Neural representations during sleep: From sensory processing to memory traces

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Abstract

In the course of a day, the brain undergoes large-scale changes in functional modes, from attentive wakefulness to the deepest stage of sleep. The present paper evaluates how these state changes affect the neural bases of sensory and cognitive representations. Are organized neural representations still maintained during sleep? In other words, despite the absence of conscious awareness, do neuronal signals emitted during sleep contain information and have a functional relevance? Through a critical evaluation of the animal and human literature, neural representations at different levels of integration (from the most elementary sensory level to the most cognitive one) are reviewed. Recordings of neuronal activity in animals at presentation of neutral or significant stimuli show that some analysis of the external world remains possible during sleep, allowing recognition of behaviorally relevant stimuli. Event-related brain potentials in humans confirm the preservation of some sensory integration and discriminative capacity. Behavioral and neuroimaging studies in humans substantiate the notion that memory representations are reactivated and are reorganized during post-learning sleep; these reorganizations may account for the beneficial effects of sleep on behavioral performance. Electrophysiological results showing replay of neuronal sequences in animals are presented, and their relevance as neuronal correlates of memory reactivation is discussed. The reviewed literature provides converging evidence that structured neural representations can be activated during sleep. Which reorganizations unique to sleep benefit memory representations, and to what extent the operations still efficient in processing environmental information during sleep are similar to those underlying the non-conscious, automatic processing continually at work in wakefulness, are challenging questions open to investigation.

Keywords: Sensory representations during sleep; Single unit recordings during sleep; Event-related potentials during sleep; Functional imaging during sleep; Expression of learning-induced plasticity during sleep; Dynamics of memory representations during sleep

1. Introduction

Although the concept of representation has been questioned, in particular by cognitive psychologists (O’Regan & Noe, 2001) and neurophilosophers (Maturana & Varela, 1987; Thompson & Varela, 2001), in the field of neurosciences the notion of neural representation has become so popular over the last thirty years that it has now come into common use (see reviews by Andersen, Snyder, Bradley, & Xing, 1997; Knudsen & Brainard, 1995; Logothetis, 1998; Maunsell, 1995; Phillips, 1993; Roland & Gulyas, 1994; Singer, 1998). This is not surprising: albeit may be naive, it is traditionally considered that brain’s function is to integrate features of the external world and to build internal representations so as to generate a “model” of the world enabling complex sensory–motor interactions and cognitive functions. However, the notion of neural representation is not univocal. From one article to another, there is a very large diversity in the level and complexity of what is represented, as well as in the type of neural code supposed to underlie the neural representations. Beyond the classical topographic representations of the sensory epithelium...
described at the cortical (Cowey & Ellis, 1969; Kaas, Nelson, Sur, Lin, & Merzenich, 1979; Merzenich, Knight, & Roth, 1975) and subcortical (Cowey & Cassetty, 1986; Malpeli & Baker, 1975; Merzenich & Reid, 1974) levels, neural representation ranges from simply a neuronal signal that has a content and performs a function (deCharms & Zador, 2000), to a response pattern obtained over a cortical area at presentation of a natural stimulus (Wang, Merzenich, Beitel, & Schreiner, 1995), and to widely distributed neuronal assemblies whose firing rate is synchronized across various brain areas in the millisecond scale (Engel, Fries, & Singer, 2001). The smallest common denominator to all these views is the idea that a neural representation contains information. The questions addressed in the present paper are thus: Do neuronal signals emitted during sleep carry information? Have they a content? Have they any functional relevance?

Addressing these questions may surprise given that loss of consciousness, loss of sensory awareness, and unresponsiveness to stimuli from the external world are among the major features defining sleep. However, sleep does not bring a little death. The neuroscience community no longer conceives of the sleeping brain as simply dormant, fully disconnected from the environment and completely quiescent. In particular, the relations between sleep and cognition have attracted considerable interest in the last decade, as attested by the recent spate of publications on that topic. In the field of sleep and cognition, now called “the cognitive neuroscience of sleep” (Hobson & Pace-Schott, 2002), it is explicitly or implicitly assumed that neural representations can be activated or can be spontaneously active and eventually modified during sleep. The present review presents some aspects of that literature, posing as many questions as it answers. Starting with the issue of sensory representations in the first two sections, we will progress by evaluating whether learned representations are accessible and can be expressed during sleep, to finally address, in the last section, the question of the dynamics of memory representations during sleep. Despite partial overlaps, the review does not cover the fields of “information processing during sleep” (see Atienza, Cantero, & Escera, 2001; Bonnet, 1982; Coenen & Drinkenburg, 2002), nor that of “sleep and memory” (see Atienza, Cantero, & Escera, 2001; Bonnet, 1982; Coenen & Drinkenburg, 2002), to a response pattern obtained over a cortical area at presentation of a natural stimulus (Wang, Merzenich, Beitel, & Schreiner, 1995), and to widely distributed neuronal assemblies whose firing rate is synchronized across various brain areas in the millisecond scale (Engel, Fries, & Singer, 2001). The smallest common denominator to all these views is the idea that a neural representation contains information. The questions addressed in the present paper are thus: Do neuronal signals emitted during sleep carry information? Have they a content? Have they any functional relevance?

Contrary to waking and PS which are both associated with fast rhythms of brain electrical activity, SWS is characterized by large-amplitude, low-frequency (<15 Hz) oscillations reflecting a massive synchronization of neuronal activities in thalamocortical networks. Spindles, delta waves, and slow oscillation are the three brain rhythms defining SWS. The neuronal patterns prevailing in thalamocortical systems, a burst-silence mode during SWS versus a sustained single-spike activity during waking and PS, are under the control of generalized modulatory systems originating in the brainstem, the hypothalamus, and the basal forebrain (review in Jones, 2005; Pace-Schott & Hobson, 2002; Steriade, 2003; Steriade & McCarley, 1990). But none of the natural states of vigilance is uniform. It is well known that within the waking state, the level of arousal modulates sensory responses (e.g., Foote, Berridge, Adams, & Pineda, 1991; Hubel, Henson, Rupert, & Galambos, 1959; Morrow & Casey, 1992), and that attentional processes strongly influence sensory processing, either facilitating responses to target stimuli or suppressing responses to non-target stimuli (review in Desimone & Duncan, 1995). Qualitatively different epochs, and thereby differences in sensory processing, also exist within a given sleep state. This is the case of the epochs with or without ocular saccades in PS (e.g., Baust, Berlucchi, & Moruzzi, 1964; Cairns, Kiang, McErlane, Fragoso, & Soja, 2003). This is also the case of the depolarizing and hyperpolarizing phases of the slow oscillation in SWS (Massimini, Rosanova, & Mariotti, 2003). Indeed, during SWS, the membrane potential of cortical neurons oscillates between depolarized and hyperpolarized levels with a periodicity of about 1 s. This cyclic alternation is reflected in the electroencephalogram (EEG) by a slow (<1 Hz) oscillation: cortical neurons are depolarized and fire spikes during depth-negative EEG waves, while they are hyperpolarized during depth-positive EEG waves (Steriade, Timofeev, & Grenier, 2000; Timofeev, Grenier, & Steriade, 2001). Lastly, some factors independent of the sleep process per se modulate sensory processing during sleep: to take only one example in human, differences in stimulus processing were observed between the first and second part of the night for the same sleep stage (Plihal, Weaver, Mölle, Fehm, & Born, 1996).

2. Sensory representations during sleep: Neuronal activity in sleeping animals

From which literature can it be inferred that sensory representations are or are not maintained during sleep? If we please cite this article in press as: Hennevin, E. et al., Neural representations during sleep: From sensory processing to memory traces, Neurobiology of Learning and Memory (2006), doi:10.1016/j.nlm.2006.10.006
except the animal studies which, in the 1960s, examined how evoked potentials along sensory pathways varied with the sleep-wake states (for review of that literature, see Coenen, 1995; Hall & Borbély, 1970; Velluti, 1997; see also Meeren, van Cappellen van Walsum, van Luijtenaar, & Coenen, 2001), two sets of data are available: single unit electrophysiological recordings in animals, and event-related brain potentials in humans. In addition, some, but still rare, data from functional neuroimaging studies in humans have been obtained. In all cases, the same experimental protocol is used: a non-awakening sensory stimulus is presented to a naturally sleeping subject, and the observed responses are compared with those obtained when the subject was awake.

Compared with the myriads of studies performed in acute anesthetized preparations, only a few studies have documented evoked responses in sensory systems of naturally sleeping animals. The technical difficulties in maintaining stable unit recordings across vigilance states are partly responsible of this paucity. In addition, the time-consuming recording sessions required to collect neuronal data during storable episodes of sleep have certainly discouraged many researchers.

2.1. Is sensory information modified before entering the thalamus?

On the basis of a few data (Coenen & Vendrik, 1972; Mukhametov & Rizzolatti, 1970; Steriade, Iosif, & Apostol, 1969), the idea prevails that prethalamic transmission is unaffected by changes in vigilance state (Steriade, 1991, 2003). This claim should, however, be reconsidered at the light of more recent results obtained by two groups working in the somatosensory and auditory modalities.

For more than a decade, Soja and colleagues have extensively explored the transmission through the ascending somatosensory pathways and have pointed out the following results. First, transmission from lumbar spinal neurons and from trigeminal sensory neurons does not differ between waking and SWS but is suppressed during PS (Cairns, Fragoso, & Soja, 1995; Cairns et al., 2003; Soja, Fragoso, Cairns, & Jia, 1996; Soja, Oka, & Fragoso, 1993; Soja, Pang, Taepavarapuk, & McErlane, 2001). Second, sensory transmission through the spinal cord and brainstem is impeded by mechanisms impinging on multiple pre- and post-synaptic sites within ascending sensory tracts (Cairns, Fragoso, & Soja, 1996a; Cairns, McErlane, Fragoso, Jia, & Soja, 1996b; Cairns & Soja, 1998). Third, the modulation of sensory transmission across behavioral states is not uniform for all types of stimuli conveyed by a single sensory tract: whereas tooth pulp-evoked responses were decreased in PS compared with waking, responses of facial hair mechanoreceptors to air puff were increased (Cairns et al., 1996b, 2003). Thus, prior to any diencephalic processing, complex state-dependent modulation of sensory transmission occurs for exteroceptive, proprioceptive and nociceptive information.

State-dependent changes were also detected in the lower stages of the auditory system (review in Velluti & Pedemonte, 2002). Whether at the level of the cochlear nucleus (Pena, Pedemonte, Ribeiro, & Velluti, 1992), the lateral superior olive (Pedemonte, Pena, Morales-Cobas, & Velluti, 1994), or the inferior colliculus (Morales-Cobas, Ferreira, & Velluti, 1995; Torterolo, Falconi, Morales-Cobas, & Velluti, 2002), a large proportion of cells (65–85%) exhibited changes in evoked firing rate from waking to SWS and from SWS to PS. However, no dominant effect emerged at any level: approximately the same number of cells displayed increased and decreased responses from one state to the other. Lastly, though the authors prevented the action of middle-ear muscles by disrupting the ossicular chain, they detected modifications of the cochlear microphonic potential and of the compound action potential of the VIIIth nerve during both SWS and PS (Velluti, Pedemonte, & Garcia-Aust, 1989).

Results corroborating the idea that sleep-related changes occur even at the most peripheral level were also obtained in the visual system. Retinal ganglion cell responses to flashes of light clearly differed between SWS and waking: they were variable during PS, resembling those in SWS or those in waking (Galambos, Szabó-Salfay, Szatmári, Szilágyi, & Juhász, 2001).

2.2. Modulation of sensory information at the thalamic and cortical levels

The thalamus has long been considered as the major station where obliteration of synaptic transmission of external signals occurs upon falling asleep (Steriade, 1989; Steriade & Deschenes, 1984). And indeed, depressed evoked responses were observed during SWS in the visual (Livingstone & Hubel, 1981; Mukhametov & Rizzolatti, 1970), somatosensory (Mariotti, Formenti, & Mancia, 1989; but see Satoh, Eguchi, Watabe, Harada, & Hotta, 1980), and auditory (Edeline, Manunta, & Hennevin, 2000; Orman & Humphrey, 1981) thalamus. Using juxtacellular recordings in visual thalamus, Coenen and Vendrik (1972) estimated that the transfer ratio (i.e., the ratio between the EPSPs and spikes) fell from 0.9 to 1.0 in waking to 0.4–0.5 in SWS. This decrease is consistent with the results of Hirsch and colleagues (Hirsch, Fournier, & Marc, 1983) who reported that visual thalamus neurons were hyperpolarized by about 4mV as the animal shifted from quiet waking to SWS. During PS, thalamic neurons were found to be depolarized by about 10mV relative to SWS (Hirsch et al., 1983), and their evoked responses were either comparable or slightly attenuated compared with waking (Edeline et al., 2000; Mariotti et al., 1989; Mukhametov & Rizzolatti, 1970; Satoh et al., 1980).

Contrasting with the homogeneity of results obtained at the thalamic level, data described at the cortical level showed more variability from one study to another. Some found that, on average, cells were less responsive in SWS than in waking (Edeline, Dutrieux, Manunta, & Hennevin, 2001; Evarts, 1963; Gücer, 1979; Livingstone & Hubel, 1981), but others did not observe response alterations.
(Murata & Kameda, 1963; Pena, Pérez-Perera, Bouvier, & Velluti, 1999). In addition, within the same study, cortical cells varied greatly from one to the next in the degree and even the direction to which they were influenced by state changes (Edeline et al., 2001; Livingstone & Hubel, 1981; Pena et al., 1999). This was also the case during PS, which explains why in the only two studies where neurons were tested in PS, there was no overall change between the evoked activity recorded in waking and in PS (Edeline et al., 2001; Pena et al., 1999).

2.3. Changes in functional properties of thalamic and cortical cells

In the vast majority of the studies mentioned above, the reported changes only concerned responses evoked by a single stimulus. They documented how sleep affects sensory transmission, but they did not provide information about the content of sensory signals. Addressing this question requires comprehensive analysis of the operations performed by sensory neurons in their receptive fields (RF). Besides the observation that low-threshold RFs of spinal dorsal horn neurons \((n = 7)\) were increased in size during PS compared with waking (Kishikawa, Uchida, Yamamori, & Collin, 1995), only three studies have evaluated how thalamocortical RFs are modiﬁed as a function of behavioral state. The well-known study by Livingstone and Hubel (1981) mentioned that arousal from drowsiness or from brief episodes of SWS did not change RF sizes in the visual thalamus, and did not change, or occasionally slightly improved, the orientation and direction selectivity of visual cortex neurons; but, as recognized by the authors themselves, some uncertainties remained because tuning curves were not quantiﬁed. In contrast, a systematic quantiﬁcation of the frequency tuning curves were performed in the thalamocortical auditory system. At the thalamic level (Edeline et al., 2000), most of the cells (69/102) displayed a reduced RF size and an enhanced frequency selectivity in SWS compared with waking. In PS, a dichotomy existed between two populations of cells, one showing RF changes still more pronounced than during SWS, the other showing RF properties comparable to those in waking. The overall shape of the intensity-function was not affected in SWS and PS. At the cortical level, though many cells displayed RF alterations during SWS, overall the RF size and the frequency selectivity were not signiﬁcantly modiﬁed due to the heterogeneity of changes from one cell to the next (Edeline et al., 2001).

High frequency (>200 Hz) thalamic bursts have long been viewed as the signature of EEG synchronized states such as SWS (Benoit & Chataignier, 1973; Hubel, 1960; McCarley, Benoit, & Barrionuevo, 1983). Although they never dominate the neurons’ mode of discharge (Massaux, Dutrieux, Cotillon-Williams, Manunta, & Edeline, 2004; Weyand, Boudreaux, & Guido, 2001), their potential role in relaying sensory processing to cortex has been recently stressed (review in Krahe & Gabbiani, 2004; Sherman, 2001), but also vigorously criticized (Llinás & Steriade, 2006; Steriade, 2001c). When auditory thalamic cells respond to acoustic stimuli, bursts are more likely to occur at the neuron’s best frequency, and they promote a shorter response latency and a smaller latency variability (Massaux et al., 2004). More importantly, compared to single spike discharges, thalamic bursts largely enhance the probability of cortical neurons firing (Swadlow & Gusev, 2001, 2002). Thus, their presence may help maintaining cortical circuits responsive to sensory inputs (see below).

2.4. What can be concluded from that literature?

First, the paucity of data is striking. Over 40 years, very few experiments have been conducted in sleeping animals even with simple stimuli; only two have quantified the neurons’ functional properties; and none has employed complex (artificial or natural) stimuli. Therefore, the conclusions are necessarily limited. Nonetheless, cortical neurons are still responsive during sleep, which argues against the disconnection of the sleeping brain from the external world. In addition, thalamocortical neurons display functional properties that are not aberrant compared with those in waking, which suggests that some analysis of the external world remains possible during sleep, at least in the auditory modality.

2.4.1. Natural sleep versus anesthetized state

Because data collection is easier and less time-consuming in anesthetized animals, one can easily succumb to the temptation of considering that changes observed under anesthesia mimic changes observed during sleep. Thus, a great interest has been devoted to results obtained when the EEG spontaneously changed under anesthesia and showing that RFs of visual cortex neurons were wider during periods of synchronized EEG than during periods of desynchronized EEG (Wörgötter et al., 1998). In the same vein, in a series of studies using brainstem reticular stimulation in anesthetized animals to mimic natural arousal, it was claimed that evoked responses of barrel cortex neurons were suppressed during arousal, which limited the spread of sensory inputs through the cortex and reduced the size of sensory representations (Castro-Alamancos, 2002; Castro-Alamancos & Oldford, 2002). However, these results are, at least, questionable for several reasons. First, the described effects are discordant with results obtained both in anesthetized and in nonanesthetized animals: on the one hand, increasing the anesthetic depth decreased, not increased, the RFs size of thalamic and cortical neurons (Armstrong-James & George, 1988; Diamond, Armstrong-James, & Ebner, 1992; Dougherty, Li, Lenz, Rowland, & Mittman, 1997; Friedberg, Lee, & Ebner, 1999; Ikeda & Wright, 1974); on the other hand, reduced thalamocortical responsiveness is not characteristic of the activated state of waking, but of SWS (see references in Section 2.2), and wider RFs sizes were found not in the EEG-synchronized state of SWS, but in waking (Edeline et al., 2000, 2001). Second, anesthesia and recent surgery alter the
activity of sensory neurons (Headley, Chizh, Herrero, & Hartell, 1999), which totally invalidates the use of anesthetized preparations for comparison with sleep or waking. And indeed, when direct comparisons were made, from the sensory periphery up to the thalamocortical system, the response patterns observed during SWS systematically differed from those observed under anesthesia (Cotillon-Williams & Edeline, 2003; Guittion, Avan, Puel, & Bonfils, 2004; Kishikawa et al., 1995; Populin, 2005; Torterolo et al., 2002). Therefore, assuming that what occurs during the anesthetic state is similar to what occurs during natural sleep is a naive oversimplification that can only contribute to generate confusions in a domain where data are rare.

2.4.2. Particularities of cortical behavior during sleep

At variance with the widely accepted belief that the cerebral cortex is deprived of external signals during sleep, changes in sensory responses are less prominent at the cortical level than at the thalamic and subthalamic levels. This comes as a surprise because the thalamus is usually considered as the gate to the cerebral cortex. However the paradox is more apparent than real. Morphological evidence indicates that thalamocortical connectivity devoted to the transfer of sensory inputs constitutes only a minor proportion of synaptic contacts in the cerebral cortex; corticocortical excitatory connections exceed by far thalamocortical ones (Guillery & Sherman, 2002; LeVay & Gilbert, 1976; White, 1978). On the functional side, neocortical and thalamic neurons do not display parallel activities during SWS; whereas thalamic neurons are under the hyperpolarizing pressure exerted by GABAergic thalamic reticular neurons, cortical neurons exhibit a relatively rich activity. It was even suggested that far from being passive receivers, cortical intrinsic networks can play an active role in amplifying incoming thalamic inputs (see Steriade, 2001a, 2003; Steriade & Timofeev, 2003).

As stressed in several studies, response changes observed at the cortical level were highly heterogenous. Two types of reasons can account for this heterogeneity. The first one is that cortical responsiveness is not stationary during SWS; it varies over a very short time scale. In sleeping humans, the amplitude of somatosensory evoked potentials changed systematically as a function of the phase of the slow sleep oscillation, approaching waking level along the negative slope of the slow oscillation and strongly decaying, but without disappearing, along the positive drift (Massimini et al., 2003). Intracellular recordings in animals confirmed that contrary to what was observed with prethalamic stimulation, sensory inputs elicited by peripheral stimulation pass the thalamic gate and are transmitted to cortex during all phases of the slow oscillation (Rosanova & Timofeev, 2005). The second reason is a high variability across cells, perhaps due to the diversity of morphological and/or physiological cell types in cerebral cortex (review in Steriade, 2001b). The effects of state changes can even differ between cells recorded via the same electrode (Livingstone & Hubel, 1981). Obviously, the fact that adjacent cells show opposite modifications of their RF properties can have drastic consequences for any type of neural representation. Unfortunately, to what extent the sleep states affect a topographic map or, more importantly, affect the pattern of activation observed over a cortical area at presentation of a natural stimulus, are areas of inquiry that have never been explored. Also unexplored is to what extent analyses based on information theory methods (Bialek & Rieke, 1992; Borst & Theunissen, 1999; Buracas & Albright, 1999) would allow a better characterization of sensory processing during sleep, compared to the classical analyses used until now. For example, quantifying the responses of auditory cortex neurons by the metric-space method of Victor and Purpura (1996) revealed that although neurons exhibited similar firing rate in response to different acoustic stimuli, they transmitted significant amount of information, i.e., they discriminated between stimuli (Huetz & Edeline, 2006). To what extent spike trains of thalamocortical neurons still carry significant amount of information during sleep deserves to be investigated in future studies.

3. Sensory integration during sleep: Event-related brain potentials and functional neuroimaging in sleeping humans

Event-related brain potentials (ERPs) have been widely used to assess the extent of information processing during sleep in humans. We only present a small facet of that literature; for a more complete vision, see the following reviews (Atienza et al., 2001; Atienza, Cantero, & Dominguez-Marin, 2002; Bastuji & Garcia-Larrea, 1999; Bastuji, Perrin, & Garcia-Larrea, 2002; Campbell, Bell, & Bastien, 1992; Cote, 2002).

In general, the earlier the component of the evoked potentials, the more it is affected by the physical characteristics of the stimulus. In contrast, the later the component, the more it is affected by factors such as the relevance of the stimulus, the subject’s level of attention, or the state of vigilance. In the auditory modality, the early components (<10–15 ms), which reflect peripheral and brainstem activation, are viewed as relatively state-independent. Data on the middle-latency potentials, which are considered to reflect the first signs of thalamocortical involvement, are much less consistent; but in any case, these components are more affected in non-REM sleep than in PS. The late components (>50 ms), whose generators are still imperfectly known, are the most profoundly altered, especially during non-REM sleep. Indeed, beyond changes in latency and in amplitude, the most impressive effect of non-REM sleep on late potentials is an increased complexity of the response due to the appearance of sleep-specific components, unique to non-REM sleep, the vertex sharp wave and the K-complex (review in Bastien, Crowley, & Colrain, 2002). The ERPs morphology in PS is much more close to that observed in wakefulness.

3.1. Automatic detection of changes in the auditory environment

Whether or not certain of the late components, those called “cognitive” (or “endogenous”) ERPs, can be elicited...
during sleep is viewed as indicating the extent of sensory integration during sleep. A first series of studies examined whether the sleeping brain is able to detect changes occurring in the auditory environment. Most of them used the oddball paradigm: a train of frequently occurring “standard” stimuli is presented and, at rare and unpredictable times, a physical feature of the standard is changed. In the awake subject, the deviant stimulus elicits the well-known mismatch negativity (MMN), an additional negative component that appears 100–200 ms from stimulus onset. As MMN is thought to reflect pre-attentive processes occurring automatically, it was expected to be elicited during sleep. However, even if several reports described deviant-related negativities, it is largely agreed that a “true” MMN was not found in non-REM sleep (Loewy, Campbell, & Bastien, 1996; Nashida et al., 2000; Nielsen-Bohlman, 1996; Bastien, 1996; Nashida et al., 2000; Nielsen-Bohlman et al., 1991; Salisbury, Squires, Ibel, & Maloney, 1992; Van Sweden, Van Dijk, & Caekebeke, 1994; Wesensten & Badia, 1988). However, because of their delayed latency and/or scalp topography, those positive waves are generally not regarded as “true” P300, but rather as components related to the K-complex which occurs more frequently and is more enhanced after rare stimuli than after frequent stimuli (discussion in Cote, 2002). Some of the late positive waveforms recorded in PS after pitch deviants are regarded as more convincing candidates P300 (Bastuji, García-Larrea, Franc, & Mauguìere, 1995; Niiyama, Fujiwara, Satoh, & Hishikawa, 1994; Sallinen et al., 1996). A large centro-parietal positivity that conformed the waking P300 in terms of peak latency but whose frontal dispersion was much more limited, was also apparent in PS in response to rare and loud intensity tones (Cote & Campbell, 1999a, 1999b; Cote, Etienne, & Campbell, 2001).

3.2. Semantic discrimination

A P300-like waveform was also described in response to another type of stimulus, highly salient because of its obvious emotional dimension and its familiarity, the subject’s own name. Our first name is one of the most relevant stimuli, and its detectability is so high that it is commonly used to evaluate severely brain-injured patients (Laureys et al., 2004; Perrin et al., 2006; Signorino, d’Acunto, Angeleri, & Pietropaoli, 1995). For a long time, there has been behavioral and electrophysiological evidence (based on number of arousals, awakening latency measured by alpha rhythm onset, number of K-complexes, finger plethysmographic responses, or heart rate changes) indicating that the sleeping subject is more receptive to his first name than to other first names, words or tones (Beh & Barratt, 1965; Langford, Meddis, & Pearson, 1974; McDonald, Schicht, Frazier, Shallenberger, & Edwards, 1975; Oswald, Taylor, & Treisman, 1960; Voss & Harsh, 1998). More recent studies have corroborated this differential processing (Perrin, García-Larrea, Mauguìere, & Bastuji, 1999; Pratt, Berlad, & Lavie, 1999). In particular, using a series of eight first names with equiprobable delivery (to avoid a rarity effect), a late positive wave considered to be an equivalent of the parietal P300 (its longer latency is supposed to be due to the longer duration of stimuli) was selectively evoked by the subject’s own name during both wakefulness and PS. During stage 2, K-complexes were evoked by all eight first names, but the early portion of the K-complex, including in particular a positive wave in the same latency range as that observed in

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1 But, in non-awake subjects, MMN-like effects might simply result from spectral interactions (see Lazar & Metherate, 2003).
waking and PS, was selectively increased by the subject’s name (Perrin, Bastuji, Mauguire, & Garcia-Larrea, 2000; Perrin et al., 1999).

To evaluate further the possibility of semantic discrimination in sleep, a last series of studies focused on the N400. This wave appears around 400 ms after the presentation of semantically unrelated information between two words or between a context and a word, and it is viewed as an electrophysiological marker of verbal discordance. For example, when word pairs are presented in which the first word of the pair (the prime) and the second word (the target) are either semantically related (animal-horse) or semantically unrelated (animal-monday), a semantic priming effect is observed in awake subjects: the N400 is greater for target words preceded by unrelated words than for target words preceded by related words. Similar results were obtained during stage 2 and PS: a negative deflection that closely resembled the waking N400 (despite its longer latency) also displayed a priming effect, being more negative for the incongruous target words than for the congruous target words (Brualla, Romero, Serrano, & Valdizán, 1998). Detection of verbal discordances during sleep was corroborated by another study which, in addition to semantically congruous and incongruous words, used also non-words (disyllabic sounds without meaning). As in waking, a higher N400-like wave was observed for semantically incongruous words than for congruous words during both stage 2 and PS. However, for non-words, there were between-state differences: non-words elicited the highest N400 in waking, a N400 of the same amplitude as incongruous words in stage 2, and a N400 of the same amplitude as congruous words in PS. Thus, the hierarchical processing of discordance that operated during waking (non-words, incongruous words, congruous words) was not maintained during sleep (Perrin, Bastuji, & García-Larrea, 2002). Finally, a sentential semantic discrimination was also reported. Sentences (definitions with two attributes) with four possible degrees of congruence as ending targets were presented during stage 2 or during PS. As in wakefulness, in the two sleep stages the amplitude of the N400 varied as a function of the degree of congruency (Ibáñez, López, & Cornejo, 2006).

3.3. Results from neuroimaging studies

Ideally, the best way for appreciating the responses of the sleeping brain to external stimuli is to combine ERP recording techniques, which have a high temporal resolution but a poor spatial resolution, with functional brain imaging techniques, which have the reverse advantages and limitations. Studies combining ERP and positron emission tomography (PET) scan methods have started in awake subjects (Perrin et al., 2005) or in comatose patients (Laureys et al., 2000, 2004), but not yet in sleeping subjects. Nonetheless, a few functional magnetic resonance imaging (fMRI) studies have already examined regional brain activation associated with acoustic stimulation during sleep, but without performing concomitant ERP recording. One study observed a reduced activation in the primary and secondary auditory cortex in all non-REM sleep stages, accompanied by a pronounced negative fMRI signal in the visual cortex and precuneus (Czisch et al., 2002). Subsequently, the fMRI signal decreases induced by acoustic stimulation were found to be more prominent in stage 2 than in stages 3–4 and to be positively correlated with increases in EEG delta power and in the number of K-complexes, suggesting that these decreases might represent cortical deactivations serving a sleep protecting role (Czisch et al., 2004). Another study compared the effects of a pure tone and of the subject’s own name. In both waking and stage 2, tones and names produced a similar pattern of activation in auditory cortex, thalamus and caudate; nonetheless, sleep was associated with lower levels of activation in thalamus and parietal, prefrontal and cingulate cortices. In addition, in both waking and stage 2, the middle temporal gyrus and orbitofrontal cortex were more activated by the subjects’ names than by the tones. Lastly, when compared with tones, names produced a higher activation in the left amygdala and left prefrontal cortex during stage 2 than during waking (Portas et al., 2000). Thus, that study complements and extends data obtained in ERPs studies by suggesting the existence of a functional network that detects emotionally relevant stimuli during sleep and potentially alerts the organism. As we will see in Section 4, this view is concordant with electrophysiological data obtained in animals.

3.4. What can be concluded from that literature?

The sleep-ERPs literature indicates that some capacities for auditory discrimination are preserved in the sleeping brain, allowing detection of a physical deviance in the auditory environment, recognition of an intrinsically meaningful stimulus (the own’s first name), and even, to a certain extent, categorization of verbal stimuli. These results support thus the idea that sensory representations can be active during sleep and, further, they suggest that semantic representations may also be accessible. The electrophysiological events from which these brain capacities are inferred are more prominent in PS than in non-REM sleep. However, more than differences in processing abilities between the two sleep states, this probably reflects differences in cortical networks dynamics, as indicated by the occurrence of evoked brain potentials unique to non-REM sleep.

Obviously, a crucial question remains open: to what extent are the “cognitive” ERP components detected in sleep functionally equivalent to their waking counterparts, i.e., do they reflect the same level of processing? The finding that sleep ERPs generally differ from those in waking in terms of latency (most often prolonged) and/or topographic distribution (often more posterior) might indicate that different anatomical networks are involved in processing sensory stimuli during sleep and wakefulness. In this line, several authors have proposed that the frontal...
contribution to cognitive ERPs would be attenuated in sleep (Atienza et al., 2002; Cote, 2002). Supportive evidence for this view comes from functional imaging of sleep states (review in Drummond, Smith, Orff, Chengazi, & Perlis, 2004; Maquet, 2000; see also Kaufmann et al., 2006; Maquet et al., 2005). These studies have revealed that primary and supramodal association cortices, in particular the prefrontal and parietal cortices, behave differentially in non-REM sleep, the latter showing activity levels much more decreased compared to wakefulness; comparable results were reported in the fMRI study of Portas and colleagues (Portas et al., 2000). Similarly, contrasting with the activation of a number of areas, including posterior cortices, thalamic nuclei, and limbic–paralimbic structures, the prefrontal and parietal cortices were relatively hypoactive during PS. Thus, though the distribution of brain activity markedly differs between the two sleep states, they share a common feature, a deactivation of prefrontal and parietal cortices. We can reasonably suppose that this deactivation and, further, the altered functional interactions between sensory and executive cortical areas limit the content of the neural representations activated in sleep. Interestingly, a recent magnetoencephalographic study compared the cortical processing of consciously perceived and unperceived somatosensory stimuli in awake subjects. Whereas phase-locked activity to perceived stimuli was detected in somatosensory, frontal and parietal regions as early as 30–70 ms after stimulus onset, the phase locking to unperceived stimuli was weak and restricted to somatosensory region (Palva, Linkenkaer-Hansen, Näätänen, & Palva, 2005). These observations are consonant with some hypotheses proposing that differences in the synchronization of neural oscillations may explain the cognitive differences between wake and sleep states (Cantero & Atienza, 2005; Kahn, Pace-Schott, & Hobson, 1997; Paré & Llinás, 1995).

4. Representation of significant stimuli: Expression during sleep of learning-induced neuronal plasticity

The ability of sleeping subjects to discriminate between relevant and irrelevant auditory stimuli is general knowledge, based on numerous anecdotal observations and experimental evidence (review in Bonnet, 1982). We are all familiar with such phenomena as mothers waking up to their baby’s cry but not to irrelevant sounds, even when louder. Sleeping mothers are even able to discriminate their baby’s cry but not to irrelevant sounds, even when they are familiar with such phenomena as mothers waking up to their own baby’s cry from the cries of other babies: on the first three postnatal nights at the hospital, 58% of the mothers’ awakenings were to their own children’s cries, and this rose to 96% on the fourth night (Formby, 1967). Another typical example is the differential processing of our first name which persists during sleep, as described above. Evidence that relevant stimuli are recognized during sleep also exists in animals. It is well known that after a stimulus has acquired significance in wakefulness, sensory thresholds for awakening from SWS or PS are lowered (Halperin & Iorio, 1981; Rowland, 1957; Siegel & Langley, 1965; Van Twyver & Garrett, 1972). Furthermore, in the absence of animals’ awakening, autonomic responses to significant stimuli were found to be increased compared to when the stimuli were neutral (Ciancia, Trigona-Leisinger, & Bloch, 1980; Maho & Hennevin, 1999). From all these observations, it is clear that behaviorally important information can be identified as such during sleep. This suggests that some filtering mechanisms operate in sleep, gating input so that relevant stimuli are recognized. What neural substrate underlies this selection process is unknown.

This question was addressed using as model the neuronal plasticity induced by associative learning. When an initially neutral stimulus (the conditioned stimulus; CS) acquires a behavioral significance through its pairing with a biologically relevant stimulus (the unconditioned stimulus; US), its neural representation is modified, needless to say. If the sleeping subject responds differently to the CS after learning, this means that the learned representation of the CS has been, at least partially, activated during sleep. In order to explore the physiological conditions and the neural network underlying the activation of the CS representation during sleep, a series of experiments examined whether brain structures exhibiting learning-induced plasticity during waking do or do not continue to express plasticity during sleep.

4.1. Expression of learning-induced plasticity during paradoxical sleep

Because external stimuli associated with a potential danger are the most able to be detected by the sleeping organism, auditory fear conditioning was first used. To limit the risks of awaking the animals, PS (the deepest state of sleep in animals) was first investigated. After a habituation session to a tone, awake rats underwent conditioning with the tone used as the CS preceding a footshock (US). Control rats received unpaired presentations of tone and footshock. After each session, the tone alone was presented, at a non-awakening intensity, during PS episodes. Multiunit activity in selected brain structures was recorded during waking and PS.

That conditioning-induced increases in tone-evoked discharges can be expressed during PS was first demonstrated in the hippocampus (Maho, Hennevin, Hars, & Poincheval, 1991). Subsequent experiments evaluated whether this enhanced responsiveness in PS already exists upstream, in the sensory pathway that conveys auditory information. Indeed, an extensive literature has established that the learned behavioral significance of an acoustic stimulus is encoded as early as the thalamocortical auditory system. During fear conditioning, and other learning situations as well, the auditory thalamus and cortex display associative plastic changes that are highly specific, robust and long-lasting (review in Edeline, 1999; Weinberger, 1995, 2004). Neuronal recordings collected in the medial division of the medial geniculate body (MGl) showed that after conditioning, the tone responses in PS were largely above...
preconditioning levels (Hennevin, Maho, Hars, & Dutrieux, 1993). This enhancement cannot be attributed to arousal from sleep, as attested by careful online inspection of EEG tracings and by offline quantification of neck-muscle electromyographic activity. It was associative in nature, since it was not observed in pseudoconditioned rats. It did result from associative plasticity induced by learning in the awake state.

There is compelling evidence that the amygdala plays a critical role in the acquisition and expression of conditioned fear (review in Davis & Whalen, 2001; LeDoux, 2000; Maren, 2001). Information from the auditory thalamus and the auditory cortex reaches first the lateral nucleus of the amygdala (LA), before being distributed to other amygdaloid nuclei which in turn mediate the expression of conditioned emotional responses. Simultaneous recordings in the MGm and the dorsal part of LA (LAd) revealed that both MGm and LAd neurons developed discharge plasticity within a few conditioning trials, and both expressed it in PS following conditioning, with a significant correlation between the response changes observed during conditioning and during PS (Hennevin, Maho, & Hars, 1998). Furthermore, conditioned heart rate accelerations to the tone CS were manifested in PS after conditioning (Maho & Hennevin, 1999). Thus, from the afferent side to the efferent side of the fear conditioning circuit, neurons express learning-induced plasticity during PS.

Whereas fear conditioning induced quite similar plastic changes (both in terms of magnitude and of time course) in MGm and LAd, this was not the case for appetitive conditioning. When an acoustic CS was associated with food delivery, increases in tone-evoked discharges developed in both MGm and LAd during waking. But whereas MGm neurons continued to express conditioned increased discharges during PS, LAd neurons did not. As a consequence, the response changes observed in MGm during conditioning and during PS were correlated, but those observed in LAd were not (Maho & Hennevin, 2002). To sum up, LAd plasticity was or was not expressed in PS depending on the aversive or appetitive value of the tone CS.

4.2. Expression of learning-induced plasticity during slow-wave sleep

To what extent neuronal plasticity can be expressed in SWS, as it can be in PS, was assessed using fear conditioning and multiunit recordings in MGm and primary auditory cortex (ACx). As a result of tone-footshock pairing, tone-evoked responses increased in MGm and ACx. However, overall, they showed no significant changes during SWS, whether in MGm or in ACx. Only the few recordings (5/29) that exhibited the strongest conditioned responses in waking expressed enhanced responding in SWS (Hennevin & Maho, 2005). Obviously, these results contrast with those described above showing that response plasticity in MGm was systematically transferred from waking to PS. But whereas waking and PS are similar in a number of respects, SWS is a fundamentally different state. The dramatic functional changes that occur from waking to SWS in the thalamocortical system may explain why MGm and ACx plasticity was not easily expressed in SWS. In particular, the neuromodulator that distinguishes SWS from waking and PS is acetylcholine (ACh) which, in contrast to waking and PS, is released at low levels during SWS (Kodama & Honda, 1996; Marrous et al., 1995; Williams, Comisarow, Day, Fibiger, & Reiner, 1994). Multiple lines of evidence demonstrate the involvement of ACh in the induction of sensory cortex plasticity (review in Dykes, 1997; Rasmussen, 2000; Weinberger, 2003), and evidence also exists for an involvement of ACh in the expression of cortical plasticity (Ego-Stengel, Shulz, Haidarliu, Sosnik, & Ahissar, 2001; Shulz, Sosnik, Ego, Haidarliu, & Ahissar, 2000). Thus, the difficulty for learning-induced plasticity to be expressed in SWS might be viewed as a physiological counterpart of the state-dependent learning phenomenon described at the behavioral level (Overton, 1964), that is, it might partly result from a too strong discordance in ACh levels (to keep this example) between the moment when plasticity was induced (i.e., during training) and the moment when it was tested (i.e., during SWS).

4.3. What can be concluded from that literature?

4.3.1. Functional roles of the plasticity expressed during sleep

By showing that associative plasticity was expressed during PS in two pivotal structures of the fear conditioning circuit, the auditory thalamus and the lateral amygdala, these results provide direct evidence that the neural representation of the fear-inducing tone is activated during this sleep state. Albeit probably partial, this activation is pervasive enough to trigger expression of a conditioned autonomic response. What can be the functional role of this activation? Behavioral responsiveness is very weak during PS: sensory arousal thresholds are high (Davis, Heins, & Van Twyver, 1972; Dillon & Webb, 1965; Trigona-Leisinger, Ciancia, Roy, & Bloch, 1977); excitability of brain activating structures is depressed (Benoit & Bloch, 1960; Piellat & Gottesmann, 1995); motor activity output is totally suppressed (review in Chase & Morales, 1990). That sensory and amygdalar associative plasticity can be conjointly expressed during PS has a clear adaptive function: in the absence of awakening, it enables the organism to detect significant environmental signals and to evaluate their biological importance; then, awakening occurs when needed. In contrast, during SWS, the expression of neuronal plasticity is attenuated, but as arousal thresholds are lower, meaningful external stimuli easily awake the subject. Note that the weak expression of neural plasticity observed in SWS (see also Bramham & Srebro, 1989; Leonard, McNaughton, & Barnes, 1987; Maho & Bloch, 1992) would logically lead to infer that spontaneous reactivation of memory traces does not easily occur in SWS (but see Section 5).

Contrasting with what was observed after fear conditioning, amygdalar plasticity was not expressed in PS after
appetitive conditioning. It seems thus that appetitive conditioning-induced plasticity was not sufficiently robust in the amygdala to be transferred across behavioral states, contrary to fear conditioning-induced plasticity. This is not particularly surprising. Even if substantial evidence from animal and human studies demonstrates that the amygdala is also involved in processing emotional material with a positive valence (e.g., Everitt, Cardinal, Parkinson, & Robbins, 2003; Gallagher, 2000), unanimous consensus is that the amygdala is primarily engaged in mediating emotionally salient, negative experiences. But what is worth noting is that, with these results, we go beyond a simple difference between significant and neutral stimuli: at the amygdala level, the tone is differentially processed during PS depending on the affective valence and/or the emotional salience that it has acquired in wakefulness.

4.3.2. Thalamic versus amygdalar plasticity

Thalamic neurons did not behave as amygdalar neurons. They exhibited enhanced responses to the significant tone in PS following both fear conditioning and appetitive conditioning. Thus, in addition to providing information on sensory processing in sleep, testing neuronal plasticity during sleep after learning allows the dissociation of thalamic and amygdalar plasticity, a matter of continual debate since several years (Cahill, Weinberger, Roozendaal, & McGaugh, 1999; Fanselow & LeDoux, 1999). The controversy concerns the relative roles of MGm and LA in fear conditioning: Which of MGm or LA is the primary site of plasticity and determines the occurrence of plasticity in the other brain region? Several authors defend the idea that the essential plasticity occurs in the amygdala, and in particular in the lateral nucleus (but see Paré, Quirk, & LeDoux, 2004): fear memories are formed and stored there (Fanselow & LeDoux, 1999; Maren & Quirk, 2004; Scharf, Nader, Blair, & LeDoux, 2001). On that account, the functional relevance of the plasticity observed upstream, in sensory structures, has been questioned, and it has been envisioned that plasticity in auditory thalamus and cortex depends on the amygdala (for argumentation, see Maren & Quirk, 2004). However, the view that thalamic and cortical plastic changes merely reflect those occurring in LA is odd with regard to the absence of direct anatomical pathway from the amygdala to the MG or the primary ACx, and also with regard to the highly specific receptive field plasticity that develops after very few training trials in auditory cortex (Bakin & Weinberger, 1990; Edeline, Pham, & Weinberger, 1993), MGm (Edeline & Weinberger, 1992), and other MG subdivisions (Edeline & Weinberger, 1991a, 1991b). Clearly, because these plastic changes are input-specific, they cannot simply result from the influence of non-auditory structures. At the thalamic level, the selective shifts of tuning to the CS frequency most likely result both from the strengthening of inferior colliculus (IC)-MG synapses conveying the CS information and from the weakening of IC-MG synapses conveying the initial best frequency information. The possibility that these opposite synaptic changes are due to an amygdalar influence is so hardly conceivable that this scenario can reasonably be discarded.

Results obtained by recording during sleep after learning can usefully contribute to this debate since, without any lesions or drug injection, they allow the dissociation of sensory and amygdalar plasticity: the LA expresses plasticity in PS after fear conditioning, but not after appetitive conditioning; the MGm continues to express plasticity after both. Thus, the plasticity developing in a region does not merely mirror the plasticity occurring in the other region. LA plasticity appears to be preferentially involved in encoding emotionally salient situations and in driving fear behavior. MGm plasticity has a broader functional role: it encodes the learned importance of the tone, independently of its emotional valence and salience, and it provides enhanced inputs simultaneously to the LA, to all cortical auditory fields, and to non-auditory cortices as well (Linke & Schwegler, 2000).

5. Dynamics of memory representations during sleep

The idea that sleep has a beneficial effect on memory formation is not new (Heine, 1914; Jenkins & Dallenbach, 1924), and it has received strong experimental support from an important stream of research that started at the end of the 1960s (review in Bloch, Hennevin, & Leconte, 1979; Ekstrand, Barrett, West, & Maier, 1977; Fishbein & Gutwin, 1977; Hennevin & Leconte, 1977; McGrath & Cohen, 1978; Pearlman, 1979; Smith, 1985: for more recent reviews see Giuditta et al., 1995; Hennevin, Hars, Maho, & Bloch, 1995; Smith, 1995). At that time, most of the data derived from animal studies (the human studies were fewer and more obscure) and concerned PS (but see Ekstrand et al., 1977). The most important conclusions of these early studies were as follows. First, as a result of prolonged PS deprivation, the memory trace continues to be in a labile state and remains susceptible to disruption (Fishbein, McGaugh, & Swarz, 1971). Second, short-term PS deprivation affects differentially retention performance depending on the learning task, suggesting a dichotomy between PS-dependent and PS-independent learning (Greenberg & Pearlman, 1974). Third, in the course of distributed learning, the time of occurrence of post-training PS increases depends on the degree of learning achieved, suggesting that they are related to critical stages of acquisition (Leconte, Hennevin, & Bloch, 1973). Fourth, the post-training “PS Window” is selective: its latency to onset and its duration vary with the learning task and the task demands (Smith & Butler, 1982). Fifth, post-training PS is a preferential time for the reactivation of newly formed memory traces (Hennevin & Hars, 1985). Sixth, according to the “Sequential Hypothesis,” SWS and PS play complementary roles in the consolidation of memory traces (Giuditta, 1985). Curiously, despite these significant advances, from the early 1980s the relationships between sleep and memory became a neglected area of research.

In 1994, two papers published side-by-side in Science have reinvigorated interest in this question. In the first one,
the performance improvement normally observed in a perceptual learning task after a night of sleep was suppressed in PS-deprived human subjects (Karni, Tanne, Rubenstein, Askenasy, & Sagi, 1994). In the second one, correlated activities between pairs of hippocampal neurons observed when rats were running for food reward were also detected during subsequent sleep (Wilson & McNaughton, 1994). In both cases, inferences are made concerning the dynamics of neural representations during sleep: the overnight improvement of perceptual performance was viewed as reflecting the beneficial effect of PS events on the sensory representations formed during initial learning; the correlated activities of hippocampal neurons during SWS were viewed as the electrophysiological signature of active neural representations and were interpreted in terms of memory trace reactivation. From these two studies, two important lines of research have developed, one inferring the effect of sleep on memory consolidation from retention performance in humans, the other inferring memory reactivation during sleep from ensemble recordings in freely behaving rats.

5.1. Human studies on sleep-dependent memory consolidation

Human studies in the last 10 years have largely substantiated the beneficial effect of post-training sleep (both nocturnal and diurnal) on retention performance. As they have been the subject of an impressive number of review articles (10 between September 2004 and September 2005), they are only briefly presented here.

5.1.1. Behavioral studies

Albeit previously questioned (discussion in Smith, 2001), recent studies have provided good evidence of a beneficial effect of sleep on declarative memory consolidation (review in Gais & Born, 2004a). Sleep is most effective when it follows shortly after learning (Gais, Lucas, & Born, 2006), and it renders the newly formed memory more resistant to subsequent associative interference (Ellenbogen, Hulbert, Stickgold, Dinges, & Thompson-Schill, 2006). Declarative memory seems to benefit preferentially from deep non-REM sleep. Using the early/latesleep design2, recall performance of two declarative memory tasks (a paired-associate wordlist and a mental spatial rotation task) was shown to particularly benefit from early night sleep, rich in stages 3–4 of non-REM sleep, as compared to an equivalent early wake interval or to late nocturnal sleep. On the contrary, two non-declarative tasks (a procedural mirror-tracing task and a wordstem completion priming task) benefited more from late sleep, rich in PS (Plihal & Born, 1997, 1999a). Likewise, a brief daytime nap (45 min) containing solely non-REM sleep benefited paired associates performance but not mirror tracing performance (Tucker et al., 2006). Furthermore, a positive correlation was found between recognition memory performance for landscape photographs and the amount of stages 3–4 gained during a nap that followed the study session (Takashima et al., 2006). The benefit of early sleep on the retention of word pairs was suppressed by increasing acetylcholine levels (Gais & Born, 2004b) or plasma glucocorticoid concentrations (Plihal & Born, 1999b) during the early part of the night. In contrast, it was enhanced by anodal transcranial direct current stimulation intermittently applied at frontal sites over a 30-min period of the first sleep cycle: this beneficial effect on retention performance was achieved though the slow oscillatory activity <3 Hz was not significantly affected (Marshall, Mölle, Hallschmid, & Born, 2004). Finally, a few studies went beyond the simple dichotomy between declarative and non-declarative memories. For example, when the contribution of explicit and implicit memory was simultaneously assessed in the same word-recognition task, sleep (and particularly early night sleep) was found to enhance recollection-based explicit recognition, but not familiarity-based implicit recognition (Drosopoulos, Wagner, & Born, 2005). When the emotional dimension was considered, late sleep was found to particularly enhance memory for emotionally arousing material: after a period of late sleep, retention of emotional texts was better than it was after a corresponding period of wakefulness, and it was also better than retention of neutral texts (Wagner, Gais, & Born, 2001). The enhancing effect of sleep on the retention of emotional texts persisted over several years (Wagner, Hallschmid, Rasch, & Born, 2006).

But so far, skill learning is the domain that has generated the greatest number of studies. Indeed, a major interest of skill learning is that it is clearly a multistep process continuing beyond the actual training experience, as indicated by time-dependent gains in performance evolving hours after practice has ended (Karni, 1996; Karni & Sagi, 1993). The development of these delayed gains in performance is regarded as a behavioral manifestation of a latent memory consolidation phase involving cortical plasticity (Karni et al., 1995; Karni & Sagi, 1991). To what extent sleep is a critical factor for the emergence of these delayed gains has been extensively investigated.

Performance improvement specifically due to sleep, rather than to the mere passage of time or to circadian factors, was repeatedly observed in perceptual learning tasks (Gaab, Paetzold, Becker, Walker, & Schlaug, 2004; Gais, Plihal, Wagner, & Born, 2000; Mednick, Nakayama, & Stickgold, 2003; Stickgold, James, & Hobson, 2000; Stickgold, Whidbee, Schirmer, Patel, & Hobson, 2000), in motor learning tasks (Fischer, Hallschmid, Elsner, & Born, 2002; Korman, Raz, Flash, & Karni, 2003; Kuriyama, Stickgold, & Walker, 2004; Walker, Brakefield, Morgan, Hobson, & Stickgold, 2002; Walker et al., 2003b), and in visuomotor tasks...
A number of factors, uncontrolled across studies, can account for these heterogeneous results. First, the amount of interference yielded by the intervening daytime experience can affect the effectiveness of consolidation processes taking place in the awake state: for example, compared to sleep or to restful wake, a 2-h period of busy waking (watching a film) after training is sufficient to decrease auditory learning performance (Gottselig et al., 2004). Other obvious factors include the type of skill, the training schedule, the amount of initial practice, the delay after training when testing was done (see Albouy et al., 2006; Censor, Karni, & Sagi, 2006; Hauptmann & Karni, 2002; Hauptmann, Reinhart, Brandt, & Karni, 2005; Korman et al., 2003; Kuriyama et al., 2004; Robertson, Pascual-Leone, & Miall, 2004; Walker, Brakefield, Hobson, & Stickgold, 2003a, 2003b), and even the instructions given to the subject, as suggested by results obtained when individual’s awareness of learning was manipulated (Robertson, Pascual-Leone, & Press, 2004). In a serial reaction time task in which visual cues guided the acquisition of a sequence of finger movements, subjects were trained with either explicit instructions (they were informed that a repeating sequence of stimuli, signaled by a change in the color of the cues, would be presented) or implicit instructions (the cues remained the same throughout training, and the possibility of a sequence to learn was never mentioned). They were then retested after a 12-h interval with or without a period of sleep. Following explicit learning, offline improvement in sequence skill was only observed when the retention interval included sleep. In contrast, following implicit learning, improvement was observed regardless of whether the retention interval did or did not contain a period of sleep (but see Spencer, Summ, & Ivry, 2006). With the implicit version of the task, disruption of the primary motor cortex (M1) by repetitive transcranial magnetic stimulation (for 10 min) prevented the overnight but not the overday performance gain, suggesting that different mechanisms, differentially involving M1, were engaged to support overday and overnight improvement (Robertson, Press, & Pascual-Leone, 2005). Consistent with this view, different aspects of the skill were found to be enhanced over the day and over a night of sleep. Skill in the serial reaction time task results from learning a series of finger movements (movement-based skill) and from learning a sequence of response buttons to push (goal-based skill). Using a design that allowed the dissociation of these two skill components revealed that movement-based improvements developed only over the day, whereas goal-based improvements developed only overnight (Cohen, Pascual-Leone, Press, & Robertson, 2005). This intriguing set of data argues in favor of distinct contributions of wake and of sleep to the offline processes of memory consolidation.

There are several indications that offline processing may involve both quantitative and qualitative changes in the representation of the training experience (Karni & Sagi, 1993; Korman et al., 2003; Kuriyama et al., 2004). In the case of sleep, the most convincing behavioral evidence suggesting that it does more than to merely increase the strength of existing memory representations comes from data showing a facilitating role of sleep in a process of insight (Wagner, Gais, Haider, Verleger, & Born, 2004). Subjects performed a number reduction task that required to analyze a 8-digit string to determine a specific digit defined as the final solution of the trial. Using two simple rules, subjects had to find the seven appropriate responses resulting from the sequential comparisons of the digit pairs. But, unknown to the subjects, a much shorter solution also existed: as the last three responses always mirrored the three preceding ones, the final solution could be discovered as early as the second response was found. Subjects were confronted with the task for only a short period, so that training was performed under implicit conditions, i.e., without awareness of the hidden rule, and they were retested after a 8-h interval of nocturnal sleep, nocturnal waking, or...
daytime waking. More than twice as many subjects gained insight into the hidden rule after sleep as after wakefulness, regardless of time of day. Curiously, sleep accelerated reaction times much less in subjects who gained insight than in those who did not, suggesting that the conscious use of the hidden rule did not simply evolve from a strengthening of procedural memories. Thus, a qualitative restructuring of the task representations might take place during sleep, facilitating extraction of explicit knowledge and insightful behavior. The idea that explicit knowledge can be gained during sleep on the basis of rules initially acquired implicitly was reinforced when the implicit version of the serial reaction time task was combined with a generation task in which subjects were explicitly asked to predict the sequential target positions. Before the retention interval, the subjects displayed no explicit sequence knowledge. But at retesting 9 h later, those who had slept in the retention interval did, contrary to those in the wake group; neither group showed further gain in skill (Fischer, Drosopoulos, & Born, 2006). The authors argue that the selective gain in explicit knowledge across sleep implies a reorganization of memory representation, presumably as a result of an interaction between explicit and implicit memory processes.

5.1.2. Brain imaging studies

Two sets of imaging studies also strengthen the idea of a sleep-dependent restructuring of memory representations: one by analyzing regional brain activation that spontaneously occurs during post-training sleep; the other by comparing the patterns of brain activation at retesting with and without an intervening night of sleep.

Indeed, learning-dependent changes in regional cerebral activity initiated during task performance continue to evolve during post-training wakefulness (Peigneux et al., 2006) and can still be detected during subsequent sleep. Using PET and regional cerebral blood flow (CBF) measurements, such changes were observed during non-REM sleep or during PS depending on the type of learning task. After extended practice on a probabilistic serial reaction time task, the cuneus and the premotor cortex, which were activated by task performance during waking, were more active during PS in trained than in non-trained subjects (Maquet et al., 2000). An interaction analysis showed that functional connectivity between the premotor cortex and the posterior parietal cortex and pre-supplementary motor area was increased during post-training PS (Laureys et al., 2001). A complementary study using a random instead of a probabilistic sequence of stimuli indicated that the increases in CBF observed during PS in learning-engaged brain areas were not merely related to the acquisition of basic visuomotor skills, but rather to the implicit acquisition of the probabilistic rules defining stimulus sequences. Further, functional connectivity between the cuneus and the striatum (which is critically involved in implicit sequence learning) was stronger in PS after practice on the probabilistic sequence of stimuli rather than on the random one (Peigneux et al., 2003). Quite different results were obtained with a spatial navigation task. Hippocampal areas (the bilateral hippocampal formation and parahippocampal gyrus) which were activated during route learning in a virtual town were again activated during subsequent non-REM sleep, predominantly deep non-REM sleep. The amount of hippocampal activity expressed during stages 3–4 was positively correlated with the improvement of performance in route retrieval on the next day (Peigneux et al., 2004). Collectively, these results corroborate and extend those obtained in behavioral studies, pointing to a differential involvement of non-REM sleep and of PS depending on the learning task and the memory system engaged.

The second approach aims at determining changes in memory representations occurring during post-learning sleep by comparing the profiles of regional cerebral activity (using fMRI) expressed at retesting with and without intervening sleep between training and retest. Whereas the overnight sleep condition was identical across studies, the without-sleep condition varied and it could be criticized in each case: retesting and fMRI scan were performed either 1 h after training without intervening sleep (but is it sleep the critical factor or is it simply time?), or after an overnight waking period (but is there no circadian modulation of performance and/or of regional brain activity?), or after a first night of total sleep deprivation followed by one or two nights of normal sleep (but does post-training sleep deprivation per se have no effect?). However, a without-sleep condition can never be neutral. In any case, and regardless of the learning task, differences were systematically observed between the sleep and without-sleep conditions.

In the declarative/spatial memory domain, only one study has been performed so far, using the spatial navigation task in a virtual town (Orban et al., 2006). Regional cerebral activity was mapped during place-finding navigation, immediately after learning and three days later, in subjects either allowed regular sleep or totally sleep-deprived on the first post-training night. In both groups, whereas hippocampal activity was decreased from immediate to delayed retrieval, activity in the caudate nucleus and several cortical areas was increased. However, striatal activity increased more at delayed retrieval in the sleeping group than in the sleep-deprived group. There was nonetheless no between-group difference in behavioral performance. The proposed interpretation stems from a broad theoretical background: Sleep would favor a shift of brain activity so that navigation, which is initially mostly based on a hippocampus-dependent spatial strategy, becomes partly contingent on a more automated, response-based strategy mediated by the striatum.

In the field of perceptual skill learning, the visual texture discrimination task was used, taking advantage of the retinotopic and monocouary specificity of the task (Walker, Stickgold, Jolesz, & Yoo, 2005). The first day at 9 P.M., the subjects were trained using one eye; the following morning at 9 A.M., they were trained using the other eye; finally, 1 h later, they were retested using each eye separately, during fMRI scanning. At retest, there was, for the eye in the sleep.
condition, both a better visual discrimination and a greater activation within a location of primary visual cortex (V1) corresponding to the trained visual target position. The activation of V1, initially proposed on the basis of psychophysical evidence (Karni & Sagi, 1991, 1993), had already been observed 24 h after intensive monocular training when comparing trained and untrained eye (Schwartz, Maquet, & Frith, 2002). Further changes extending beyond V1, into higher order visual processing areas including the inferior temporal and inferior parietal regions, were also observed.

Motor skill learning is known to be associated with fast and slow changes in several brain regions (Karni et al., 1995, 1998; Ungerleider, Doyon, & Karni, 2002). Three studies examined whether sleep contributes to the development of this motor plasticity. In all three, right-handed subjects were trained with their left hand for a brief period of time (5–10 min). In the first experiment (Maquet et al., 2003a), subjects were trained on a visuomotor pursuit task, and half of them were totally sleep deprived during the first post-training night. At retest, three days after training, they were exposed to the previously learned trajectory and to a new one. In the sleeping group, as compared with the sleep-deprived group, performance was improved, and brain activity for the learned trajectory was greater in the posterior superior temporal sulcus. Furthermore, the functional connectivity between this region and the cerebellum, as well as between other areas involved in smooth pursuit eye movements, was augmented. A finger-sequence tapping task was used in a second experiment (Walker, Stickgold, Alsop, Gaab, & Schlaug, 2005). Following a night of sleep, and relative to an equivalent intervening wake period over the day, increased activation was observed in the right primary motor cortex and left cerebellum. There were also regions of increased activation in the medial prefrontal lobe and the hippocampus. In contrast, decreased activity was observed bilaterally in the inferior parietal cortices, a decrease supposed to reflect improved sequence automation. In the third experiment (Fischer, Nitschke, Melchert, Erdmann, & Born, 2005) in which a sequential finger movement task (the finger-to-thumb opposition task) was also used, training was followed by either a night of regular sleep or sleep deprivation, and fMRI was performed both during initial training and at retesting, 48 h later. Post-training sleep, but not sleep deprivation, led to improved performance at retrieval testing. Relative to initial learning, this improvement was accompanied by reduced activation in prefrontal, premotor, and primary motor cortical areas, along with a stronger activation in left superior parietal cortical regions (supposed to support automated performance). The prevalence of brain areas with decreasing activation at testing after sleep leads the authors to propose that a central function of the sleep-associated consolidation process refers to an extinction of network activity that has become irrelevant for optimal performance. Because of task differences but also of methodological differences (the sleep condition was contrasted with control conditions that were never the same from one study to another), the results are heterogeneous. Nonetheless, all these studies converge on the idea that sleep would promote the restructuring of memory representations toward enhanced efficacy and increased automation of behavioral performance.

5.2. Animal electrophysiological studies on neuronal reactivation during sleep

Needless to say, a coherent neural representation of any learning situation involves coordinated activities of large ensembles of neurons that are only very partly sampled even with the most modern electrophysiological recording techniques (Buzsáki, 2004; Nicoletis & Ribeiro, 2002). Nonetheless, the search for electrophysiological signs of neuronal reactivation during sleep has progressed over years: whereas initial studies simply quantified the firing rate of neurons, the following ones looked for multiple cross-correlations between simultaneously recorded neurons, then for between-cell temporal sequences of neuronal discharges. Except in few cases, these studies focused on hippocampal pyramidal cells, using the functional properties of place field CA1 neurons to infer mnemonic operations.

The source of all these investigations was a study by Pavlides and Winson (1989). Pairs of CA1 cells were recorded in waking, SWS and PS before and after confining rats during 15 min in a particular location that was the place field of one cell of the pair. After exposure, that cell, but not the other, exhibited increased firing rates in both SWS and PS. Although these data were from a limited sample of 13 cells, they have strongly impacted the domain of sleep and memory because they were viewed as the first electrophysiological evidence of reactivation of memory traces during sleep. Subsequent experiments, using large-scale recordings, could not confirm the relationship between firing rates in the awake and sleeping animal (Kudrimoti, Barnes, & McNaughton, 1999; Wilson & McNaughton, 1994). To elucidate this point, discharge activity of pyramidal cells was examined during brief “sleep” sessions (15 minutes) recorded before and after wheel-running behavior (rats daily exercised in a running wheel placed in a location that matched the place fields of several of the recorded neurons). The global firing rate of the cell population was found to be unchanged after wheel running in the familiar environment (Hirase, Leinekugel, Czurko, Csicsvari, & Buzsáki, 2001). So it was when rats were placed in a novel environment. However, whereas the firing rates in sleep before and sleep after running were highly correlated in the familiar environment, they were no longer in the novel one, an effect that the authors interpreted as a result of bidirectional, homeostatic, changes in discharge rate (some cells increased their firing and others decreased it).

To determine if hippocampal neurons retained during sleep changes in functional connectivity expressed during preceding active behavior, Wilson and McNaughton (1994)
collected simultaneous recordings from neuronal ensembles and evaluated the cross-correlation functions between all pairs of cells. In that study and in subsequent ones, rats’ behavioral experience was simply to run in a linear, triangular, or rectangular track where food was available at fixed locations. Cross-correlation functions were computed during track running and during the preceding (Rest1) and the following (Rest2) resting period. Cells that showed strong temporal correlations during the running session, because of overlapping place fields, were more correlated during the Rest2 period (which included both quiet waking and SWS) than the bulk of the other pairwise comparisons, and they were also more correlated than they had been during Rest1. This effect, observed for cross-correlations computed with large temporal windows (up to 200 ms), dissipated in about 10–15 min (Skaggs & McNaughton, 1996; Wilson & McNaughton, 1994). The maintenance of correlated patterns of firing was more apparent during the ripple events (i.e., 150–200 Hz field oscillations in the hippocampal EEG, lasting 50–100 ms and coupled to hippocampal sharp waves) than during the inter-ripple intervals (Kudrimoti et al., 1999). Similar results were described for cells in the ventral striatum but, contrary to hippocampal results, the effect was still significant 20 min after the running session (Pennartz et al., 2004). As the hippocampo-neocortical dialogue has long been the object of intense interest (Buzsáki, 1989, 1996; McNaughton, Leonard, & Chen, 1989), the correlation patterns between hippocampal and neocortical neurons were examined (Qin, McNaughton, Skaggs, & Barnes, 1997). Ensemble recordings obtained in posterior parietal cortex and in CA1 indicated that neocortical cells essentially behaved as hippocampal cells: higher cross-correlations were found during Rest2 (a 20-min period comprising a mixture of SWS, quiet wakening, and PS). When cross-correlations were quantified between hippocampal and neocortical cells, broad correlations (quantified over 200 ms) were found after the running session (but not before). Temporal order of correlations was preserved between hippocampal cells, between neocortical cells, but not between hippocampal and neocortical cells. Note that functional correlations between recordings collected in posterior parietal cortex and CA1 are hardly interpretable because the anatomical connections between these two areas are quite indirect (Kolb & Walkey, 1987; Reep, Chandler, King, & Corwin, 1994). In fact, recording in parietal cortex was probably dictated more by practical reasons (the tetrodes have to pass through the parietal cortex before reaching CA1) than by theoretical reasons. Note also that when temporal relationships between neocortical and hippocampal neuronal discharges were examined independently of any behavioral experience, heterogeneous results were found. An overall tendency for hippocampal events to precede neocortical events was reported by some authors (Siapas & Wilson, 1998), whereas a precession (of about 50 ms) of neocortical discharges (during both spindles and delta waves) relative to hippocampal events was found by others (Siroti, Csicsvari, Buhl, & Buzsáki, 2003).

Because cross-correlograms do not allow descriptions of temporal patterns of firing on more than two cells (see for discussion Quirk & Wilson, 1999), the approach initiated by Buzsáki and colleagues privileged the detection of temporally organized spike sequences within neuronal ensembles. The search for repeating spike sequences (typically less than 200 ms in duration) was performed using modified versions of well-established methods (template-matching method: Abeles & Gerstein, 1988; Dayhoff & Gerstein, 1983; JPTH method: Aertsen, Gerstein, Habib, & Palm, 1989). Rats ran in a fixed spatial position (in a running wheel) to activate a selected group of hippocampal pyramidal cells (Czurkó, Hirase, Csicsvari, & Buzsáki, 1999). Recurring spike sequences (in significantly higher numbers than their surrogates generated by various shuffling methods) were found during waking behavior (Run) and sleep (Nádasdy, Hirase, Czurkó, Csicsvari, & Buzsáki, 1999). Two rats provided stable recordings during the Run, Sleep1 (before Run) and Sleep2 (after Run) sessions. Among the significant (above chance level) triplets, more triplets were common to Sleep2 and Run than to Sleep1 and Run: in one rat, there were 9% of common triplets between Sleep2 and Run versus only 5% between Sleep1 and Run (but there were 8.8% of common triplets between Sleep1 and Sleep2); in the other rat, it was only mentioned that common triplets were only found between Sleep2 and Run. Long sequences (100–200 ms in duration), associated with increased power in the theta frequency, were detected in waking and PS, whereas short sequences (<50 ms in duration), associated with increased power at the ripple frequency, were usually detected in SWS. Unknown is whether these sequences were derived from Sleep1 and/or from Sleep2, and, in the latter case, how long after the Run session they were detected. In any case, the correlation between the occurrence of short sequences and ripples led the authors to propose that spike sequences observed during wheel running were replayed in a time-compressed manner during SWS ripples.

The work of Wilson and colleagues also searched for repeating spike sequences in post-behavior sleep. Based on ensemble recordings from 8 to 13 CA1 hippocampal cells, these authors first looked for between-cell patterns during PS episodes, then evaluated if these patterns were also present when the rat was running in a circular track (Louie & Wilson, 2001). At variance with all previous studies that described spike sequences on the timescale of milliseconds to seconds (Abeles, Bergman, Margalit, & Vaadia, 1993; Abeles & Gerstein, 1988; Gerstein, 2004; Nádasdy et al., 1999), Louie and Wilson searched for the recurrence of multispike sequences during much longer durations (from tens of seconds to minutes) and with a lower temporal resolution (one second or less). Out of 45 PS episodes from which spike sequences were obtained, 20 exhibited...
sequences that correlated with those detected during the track-running session (Run). Surprisingly, 19/20 corresponded to correlations between Run and preRun PS, and only one to correlation between Run and postRun PS. The duration of spike sequences was roughly the same during PS and Run (compression factor of 1.4). Having in mind that the patterns observed in preRun PS reflected persistent mnemonic activation from the day before, the authors engaged one rat in three novel running tracks. In that case, no correlation was obtained between preRun PS and Run, nor between postRun PS and Run. The same laboratory developed another combinatorial method, particularly complex and published two years later (Lee & Wilson, 2004), to look for matches between temporal spike sequences during SWS and track running (Lee & Wilson, 2002). Contrary to PS, matches were found between Run and postRun, not preRun, SWS. These matches concerned sequences named “low probability trials” that involved up to 8–10 cells, occurred during high frequency ripples, and exhibited a compression factor of 20 (this means that a sequence lasting 5–10 s during waking was matched by a sequence of 100–200 ms during SWS). It was thus concluded that long spatial sequences occurring during waking behavior were replayed at a highly compressed time-scale during SWS ripples. This “compressed replay” during postRun SWS contrasts with the “extended replay” during preRun PS described by the same authors. But the use of two fundamentally different analytical methods to detect spike sequences in SWS and in PS prevents any direct comparison between the two sleep states and precludes any valid conclusion. Still, searching for spike sequences during SWS and PS in the same animals and using the same method would have been of great interest, for instance to determine whether, in a familiar environment, the same sequences are expressed during both sleep states.

Although no functional significance has ever been demonstrated, and not even evaluated, for these replayed pattern activities, they are unanimously regarded as undisputable evidence that memory traces are reactivated during SWS. Still this conclusion is unjustified: the terms SWS, reactivation, and memory traces are misused.

SWS: Electrophysiological results were collected right after the running session and generally for a short period of time (sometimes ≤ 15 min) which included quiet waking, drowsiness and SWS (one exception being the initial study by Pavlides & Winson, 1989). Absent are the classical indices (global cortical EEG and electromyographic activity) allowing unambiguous distinction between behavioral states (focal hippocampal EEG recorded through tetrodes only provides limited information). Aware of these problems, some authors used the word “rest” rather than “sleep,” and in some of their articles they recognized that actual sleep was not necessary for observing pattern reactivation which also occurred during quiet waking (Sutherland & McNaughton, 2000).

Reactivation: The concept of reactivation stems from the active/inactive memory distinction proposed long ago (Lewis, 1979; Misanin, Miller, & Lewis, 1968; Spear, 1973). A reactivated memory is an inactive memory that has returned to the active state. In the present case, the “traces” were not reactivated: the enhanced cross-correlations observed during running did not disappear then reappeared; they were maintained for a certain period of time, progressively dissipated and disappeared in 15–30 min. Interestingly, a similar temporal decay was observed when an enhanced cross-correlation between two cells was artificially imposed in behaving and non-behaving animals (Ahissar et al., 1992). It cannot be argued that “peaks of reactivity” occurred during the ripple events because the enhanced cross-correlations also progressively vanished across ripple episodes.

Memory traces: For a memory trace to be formed, some information has to be acquired. In the above described experiments, the animals simply ran, in a very stereotyped way, in a totally predictable environment. When no uncertainties exist about a stimulus or about the consequences of an action, no information is acquired (Dickinson, 1980; Mackintosh, 1974; Pearce, 1997; Rescorla & Wagner, 1972). Thus, the use of behavioral protocols in which all the stimuli and the interactions between stimuli and behavior are entirely predictable precludes the acquisition of new information. It could be argued that, in several experiments, neuronal data were collected while rats were running in new environments (assuming that running in another rectangular track, or running 90° instead of 270°, is a new environment). Ironically, under these conditions, the postulated memory traces were not observed during the resting period (Gerrard, Kudrimoti, McNaughton, & Barnes, 2001; Hirase et al., 2001; Kudrimoti et al., 1999; Lee & Wilson, 2002; Louie & Wilson, 2001).

In short, by their spatial and sensory–motor aspects, the behavioral tasks are tailored to impose robust and sustained network activities during waking behavior. These forced network activities have no mnemonic content, but they persist for a certain amount of time. The enhanced cross-correlations accompanying these activities are more easily detected when ripple events, which synchronize the entire network, boost all between-cell correlations.

Aware of some of these problems, Ribeiro and colleagues (Ribeiro et al., 2004) continuously collected for 4 days ensemble recordings from five rats which, at the end of the second day, were allowed to explore for 1 h four novel and salient objects. They sought for correlations between five activity patterns sampled in hippocampus, cortex, thalamus and striatum during object exploration and during the pre- and post-exploration periods. Overall, neuronal ensemble correlation was higher after exploration than it was before. However, both the duration and the strength of the effect were variable across rats. Enhanced correlation was found up to 48 h post-exploration in two rats, for less than 24 h in two other rats, and there was no enhancement for the last one. In some rats enhanced correlation was mostly observed in striatum and/or cortex, whereas in others it was mostly found in hippocampus and thalamus. It
peaked during SWS, but was also significant during waking and PS. The authors stressed that their results differ from the previous ones regarding three points. First, rather than discrete reactivation of memory traces, they suggest a persistent neuronal activity, called “neuronal reverberation” by the authors. Second, as in all the animals and all brain areas the correlation values were quite small (0.1–0.3), they argue against a high fidelity replay during sleep. Third, there was no evidence for better correlations when the analyses were aimed at detecting compressed or expanded patterns. It can be added that if some information was probably acquired by the animals concerning the novel objects, unknown is which information was reflected by the persistent neural activity. As correlations between neural patterns collected during object exploration and patterns collected in the pre-exploratory period already existed (they were only slightly increased in the post-exploratory period), the behavioral correlate of these patterns remains to be determined. In fact, in this study as in the previous ones, the enhanced correlations detected during SWS might simply be the consequence of the high synchronization that naturally exists in SWS. And an increased synchronization is not necessarily the signature of memory consolidation: general anesthesia and epileptic seizures are also brain states persistently exhibiting high neuronal synchronization, but are obviously not states of memory consolidation.

5.3. What can be concluded from that literature?

5.3.1. The gap between human and animal studies

Following effective acquisition of new information or new skills, a specific memory representation is formed, which can then undergo further modifications through consolidation processes. Over the past decade, human and animal studies have held the idea that some of these processes take place during post-learning sleep, allowing the strengthening, enhancement, and/or reorganization of the newly formed representations (for discussion on presumed stages of memory consolidation, see Walker, 2005; Walker et al., 2003a). All along these years, the human and animal literatures have benefited from each other and have reinforced mutually. Still, they fundamentally differ. Whereas behavioral acquisition is central in the human studies, it is neglected in the animal studies. This gap between the human and animal literatures is not merely the consequence of limitations inherent to rodent’s learning abilities. It rather reflects a fundamental difference in the way of conceiving what is memory and from which kind of data it can be inferred. Memory cannot be inferred simply on the basis of the occurrence of neural events, whatever they are, and data collected in freely behaving animals do not necessarily relate with the acquisition and memorization of information. An interpretation in terms of memory processes requires that a learning task be designed and that a behavioral performance be obtained and attest the retention of the learning experience.

In human studies, the learning tasks and behavioral protocols have been diversified and refined across years, allowing more and more specific investigations on which types and subtypes of memory, and which memory components benefit from sleep. They have substantiated the notion that memory representations continue to evolve and are reorganized during post-learning sleep but, of course, a lot of questions remain open. Some concern the necessity of sleep for effective consolidation and the relative contribution of sleep and of time per se: To what extent both wake and sleep make unique and distinct contributions to memory consolidation needs to be clarified. It also remains to specify the relationships between the different forms of memory and their different aspects, the individual sleep stages, and the various processes that can be engaged in consolidating memory traces, as well as, obviously, the respective physiological mechanisms put into play.

5.3.2. The question of memory reactivation during sleep

It is now widely accepted that neuronal populations previously engaged in a learning task are reactivated during sleep and that this reactivation is a key process for the consolidation of memory traces during sleep. This view is based on electrophysiological experiments in animals and imaging experiments in humans which both showed that neural patterns expressed during waking experience are also expressed during subsequent sleep periods. However, that brain activities during sleep are influenced by the previous waking activities must not be systematically interpreted in terms of memory reactivation. As already pointed out (Maquet, 2001), other explanations involving use-dependent rather than learning-dependent changes must also be considered, such as the persistence of activities that occurred during the waking period, a short-term adaptation to previous waking conditions, or restorative processes.

In fact, the concept of memory reactivation during sleep was initially proposed on the basis of theoretical considerations (Spear & Gordon, 1981) and of behavioral results (Hennevin & Hars, 1985), but it has begun to be considered with interest only several years later, from the study by Wilson and McNaughton (1994). However, as extensively discussed above, despite impressive advances in collecting and analyzing large scale neuronal ensembles, none of the electrophysiological studies performed up to now has provided acceptable evidence for a reactivation of memory traces during sleep. These studies only showed that patterns of neuronal firing detected during running or exploratory behavior continued to be expressed thereafter, including during sleep periods. These patterns are simply the neuronal correlates of a prolonged, stereotyped sensory–motor experience, and their vanishing traces remain detectable for a certain amount of time. That a biological phenomenon persists after a sustained and repetitive behavior is not sufficient to consider that it participates to a memory trace.

In neuroimaging studies in humans, the subjects do acquire new information or new abilities. But whether the
increases in regional brain activity observed during post-training sleep in task-related brain areas reflect use-dependent or learning-dependent processes is a central question, specially because quantification relies on metabolic activity. The findings that (i) different brain areas are activated during sleep depending on the nature of the task and that (ii) the amplitude of activations during sleep is correlated with learning performance, do not allow to discard the possibility of use-dependent processes. On the other hand, the findings (i) that cerebral activations are observed during deep Non-REM sleep or during PS (thus, early or late in the night) depending on the task, (ii) that the amplitude of activations during sleep is correlated with the overnight performance improvement, and (iii) that it depends on the temporal structure (probabilistic vs random) of the visuo-motor task, strongly suggest learning-dependent processes and a reactivation of specific memory traces during sleep.

6. Conclusions

From the single cell to human behavior, studies converged and their results agreed to support the notion that neural representations, or at least parts of neural representations, can be in an active form during sleep. First, environmental stimuli do penetrate the sleeping organism: Although impoverished, the messages sent by sensory neurons provide information about the external world which is accurate enough to allow detection of behaviorally relevant stimuli; event-related brain potentials in humans also attest the preservation of some sensory integration and discriminative capacity. Second, convergent evidence from behavioral and neuroimaging studies suggest that memory traces are reactivated and are reorganized during post-learning sleep: these reorganizations may underlie the extensively described beneficial effects of sleep on behavioral performance. Therefore, from the most elementary sensory levels to the most cognitive ones, it appears that we can give positive answers to the questions raised in introduction: Neural signals emitted during sleep carry some information; they have some content; they have some functional relevance. But obviously, the absence of attentional and intentional processes considerably limits the online processing of environmental stimuli. Substantial evidence from the field of cognitive psychology suggests that non-conscious processes are continually at work during wakefulness, allowing for example an automatic evaluation of environmental stimuli (e.g., Duckworth, Bargh, Garcia, & Chaiken, 2002). Non-conscious processing can extend to complex stimulus analyses such as semantic processing of words (e.g., Gaillard et al., 2006). The maintenance of such automatic processes holds true for memory representations: to what extent the reactivation and consolidation processes taking place during sleep differ from those occurring during wakefulness still needs to be clarified. Undoubtedly, the last decade has offered a rich literature that has opened large avenues for research in the cognitive neuroscience of sleep. In the future, imaging techniques with a cellular resolution in behaving animals and with a high temporal resolution in humans, combined with elaborate behavioral protocols, will certainly provide a deeper understanding of the dynamics of neural representations during sleep.

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