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Sleep and Sensory Information.

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Running Title: ***sleep & sensory systems.***

The information coming from the outer and the inner worlds during life is a meaningful influence on the brain phenotypical development and, in our particular topic, on sleep organization. In early developmental stages, from phylogenetic and ontogenetic viewpoints, the sensory information constitutes a relevant drive controlling the brain function and the general physiology. Each brain develops genetically conditioned, although a germane component is the sensory information from both the two worlds and the way the brain handled it throughout life, i.e., an endless process.

The natural light-dark sequence, a phylogenically archaic information, through the light receptor and its processing system, profoundly influences the sleep-wakefulness cycle. The circadian rhythm of melatonin secretion -the notion of darkness- is generated in mammals by a central pacemaker located in the suprachiasmatic nuclei of the hypothalamus, largely synchronized by cues from the light-dark cycle.

Early in the twentieth century, the concept of the sleep as being the result of a blockade of the auditory inflow was introduced [see 16]. Later, Bremer [1] made the proposal of an extensive deafferentation of ascending sensory impulses to the isolated brain that resulted in sleep. He became the outstanding proponent of the deafferentation sleep theory known as the "passive theory", implicating the existence of a *tonus* on the central nervous system (CNS) dependent on the sensory information. The activating ascending reticular system described [2] seemed to confirm Bremer's concepts: every sensory input would also release information (*tonus?*) to the brain stem activating reticular formation.

Brief history of sleep active processes.

A clinical observation of a continuous and prolonged sleep easily arousable at the beginning- made in Montevideo and published in France by Soca [3] - was reported in a young patient with a tumour located over the *sella turcica*, probably a craneopharyngioma, which compressed the anterior hypothalamic region. von Economo [4] proposed the anterior hypothalamus as a sleep facilitatory area in patients suffering from encephalitis with *post mortem* lesions in this region.

Hess[5] electrical stimulation of thalamic areas provoking sleep was the final step towards admitting sleep as an active process. Later it was shown [6] that electrical stimulation of the lateral preoptic area evoked bilateral EEG synchronization. On the neurotransmitter side of sleep generation, acetylcholine (ACh) was one of the first used in that sense by the pioneering work carried out by Dikshit [see16] and particularly by Hernández-Peón et al. [7], who introduced ACh crystals directly into the medial forebrain bundle and produced sleep in cats; ACh microinjections into the brainstem led to the occurrence of paradoxical sleep in cats [8]. Furthermore, the sleep generated by ACh

crystals applied into the preoptic area could be blocked by atropine in posterior regions of the basal forebrain bundle [9]. Active processes in the sleep production were also proposed by Moruzzi [10] and by Jouvet [11]. Several recent reports support the tenet of sleep as actively produced. Electrophysiological approaches as unitary recordings, immunoreactive staining techniques as well as functional magnetic resonance imaging in human, are some contributions to such concept [12, 13, 14]. Now, we are postulating the sensory systems hereby included as relevant factors actively participating in sleep processes [15-18].

A special consideration should be restated: sleep generation, maintenance and every related event, are part of central processes that involve the whole brain, obviously including the always forgotten neocortex.

Interactions between sensory activity and sleep neurophysiology.

The processing of sensory information is definitely present during sleep, however with profound modifications. All sensory systems reviewed, visual, auditory, somesthetic, olfactory as well as temperature receptors, etc., demonstrated some influence on sleep and, at the same time, the sensory systems undergo changes that depend on the CNS sleep or waking condition. We would like to suggest that the neural networks/cell assemblies responsible for sleep processes are actively modulated by sensory inputs in order to support the widely distributed brain changes occurring on entering sleep. Thus, the CNS and its sensory input have reciprocal interactions on which the normal sleep-waking cycling and behaviour depend to a great extent [15,16].

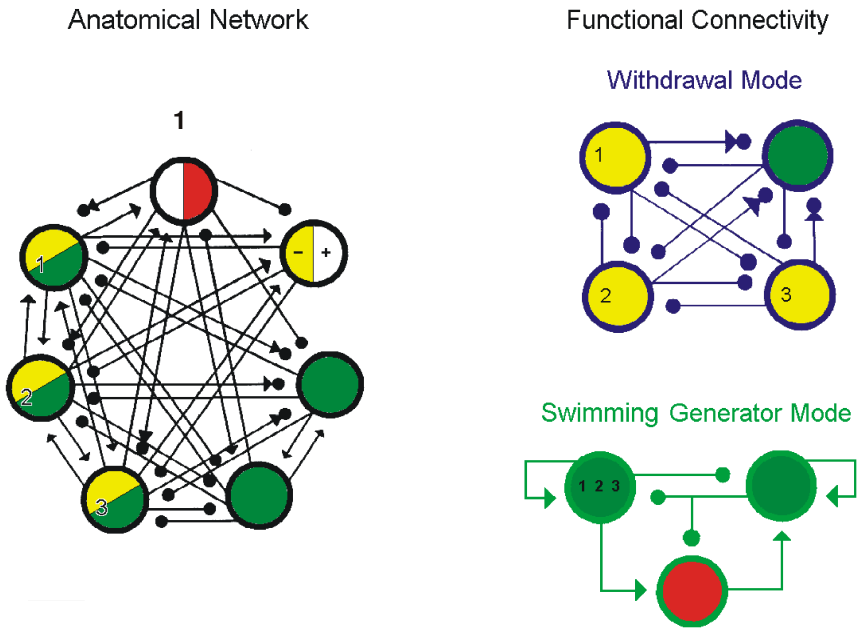

***Figure 1**. Neuronal network of a mollusc, the Tritonia, anatomical connectivity and the two possibilities for functional-behavioural networks are shown acting as, a) withdrawal mode and, b) swimming generator mode. The neurone 1 (top, left) activation-deactivation is the first action to produce the functional shift changing the animal behaviour. Modified from [19]*

The *Tritonia* simplistic approach is intended to suggest/evoke what may happen in a complex CNS on passing from wakefulness to sleep.

Getting [19] postulated that "…If a network, synaptic and cellular mechanisms are under modulator control, then an anatomical network may be configured into any one of several *modes*,…The term *modes* is intended to imply a manner in which a network processes information or generates and output pattern,…" **(Fig. 1)**. When afferent or modulator inputs alter the properties of the basic constituents of a set of networks, a transition among modes may occur, e.g., in our case passing from W to sleep. A neurone as a basic constituent of a network or cell assembly may fire an action potential or not, or may increase or decrease firing while still belonging to the same network although running for a new particular function. Thus, increasing firing does not necessarily mean that a cell is sub-serving to sleep or waking, because in the sleep case for instance, the recorded neurone may belong to a network in which, although engaged in sleep, should play a decreasing firing *mode*. Further, the imbalance introduced by cell 1 in the *Tritonia* very simple CNS **(Fig. 1)** may be provoked, in a complex brain, by a summation of factors that, after some signal on a group of neuronal networks/cell assemblies -perhaps decreasing light intensity- progressively begin to condition the system.

Neuronal Network/Cell Assembly. Neuronal assemblies is a concept defined by the temporally correlated neuronal firing associated to some functional end. The most likely information coding is the ensemble coding by cell assemblies [20]. Neuronal groups connected with several other neurons or groups can introduce cooperation and integration among widely distributed cells even with different functional properties to sub-serve a new state or condition. A neurone firing in a functional associated group may process some information and, some time later may become associated to other competing and activated neuronal groups for different functional purposes, e.g., on passing from wakefulness to sleep.

The auditory system in sleep.

From several viewpoints the auditory is a special system related to sleep neurophysiology, exhibiting a series of unique associated changes [16,17,18]. The auditory incoming signals to the CNS may change the sleep characteristics, while, conversely, the CNS can control by feed-back mechanisms the auditory input in close correlation with the sleep-wakefulness cycle [15].

Receptor and auditory nerve action potentials exhibited amplitude changes when analysed during quiet wakefulness (W), slow wave sleep (SWS) and paradoxical sleep (PS or REM sleep) in guinea-pigs [21]. Auditory evoked potentials recorded from the primary cortical area in rats and far-field potentials in humans, also exhibited amplitude shifts on passing from W to sleep. All evoked potentials components of the averaged waveform were larger during SWS than in W or PS [see16,22].

Auditory single cell recordings

The effects of sleep and wakefulness on auditory evoked activity at the mesencephalic reticular formation was reported showing the activity of the non-lemniscal neuronal auditory pathway to vary between sleep and W in cats [23]. The analysis of the

unitary responses to sound, now at the specific auditory nuclei and cortex, revealed the following scenery:

Neuronal discharge rate shifts. Around 50% of the auditory cortical (AI) units recorded during SWS and PS maintained a firing similar to the one recorded during quiet W, postulated to continue monitoring the environment. Another set of cortical neurones are divided into those that increase and those that decrease their firing on passing from W to SWS or from SWS to PS. The latter group, although responding to the sound stimuli, are proposed to be engaged- then associated to other neuronal network/cell assembly- in sleep-active processes **(Fig. 2)**. A different proportion of auditory units firing are seen in the brainstem nuclei. In those *loci* most of the units exhibit increasing and decreasing firing, while those units responding in sleep as during quiet W, are present in a smaller number than in the auditory cortex. This suggests that the auditory brainstem neurones that increase/decrease firing in sleep are engaged in some sleep process, particularly, we propose, participating in sleep-active cell assemblies/networks **(Fig.2)**. A most salient fact is that no auditory neurone exhibited a firing stop on passing to sleep [16].

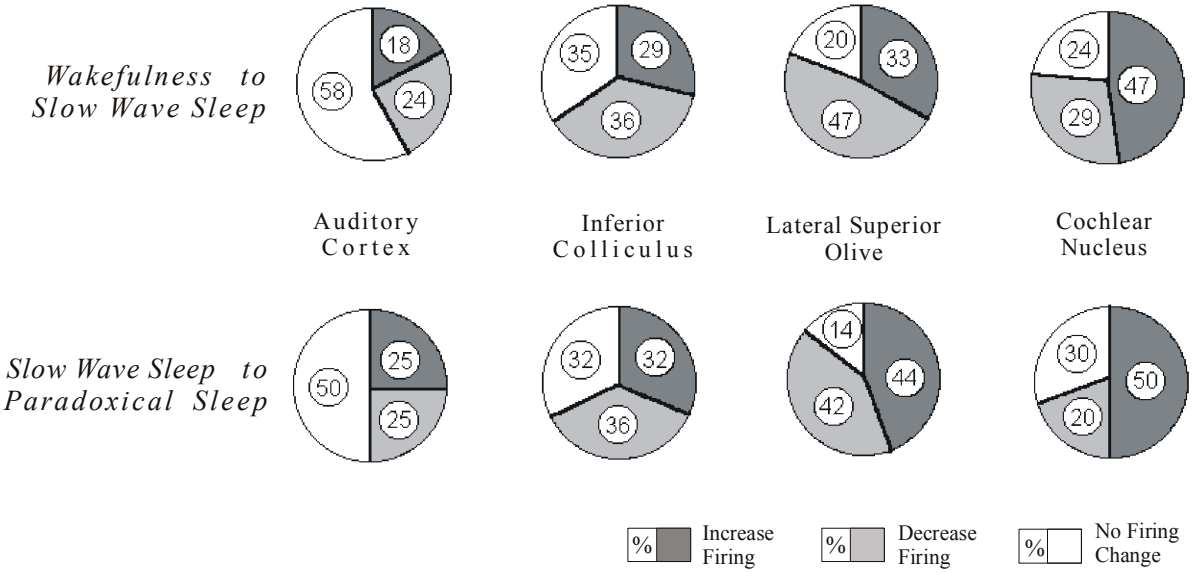

Figure 2. *Guinea pig unitary evoked activity (n=293) along the auditory pathway in the sleep-waking cycle. Pie charts show percentages of neuronal firing shifts on passing from Wakefulness to Slow Wave Sleep and from Slow Wave sleep to Paradoxical Sleep. The lower the locus the majority the increasing-decreasing firing neurones. No silent neurone was detected on passing to sleep or during sleep in any pathway level. Data from* ***see 16****.*

Neuronal discharge pattern shifts. The firing pattern change may support a different possibility of sound analysis as well as suggesting a different mode of relation to other cell assembly/network which we are postulated as active sleep-related. The same neurone may exhibit a pattern when in SWS and a different one when in PS, to recover, e.g., the initial W firing distribution at the following W epoch. Moreover, diverse patterns could be observed throughout the sleep-waking cycle [17,18].

Hippocampal theta rhythm. Time is a variable that could be controlled by the hippocampus, represented by the theta rhythm, postulated as a meaningful factor in the temporal processing of auditory signals [17,18]. Vinogradova [24] supports the notion of theta rhythm influences, e.g., a regulatory system, linking the hippocampus to brainstem structures, sensing the attention level and, most important to our proposal, introducing information on the changes in the environment. Recordings carried out in the primary

auditory cortex are indicative of an interconnection between these brain regions, supporting the notion that an auditory-hippocampal shared functional interaction may be present [see 16]. New data- auditory units phase-locked with theta rhythm- may be not only part of the sensory processing but also part of sleep processes in the context of neuronal networks/cell assemblies dynamics, and the known relationship between paradoxical sleep and hippocampal theta rhythm.

Absence of auditory input

The surgical section of the olfactory, optic, statoacoustic, and trigeminal nerves, one vagus nerve and the spinal cord posterior paths in cats, that is, *quasi* total deafferentation, carried out by Vital-Durand et Michel [25], revealed a sleep-waking cycle showing several relevant changes, demonstrating the influence of the sensory inputs on sleep organization.

The total auditory deprivation in guinea-pigs, by surgical removal of both cochleae, enhances SWS and PS by a similar proportion while reducing W, for the 45 post-lesion days studied [26]. We propose that the relative isolation from the outside world may provoke part of the change observed in deaf guinea-pigs, although it can not be discarded that it may mean the lack of an active influence. Thus, eliminating an input to a complex set of networks/cell assemblies as the ones that may regulate the sleep-waking cycle, would introduce functional shifts meaning that such input is significant for the sleep/waking behaviour.

Human´s event related potentials

The late components of the far-field evoked potential, also called the slow potentials or late auditory evoked responses, are most altered during sleep. Bastuji and García-Larrea [27] studies on evoked potentials during human sleep support the view that sophisticated auditory information processing persists during all sleep stages. Semantic information is possible in stage II and PS, whereas the presence of P3 seems to be essential to stimulus encoding despite the fact that the question if W and sleep P3 can be considered equivalent remains to be studied.

The recording of mismatch negativity, a component of auditory evoked activity, was reported to be present in SWS [see 16] and during PS [28], after a training period in humans. Moreover, this negativity has recently been observed also in newborn “quiet sleep” and linked to learning [see 16]. A possible learning-memory storage process has been already reported through several technical approaches including our units studies in guinea pigs (**Fig. 3**, Auditory Cx Unit).

Conclusions and final proposal.

Sleep and sensory input in general

The sensory functions analysis during sleep-waking cycle leads to the conclusion that normal sleep depends in many ways on the sensory input. We are suggesting that the sleep and waking control networks are modulated by several inputs, and therefore a proportion of “passive” effects must be associated with active functions for entering and

maintaining normal sleep. Hence, the total amount of sleep increases under some experimental conditions: a) continuous somatosensory stimulation. b) the total darkness. c) the total silence, after bilateral cochlear destruction. Furthermore, partial increments in the frequency of specific sleep stages are observed: a) when rats are stimulated by sounds during any sleep stage. b) with bright light stimulation in humans. c) with electrical stimulation of the olfactory bulb in cats [15]. On the other hand, the sensory influence on sleep, e.g., the abolition or decrement of a sleep sign or stage is produced by: a) continuous light stimulation in rats. b) bilateral lesions of some vestibular nuclei. c) the long exposure to cold which decrements PS leading to PS deprivation. d) the olfactory bulbectomy which decreases PS frequency episodes [15].

The lack of sensory inputs as well as their enhancement can produce sleep/ waking imbalances, augmenting or diminishing their proportions. Thus, the induced changes in the waking and sleep networks lead to the cited imbalances not simply for passive sleep production but also by introducing sensory sleep-active influences.

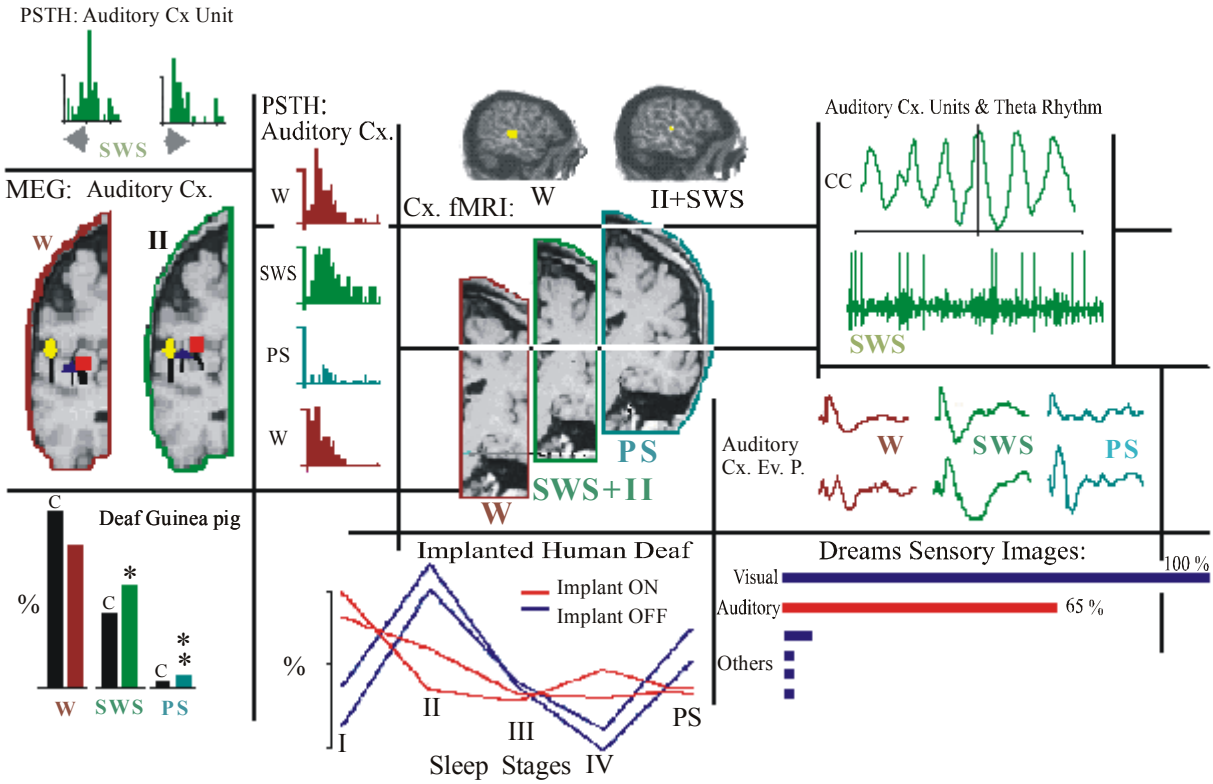

Figure 3. *Diverse technical approaches supporting the postulated notion of the importance and possible active participation of the auditory input on sleep processes. Three human half brain tomographic cuts (centre) represent the three main functional possibilities: wakefulness (W), slow wave sleep (SWS) and paradoxical sleep (PS).*

Post stimulus time histogram (PSTH) changes of a cortical auditory neurone firing shift when stimulated with natural sound played directly or backwards [see 16]. PSTH of a cortical unit on passing from wakefulness (W) to slow wave sleep (SWS) and paradoxical sleep (PS) exhibiting firing and pattern shifts [see 16]. Human auditory cortical imaging (fMRI) demonstrating activity during sleep. Modify from [30]. The cortical auditory neurones can be phase-locked to hippocampal theta rhythm [see 16]. Rat auditory cortical evoked potentials through the sleep-waking cycle showing amplitude changes [22]. The dream auditory "images" are present in 65% of dream recalls [see 16]. Deafness, in human and guinea pig, influences sleep. The human recorded with the intra-cochlear implant "off" and "on" shows different sleep stages percentages while the guinea pig exhibits (bars) an increase in sleep time with decreasing wakefulness [26]. The human magnetoencephalography (MEG) shows a place shift of the dipole evoked by three sound stimulating

frequencies on passing to sleep Stage II, demonstrating a change of neuronal network/cell assembly [29]. Modified from [16].

A magnetoecephalographic (MEG) approach described amplitude changes and anatomical place shifts of the sound evoked dipole in the human primary auditory cortex (**Fig. 3**, MEG) on passing from W to sleep Stage II [29]. The MEG dipole anatomical position shift obtained implicates a change to a new neuronal group/network, already indirectly supported by our unitary studies [16]. The evoked activity during sleep- its dipole- appears in a different cortical region than during W, thus suggesting a new cell assembly/neuronal network participation.

The functional magnetic resonance imaging (fMRI), when combined with EEG recording, showed that the auditory stimuli produced bilateral activation in the human auditory cortex (**Fig. 3**, Cx fMRI) and other areas related to cognitive aspects, both during W and sleep [30]. Maquet [14] fMRI studies support the notion that the primary sensory cortices are the least deactivated during sleep, in total agreement with our unitary results which never showed an auditory unit to stop firing on passing to sleep [16]. The data exhibited by fMRI strongly support the notion that the sleeping brain can process auditory information, detecting meaningful events [30], as it can be observed in the unitary cortical and inferior colliculus responses in guinea pigs when a complex stimulus (the animal call) is played normally or in reverse [16] (**Fig. 3**, PSTH: Auditory Cx Units).

Some sleep researchers are, unconsciously, looking for a “sleep centre” that does not exist. A CNS centre may be real and useful for controlling a function as the cardiovascular, the respiratory, etc., while, totally on the other hand, sleep is not a function but a complete different CNS state. This means different brains for the diverse W conditions, for sleep Stages I, II and SWS and for PS with or without phasic components. Hence, sleep signifies a whole change of networks/cell assemblies, a new cooperative interaction among them, considering that a single network may sub-serve several different functions.

The many technical approaches reviewed support the notion of the sensory in general and the auditory incoming information in particular, as exerting influences on sleep through a dynamic neuronal participation in different sleep-related cell assemblies.

A special point is the environmental reduction of sensory information, as occur during the night, allowing the auditory system neurones to become engaged, as we are postulating, in active sleep-related processes. Thus, the sensory input is not only a passive but an active contributor to the whole brain change on passing from W to sleep, maintaining the environment monitoring.

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