Chapter 16
Genes, Sleep and Dreams

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16.1 Dreams in Medicine and Psychology

Dream interpretation, religion and medicine were once closely linked. Dream soothsayers prospered during all of the antiquity (Jung et al., 1969; Miller, 1997). In ancient Greece, a ritual known as "Dream Incubation" took place in sanctuaries named *asklepieia* in honor to Asclepius, the god of medicine. Greeks would travel long distances to visit these healing temples in search for cures for their ailments. Each *asklepieion* contained a sacred large hall, the *enkoimeterion*, where Dream Incubation took place. The patient would sleep overnight and the next day a priest would listen to a description of the patient's dream to diagnose the illness and determine the right treatment (Meier, 2003). Sometimes, Asclepius himself would appear in dreams to prescribe the treatment (Horstmanshoff, 2004). Similar rituals also existed in Ancient Egypt in the temples of the God Serapis and were preserved throughout the Middle Ages in some Byzantine Christian sects (Meier, 2003). Indeed, dreams play a major role in the Christian tradition, as remarkable instruments by which God reveals His wishes to the chosen people. The newborn Jesus was protected a number of times due to advice received in dreams by his father Joseph. The first such episode occurred before Jesus' birth, when Joseph intended to leave

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Mary because of her pregnancy prior to marriage. An angel of the Lord appeared to Joseph in a dream and told him not to be afraid of taking Mary as his wife, because the baby she carried was the son of God and should be called Jesus. Joseph obeyed, saving the pregnant mother from being stoned (Matthew 1:18–25). When Jesus was born, three magi came to Bethlehem from the East to worship the King of Jews. The local ruler Herod, troubled by the prophecies regarding Jesus, asked the magi to search for the child and bring back news as soon as possible, so that he could honor the new king himself. The magi were warned in their dreams that Herod's request was deceptive, for his real intention was to kill the baby. At the same time, in his dreams, Joseph was advised by an angel to take his family away to Egypt, for Herod had ordered the assassination of all children under the age of two. After Herod's death, the angel visited Joseph's dreams once again to tell him that it was now safe to return home (Matthew 2:1–20).

Given the great importance attributed to the predictive and healing power of dreams in so many ancient cultures, as well as in present-day "primitive" traditions (Kilton, 1951; Cawte, 1984; Shulman et al., 1999; Lincoln, 2003), it is interesting that dreams achieve such poor status in contemporary western society. The arcane relationship between dreams and divinity is likely the explanation for the decay of dream status in a world in which rationalism progressively replaced religiosity. Any effort to rescue the prominent role of dreams in the new rationalist world would require dreaming to be brought inside the scientific arena. Even though dreams are quite accessible as inner reality to most people, they are rather hard to assess empirically. This is related to the high degree of subjectivity involved in dream symbiology. Any introspective dreamer can recall a wide variety of dreams, ranging from fleeting impressions to complex time-evolving narratives. Dreams comprise the reproduction of trivial situations of daily life, such as walking on the street, but they also include impossible feats such as flying like a bird or breathing under water. Familiar and unfamiliar characters can show up in coherent settings or absolutely bizarre contexts and places. Dreams can depict completely unreal situations, as Kafkian as having hair growing on teeth. Anyone who has awakened from a bad dream in the middle of the night knows that dreams can also be diverse in respect to their emotional tone, ranging from the pleasant fulfillment of a secret wish to a gory nightmare. The weird fantasies experienced in dreams are often vivid. Although visual images tend to be prevalent, dreams can also involve combinations of auditory, olfactory, tactile, gustatory, motor, vestibular and linguistic modalities in a mix of senses and emotions.

The first attempt to explore dreams scientifically occurred at the dawn of the 20th century, when Sigmund Freud published "The Interpretation of Dreams" (Freud, 1900). Freud's research program was not yet a quantitative approach of the oneiric phenomenon, but it sought to identify the underlying causes of dreaming in a very objective manner, dissecting the complex oneiric symbology with reference to the patient's own memories and recollections. Freud stated that dreams, far from being nonsense or chaotic, are highly meaningful reflections of the emotions, desires and concerns of the dreamer. He postulated that dream narratives fulfill wishes (or anti-wishes) of the awake subject, simulating the realization (or frustration)

of specific desires (Freud, 1920). He also noted that mnemonic images and the wishes that bring them together tend to remain unconscious most of the waking time, surfacing during dreams in a very special manner. Freud's recognition that dreams are usually stamped with impressions from the waking period advanced the important concept of "day residue", i.e. the part of a dream that derives directly from experiences of the previous day(s). The intensity of this waking intrusion varies according to how recent, novel and behaviorally relevant waking events are.

Although implicit in the concept of "day residue", the beneficial role of sleep for learning was not foreseen by Freud himself. The discovery of the cognitive role of sleep occurred more than 20 years later, with pioneering studies of the effect of sleep on the retention of nonsense syllables (Jenkins and Dallenbach, 1924). These first findings remained obscure for several decades, and it was only in the late 1960s that the relationship between sleep and memory consolidation began to be systematically subjected to experimental tests in rodents and humans. The studies concluded that sleep is a powerful learning booster (Fishbein et al., 1966, 1971, 1974; Leconte and Bloch, 1970; Fishbein, 1971; Leconte and Hennevin, 1971, 1973; Leconte et al., 1973, 1974; Smith et al., 1974, 1980; Fishbein and Gutwein, 1977; Hennevin and Leconte, 1977; Smith and Butler, 1982; Hennevin and Hars, 1985, 1992; Smith and Lapp, 1986, 1991; Smith and Kelly, 1988; Hennevin et al., 1989, 1993, 1995a, b; Smith and Wong, 1991; Smith and MacNeill, 1993). Freud's ideas concerning the importance of dreams for mental health remain controversial to this day, mostly due to rifts within the field of psychology. While the Freudian psychoanalytic tradition focused on wish fulfillment and dream meaning (Freud, 1900; Jung, 1953a, b, 1974; Jung et al., 1969; Fosshage and Loew, 1978; Solms, 2004), experimental psychologists pursued the more objective dream aspects related to sleep-dependent memory consolidation (Bryson and Schacher, 1969; Pearlman, 1969; Leconte and Bloch, 1970; Lucero, 1970; Fishbein, 1971; Leconte and Hennevin, 1971; Smith and Butler, 1982; Smith and Lapp, 1986; Karni et al., 1994; Smith, 1995, 1996, 2001; Maquet, 1996, 2001; Maquet et al., 1996, 1997, 2000; Maquet and Phillips, 1998; Stickgold, 1998, 2001, 2003; Stickgold et al., 1999, 2000a, b, 2001, 2002; Mednick et al., 2002, 2003; Walker et al., 2002a, b, 2003; Born and Wagner, 2004a, b; Walker and Stickgold, 2004; Stickgold and Walker, 2005; Born et al., 2006).

If dreams are normally directed by the anxieties and expectations of the dreamer and tend to recapitulate the past and the present (Winson, 1985), dream narratives sometimes contain anticipatory simulations of expected challenges. A good example is provided by the dreams of students facing difficult exams in the near future. In these cases, the occurrence of dreams related to test questions in the night preceding the exam is common. Such simulations of future events can simply deliver emotional readiness, or sometimes bring forth the solution for some puzzling situation. This unique way of learning is called insight (Kohler, 1947) or abduction (Peirce, 1958) and corresponds to the creation of new memory traces through the restructuration of pre-existing ones. Although insights occur often during waking (Jung-Beeman et al., 2004), they are greatly facilitated by sleep (Wagner et al., 2004). Notorious examples of sleep-dependent insight can be drawn from both science and art (Barrett, 2001). August Kekulé was puzzled by the number of carbon and hydrogen

atoms in benzene, which did not fit any linear diagram he could conceive. He then saw in a dream the famous alchemical symbol called *Ouroboros*, the snake that eats its own tail. After giving thought to this dream, he inferred that benzene has a circular structure, the benzene ring that is so important in organic chemistry. Dimitri Mendeleyev, the great discoverer of the periodic table, visualized his breakthrough concept in a dream. Intense dreams have greatly inspired artists like Albrecht Dürer, William Blake, Salvador Dalí, Frida Kahlo and many others (Barrett, 2001). Learning from insight gained through dream evaluation is reminiscent of the old view of dreams as oracles, a strong belief even to this day among lay people with little education. Why would dreams appear to predict the future? Studies comparing dream reports of children exposed to different degrees of environmental threats suggest that dreaming simulates actions that lead to undesirable consequences and therefore should be avoided in the real world (Revonsuo, 2000). This "threat simulation" theory has been generalized to include dreams regarding actions that lead to a desirable outcome and therefore should be performed in the real world (Ribeiro and Nicolelis, 2006). The main function of these simulations would be to test specific novel behaviors against a memory replica of the world, rather than the real world itself, thereby leading to learning without risk. An investigation of REM sleep mentation found that over 70% of the reports included emotions, with a balanced proportion of positive and negative ones (Fosse et al., 2001). The notion that nightmares evolved as a way to negatively modulate particularly dangerous behavior simulations, while blissful dreams correspond to the association of pleasure (reward) with dream simulations of especially adaptive behaviors, is analogous to the concepts of Eros and Thanatos proposed by Freud as life and death drives (Freud, 1920).

16.2 The Search for Mechanisms: Active Versus Passive Sleep

Even if both branches of psychology agree that sleep and dreaming are active mental processes that play a key role in cognition, such certainty is not held by all biologists, nor by all philosophers. The past several decades of investigation have witnessed a fierce clash between two major notions regarding the existence of active, adaptive and cognitive processes during sleep and dreams. While the biological mechanisms underlying the generation and maintenance of the sleep-wake cycle are fairly understood (Aserinsky and Kleitman, 1953; Dement and Kleitman, 1957a, b; Dement, 1958; Jouvet et al., 1959; Grastyan and Karmos, 1961; Roffwarg et al., 1962; Jouvet, 1967; Rechtschaffen and Kales, 1968; Timo-Iaria et al., 1970; Siegel, 1990; Steriade, 1992; Steriade et al., 1993; Sutcliffe and de Lecea, 2002; Lee and Jones, 2004; Luppi et al., 2004), no consensus has been achieved about the biological function of sleep and dreams (Maquet, 2001; Siegel, 2001; Stickgold et al., 2001). Some authors even stand for the opinion that dreams play no relevant biological role at all, being nothing but an epiphenomenon of sleep. The anti-Freudian philosopher Owen Flanagan, for instance, argues that dreams cannot possibly be the result of a biological adaptation, based on his failure to recognize fitness-enhancing elements on his own dreams. In his opinion, "dreams are the spandrels of sleep" (Flanagan,

2000). The neural corollary of this point of view is that the bizarreness and hyper-associativeness of dreams can be trivially explained as a side effect of random engram activation during sleep, due to a generalized bombardment of the cerebral cortex by neurons located in deep brain nuclei (Crick and Mitchison, 1983, 1995) Dreams would in this case reflect some sort of "house cleaning" process by which randomly activated memories would be washed away. If this was the case, dreams would have no relevant meaning, and would serve no function *per se*. Despite its ingenuity, the "random cortical activation" theory does not survive confrontation with the fact that dreams can sometimes be very repetitive. This phenomenon occurs in healthy subjects but becomes much more frequent in patients with post-traumatic stress disorder (PTSD). Recursive nightmares related to major trauma are indeed an important symptom of this syndrome, and are very common among war veterans (Ross et al., 1994, 1999). Typically, PTSD dream narratives represent battle events that may recur decades after the end of combat (Neylan et al., 1998; Schreuder et al., 1998; Esposito et al., 1999). Given the colossal number of neurons and synapses in the human neocortex, it is clearly impossible to explain the activation of nearly identical neuronal firing patterns over several consecutive dreams by way of random neocortical activation.

To consider sleep as nothing more than an opportunity for the body and mind to rest is very intuitive, since most of sleep coincides with behavioral quiescence and the slumber experience of slow-wave sleep (SWS). The typical mental content of a person woken up during SWS is a dark visual scene plus thoughts related to waking preoccupations (Kales et al., 1967; Fosse et al., 2004). The subjective experience of being in SWS is in line with the fact that SWS is concomitant with slow neural oscillations under 4 Hz, and decreased firing rates in the cerebral cortex (Timo-Iaria et al., 1970; Steriade et al., 1993; Gervasoni et al., 2004; Ribeiro et al., 2004a). On the other hand, the discovery of a sleep state characterized by dreaming and high neuronal activity in most of the cerebral cortex (Aserinsky and Kleitman, 1953; Dement and Kleitman, 1957b), supported the active sleep paradigm. This second sleep state, called rapid-eye-movement (REM) (Aserinsky and Kleitman, 1953) or paradoxical sleep (Jouvet et al., 1959; Jouvet, 1967), is highly correlated in humans with widespread atonia, except for fast eye movements and occasional localized muscle twitches (Dement and Kleitman, 1957a; Dement, 1958; Jouvet et al., 1959; [Au2] Roffwarg et al., 1962; Kleitman, 1963; Grastyan, 1961, p. 12008; Jouvet, 1967; Rechtschaffen and Kales, 1968; Timo-Iaria et al., 1970). Despite the motionless body, increased neural activity during REM sleep gives life to a succession of mental representations that constitutes the vivid subjective experience of dreaming. Conceived by Freud as "a conglomerate of psychic formations" (Freud, 1900), the dream therefore seems to reflect the fragmented activation of the very stuff the unconscious is made of, i.e. latent memories (Freud, 1915). It is amazing that such high levels of brain activity fail to be converted into behavior. The explanation lies in the activation of glycinergic neurons in the pons that inhibit the efferent control of muscles during REM sleep (Jouvet, 1994). Cats with lesions on these brainstem cells sleep quietly during SWS, but become agitated during REM sleep by vigorous species-specific behaviors, such as meowing and pouncing (Jouvet and Delorme, 1965).

Neural activity during REM sleep is grossly similar to that of waking in intensity and spectral content, with a predominance of high oscillatory frequencies above 30 Hz (Cantero et al., 2004; Gervasoni et al., 2004). A selected set of forebrain areas becomes activated during human REM sleep, including portions of the hypothalamus, amygdala, septum and ventral striatum, as well as the orbitofrontal, anterior cingulate, entorhinal and insular cortices (Maquet et al., 1996; Braun et al., 1997; Nofzinger et al., 1997). In addition, dreaming ceases upon lesion of mesolimbic pathways connecting reward centers with the cerebral cortex, striatum and thalamus (Solms, 1997, 2000). This suggests that dreams promote the "integration of neocortical function […] with motivational and reward mechanisms"(Nofzinger et al., 1997). Deactivation during REM sleep of the dorsolateral prefrontal cortex (Maquet et al., [Au3] 1996; Muzur et al., 2002), a brain region essential for the planning, execution and evaluation of goal-directed behaviors (Tanji and Hoshi, 2001; Schultz, 2002), is the likely basis for the limited volitional power of the self-representation during dreams.

The discovery that waking patterns of neuronal activity reverberate throughout both phases of subsequent sleep provided a mechanism to explain memory reactivation during REM sleep dreams, as well as SWS mentation (Pavlides and Winson, 1989; Wilson and McNaughton, 1994; Skaggs and McNaughton, 1996; Qin et al., 1997; Nadasdy et al., 1999; Dave and Margoliash, 2000; Maquet et al., 2000; Hirase et al., 2001; Louie and Wilson, 2001; Hoffman and McNaughton, 2002; Lee and Wilson, 2002; Peigneux et al., 2003; Ribeiro et al., 2004a, 2007). But SWS and REM sleep are different states when it comes to the stability of neuronal reverberation. While SWS exhibits a steady reactivation of memory traces that is likely to strengthen the networks involved, REM sleep exhibits less stationary reverberation (Winson and Abzug, 1977; Pavlides and Winson, 1989; Ribeiro et al., 2004a, b; Pereira et al., 2007). Such 'noisy' reverberation during REM sleep, long postulated by psychology (Hartmann, 1967, 1998), has been proposed to promote the reconfiguration of neuronal networks, assembling pre-existing memory fragments to give origin to novel engrams underlying sleep-dependent insight (Ribeiro et al., 2004a; Ribeiro and Nicolelis, 2006).

16.3 Long-Lasting Memories and Gene Expression During Sleep

Altogether, the electrophysiological studies of neuronal reverberation performed in animal models support the theory that sleep is an active state linked to mnemonic processing and cognitive work (Pavlides and Winson, 1989; Wilson and McNaughton, 1994; Skaggs and McNaughton, 1996; Qin et al., 1997; Nadasdy et al., 1999; Dave and Margoliash, 2000; Hirase et al., 2001; Louie and Wilson, 2001; Hoffman and McNaughton, 2002; Lee and Wilson, 2002; Ribeiro et al., 2004a, 2007). Equivalent results were obtained in human subjects using brain scanning techniques such as positron emission tomography (Maquet et al., 2000; Peigneux et al., 2003). Still, increased blood oxygenation and neuronal depolarization *per se* cannot produce long-lasting memories. The long-term storage of newly acquired memories depends

crucially on *de novo* protein synthesis related to neuronal plasticity, resulting from the activation of gene expression programs that promote durable changes in synaptic abundance, localization and efficacy (Bliss and Collingridge, 1993; McGaugh, 2000). Mnemonic changes are triggered by sustained neuronal depolarization and mediated by calcium-dependent kinases (Frankland et al., 2001; Lisman et al., 2002; Bozon et al., 2003). The first wave of gene expression after memory formation corresponds to the transcriptional upregulation of fast response genes that couple membrane depolarization to genomic regulation inside the cell nucleus. The proteins coded by such immediate early genes (IEG) may be direct effectors of plasticity within the cell, or indirect modulators of cellular change, functioning as transcriptional regulators for other genes. An example of memory-related effector gene is the activity-regulated cytoskeleton-associated protein (arc), a calcium-dependent IEG that interacts with glutamatergic AMPA receptors, actin and calcium-calmodulin kinase II to promote synaptic remodeling; arc mRNA is transported to dendrites for local translation, leading to retrograde effects with respect to the cell soma (Lyford et al., 1995; Steward et al., 1998; Guzowski et al., 2000; Waltereit et al., 2001). The calcium-dependent gene zif-268 (a.k.a. egr-1, krox-24, NGFI-A and ZENK) is an example of memory-related gene with indirect regulatory function. Zif-268 encodes a transcription factor potentially involved in the expression of hundreds of different genes (Milbrandt, 1987; Christy and Nathans, 1989; Wisden et al., 1990). There is *in vitro* evidence that the zif-268 protein controls the transcription of synapsins (Thiel et al., 1994; Petersohn et al., 1995), the most abundant protein constituent of synapses, required for synaptic vesicle release (Hilfiker et al., 1999). The control of synapsin levels by the zif-268 protein illustrates how neuronal depolarization can effect anterograde synaptic remodeling with respect to the cell soma (Ribeiro and Nicolelis, 2004).

An early attempt to address the role of *de novo* protein synthesis for the cognitive role of sleep found that the blockade of protein synthesis during sleep impairs memory consolidation (Gutwein et al., 1980). When calcium-dependent IEG were discovered in the late 1980s, many researchers envisioned a link between neuronal reverberation at the electrophysiological level and memory consolidation at the genomic and proteomic level. If sleep benefits memory consolidation and IEG are required for long-lasting plasticity, at least some of those genes should be upregulated during sleep. But the first measurements of the c-fos and zif-268 gene expression in the rat telencephalon across the sleep-wake cycle detected upregulation during waking and downregulation during sleep (Pompeiano et al., 1994). This result was soon corroborated by another other team (O'Hara et al., 1993) and extended to other IEG (Tononi et al., 1995; Cirelli and Tononi, 1998, 1999a, b, 2000a, b; Cirelli [Au4] et al., 2004, 2006; Cirelli, 2005, p. 12636), as well as calcium-dependent kinases and other molecular markers of plasticity (Vyazovskiy et al., 2008). Further studies in flies by the same group detected a sleep-related increase in transcripts encoding membrane trafficking proteins, and a general decay in the expression levels of metabolic enzymes, such as cytochromes necessary for respiration inside mitochondria (Shaw et al., 2000; Huber et al., 2004; Cirelli et al., 2005a, b; Cirelli, 2006; Bushey et al., 2007). The fly studies seemed to confirm the experiments in

mammals, i.e. sleep correlated with a transcriptional downregulation of plasticity-related genes such as arc, brain-derived neurotrophic factor (BDNF), homer and zif-268 (Cirelli et al., 2004). Taken together, these results produced an unexpected revival of the passive sleep paradigm, leading to a synaptic downscaling theory of sleep (Tononi and Cirelli, 2003) which proposes that "periods of wakefulness are associated with a net increase in cortical synaptic strength and periods of sleep are associated with a net decrease" (Vyazovskiy et al., 2008). Sleep, in this case, would play a role in "an overall balance of synaptic strength" by favoring "global synaptic depression" (Vyazovskiy et al., 2008).

But other research groups have generated divergent results, based on different assumptions and consequently different experimental strategies. One such assumption is the necessity to compare animals with and without exposure to novel experience in order to investigate the cognitive role of sleep (Giuditta, 1985). Another key point is the need to distinguish the contributions of SWS and REM sleep for the biological variable of interest, since the two main sleep states show very different neural dynamics. In addition, SWS is considerably more abundant than REM sleep (Gervasoni et al., 2004), and therefore experiments that do not sort sleep states tend to be dominated by SWS (Cirelli et al., 2004). Using an experimental strategy that comprised sleep state sorting and pre-sleep novel experience, we found that zif-268 mRNA levels in the cerebral cortex and hippocampus are upregulated during the first REM sleep episode that follows exposure to a novel environment (Ribeiro et al., 1999). In a follow-up study (Ribeiro et al., 2002), we found similar results when exposure to novel environment was replaced by the induction of long-term potentiation (LTP) in the hippocampus, a well-known neurophysiological model of memory (Bliss and Collingridge, 1993). Our experiments revealed a sequence of three spatiotemporally distinct waves of *zif-268* expression, beginning locally at the hippocampus 30 min after stimulation, still during waking, and proceeding to distal extrahippocampal areas during the two subsequent REM sleep episodes. Each *zif-268* upregulation wave was interrupted by the next SWS episode, indicating the existence of recurrent plasticity cycles as the two sleep states alternate.

In 2005, our reports of experience-dependent upregulation of *zif-268* mRNA during REM sleep were extended to other plasticity-related molecules by an independent research team. The study, which employed the active avoidance learning task as behavioral paradigm, linked REM sleep and pontine waves typical of that state to the experience-dependent upregulation of arc and brain-derived nerve growth factor (BDNF) levels, as well as to the increased phosphorylation of the cyclic AMP response element-binding (CREB) protein (Ulloor and Datta, 2005). In 2006, a study of sleep in flies investigated the effects of enriched environment exposure on sleep-related gene expression. The researchers found evidence that sleep is increased in flies exposed to socially enriched environment. Most importantly, during sleep these flies showed increased expression of 17 genes related to long-term memory (Ganguly-Fitzgerald et al., 2006). More recently, our research team showed that the mRNA levels of *zif-268* and *arc* are upregulated in the cerebral cortex during late REM sleep episodes (Ribeiro et al., 2007). Taken together,

these findings corroborate the notion that sleep harbors active experience-dependent processes related to neural plasticity.

Karl Popper prescribed that scientists should constantly attempt to falsify their own theories, subjecting them to critical tests in order to best advance knowledge (Popper, 1963). The refutation of a conjecture derived from a well established theory produces anomalous results with respect to that theory. According to Popper, it is the accumulation of such anomalies that allows other scientists to challenge and eventually substitute a faulty theory with a better one. However, Thomas Kuhn showed that when different theories collide, they tend to coexist for a while (Kuhn, 1962), because scientists become partisan about their own theories. Rather than convincing each other, believers of opposite theories tend to build separate edifices, sometimes even reaching the point of completely ignoring the contribution of others. When additional experiments performed by competitors produce results that do not fit the theory, its proponents often neglect to seriously consider these anomalies. Far from trying to kill their own theories, real life scientists tend to protect their own theories from critical tests, and may avoid performing experiments that could directly refute their theories (Kuhn, 1962).

The issue of molecular markers of plasticity during sleep constitutes a good example of paradigm clash in neuroscience. Despite the fact that three independent groups reported an increase in learning-related gene expression during sleep (Ribeiro et al., 1999, 2002, 2007; Ulloor and Datta, 2005; Ganguly-Fitzgerald et al., 2006), these results have been completely ignored by the proponents of the "synaptic downscaling" theory. The neglect was so strong that it even precluded citation of any divergent results in the 40 publications regarding sleep and plasticity produced in the last decade by the proponents of the "synaptic downscaling" theory. In fact, none of these studies attempted to run the critical experiments involving learning and separation of SWS and REM sleep. Only in their most recent article has this issue begun to be contemplated, by way of measurements of evoked electrical responses after novel object exposure and post-exposure sleep. However, post-exposure sleep was simply not investigated at the molecular level, as if the question was not pertinent to contemporary neuroscience (Vyazovskiy et al., 2008).

Remarkably, synaptic upscaling and downscaling are not mutually exclusive. Experience-dependent IEG expression during REM sleep is compatible with the notion of sleep-dependent synaptic downscaling, as long as the latter happens more strongly in neuronal circuits that were not activated by waking experience (Ribeiro and Nicolelis, 2004). Synaptic downscaling during SWS is likely to be essential for learning, but if it occurred with equal strength in activated and non-activated circuits, it should promote generalized forgetting, not learning. We have proposed that the combination of synaptic upscaling in activated circuits and synaptic downscaling in non-activated circuits should markedly increase the signal-to-noise ratio of memory consolidation during sleep. In principle, such differential plasticity should be sufficient to carve high-relief memory traces in a background of disengaged synapses [Au5] (Ribeiro, 2004, 2006). Recent results comparing stimulated and non-stimulated regions of the cerebral cortex indicate that this is exactly the case, at least with regard to different sensory modalities (Ribeiro et al., 2007).

16.4 Conclusion

Can passive quiescence fully explain the cognitive role of sleep? The ancient Greeks were surely unaware of the neural mechanisms activated during sleep, but in a very intuitive way they knew that a powerful learning tool was effective at night. They believed that dreams could predict the future as a result of divine intervention. The abundance of votive offers at *asklepieion* archaeological sites is intriguing, suggesting that Dream Incubation often resulted in healing (Meier, 2003). During this ritual, the god of medicine Asclepius had the assistance of Hypnos, the god of quiescent sleep who was the twin brother of Thanatos, god of death. Hypnos would first induce the subject into gentle sleep, and then he would request the help of his son Morpheus, god of dreams, to open the mental window that allowed Asclepius to bring prescription of the right treatment for the subject's illness. The dichotomy between Hypnos and Morpheus illustrates the ongoing scientific debate regarding the mechanisms underlying the cognitive role of sleep. One of the competing theories proposes that the function of sleep is to trigger generalized synaptic downscaling, so as to restore homeostatic balance and enable further waking potentiation. This theory focuses on SWS, disregards REM sleep, and does not take into account experience-dependent changes (Tononi and Cirelli, 2003). Our theory proposes that the cognitive role of sleep derives from the cooperative interaction of its two major states: While SWS reverberates waking memories in the absence of distracting stimuli, REM sleep elicits plasticity-related IEG expression in previously activated neurons (Ribeiro and Nicolelis, 2004). According to this view, sleep harbors decreased and increased plasticity in separate circuits, leading to experience-dependent differential plasticity. Further experimentation is required to convincingly refute either theory.

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[Au2]: Grastyan, 1961 is not included in the reference list.
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