REM Sleep: Tear Secretion and Dreams

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ABSTRACT **Although a number of hypotheses exist to explain the reasons for the rapid eye movement (REM) phase of sleep, the physical movements themselves have not been explained or interpreted in the literature. The author theorizes that REM during sleep serves not only to increase the lacrimal secretion and to humidify and lubricate the ocular surface, but also to redistribute the secretion on the ocular surface and to inform the conjunctiva-associated lymphoid tissue (CALT) system. He hypothesizes that when eyes move in REM periods to humidify the ocular surface, they indirectly release phenomena of the visual activity, producing dreams.**

KEY WORDS **dry eye during sleep, rapid eye movements (REM), sleep**

When mothers gaze with fascination at the faces of their sleeping children, lovers at the faces of their partners, nurses at their patients, they have doubtlessly observed that the eyeball of the sleeping person sometimes moves and flutters under the closed lids, then stops. Yet, these eye movements have not been explained or interpreted in the literature.

The movement of the eyes under closed lids is easily observable. The protrusion of the cornea (having a convexity with a radius of about 8 mm of curvature) over a flatter sclera (with a curvature radius of about 12 mm) under the closed upper lid produces a protuberance of the central part of the lid (Figure 1). The changes in this position show the movements of the eyeball.

This work was performed with the help of a grant from the Fundación Mutua Madrileña FMM.

HISTORY OF RAPID EYE MOVEMENTS (REM) DURING SLEEP

Until recently, sleep was considered a passive state of brain activity produced by fatigue. Now we know that sleep is not a period of inactivity, but of rearrangement of the physical and psychic aspects of humans. Great activity takes place in the human body during sleep.The sleeping human can be compared to an office in which, during the day, rooms, books, computers, papers, tables, chairs, and facilities are used by the workers, and, during the night, a cleaning and tidying service organizes everything for re-initiation of work the next day.

Cajal observed the histological differences of the brain neurons of animals when asleep and when awake.[1] In 1913, Piéron first published the concept that sleep is not a passive state, but an active physiological function.[2] Electroencephalography (**EEG**) was initiated by Berger in 1926-1929.[3] The first electroencephalogram during sleep was done by Loomis et al in 1936; they described five stages of sleep, but failed to observe the presence of REM.[4] In 1949, while performing an EEG, Moruzzi and Magoun made the first observation of rapid eye movements.[5] In 1953, Kleitman and Aserinsky confirmed the previous observation, and with the addition of an electrooculogram (**EOG**) to the EEG during sleep, they observed alternate periods without eye movements and with rapid eye movements, which repeated cyclically several times during a normal sleep pattern.[6] It is possible to perform an EOG because the anterior part of the eye is electropositive in relation to the posterior pole of the eye. Thus, an electrode placed near the lateral canthus allows the ocular movements to be detected (Figure 2).

Figure 1. Protrusion of the cornea on the lid surface.

Other researchers and clinicians[7-10] added an electromyogram (**EMG**) of skeletal and visceral muscles, including an electrocardiogram, vascular tension, respiration, and blood oxygenation; as a result, associated or concomitant coincident phenomena in the periods of REM and in the periods without REM (non-REM or **NREM**) were discovered. This was the beginning of the overnight polysomnography that is currently used. The discovery of the occasional saccadic eye movements during sleep led Aserinsky and Kleitman to divide sleep into cyclic and repetitive NREM and REM periods.[6] Oneiric dreams were

associated with the REM periods.

Before describing the characteristics of the ocular surface and tear in relation to sleep, some aspects of nocturnal rest should be explained.

WHY AND HOW DO WE SLEEP?

Circadian sleep exists in all animals, including mammals, birds, reptiles, amphibians, fish, insects, etc, with specific different characteristics. The reason for sleep is unknown. Possible reasons are: (1) to reduce the activity of animals when they are more vulnerable and protect them from their predators; (2) to save energy, as occurs in the hibernation of bears and many other animals; (3) to allow brain concentration in some activities (learning, memory) without the interference of waking activities; or (4) to revitalize neutrotransmitters and hormones.

Newborns sleep between 17 and 18 hours a day, 5-year-olds 10-12 hours, young adults 8 hours, and elder adults 7 hours. Sleep in nonhuman animals is very different from species to species. For instance, it lasts 18 hours in bats, 8 hours in most diurnal birds, 4-5 hours in giraffes and elephants, and only a few minutes in some fish.

The position of the species when sleeping is characteristic. Most animals close their eyes and adopt particular body positions. A human lies down with closed eyelids, a giraffe kneels and bends its head in the crook of its hind knee, a dolphin sleeps while moving against the current, some horses sleep while standing, others sleep belly up, and vampire bats sleep hanging upside down.

The brain regions mainly involved in the sleep phenomena are in the nuclei of the preoptic area of the basal telencephalus, anterior hypothalamus, raphe of the cerebral trunk, tractus solitarius, reticular formation, and area postrema. And the arousal regions, whose stimulation provokes arousal and vigilance, are the gigantocellular tegmental fields of the pontine reticular formation, the posterior hypothalamus, locus caeruleus, substantia nigra, and nearby midbrain.

Figure 2. Nathaniel Kleitman, the father of modern sleep research, preparing to experiment on himself to detect ocular movements when sleeping. The electrodes placed on the temples will indicate the changes of potential when the eyes move.

SLEEP CYCLES OF NREM/REM PERIODS AND THEIR NORMAL ASSOCIATIONS

The many cerebral functions that are improved or restored during sleep have been grouped along the phylogenetic evolution in several categories of activity. Aserinsky and Kleitman's division into NREM and REM periods is still maintained today.[6] These two periods group and associate functions that serve different biological purposes, because when either of these two periods is lacking, the deprived period is larger in the next cycle or in the next sleep.

The actual movements of the eyes seem to be trivial, or, at least, unrelated to the many different, important and complex activities grouped under NREM or REM periods. Nevertheless, the rapid movement of the eyes remains the key reference that gives the name to the primary division of the sleep in cycles NREM-REM because a better practical classification has not been found. The meaning of the eye movements when sleeping is still unknown. A theory, perhaps the only one at present, will be expounded in this paper.

NREM periods are characterized in the EEG by large and slow δ waves, and thus can be termed *slow-wave sleep* (**SWS**). During the NREM period, parasympathetic activity predominates over sympathetic activity (miosis, bradycardia, etc.). Muscular tonus and muscular reflexes are, or return to, normal. Heart and breathing rates slow down. Body temperature and blood pressure decrease. Dreams are absent, or they are not vivid. Sleep-talking, sleep-walking (somnambulism), and nocturnal enuresis (bed-wetting) occur during NREM sleep.

REM periods are characterized in the EEG by brainwave activity, and rapid, short, low-voltage β waves in a pattern similar to that of the waking periods. Thus, REM sleep has been termed *light sleep* or *desynchronized EEG activity sleep* (D sleep).

The most obvious characteristic of D sleep is the rapid ocular movements. These movements are frequently associated with lid contractions (orbicularis oculi and levator palpebrae superioris), especially in sucklings. These eye movements do not seem to have a direct relation with other simultaneous concomitant functional activities, such as breathing, cardiac rhythm, or memory consolidation. Nevertheless, the evidence of the ocular movements is the basis for the term *REM period*, and the other nonsimultaneous phenomena were included in an NREM period.

The second obvious characteristic of REM sleep is skeletal muscular hypotonia**,** particularly the complete atony in the back, neck, arms, and legs. Breathing and extrinsic eye muscles are less affected, and so the eyes can move with saccadic movements under the closed or fluttering lids.

During REM sleep, respiration is more active and frequent, the heart rate is more dynamic and irregular, the penis becomes erect and the clitoris enlarges in normal males and females, respectively, of all ages,[11] and body temperature is not well regulated and is influenced by the environmental temperature (as in poikilothermal animals, such as amphibians and reptiles).

The main psychical characteristics of REM sleep are related to memory and oneirism (related to dreams or dreaming). The three main types of

memory are 1) verbal episodic memory (recollection of experiences), 2) procedural memory (learning of perceptual-motor or cognitive skills), and 3) working memory. The three types need a normal REM sleep to transfer, develop, and satisfactorily consolidate the temporary memory to the long-term memory.[12] During sleep the human brain memorizes, fixes, files, selects, and relates knowledge and experiences, mainly those received the previous day. Only a thousandth part of this activity is sometimes expressed in the conscience in form of dreams.

Dreams are very typical of REM sleep. In 1957, Dement and Kleitman reported the synchronism between REM sleep periods and dreaming.[7] When this was confirmed by other researchers, some authors termed the REM periods *oneiric,* and the NREM ones *nononeiric*. Today this is not totally accepted[13] because dreams can occur in all stages of the sleep/wake cycle, and there is evidence that the REM sleep phase and **PGO** (ponto-geniculate-occipital) waves are strongly associated with visual imagery during dreaming.[14] Moreover, the emotional manifestation associated with the scenic images (anxiety, fear, sadness, love, eroticism, joy) is more frequent, more scenic and intense, and larger in the REM than in NREM phases (Figure 3).[15,16] REM sleep disorders are frequently associated with depression, Alzheimer disease, myotonic dystrophy, narcolepsy,[17,18] and chronic glaucoma.[19-21] Nocturnal activity (laboral or recreative activity) and transoceanic travel alter and change the NREM/REM cycles. Gastaut et al discovered apnea during sleep,[22] and today this is the main reason for polysomnographic study in clinics.

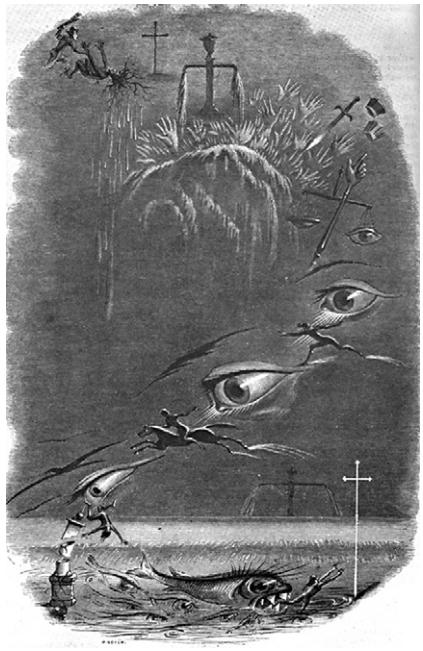

Figure 3. Lithograph by J. J. Grandville: "First dream: Crime and expiation." *Le Magasin Pittoresque*, Paris, 1847. A sexist crime promotes a succession of images, in which the plates of a balance are being transformed on the ocular surface. A fish devours the murderer, eyebrows are transformed into a bird, etc., representing in an instantaneous image a temporal succession of acts.

WHY REM PERIODS?

There are several hypotheses for explaining the development of REM sleep periods.

1. Jouvet stated that REM sleep is an independent "state of **alertness"** intercalated intermittently in the sleep.[9]
2. The REM sleep period is the **ontogenic evolution** of the "active sleep" of neonates and is very important in the formation of mature neural connections in the developing brain of children.[23,24] Therefore, *active sleep deprivation* in early life can result in decreasing brain mass and behavioral problems.[25]
3. The greater the **organic maturity** at birth of an animal species, the shorter its duration of REM sleep.[26] There is speculation about this fact. Intelligence does not seem to play a role, and 20% of sleep time in humans is in an REM period because of their organic immaturity at birth. However, whales and dolphins (with a high level of intelligence in comparison with other mammals, but also with high organic maturity at birth) have the lowest REM seen in mammals. So, the physical immaturity at birth seems to be the most important reason for longer REM periods.
4. REM sleep allows the **consolidation of memory**. Nevertheless, people with brain damage that suppresses REM sleep have a normal memory function.
5. REM sleep allows **reorganization of the neurotransmitters**. The monoamine neurotransmitters (norepinephrine, serotonin and histamine) and monoamine receptors in the brain need to shut down during the phase of REM sleep in order to recover and to regain full sensitivity. So, during the periods of REM sleep, there is a general muscular atony, the motor neurons are not stimulated, and the muscles do not move.

All these hypotheses attempt to explain why there is a specific period called the REM period, but they do not explain the reason for the eye movements.

REM SLEEP CHARACTERISTICS IN MAMMALIANS AND BIRDS

REM sleep does not exist in fish, amphibians, and reptiles, although they do sleep. It occurs in birds and mammals. As neither reptiles nor the Australian ant bear (*Monotrema echidna*), the most primitive present-day mammal, have REM sleep, it is assumed that REM sleep appeared later on in mammals, and that REM sleep in birds developed independently from that in mammals. Another mammalian without REM sleep is the dolphin, which alternates both cerebral hemispheres when sleeping.

In humans, when a normal adult falls asleep, he/she goes first into an NREM sleep period, which lasts for about one-and-a-half hours (only sucklings can enter directly into a REM sleep period). Then comes the first REM period, which usually lasts for only about 5 minutes. Then, the cycle NREM/REM repeats, and the sleeper enters into a new NREM period for about 1 hour, followed by a new REM period, that lasts longer than the first one. These NREM-REM cyclings continue 4 or 5 times throughout the night, and the length of the REM periods progressively increases. In the early hours of the morning, a REM period can last up to 30 minutes. The normal adult frequently awakes definitively after this last REM period; therefore, the last oneiric episodes are often remembered, but usually they are gradually forgotten in the 5 minutes after awakening.

The cycling of NREM/REM periods changes with age. REM periods

occupy in human newborns 50-80% of the total sleep, in children aged 5 years, 25-30%, and in adults and the elderly, 20-25%. In the fetus, almost all the time corresponds to characteristics of atypical REM periods (isothermic with the mother, a certain sympathetic predominance, active cardiac rhythm), but eye movements are very poor or absent and, of course, there is no respiration.[27]

The proportion of NREM/REM periods in adult non-human animals is different: REM sleep is 5% in most birds, 10% in baboons and Guinea pigs, and 25% in dogs, giraffes, and hedgehogs.[28,29] In mammals, the more immature the mammal is at birth, the longer is the period of REM sleep during lactation and in adulthood.

WHY ARE THERE EYE MOVEMENTS IN REM SLEEP?

Each eyeball is moved by the action of six muscles, innervated by three cranial nerves: The medial rectus, superior rectus, inferior rectus and inferior oblique muscles are innervated by the III cranial nerve; the superior oblique, by the IV nerve; and the lateral rectus, by the VI nerve.

To move simultaneously and to unite both eyes, the nuclei of the cited nerves are coordinated by three main groups of centers that respectively associate and co-relate their activation for the vertical, lateral, and convergent gaze. They are distributed in the pontine and parapontine centers.[30]

The reticular formation is a part of the brain, roughly centered in the pons Varolii. It is phylogenetically one of the oldest parts of the brain and is involved in autorhythmic stereotypical actions, such as respiration, walking, mastication and eating, eye saccadic movements, urination, defecation, sexual activity, sleep-arousal, changes in NREM/REM sleep, and many other automatic or semiautomatic functions. The reticular formation has an ascending activating system connecting to the hypothalamus, thalamus and cortex, and a descending activating system connecting to the cerebellum, vestibular system, and sensory nerves.

The brain regions mainly involved in the sleep phenomena are in the nuclei of the preoptic area of the basal telencephalus, anterior hypothalamus, raphe of the cerebral trunk, tractus solitarius, reticular formation, and area postrema. The arousal regions, whose stimulation provokes arousal and vigilance are the gigantocellular tegmental fields of the pontine reticular formation, the posterior hypothalamus, locus caeruleus, substantia nigra, and nearby midbrain.

In the REM active periods, the extrinsic ocular muscular system is activated rhythmically, and the eyes flutter simultaneously for a time with variable cadences. As previously mentioned, the reason for and utility of these movements are still unknown.

TEAR SECRETION DURING SLEEP

Quantitative Tear Production with Eyes Closed While Awake

Some authors say that when mammals are awake with their lids closed, their basal tear secretion has the same quantity as with normal blinking. Mizukawa, using a test of dilution of isotopes in humans and rabbits, determined that when the eyes are closed, tear secretion is about the same as when they are open.[31] Lamberts et al observed with the Schirmer-Jones test (Schirmer I with topic anesthesia) that the lacrimal basal secretion is the same with open and with closed eyes.[32] However, other researchers say that tear secretion is less with closed than with open eyes, and Maruyama determined that rabbits with open eyes produced 42.9 µl/hour of tear, and with closed eyes they produced 4 times less (11.7 µl/hour). [33]

Quantitative Tear Production During Sleep

Schirmer (1903) wrote that when closed during sleep, the normal eye does not produce tear, basing this affirmation on the fact that patients without a lacrimal sac (dacryocystectomy was the most frequent surgery in those times to treat the dacryocystitis) do not accumulate tear in the lacrimal lake when sleeping.[34] However, Szmyt found that during sleep, there is lacrimal secretion, although very reduced.[35] Chodan et al applied a variation of the Schirmer test to 30 normal children and found that the wetting of the test strip was the same during sleep or when the child was awake and deduced that because evaporation does not occur during sleep, the tear secretion is lower.[36]

Using Chodan's test in children 1-10 years old, I found that the wetting of the strip varied between 1 and 8 mm. I deduced that the tear secretion during sleep is poor, not continuous but intermittent, and may exist only during the REM periods.[37] When awaking, humans frequently rub their closed eyes and stretch their limbs. Could this be to unconsciously stimulate tear secretion and activate the skeletal muscles?

Characteristics of Tear During Sleep

During sleep, tear becomes hypoosmolar and hypoxic as compared to its condition in the waking person, the first because of the diminished evaporation, the second because of the diminished contact with the atmosphere.

Somnial hypoosmolarity has been frequently demonstrated.[38] Terry et al determined that during the waking day, the tear osmolarity is 310mOsm/l, equivalent to an aqueous solution of NaCl 9.7%°, but during sleep is 285 mOsm/l, equivalent to a 8.9%° NaCl aqueous solution.[39,40] Thus, lid closure results in a decrease in tear osmotic pressure.

Somnial hypoxia is due to the isolation of the lacrimal lake. When the eyes are closed for a long time, atmospheric oxygen is diminished, and a substitutive anaerobic glycolysis is necessary.[40] Lipid (gl. Meibomio y Zeis) and mucinic secretion are also diminished.

Corneal Changes During Sleep

Von Bahr reported that corneal thickness does not have night/day (sleeping/waking time) variations.[41,42] Other researchers are not in agreement and have reported thickening of the cornea during sleep, which has been attributed by some to the hypoosmolarity of the sleeping tear, and by others to the lack of oxygen[40,43] or to the combination of both factors. Mishima et al observed that even during waking time, with prolonged eye closure

Figure 4. A. Humidimeter model TestoStor-171-1. B. Sensor of the humidimeter placed in the posterior part of the bridge of semihermetic spectacles. C. Subject prepared to sleep, wearing spectacles with the humidimeter, and other polysomnography registers as electroencephalogram, breathing register, and sterno-cleido-mastoid electromyography.

evaporation in rabbits decreases and corneal thickness increases.[44] Mandell et al observed in a human that the cornea on awakening is 3.6% thicker than after about 1 hour with normal blinking open eyes.[43] Terry et al attributed this to the fact that during overnight sleep, the reduced evaporation diminishes the osmolarity of the cornea, producing corneal edema.[40]

A THEORY ON TEAR STIMULATION DURING REM SLEEP

Definition of "Theory:" A supposition explaining something based on principles independent of the phenomenon (as opposed to hypothesis).[45]

In my review of the literature, I found no explanations for the REM phenomenon. I suggested in 1980 that the REM during sleep may represent an attempt to correct the nocturnal dryness of the ocular surface by stimulating tear secretion.

Humidimetry of the preocular space is a technique to measure tear evaporation.[46-50] The patient is fitted with semi-closed spectacles, and the humidity and temperature are measured in the space between the spectacles and the eye. The relative humidity increases when the lacrimal lake is increased by artificial tears or by secretion; because the lids do not close hermetically, they flutter frequently, and the evaporation through the interpalpebral zone and lacrimal lake is constant.

Recently, we have performed polysomnography in normal and dry eye patients wearing semihermetic goggle-spectacles with a humidimeter (Figure 4).[51] We found in eight persons that preocular evaporation and humidity increase in the periods of REM sleep and decrease when the eyes stop moving (Figure 5). The values of relative humidity under the goggles went up clearly minutes after the REM sleep period began. The evidence of poor tear secretion during sleep, and of an increase of production in the periods of REM sleep, is suggestive that the eye movements are intermittent episodes for humidifying the eye surface (Figure 6).

A complement to the theory that sleeping REMs are for the purpose of producing tear and humidifying the ocular surface is that the cornea itself does not contain its own lymphoid cells, as does the conjunctiva.[52-54] Thus, during sleep with the eyes closed and quiet, the cornea is separated from the protective system of microbial antigens, inflammatory cytokines, etc. The REM serves not only to increase the lacrimal secretion and to humidify and lubricate the ocular surface, but also to redistribute it on the ocular surface and to inform the conjunctiva-associated lymphoid tissue (CALT) system.[54]

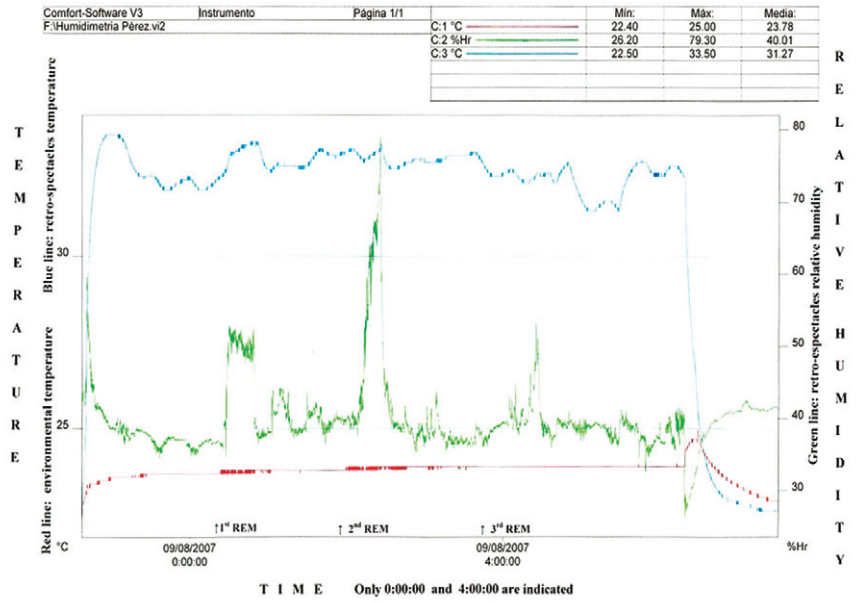

Figure 5. Humidimetry in a patient sleeping between 11:00 pm and 6:30 am. The time is marked only at 12:00 am and 4:00 am, with addition of the three REM periods 12:20 am to 12:31, 2:09 am to 2:24 am and 4:02 am to 4:28 am taken from the polysomnography. On the left, temperature from 22ºC to 34ºC, in red, outside the spectacles, and in blue in the space between the spectacles and the palpebro-ocular surface. On the right, relative humidity in the space between the glasses and the eye, in green showing the base line in NREM sleep, about 38% , and the peaks to 53%, 78% and 52% in the periods of REM.

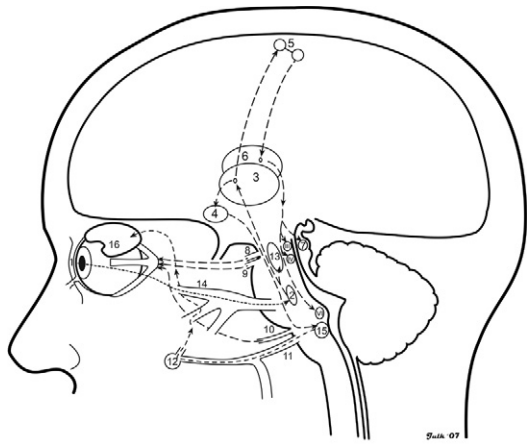

Figure 6. Theoretic diagram illustrating the stimulation of REM sleep activity and tear secretion. 1) Ocular surface. 2) Sensory nucleus of the nervus trigeminus. 3) Thalamus. 4) Hypothalamus. 5) Cortex cerebri. 6) Corpus striatum: nuclei lentiformis et caudatus. 7) Colliculus superior. 8) Nervus oculomotorius. 9) Nervus throclearis. 10) Nervus abducens. 11) Nervus facialis. 12) Ganglion pterygopalatinum. 13) Nuclei reticulares. 14) Nervus ophthalmicus. 15) Nucleus lacrimalis. 16) Glandula lacrimalis

The ocular surface dryness [and maybe the corneal hypoxia and tear hyperosmolarity] (1) stimulates the sensitive nucleus of the trigeminal nerve (2), initiating a cascade that will increase the tear secretion: The trigeminal efferences reach the optic thalamus (3) and the trunco-encephalic reticular nuclei (13). The efferences of the optic thalamus project to the cerebral cortex (5) and hypothalamus (4). Motor extrapyramidal cortical efferences (5) project to the nuclei of the corpus striatum (6). These nuclei send efferences to the trunco-encephalus, stimulating the superior colliculi (7) and to the motor nuclei of the III, IV and VI cranial nerves (III, IV, VI), producing (8, 9 and 10) the REM ocular movements. The inhibitor and facilitator reticular nuclei in the encephalic trunk (13) modulate this activity. The active rubbing of the ocular surface against the lids strongly stimulates the sensory nucleus of the trigeminal nerve, which connects with the hypothalamus. The hypothalamus sends motor efferences to the lacrimal nucleus (15), which vigorously spurs the lacrimal gland secretion (16) through the facial nerve (11), greater petrosal nerve, and pterygopalatine ganglion (12).

A HYPOTHESIS ON ONEIRISM DURING REM SLEEP

Definition of "Hypothesis": A supposition made as basis for reasoning, without reference to its truth, or as starting point for investigation.[45]

Another association with REM sleep that occasionally may be related to the eye movements are dreams. Ocular motility has been developed to direct the eyes to the objects when awake, to fix and follow them, and to break out the complex process of receiving and focusing their images on the retina, to computerize their transmission from the retina to the lateral geniculate body and to the visual occipital cortical area, and to associate this sensation to other areas. In this way, they are interpreted and correlated with other simultaneous perceptions, memory, associations with reading, writing, and phonic engrams, stimulating past histories and personal experiences, adding emotional context, and integrating in a complex episode the perception that has been initiated by a simple eye movement.

Figure 7. S Dalí, 1944: "Dream caused by the flight of a bee around a pomegranate a second before awaking."

It may be hypothesized that it is possible that when eyes move in REM periods to humidify the ocular surface, they indirectly release phenomena of the visual activity, producing dreams. It may even be that the impulse that initiates this process is not the ocular extrinsic movements, but rather the activation by eye dryness of the pontine and parapontine conjugate nuclei of the ocular muscles, which contribute to an oneiric visual imagery, and dreams. This hypothesis is not in agreement with that of Kleitman, who suggested that "… some sort of emotional disturbance, such as might be caused by dream, may cause the eye movement during sleep." In fact, it is just the opposite.

External stimuli, even auditory ones that provoke a spatial identification and seeking by the eyes, activating the oculomotor musculature, may be stimulators of visual dreams (Figure 7).

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