890; Villringer and Chance, 1997). With increased neural activity, more blood is required to supply metabolic demand. Of particular importance is whether there is a physiological limit to the amount of blood that can be delivered. Under pathological conditions, such as epilepsy or stroke, the blood vessels may reach a limit in their capacity to expand and deliver metabolites, leading to further tissue trauma. Waking activity does not normally require as many resources as severe pathological conditions; however, wake is characterized by neural depolarization and frequent spontaneous action potentials, a period of activity with high metabolic demand. Thus, it is possible that vascular smooth muscle expansion during extended waking and sleep deprivation may also cause vessels to approach their limit of metabolite delivery, with the possibility of limited tissue resources during these periods. Alternatively, quiet sleep is characterized by a synchronous membrane potential oscillations between hyperpolarized and depolarized states at a Delta frequency (0.3–3 Hz), where neurons spend roughly half of the time in a hyperpolarized, less metabolically demanding state. Since regional cerebral blood flow and metabolism, as measured from resting brain activity, is decreased during quiet sleep compared to wakefulness (Braun et al., 1997), sleep maybe required to restore the vascular compliance back to a more relaxed state.

Several lines of evidence support the notion that blood vessels exhibit compliance limits under nonpathological conditions. First, regional evoked vascular responses to external stimuli are larger during quiet sleep compared to wake (Larson-Prior et al., 2009; Schei et al., 2009), suggesting that blood vessels exhibit lower compliance during wake due to their larger volume, causing a blunted evoked response. Conversely, since basal cerebral blood flow and metabolism levels are lower during quiet sleep, vessel relaxation may allow a larger evoked vascular response, resulting in a larger influx of blood. Second, healthy, older adults exhibit decreased blood oxygen level-dependent (BOLD) responses, requiring age-sensitive fMRI studies (D'Esposito et al., 1999). Thus, age related changes may result from reduced smooth muscle compliance, impacting vascular responsiveness, and reducing local perfusion.

While limits to vascular dilation may not impact the tissue under normal conditions, over the long term, sleep restriction, and deprivation have detrimental consequences on cerebral processing and cognitive performance (Goel et al., 2009; Van Dongen and Dinges, 2005). Conditions of impaired perfusion and overdriven cells underlie significant injury described for obstructive sleep apnea (OSA; Macey et al., 2008). In addition, studies following total sleep deprivation in humans showed decreased glucose metabolism in subcortical structures and increased in the visual cortex associated with a visual vigilance task, yet with no overall change in whole brain metabolism (Wu et al., 1991).

To test the hypothesis that prolonged high basal neural activity can decrease blood vessel compliance and blunt evoked hemodynamic responses, we investigated both electrical and hemodynamic responses to auditory stimulation following varying amounts of sleep deprivation. Combined electroencephalographic (EEG) and NIRS allow simultaneous assessment of electrical neural activity with vascular changes associated with increased metabolite demand during stimulation. With longer sleep deprivation periods, we expect the evoked vascular response will become smaller as blood vessels stretch and become less compliant.

Methods

Chronic implantation

We implanted four adult female Sprague–Dawley rats (250–300 g, Simonsen Laboratories, Gilroy, CA, USA) with two screw electrodes (Fig. 1, closed circles; J. I. Morris, Southbridge, MA, F00CE188), one over the frontal lobe and one over the parietal lobe, measuring electric potential differences from a reference screw placed over the occipital lobe. The remaining screws secured the headstage to the skull (open circles). A light emitting diode (LED; 1.6 mW, B5b-436-30, Roithner Lasertechnik, GmbH, Vienna, Austria), placed 6 mm caudal to bregma and over the temporal ridge, illuminated the cortex with 660 nm light. A photodiode (PC1-6, Pacific Silicon Sensors, Westlake Village, California, USA), placed 3 mm rostral to the LED, measured changes in light scattered from the cortex. An insulated stainless steel wire (New England Wire, Lisbon, NH, 212-50F-357-0), with 1 mm end exposed, was placed subcutaneously beside the thoracic cavity to measure electrocardiographic (ECG) activity and another wire was placed in the neck muscle to measure electromyographic (EMG) activity. Wires were assembled to a miniature plug and secured with dental cement. All procedures were approved by the Washington State University Animal Care and Use Committee.

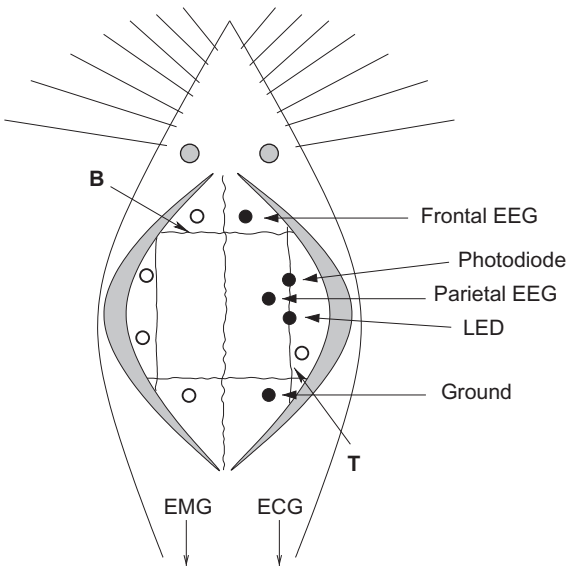

Fig. 1. Rats were implanted with stainless steel screw electrodes (closed circles), with blunted ends, placed over the frontal and parietal lobes measuring the electric potential relative to a ground reference in the occipital lobe. A light emitting diode (LED) providing 660 nm illumination was implanted 6-mm caudal from bregma (B) over the temporal ridge (T). A photodiode placed 3-mm rostral from the LED collected light back-scattered from the cortex. Anchor screws secured the headstage to the skull (open circles). A wire inserted subcutaneously along the thoracic cavity measured electrocardiographic activity (ECG) and a wire inserted into the neck muscle measured electromyographic activity (EMG).

Sleep deprivation paradigm

At least 2 weeks after surgical recovery, we recorded animals under freely moving conditions, using an acrylic chamber (26.5 cm × 26.5 cm × 34 cm) and tethered their headstage to a 55-cm cable connected to a swivel commutator (ProMed-Tec, Bellingham, MA, USA, Pro-ES24). Food and water were available *ad libitum* and animals were housed under a 12–12-h light cycle where ambient lights came on at 00:00. Ambient room temperature was approximately 22 °C. Two hours after lights on (02:00), animals were brought from their housing area to the recording room and tethered to the data acquisition system. Animals were sleep deprived for 2, 4, or 6 h by gentle handling, gentle petting with a paintbrush, and introducing novel objects, then recordings proceeded for 1 h after each deprivation session (Fig. 2). To control for time-of-day and novel environment effects, all animals were also recorded continuously during nondeprived conditions and were allowed to sleep normally for 7 h, from 02:00 to 09:00. The order of sleep deprivation duration/control condition was randomized within and across animals, and each condition was repeated two to six times. Each animal was allowed 1 week recovery

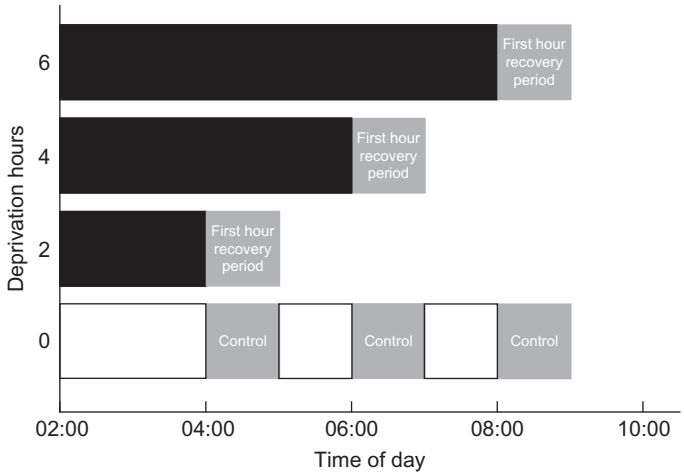

Fig. 2. Sleep deprivation began 2 h after lights on (02:00) and lasted for 2, 4, or 6 h (black blocks). The first hour of the recovery period began at 04:00, 06:00, or 08:00, respectively, illustrated by the gray blocks. All results represent evoked responses collected during quiet sleep within this first hour recovery period. In the control condition, animals were freely behaving and responses were measured during a 1-h period beginning at 04:00, 06:00, and 08:00.

between recordings and sessions continued over a period of 8 months.

To generate evoked responses, we stimulated the auditory cortex using a train of five auditory clicks (10 Hz, ~65 dB) delivered by a speaker placed 3 cm above the recording chamber. Stimuli occurred at random intervals between 2 and 13 s. Physiological data were amplified (AC photodiode ×200, DC photodiode ×1, EEG ×1000, ECG ×1000, EMG ×1000), filtered (0.1 Hz–3.2 kHz), and digitized (10 kHz) using custom built hardware (Rector and George, 2001). In addition, we collected images using a digital USB camera (1 Hz) to aid in sleep scoring. All data were archived to a hard drive for *post hoc* analysis.

Sleep scoring

Electrophysiological data were sorted into 2-s epochs and fast Fourier transform (FFT) analysis was performed to calculate a power spectrum for different frequency ranges. A scatter plot of the EEG Delta power versus the total EMG power was generated using each 2-s epoch in the recording (Rector et al., 2009b). Data point density clusters revealed the animal state such that high EMG power and low EEG Delta power corresponded to wake; low EMG power and high EEG Delta power corresponded to quiet sleep; and very low EMG power, low EEG Delta power, and high EEG Theta power corresponded to rapid eye movement (REM) sleep. Quiet sleep was further sorted into light quiet sleep (LQS) corresponding to higher EMG power and high EEG Delta power, and deep quiet sleep (DQS) corresponding to lower EMG power and high EEG Delta power (Rector et al., 2009b). Once clusters were sorted by state, we visually reviewed the physiological traces and camera images to confirm each epoch. Since the evoked vascular response lasted several seconds, state changes during the response may alter the signal, and such events were excluded from analysis. While arousals following the stimulus were rare (Phillips et al., 2010), if a state change occurred within 6 s of a stimulus, the stimulus was ignored, resulting in elimination of 5.7 ± 3.5% of the total stimuli.

Optical measurements

The vascular response was measured using the same principles as pulse oximetry. Light from the 660-nm LED illuminated the cortex and was attenuated through scattering and absorption as it traveled through the tissue, described by the modified Beer–Lambert law (Boas et al., 2001). Changes in the amount of light collected by the photodiode were dominated by light absorption changes due to fluctuations in the oxyhemoglobin and deoxyhemoglobin concentrations. At 660 nm, deoxyhemoglobin absorbs 10 times more light than oxyhemoglobin. However, changes in oxygen concentration are also accompanied by changes in blood volume. Therefore, our signals originated from a convolution of changes in deoxyhemoglobin concentration and blood volume (Schei et al., 2009). Absorption changes were recorded simultaneously with the EEG for assessment of correlated electrical and hemodynamic changes.

Data analysis

All data were analyzed using Octave, an open source analysis and mathematical modeling program (www.octave.org). After sleep scoring the data file, we averaged stimuli during LQS and DQS for the first hour of the recovery period following deprivation, since movement artifact disrupted the signals during deprivation and we expected this time period to exhibit the largest sleep deprivation effects. During the first hour recovery period, the number of stimuli in each state was divided by the total number of stimuli, indicating percent time spent in each state. Evoked response potential (ERP) amplitudes were measured from the P1 and N1 components (Knight et al., 1985) and values were normalized to the average P1 amplitude during LQS in the first hour recovery period following the 2-h deprivation condition. Since evoked responses were different between states, and since waking periods exhibited high noise due to movement artifact, we narrowed our analysis to responses that occurred only during quiet sleep during the first hour recovery period.

We displayed the vascular response by inverting the optical signal to correspond with changes in blood volume and deoxyhemoglobin concentration. In order to account for changes in baseline light levels, we divided the response by the normalized baseline light levels during the first hour of sleep deprivation for each animal. As with the electrical signal, we normalized the optical responses to the peak amplitude during LQS in the first hour recovery period following 2-h sleep deprivation. The peak was identified as a local maximum occurring around 2.5 s after the stimulus and the trough was identified as a local minimum occurring after the peak, around 3.9 s after the stimulus. We filtered the optical response using a high pass filter of 0.1 Hz and a low pass filter of 1 Hz to remove noise. To assist in identifying peak and trough amplitudes, optical signals were fit to a standard response curve. Statistical significance was calculated using a Mann–Whitney *U*-test with data from four animals, because normal distributions could not be assumed.

Results

Increased sleep deprivation altered sleep patterns significantly during the first hour of the recovery period (Fig. 3a). Compared to the 2-h deprivation condition, there was significantly less time spent in wake and more time spent in LQS, DQS, and REM in the 4- and 6-h deprivation conditions ($p < 0.05$). While the percent time spent in REM sleep increased with longer deprivation periods, it composed less than 15% of the total time. Consequently, there were too few stimuli present during REM, and the optical responses showed small signal-to-noise ratios. The data during waking states was convoluted with movement artifact, making the interpretation of the hemodynamic

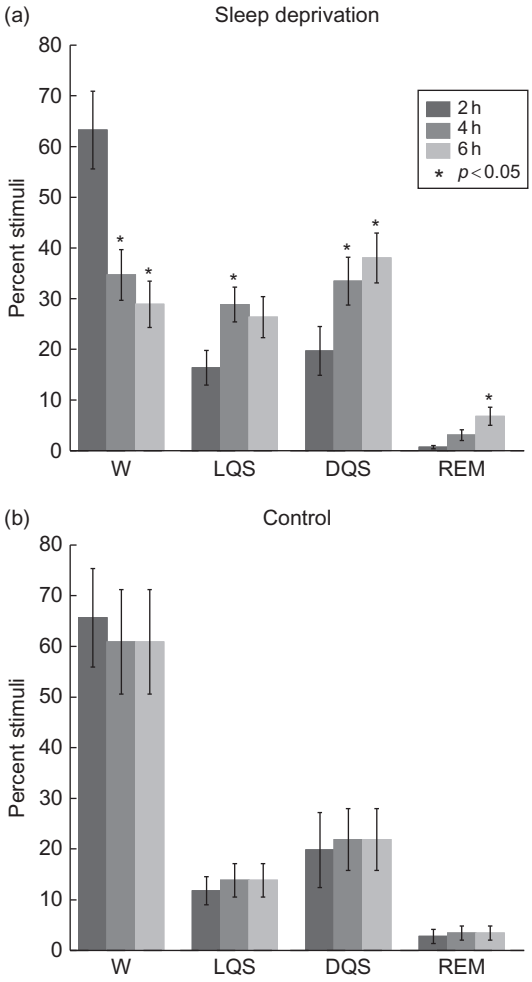

Fig. 3. The percent time spent in each state for the first hour recovery period (a) from four animals shows that increased amounts of sleep deprivation caused a significant decrease in the percent time spent in wake (W) and a significant increase in the percent time spent in light quiet sleep (LQS), deep quiet sleep (DQS), and rapid eye movement (REM) sleep. Significant changes are denoted with *($p<0.05$; Mann–Whitney *U*-test). During the no deprivation, control condition (b), no significant difference in the amount of time spent in wake or sleep across the three time periods was found, suggesting no significant time-of-day effect.

response difficult. Therefore, we focused our analysis on the LQS and DQS states. In the control condition, the total amount of time spent in wake and sleep did not significantly differ across the different time periods (Fig. 3b). While we might expect to observe small time-of-day differences in sleep structure, the novel environment may have artificially increased the amount of waking these animals experienced over the recording period.

Two example traces are shown in Fig. 4 from recordings conducted with no sleep deprivation. Evoked electrical responses showed larger P1 amplitudes during LQS and DQS compared to wake (Fig. 4a and b; $p<0.05$), as expected (Rector et al., 2009b), at a 65-dB stimulus intensity. The simultaneous evoked hemodynamic response peak amplitude was larger during LQS and DQS compared to wake (Schei et al., 2009; Fig. 4c and d; $p<0.05$).

A plot of the ERP mean P1 and N1 amplitude from all four animals after sleep deprivation and control conditions, along with standard error, is shown in Fig. 5a. There were no statistically significant within-state differences in the P1 and N1 amplitudes for LQS and DQS during the first hour recovery period following 2, 4, or 6 h of sleep deprivation. Figure 5b shows the ERP P1 and N1 amplitudes for the no deprivation, control condition. The only difference we observed occurred between the second and sixth hour recording time periods where there was a small but significant decline in the ERP P1 amplitude ($p<0.05$).

Two examples of the evoked vascular responses during LQS (Fig. 6a and b) and DQS (Fig. 6c and d) for the first hour recovery period show that the evoked vascular response became smaller for DQS with longer deprivation periods. We focused on the changes in the peak and trough amplitudes, indicated by the arrows, during LQS and DQS for the first hour recovery period following sleep deprivation. Figure 7a shows the average and standard error of the peak and trough amplitudes from four animals after sleep deprivation. During the LQS state, the hemodynamic response peak and trough amplitudes did not significantly differ across sleep deprivation duration. However, the DQS peak amplitude was significantly smaller after 6 h

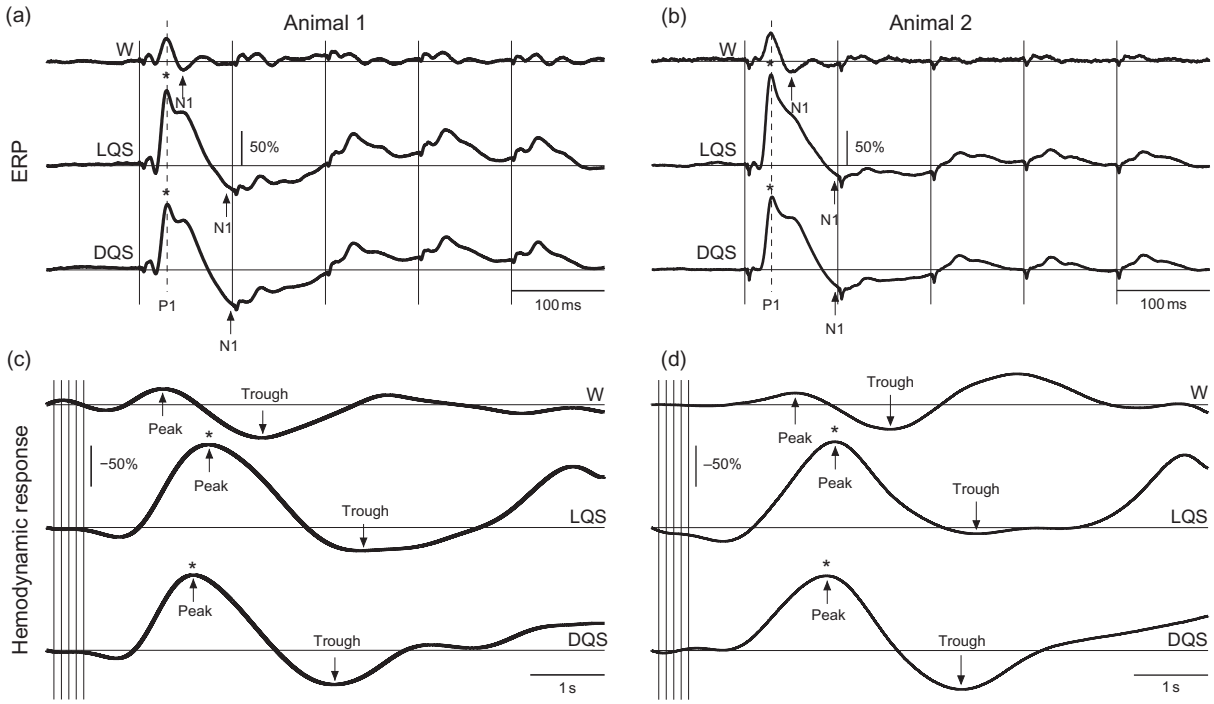

Fig. 4. Example evoked electrical response potentials (ERPs; a and b) and inverted evoked hemodynamic responses (c and d) from two animals recorded under no sleep deprivation conditions. We measured the ERP P1 and N1 amplitudes and the hemodynamic response peak and trough amplitudes, as indicated by the arrows. In agreement with our previous report (Schei et al., 2009), the ERP P1 amplitude was larger during light quiet sleep (LQS) and deep quiet sleep (DQS) compared to wake (W), and the hemodynamic peak amplitude was larger during LQS and DQS compared to W. Significant changes are denoted with *($p < 0.05$; Mann–Whitney *U*-test).

deprivation compared to those obtained after 2 h deprivation ($p < 0.1$). The trough amplitude did not significantly differ across sleep deprivation periods. In the control condition, the peak and trough amplitudes did not significantly differ (Fig. 7b).

Discussion

In corroboration with our earlier studies, evoked hemodynamic responses were largest during quiet sleep (Fig. 4; Schei et al., 2009), and the control condition showed no significant difference in hemodynamic response amplitude during LQS or DQS across 7 h. However, with increased sleep deprivation, we observed a significant decrease in the evoked hemodynamic response amplitude during DQS in spite of the observation that the ERP amplitude did not change. High neuronal use requires metabolites, stretching blood vessels, and blunting the evoked hemodynamic response during wake. With prolonged use over extended waking periods, the surrounding vasculature may reach a limit in its ability to expand and supply metabolites to the activated tissue, further blunting evoked responses during sleep immediately following deprivation.

Mounting evidence suggests that basal neural activity has a significant effect on the evoked

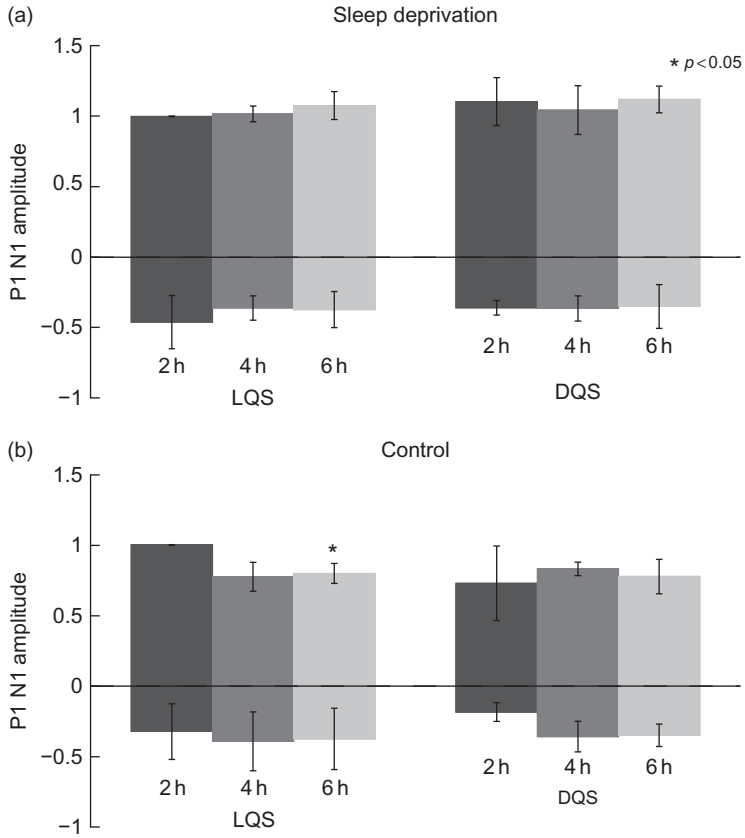

Fig. 5. The evoked electrical response potential (ERP) P1 and N1 amplitudes across light quiet sleep (LQS) and deep quiet sleep (DQS) during the first hour recovery period measured from four animals showed no significant difference across deprivation hours (a). Under the no deprivation control (b), we observed a small but significant decline in the ERP P1 amplitude in the sixth hour compared to the second hour ($p < 0.05$; Mann–Whitney *U*-test).

hemodynamic response. Cerebral blood flow and the BOLD response are correlated to Delta rhythms and *k*-complexes (Czisch et al., 2004) as well as isoflurane bursting EEG activity (Liu et al., 2010). The waking state is characterized by high basal neural activity and is highly demanding of metabolites to replenish the tissue, and in response, blood vessels expand to allow for sufficient nutrient delivery, which may reduce vessel compliance, blunting the evoked hemodynamic response. Thus, during wake, the evoked vascular response was smaller in amplitude compared to quiet sleep due to these potential limits. Consequently, smaller vascular responses in DQS were observed following sleep deprivation, which may be due to decreased vessel compliance. Synchronous Delta rhythms of membrane potential fluctuations between depolarized and hyperpolarized states during quiet sleep may be less metabolically demanding, allowing blood vessels to relax and become more compliant during sleep.

The data from LQS showed a similar trend of decreasing vascular responses with longer sleep deprivation; however, this result did not reach significance due to high variability in the data.

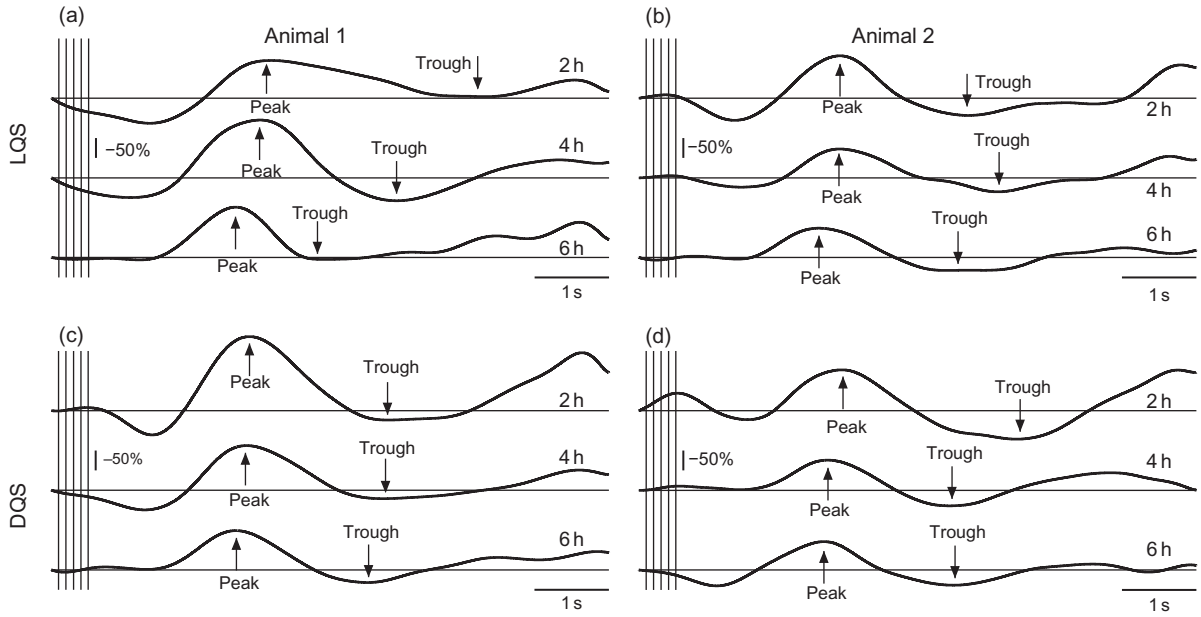

Fig. 6. Two example inverted evoked optical response traces during the first hour recovery period across light quiet sleep (LQS; a, b) and deep quiet sleep (DQS; c, d) from two animals shows progressively smaller responses after sleep deprivation, particularly in DQS. When using 660 nm light, the optical response was dominated by changes in absorption due to blood volume and deoxyhemoglobin concentration changes. Therefore, the trace was inverted such that a peak in the signal corresponded to an evoked increase in blood volume/deoxyhemoglobin concentration. We measured the peak and trough components of the response, marked by arrows. The vertical scale bars represent the normalized percent change from the peak during LQS following 2-h sleep deprivation. With longer sleep deprivation, the peak decreased, suggesting a blunted evoked response.

Future studies must reduce the variability in the hemodynamic signals to allow further assessment of extended neural use and sleep deprivation across all states, including wake and REM. Modifying the stimulation paradigm could produce more robust hemodynamic responses and enhance signal-to-noise ratios. With further miniaturization of the headstage, currently in progress, such studies could be less labor-intensive and the number of animals could be increased. These results could lead to additional studies into novel mechanisms of sleep control and be incorporated into theories of sleep regulation which propose more localized control over sleep states within the cortex (Krueger et al., 2008; Rector et al., 2009a). For example, if limits to blood delivery could lead to metabolic deficiency, then local sleep maybe required to restore vascular compliance and resources to the tissue.

Conclusion

The present study provides preliminary evidence for a novel mechanism in the control of sleep. If high basal neural activity during wake can cause vessels to approach their limits in blood delivery due to stretching and low compliance, sleep may serve as a mechanism to circumvent tissue damage associated with metabolic deficit. Furthermore, sleep deprivation puts additional strains on the system and longer sleep bouts may be

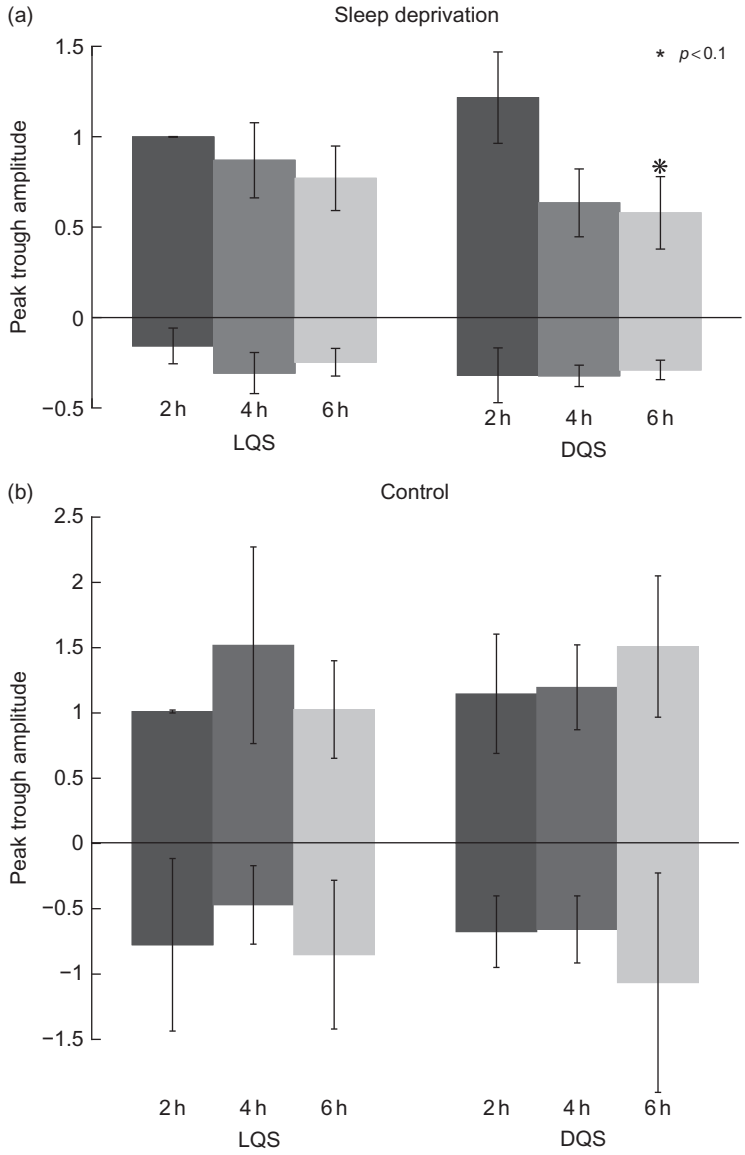

Fig. 7. The peak and trough mean amplitude and standard error of the vascular response was measured from four animals during light quiet sleep (LQS) and deep quiet sleep (DQS) for the first hour recovery period following 2, 4, or 6-h sleep deprivation (a). There was a trend for the response to be smaller during LQS with increased sleep deprivation; however, due to small signal-to-noise, the differences were not significant. During DQS, the peak amplitude significantly decreased in 6-h deprivation compared to 2-h deprivation. A mean decrease was also observed after 4 h of sleep deprivation, but again, the variability was too high to reach significance. Significant changes are denoted with *($p<0.1$; Mann–Whitney *U*-test). (b) The peak and trough mean amplitude and standard error of the vascular response from a no deprivation control condition during the same recovery time periods as the 2, 4, and 6-h deprivation data. The peak and trough amplitudes did not significantly differ, suggesting no time-of-day effect on the vascular response.

needed for the restoration period (Friedman et al., 1979). Chronic sleep restriction, deprivation, and other sleep pathologies may be consequential to the limits of the cerebral vasculature over the long term and lead to processing deficits, performance impairments, and tissue damage.

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Abbreviations

BOLD	blood oxygen level-dependent
DQS	deep quiet sleep
ECG	electrocardiographic activity
EEG	electroencephalographic activity
EMG	electromyographic activity
ERP	evoked response potential
FFT	fast Fourier transform
fMRI	functional magnetic resonance imaging
LED	light emitting diode
LQS	light quiet sleep
NIRS	near infrared spectroscopy
OSA	obstructive sleep apnea
PET	positron emission tomography
REM	rapid eye movement

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