Deep Brain Stimulation and Sleep

BY REGINA PATRICK, RPSGT, ASSOCIATE EDITOR

In 1995 in Europe, Canada and Australia, a newly-approved medical device—a deep brain stimulator—was used to treat people who had essential tremors (i.e., tremors with no apparent cause). Two years later in 1997, the United States Food and Drug Administration gave its approval for the device to treat people with essential tremors. Since its introduction, use of deep brain stimulation has been expanded to treat other disorders such as epilepsy, depression, and especially the rigidity, tremors, bradykinesia (slow movement), and gait difficulties of advanced Parkinson’s disease. More than 30,000 people worldwide have been implanted with a deep brain stimulator since 1995. Scientists are beginning to investigate the possibility of using deep brain stimulation (DBS) to treat certain sleep disorders. DBS stimulates areas in the brain involved in sleep and some studies show that it can modify sleep architecture.

Deep brain stimulation (DBS) initially came about as a treatment for pain. One theory on the genesis of pain viewed pain as the result of somatic signals being blocked from stimulating certain areas (e.g., ventrotetoposterior nuclei) of the thalamus. With this view in mind, G. J. Mazars and other scientists in the 1970s began experimenting with artificially stimulating the thalamus in an effort to reduce pain. Artificial stimulation was accomplished with the implantation of an electrode to the brain which was attached to a device that generated pulses.

Scientists soon began to note that the surgery also stopped abnormal movements (e.g., “jumping stumps” in amputees) in intractable pain patients. This led to the speculation that the thalamus plays a role in intractable pain and movement and that stimulating the thalamus may also reduce abnormal movements. Many studies subsequently investigated the use of thalamic surgery to improve movement.

Initially, thalamic surgery for restoration of movement involved destroying tiny areas of the thalamus or nearby structures such as the globus pallidus and subthalamic nucleus. However, in the 1980s, neurosurgeon Alim-Louis Benabid noted during surgery that when a stimulating electrode was placed on thalamic areas involved in movement, the person’s movement immediately improved although the area had not yet undergone tissue destruction. This observation led him to suggest that permanent stimulation of the areas rather than destruction of the tissue may be able to reduce tremors in people. He worked in collaboration with a medical device company to develop an implantable neurostimulator to specifically treat tremors.

Deep brain stimulation surgery now typically involves implanting a lead into two areas near the thalamus: the globus pallidus and the subthalamic nucleus (STN, a mass of gray matter is located just below the thalamus). The tip of the lead contains four electrodes which each stimulates a discrete area of tissue. An extension wire connects the other end of the lead to a neurostimulator. The neurostimulator produces the stimulatory pulses which are transmitted through the extension wire to the lead.

Before surgery, the person’s head is placed within a stereotactically made frame (e.g., Leksell G frame) so that measurements can be made in order to determine precisely where to insert the lead. The frame also keeps the person’s head stabilized during the surgery.

Once measurements are made, a small area on the scalp is anesthetized and a small circular (approximately 0.5 inch diameter) opening is bored in the skull near the coronal suture (the junction line of the frontal bone with the parietal bone). The lead is inserted until it reaches the basal ganglia. Since the patient remains awake during this portion of the surgery, a surgeon does neurological tests and asks the patient to describe sensations the patient is experiencing. This helps the surgeon to more accurately determine that the lead is being inserted into the correct area. Once the lead is in the right position, the patient then undergoes general anesthesia so that the neurostimulator can be implanted.

The neurostimulator is a small device about 3 inches round and 1/2 inch thick. It is inserted through an incision made beneath the collar bone. An extension wire from the neurostimulator is passed up beneath the skin through the neck toward the bore hole in the skull. The extension wire connects the lead at the bore hole. Depending on whether one side or both sides are affected by impaired movement, a person may be implanted with a unilateral or bilateral stimulator system.

After surgery, a physician adjusts the neurostimulator’s stimulation parameters (i.e., amplitude [voltage], signal frequency, and pulse width [length of stimulation]). The usual stimulation parameter ranges are an amplitude of 1 to 3 volts, signal frequency range of 135 to 185 cycles per second, and a pulse width of 60 to 120 microseconds.

The subthalamic nucleus (STN) and globus pallidus are located in close proximity to each thalamus. The STN and globus pallidus have many interconnecting pathways with each other. The globus pallidus also has connections to the thalamus, midbrain, and other basal ganglia such as the caudate nucleus.

The role of the STN and globus pallidus in sleep is unclear. However, scientists have begun to discern the neural activity of these structures during sleep and wake. For example, studies show that cortical activity has an excitatory influence on the STN but the ability of the STN to respond to the excitatory effects of cortical neurons is modulated by the inhibitory influence of the globus pallidus which contains many GABAAergic neurons. (GABA, gamma-amino butyric acid, is a neuroinhibitor.)
The STN-globus pallidus network has connections to the reticular nuclei of the thalamus which in turn has connections to the midbrain reticular activating system. Increased activity of the midbrain reticular activating system from sleep to wake increases the activity of the globus pallidus.

The globus pallidus fires in a random pattern rapidly during wake and less rapidly during slow wave sleep but during rapid eye movement (REM) sleep its firing rate increases dramatically. The STN fires at a virtually constant rate throughout sleep and wake but the quality of the firing changes from a random pattern in wake to a burst pattern in slow wave sleep. The function of changes in activity of the STN-globus pallidus network from sleep to wake is unknown but they may play a role in information processing.

Researchers Alex Iranzo et al.1 and Isabelle Arnulf et al.2 in separate studies found that stimulation of the STN in people with Parkinson’s disease subjectively improved sleep quality and improved objective measures of sleep. For example, in the Iranzo study, polysomnography revealed that the subjects’ arousal index (number of arousals/hour) decreased by 37.7%; wakefulness after sleep-onset (WASO) decreased by 10.6%; the amount of slow wave sleep (stage 3/4) increased by 43.2%; and the longest period of uninterrupted sleep increased by 53.5%. In the Arnulf study, polysomnography showed that the subjects’ total sleep time increased by 47%; wakefulness after sleep-onset (WASO) decreased by 51 minutes; and sleep efficiency (the ratio created by dividing total sleep time divided by duration of the sleep period) increased by 36%.

Both Iranzo and Arnulf note that symptoms of REM sleep behavior disorder (e.g., vocalizations, movements during sleep, restless legs/arms) remained despite improvement of other sleep characteristics. Both researchers theorize that this may occur because pathways affected by STN stimulation do not affect the neurons of the upper brainstem which play a role in REM sleep atonia. Since the upper brainstem neurons are not stimulated, REM sleep behavior symptoms can manifest.

Other researchers3 have similarly found that DBS increases in slow wave sleep (stage 3/4), decreases in WASO, and increases periods of uninterrupted sleep. However, French physicians Christelle Monaca et al.4 in 2004 reported the case of DBS therapy inducing insomnia in a patient. The patient, a 48 year old woman with Parkinson’s disease, complained that after surgery she was able to sleep for about 1 hour at night. The patient would wake up, eat, and feel compelled to remain active at night. A polysomnogram performed three months after DBS surgery confirmed the patient’s insomnia — during the study night she slept for about 80 minutes. Interestingly, the patient’s insomnia did not result in the expected excessive daytime sleepiness.

Nine months after surgery, the patient’s right side had not fully responded to DBS. The surgeons as a result decided to reposition the left DBS lead. Magnetic resonance imaging (MRI) performed before repositioning revealed that the right lead was placed in the posterior part of the STN while the left lead had been placed on the outer front portion of the STN. After repositioning the left lead, the patient’s right-sided movement improved and her insomnia and nocturnal eating immediately stopped.

Monaca et al. theorize that insomnia may have resulted from the position of the left electrode. It may be that at its more anterior position on the STN, the lead may have been stimulating descending fibers to the hypothalamus. The hypothalamus controls appetite as well as certain aspects of sleep. Monaca et al. point out that animal studies and similarly some human studies show that severe insomnia can result when the thalamus is removed. They believe that thalamotomy affects the ability of the STN to receive inhibitory input from midbrain reticular neurons and other structures. Consequently, waking activity of the STN is not inhibited and insomnia results. Although DBS does not destroy tissue, it neurologically mimics the effect of thalamotomy and inadvertently resulted in insomnia.

Scientists are trying to determine if DBS could be used to treat restless leg syndrome, periodic limb movement, or REM sleep behavior disorder. Results have been conflicting.

A 2006 Baylor College of Medicine study5 found that stimulating the ventralis intermedius nucleus (Vim) of the thalamus did not reduce restless leg syndrome in people who also had essential tremors. Okun et al.6 report the case of a woman whose symptoms of restless legs improved after she had undergone DBS surgery to stimulate the globus pallidus. Kedia et al.7 report that restless legs syndrome appeared in their subjects after STN stimulation; they concede that reduction of medication after surgery may have played a role in the manifestation of the disorder. Several researchers (e.g., Arnulf and Iranzo) have noted no improvement of REM sleep behavior disorder with DBS despite the improvement in muscle control after surgery.

Such conflicting results are not discouraging. Apparent failures of DBS treatment to alleviate symptoms in these disorders help scientists to more clearly understand pathways involved in sleep and wake. This understanding may yet be utilized in the future to improve sleep. ★

References

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