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Physiological Markers of Local Sleep

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Abstract

Substantial evidence suggests that brain regions that have been disproportionately used during waking will require a greater intensity and/or duration of subsequent sleep. For example, rats use their whiskers in the dark and their eyes during the light which manifests as a greater magnitude of electroencephalogram (EEG) slow wave activity in the somatosensory and visual cortex during sleep in the corresponding light and dark periods respectively. The parsimonious interpretation of such findings is that sleep is distributed across local brain regions and is use-dependent. The fundamental properties of sleep can also be experimentally defined locally at the level of small neural assemblies such as cortical columns. In this view, sleep is orchestrated, but not fundamentally driven, by central mechanisms. We explore two physiological markers of local, use-dependent sleep, namely, an electrical marker apparent as a change in the size and shape of an electrical evoked response, and a metabolic marker evident as an evoked change in blood volume and oxygenation delivered to activated tissue. Both markers, applied to cortical columns, provide a means to investigate physiological mechanisms for the distributed homeostatic regulation of sleep, and may yield new insights into the consequences of sleep loss and sleep pathologies on waking brain function.

Keywords

Evoked Response Potential; Model; Homeostasis; Optical; Hemodynamic Response

Introduction

Natural rhythms in sleep propensity are easily observed in most animals that exhibit consolidated sleep and waking periods. Under normal conditions, these cycles appear as a regular pattern and can be modeled on the basis of two processes: a homeostatic drive for sleep that builds up during wakefulness and dissipates during sleep; and a near-24-hour oscillatory, circadian rhythm that interacts with it. The two-process model (Borbély, 1982; Daan et al., 1984; Borbély and Achermann, 1999) provides a sound platform for making predictions about the timing and duration of sleep under normal night conditions and following sleep deprivation. However, the two-process model does not provide information about underlying sleep mechanisms or sleep functions. Investigations and modeling of sleep control at a more mechanistic level are needed. We posit that basic sleep control mechanisms exist locally within individual neural assemblies throughout the brain, and that specific electrophysiological and metabolic markers can be used to assess the local state of the tissue.

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Mechanisms of Sleep Regulation

Circadian mechanisms involved in sleep regulation have been studied in great detail (for reviews see Silver and Lesauter, 2008; Turek, 1994; Kolker and Turek, 1999). They involve the near-24-hour cyclic suprachiasmatic nuclei (SCN) influence as driven by daily rhythms in clock gene expression. The mechanisms that underlie the homeostatic component of the two-process model are beginning to be understood at a biochemical level (Krueger et al, 2008), and are affected by a wide range of variables such as food and water intake, gender, immune and stress status, activity levels, etc, many of which influence duration and intensity of sleep for several days. Several measures correlate with homeostatic sleep pressure, including sleep latency, electroencephalogram (EEG) slow wave activity (SWA), brain metabolic levels, and cognitive task performance. SWA is measured by recording the amplitude of 0.5 to 4 Hz EEG oscillations (delta waves) and has been used as an index of non-rapid eye movement (non-REM) sleep intensity. Energy balance (Vanitallie, 2006) and changes in synaptic strength (Tononi and Cirelli, 2006) have also been linked to sleep homeostasis. However, none of these parameters provide a direct causal mechanism for the occurrence of sleep in the brain, although some biochemicals involved in sleep regulation promote sleep (Krueger et al., 2008). A more in-depth understanding of the underlying mechanisms for sleep and sleep homeostasis would significantly advance our knowledge of sleep function and control.

Not only has the sleep field lacked a full understanding of the basic sleep control mechanisms, it has also lacked a clear definition of what it is that sleeps. Prevailing theories about sleep homeostatic components rely on time-dependent or use-dependent processes such that the longer an animal remains awake or the more intense the activity, the more sleep it will need (Feinberg, 1974; Franken, 2007). Additionally, sleep is currently defined in terms of whole animal behavioral state, in spite of mounting evidence that aspects of sleep can be observed in something less than the whole animal; including unihemispheric sleep, regional increases in SWA depending on prior use, and sleep patterns present in any living brain, no matter how badly damaged (reviewed in Krueger et al., 2008). For example, dolphins exhibit high amplitude EEG delta waves characteristic of non-REM sleep unihemispherically, suggesting that they may sleep in one hemisphere at a time (Mukhametov et al., 1977). However, each hemisphere contains essentially all the components of the whole brain and unihemispheric sleep could therefore involve the same centrally controlled sleep regulatory mechanisms. In contrast to unihemispheric sleep, locally altered sleep is fundamentally more difficult to explain in terms of central mechanisms, because not all components/nuclei are duplicated at the local level.

Strong evidence supports that notion that a part of the brain that is disproportionally used during wakefulness may require more sleep because use-dependent local increases in SWA have been observed in several mammalian species (reviewed in Krueger et al., 2008). In humans, sensory stimulation of one hand increases EEG slow waves in the opposite hemisphere during subsequent sleep (Kattler et al., 1994). A learning task involving a circumscribed brain region produces local increases in SWA during sleep (Huber et al., 2004). In contrast, if an arm is immobilized during the day and motor performance deteriorates, both somatosensory and motor evoked potentials decrease over the contralateral sensorimotor cortex and SWA over the same cortical area is markedly reduced (Huber et al., 2006). Similarly, during sleep, SWA is greater in the somatosensory cortex of rats during the dark period when they use their whiskers more, and greater in the visual cortex during the light period when they use their eyes more (Yasuda et al., 2005). Rats that use one paw more than the other during the wake period exhibit greater SWA in the contralateral hemisphere during sleep (Vyazovskiy and Tobler, 2008), a phenomenon which is even more dramatic during different developmental stages (Miyamoto et al., 2003). While SWA has been a useful measure of homeostatic regulation in mammals, SWA generation requires synchronization of large cortical regions. In order to

extend the definition of sleep to include small neural assemblies (such as cortical columns), or in organisms that do not have a cortex, we need to define other measures. For example, we focused on the input/output relationships of cellular groups by stimulating the system and observing the output responses.

Defining what sleeps

Most studies focus on sleep as a whole animal property because sleep is traditionally defined in terms of whole animal behavior and/or electrical markers measuring activity of the whole brain and body. However, since some aspects of sleep manifest as something less than the whole animal or brain, it has become important to define the minimal component of the brain that can exhibit the contrasting states of sleep and wake. While individual cells and single cell organisms demonstrate aspects of rest/activity cycles perhaps related to sleep, it has been difficult to frame the current sleep paradigms in the context of single cells because it is not yet possible to causally link single cell activity to whole animal behavior in mammals. The next level up in neural complexity from the single cell is represented by assemblies of neurons (e.g., small brain nuclei, individual cortical columns) which exist as highly interconnected groups of cells that are believed to constitute the basic units of information processing (Koch, 2004; Panzeri et al., 2003). We hypothesize that the fundamental level at which sleep occurs is within these neuronal assemblies. Since the cortical surface is accessible by a variety of invasive and non-invasive techniques we have focused our studies on cortical columns.

In the predominant view of sleep regulation, sleep is imposed on the animal by sub-cortical structures in a centrally directed manner. However, this idea invokes issues of infinite regress, or a fundamental question of what tells the sub-cortical structures that sleep is required. In Saper's flip-flop, bistable sleep-switch model, homeostatic input to the ventro-lateral preoptic nucleus (VLPO) may provide the required input; however what "homeostatic input" is or where it comes from is not specified (Saper, et al., 2005). Our studies show that the homeostatic input can be biochemically defined, and comes from multiple neuronal assemblies sending their inputs to the VLPO (Yasuda et al., 2007). We hypothesize that whole organism sleep is an emergent property of the collective neuronal assemblies, and that a sleep-like state can be initiated independently within each assembly. Since networks of neuronal assemblies are coupled, they will tend to synchronize (Strogatz, 2003; Manoranjan et al., 2006; Roy et al., 2007). As such, when a significant number of neuronal groups enter the sleep state, other groups will follow suit. This emergent property of state synchronization of multiple neuronal assemblies represents whole animal sleep. Such an emergent whole animal state would not require any central regulatory control for its existence; although, central regulatory control of its timing could enhance its evolutionary fitness.

While there is no question that sub-cortical mechanisms can influence sleep in a top-down fashion, understanding what drives these systems to affect sleep remains limited. Central regulatory control may serve to consolidate sleep into ecological niche-appropriate, consolidated sleep/wake periods; sub-cortical structures such as the SCN, lateral hypothalamus and VLPO might consolidate sleep into contiguous blocks of time, without numerous unwanted state transitions (Saper et al., 2005). Sub-cortical structures may also serve to time sleep to periods when the animal is not disadvantaged by being asleep. They may further serve to avoid mixed whole animal states with only portions of the neuronal networks being awake. By inhibiting arousal systems (Szymusiak and McGinty, 2008; Saper et al., 2005), they may prevent the animal from behaving at a time when some of its neuronal groups are in the sleep-like state. In fact, such phenomenon may be evident when normal sleep is disrupted, either by pathological conditions (Mahowald and Schenck, 2005), or by restricted sleep. Thus, local sleep mechanisms can provide a framework for conditions associated with sleep disturbance or with performance variability associated with sleep loss (Doran et al., 2001).

From an evolutionary point of view, activity dependent rest cycles appear in many types of neuronal assemblies in general and not just mammalian cortical columns. Considering that single celled organisms and primitive animals such as sponges (Amano, 1986), jellyfish (Kavanau, 2006) and *Drosophila* (Cirelli and Bushey, 2008) show behavioral and biochemical correlates of sleep, the principles of sleep homeostasis are not unique to those animals with a cortex. Additionally, cortical EEG activity (as a correlate of sleep) does not have to be regulated centrally since cortical columns can produce delta rhythms in isolation, whether as cortical islands (Kristiansen and Courtois, 1949), or in slices (Steriade, 2003).

Fundamentally, the mechanisms of sleep homeostasis may reside in any neuronal assembly within the brain; however, these brain units must demonstrate established properties of sleep such as homeostasis and use-dependence, in a similar manner as the whole animal and larger cortical regions (Krueger and Obál, 1993). In order to explore mechanisms of localized sleep within neuronal networks, we have examined cortical columns, which are experimentally accessible and thus are useful for investigating the electrophysiological and metabolic consequences of activity in the brain. Several investigators have demonstrated how electrical (e.g. Weitzman and Kremen, 1965; Hall and Borbély, 1970; Velluti, 1997) and hemodynamic (e.g., Braun et al., 1997; Drummond et al., 2005) measures change across whole animal sleep and waking, but a detailed look at these measures within individual cortical columns has yet to be fully explored.

The functional connections between cells within a cortical column are much denser than connections between columns, thus we would expect greater synchrony of activity and state between cells within a column (Panzeri et al., 2003). Under normal conditions, we would not expect cortical columns to sleep much in isolation, and indeed, our measurements support this idea (Rector et al., 2005). The farther removed two structures are in space and connectivity, the less likely they exhibit synchronous states. Thus, different functional brain regions might be more asynchronous (e.g. somatosensory vs visual), and show stronger differences in sleep-like behaviors. We focused on cortical columns because they represent a basic unit of information processing, and thus the smallest functional unit that might independently exhibit sleep-like states if driven individually. The same holds for other neuronal assemblies, but cortical columns are the most suitable for theory development and measurement because they are easily observable through evoked responses and local blood volume regulation. While the full temporal structure of the evoked response is ultimately generated by more components than a single cortical column, we focused specifically on the P1/N1 components which arise largely from the initial activation of specific pathways from the sensory system (Panzeri et al., 2003). Since we implanted high density cortical ECoG arrays over the somatosensory cortex, we were able to create electrical maps of the cortical surface that allowed us to visualize individual cortical column activation by localizing the P1/N1 potentials with high resolution (Hollenberg, et al., 2006; Topchiy et al., 2009). In order to emphasize the differences between columns, we used two whiskers that were separated in space by at least one column, which also allowed easier distinction between columns.

Assessment of state

There are several passive and active methods to assess the state of an organism. Passive measurements include observing the organism for characteristic postures; typically, a sleeping animal is recumbent and inactive. For most animals, characteristic EEG and electromyogram (EMG) patterns appear during sleep, and there are other characteristic, measurable changes: the body temperature drops, a variety of different genes are expressed and chemicals are produced, metabolism decreases, and correlates of metabolism (such as blood flow and volume) change. We have recently shown that population action potentials can be recorded with EEG and ECoG electrodes (Rector et al., 2009), thus when the cells within the column

are in their “up” or depolarized state, they produce more spontaneous action potentials which can be measured as an increase in the high frequency power of the signals recorded from the electrode. We are also developing a new optical probe that will spectroscopically assess hemodynamic parameters over long time periods enabling us to find local shifts in blood volume, flow or oxygenation that are state related.

Active state measures can also be used, but they have the potential for altering the state being measured. For example, arousal thresholds have been used as an index of sleep depth, but the arousals themselves induce a transition toward wakefulness. If the cortical columns are otherwise silent, one of the only ways to determine the state of the cells within the column is to probe it with an input stimulus, and measure the output. Thus, the electrical state of neurons may be altered during sleep such that when probed with external stimuli, they will provide a different response. Additionally, if the neuronal electrical state is altered during sleep, then the neurovascular coupling might also be different, and a given stimulus may provide a different evoked blood flow or volume change during sleep compared to waking. Active methods to assess state require that the system be probed with a stimulus, and the resulting output from the same stimulus be different depending on the state of the system. At the whole organism level, we define sleep and wake states in part by different outputs elicited by an input. For example, when asleep, the animal does not respond to a given stimulus. Similarly, we may use this feature to define local sleep, requiring that the output changes locally in response to a probing input stimulus. At a neuronal assembly level, we propose to use such a definition of sleep.

Electrophysiological Markers

A close look at the structure of the cortex reveals clusters of highly interconnected cells grouped into cortical columns. Each column responds to specific external stimuli, as evidenced by generating an electrical evoked response tied to the input signal. The evoked response, as measured by EEG, local field potential (LFP) or electrocorticogram (ECoG) electrodes, consists mostly of populations of synchronized synaptic potentials that sum as a consequence of many hundreds or thousands of cells being simultaneously active. The temporal structure of the evoked response waveform is determined by a number of factors including the strength of the stimulus, other ongoing activity, the resting membrane potential, the number of cells that respond, and their responsiveness (e.g. receptor populations).

When stimuli are provided during non-REM sleep states, as defined by traditional whole animal metrics such as EEG delta power and EMG amplitude, we and others observed that the average evoked responses are higher, with longer latency, than those observed during waking or REM sleep (Hall and Borbély, 1970; Velluti, 1997; Rector et al., 2005). We posit that one could use the size and shape of the evoked response to assist in determining sleep state (Figure 1). By utilizing a basis-decomposition fitting function (Kisley and Gerstein, 1999; Rector et al., 2009), the temporal components of each evoked response can be identified and tracked over time. A detailed examination of individual evoked response potentials shows a large amount of trial-to-trial variability in the size and shape of the response to any given stimulus (Rector et al., 2005). While the average evoked response demonstrates a significant state dependence, individual evoked responses may be large or small in any whole animal state, although they are usually large during sleep, and usually small during waking and REM (Figure 2). While some of this variability may result from ongoing EEG fluctuations, we found that the size of the evoked response is also use-dependent (Rector et al., 2005). Since a wake-like column state can be observed during whole animal sleep and conversely that a sleep-like column state sometimes occurs during whole animal waking, our data suggest that sleep is a fundamental property of the column, and modulated by the local column state.

When two whiskers of a rat are repeatedly stimulated in an identical manner (Rector et al., 2005), they produce identical evoked response potentials (ERPs) on average, but different individual response profiles over time (Figures 2 and 3). During whole animal waking, at least part of this variability may be explained by surrounding ongoing activity that could interfere with accurately measuring the response characteristic (Arieli et al., 1996); however, when stimuli are presented during brief periods of relatively flat EEG, regardless of whole animal sleep state, we still observe high variability in individual evoked responses. Given identical input stimuli, if we accept that the large amplitude ERP is the output produced by a cortical column in its sleep-like state, and the low amplitude ERP is produced by a cortical column in its wake-like state, then we can perform specific experiments to test the cellular mechanisms that underlie the differences in the ERP size. In this manner we found that the ERP size shows use dependence such that the longer a cortical column produces low amplitude wake-like ERPs, the more it will begin to produce large amplitude sleep-like ERPs, irrespective of whole animal state (Rector et al., 2005). Additionally, the ERP size can be modulated by sleep regulatory substances such as tumor necrosis factor (TNF) (Churchill et al., 2008), in congruence with the local sleep states these substances should induce. Thus, ERP amplitude may provide a marker of the local state of an individual cortical column.

Since the pathway between the rat whisker follicle and the whisker barrel cortical columns is well understood, a detailed look at stimulus responses along the pathway provided some clues about the origin of the ERP variability observed in the cortex. When depth electrodes were implanted into the thalamic region that projects to the whisker barrel (cortical column) receiving input from the whisker being stimulated (Rector et al., 2004), we were able to record local field potentials arising from neural structures that provide input to the cortex (Figure 4). Thalamic local field potentials exhibit much less variability than cortical evoked responses; therefore, we assume that the variability observed in the cortical columns must arise from processes within the cortex, or processes in thalamo-cortical communication. Since cells in the cortex exhibit synchronous depolarized and hyperpolarized (up and down) fluctuations in membrane potential during slow wave EEG (Steriade et al., 1993), it is possible that the up and down membrane potential states might correspond to the low and high amplitude evoked responses, and thus may also correspond to the wake- and sleep-like states within the cortical column (Massimini et al., 2003; Rosanova and Timofeev, 2005; Rector et al., 2009). Thus, during non-REM sleep, each slow wave may indicate that the cortical column is fluctuating between sleep- and wake-like states.

Metabolic markers of local sleep

If the homeostatic component of sleep depends at least in part on energy and resource utilization and recovery of those resources, then changes in blood delivery may be involved. A number of positron emission tomography (PET) and functional magnetic resonance imaging (MRI) studies have shown increased blood flow and volume through increasing vessel diameter and compliance to a part of the brain that is used more (e.g. Logothetis and Wandell, 2004; Stephan et al., 2004). Since each cortical column is supplied by its own bed of capillaries which are tightly regulated by activity within the column (Jones et al., 2008; Devor et al., 2005; Filosa and Blanco, 2007), we might expect localized differences in hemodynamic measures in tissues to reflect use-dependent activity levels, and this could yield a measure of use dependence.

By implanting light emitting diodes and photodiode detectors over the rat cortex, we measured the consequences of sleep on neurovascular coupling as recorded using light absorbance correlates of blood volume. This technique is similar to pulse oximetry used to assess relative oxy- and deoxy-hemoglobin levels from skin. When a whisker was stimulated, or an auditory click was given to an animal, the cortex generated an electrical evoked response and a corresponding optical absorption change, the latter presumably in response to the increased

demand for blood and metabolic substrates. On a larger scale, metabolism within the cortex decreases during quiet sleep (Braun et al., 1997). We observed a dynamic state dependent hemodynamic change in the auditory cortex that was largest during quiet sleep, and smaller during waking and REM (Schei et al., 2009). While our initial measurements have established that hemodynamic changes occur over the auditory cortex using a single photodiode, further studies are required to establish state dependent local control of blood volume and oxygenation (Figure 5).

The larger evoked changes in blood volume during quiet sleep demand further investigation because there are several potential mechanisms that could underlie these observations, and distinguishing them is critical for our understanding of state dependent neurovascular coupling. First, the larger blood volume response during quiet sleep may simply reflect an increased demand for metabolites to support the increased depolarization associated with the larger evoked response described above. Yet, if all input to the cortex during sleep initiated a larger blood volume response, then we would not expect total metabolism and blood volume to be lower during sleep. Since all well characterized sleep regulatory substances (SRS, i.e. adenosine, nitric oxide, interleukin 1, TNF and prostaglandins) are cerebral dilators yet they all enhance sleep, we might expect increased blood volume in the brain during sleep. Indeed, SRS involvement with the responses we observed is consistent with the SRS literature; however, we cannot as yet explain why whole brain metabolism and blood volume appear to decrease during sleep. Second, sensory stimulation during sleep could elicit a similar blood volume response as during wake, but arising from a lower baseline level. This mechanism would parallel previous observations that baseline blood volume and flow are lower during sleep. Third, there could be a fundamental difference in the compliance and responsiveness of the vasculature to metabolic demand during sleep which is modulated by cortical column activity and is use-dependent. Fourth, glia outnumber neurons by about 10:1; small corresponding reductions in their metabolism during sleep would have a large effect on whole brain metabolism. Nonetheless, the hemodynamic response may provide another marker of use dependence and local sleep states within cortical columns.

Conclusions

The electrical and optical measures of neuronal assembly state described here may provide markers of the local sleep/wake state of the tissue. Of particular interest is the potential to use information about the level of activity the tissue has maintained in the past to make predictions about performance in the near future. From this, we may be able to predict whole organism homeostatic sleep drive, and ultimately forecast whole organism sleep/wake state changes. This would not only have important theoretical value, but might also have practical implications, such as gaining the ability to anticipate and prevent people falling asleep while driving.

The markers of local sleep described in this manuscript provide a path to make specific predictions about the use-dependent behavior of cortical columns, which can be experimentally tested. For example, if one whisker is stimulated more often than another whisker, then we expect subsequent evoked responses to be larger (i.e., indicative of sleep) for the corresponding cortical column that was the more active. Conversely, the performance of an animal on a given task that depends on the cortical column at hand should vary with the size of the evoked response generated during the task, such that the animal should perform poorly when the cortical column is in its large amplitude ERP, sleep-like state. Our preliminary studies (Walker et al., 2005) suggest that animals make more mistakes in a performance task when the cortical column produces a large (sleep-like) evoked response. Humans may show a similar phenomenon in the form of wake state instability (Doran et al., 2001), a phenomenon seen

under conditions of sleep deprivation and unexplained by bistable central regulatory mechanisms (Saper et al., 2005).

Some key experiments must be performed to link sleep homeostasis to the markers of local sleep described here. First, several reports have connected large ERPs to the hyperpolarized (down) membrane potential state and small ERPs to the depolarized (up) state of cells in the cortical column (Steriade et al., 2001; Rosanova and Timofeev, 2005); however, further intracellular measurements are required to confirm that this relationship is maintained in the unanesthetized animal progressing through natural sleep and waking states, and that the local depolarized and hyperpolarized states of cells within a cortical column are use-dependent. Since the delta rhythm is characterized by fluctuations between the depolarized (up, or wake-like) and hyperpolarized (down, or sleep-like) states, we posit that if the cells never entered the depolarized state, then they could not process incoming information. Second, we hypothesize that the large amplitude ERP, hyperpolarized state is less metabolically demanding. Further experiments are required to link changes in vascular coupling to the changes we observed in the evoked response and metabolic demand. Thus, when a group of cells within a cortical column is active to the point that some of its resources are depleted, then the cells within that column may enter the hyperpolarized state to conserve and/or replenish resources.

This latter idea leads to a new hypothesis: when the demand for metabolites exceeds the ability of the vasculature to supply the demand, then the cortical column enters the sleep-like state. While resource depletion and limited vascular supply have never been experimentally demonstrated in an intact, freely-behaving and fully functioning animal, we believe that the hyperpolarized, sleep-like state may serve as a protection mechanism to reduce the possibility that cells within the column experience a severe limit in resources in a similar way that muscles fatigue before metabolic resources become limited (Enoka and Duchateau, 2008).

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Abbreviations

ECoG, Electrocorticogram
 EEG, Electroencephalogram
 EMG, Electromyogram
 ERP, Evoked Response Potential
 LFP, Local Field Potential
 MRI, Magnetic Resonance Imaging
 PET, Positron Emission Imaging
 REM, Rapid Eye Movement
 SCN, Suprachiasmatic Nucleus
 SRS, Sleep Regulatory Substance
 SWA, Slow Wave Activity
 TNF, Tumor Necrosis Factor
 VLPO, Ventro-Lateral Preoptic Nucleus

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Figure 1.

Typical evoked electrical responses (ERP) to auditory clicks in the rat. ERPs for wake, quiet sleep, and REM were averaged across stimuli and plotted across time (thick black lines). The gray regions illustrate the standard deviation from 100 trials. The vertical line represents the time of the stimulus. The ERP amplitude, measured from the first peak to the first trough, was significantly larger during quiet sleep than during both wake and REM.

Figure 2.

Temporal changes in the amplitude of event-related potentials. Animals were presented with single auditory clicks randomly at intervals from 2 to 3 seconds and the size of each individual evoked response was measured and plotted across time (~10 minutes of data from one rat are shown here). The dark gray trace shows an 8 point moving boxcar average over time, while the black trace shows the data smoothed with a 50 point moving boxcar average to illustrate the evoked response amplitude trend over time. The horizontal line represents the average response from all trials in the period. When the animal was awake (white background), the evoked response usually exhibited low amplitude. When the animal was in quiet sleep (gray background), the evoked response usually showed high amplitude. However, across time, the evoked response was highly variable, sometimes of high and sometimes of low amplitude.

Figure 3.

Comparison of evoked response potentials from adjacent whisker barrels. When two rat whiskers were simultaneously stimulated, two evoked responses were generated over the corresponding whisker barrel cortical columns in the cortex. The average traces (top) showed that the evoked responses were almost identical on average, but the individual trials showed large variability both among trials (downwards) and between the two different whiskers (left traces vs. right traces).

Figure 4.

Comparison of variability in a cortical column and its associated thalamic region. Evoked electrical responses from the rat whisker barrel cortical columns in the cortex (left panel) showed much higher variability than local field potentials recorded from the corresponding thalamic region that projects to the respective cortical column (right panel). The thick black line represents the average of all responses and the traces with varying shades of gray are the individual responses. Each response was generated by identically deflecting the rat whisker by 1mm in 0.2ms. The stimulus time is indicated by the vertical line.

Figure 5.

Averaged evoked optical (lower panel) and electrical (upper panel) responses to a 10 Hz burst of five auditory clicks across wake, quiet sleep, and REM sleep. The responses showed significantly larger hemodynamic optical changes (as recorded by changes in 660 nm light absorption) during quiet sleep than during wake and REM. The electrical evoked responses followed a similar state-dependent trend as shown in Figure 1. The vertical scale bar indicates percent change from baseline, pre-stimulus conditions. An upward deflection in the evoked optical signal corresponded to a decrease in backscattered light, an increase in 660 nm light absorption, and an increase in deoxyhemoglobin and blood volume. Note the time scale differences between the electrical and optical plots. The five thin vertical lines correspond to each of the five auditory clicks.