Commentary

A Brief History of the Biology of Sleep

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Glaswegian physician, Dr Robert Macnish, was half right when he stated in 'The Philosophy of Sleep' that "sleep exists in two states; in the complete and incomplete."[1] His postulation that incomplete sleep was "the active state of one or more of the cerebral organs while the remainder are in repose" beared some vague semblance to our current concept of rapid eye movement (REM) sleep. However, his concept of complete sleep being "characterised by a torpor of the various organs which compose the brain" typified the erroneous perception of sleep being a state of passivity.

This philosophical proposition of sleep being a passive state was seemingly demonstrated in the 1930s by Frederick Bremer who conducted electroencephalography (EEG) on cats' brains (encéphale isolé) preparations and concluded that sleep was a consequence to the brain being "turned off."[2] Subsequently in 1970, when it was proven by others that active stimulation at the "basal optic focus" and "bulbo-pontine area" produce slow wave sleep through direct inhibition of the reticular activating system (RAS),[3] Bremer performed stimulation studies on cat encéphale isolé in the basal preoptic area which resulted in EEG synchronisation and sleep.[4] This debunked his previous theory that sleep was due to de-afferentisation.

Research into the anatomy and physiology of the brain has revealed that sleep is an active process. One of the earliest evidence that sleep is an "activated" state originated from Constantin von Economo.[5] He studied histological sections of brains of influenza-afflicted patients who had encephalitis lethargica and discovered that cell loss in the anterior hypothalamus and preoptic regions was linked to profound insomnia in a small group of these patients. It was postulated that the activation of these regions of the brain was required to effect sleep.

The discovery of the EEG in 1928[6,7] allows for non-invasive recording of brain activity during sleep and sets the stage for further demonstration that sleep is, indeed, an active process. Loomis et al demonstrated that trains of "spontaneous" bursts of waves – "spindles", "trains", "saw-tooth waves" and "random waves" occurred at certain hours of sleep.[8] He also described the locations and transitions of such waves as sleep progressed.[9] Analysis of 84 records of 30 subjects during sleep allowed the authors to conclude that there was a "continual shift of a person from one state of sleep to another."[10]

The discovery of REM sleep and its association to dreams sets another milestone in establishing sleep as an active process.[11] The discovery of REM by Aserinsky and Kleitman in 1953 reinforced the concept of an activated state in sleep.[12] The authors correlated electrooculograms (EOG) recordings with EEG, respiratory rates and the presence of dreams in normal adult subjects and found that REM was linked to a distinct pattern of EEG recordings, autonomic nervous system activation and probably, dreaming and concluded that this state of REM sleep was a manifestation "of a particular level of cortical activity which is encountered normally during sleep".

Shortly after, in 1959, Jouvet coined the term "paradoxical sleep"[13] which corresponds to the current REM sleep. He was referring to the paradoxical state of cortical activation and REM in the presence of muscle atonia in sleeping cats. The modern day sleep profile in adults is characterised by non-rapid eye movement (NREM) stage 1, NREM 2, NREM 3 and REM sleep. Each stage is characterised by a unique set of EEG, EOG and electromyogram (EMG) manifestations.[14] Transitions between these sleep stages form the sleep cycle. If sleep were a passive process, then we would expect brain processes to be quiescence, i.e. in a "turned-off" state. On the contrary, in NREM and REM sleep, neurons in the ventrolateral preoptic (VLPO) nucleus are in an active state and cause active inhibition of the awake activating neurons in the tuberomammillary nucleus (TMN), locus coerulus (LC) and dorsal raphe nucleus (DRN).[15] Destruction of the VLPO disrupts sleep. Similarly, REM sleep is associated with high level of brain activity. One of

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the postulations was that REM-on cholinergic neurons in the lateral dorsal tegmentum (LDT) and pedunculopontine tegmentum (PPT) exerts a positive feedback on itself and on the REM-off neurons in the TMN, LC and DRN. When this excitatory effect on the REM-off neurons reaches a threshold, the REM-off neurons will inhibit the REM-on neurons, thereby terminating the REM episode.[16] Yet another sign of brain activation in REM sleep is the emergence of ponto-geniculo-occipital (PGO) waves[17-20] in EEG. PGO waves are generated from the pons, and these waves project to the lateral geniculate nucleus (LGN) and visual occipital cortex. The nucleus subcoeruleus had been shown, in rats, to be the origin of these waves.[21] The pontine reticular formation (PRF) was found to be central in the generation and maintenance of REM sleep.[22] Neurons in the PRF remained polarised throughout REM sleep.

Also pivotal to the concept of the active state of sleep is the presence of dreams. Following the discovery of REM in sleep in 1953 and its possible relationship with dream,[12] Dement tested the relationship between REM and dreaming in 9 subjects and found that there was a high incidence of dream recall after REM versus NREM awakening.[23] Interestingly, eye movements, i.e. vertical, horizontal etc. that occurred during sleep while in the state of dream corresponded with those in the awake state when the respective dreams were "re-enacted". Dreams are known to occur in NREM sleep though they are often more frequent and bizarre in REM sleep.[24]

Recent advances in neuroimaging has extended our understanding of the functional neuroanatomy of sleep and brain activity during sleep. Positron emission tomography (PET) was employed to map the metabolically active areas of the brain during REM, namely the brainstem, the limbic system and the cingulate cortex.[25] Functional MRI (fMRI) had demonstrated the active anatomical origins of the slow and fast spindles during NREM sleep.[26] The same technology also revealed significant activity in the parahippocampal gyrus, cerebellum and brainstem during slow wave sleep illustrating that it is not a period of cerebral quiescence or passivity.[27]

There were, previously, philosophical vascular theories relating the "passive" state of sleep to the redistribution of blood from the brain to the digestive system.[28] This was debunked by Reivich et al in 1967 who showed that there was an increase in cerebral blood flow during the state of REM which signified increased brain activity and metabolism.[29] A recent study in mice had demonstrated a 60% increase in convective clearance of β-amyloid, one of the proteins implicated in neurodegeneration, from the cerebrospinal fluid to the interstitial fluid through the glymphatic system during sleep.[30]

Sleep is postulated to be essential for brain processing and memory consolidation. Studying subjects with narcolepsy, Scrima et al demonstrated that recall of prior tasks consisting of anagrams and trigrams was the most accurate after isolated REM sleep. Recall was also significantly better after NREM sleep than after an awake state.[31] Hence, it was concluded that there were active processes in REM sleep that were essential for memory consolidation. The sequential hypothesis of the function of sleep postulates that the information acquired during the awake state will undergo the processing stage in slow wave sleep and consolidation takes place during REM sleep.[32]

The active state of sleep is also evidenced by extracranial manifestations. Haemodynamic changes reflecting an increase in sympathetic drive had been observed in REM sleep. Transient increases in heart rate, predominantly in phasic REM sleep, results in increases in blood pressure.[33,34] Excitatory inputs to the respiratory system during REM sleep resulted in tachypnoea and irregular breathing.[35] These were clearly atypical of passivity.

Sleep also represents a state of active development and tissue restoration. Growth hormone surges occur at sleep onset and during slow wave sleep in prepubertal children.[36] Sexual maturation in boys is facilitated by peaking testosterone and luteinising hormone levels during sleep in pubertal boys.[37] Bone growth and increase mitotic rate of lymphoctyes had been shown to be enhanced during sleep.[38]

Though controversial, sleep has been postulated as a modulator of immune function. Lymphocyte activity and antibody synthesis had been shown to be lower after sleep deprivation.[39] Brown et al reported that there was inferior clearance of influenza virus and lower virus specific antibody in sleep-deprived immunised mice.[40] Similar effects were demonstrated in sleep-deprived humans who were given influenza vaccinations.[41]

Hence, sleep is an active process. And as illustrated above, certain processes in the brain and body can be more active in sleep than awake.

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