

Sleep Hippocampal Theta Rhythm and Sensory Processing

Marisa Pedemonte and Ricardo A. Velluti

Introduction

Ancient human cultures have developed diverse forms of a device that, based on sensory stimulation, is used to put babies to sleep: the rocking cradle. Vestibular and somatosensory stimulation produced by the rocking movements, complemented by eye closure and other stimulation such as constant temperature and the mother's voice/song (lullaby) activating the auditory system, are able to induce sleep. On the other hand, it is a common experience that reducing the sensory afferent volleys to the brain can facilitate sleep.

A series of experimental data will be presented demonstrating the sensory input relevance in the organization of the sleep and wakefulness cycle. Firing rate shifts in auditory and visual neurones, changes in the pattern of discharge, and, most important, the temporal correlation of the spike timing with the hippocampal theta rhythm, will be set forth.

Sleep, a huge change in the brain physiology, depends on both, a series of active processes and passive mechanisms, e.g., functional sensory deafferentation^{3,19} and neural networks changing organization. Although many signs of active processes have been shown, there are not enough experimental data to support a final decision about the relative contribution of passive processes.^{16,27,43,46} However, both approaches may be partially reconciled conceding that the deafferentation may be provoked by an inhibitory influence acting, e.g., upon the ascending activating reticular system.

Our main purpose is to provide an experimental aspect of sensory data analysis, its relation to sleep and the hippocampal theta rhythm as an internal *zeitgeber* (time giver) for auditory and visual information processing.

The Hippocampal Theta Rhythm

The hippocampal theta rhythm is a well-known feature of the hippocampal electrogram in humans and other mammals although its functions remain partially unknown.^{15,29,39,49}

Since the beginning, attention processes have been associated to the theta rhythm. Figure 1 shows a classical example on this matter. When a cat observed himself in a mirror exhibited a theta rhythm burst in the hippocampus.¹⁴

Although more prominent in active wakefulness and paradoxical sleep, the hippocampal theta can also be observed during slow wave sleep.^{12,21} It has been related with phasic phenomena during paradoxical sleep,^{11,22} with movements⁵ and with autonomic control of the heart rate.^{32,34}

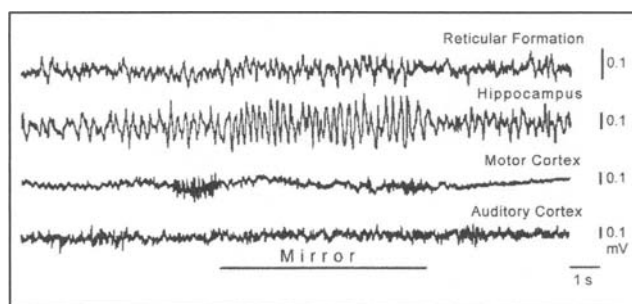


Figure 1. Recording in an awake cat showing enhancement of theta rhythm in the hippocampus when the animal see itself at a mirror (black bar). (Modified from Grastyan et al, 1959.)

Since the pioneering work of Scoville and Milner,⁴⁰ almost five decades of research resulted in the recognition of the hippocampus as a brain region implicated in learning and memory processes^{4,42} in several species including humans.^{1,45} Besides, theta blocking by septal lesion provokes memory impairment.¹³

Moreover, the hippocampus is involved in the neural coding of spatial position^{2,28,51} necessarily associated with the sensory input and its processing. As an experimental animal traverses space, the hippocampal place neurones firing progressively changes to an earlier phase of the ongoing theta rhythm.^{23,44} This may be relevant to long-term potentiation which is sensitive to the theta phase, i.e., potentiation increases at the theta peak while depression is associated with the troughs.

The theta wave may affect spatially distant neurons by inducing fluctuations in cellular excitability due to membrane potential oscillations.^{11,20} Moreover, intracranial recording from human cortices have revealed theta oscillations in several brain regions including the neocortex, suggesting that theta waves may not reflect volume conduction from the hippocampus but the existence of theta generators in the brain surface.^{17,18}

Our approach was to study the hippocampal theta influences on the unitary activity of the sensory systems in the context of wakefulness and sleep. The interactions were present in both, sleep and waking behaviour.

By studying the unitary activity of several auditory nuclei, the lateral geniculate visual thalamic neurones and their relationship to the hippocampal theta, we have found that this rhythm may play a role as an internal clock. We postulate it constitutes a low

frequency *zeitgeber* associating a temporal dimension to the processing of auditory signals in the lateral superior olive,⁴⁷ inferior colliculus,^{31,47} primary auditory cortex,^{33,48} and to the visual processing in the thalamus.¹⁰

Auditory and Visual Neuronal Activity in Sleep and Wakefulness

Auditory Neurones

Changes in the Discharge Rate

Since sleep is a special physiological condition, it is possible to maintain that the incoming auditory information- always present- is differently processed in different states. Accordingly, the brain will select what input to focus on and determine to what neuronal network sensory neurones are engaged.

Approximately half of the auditory cortex neurones studied showed changes in the response to tone bursts in sleep compared to quiet wakefulness (Fig. 2). Those neurones that changed can be related to sleep processes still unknown, participating in a different neuronal assembly. There has been no auditory unit that stopped firing as the guinea pig enters sleep, thus, the auditory system is continuously monitoring the environment.^{7,26,30,35,36,47,48}

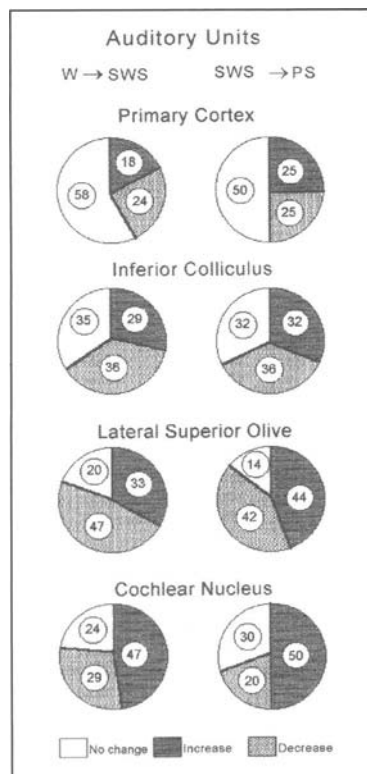


Figure 2. Neuronal sound evoked activity along the auditory pathway during different behavioural states in guinea pigs. Pie charts show percentages of neuronal firing changes on passing from wakefulness (W) to slow wave sleep (SWS), and from SWS to paradoxical sleep (PS) at four auditory loci: auditory cortex (A1), central nucleus of the inferior colliculus, lateral superior olive and ventral cochlear nucleus. No neurons were recorded that became silent on passing to sleep in the auditory regions studied (modified from Velluti and Pedemonte, 2002).

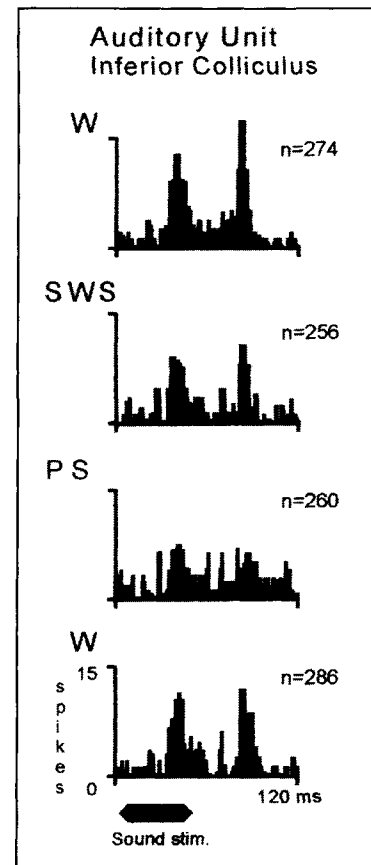


Figure 3. Tone-evoked response of an inferior colliculus neuron during waking (W), slow wave (SWS) and paradoxical sleep (PS) in guinea pig. Post-stimulus time histograms showed no significant changes in the firing rate (Mann-Whitney U-test) on passing from W to sleep phases, meanwhile the pattern of discharge during 120 ms exhibited differences. Two peaks present during W decrease in SWS and almost disappear during PS to recover, in the following W control, the same pattern and firing rate as the initial W. Preceptorial effects were eliminated by removing the middle ear ossicles and delivering the sound directly to the ear. Sound stimulation: tone-burst at the characteristic frequency; intensity of 10 dB above the threshold; 50 ms duration and 5 ms rise-fall. Modified with permission from Morales-Cobas et al. J Sleep Res 1995; 4:242-251. ©1995 Blackwell Publishing.

Changes in Discharge Pattern

Besides discharge rate, the pattern in which the firing develops may be relevant for the processing. In addition to changes in the firing rate throughout sleep and waking, a set of neurons exhibited shifts in the pattern of discharge (Fig. 3). Although some neurones showed no significant changes in discharge rate, the temporal distribution of spikes was different when the animal entered slow wave or paradoxical sleep. The discharge pattern was recovered in the following waking period, used as control.²⁶

Response to Natural Guinea Pig's Calls

The study of neuronal response to natural stimuli may introduce to the analysis of their processing during sleep. It is known that a significant auditory stimulus may awake a person more easily than a non significant one. Besides, we have carried out stimulation with non significant natural call by just inverting it in time. Cortical auditory neurons (A1) exhibited firing shifts on passing from

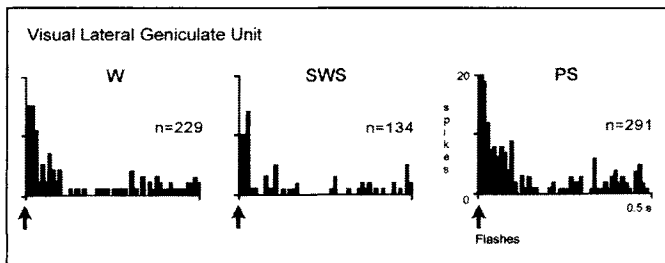


Figure 4. Visual evoked unitary firing in the lateral geniculate nucleus during wakefulness (W), slow wave (SWS) and paradoxical sleep (PS) in guinea pig. Post-stimulus time histograms showed statistically significant changes in the firing rate (Mann-Whitney U-test), both on passing from W to SWS and from SWS to PS. Light stimulation: flashes, 2/s, high intensity, 30 cm distance of the animal head, pupils pharmacologically dilated. The flashes' intensity and the pupils' dilation allowed a constant stimulation of the retina even during periods of eye movements.

wakefulness to slow wave sleep when stimulated with a natural call. Moreover, the pattern of discharge exhibited differences when the stimulus was presented direct or inverted in time.³⁷

Visual Neurones

Unlike the auditory system, which is always relatively "open" to the environment, the activity in the visual system is expected to decrease during sleep due to closing of the eyelids. However, the discharge rate of visual neurones also showed changes during sleep. Figure 4 exhibits an increase in firing rate during paradoxical sleep. Visual neurons keep responding to a flash during sleep.

Not only the discharge rate but also the firing pattern may vary on passing from waking to sleep phases (Fig. 4). The incoming visual information reaches the visual centres differently depending on the current behavioural state. The central nervous system, acting through its sensory efferent system, may control its own input (see review ref. 46).

Role of the Theta Rhythm

The theta rhythm may be activated by several physiological variables, such as attention, movements, etc. Thus, the resulting cross-correlation may be dependent on the most relevant signal at a particular time. The changes associated with attention may appear when the input varies or when an unknown internal factor becomes relevant. There is a relationship between the theta power and the presence of phase locking with a sensory neuron, although other factors could condition such temporal correlation.

Auditory neurones from the lateral superior olive and central nucleus of the inferior colliculus exhibited phase locking to the hippocampal theta rhythm.⁴⁷ Although being nonrhythmic, the spontaneous activity of inferior colliculus neurones analysed during wakefulness exhibited phase locking to the hippocampal theta (Fig. 5). When the same unit was stimulated with a continuous pure tone at the neurone's characteristic frequency—adding a specific evoked activity—the neurone became more synchronized with the theta rhythm's frequency. Since there was no significant increase in the firing number ($n=287$ vs. $n=289$), it means that the theta rhythm input was, in this case, a relevant influence resulting in a spike autocorrelation increased rhythmicity.³¹ This led us to conclude that the temporal correlation between both the rhythm and the unit is functionally significant.

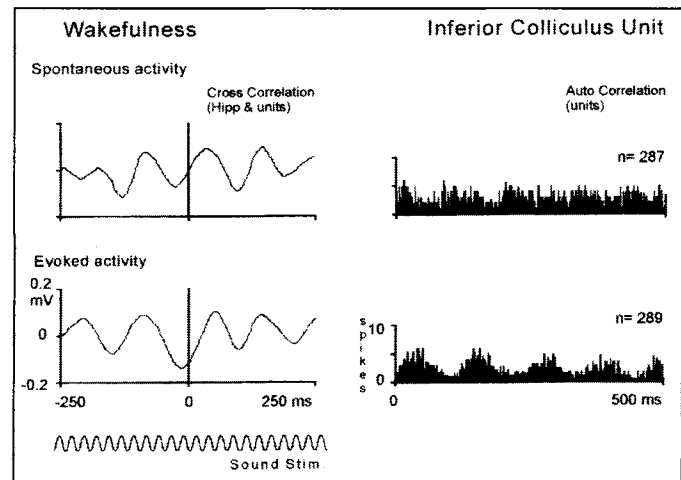


Figure 5. Temporal correlation between hippocampal theta rhythm (Hipp) and the spontaneous activity of an inferior colliculus neurone in an awake guinea pig. The correlation of the spikes with the theta rhythm was studied with spike-triggered averaging of the hippocampal electrogram. Both, spontaneous and evoked activity showed temporal correlation with hippocampal theta rhythm (bipolarly recorded). The cross-correlation was considered positive when it became flat after "shuffling" the spikes series included in the data.⁸ The autocorrelation histograms showed that the almost nonrhythmic discharge pattern during spontaneous activity (upper recording) becomes rhythmic at theta frequency during the evoked activity (lower recording), thus stressing the relevance of theta input onto the auditory cell. Sound stimulation: continuous tone at the unit's characteristic frequency (1.1 kHz), 10 dB above threshold (modified from Pedemonte et al, 1996).

Since visual information includes temporal cues, our analysis was centred on the correlation between hippocampal theta rhythm and lateral geniculate activity.¹⁰ Phase-relationships between hippocampal theta and unitary firing were found with both spontaneous and light evoked activity during wakefulness, slow wave and paradoxical sleep. This temporal correlation was dynamic, exhibiting changes related to the sleep-waking cycle and perhaps to attention shifts, e.g., in Figure 6 (right) the cross-correlation appeared when the flash stimulation ceased during a slow wave sleep epoch.

Auditory and visual units exhibited temporal correlation with the hippocampal theta rhythm during wakefulness, slow wave and paradoxical sleep.³³ An interesting finding is that the phase locking with hippocampal theta may be provoked by changes in the sensory input. We have found that auditory as well as visual neurones, may change from a nonphase-locked condition into a phase locked one after a change in its sensory input.

Figure 6 shows an example of an auditory cortex (A1) neurone (left) and a visual geniculate neuron (right), that became phase locked to theta when the stimulus changed during a slow wave sleep period.

The following experimental approach included guinea pig's natural call ("whistle", 700 ms duration). During rhythmic and random presentations of natural calls, most A1 neurones exhibited phase locking to the hippocampal theta waves in wakefulness, slow wave and paradoxical sleep. The theta phase locking was also observed when the sound (natural call) was presented in reverse, i.e., inverted in time.³⁷

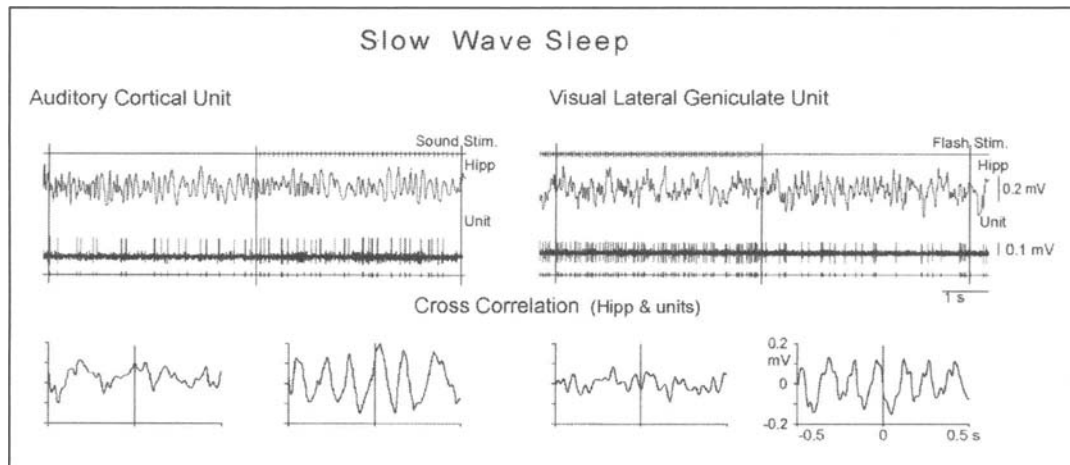


Figure 6. Firing and cross-correlation of two sensory unit- auditory and visual- when their input is changed during slow wave sleep. Top, single recordings of the hippocampus (Hipp), the unitary discharge and the digitised signals. Sound and flash stimulation (Stim) represent the synchronizing pulses. Bottom, four cross-correlations performed on the data sets limited by vertical lines in the above traces. Both are showing a change from the no phase locked condition to a temporal correlation (phase locking) with the hippocampal theta rhythm, when a shift in the sensory input occurred. Whereas the auditory cortical unit (A1) phase locked to the hippocampal theta only when the sound stimulation began, the visual neurone showed the opposite phenomenon. The lateral geniculate neuron exhibited no phase locking to the theta when the flashes of light were present. With the flashes off, the correlation with hippocampal theta appeared (modified from Velluti and Pedemonte, 2002).

Conclusions

Our experimental approaches have assessed different aspects of the neuronal activity that give us an insight on how sensory information processing and sleep mechanisms reciprocally affect each other, participating in the processing and/or in sleep promoting functions. The neuronal discharge level and pattern of discharge changes in response to constant stimuli indicate that the CNS is modulating (selecting?) and perhaps distributing the incoming auditory information according to its current state. Auditory,⁴⁶ somatosensory,^{38,41} and visual neurones studied^{9,23,25} exhibited changes in their firing rates in correlation with stages of sleep and wakefulness. This is consistent with the hypothesis of a general shift in the neuronal networks involved in sensory processing during sleep that may participate in the switch to a sleeping mode of cell assemblies. A number of neurones at different auditory *loci*, from brain stem to the cortex itself, presented significant quantitative and qualitative changes in their evoked firing rates and pattern. On the other hand, another group of neurones, recorded in every nucleus of the pathway, did not show behavioural related changes in firing rates on passing to sleep. Moreover, no neuron belonging to any pathway level or cortex was observed to stop firing on passing to sleep.

A close temporal correlation between hippocampal theta rhythm and unitary firing was also demonstrated at several stages in the auditory pathway,^{31,33,47,48} and in visual neurons at the thalamic lateral geniculate nucleus.¹⁰ At a neural population scale, this phase-locking may result in a composite final signal that could be used in processes like attention, movements, and, in particular auditory/visual sensory input processing. Furthermore, we hypothesize that the phase locking to the hippocampal theta adds a temporal dimension to the sensory processing, perhaps necessary for time related perception also during sleep. Given that every stimulus develops in time, the CNS must have a way to encode this parameter. Hippocampal theta, being one of the most regular brain-generated low frequency rhythms, may participate in this internal clock.

The temporal relationship between the sensory neuronal firing and the hippocampal theta field activity is a changing phenomenon whose variation may depend on the interaction of a set of signals: (a) the hippocampal theta rhythm amplitude and frequency, (b) the current state of the brain, awake or asleep, and (c) the incoming sensory information. A neuronal assembly may shift its discharge pattern by changing the interaction between these three input signals, e.g., facing a novel stimulus may change the brain condition evoking a new phase locking with a higher power of hippocampal theta waves.

The parallel recording of hippocampal theta field activity and cortical auditory multiunit firing revealed a precise temporal organization of population events during wakefulness, slow wave and paradoxical sleep. The notion of a discontinuous exchange of information between hippocampus and cortical areas is supported by the data. The phase locking of cortical auditory units and hippocampal theta mainly occurs when a novel stimulus or an on/off condition of the same one are applied during wakefulness, slow wave or paradoxical sleep, indicative of a "top down" theta action.⁵⁰

Corollaries

- The auditory units that did not change firing in sleep may be related to the environmental monitoring during sleep.
- Those units that shift their firing may be related to unknown processes during sleep, or perhaps, act as active signals in sleep related neuronal networks.
- The auditory neurons that keep responding during sleep, as well as those exhibiting theta phase-locking, convey information that could be the first step in the complex auditory learning function, which is consistent with a recent report of learning during sleep in human newborns.⁶
- The activity-dependent development of the brain during early life may not only occur during wakefulness.²⁴ We suggest that it also occurs associated to auditory and visual incoming information during the long periods of sleep in newborns and infants.

During early ontogenetic development, and maybe in adults, the sensory information reaches the CNS not only during wakefulness but also during sleep. This continuous sensory input may "sculpt" the brain and participate in the adaptation to novel conditions.

References

- Basar E, Schürmann M, Sakowitz O. The selectively distributed theta system: Functions. *International J Psychophysiol* 2001; 39:197-212.
- Best PJ, White AM, Minai A. Spatial processing in the brain: The activity of hippocampal place cells. *Annu Rev Neurosci* 2001; 24:459-486.
- Bremer F. Cerveau "isole" et physiologie du sommeil. *C R Soc Biol* 1935; 118:1235-1241.
- Brown MW, Aggleton JP. Recognition memory: What are roles of the perirhinal cortex and hippocampus? *Nat Rev Neurosci* 2001; 2:51-61.
- Buño W, Velluti JC. Relationship of hippocampal theta cycle with bar pressing during self-stimulation. *Physiol Behav* 1977; 19:615-621.
- Cheour M, Martynova O, Naatanen R et al. Speech sounds learned by sleeping newborns. *Nature* 2002; 415:599-600.
- Edeline JM, Dutrieux G, Manunta G et al. Diversity of receptive field changes in auditory cortex during natural sleep. *Eur J Neurosci* 2001; 14:1865-1880.
- Fuentes J, Buño W, García-Austt E. Simulation of post-synaptic activities in hippocampal cells during theta rhythm. *Brain Res Bull* 1981; 7:157-162.
- Gambini JP, Pedemonte M, Velluti RA. Sleep-wakefulness modulation of lateral geniculate visual information: Unitary study and hippocampal theta phase-locking. *Sleep Res Online* 1999; (Suppl 1) 2:99.
- Gambini JP, Velluti RA, Pedemonte M. Hippocampal theta rhythm synchronized visual neurons in sleep and waking. *Brain Res* 2002; 926:137-141.
- García-Austt E. Hippocampal level of neural integration. In: Ajmone-Marsan E, Reinoso-Suárez F, eds. *Cortical integration. Basic archicortical and cortical association levels of neuronal integrations*. New York: Raven Press, 1984:91-104.
- Gaztelu JM, Romero-Vives M, Abaira V et al. Hippocampal EEG theta power density is similar during slow-wave sleep and paradoxical sleep. A long-term study in rats. *Neurosci Lett* 1994; 172:31-34.
- Givens BS, Olton DS. Cholinergic and GABAergic modulation of medial septal area: Effect on working memory. *Behav Neurosci* 1990; 104:849-855.
- Grastyán E, Lissák K, Madarász I et al. Hippocampal electrical activity during the development of conditioned reflexes. *Electroenceph Clin Neurophysiol* 1959; 11:409-430.
- Green JD, Arduini AA. Hippocampal electrical activity in arousal. *J Neurophysiol* 1954; 17:403-420.
- Hess WR. Le sommeil comme une fonction physiologique. *J Physiol* 1949; 41:61A-67A Paris.
- Kahana MJ, Sekuler R, Caplan JB et al. Human theta oscillations exhibit task dependence during virtual maze navigation. *Nature* 1999; 399:781-784.
- Kahana MJ, Seelig D, Madsen JR. Theta returns. *Curr Opin Neurobiol* 2001; 11:739-744.
- Kleitman N. *Sleep and Wakefulness*. Chicago, London: The University of Chicago Press, 1963.
- Kocsis B, Vertes RP. Dorsal raphe neurons: Synchronous discharge with theta rhythm of the hippocampus in the freely behaving rat. *J Neurophysiol* 1992; 68:1463-1467.
- Komisariuk B. Synchrony between limbic system theta activity and rhythmic behaviour in rats. *J Comp Physiol Psychol* 1970; 10:482-492.
- Lerma J, García-Austt E. Hippocampal theta rhythm during paradoxical sleep, Effects of afferent stimuli and phase-relationships with phasic events. *Electroenceph Clin Neurophysiol* 1985; 60:46-54.
- Livingstone MS, Hubel DH. Effects of sleep and arousal on the processing of visual information in the cat. *Nature* 1981; 291:554-561.
- Marks GA, Shaffery JP, Oksenberg A et al. A functional role for REM sleep in brain maturation. *Behavioural Brain Res* 1995; 69:1-11.
- McCarley R, Benoit O, Barrionuevo G. Lateral geniculate nucleus unitary discharge in sleep and waking: State- and rate- specific aspects. *J Neurophysiol* 1983; 50:798-817.
- Morales-Cobas G, Ferreira MI, Velluti RA. Sleep and waking firing of inferior colliculus neurons in response to low frequency sound stimulation. *J Sleep Res* 1995; 4:242-251.
- Moruzzi G. The sleep-waking cycle. *Ergebnisse der Physiologie* 1972; 64:1-165.
- O'Keefe J, Recce ML. Phase relationship between hippocampal place units and EEG theta rhythm. *Hippocampus* 1993; 3:317-330.
- O'Keefe J, Burgess N. Theta activity, virtual navigation and the human hippocampus. *Trends Cognit Sci* 1999; 3:403-406.
- Pedemonte M, Peña JL, Morales-Cobas G et al. Effects of sleep on the responses of single cells in the lateral superior olive. *Arch Ital Biol* 1994; 132:165-178.
- Pedemonte M, Peña JL, Velluti RA. Firing of inferior colliculus auditory neuron is phase-locked to the hippocampus theta rhythm during paradoxical sleep and waking. *Exp Brain Res* 1996; 112:41-46.
- Pedemonte M, Rodríguez A, Velluti RA. Hippocampal theta waves as an electrocardiogram rhythm timer in paradoxical sleep. *Neurosci Lett* 1999; 276:5-8.
- Pedemonte M, Pérez-Perera L, Peña JL et al. Sleep and wakefulness auditory processing: Cortical units vs. hippocampal theta rhythm. *Sleep Res Online* 2001; 4:51-57.
- Pedemonte M, Goldstein-Daruech N, Velluti RA. Temporal correlation between heart rate, medullary units and hippocampal theta rhythm in anesthetized, sleeping and awake guinea pigs. *Autonomic Neurosci* 2003; 467:107: 99-104.
- Peña JL, Pedemonte M, Ribeiro MF et al. Single unit activity in the guinea-pig cochlear nucleus during sleep and wakefulness. *Arch Ital Biol* 1992; 130:179-189.
- Peña JL, Pérez-Perera L, Bouvier M et al. Sleep and wakefulness modulation of the neuronal firing in the auditory cortex of the guinea-pig. *Brain Res* 1999; 816:463-470.
- Pérez-Perera L. Actividad unitaria de la corteza auditiva: Ritmo theta del hipocampo y respuesta a vocalizaciones en el ciclo vigilia-sueño. Tesis de Maestría. Programa de Desarrollo de Ciencias Básicas-Facultad de Ciencias. Montevideo Uruguay 2002.
- Pompeiano O. Mechanisms of sensorimotor integration during sleep. In: Stellar E, Sprague JM, eds. *Progress in Physiological Psychology*. New York, London: Academic Press, 1970:1-179.
- Raghavachari S, Rizzuto D, Caplan J et al. Gating of human theta oscillations by a working memory task. *J Neurosci* 2001; 21:3175-3183.
- Scoville WB, Milner B. Loss of recent memory after bilateral hippocampal lesions. *J Neurol Neurosurg Psych* 1957; 20:11-21.
- Soja PJ, Cairns BE, Kristensen MP. Transmission through ascending trigeminal and lumbar sensory pathways: Dependence on behavioral state. In: Lydic R, Baghdoyan HA, eds. *Handbook of Behavioral State Control*. Boca Raton, London, New York, Washington: CRC Press, 1998:521-544.
- Sutherland GR, McNaughton B. Memory trace reactivation in hippocampal and neocortical neuronal ensembles. *Curr Opin Neurobiol* 2000; 10:180-186.
- Szymusiak R. Magnocellular nuclei of the basal forebrain: Substrates of sleep and arousal regulation. *Sleep* 1995; 18:478-500.
- Skaggs WE, McNaughton BL, Wilson MA et al. Theta phase precession in hippocampal neuronal populations and the compression of temporal sequences. *Hippocampus* 1996; 6:149-172.
- Tesche CD, Karhu J. Theta oscillations index human hippocampal activation during a working memory task. *Proc Natl Acad Sci USA* 2000; 97:919-924.
- Velluti RA. Interactions between sleep and sensory physiology. *J Sleep Res* 1997; 6:61-77.
- Velluti RA, Peña JL, Pedemonte M. Reciprocal actions between sensory signals and sleep. *Biol Signals Recept* 2000; 9:297-308.
- Velluti RA, Pedemonte M. In vivo approach to the cellular mechanisms for sensory processing in sleep and wakefulness. *Cell Mol Neurobiol* 2002; 22:501-516.
- Vertes RP, Kocsis B. Brainstem-diencephalo-septo-hippocampal systems controlling the theta rhythm of the hippocampus. *Neurosci* 1997; 81:893-926.
- von Stein A, Sarnthein J. Different frequencies for different scales of cortical integration: From local gamma to long range alpha/theta synchronization. *Int J Psychophysiol* 2000; 38:301-313.
- Wallenstein GV, Eichenbaum H, Hasselmo ME. The hippocampus as an associator of discontinuous events. *Trends Neurosci* 1998; 21:317-323.

Sleep and Sleep Disorders:

A Neuropsychopharmacological Approach

Lader, M.H.; Cardinali, D.P.; Pandi-Perumal, S.R. (Eds.)

2006, XIII, 309 p. 121 illus., Hardcover

ISBN: 978-0-387-27681-6