The Brain That Never Fully Sleeps

... and the body's consequences

Sleep is a process that takes place in the brain. When you are asleep, it is commonly assumed that your whole brain is deep in slumber, but is this really the case?

James Krueger, Ph.D., of Washington State University in Pullman, points out situations in which people appear to be awake and asleep at the same time. Sleep walking is a clear example. "These individuals are awake (evidenced by their ability to negotiate around objects) and asleep simultaneously," says Krueger.[1]

Dolphins present another interesting example of sleep and wake occurring at the same time. "One side of the brain sleeps while the other side remains awake," says Krueger, adding that sleep is not a "whole brain" phenomena.

Many fibromyalgia (FM) patients describe their sleep as light and unrefreshing. Others state that they seem to have one leg in sleep and the other leg out of it at night ... sort of like being half asleep or half awake. Based on Krueger's research and his lecture at the annual SLEEP 2008 meeting, this analogy may be true. Also, your inability to obtain deep, restful sleep likely explains other symptoms besides being fatigued, achy, and brain-fogged during the day.

One Eye Open

The concept that sleep is a "whole brain" phenomena, meaning that all of the brain cells are asleep, probably does not make sense to people with FM. You can lie in bed night after night, feeling that you hardly slept at all. But, perhaps your bed partner or overnight sleep study indicates otherwise. How can this apparent discrepancy occur? The answer has to do with the concept of sleep being a local process of cellular units, called cortical columns. Think of the surface of your brain as being made up of tiny pins, each one extending beneath the surface as columns (see graphic below). The brain is made up of roughly 100,000 cortical columns, with each one consisting of several thousand brain cells that are neurologically linked together. The more cortical columns that are in a sleep state at the same time, the deeper your sleep will likely feel, and it will probably be more restorative as well. But what causes these columns to fall asleep?

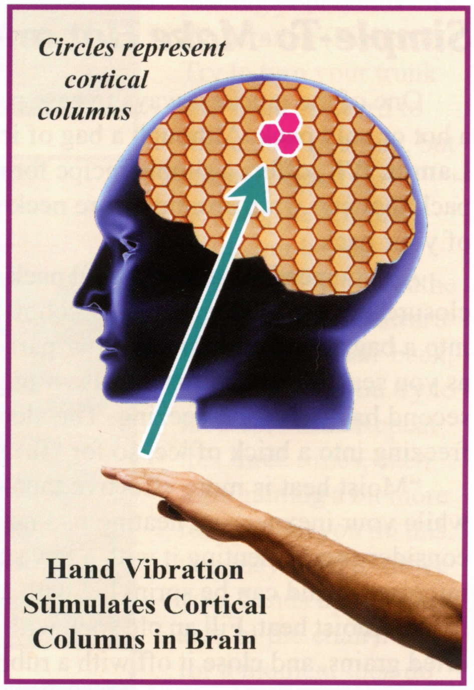
There are a number of sleep promoting substances, but tumor necrosis factor (TNF) is the most thoroughly researched. Injecting a minuscule amount of TNF on a tiny region on one side of a mouse's brain, Krueger measured the brain waves generated by both sides. Very slow brain waves represent deep level sleep. "We observed an increase in slow wave sleep on the side injected with TNF," says Krueger, while the rest of the brain did not enter sleep.

Krueger has also shown that the more active a cortical column is, the more likely it will enter the sleep state. The human body demonstrates this as more activity leads to exhaustion and the desire to sleep. Mice rely upon their whiskers when traveling through dark tunnels. "Each one of these cortical columns corresponds to a single whisker," says Krueger. "You can map this very accurately in mice." What if you stimulate a whisker (painless touch) on one side twice as fast as a whisker on the other side of the face? "The probability of the cortical column entering a sleep state following the rapid stimulation was much higher," says Krueger. The research demonstrates that a cortical column can fall asleep in an otherwise awake animal while not effecting the whole brain. Also, a more active column is more likely to enter sleep first, showing that sleep is dependant on prior activity.

Studies in healthy people have confirmed Krueger's animal findings. Researchers intermittently vibrated the right hand of eight men before bedtime on two of five nights in a sleep lab.[2] The cortical region that corresponded to the right hand entered deep sleep faster and longer on the nights the subjects were given the stimulus (see graphic below).

If activity enhances the odds of cortical columns entering sleep, then inactivity should do the opposite. Following an overnight sleep study, the left arm and hand of 15 healthy subjects was immobilized with a sling for 12 hours.[3] Participants went about their daily activities and returned to the lab for a second sleep study. Comparing the two nights, the amount of deep level sleep on the side of the brain corresponding to the immobilized arm was significantly reduced.

"The idea that sleep is a local process that depends on prior activity allows for parts of the brain to be



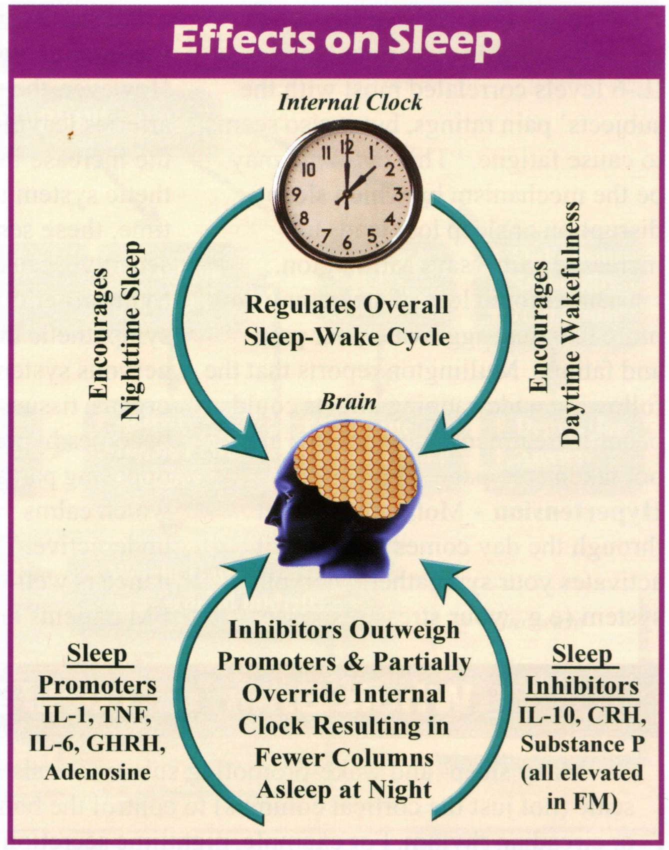
asleep while other parts are awake at the same time," Krueger adds.

A Balancing Act

TNF is just one of many substances that promotes sleep. Adenosine, interleukin-1 (IL-1), interleukin-6 (IL-6), and growth hormone releasing hormone (GHRH) all act on different areas of the brain to enhance deep level sleep. But how do you get these sleeping agents secreted at night when you need them? Based on studies in rats, stimulation of a whisker leads to the production of these substances in the cortical column that receives the stimulus. So more activity or increased neurological signals traveling to the brain's cortical columns during the day will enhance the release of sleep promoting substances at night.

For healthy people who are on the move and exercise vigorously each day, this regulation process helps them drift off into deep snooze-land each evening. Yet, for people with FM, their bodies may feel tired but their brains are wired at the end of the day. Brain imaging studies in FM patients have shown that a large percentage of the cortex is "lit up" or "hyperactive" due to the pain-related signals that bombard the brain day and night.[4] In fact, the greater the hyperactivity of the brain cells, the more severe the patient's pain and other symptoms. This persistent activity, according to Krueger, could try to drive the associated cortical columns into a sleep-like state, even during the day!

Sleep promoters are counterbalanced by sleep-inhibiting substances, such as corticotropin releasing hormone (CRH), substance P, and interleukin-10 (IL-10). Sleep inhibitors may help you stay awake during the day, but if present in high concentrations at night, they will disrupt your sleep (see diagram above).



Studies in FM patients show that their spinal fluid, which bathes the cortical columns in the brain, contains almost twice the normal amount of CRH and three times the usual amount of substance P.[5,6] These concentrations are high around the clock. In addition, a recent report looking at the nighttime ratio of IL-10 to that of the two sleep-promoting cytokines (TNF and IL-1) in people with FM showed that IL-10 was elevated compared to healthy subjects.[7] Ironically, IL-10 works in the body as an anti-inflammatory cytokine to fight pain, while TNF and IL-1 are pro-inflammatory cytokines and they produce more achiness. Although your body may be using IL-10 to stomp out pain, the high levels of IL-10, CRH, and substance P could be keeping you awake at night.

Link to Brain-Fog

Wondering what cortical columns have to do with your clouded thinking? Krueger describes a study in which rats were trained to lick when a single whisker was stimulated, and the error rate of their licking response was measured during the awake and sleep states. "When the rats were awake, they didn't make mistakes," says Krueger. "When the animals were asleep, they had incorrect responses. So the state of the cortical columns matters whether or not the animal makes mistakes."

Putting the animal studies into the context of FM, you likely have too many cortical columns sleeping on the job during the day. This could account for your brain fog and the physical feeling of fatigue. Krueger cautions, however, that these symptom explanations are based on animal studies and human experiments are needed to prove these concepts.

Taking this hypothesis one step further, if too many cortical columns are in the sleep-state during the day, they probably will not go to sleep in the evening. In addition, this could slow down metabolic processes and make you feel sluggish or lethargic. As a result, your brain and your body could be trying to function in a foggy and energy-drained state.

The Consequences

What do chronic illnesses or hectic schedules that short-change sleep do to your body? Partial sleep restriction studies in healthy people are often performed to answer this question. Speaking at the SLEEP 2008 meeting, **Janet Mullington, Ph.D.**, of Harvard Medical School, says, "One of the most striking observations from this research is the continual decline in optimism and sociability throughout the sleep-deprivation period." Fatigue, irritability, and muscle aches also occur and appear to be linked to the production of interleukin-6 (IL-6), a pro-inflammatory cytokine.[9] In fact, IL-6 levels correlated most with the subjects' pain ratings, but it also seems to cause fatigue. "This cytokine may be the mechanism by which sleep disruption or sleep loss leads to increased pain," says Mullington.

But chronic loss of sleep may do more than just aggravate your pain and fatigue. Mullington reports that the following wide-ranging effects could occur if treatment interventions are not taken (see page 15 diagram):[10]

Hypertension - Motivation to get through the day comes at a cost: it activates your sympathetic nervous system (e.g., your stress response mechanism) and this leads to an increase in blood pressure (BP). However, the sensors in the main arteries leaving the heart will detect the increase in BP and tell the sympathetic system to mellow out. Over time, these sensors become less sensitive, causing BP to gradually rise.

Sympathetic Activation - The sympathetic branch of your autonomic nervous system that controls your organs, tissues, and blood vessels becomes hyperactive while the opposing parasympathetic branch, which calms your body, becomes underactive. This sympathetic dominance is well-documented in studies of FM patients and produces many undesirable symptoms (see the January 2009 *Journal* for details).

Weight Gain - Hormones involved in appetite regulation can be altered by sleep. Leptin, which helps control appetite, drops with less sleep. Ghrelin, which stimulates appetite, becomes elevated. This coupled with reduced physical activity results in continued weight gain. As you put on more pounds, activities become increasingly difficult and the battle of the bulge snowballs.

Metabolic Changes - With the aid of insulin produced by the pancreas, cells draw in glucose from the bloodstream to use as fuel, such as powering muscle function. In situations of poor quality sleep, insulin becomes less effective at helping the cells draw in glucose. It is compounded by increased appetite and carbohydrate cravings. As a result, the excess blood glucose is stored as fat around the waist. If the process is not halted, metabolic syndrome develops, which may eventually lead to type 2 diabetes.

Immune Activation - Insomnia patients show an increased production of both TNF and IL-6 during the day. IL-6 is a potent stimulator of C-reactive protein (CRP), a marker of immune activation and inflammation. These immune substances make people feel achy and tired, leading to restricted activity and contributing to weight gain. In turn, these fat cells can become a major source of IL-6 and other inflammatory substances.

Cardiovascular Disease - As you can see from the diagram, all of the factors linked to chronic sleep disruption may enhance your risk of developing hypertension and other cardiovascular diseases.

Whole Brain vs. Local Sleep

Many sleep- and wake-promoting substances also work on a "global" scale (not just the cortical columns) to control the body's sleep/wake cycle or circadian rhythm. For example, nighttime secretion of melatonin and growth hormone releasing hormone (GHRH) are hypnotic, while daytime release of histamine increases alertness.

The individual cortical columns become synchronized or more connected by the control of the body's internal clock mechanisms that keep track of the time of day, sensory input, and mental activity. This is the process that is commonly viewed as the "whole brain sleeps." So while sleep occurs locally in the cortical columns, there are also controls in place that regulate the body's overall sleep-wake cycle.

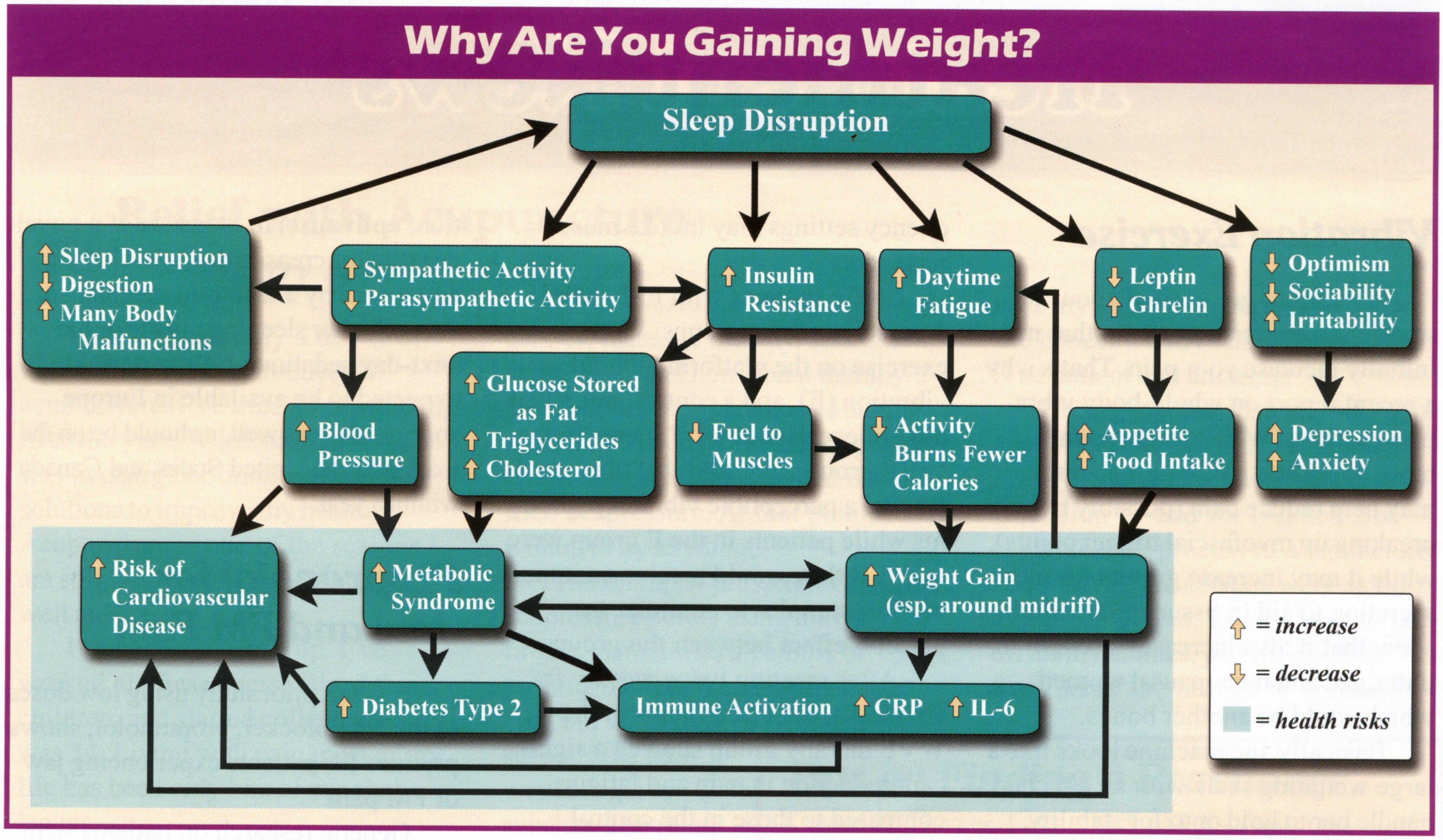
"At the whole-animal behavioral level, sleep functions seem clear; calories are saved, performance is restored, and (in humans) mood becomes more positive as a result of sleep," writes Krueger. "Such findings have led to the universal acknowledgment that sleep restores brain function."[1] He adds that the sleep field is dominated by the theory that the whole brain sleeps under the control of the sleep regulatory circuits, but points out that this theory fails to explain the following:

- In people with Alzheimer's, parts of their brains do not work but nevertheless, they sleep.
- A person who survives the removal of a brain lesion or tumor will sleep.
- Many people have insomnia and clinical conditions that cause symptoms of fatigue or sleepiness.

Referring to the last point, Krueger says the degree of sleepiness may depend upon the proportion of cortical columns that are in a sleep-like state compared to an awake-like state. He also references a study that measured the brain activity of insomnia patients while they were sleeping.[8] "Some areas of the brain show activation that is characteristic of waking while simultaneously other areas show the reduced activity that is characteristic of sleep," says Krueger. Indeed, the researchers found that the amount of time spent awake at night correlated with increased activity in 12 areas scattered throughout the brain.

Fibro Studies

How likely is it that the above consequences of poor sleep might be relevant to people with FM? A 2007 study showed that FM patients were five times more likely than healthy controls to develop metabolic syn-



drome.[11] Earlier this year, a published report showed that people with FM had elevated levels of IL-6 and CRP.[12] These inflammatory substances both correlated with measures of disturbed sleep. Unfortunately, the patient's BMI (measure of obesity) increased as the concentrations of IL-6 and CRP became higher. This prompted the authors to recommend a dietary approach rather than a sleep specialist for evaluation. But the data imply that metabolic and cardiovascular risk factors are present in FM, even if these connections are not recognized.

What Can You Do?

"Sleep must serve a crucial, primordial function. During sleep we are subject to predators and give up the opportunity to reproduce, eat or drink. It could only have evolved despite these high evolutionary costs," states Krueger.[1] Likewise, you and your doctor need to place top priority on improving the quality and quantity of your sleep. Medications, positive airway pressure (PAP) for those with sleep-disordered breathing, and self-help measures all need to be considered:

- Try to enhance the difference between your wake and sleep times by being more active during the day.
- Sit in a hot tub or take a hot shower before bedtime to enhance deep sleep.
- Put your circadian rhythms to work for you by going to bed around 10 p.m. and getting up around 6 a.m. regularly.
- Avoid heavy meals before bedtime because foods high in fat interfere with sleep, and the excess calories go to your waist. In fact, you may try to increase the protein content of your diet to curb your appetite and balance blood sugar. Also avoid caffeine in the evening because it blocks adenosine, which is a strong sleep promoter.
- Reduce stress to decrease the hyperactivity of your sympathetic system. This will lower blood pressure and improve the activity of the parasympathetic system to aid with sleep.
- Eat small, nutritious meals throughout the day because they may help decrease production of IL-6 and CRP.[9]
- If you are concerned that you might have metabolic syndrome, ask for a blood test for CRP and glucose tolerance. (*See Patient Resources on page 20.*) END

Medically reviewed and edited by James Krueger, Ph.D.

1. Krueger JM, *et al.* Nat Rev Neurosci 9:910-19, 2008.
2. Kattler H, *et al.* J Sleep Res 3:159-64, 1994.
3. Huber R, *et al.* Nat Neurosci 9:1169-76, 2006.
4. Giedk E, *et al.* J Nuclear Med 49:1798-803, 2008.
5. McLean SA, *et al.* Neuropsychopharm 31:2776-82, 2006.
6. Andersen ML, *et al.* Behav Brain Res 167:212-8, 2006.
7. Togo F, Natelson BH, *et al.* Exp Biol Med 234:232-40, 2009.
8. Nofzinger EA, *et al.* J Clin Sleep Med 2:316-22, 2006.
9. Haack M, *et al.* SLEEP 30:1145-52, 2007.
10. Mullington JM, *et al.* Prog Cardio Dis 51:294-302, 2009.
11. Loevinger BL, *et al.* Metab Clin Exp 56:87-93, 2007.
12. Okifuji A, *et al.* Clin Rheumatol [epub ahead of print] January 27, 2009.