The Neural Mechanism for Sleep Initiation in the Mammalian Brain

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Abstract

Many areas of the brain have been implicated in the sleep cycle, but a holistic picture of their involvement is hard, if not impossible, to find. This paper is meant to summarize in relevant detail the major players in sleep initiation in the mammalian brain. The major players in sleep were broken into two categories: sleep-agonists and sleep-antagonists. The sleep-agonist areas are the median pre-optic nucleus, the ventrolateral pre-optic nucleus, and the Pineal Gland; the sleep-antagonist areas are the raphé nucleus, the locus coeruleus, the perifornical lateral hypothalamus, and the tuberomammillary nucleus. Also included in the paper are introductions to sleep and general neural mechanisms; information on Narcolepsy, Hypersomnia, and Insomnia; and a description of the typical American sleep lab.

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The Neural Mechanism for Sleep Initiation in the Mammalian Brain

Sleep is a marvelous, complex, and mysterious phenomenon, or at least it is to many people. Although acronyms like REM and NREM (Non-REM) are recognizable to many educated citizens, a true understanding and implications of such terms are often non-existent. Neurological professionals can cite various parts of the brain involved, like the Reticular Activating System, the Pre-Optic Area, or the Hypothalamus, but the mechanisms that exist among these distinct areas and cell populations of the brain are often too recently discovered to be understood by such professionals. However, knowledge of what truly happens when a tired truck driver falls asleep behind the wheel, or when an infant drifts silently off to sleep is better understood now than ever. While much of the information needed to understand sleep is out there waiting to be found in various scientific journals and websites, much of it is scattered or incomplete, or worse, dry and difficult for a layperson to understand and follow.

Thus, the objective of this paper is bifold: to present a compilation of the publications of many hardworking researchers in a format that can educate laypeople on the concept of sleep, and to help medical doctors and other professionals to catch up with the scientific community concerning the areas and mechanisms of sleep initiation in the brain. However, because the majority of the cited sources were published within the past five years, some of this information may be incorrect as the professional community may not have had adequate time to test and retest the results of these sources. Another shortcoming of the current

research is that all the invasive physiological testing done thus far has been conducted on mammals other than humans, and much of it has yet to be confirmed adequately in humans. For this reason, this paper will target a generalized explanation of sleep initiation for mammals.

This paper is meant to provide a solid and yet easy-to-read collection of information, and to achieve this goal, any theoretical implication or inference supported by true scientific research will be treated as fact to avoid annoying repetitions such as “supported by” and “supposedly”. However, to assure reliable and valid conveyance of the material, anything strictly theoretical will be referred to as such. Also, it is completely possible that contradictive or supplemental data was not found or was not published by the time this literature review ended.

Theories of Sleep

In reviewing the literature on theories of sleep, the names of sleep theories tend to be descriptive, rather than titled after the creator of the theory. This is probably because the presumptive cause of sleep has been “known” or “understood” throughout history and the theorists simply elaborated on a previous thought rather than constructing their own unique theory. The fact of the matter is that much like the question of “Nature vs. Nurture,” a full understanding of sleep may only be fully accounted for by an eclectic, or mixed, view. As a discipline, this lack of a single, encompassing theory can be explained by the fact that almost every reason for sleep has been scientifically substantiated and yet no one theory accounts for all that is known at this time.

It is widely accepted that sleep is necessary, but for whom is it necessary? It has been shown that most mammals and many other animals sleep (Rechtschaffen, 1998); however, this is not the question that sleep theories seek to substantiate. The question is why animals sleep. The mechanisms for explaining how animals sleep are all but concretely defined, pushing the majority of theoretical publications onto the subject of why animals sleep.

In one way or another, many of the most accepted sleep theories revolve around a central physiological entity or process, such as metabolism. Some of these theories are so very similar that it seems as if they are the same theory, just with different words. The easiest theory to understand falls under the heading of Energy Conservation. The basic idea is that because the body is in an exhaustive state of energy consumption, there must be a period of energy conservation (Shapiro & Flannigan, 1993). Some studies have suggested that the body's internal processes are less than a quarter as active during sleep as compared to the waking state (Rechtschaffen, 1998; Shapiro & Flannigan, 1993); however, this difference, in and of itself, is not enough to make the immediate need for sleep life threatening, and could be easily compensated for in today's more advanced societies where nutritional diets and healthcare are commonplace (Greier, 1997; Rechtschaffen, 1998).

There are multiple other theories that are based on restoration, which is very similar to conservation once the details of metabolism are understood. High metabolism indicates a greater amount of catabolism and a lesser amount of

anabolism. Catabolism is the breaking down of tissues and associated proteins, while anabolism is the production and synthesis of tissues and associated proteins. Catabolism usually yields and expends energy while anabolism stores energy (Fox, 2004). During sleep, the conservation and restoration theories refer to the observation that metabolism is lower, meaning that anabolism is higher than catabolism. However, restoration theories expand on by suggesting that the body compensates for its previous expenditures during waking by refilling the reserves during sleep. This production of reserves correlates with the higher levels of many hormones and many other trends during sleep (Shapiro & Flannigan, 1993).

The above two sleep theories are more comprehensive than some others which work to explain sleep based on one narrowly focused type of observation. Such theories do not explain everything but are useful to an eclectic approach. A good example of this type is a theory based on the thermoregulation of the body. The body's lowest temperature occurs during the early morning hours of sleep, and the body is relatively cooler while sleeping than during waking activity (Rechtschaffen, 1998). Furthermore, increased body heat levels tend to promote sleep, probably because the increased heat levels indicate the need for the cooling effects of sleep. This concept was explored by an experiment in which sleep-deprived rats were allowed to change the temperature of their immediate environments. These rats voluntarily increased their cage temperatures by an incredible average of ten degrees Celsius (Greier, 1997), possibly in an unconscious attempt to force the initiation of sleep. Similarly, professional

athletes have been shown to sleep considerably more when their body temperatures are significantly raised during workouts (Greier, 1997).

The final type of theory is that which is based almost solely on an evolutionary explanation for the phenomena, rather than the physiological mechanism. The most widely accepted example is that sleep is meant to keep animals out of harm's way (Greier, 1997). This theory is best used to explain the sleeping behavior of prey, and does not work as well for predators with few or no natural predators. As is widely known, many predators are nocturnal and are naturally equipped with specialized sensory organs that give the predator an advantage in the dark. Because of these special advantages, small or vulnerable prey, such as humans, should stay out of the way of predators throughout the night. This theory is supported by the observation that most prey sleep in an area with minimal danger or chance of attack; some animals burrow themselves deep in the ground, and some sleep high up in trees or other structures to avoid predators on the ground. Other evolutionary arguments are that of specialization, which focus on specialized forms of sleep in certain animals. Hibernation is one example and the common sleeping behavior of fish is another. The common sleeping behavior of fish involves the staggered sleeping of only one half of the fish's brain at one time. It should be noted that the sleeping behavior exhibited in some fish is not completely accepted to be sleep because many mammalian characteristics of sleep are not present (Rechtschaffen, 1998). These observations and others led

some researchers to suggest that the function of sleep was to force a life-saving and defensive behavior (Greier, 1997).

Most extant theories have supporting evidence, but none fully account for the complexity of sleep. Because of the lack of a definitive sleep theory, an eclectic theory of sleep is required. The eclectic theory of sleep combines the best portions of individual theories together in an attempt to better understand sleep.

Characteristics of Sleep

Many people are aware that the brain exhibits brain patterns or brain waves, yet many do not understand how such phenomena exist. The brain waves that are characteristic of sleep and waking are really just the resulting image created by a machine that reads all available electrical patterns and records the amplitude, frequency, and other details of the electrical impulses traveling through the brain. These impulses are the result of action potentials, which, consequently, are the result of the culmination of excitatory and inhibitory post-synaptic potentials (EPSPs and IPSPs). Action Potentials, EPSPs, and IPSPs will not be explained in any detail other than to say that these are the processes involved in the electrical conduction of signals within the brain and, furthermore, within any nerve cell (or neuron) in the body. More information can be found on these topics in almost any local library or on the World Wide Web (e.g. http://www.winchestersleep.com/content/view/3/5/; http://en.wikipedia.org/wiki/Sleep; http://health.howstuffworks.com/sleep1.htm).

Brain Waves

The overall electrical patterns in the brain indicative of sleep and the varying levels of arousal have been found to be relatively constant across all healthy humans. The typical brain waves found in mammals are called beta, alpha, theta, and delta waves, and are observed in waking, drowsy, light sleep, and deep sleep phases, respectively.

When a person is fully awake, the brain exhibits what is known as beta waves, which are high frequency, and very low amplitude waves; furthermore, these waves are characterized as being random and erratic. When a person is conscious and becomes relaxed or drowsy, alpha waves appear, which are also relatively high frequency and low amplitude, but display more organization and have slightly higher amplitude than beta waves. The brainwaves observed during first two stages of sleep continue to increase in synchrony and amplitude, while lessening in frequency. Stage 1 displays theta waves, while stage 2 displays a variation of theta waves, which includes spindles and K-complexes. These complexes can be thought of as the beginning of delta waves, which exist in stages 3 and 4. Stage 3 actually exhibits a combination of theta and delta waves with more perceived organization than stage 2, but will turn more and more toward delta waves as stage 3 progresses. Delta waves are very organized, large amplitude, and synchronous brain waves. During stages 1 through 4, there is little to no eye movement, and the body is free to move around to some extent, such as rolling over, bending the legs, or anything else that is needed to keep the sleeper comfortable; however, any strenuous movement such as walking around, standing

up, or other physical activities that disrupt the individual or cause stress to the individual are often indicative of a parasomnia, which is a sleep disorder that takes place during sleep which often involves a particular behavior. For example, somnambulism (sleep walking) and night terrors are parasomnias. If the physical activity does occur regularly and results in awakening or the prevention of sleep, then these symptoms may also be indicative of a sleep disorder, such as hyposomnia or restless legs syndrome.

Stages 1 through 4 are all known as non-rapid eye movement (NREM) sleep. Stages 3 and 4 are further classified as deep sleep, and these are the stages during which the most rest is achieved for the sleeper. Rapid Eye Movement sleep, also known as REM, is very different from NREM. This phase is characterized by brain waves very similar to beta waves. REM sleep is the stage in which the most vivid dreaming occurs; most dreaming that is remembered upon awakening occurs during REM. Paralysis is known to occur during REM episodes in humans, and probably most other mammals. This paralysis is useful in preventing the acting-out of dreams during an REM episode.

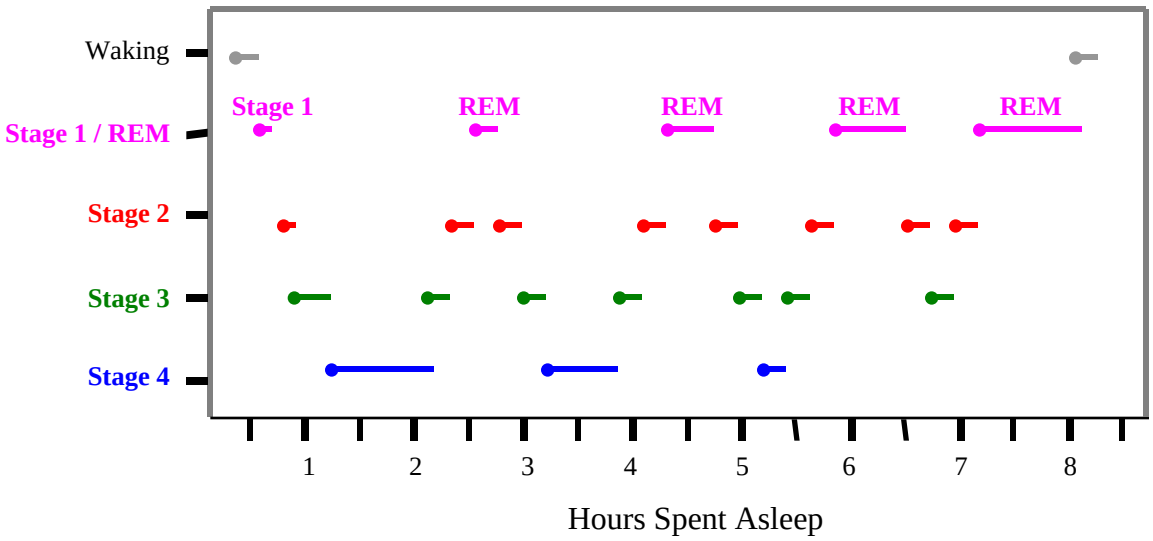
The Sleep Cycle

The cycle of sleep tends to be much more convoluted than many people think and does not simply follow from stage one through four, and then to REM. Because the concept of the sleep cycle tends to be difficult to grasp, especially in paragraph form, Figure 1 is included to help clarify this material. More information

on the sleep cycle and other information about sleep can be found at

http://en.wikipedia.org/wiki/Sleep.

Figure 1.



One night's sleep is diagramed with lines indicating relative amounts of time spent in each stage of sleep. One sleep cycle goes from stage 1/REM to Stage 4 and back to stage 1/REM. Stage 1 only occurs at sleep onset, and REM replaces stage 1 until awakening and subsequent initiation of sleep, at which time stage 1 will occur only once. Also, notice that as sleep progresses throughout the night, stage 4 lessens until it is non-existent at the end of a full night's sleep. Meanwhile, time spent in REM increases throughout the night. Time spent in each stage starts with a dot and ends with a straight line. Transitions from one stage to another are considered instantaneous, thus no time is allotted for the transition.

To fully understand the cycle of sleep, it will be outlined from the time preceding sleep through awakening after a full night's sleep. To start, the typical person exhibits beta waves during the waking hours. Next, the typical person will become drowsy and begin showing alpha waves as the standard bedtime comes closer, and will drift from the typical alpha waves of drowsy awakening to the theta waves of Stage 1 sleep. This change from alpha to theta waves corresponds to

the time when consciousness will most often be lost, but this loss can be reversed by a sudden change in the immediate environment, such as a sound or change in lighting. The time spent in the transition from beta to theta will vary from person to person, and could easily fall between five and thirty minutes. The transition from stage 1 to 2 sleep is slight, as is the change from stage 2 into the delta waves present in stage 3. The change from stage 3 to stage 4 is more pronounced, and it is in stage 4 that brain waves will be the most organized. After stage 4 is complete, the process of NREM reverses itself and stage 4 transitions to stage 3 and then to stage 2. The obvious anticipation is that stage 1 will be next.

However, unless a person is awakened, stage 1 will not follow stage 2; stage 1 sleep only occurs when sleep is initiated. After the initiation of sleep, REM replaces stage 1. At the end of the REM stage, the pattern begins again, starting with stage 2. This process repeats over and over, with approximately 90 minutes from the start of one stage 2 to the next stage 2.

The individual time spent in each stage of sleep varies from one cycle to another, yet these changes also follow a predictable pattern. The first occurrence of stage 3 and stage 4 sleep is the longest (with stage 4 being longer than stage 3), and the first occurrence of REM is the shortest. Subsequently, the final occurrence of stage 3 and stage 4 will be the shortest, and the final REM episode will be the longest. The predominance of REM sleep toward the end of a night's sleep is the reason why the most dreams that are remembered happen directly before waking. Also, the final dreams before waking tend to be the longest, and

possibly the most intricate. An important fact to keep in mind is that the body can reach a saturation point for time spent in deep sleep. Thus, as the night continues, less and less time is spent in the deep sleep stages.

Night-Sleep Duration

A very common question among laypeople and many professionals is how much sleep is adequate. There are many college students who run on extreme sleep deficits during the week and then try to catch up over the weekend. This especially tends to be the case during mid-term and final exam weeks. Students and many others learn to live through these periods of inadequate sleep, and many perform just fine while doing it. So who is to say that one amount of sleep is ideal? In a study of children, from infancy to adolescence, Iglowstein, Jenni, Molinari, and Largo (2003) found that the average number of hours of sleep per day for infants is about fourteen and decreases steadily to 8 hours of sleep at age sixteen; however, these numbers are simply averages and only a small number of participants actually sleep the average amount. These averages simply work as a good baseline for comparison, but are often misinterpreted to be exact.

Susman (1989) noted that how much time is spent in the different stages as well as the total time spent asleep changes throughout adulthood. As overall sleep time decreases, the time spent in deep sleep decreases while time spent in the light sleep increases. However, REM sleep accounts for the same proportion of overall time spent asleep in late adulthood as in early adulthood. In addition to complaints about time spent asleep, many elderly complain of an increase in sleep

latency, or the time it takes to fall asleep, but this change is fairly normal with age (Susman, 1989).

The best way to know how much sleep a person needs is by experience. If someone wants to discover how much sleep works best for him or her, the person should keep track of how much time is spent asleep, and separate these data according to when the person does and does not feel rested; these data can be recorded and used to guesstimate the amount of sleep that is optimal (Linley, 2005; Sateia & Nowell, 2004). However, even this technique does not insure accuracy because other influences such as stress, medications, and recreational drugs have a strong affect on sleep (Linley, 2005).

The information contained in this introduction is considered to be common knowledge by neurological professionals. Most of this information, with the exception of some of the sleep theories can be found in textbooks such as *Human Physiology* by Fox (2004)*, Biopsychology* by Pinel (2003), *Biological Psychology* by Kalat (2003), and *Psychology: In Search of the Human Mind* by Sternberg (2001).

The Basics of a Neural Mechanism

Trying to learn information on a new topic solely through journals and professional articles can often be overwhelming. The learning process is often made more difficult with the extensive use of abbreviations. Many neurological journals use abbreviations and acronyms to save time and valuable space. Additionally, many journal articles expect the reader to know ahead of time

what an abbreviation or acronym represents. This paper will be using many acronyms and abbreviations, but will try not to allow their use to become too cumbersome for the reader. Table 1 gives a list of all abbreviations used in this paper along with their full names and page number of their first use.

The initiation of sleep in the brain involves multiple regions of the brain, and within some of those regions distinct and functionally different nuclei exist. A nucleus in the brain is a group of neurons whose function is related and often identical. Although the individual neurons of a nucleus have a unique network of connections to other neurons, much of the electrical communication within a nucleus is meant to achieve one or more particular functions. The network of connections is developed and strengthened during fetal and early childhood development, and in some areas, throughout the life of the individual. Connections that do not help achieve the desired function are almost always eradicated or otherwise modified for completion of the objective of that nucleus or pathway. A pathway is a group of neurons that carry, and sometimes modify, electrical impulses between two nuclei. These pathways can be routed through one or more nuclei on the way to the target or may make one uninterrupted passage.

Table 1. Acronyms Used and Their Meanings

Acronym	Full Name	Page of First Use
5-HT	Serotonin	15
ACh	Acetylcholine (an NT)	15
DRN	Dorsal Raphé Nucleus	22
EPSP	Excitatory Post-synaptic Potential	36
GABA	_-aminobutyric Acid (an NT)	15
IGL	Intergeniculate Leaflet	22
IPSP	Inhibitory Post-synaptic Potential	36
LC	Locus Coeruleus	19
MnPN	Median Pre-optic Nucleus	31
MRN	Median Raphé Nucleus	22
NA	Noradrenaline (an NT)	15
NT	Neurotransmitter	15
PFLH	Perfornical Lateral Hypothalamus	27
POA	Pre-optic area	31
RE-cell	Regulatory cell	37
REM	Rapid eye Movement (Sleep)	1
RF	Reticular Formation	21
RN	Raphé Nucleus	21
SCN	Suprachiasmatic Nucleus	19
TC-cell	Thalamocortical cell	37
TMN	Tuberomammillary Nucleus	26
VLPO	Ventrolateral Pre-optic Area	31

The electrical signals that travel within neurons are passed from one neuron to another by way of chemical messengers called neurotransmitters. Neurotransmitters can cause either the excitation or inhibition of the innervated neuron by instigating the influx of ions into the receiving cell. Innervation is the

connection between neurons that allows for chemical communication. An excitation of a neuron can cause the neuron to fire (the act of sending a signal), which involves the production of an action potential which will be transmitted via neurotransmitters to all connected dendrites (the receiving end of neurons). Inhibition of a neuron is best described as the prevention of the creation of an action potential. However, because the brain is composed of about one-hundred billion neurons, most of which have many connections and produce many action potentials per second, the inhibition or excitation of a single cell is very complex and involves many inputs. In the end, if there are enough excitatory impulses to overpower the inhibitory impulses and exceed the threshold necessary for the creation of an action potential, then the neuron will fire.

The major neurotransmitters (NT) used in the brain are gamma-aminobutyric acid (GABA), epinephrine, norepinephrine (NA), serotonin (5-HT), glutamate, and acetylcholine (ACh). The abbreviations listed after the neurotransmitter's names in parenthesis are common abbreviations that will often be found in the professional literature. Some NTs receive more coverage than others in the media. For example, Serotonin is a common term in today's society due to its role in depression and euphoria. Epinephrine is also well known, but under a different name: Adrenaline. Likewise, norepinephrine is also known as noradrenaline. However, the terms adrenaline and noradrenaline often refer to the chemical when present in the peripheral nervous system, which includes all of the

body except the brain and spinal cord. GABA, NA, 5-HT, and ACh are the most commonly implicated NTs in sleep.

There are numerous factors to be taken into account when discussing what effect a NT will have on the recipient cell, but there are some consistencies. For example, GABA is the brain's predominant, endogenous inhibitory NT, while glutamate is the brain's predominant, endogenous excitatory NT. Chemicals which are synthesized naturally in the body are described as being endogenous. Epinephrine, norepinephrine, and acetylcholine tend to be excitatory, but their effect ultimately depends on the properties of the receptor. Serotonin usually inhibits neurons that release an inhibitory NT. There are often many different receptors for each NT that exist in various parts of the body, and these receptors may cause very different effects. Individual receptors will not be considered in this paper because the complex effects of multiple NT receptors are out of the scope of this paper.

Neurotransmitters are important for passing and regulating signals between neurons, and their production is most often regulated by the neurons themselves. Another class of chemicals used in intercellular communication is the hormone, which is also very important to the body's ability to regulate its various processes. While NTs are used for inter-neuronal communication, hormones are more for inter-system communication and are transferred from one system to another by the blood and interstitial fluid (the fluid that exists and flows between all types of cells in the body but exists outside of the vascular system). The only hormone

produced by the brain that will be discussed in this paper is Melatonin because of its role in sleep and its recent exposure in the media.

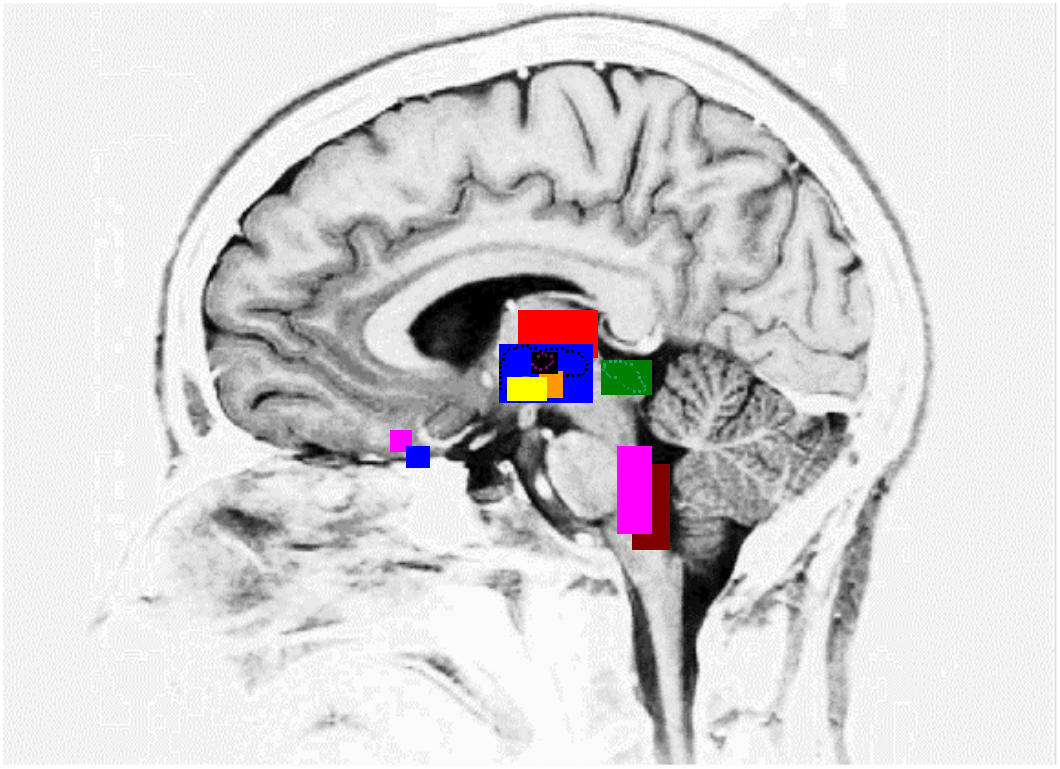
Not all chemicals are used strictly as either NTs or hormones. Epinephrine and Histamine are good examples of chemicals that are usually hormones everywhere but in the brain, where these chemicals are principally used as NTs.

The Neural Mechanism for Sleep Initiation

As is the case with most complex neural mechanisms, there are many parts of the brain that are involved simultaneously. In order to simplify the description of the sleep mechanisms, the individual neural components or areas will be described in relevant detail with minimal references to interactions with other areas. Following the descriptive accounts of these areas will be an explanation of how these areas interact with each other to produce the complex interaction known as of sleep. Figure 2 illustrates the approximate relative positions of all the major sleep centers in the sagittal cross-section of the human brain.

The first part of the brain to be discussed is the Suprachiasmatic Nucleus because it is the pinnacle of the sleep-wake switch and central to the connections of most other sleep-involved brain regions. Following this section will be the sleep-antagonist areas and then the sleep-agonist areas. Antagonists work to prevent, disable, or counteract a particular process, while agonists

Figure 2



Suprachiasmatic Nucleus

Thalamus

Hypothalamus

Tuberomammillary Nucleus

Raphé Nucleus

Locus Coeruleus

Perifornical Lateral Hypothalamus

Ventrolateral Pre-optic Nucleus

Median Pre-optic Nucleus

Pineal Gland

Sleep-related structures in the brain as discussed in the neural mechanism section. Notice that some structures like the Tuberomammillary Nucleus are located within another structure, the hypothalamus. The positions indicated are strictly meant to be relative, and will vary from one organism to another.

promote and strengthen a particular process. The process that is being antagonized or agonized is sleep initiation. Sleep-antagonists will be mentioned first because they are more numerous and because their interactions and connections are less convoluted. Following the sleep-antagonists will be the sleep-agonists. Then, the overall sleep-wake switch will be defined and its interactions elaborated. Following that, the thalamus will be described; it is the region believed to create the brain patterns indicative of the sleep-wake cycle.

Suprachiasmatic Nucleus

The body has many ways of regulating the different processes that are necessary for survival. The Suprachiasmatic Nucleus (SCN) maintains the circadian cycle in the mammalian body. The circadian cycle corresponds to one revolution of the earth which is just slightly longer than one 24-hour day. The output and maintenance of the circadian cycle is crucial to the sleep-wake cycle and to other behaviors (Aston-Jones, Chen, Zhu, & Oshinsky, 2001; Glass, Grossman, Farnbauch, & DiNardo, 2003). The SCN receives both photic and non-photic information from multiple sources (Glass et al., 2003). The term photic refers to light; therefore, photic information comes from light input, primarily through the eyes. Non-photic inputs vary widely, and many are the neural systems that promote or antagonize sleep.

Although the SCN is often considered to promote arousal, this is not completely true. The SCN alters and relays the information it receives, and it acts as a central convergence point for both the sleep agonists and the sleep-

antagonists. Some portion of the SCNs afferents come from sleep-agonists (Aston-Jones et al., 2001), and during sleep, these are the most major inputs. However, during waking hours the sleep-antagonists provide the largest influx of information. When the circadian cycle is uninterrupted, the hundreds of cells in the SCN tend to peak their firing rates around midday and reach their lowest point, or trough, late at night. The trough experienced tends to coincide with the body's lowest temperature during the night and sunrise, usually somewhere between 2 and 6 a.m. Although the SCN neurons all tend to have the same basic circadian rhythm, their individual rates of firing at any given time differ. The circadian rhythms are influenced by individual gene expression in each cell. However, the cells' individual rhythms interact to stimulate and reinforce other rhythms in adjacent cells of the SCN. The result of the cellular rhythms is a seemingly beautiful interaction of neural activity (Yamaguchi et al., 2003).

Yamaguchi et al. (2003) conducted an experiment in which the signals of all neurons in the SCN were shut down in vitro (an artificial and controlled environment). When the shut down lasted for at least one circadian phase (either sleeping or waking), all the cells begin firing again at approximately the same circadian phase and firing rate. After a short period of uniform firing, the neurons will begin to interact with each other and change the overall rhythm of the SCN.

Although the changes that occur in the brain across the sleep-wake states are facilitated by the SCN, the changes, such as the different brain waves, are not

necessarily present in the SCN. The changes influenced by the SCN will be discussed near the end of the neural mechanism section.

Sleep-Antagonists

Raphé Nucleus

Conscious arousal of the human mind exists because of neural activity in many different regions. The parts of the brain responsible for antagonizing or inhibiting sleep are composed of one hormone-based and three neurotransmitter-based centers. The Reticular Activating System, also known as the Reticular Formation (RF), is a major region in the brain involved in many different activities including arousal. One subregion involved in sleep antagonism within the RF is the Raphé Nucleus (RN). The RN has many functional influences in the brain, such as pain, eating, anger, motor functions, and also almost everything associated with arousal (Sakai & Crochet, 2001). One particular sub-nucleus within the RN has been shown to display tonic (full speed) firing during both waking and drowsiness. The firing rate begins to decrease with the transition to sleep and continues to slow until the initiation of REM, when this portion of the RN is reportedly completely quiescent (Manfridi et al., 2003). It can be assumed, due to reasons to be presented later in this section, that all other areas of the RN relevant to sleep display the same pattern of firing.

The RN facilitates its involvement in sleep by connections to other brain areas, notably, the SCN (Glass et al., 2003). Two pathways are influential in the connection between the RN and SCN: the extra-RN pathway and the intra-RN

pathway. The extra-RN pathway involves a serotonergic RN efferent to the Intergeniculate Leaflet (IGL) which then follows an optical pathway to the SCN. The RN increases 5-HT output to the IGL when conscious arousal increases, and decreases output with a loss of conscious arousal. The 5-HT output to the IGL can phase-forward the circadian clock, meaning it causes an increase in total arousal (Glass et al., 2003). The mere existence of the optical pathway between the IGL and the SCN is relevant to the simplified mechanism of sleep initiation (Glass et al., 2003). Therefore, the details of this optical pathway will not be elaborated upon here.

The intra-RN pathway defined by Glass et al. (2003) involves two distinct parts of the RN: the Dorsal Raphé Nucleus (DRN) and the Median Raphé Nucleus (MRN). Figure 3 defines the parts of the intra-RN pathway that are active in response to excitation or inhibition of the RN. The intra-RN pathway can appear to be very convoluted because numerous steps and neurotransmitter interactions are included. The most reader-friendly way to present these interactions is to outline the three interactions within the RN, and then discuss what happens with the different inputs that arrive in the DRN from the MRN. All involved groups of neurons will be named by the nucleus they inhabit and the primary neurotransmitter they release. For example, a serotonergic (5-HT) neuron in the MRN will be named MRN-5-HT. The first interaction

Figure 3

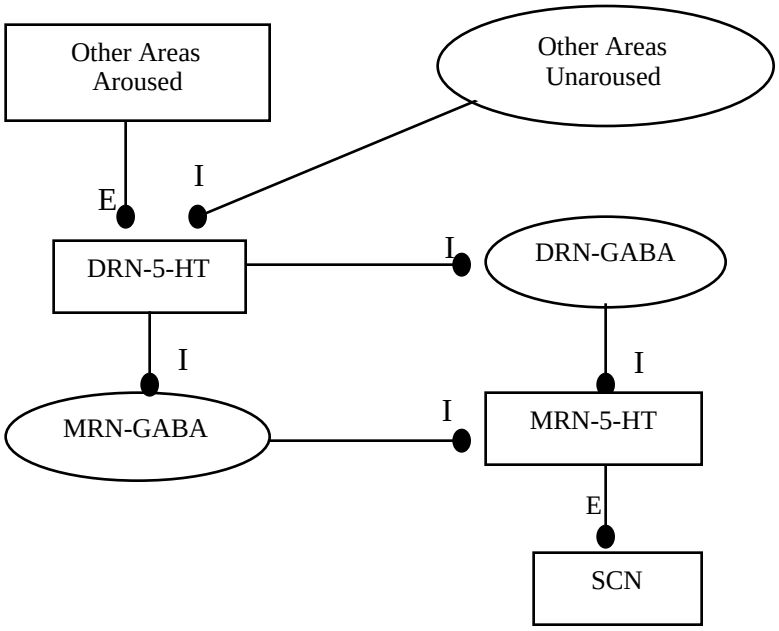
If RN is excited:

Excited (Active) Cells

Inhibited (Inactive) Cells

I = Inhibitory Synapse

E = Excitatory Synapse



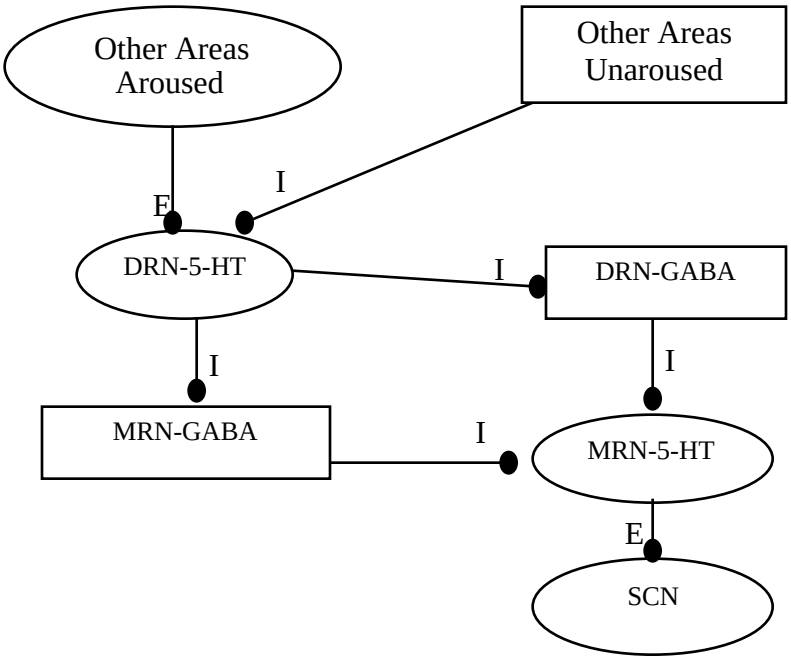
If RN is inhibited:

Excited (Active) Cells

Inhibited (Inactive) Cells

I = Inhibitory Synapse

E = Excitatory Synapse



The intra-Raphé nucleus pathway as described in the neural mechanism works as a switch. Notice that if the RN is excited by other brain structures, an output to the SCN is observed by inhibiting (I) the MRN- and DRN-GABA cells. When the RN is inhibited by other brain structures, the MRN-GABA and DRN-GABA cells are allowed to fire tonically, thereby suppressing the output of the RN to the SCN.

is between the DRN-5-HT cells, which serotonergically inhibit both the DRN-GABA and MRN-GABA cells. The second interaction to be defined is an inhibitory innervation of the MRN-5-HT by both the DRN-GABA and the MRN-GABA. The final interaction is serotonergic innervation of the SCN by the MRN-5-HT cells. The serotonergic innervation from the MRN-5-HT cells tends to cause the arousal and activation of the SCN. The MRN-5-HT, DRN-GABA, and MRN-GABA cells are the only cells in this pathway to fire tonically, which refers to firing as often as possible, even without excitatory input.

Once the three intra-RN interactions are fully understood, it becomes clear that when the DRN-5-HT cells fire, they release the inhibitory hold over the MRN-5-HT cells propagated by the DRN- and MRN-GABA cells, thus allowing the MRN-5-HT cells to fire. Therefore, the firing rate of DRN-5-HT cells should be proportional to that of the MRN-5-HT cells. The RN receives input from other areas of the brain important to arousal but not directly relevant to sleep-initiation. When an arousal center excites the RN, it does so by exciting the DRN-5-HT cells, thereby increasing the firing of the MRN-5-HT cells, and resulting in the excitation of the SCN. In turn, when inhibitory inputs arrive in the RN, they will inhibit the DRN-5-HT cells, thereby decreasing the excitation of the SCN (Glass et al., 2003).

Locus Coeruleus

Contained within the Reticular Formation of the mammalian brain are two distinguishable sub-areas that are strongly implicated in conscious arousal: the Raphé Nucleus and the Locus Coeruleus. The Locus Coeruleus (LC) has long

been implicated in arousal and waking functions. Because of this longstanding implication of arousal, the LC is often found to be over-emphasized, as is evident when scanning neurological journals. However, no one sleep-antagonist can provide or sustain the arousal that humans and other mammals need to survive. Although the LC is distinct from the other sleep-antagonists in that it is the only noradrenergic nucleus (Aston-Jones et al., 1991; Aston-Jones et al., 2001; Berridge & Foote, 1991; Sakai & Crochet, 2001), the firing rates of the LC are very similar to the firing rates of the RN (Manfridi et al., 2003; Aston-Jones et al., 2001). The firing trends and inherent noradrenergic properties of the LC help make it vital to the creation and sustaining of arousal (Berridge & Foote, 1991).

The SCN is the central convergence point for most of the sleep-relevant centers, and the LC does communicate with the SCN. Yet, unlike the RN, the LC does not directly connect to the SCN. Rather, the LC's efferent to the SCN is relayed through the Dorsomedial Hypothalamus (Aston-Jones et al., 2001). The Dorsomedial Hypothalamus is merely an area within the Hypothalamus and is not a nucleus, as it contains diverse nuclei within it. It should also be noted that while Aston-Jones et al. refer to this particular area within the hypothalamus as the Dorsomedial Hypothalamus, this paper will speak later of the Perifornical Lateral Hypothalamus, which is a different name for the same region.

Tuberomammillary Nucleus

The Tuberomammillary Nucleus (TMN) is not found in the RF like the LC and RN. The TMN is unique in that it is the only part of the brain to use Histamine

as a neurotransmitter (Sherin, Elmquist, Torrealba, & Saper, 1998). Many laypeople are familiar with histamine, if only from the common over-the-counter use of anti-histamines to prevent allergenic side-effects. The histamine found in the TMN is the same as the histamine released in allergic reactions, but in the TMN (and in the mammalian brain) the histamine is used as a neurotransmitter to convey neural information. Therefore, the histaminergic pathway that the TMN utilizes is completely separate and distinct from the histamine pathway utilized in other parts of the body. It should also be understood that histamine will be found in other parts of the brain, but the key idea is that the TMN is the only part of the brain in which histamine is formed.

Much like the other sleep-antagonists, the TMN maximizes firing during the waking state and gradually decreases firing with decreased arousal. The TMN continues to decrease its firing through NREM, and is all but quiescent during REM (Sherin et al., 1998). Although the role of the TMN in reference to sleep has not been widely published, there exists a good deal of information on afferent and efferent interactions with the Ventrolateral Pre-Optic area, some of which can be applied to the neural mechanism of sleep initiation.

Perifornical Lateral Hypothalamus

The Perifornical Lateral Hypothalamus (McGinty & Szymusiak, 2003) has been referred to as the source of Hypocretin (Orexin) in the mammalian brain. Although it has been found that Hypocretin activates many arousal centers, the nuclear source of Hypocretin has many names. Hypocretin's primary source has

been claimed to be the Perifornical and Lateral Hypothalamus, the Lateral and Posterior Hypothalamus (Eriksson, Sergeeva, Brown, & Haas, 2001), the tuberal region of the Hypothalamus (Peyron et al., 1998), and also the dorsomedial Hypothalamus (Aston-Jones et al., 2001).

Regardless of the lack of a definitively named source, it is clear that Hypocretin causes arousal. Kiyashchenko et al. (1998) found a technique to measure the concentrations of Hypocretin across a long period of time. Before this technique was discovered, Hypocretin concentrations could only be measured for short periods of time. This new technique allowed Kiyashchenko and his colleagues to monitor the concentrations of Hypocretin throughout specific points in the brain across the natural sleep-wake cycle. Kiyashchenko et al. (1998) discovered that Hypocretin concentrations were positively correlated with the increased firing rates of the other sleep-antagonists, which indicates that Hypocretin most likely plays a role in arousal.

When searching the literature on Hypocretin and the sleep-wake cycle, it was clear that the LC and the TMN are affected by the Perifornical Lateral Hypothalamus (PFLH). However, the LC and TMN are not the only areas in the mammalian brain that are reactive to Hypocretin. It has been shown that Hypocretin reacts with all major players in the circadian system, except the SCN and possibly the Ventrolateral Pre-optic Area (Peyron et al., 1998). This vast Hypocretin interaction with the circadian system is a major distinction to be considered when comparing the PFLH and the Pineal Gland because the Pineal

Gland is not known to directly influence any part of the mammalian brain other than the SCN.

Although it is clear that Hypocretin plays a role in arousal, Hypocretin is also known to impact other systems in the brain. For example, Hypocretin plays a major role in the neural control of feeding behavior (Eriksson et al., 2001). In addition, extreme deficits in Hypocretin have been heavily implicated in Narcolepsy (Aston-Jones et al., 2001; Eriksson et al., 2001; Kiyashchenko et al., 2002). The effect of Hypocretin in Narcolepsy will be discussed in the Sleep Disorders section of this paper.

Sleep-Agonists

Pineal Gland

As is true in the sleep-antagonistic centers, the sleep-agonists also have a group of neurotransmitter based centers along with one hormone-based center, the Pineal Gland. Although many non-mammalian animals have Pineal Glands, the mammalian version has greatly evolved, and is now more specialized for sleep regulation than that of lower vertebrates and other animals (Ekström & Meissl, 2003). The mammalian Pineal Gland is almost in the exact center of the brain (Hilton, 2002), and near the ventricles of the brain (Pinel, 2003). The Pineal Gland is different from other areas of the brain in that it is a neuroendocrine gland, and Melatonin, its primary excretion, is released into the bloodstream, rather than being transported to its targets via neural connections (Ekström & Meissl, 2003).

As was mentioned above, the mammalian Pineal Gland has evolved from that of lower species. It evolved to sense basic light levels indirectly by receiving input from other areas and organs, rather than being directly connected to photosensory cells (Ekström & Meissl, 2003). Some non-mammalian species, like fruit flies, have many organs that both sense basic light levels and process the subsequent photosensory experience. However, humans are believed to have many light-sensing regions while the brain processes the photosensory experiences (Travis, 1998). For example, Travis (1998) reported that light shown on the back of the knees creates almost identical responses in the brain as does light shown on the eyes. The responses discussed by Travis are related to basic light levels, and not complex visual stimuli (Travis, 1998). One of the measured effects of the applied light was the increased concentration of Melatonin in saliva which indicates the increased production of Melatonin by the Pineal Gland.

Because the Pineal Gland is an endocrine gland, it releases its secretion directly into the bloodstream, and this secretion travels wherever the blood goes; however, it is important to realize that Melatonin will only have an effect wherever there is a receptor for it. A major receptor site for Melatonin in the mammalian brain is in the SCN. The Pineal Gland increases Melatonin production with decreases in the levels of light entering the eye, and possibly other parts of the body. When the Pineal Gland increases production, it does not store Melatonin, but rather releases it immediately into the bloodstream upon production. Melatonin tends to reset the circadian clock, meaning that the typical person will

become sleepy and the other sleep-agonistic centers might be able to take over and cause the initiation of sleep; however, if a human who is producing Melatonin does not reduce physical and mental activity, the hormone will likely have little effect. In other words, the effect of Melatonin will most likely induce sleep, unless the organism is antagonizing this process with increased physical and mental activity.

The use of Melatonin supplements and the manipulation of endogenous Melatonin production are very useful to those enduring jet-lag, night-time shifts (and subsequent daytime sleep), and other changes in the sleep schedule. Melatonin is currently available for sale in the United States. It has increased in its popularity and is an over-the-counter drug about which few people ask their doctors before consuming. However, while Melatonin is a harmless drug when taken appropriately, abuse of this drug can reduce the effectiveness of endogenous Melatonin. The dosages sold in the United States are probably more than enough to mimic the effects of endogenous secretion, but much like any other drug, the human body can develop a resistance to it. Such a resistance would mean that the effects of endogenous Melatonin would not be enough to have the same effect as it did before the use of the supplement. Anyone considering taking Melatonin supplements should consult a doctor before use, especially if they are on any prescription medications.

Pre-optic Area

As a whole, the Pre-optic Area (POA) of the mammalian brain has many hypnogenic (sleep-inducing) characteristics. The hypnogenic effects of the POA are primarily thought to be due to efferent inhibitory projections to the RAS and possibly to the SCN. Two specific areas of the POA, the Ventrolateral Pre-optic Area (VLPO) and the Median Pre-optic Nucleus (MnPN), have been implicated in sleep initiation. These are the only two areas of the brain found to specifically promote sleep. Much like the difference in interactions between the RN and the LC, the MnPN has complex inner workings, while the VLPO has a relatively simple internal mechanism. Although the MnPN is believed to have some efferents, the VLPO most likely has more, and targets all known major sleep-antagonists (Chou et al., 2002). In addition to POA efferents to sleep-antagonists, there is also a great deal of communication between the VLPO and MnPN (Chou et al., 2002). This communication between the VLPO and the MnPN suggests that these two POA sleep-agonist centers may work together in a way unique to the sleep-agonists.

Pre-optic Area: Median Pre-optic Nucleus

Suntsova, Szymusiak, Alam, Guzman-Marin, and McGinty (2002) discovered that the MnPN contains pace-setting cells. These pace-setting cells change firing rates across the sleep-wake cycle, but on average, the MnPN fires more frequently in NREM than in waking, and more so in REM than in NREM. Within this unique population of cells exists multiple sub-populations exhibiting specific firing patterns, all of which create a sort of sleep-initiation pacemaker.

The first sub-population (S1) discussed by Suntsova et al. (2002) has a straight-forward internal dynamic and comprises the majority of the sleep-related cells in the MnPN. S1 contains neurons which, on average, increase their activity greatly from waking to NREM, and show lesser (but still substantial) increases from NREM to REM. All the S1 cells do not fire all at once, but instead fire in a tonic manner at all times. Within S1, some cells ($S1_a$) preferentially peaked their activity during NREM sleep and were more similar than different during waking and REM. Also in the S1 population, other cells ($S1_b$) peaked during REM and were insignificantly different between waking and NREM; interestingly, $S1_b$ cells exhibited the peak occurring in REM almost instantaneously, in accordance with the observable state transition. Most likely, S1, as a whole, would be primarily responsible for the transition from waking to NREM, and from NREM to REM. However, these cells seem to have little to do with the stage transitions occurring within NREM. This lack of influence is assumed because these cells were not recognized to increase substantially within NREM or REM, but rather fire tonically throughout these individual sleep stages.

In a second sub-population (S2) found by Suntsova et al. (2002), all cells increased their firing rate during waking, and presumably, decreased across all other phases of sleep. In addition, these cells tend to significantly decrease their rates between the first NREM and last NREM episode during constant sleep. Within S2, some cells ($S2_a$) increase firing rates during W in association with

muscle movement and activity, while others ($S2_b$) increase during W independent of muscular activity. The combined effects of $S2_a$ and $S2_b$ can account for the fact that doing nothing can still result in exhaustion, but that physical activity can often produce fatigue more quickly than doing nothing. For example, if a person does strenuous work, both the muscle-related ($S2_a$) and non-muscle-related ($S2_b$) neurons of the MnPN will increase their firing rates. During static activities, only the $S2_b$ neurons would increase firing. Also, if higher cognitive functioning is not utilized, such as when watching TV or whenever boredom occurs, there is no inhibition of $S2_b$ cells by arousal and higher cognitive centers. However, it is important to consider that strenuous physical activity can also raise arousal by activating the sleep-antagonist centers, possibly counteracting any added effect the S2 population might have on fatigue.

A third sub-population (S3) was identified by Suntsova et al. (2002) that is simply more active during W and REM than during NREM, with no significant difference between the W and REM states. Although Suntsova et al. (2002) did not remark on the possible functions of these MnPN sub-populations, the S3 cells could function antagonize the S1 cells, thereby creating a balance and strengthening the pacemaker function of the MnPN. However, too little is known about the interactions between sub-populations of the MnPN to infer functions at this time.

Suntsova et al. (2002) made reference to a final sub-population (S4), that consists of neurons whose firing rate does not depend on sleep states. The function of S4 cells could be to serve as the control group for the MnPN, but, more likely, their function lies with the non-sleep-related functions of the MnPN, which include many autonomic processes such as blood volume regulation. The highly specialized organization of the MnPN for sleep might indicate that it functions most vital function is sleep initiation and maintenance, but this fact remains to be confirmed (Suntsova et al., 2002).

Pre-optic Area: Ventrolateral Pre-optic Area

The VLPO has efferents that reach almost all of the sleep-antagonists, and these projections utilize two different inhibitory neurotransmitters, GABA and Galanin (Chou et al., 2002; Sherin et al., 1998). The VLPO displays a very straight-forward firing rate, as opposed to the convoluted inner workings and sub-populations of the MnPN. In general, the VLPO is most active during deep sleep, and damage to it tends to decrease the number of delta waves (Chou et al., 2002).

A major component to the sleep-wake cycle is the sensitivity of the VLPO to Adenosine, one of the numerous endogenous chemicals of the mammalian brain. Adenosine has been shown to increase in concentration during the waking state, and is only reduced in concentration during slow-wave sleep (Porkka-Heiskanen et al., 1997). The existence of Adenosine has been shown to increase slow-wave sleep and decrease REM sleep. Adenosine is not known to increase the efficiency of slow-wave sleep, but rather to increase the time spent in slow-wave sleep.

Some stimulants, such as caffeine, actually inhibit the effects of Adenosine, which can account for the waking effect of caffeine (Porkka-Heiskanen et al., 1997).

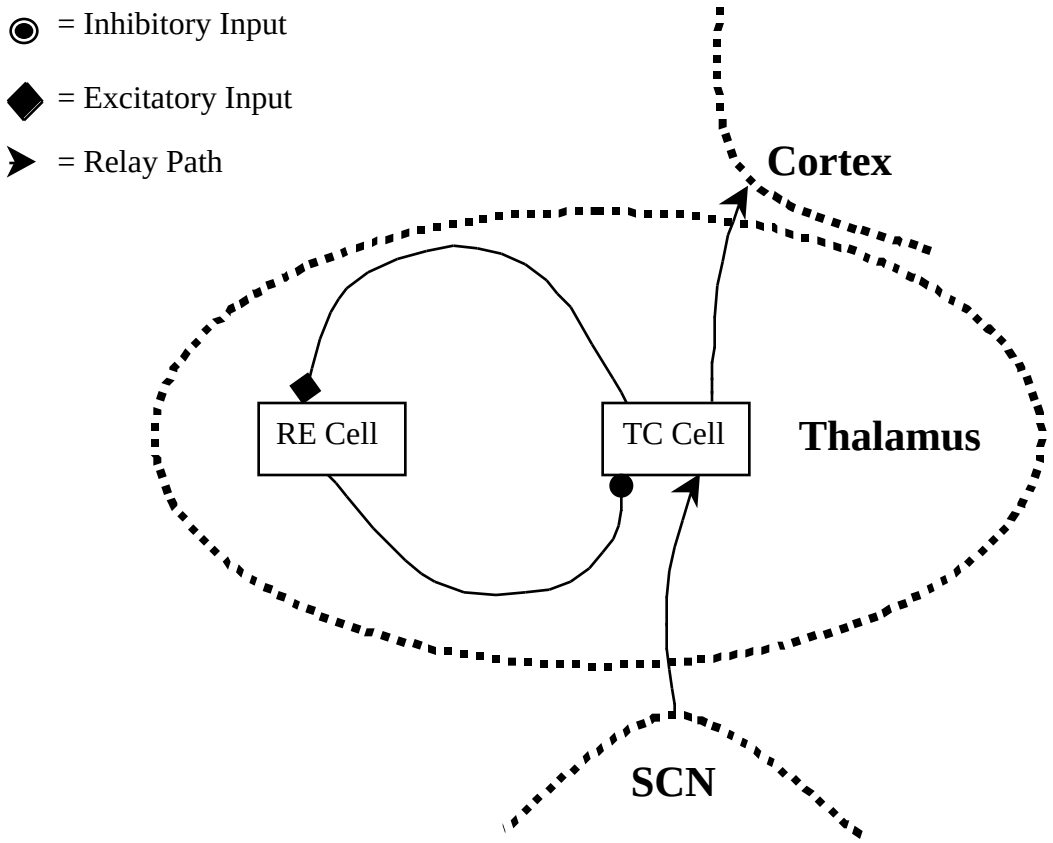
Thalamus

The thalamus is a very well known structure in the brain, yet the involvement of the thalamus in sleep is not often referenced in the professional literature. However, Destexhe and Seinowski (2003) wrote a detailed and interesting account that, among other things, explained the involvement of the thalamus in the propagation of brain waves. The existence of brain waves has been known for quite some time, but the way these intrinsic conditions are created and sustained within the brain is still being investigated. Progress has been made and some of the more recent theories can account for most or all of the data on the subject of brain wave propagation. The oldest published theory explaining the brain's rhythmic properties was the "Circus Movement Theory," which postulated that traveling action potentials in the brain set off the waves recorded by the EEG. Although the Circus Movement Theory sounded good, this explanation was lacking in numerous ways, as most early theories were found to be. Another early theory, the "Thalamocortical Reverberating Circuit" theory, was more locationally on target, but still fundamentally wrong. This theory suggested that the traveling action potentials between the thalamus and cortex caused the rhythms indicative of the sleeping mammalian brain. Both of these theories imply that the electrical activity simply spreads or diffuses across brain tissue. These two theories tend to be less comprehensive than the current theory which is based on scientific data.

The current theory, which lacks a specific name, suggests that the oscillations are due to thalamic pacemakers interacting with both intra-thalamic and thalamocortical excitatory and inhibitory post-synaptic potentials (EPSP-IPSP) loops. Figure 4 diagrams a single theoretical thalamocortical loop.

Destexhe and Seinowski (2003) explained how the rhythmic properties of the thalamus are transferred to the different areas of the cortex via various routes and relays in the brain. The rhythmic wave arrives in almost every part of the brain and the results of this wave are readily recorded by an EEG. The spreading of the signal through the cortex is theoretically achieved in a very similar way to the transition of the waves from the thalamus to the cortex. The path of these waves involves an intermediary between the thalamus and initial cortical relays. This intermediary between the thalamus and initial cortical relays is the thalamocortical loop. One of the cells involved in the thalamocortical

Figure 4.



The thalamocortical loop as described in the neural mechanism. Notice that the input to the loop is from the SCN, and that the output of the loop leaves the thalamus and proceeds into the cortex, thus theoretically initiating brain waves. The TC cell excites the RE cell. When the RE cell is excited, the RE inhibits the TC cell. The inhibition of the TC cell could prevent the next occurrence of firing.

loop is the distributor "TC cell". The TC cell is connected to the cortical relays in addition to an "RE cell". The RE cell responds to the excitatory potential of the TC cell with an inhibitory potential that is transmitted back to the TC cell (Destexhe & Seinowski, 2003).

Complicated neural relays can often be easier to understand if considered from start to finish of a single cycle. The cycle of a thalamocortical loop starts with the thalamus exciting the TC cell of the thalamocortical loop. Next, the TC cell will

fire, causing an EPSP in both the cells of the cortical relays and the RE cell. Then, the RE cell will fire, causing inhibition of the TC cell. The inhibited TC cell is hyper-polarized by the inhibition, meaning that it requires more excitatory potential than when not inhibited to fire. Once the TC cell is hyper-polarized, the thalamus must transmit more excitatory potentials to the TC to cause the firing of the TC cell. The cycle is over once the TC cell is no longer hyper-polarized. The cycle begins again when the TC cell receives enough excitatory potentials to fire. However, the idealization of this cycle breaks down in real time, primarily because the inhibition by RE cells and the excitation of TC cells by the thalamus can and will happen at roughly the same time (Destexhe & Seinowski, 2003).

Destexhe and Seinowski (2003) suggest that although the thalamus appears to be pivotal in the creation of brain waves, the thalamus cannot maintain synchrony by itself. In experiments, the thalamus only maintained large-scale synchrony if part or most of the cortex was intact. Without the cortex, the intrathalamic and extrathalamic rhythms were broken down and synchrony was only recorded within a 1 mm distance. This loss of synchrony demonstrates that the thalamus relies on feedback from portions of the cortex to maintain the rhythms of its internal and efferent processes. However, the process involved in the feedback to the thalamus by the cortex has not been published widely at this time (Destexhe & Seinowski, 2003).

Sleep-Wake Switch

The sleep-wake switch (McGinty & Szymusiak, 2003; Suntsova et al., 2002) works much like a dimmer switch for a light bulb: a strong force or push in any one direction can increase or decrease the strength of result, which, in this case, may be either the initiation (agonism) or inhibition (antagonism) of sleep. The loss of consciousness that follows, or occurs simultaneously with, sleep initiation is theoretically due to the work of the thalamus.

Because the actors in sleep initiation and arousal have been described, the overall process of sleep initiation or cessation can be formed properly. The best way to describe the actual processes of the sleep-wake switch is to move through the stages involved when the typical person is conscious and aroused, and then proceed through the occurrence of sleep. When the typical person is conscious, all of the sleep-antagonists are very active, managing one function or another. The Locus Coeruleus, Raphé Nucleus, and Tuberomammillary Nucleus are all exciting the Suprachiasmatic Nucleus with Norepinephrine (Aston-Jones et al., 1991; Aston-Jones et al., 2001; Berridge & Foote, 1991; Gervasoni et al., 1998), Serotonin (Manfridi et al., 2003; Sakai & Crochet, 2001), and Histamine (Eriksson et al., 2001; Sherin et al., 1998), respectively. Although the Locus Coeruleus, Raphé Nucleus, and Tuberomammillary Nucleus do not directly connect to one another, the Perifornical Lateral Hypothalamus is stimulating all three areas, but does not directly interact with the Suprachiasmatic Nucleus (Peyron et al., 1998). The individual outputs of the sleep-antagonists may vary throughout the day with levels of concentration, attention, and physical activity, but as long as the typical

person is fully awake and not drowsy, the sleep-antagonists' outputs are at or near full functioning.

If it is accepted that the Tuberomammillary Nucleus, Raphé Nucleus, and Perifornical Lateral Hypothalamus all innervate both the Ventrolateral Pre-Optic Area and the Median Pre-optic Nucleus (Berridge & Foote, 1991; Chou et al., 2002; Sherin et al., 1998), and that the Locus Coeruleus does not innervate either the Ventrolateral Pre-optic Nucleus or Median Pre-optic Nucleus (Chou et al., 2002), then Serotonin, Histamine, and Hypocretin must all inhibit the activity of the Ventrolateral Pre-optic Nucleus and Median Pre-optic Nucleus. Therefore, Serotonin, Histamine, and Hypocretin lessen the efferent inhibitory outputs of the Ventrolateral Pre-optic Area and Median Pre-optic Nucleus, but do not completely sedate the Ventrolateral Pre-optic Area and Median Pre-optic Nucleus. The simple inhibition and lack of complete sedation would allow the Median Pre-optic Nucleus to release the inhibition of the Ventrolateral Pre-optic Area and inhibit the Suprachiasmatic Nucleus and sleep-antagonists according to phase-change indications within the Median Pre-optic Nucleus. In response to excitation by the Median Pre-optic Nucleus, the Ventrolateral Pre-optic Area would increase its firing rate, thus strengthening the Median Pre-optic Nucleus, regulating the Suprachiasmatic Nucleus, and inhibiting the sleep-antagonists. The back-and-forth excitatory interaction between the Ventrolateral Pre-optic Area and Median Pre-optic Nucleus inevitably tips the scales in favor of the sleep-agonists, meaning

the sleep-antagonists would be inhibited. The sleep-wake switch can easily be reversed by the sleep-antagonists when sleep is interrupted.

The sleep-agonists are very different from the sleep-antagonists, in terms of their interactions with each other. The two neurotransmitter-based sleep-agonist centers (Ventrolateral Pre-optic Area and Median Pre-optic Nucleus) heavily interact with each other. In fact, one of the heaviest inputs to the Ventrolateral Pre-optic Area is from the Median Pre-optic Nucleus (Chou et al., 2002). This input to the Ventrolateral Pre-optic Area has been postulated to be a major source of synchronization for the sleep-agonists (Chou et al., 2002). The Ventrolateral Pre-optic Area is known to have efferents to all the sleep-antagonists with the exception of the Locus Coeruleus, while the Median Pre-optic Nucleus is known to project to both the Locus Coeruleus and the Raphé Nucleus. The Pineal Gland has a very different style of sleep-center modulation from the Perifornical Lateral Hypothalamus in that it does not directly affect the sleep-agonists, but rather regulates the Suprachiasmatic Nucleus directly (Hilton, 2002). Although the sleep-antagonists and sleep–agonists have different methods of interaction with sleep centers, both groups can take control of the sleep-wake switch efficiently when prompted.

Sleep Disorders

The neural mechanism of sleep initiation is the process by which sleep occurs in healthy, average mammals. However, even a mild deviation within a single sleep center can disrupt the cycle of sleep. The symptoms observed in

sleep disorders are often the direct results of deviations in the sleep centers involved in either sleep initiation or sleep-antagonization. In this section the basic causes of a few sleep disorders will be mentioned, along with the symptoms used to diagnose the particular sleep disorder.

Narcolepsy

Few sleep disorders are as well known as Narcolepsy, and possibly even fewer as misconstrued in the media. Although the actual combination of symptoms in Narcolepsy can vary, the symptoms usually associated with Narcolepsy include cataplexy, excessive daytime sleepiness, hypnagogic hallucinations, and sleep paralysis (each is described below). The existence of cataplexy and excessive daytime sleepiness are often considered to be the most distinguishing characteristics, while sleep paralysis is a symptom found in other disorders and can occur spontaneously in the general public. Hypnagogic hallucinations are also not found exclusively in Narcolepsy and have been occasionally observed in people without any known sleep-cycle affliction (Parkes, Chen, Clift, Dahlitz, & Dunn, 1998).

Cataplexy is a sudden loss of muscle tone and often involves characteristics indicative of REM (Parkes et al., 1998). This occurrence of REM-like conditions suggests that subjects are asleep while experiencing a cataplectic attack. Cataplexy is often brought on by a strong emotional response, such as laughter or surprise (Parkes et al., 1998). Cataplexy should not be confused with a simple loss of muscle tone, termed atonia, which does not display the features of

REM and may or may not be brought on by an emotional response (Parkes et al., 1998). Although it may seem like the existence of cataplexy would be easy to identify, individuals experiencing a cataplexy episode may not realize they experienced such an episode unless a violent fall or disruption in stance occurs. A clinician may want to personally view an episode of cataplexy before an actual diagnosis is made, meaning a formal diagnosis may take years to complete because cataplectic attacks may be very infrequent or occur only once (Parkes et al., 1998).

Excessive daytime sleepiness is what the name implies, drowsiness to the point that it impedes the ability to function. Excessive Daytime Sleepiness is a condition in which a person's ability to stay awake and alert is impeded by constant or periodic drowsiness. This drowsiness can cause involuntary sleep initiation which could happen in a potentially life-threatening situation, such as while driving a car. Excessive Daytime Sleepiness comes in varying intensities and may or may not include sleep drunkenness (Billiard et al., 1998; Mukai et al., 2003). Sleep drunkenness is a condition that results in the inability to achieve full waking arousal in a reasonable amount of time and will most likely lead to confusion, dysphoria (an anxious and uncomfortable state of being), and possible motor coordination problems upon awakening (Billiard et al., 1998). A good conceptual image of this disorder is the small child that must be dragged out of bed or splashed with cold water to be awakened. However, someone exhibiting true sleep drunkenness has no control over the condition and will most likely

exhibit the sleep drunkenness across all situations, no matter the desire for alertness involved.

Hypnagogic hallucination is the old term for Sleep-onset REM (SOREM) and occurs when a REM episode is experienced at the onset of sleep, rather than the typical stage 1 sleep. Sleep-Onset REM episodes can and do happen in the general population and do not conclusively indicate the existence of Narcolepsy, nor do the lack of such episodes discount the existence of Narcolepsy (Billiard et al., 1998).

Sleep paralysis is a condition in which the paralysis that normally occurs only during a REM episode extends through to the waking state for a short period of time. People exhibiting sleep paralysis wake up and have little to no voluntary muscle control for a limited period of time. This condition does not indicate a disorder, but lack of knowledge about this condition can be responsible for considerable stress and anxiety in an individual and can cause a fear of sleep in general. In general, sleep paralysis is more likely to occur when circadian rhythms are shifted or interrupted.

The symptoms that occur in Narcolepsy are largely believed to be due to drastically insufficient amount of Hypocretin in the mammalian brain (Aston-Jones et al., 2001; Eriksson et al., 2001; Kiyashchenko et al., 2002; Peyron et al., 1998). The lack of sufficient Hypocretin can impede the brain's ability to maintain arousal regardless of attention and concentration levels. In addition to limiting arousal levels, a lack of sufficient Hypocretin seems to cause abnormal effects in the REM

system. The effects on the REM system are demonstrated by multiple symptoms including cataplexy, hypnagogic hallucinations, and sleep paralysis. The role of Hypocretin in the other symptoms present in Narcolepsy has not yet been substantiated.

The treatment of Narcolepsy has historically utilized stimulants of all types, but especially those stimulants that are agonists for excitatory neurotransmitters like Glutamate and Norepinephrine. These types of stimulants often provide limited help (Guilleminault, Aftab, Karadeniz, Leger, & Leger, 2000) and are outlawed or carry heavy restrictions in some countries due to their potential use as recreational drugs (Billiard et al., 1998). A new drug, Modafinil, has been found to be very useful in treating Narcolepsy. This drug is also revolutionary because it is not believed to be a traditional stimulant, but the way Modafinil works is still unclear at this time (Guilleminault et al., 2000). The side-effects of Modafinil are generally mild and the primary side-effect is headaches. Among patients who previously have been treated with other stimulants, the side-effects tend to be worse. Overall, Modafinil seems to be a push in the right direction for the treatment of Narcolepsy.

Idiopathic Hypersomnia

Idiopathic Hypersomnia literally means excessive sleep. It has various sub-types, and has been recognized as a distinct disorder for only two-to-three decades (Billiard et al., 1998). One way to conceptualize this disorder is to organize it into complete and incomplete sub-types. It should be noted that the

term Essential Hypersomnia is a disorder that was acknowledged around the same time as Idiopathic Hypersomnia (Billiard et al., 1998), but that is actually the same as incomplete Idiopathic Hypersomnia (Billiard et al., 1998; Mukai et al., 2003). The complete sub-type exhibits all possible symptoms while the incomplete sub-type displays only some of the possible symptoms. The symptoms displayed in complete Idiopathic Hypersomnia are severe Excessive Daytime Sleepiness with sleep drunkenness and instances of excessively long periods of sleep. For people with complete Idiopathic Hypersomnia, naps may be detrimental due to the possibility of sleep drunkenness after even short periods of sleep. Incomplete Idiopathic Hypersomnia is different from complete Idiopathic Hypersomnia in that the incomplete form does not cause sleep drunkenness, and the majority of people with the incomplete sub-type studied by Billiard et al. did not exhibit an excessively long period of sleep. Also, people with incomplete Idiopathic Hypersomnia tend to have varying degrees of Excessive Daytime Sleepiness.

The treatment options for people with Idiopathic Hypersomnia have often been the same as that for Narcolepsy (Billiard et al., 1998; Guilleminault et al., 2000; Parkes et al., 1998). Many of the same stimulants are used for both disorders, but these stimulants have less success when used to treat Idiopathic Hypersomnia. Modafinil is also used in the treatment of Idiopathic Hypersomnia but its usefulness in treating Idiopathic Hypersomnia is still being evaluated.

Insomnia

Insomnia is a sleep disorder very different from most other sleep disorders. Insomnia is common as far as disorders go, causing sleep dissatisfaction in approximately 10-15% of people (Sateia & Nowell, 2004). Insomnia is often believed to be sustained by other disorders or conditions, but usually does exist in its pure form. Generally, disorders are not considered to exist in their true form if caused by another disorder, such as drug abuse, but Insomnia does not follow this rule of thumb (Sateia & Nowell, 2004).

Although the layperson's traditional idea of insomnia may be characterized by difficulty falling asleep and staying asleep, Insomnia has many features other than an increase in sleep latency, which is the time it takes for a person to fall asleep. The symptoms of Insomnia may include various mental deficiencies, impaired coordination and strength, and muscle and digestive problems, most of which result from sleep deprivation (Sateia & Nowell, 2004). Most of the symptoms of insomnia are measured by subjective responses and self-evaluations from the patient that often involve the use of sleep logs and schedules (Linley, 2005; Sateia & Nowell, 2004). The primary complaints of insomniacs involve increased sleep latency (time spent going to sleep), increased numbers and duration of sleep disruptions, and early waking from sleep. For insomnia to exist, these symptoms and schedule issues must cause distress to the patient. As mentioned in the section on sleep duration, it is normal for sleep periods to differ greatly from one person to another and from one night to another. Therefore, a

shorter time spent asleep that does not cause distress to the individual may be the result of an adaptation to the current situation or the result of age.

Sometimes, patients attribute their low sleep quality or quantity to Insomnia, when really they have a different sleep disorder. Sleep Apnea is a sleep disorder in which the patient can stop breathing temporarily or where breathing quality can be diminished drastically (Heinzer et al., 2001). Sleep Apnea is heavily influenced by overall health, and can be caused or worsened by certain health conditions, including obesity and excessive alcohol consumption (Bayadi et al., 1990). In Obstructive Sleep Apnea, one or more parts of the airway can be blocked causing a temporary cessation of breathing. A continuous positive airway pressure machine (CPAP) can improve the quality of sleep by maintaining a patent (unblocked) airway at all times (Heinzer et al., 2001).

Insomnia exists in both the acute and the chronic form. Either form of Insomnia can result from an existing medical disorder; however, the acute form of insomnia is normally brought on by short-term illnesses, stress, schedule changes, or possibly maturation (Linley, 2005; Sateia & Nowell, 2004). The acute form may require no more than a little time to adapt and some helpful advice. In contrast, chronic Insomnia is almost always due to an accompanying pathological disorder. Furthermore, the pattern of chronic Insomnia will probably follow the periods of severity of the accompanying disorder, meaning when the accompanying disorder is worse, the Insomnia will be worse (Sateia & Nowell, 2004). For example, Insomnia and other sleep disorders occur frequently in people with Parkinson's

disease, and Insomnia is likely to be worst during a flare-up of Parkinson's symptoms than during remission or lessening of symptoms (Stocchi et al., 2000).

Many treatment options for insomnia currently exist in developed countries and most can be placed into one of two categories: drug-based or therapy-based (Linley, 2005; Sateia & Nowell, 2004). In America, most sleep professionals tend to agree that therapy techniques are the most helpful over a longer period of time (Linley, 2005; Sateia & Nowell, 2004). This is because non-drug treatments teach the patient to control when and where sleep happens, and they do not reinforce dependency on a drug. In contrast, drugs tend to be much better for short-term treatments because they do not involve the learning of a skill. However, hypnotic (sleep-inducing) drugs usually have addictive properties, suggesting that hypnotic drugs should only be used under close clinical supervision (Sateia & Nowell, 2004). The most common hypnotic drugs include benzodiazepines and their agonists, various antihistamines which tend to be sold over-the-counter, natural medicines such as Melatonin, and various other drugs with hypnotic properties.

The Modern Sleep Lab

In the eyes of a child, the concept of a sleep lab can be a scary place. When a family member disappears for a night to have tests done, the visualization of a mad scientist's lair with all sorts of terrible machines and instruments is certainly not beyond the realm of imagination. However, the true nature of the modern sleep lab is much different than this plausible depiction. The "mad scientist's lair" may resemble a hotel room more so than any lab. The truth of the

situation is that the modern sleep lab is designed to be comfortable, and usually described as either home- or hotel-like.

In order to more systematically investigate the modern sleep lab, thirteen major American cities were chosen arbitrarily and sleep labs in those cities were randomly chosen using the “local results” feature of the Google search engine. Four cities, New York, San Francisco, Raleigh, and Minneapolis, returned no Google local results and no sleep labs were contacted in these cities. The information collected from the sleep labs in the remaining nine cities is in Table 2. The final column in Table 2 indicates whether the sleep lab is accredited by the American Academy of Sleep Medicine. Only full service labs can be accredited.

Although all the facilities in Table 2 are sleep diagnostic facilities, some call themselves sleep labs, and others sleep centers. The term lab, when referring to a sleep lab, does not necessarily indicate the occurrence of research at that facility, just as the term center does not only correspond with medical diagnostics and treatment. Aside from whether or not research is performed, the environment in a sleep lab is necessarily going to be comfortable in almost all cases. The only reason why a sleep lab might not be designed around the comfort of the patient is if research is being done that requires the prevention of sleep. When the representatives of the individual sleep labs were asked to describe their own facilities, the phrases “like a hotel” or “like being at home”

Table 2. Information on Sleep Labs Across the US

Name of Facility	Location	Disorders Diagnosed	# of Testing Rooms	# of Physicians on Staff	# of Patients Seen	% of Patients with OSA	Tests Given at Facility	In-House Treatments	Academy Accredited
Swedish Sleep Medicine Institute	Seattle, WA	FS	18	4	130-135/ week	—	PS, MSLT, PaS	CPAP Titration	Yes
St. Elizabeth Sleep Disorder Lab	Lincoln, NE	OSA, PLM	2	5-6	—	90	PS, MSLT	CPAP Titration	No
St. Anthony Hospital SL	Oklahoma City, OK	OSA, N	4	4	18/ week	90-95	PS, MSLT	CPAP Titration	No
Somnitech, Inc.	Kansas City, KA	FS	48	2	500-600 /month	75-80	PS, SNS, MSLT	CPAP Titration	Yes
North Texas SL	Dallas, TX	OSA, RLS, N, I	4	—	20/ week	—	PS, SNS, MSLT	CPAP Titration	No
Gateway SL	Los Angeles, CA	OSA	2	—	14/week	90-95	—	—	No
Comprehensive Sleep Solutions	Phoenix, AZ	OSA, PLM, I, N	6	10	200 /week	95	PS, MSLT, MWT	CPAP Titration	No
Comprehensive Sleep Disorder Center	Orlando, FL	FS	14	8	98/week	95	PS, MSLT, MWT	CPAP Titration	No
Bon-Secours SL	Richmond, VA	OSA, N, RLS	6	7	75-80/week	80	PS, SNS, MSLT	CPAP Titration	No

Abbreviations: FS: Full Service; I: Insomnia; MSLT: Multiple Sleep Latency Test; MWT: Maintenance of Waking Test; N: Narcolepsy; OSA: Obstructive Sleep Apnea; PaS: Parasomnia Studies; PLM: Periodic Limb Movement Disorder; PS: Polysomnography; SL: Sleep Lab; RLS: Restless Legs Syndrome; SNS: Split-night Studies (a form of polysomnography)

occurred repeatedly. The Swedish Sleep Institute in Seattle prides itself with providing a home-like environment, and specifically avoids furniture and furnishings characteristic of hotels. Meanwhile, the Gateway Sleep Lab in Los Angeles utilizes actual hotel rooms. The Comprehensive Sleep Disorder Center in Orlando modified rooms at their facility to accommodate patients for various sleep studies. Figures 5a and b are copyrighted pictures of the Comprehensive Sleep Disorder Center in Orlando and show what the typical hotel-style room is like. Notice that the furniture looks normal but that the overall situation is more similar to a hotel than the stereotypical residential bedroom.

Whether or not a sleep lab testing room is more similar to home or a hotel, the process of making a testing room comfortable can be difficult and costly. Somnitech, Inc. is a company that provides sleep labs to hospitals lacking their own sleep-related facilities. Somnitech works with multiple hospitals and medical labs all over the western United States. The Somnitech sleep lab in Kansas City was professionally decorated and is described as being the equivalent of a three-star hotel room. Of course, not all sleep labs go to that much trouble, but, in any case the art of making a patient feel comfortable is the ultimate goal of any good sleep lab.

When going to a sleep lab, doctors often perform a clinical interview first, to assess the medical history of the patient. If an EEG is needed, it may be done right away if there are no scheduling issues. Due to the limited number of sleep labs and the overwhelming need for their services, elaborate tests such as

Figure 5a

Figure 5b

Two pictures from the Comprehensive Sleep Disorders Center in Orlando, Florida detailing the setup of a patient testing room. In figure 5a, notice how the electronics are well concealed and organized. The rooms do not resemble the stereotypical residential bedroom, but appear comfortable and homely, nonetheless. On the bedside table is a white CPAP machine, and on the headboard are some electronic hook-ups that can be used for EEGs and possibly other machines. The recliner in figure 5a may be used for short EEGs. In figure 5b, there is a TV on the wall beside an observation camera and a few small paintings. There is a dresser for the patient's use, although most patients would use the room for no more than eight to ten hours at a time. There is some other furniture in the room, some of which is purely for aesthetic appeal.

Multiple Sleep Latency tests, which last about eight hours, will often need to be scheduled for a future time. If an over-night study is needed, patients may be asked to arrive around bedtime (e.g. 8 to 10 p.m.). Few tests, if any, require the removal of clothing, so patients are usually instructed to dress comfortably. Sleep labs will always have over-night lab technicians to supervise any sleeping patients, and many facilities are safer than the traditional home. The key to a successful sleep study is comfortable surroundings, so patients are often provided anything reasonable to enhance the pleasantness of the environment. If a common sleep disorder is diagnosed, treatment can often easily be added to the patient's routine, such as a timed heating blanket for Hypersomnia or a CPAP machine for Obstructive Sleep Apnea.

American sleep labs vary greatly in size and function. Almost all sleep labs will treat and diagnose Sleep Apnea, especially the Obstructive type. Many non-accredited labs tend to specialize in two or three specific disorders and may or may not be equipped to handle other disorders. The average sleep lab, academy accredited or not, does not provide any in-house treatments other than CPAP titrations. Most sleep labs simply provide diagnostic services, and allow medical retailers to provide the supplies needed for treatment. If Sleep Apnea is diagnosed in a patient, continuous positive airway pressure machines (CPAP) can be used to treat Sleep Apnea, especially the obstructive type. CPAP titrations are used to find the minimal amount of pressure needed from the CPAP to keep the patient's airway open. A CPAP titration takes approximately six to eight hours to

complete and can be done over two nights (a split-night titration) or all at once (a full-night titration). A CPAP titration is performed by sleep labs, and a prescription is prepared for the patient.

If a patient suffering from a sleep disorder has a choice, an Academy accredited sleep lab will most likely provide the largest selection and highest quality of services. A list of accredited sleep labs can be found on the Academy's website (www.aasmnet.org). It should be noted that the number of doctors at a sleep lab does not necessarily indicate the quality of service provided. Most tests are performed by lab technicians, not doctors. However, all test results are supposed to be interpreted by medical doctors or other trained research professionals.

Discussion

Sleep, its causes, and its benefits, have been discussed for many years, and the discussion is not nearly over. More is known about the causes of sleep initiation now than ever before. Because this paper was designed to sum up the past and current literature and because of the delay inherent in scientific publication, this paper is likely to be outdated before it is published. However, the point of this paper is to serve as a starting point for those looking to understand the intricacies of sleep and is not meant to be the definitive source of information on sleep.

There are some portions of the neural mechanism for sleep initiation that need to be researched more in depth. The process of how the thalamus creates

and sustains brain waves needs to be further examined and researched. Although Destexhe and Seinowski (2003) provided a good examination of the role of the thalamus in the creation of brainwaves, their model is largely theoretical and possibly oversimplified, and needs to be tested and substantiated in the mammalian brain. The connection between the Suprachiasmatic Nucleus and the thalamus is largely unknown, and little recently published research concerns itself with this connection. Also, the intricacies of the sleep-wake switch as a whole have yet to be studied in enough detail.

A seemingly necessary gap in the literature is in reference to sleep initiation in humans. Because most of the research in this area requires invasive procedures, and thus, animals, the current models cannot be shown to exist concretely in humans. Perhaps as non-invasive functional testing (e.g. fMRI and PET scans) evolves so will our view of sleep initiation in humans. Until non-invasive human testing yields more answers, animal models will continue to be designed and perfected in an attempt to better understand human sleep.

Finally, the current literature on theories of sleep tends to be fragmented or one-dimensional. If society wants to understand the evolutional and functional aspects of sleep, then eclectic views and models must be considered and published for peer review. As animal models of sleep progress, more and more will be understood, and maybe someday the reasons for and implications of sleep will be common knowledge. However, until all is understood, society will need to understand the two basic facts of sleep: sleep serves an incredibly important

function in human health and proper sleep etiquette is as important as regular diet and exercise are to general health.

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