Biomedical Correlates of Sleep

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Sleep has always held a special fascination for me much before my medical school days. I recall how I used to meticulously peruse every article on sleep that appeared in the newspapers or the periodicals during my time in the boarding school. The school library, although very well equipped by contemporary standards, did not have much material on sleep and I recall the bemused expression on my school librarian's face when I requested him to obtain a few tomes on the topic.

Slumber is clearly one of the most fundamental drives regulated by the innate biological clocks all of us carry within ourselves. But what is most intriguing is that we still do not understand fully its function. I recall very clearly asking my biology teacher why sleep as a physiological activity was in any way preferable to a state of conscious rest where the brain would continue to receive external inputs. His response, now almost 55 years ago, was that while the area was not fully understood, an unconscious sleep offers an advantage to the brain. And unfortunately, despite all the scientific advances, we have still not been able to solve this riddle. There is a tacit acceptance that sleeps impacts nearly every system governing human physiology. It is an important ingredient of neurosciences. It is crucial in pulmonary functions. And of course, it does have a bearing in psychiatry.

During my medical school years, I had managed to buy a copy of the book called Sleep by Ian Oswald,[1] one of the most respected sleep researchers in the world. It intrigued me even further and I seriously began to dream and aspire for a career as a full-time sleep researcher. When I was selected for my residency training in Edinburgh, I noted a name of a senior professor at the hospital being Ian Oswald. I had absolutely no idea that he was the same man whose bestselling book had influenced me so much during my formative years and prompted me to seek a career in sleep research. And my thrill and excitement knew no bounds when I was assigned to his unit in the next few months.

However, things did not work out as I had hoped as I had a severe altercation with Oswald over one of his remarks which I objected to and perhaps over-reacted. That put paid to my dream of becoming a sleep researcher. But all credit to Oswald who was big enough to impart crucial insights into this area. While I could no longer rely on him to help me with my stated ambitions, Oswald was always willing to help me with his phenomenal insights despite our mutual antipathy towards each other. And while I could not become a sleep researcher, I did learn an awful lot from Oswald; and his teachings have always held me in good stead.

Functions of Sleep

There is an abundance of data to suggest that proper sleep is beneficial for memory and general neural functions.[2] Recent researches have established that sleep tends to reverse the exhaustion and over-elaboration of the nerves hence it is important for neural homeostasis.[2] There is another hypothesis that suggests that sleep is important for the consolidation of important memories for long term storage.[3] Ironically these two theories somewhat contradict each other at the synaptic level. The homeostatic hypothesis would suggest that neural synapses are weakened but the consolidation hypothesis would suggest that specific synaptic connections should be strengthened during sleep to consolidate memory. This is an area that might interest today's budding researchers.[3] My own belief always has been that electrical brain rhythms are the most important biomedical correlate that enables the brain to

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perform all the important functions of sleep.

Electrical Signals in the Brain

The contemporary understanding of the brain would suggest that the basic unit of computation are electrical signals transferred from one cell to another.[4] And this takes place when neurons have received adequate excitatory input. These action potential signals are produced by individual neurons at rates that may range from one per minute to hundreds every second. They are large enough to be measured outside the neurons.[3] These recordings outside the cells are a measure of information by a given set of neurons. The synaptic connections between the neurons are mostly sparse and mostly structured thereby conveying the impression of a circuit. As a consequence, several volleys of action potentials emerge from a set of neurons in a cohesive manner. Spatial segregation of neurons into subdivisions of the brain lead to the emergence of structures like the thalamus, neocortex and hippocampus. Each of these regions is responsible for the performance of a specific physiological function like controlling respiration, visual perceptions, memories etc.[3] To regulate these very distinct functions, the brain utilizes a temporal organisational scheme with periodic electrical oscillations to realise two very fundamental operations.

The first of these is routine local-global communications whereby local computations are transmitted to the entire brain so that all the distinct structures are notified of the local effect if any. Similarly, global brain activity is made available to the individual local circuits in the reverse direction. Many neuroscientists have described this as 'top down control'. The second fundamental feature perhaps more important is the ability of input to sustain a long-lasting activity trace must after the input has vanished -even during the state of slumber.[4]

Both during sleep and wakefulness, local field potential recording (LFP) as well as the electroencephalogram (EEG) display constant changes. There are occasions when large-amplitude slow oscillations are more prominent while on other occasions low amplitude fast oscillations are more prominent. Most of the time though, these two oscillations co-exist.[3]

While neuronal oscillations have been discovered in the brains of all the animals, in mammals the range is much greater-from one wave every forty seconds to almost seven hundred waves per second.[2] Interestingly and very importantly, the spectral features of EEG and LFP are similar in all mammals totally independent of the brain size. Neuroscientists have been able to identify and classify about 10 mutually oscillating bands that are defined by behavioural correlates. Most forms of brain rhythms have their provenance in the inhibitory rhythmic synaptic transmission onto the other neuronal systems including the information carrying excitatory neurons. An excellent illustration of the effect of brain rhythms is the interaction between theta rhythm in the hippocampus (5-8 Hz) and the higher frequency gamma rhythm in the neocortex (30-90 Hz). The theta oscillations enable the hippocampus to occasionally reroute and coordinate impulses from other cortical regions so that diverse information can be processed by the receiver hippocampus.[2]

Oscillations play a crucial role in another very important function ie learning new information to effectively consolidate future action. To sum up, neuronal oscillations are essential to the brain's basic functions of information transmission and proper computation.[4]

Neurophysiological researches in the last two decades have empirically defined the relationship between memory, learning and sleep. Early studies had indicated that while all memories tend to die with time, they do so more slowly during sleep than wakefulness. Later studies lead the researchers to infer that new experiences can interfere with earlier memories and sleep may be a physiological sanctuary where memories tend to persist better than the state of wakefulness.

REM and nREM Sleep

Subsequent neurophysiological researches revealed that sleep is composed of two distinct electrochemical substates known as rapid eye movement (REM) sleep and slow-wave sleep (commonly referred to as non-REM or nREM sleep). These states play different roles in the regulation of memory. During an episode of sleep, REM and nREM appear in stereotypically cyclical patterns. Sleep generally commences with a very light form of nREM sleep which then transforms into a deeper nREM sleep. During this phase, it is very difficult to awaken the person and the slow waves are more prominent. The individual then retreats back into shallow nREM sleep which finally gets transformed into REM sleep before the commencement of a new cycle. As elaborated nREM is characterised by very large slow waves occurring at 0.5 to 4 Hz which is very different from the waking rhythms. By contrast, the recordings of the REM sleep bear marked semblance to those obtained during wakefulness where smaller amplitude gamma waves dominate the neo-cortex and the theta nested gamma waves are found in the hippocampus. Even chemically these two states are quite different; nREM sleep corresponds with a decrease in the activity of brain systems that secrete acetylcholine, histamine and serotonin. REM sleep on the other hand involves the reinstatement of waking like acetylcholine activity. In addition, nREM and REM are associated with the activation of distinct regions in the brain.[4]

It was REM sleep that initially attracted the sleep researchers who found correlations between pre-sleep learning and the duration of REM sleep. They also discovered that increased REM sleep produced better performance in later post-sleep tasks. Deprivation of REM sleep tends to impair memory for complex tasks but not the simple ones. REM sleep is also increased in those suffering from depression and in the elderly population memory is known to be significantly impaired. What is very noteworthy here is that successful pharmacological treatment of depression with ant depressives eliminates REM almost in its entirety.[1]

In human subjects, REM was associated with the most bizarre dreams while the dreams in the nREM phase are generally more in keeping with reality. Interestingly it was also noted that when people were awakened during REM sleep, they made significantly more association between ideas and were capable of performing complex tasks. It is generally believed that during the daytime, the brain processes information and coordinates perception while nighttime is meant for maintenance of the entire system. Borbely way back in 1982 had presented a hypothesis where he conceptualised sleep as a homeostatic mechanism.[5] Synaptic connections are continually built during wakefulness whenever new associations are made. As more and more associations emerge, the brain may become dysfunctional and sleep serves to scale back synapses which is an important homeostatic mechanism. This was further corroborated by the path-breaking researches conducted by the neurophysiologist Giulio Tononi. But Tononi also suggested that some new synapses are also formed during sleep and this is an area that needs further research as to how this happens is still very unclear.[6]

There is also a major problem when we begin to see sleep as an activity that is just involved in synapse reduction. Plenty of researches have shown sleep to spur the process of memory consolidation which simply would not be possible if sleep was only reducing synapses. Many recent types of research have supported the two-stage model of consolidation of memory. During sleep, memories are often found to be improved. This would support the hypothesis that new skills can actually be acquired and built during sleep which would suggest that sleep may actually be performing an actively constructive role.

Memory Consolidation and Homeostatic Models in Sleep Neurophysiology

The most important factor in memory consolidation is nREM ripple which is a very brief electrical rhythm generated by self-organisation within the hippocampus. neurophysiological researches have established that the more often the two neurons fire together, the stronger the synapse between them. This hypothesis states that when neurons fire repeatedly with a particular timing relative to each other, the synapse between them will strengthen and weave them together to represent a given percept. Neurophysiologist Jan Born and his team have established that increased power of slow oscillations leads to increased memory gain on waking.[5]

One of the major problems with both the homeostatic and consolidation models is the fact that they tend to ignore REM sleep and do not fully explain the very complex choreography of nREM-REM sleep process. In its simplest form, the nREM may be regulating the consolidation process and selective enhancement of neuronal learning-related firing systems while the REM sleep may be responsible for homeostatic dimunition of synaptic weights.[5]

As stated, sleep always commences with nREM. Therefore, consolidation and strengthening of important synapses emerge before the REM regulated downscaling of synapses. Of course, with the advancement of neurosciences, the homeostatic and consolidation model may be proven to be too simplistic. Certain synapses and neurons may have varying and multiple roles. But as of today, this particular mode of understanding the sleep process as a tool by mammals to finetune their nervous system seems to be the best way to understand the functions of sleep.[1]

We do understand that without sleep, the brain during wakefulness may have to take on many more additional roles like preventing the formation of more connections than it can handle. Perhaps nature has in its wisdom prescribed for us to deal with motor control, perception and learning during the state of wakefulness. To understand how crucial sleep is, one only has to look at the researches on sleep deprivation.

Sleep deprivation can lead to seizures, poor memory, emotional lability, mood swings, impaired cognition, and at times frank psychosis. The relationship between sleep and mood disorders is well documented although the exact understanding is still hazy.

It would therefore be entirely appropriate to visualise sleep as a pair of special modes within the brain - nREM and REM. Both these states are impervious to outside inputs and coordinate with each other to clean the learning and memory apparatus available to us. It also retains important information for subsequent use enabling the brain to maximally focus on learning and adapting to its surrounding for the next cycle of wakefulness.

Dedication: *I would like to dedicate this piece to late Professor Ian Oswald, ace sleep researcher under whom I had the good fortune to work nearly 45 years ago. While I could not realize my ambition of pursuing a career in sleep research, his valuable instruction at the time sustained my interest in this area.*

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