

NEUROIMAGING IN SLEEP RESEARCH WORKSHOP
MARCH 29-30, 2006
SUMMARY

BACKGROUND

The National Heart, Lung, and Blood Institute, the NIH Office of Rare Diseases, and several member Institutes and Centers of the Trans-NIH Sleep Research Coordinating Committee convened a Conference of experts in both neuroimaging and in sleep disorders to assess the current state of knowledge, identify gaps in our understanding of how neuroimaging can be best utilized to identify and test critical hypotheses to advance sleep research, and to provide recommendations for future collaborative and interdisciplinary research opportunities.

DISCUSSION SUMMARY

Quantitative neuroimaging can provide in vivo evidence for brain structural, biochemical, and functional mechanisms. Neuronal mass and integrity can be indexed with in vivo magnetic resonance imaging (MRI) measures of gray matter volume and proton MR spectroscopy (MRS) with measures of N-acetylaspartate (NAA), a marker for living neurons. Connectivity requires the integrity of white matter tracts within cortex and from deep brain structures and can be indexed with Diffusion Tensor Imaging (DTI).

Neuroimaging studies to date have revealed some distinct patterns associated with sleep and sleep deprivation, including altered local blood flow in rapid eye movement (REM) and non-REM (NREM) sleep compared to wakefulness. Neuroimaging techniques have only recently been used to analyze a range of sleep functions. Electroencephalography (EEG) and electromyography (EMG) signals, for example, can detect different stages of sleep and can follow NREM stages as well as REM cycles across the night, with durations that are longer and more phasic. However, many neuronal groups involved in sleep regulation are below the spatial resolution of typical neuroimaging techniques. Continuous wave optical approaches such as Near-Infrared Spectroscopy (NIRS) and Diffuse Optical Tomography (DOT) enhance temporal and spatial resolutions and can be combined with other measures to evaluate functional information in sleep and sleep disorders.

Basic science investigations and correlative studies using positron emission tomography (PET) and polysomnography (PSG) are beginning to reveal some of the neurochemical changes that may be responsible for sleep related movement disorders, particularly REM Behavior Disorder (RBD) in both animal models and human studies. RBD is characterized by loss of normal voluntary muscle atonia during REM sleep and is thought to be associated with individuals physically acting out their dreams. PET has also been used to assess NREM sleep in relation to waking. The findings indicate a relative decrease in metabolism in the prefrontal cortex during typical sleep. The prefrontal cortex appears to be less deactivated during sleep in those affected by insomnia, aging, and depression suggesting a potential association with local mechanisms regulating sleep and sleep homeostasis.

Global spatial organization of activity patterns in the deep brain and during different stages of sleep is not well understood but imaging techniques such as functional MRI (fMRI) promise to provide useful information. However, the signature of specific sleep-related local field potential (LFP) patterns—like spindles reflected in BOLD (blood oxygen level-dependent)—remain elusive. BOLD strength may correlate better with inputs and intracortical processing rather than with spiking activity. Patterns of BOLD activity may reflect different states of sleep.

Recent studies using high-density EEG illustrate that slow oscillations characteristic of NREM sleep behave as traveling waves and occur hundreds of times each night. The study of such waves should further the understanding of sleep disturbances as well as related neurological and psychiatric disorders. Studies using high-density EEG demonstrate that slow-wave sleep homeostasis associated with plasticity is increased by wake-related induction of synaptic potentiation in local cortical circuits as well as by transcranial magnetic stimulation (TMS) potentiation of local synaptic circuits. EEG, in combination with TMS, has provided evidence that brain region connectivity is dramatically different in waking and sleep states. Specifically, pathways linking cortex and lower brain regions are effectively weaker during sleep.

Comparative studies in multiple species suggest that the functional changes in connectivity during sleep have significant implications for brain tissues generally. For instance, genes that are upregulated during prolonged sleep loss are also related to cell stress response, autoimmune response, and glial dysfunction.

Considering the range of available neuroimaging methodologies, fMRI appears to be the most widely used modality for functional brain imaging because it is noninvasive, widely available, and provides good spatial and temporal resolution. In addition, fMRI is also well suited to studies of sleep since it can compare resting and activated CBF (cerebral blood flow) related to cognitive mapping. Most fMRI has been carried out using BOLD contrast, which is best suited for studying functional connectivity analysis to detect regional changes with task performance. Another technique—direct quantification of CBF using arterial spin labeled (ASL) perfusion fMRI—is best suited to resting studies of physiological and behavioral states and has greater reproducibility across subjects and time. The two techniques offer complementary benefits; BOLD is best for localization of short-term events, while ASL is best for long-term longitudinal studies.

The working group determined that while there are many areas in which current neuroimaging methodologies can be helpful in furthering sleep research, the major challenge is in determining how brain areas communicate during sleep and wakefulness. Inter-disciplinary efforts involving both neuroimaging and sleep researchers are necessary to juxtapose the scientific opportunities presented within each discipline.

RECOMMENDATIONS

- Consider options for development of a ‘Sleep Atlas’ imaging resource to facilitate temporal and spatial comparisons of normal waking and sleep, and to assess the effect of factors such as age and cortical thickness across the entire lifespan. The resource would also facilitate functional imaging studies of those with sleep disorders and identifying the most important biological differences. This would be a significant improvement over existing neuroimaging atlases which consider population variation but not sleep-wake differences in function.
- Use functional imaging techniques to investigate how sleep changes brain activity across sleep stages, in sleep disorders, and the effect of pharmaceuticals on sleep and sleep deprivation.
- Use the speed of ocular motor changes associated with sleep changes as a model in which investigate the sleep associated changes in neurobiological function. Noise, motion, and body posture would be factors to consider in this analysis. For example, lying down may initiate changes in function that are distorted during sleepiness, while the speed of acquiring images and cognitive variables may be variables reflecting individual differences in the response to sleepiness. Imaging techniques used in such studies over time, could be coupled to changes in gene expression observed in such models.
- Use basic science approaches to elucidate the neurological mechanisms underlying altered connectivity between brain regions during sleep and wakefulness.
- Develop neuroimaging strategies capable of elucidating the temporal progression of functional brain changes accompanying the sleep/wake process, the homeostatic pressure to sleep, and the restorative functions of sleep in brain.

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NHLBI website and publication

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