Published in final edited form as:

Neurobiol Learn Mem. 2011 November ; 96(4): 564–582. doi:10.1016/j.nlm.2011.07.004.

The cognitive cost of sleep lost

John G. McCoy* and Robert E. Strecker*

VA Boston Healthcare System, Research Service and Harvard Medical School, Department of Psychiatry, 940 Belmont St., Brockton, MA 02301-5596, USA¹

Stonehill College, Department of Psychology, Easton, MA 02357, USA

Abstract

A substantial body of literature supports the intuitive notion that a good night's sleep can facilitate human cognitive performance the next day. Deficits in attention, learning & memory, emotional reactivity, and higher-order cognitive processes, such as executive function and decision making, have all been documented following sleep disruption in humans. Thus, whilst numerous clinical and experimental studies link human sleep disturbance to cognitive deficits, attempts to develop valid and reliable rodent models of these phenomena are fewer, and relatively more recent. This review focuses primarily on the cognitive impairments produced by sleep disruption in rodent models of several human patterns of sleep loss/sleep disturbance. Though not an exclusive list, this review will focus on four specific types of sleep disturbance: total sleep deprivation, experimental sleep fragmentation, selective REM sleep deprivation, and chronic sleep restriction. The use of rodent models can provide greater opportunities to understand the neurobiological changes underlying sleep loss induced cognitive impairments. Thus, this review concludes with a description of recent neurobiological findings concerning the neuroplastic changes and putative brain mechanisms that may underlie the cognitive deficits produced by sleep disturbances.

Keywords

Sleep loss; Learning; Memory; Cognition; Attention; Sleep deprivation; Executive function

“It is a common experience that a problem difficult at night is resolved in the morning after the committee of sleep has worked on it.”

~John Steinbeck

1. Introduction: sleep disruption in rodents

1.1. Overview

Sleep, an essential part of human life, is needed for optimal health and performance. Sleep disturbance caused by disease and vocational demands contributes to decreases in work/school efficiency, and sleepiness is now recognized as a major contributor to accident rates (Phillip & Akerstedt, 2006). Indeed, the diminished cognitive function associated with sleep disruption caused by sleep disorders and/or occupational factors is increasingly being recognized as a major public health and safety issue that has large financial and social costs (Czeisler, 2009; Durmer & Dinges, 2005). It is now well established that sleep disruption

*Corresponding authors at: VA Boston Healthcare System and Harvard Medical School, 940 Belmont St., 151C, Brockton, MA 02301-5596, USA. Fax: +1 774 826 1876. jmc coy1@stonehill.edu (J.G. McCoy), robert_strecker@hms.harvard.edu (R.E. Strecker).

¹Institution where work was performed.

Conflict of interest

There are no conflicts of interest to disclose for any of the authors related to this work.

can interfere with almost all specific behavioral processes studied to date in humans (Balkin, Rupp, Picchioni, & Wesensten, 2008; Killgore, 2010). Thus, sleep disturbance produces specific cognitive impairments in humans including deficits in attention, executive function, non-declarative and declarative memory, as well as emotional reactivity and sensory perception (Durmer & Dinges, 2005; Jones & Harrison, 2001; Walker, 2008). A separate body of literature has demonstrated the beneficial effects of a good night's sleep on human cognitive performance, a literature that will not be covered in the present review (see Ellenbogen, 2005; Stickgold & Walker, 2007; Walker, 2008). Instead, this review focuses on the cognitive impairments produced by sleep disruption in rodent models of several human patterns of sleep loss/sleep disruption and compares the rodent findings to the findings described in the human literature. Unlike some early rodent work which investigated the effects of long periods of total sleep deprivation (reviewed in Rechtschaffen and Bergmann (2002)), contemporary sleep research focuses on rodent models (described next) of the conditions that mimic typical human sleep disruption. Finally, this review concludes with a brief summary of the neurobiological findings that promise to illuminate the mechanisms that underlie the cognitive impairments produced by sleep disruption in rodents, although much work remains to be done (see Poe, Walsh, and Bjorness (2010) for a recent review on this topic).

1.2. Sleep disruption

The term “sleep disruption” is used herein as an “umbrella term” that encompasses several types of sleep disturbance seen in humans. Another general term, “sleep loss” can be misleading because, at times, it has been used to mean “total acute sleep deprivation”. Sleep in rodents can be experimentally disrupted in several ways in order to model human sleep disorders, or to model human occupational/behavioral patterns of sleep disruption. The types of sleep disruption described in this review are defined next.

1.3. Sleep deprivation (SD)

Is used to refer to acute total sleep deprivation (typically short periods of wakefulness (<72 h) accompanied by a nearly complete loss (>90% of both NREM sleep and REM sleep). This type of sleep disruption is often produced by voc demands such as experienced by shift workers, emergency workers & physicians on 36 h to 48 h work shifts, and in military situations, or by clinical conditions such as insomnia.

1.4. Experimental sleep fragmentation (SF)

The clinical term “sleep fragmentation” describes the pattern of sleep disruption seen in many clinical disorders, such as obstructive sleep apnea (Roehrs et al., 1985), restless leg syndrome (Saletu et al., 2000), depression (Perlis et al., 1997), post-traumatic stress disorder (Mellman, Nolan, Hebding, Kulick-Bell, & Dominguez, 1997), and narcolepsy (Tafti, Villemin, Carlander, Besset, & Billiard, 1992) to name a few. The rationale for assessing the behavioral consequences of SF is to develop a valid rodent model that mimics the disturbances in continuity, deep sleep, and rapid eye movement sleep (REM sleep) observed in patients with sleep apnea (Tartar et al., 2006) and these other disorders. When clinical sleep fragmentation has been modeled in the experimental laboratory it has been called “sleep interruption”, or “experimental sleep fragmentation”. This review uses the term “experimental sleep fragmentation” abbreviated as SF. Following exposure to experimental SF rats exhibit marked sleepiness, as indicated by a decrease of sleep onset latency in a multiple sleep latency test, an increase in delta power (i.e., cortical slow wave activity), and elevated adenosine levels within the BF (details below, McKenna et al., 2007). These changes mimic the alterations in sleep architecture observed in patients diagnosed with sleep apnea.

1.5. Selective REM sleep deprivation (REM SD)

During normal mammalian sleep, REM sleep is entered from NREM sleep (also known as Slow Wave Sleep, due to the presence of high amplitude, low frequency signals in the cortical electroencephalogram). Experimental methods exist that selectively disrupt REM sleep, while leaving NREM sleep largely intact (Smith & Rose, 1996; Youngblood, Zhou, Smagin, Ryan, & Harris, 1997). The use of REM SD methods allows the partial disassociation and comparison of the roles that NREM sleep and REM sleep play in cognitive processes. Thus, a discussion of the effects of sleep disruption on cognition and behavior is intimately associated with a discussion of the roles that NREM sleep and REM sleep play in cognitive information processing and memory consolidation.

1.6. Chronic sleep restriction

Many people in modern society reduce the amount of time they sleep each day for vocational or lifestyle reasons. Recent experimental studies in humans reveal that sleeping 2–3 h less than their normal sleep time, even for only a few consecutive days, leads to significant impairment in cardiovascular, immune, endocrine, as well as cognitive functions (for review see Banks & Dinges, 2007; Dinges, Rogers, & Baynard, 2005). In fact, the impairments in humans produced by 2 weeks of sleep restriction (i.e., 6 h of sleep/night) on psychomotor vigilance response times are comparable to the deficits caused by two nights of total sleep deprivation (Van Dongen, Maislin, Mullington, & Dinges, 2003). Consistent with these reports are epidemiological studies which suggest that habitual short sleep duration is associated with increased obesity (Spiegel, Knutson, Leproult, Tasali, & Van Cauter, 2005), heart disease (Gangwisch et al., 2006), and mortality (Cappuccio, D'Elia, Strazzullo, & Miller, 2010). Rodent models of chronic sleep restriction have recently been developed (Caron & Stephenson, 2010; Everson & Szabo, 2009; Kim, Laposky, Bergmann, & Turek, 2007; Leemburg et al., 2010), but little work has been done with these models to date. Finally, although other types of sleep disruption exist along with their relevant animal models (e.g., insomnia, jet lag and other circadian disorders affecting sleep patterns), this review will focus on the four types of sleep disruption defined above, with an emphasis on the published work of the authors.

1.7. How is sleep disruption produced in rodents?

Rodent studies of sleep disruption have often relied on human intervention to keep the subjects awake using a procedure called “gentle handling” to produce acute sleep deprivation. The gentle handling method uses light tactile and sensory stimulation to keep the rodents awake; a process that is very labor intensive and becomes more difficult as the duration of sleep deprivation increases (e.g., beyond 6 h). Hence, computer controlled automated devices that awaken rodents due to the movement of the cage in which the rodents are housed have gained in popularity. One of the first automated devices was developed by Rechtschaffen and co-workers in the 1980s (the disk over water method; reviewed in Rechtschaffen and Bergmann (2002)), but this device has not been widely adopted. Other researchers have used automated treadmills, activity wheels, and carousels that can be programmed to produce the different types of sleep disruption described above. Unlike treadmills (Tartar et al., 2009), recent findings indicate that the activity wheels and carousels produce a negligible corticosterone stress response (Leenaars et al., 2011, and our unpublished findings). Hence, the use of these less stressful sleep disruption devices promises to allow better separation of the effects of sleep disruption from the possible confounds of non-specific hormonal stress. Using automated devices to keep a rodent awake requires the addition of a treatment condition that mimics the cage movement of the sleep disruption condition, but distributes the timing of cage movement to allow for longer periods of normal deep and consolidated sleep. This control group has been called an “exercise control” or a “movement control” (the term used herein). The importance of the movement

control condition is that it helps separate the sleep disruption from other non-specific effects experienced by the rodent subject such as the possibility of increased locomotor activity and/or stress.

2. Sleep and sleepiness

2.1. Homeostatic and circadian influences on sleep

The two main regulators of wakefulness and sleep are the duration of prior wakefulness, which produces the homeostatic sleep drive, and circadian influences (Borbely, 1982). The circadian process (not covered in this review) directs the timing of sleep and wakefulness, whereas the homeostatic process regulates the amount of sleep based on the duration of prior wakefulness. Increases in the homeostatic sleep drive are associated with sleepiness, diminished alertness and neurobehavioral function (reviewed in Durmer and Dinges (2005)). Thus, the recovery sleep response to total SD depends on several factors including the duration of deprivation, and the circadian time at which deprivation and recovery sleep occur.

2.2. The multiple sleep latency test

The sleepiness produced by sleep disruption can be measured directly by assessing the latency to sleep onset, a measure that can be quite variable. To reduce variability in the data obtained, human studies typically perform multiple trials in what is called the “multiple sleep latency test” or MSLT. Sleep onset latencies can also be measured in rodents and several papers have described specific procedures to measure these latencies in rodents (for review, see McKenna et al., 2008). Rodents must be awakened for a fixed duration (typically 5 min) prior to each trial measuring sleep onset latency. The number of trials used can be adjusted to take into account issues such as the variability between and within subjects, while balancing the concern that waking the rodent up regularly (even if only for 5 min) can, in itself, add to the amount of sleep disruption.

2.3. Electroencephalographic measures of sleepiness

A large literature has used electroencephalographic measures to identify brain signals that correlate with the homeostatic sleep drive and sleepiness. Similar results are seen in humans and rodents. Laboratory rats are nocturnal, sleeping more during the light period (their inactive period). Short periods of total SD (3–12 h) in the light phase leads to a compensatory increases in the amount of cortical electroencephalographic slow wave activity (also known as delta power) and the amount of NREM sleep during the recovery period following SD, with smaller increases observed in REM sleep compared to baseline levels (Lancel & Kerkhof, 1989; Shiromani et al., 2000; Tobler & Borbely, 1990). Light-phase recovery sleep following 12-h SD during the dark phase shows little or no increase in NREM and REM sleep amounts versus baseline (likely due to a ceiling effect since rats sleep a lot in the light period which was used as the baseline reference; Lancel & Kerkhof, 1989; Shiromani et al., 2000). In summary, for up to 12 h of total SD the amount of delta power during recovery sleep appears to be a more sensitive measure of the homeostatic sleep drive than is the increase in sleep amount. However, 1–4 days of total SD produces more variable changes in sleep amount and delta power during the recovery period (for review see Rechtschaffen & Bergmann, 2002), suggesting that some aspects of the homeostatic sleep drive adapt to longer periods of sleep disruption (e.g., see Kim et al., 2007), and, therefore sleep onset latency may be a more reproducible measure of sleepiness during periods of chronic sleep disruption/restriction (see Fig. 1).

3. Attention/vigilance

3.1. Attention is important in all cognitive processes

Decades of experimental and clinical research on humans have revealed that sleep loss impairs a wide variety of cognitive processes (reviewed in Killgore (2010)), ranging from the most basic (e.g., attention, alertness, vigilance) to the most advanced cognitive abilities (e.g., decision making, problem solving, etc.). These findings have been interpreted to suggest that sleep loss impairs a process (or processes) such as attention that is (are) essential to virtually all other cognitive processes (Balkin et al., 2008). Relatively recent advances in methods used to image the human brain in vivo have revealed that sleep loss results in changes in the activity of numerous brain structures, including several cortical regions (Chee & Chuah, 2008; Desseilles, Vu, & Maquet, 2011; Drummond et al., 2005; Thomas et al., 2000), all cortical regions known to play important roles in higher-order cognitive functioning. Although higher level cognitive processes are clearly affected the most reliable and robust behavioral impairments following sleep loss are the effects observed on alertness and attention (Lim & Dinges, 2010). Proper functioning of lower-level processes, such as attention, is a necessary condition for optimal functioning of neural circuits that mediate higher cognitive functions. Thus, in order to understand the impact of sleep loss on cognition in general, one must develop reliable experimental models that will allow us to understand precisely how sleep loss interferes with basic attention processes.

3.2. Multiple types of attention

At least three separable attention processes have been characterized at the behavioral and neurochemical levels (Robbins, 1997). Sustained attention, used as a synonym for vigilance in the psychology literature, refers to the continuous allocation of processing resources for detecting an important event. Deficits in vigilance are often detectable at the end of a long test session, even without any sleep disruption. Impairments in sustained attention performance are widely considered to be the most sensitive and easily measured behavioral deficit produced by sleep disruption (Balkin et al., 2004). Hence, sustained attention impairments are widely used as an indirect measure of sleepiness. Divided attention involves situations in which several different contingencies must be monitored simultaneously, thus, requiring the optimal allocation of limited cognitive resources. Selective (focused) attention requires the ability to focus resources on a restricted number of sensory channels whilst filtering out irrelevant sensory information and/or background noise. While the multiple aspects of attention may be differentiated under controlled experimental conditions, it is generally recognized that two or all three aspects of attention may be activated and interacting in many situations outside the laboratory (Robbins, 1997).

3.3. Rodent tests of sustained attention

1. *The 5-choice serial reaction time (5-CSRT).* The 5-CSRT task has been proposed to offer the advantage of being able to use several different performance measures in order to dissociate these three different “types” of attention, while also providing an index of response inhibitory control (Robbins, 2002). Response inhibitory control, which is one aspect of executive function, is assessed in the 5-CSRT task by measuring premature responses and perservative responding; these measures serve as indices of impulsive and compulsive behavior, respectively. As little as 4, 7, and 10 h of total sleep deprivation with gentle handling has been shown to impair vigilance (sustained attention) in rats using the 5-CSRT. Specifically, both response latencies and the number of errors of omission were increased by SD (Cordova et al., 2006; see Fig. 3). Broad application of the 5-CSRT task is difficult because it can take several months to train rats to perform this task. Furthermore, the human sleep literature uses a simple reaction time test known as the “*psychomotor*

vigilance test” (PVT) to detect decrements in sustained attention; this test is one of the most sensitive measures for the detection of impaired vigilance caused by sleep disturbance (Balkin et al., 2004). The PVT is also very easy to use; for example, it can be applied in field studies using a handheld device that measures responses to visual stimuli. Hence, more recent animal studies have used a rat analogue of the human PVT (Christie et al., 2008; Christie, McKenna, Connolly, McCarley, & Strecker, 2008; see Fig. 2).

2. *The rat psychomotor vigilance test.* Similar to the human PVT, the rat PVT is a simple reaction time test. The rat PVT requires the rat to monitor a central stimulus location (light) for a brief and unpredictable signal (light flash) and then respond with a simple species-specific response (a nose poke for rats). The primary measures in the rat PVT and human PVT are the same: response latency and number of lapses (i.e., failure to respond within a specified amount of time, ~1.0 s for the rat PVT). Training rats to perform the rat PVT to stable baseline criteria takes only 4–6 weeks, and 95% of the rats can be successfully trained. The rat PVT has been validated by exposing rats to 24 h SD and comparing the effect on rat PVT performance to changes in objective sleepiness using a rat “multiple sleep latency test” (Christie, McKenna, et al., 2008). After 24 h SD, response latencies slowed, and lapses increased significantly (compared to baseline and movement control conditions), changes indicative of impaired vigilance. Sleepiness was confirmed by both polysomnography and by the rat multiple sleep latency test (see McKenna et al., 2008 for methods). Taken together, these results suggest that the decrement in vigilance was due to increased sleepiness, and not other nonspecific factors such as fatigue or stress (Christie, McKenna, et al., 2008).

3.4. Comparing the human and rat psychomotor vigilance tests

Fig. 2 shows that PVT lapses/omissions are increased by sleepiness in both humans and rats. Quantitative comparisons between studies are very difficult due to the inherent differences between the species and the specific experiments shown in Fig. 2. The data shown are normalized to baseline performance of the subjects in each study, in order to illustrate that attention is impaired in each of the studies. Rat studies require food or water restriction in order for them to perform the operant tasks for a reward; for rats this effectively limits the number of trials per operant session to about 120–150 total trials/session. In contrast, humans are motivated only by the request of the investigator and a PVT session duration of 20 min (shown here in Panel A; data modified from Van Dongen, Baynard, Maislin, and Dinges (2004)) produces approximately twice as many lapses as does a PVT session of 10 min duration (Van Dongen et al., 2003). Evidence for trait-like individual differences in vulnerability to performance impairments produced by sleep loss has been observed in several cognitive parameters including self evaluation of sleepiness/fatigue & mood, cognitive processing ability, and sustained attention (vigilance) performance in the PVT (Van Dongen et al., 2004). Though one cannot model subjective sleepiness ratings in rodents, it is certainly possible to examine individual differences in vigilance impairments using both the 5-CSRT and rPVT in rats. Inter-individual differences in the neurobehavioral response to sleep disruption are illustrated in panels B (rat) and C (human; see the figure legend and Cordova et al. (2006) and Van Dongen et al. (2004) for details). Interestingly, the response of individual human subjects to the effects of SD on cognitive performance is task specific. Thus, the human subject that performed the best on the PVT actually performed at an average level on the measures of subjective sleepiness, and worse than average on a word detection task assessing cognitive processing (data not shown; see Van Dongen et al. (2004) for details).

3.5. The basal forebrain and rat PVT performance

The rat PVT has also been used to test the widely investigated hypothesis that elevations in basal forebrain (BF) adenosine levels mediate the homeostatic sleep drive and increases sleepiness associated with periods of prolonged wakefulness (Basheer, Strecker, Thakkar, & McCarley, 2004; McCarley, 2007; Porkka-Heiskanen, Strecker, & McCarley, 2000; Porkka-Heiskanen et al., 1997; Strecker et al., 2000). Adenosine is an inhibitory neuromodulator at the A1 receptor, and is thought to be an endogenous hypnogen. Thus, it follows that the adenosine receptor antagonists caffeine and theophylline, found in coffee and tea, are widely consumed beverages used to promote wakefulness/alertness in man (see Basheer et al. (2004) for review). The central adenosine hypothesis has been tested by infusing adenosine directly into the BF (via reverse microdialysis), and evaluating vigilance performance with the rat PVT (Christie, Bolortuya, et al., 2008). Pilot studies were conducted to determine a dose range of adenosine that increases sleepiness, but did not incapacitate or induce excessive sleep in rats. Infusion of 300 μ M adenosine into the BF slowed response latency and increased lapses on the rat PVT (Christie, Bolortuya, et al., 2008), effects that mimicked the effects of 24 h SD in the rat PVT test (Fig. 2, panel A). This vigilance impairment was blocked by co-dialysis of a selective adenosine A1-receptor antagonist, demonstrating that decrements in performance were due to the elevated adenosine in the BF, not to other nonspecific factors.

4. Executive function

4.1. Definitions of executive function

Despite an increase in interest and publications on the topic of 'executive function' in recent years, the construct of executive function is difficult to define and specify, as the term has been used to cover many functional abilities, and has been used in different ways. Executive function (or control) involves "selection, control and coordination of computational processes that are responsible for integrating perception and action" (Verstraeten, 2007; Verstraeten & Cluydts, 2004). Others refer to executive function as the parceling out attentional resources in response to changing environmental demands by components of the working memory system, which holds information on-line for immediate use (Baddeley, 1996). Norman and Shallice (1986) refer to the 'supervisory attention system,' which is required in situations that are novel or highly competitive, when selection of routine behaviors is inadequate. The supervisory attention system coordinates the following. "planning or decision making, error correction or troubleshooting, learned or novel sequences of actions, in situations judged to be dangerous or technically difficult, or situations that require overcoming a strong habitual response (Norman & Shallice, 1986)." Basic research using rodents has thus only been able to model certain aspects of executive function. The attentional set-shifting task (described below), used both in human and animal basic research, evaluates the last of these conditions, the ability to overcome a strong habitual response (Birrell & Brown, 2000; Owen, Roberts, Polkey, Sahakian, & Robbins, 1991).

4.2. Sleep loss induced executive function impairments in man

In humans, manipulations used to reduce or fragment sleep have been shown to impair "executive function," including the loss of focus on relevant cues, cognitive flexibility, and behavioral adaptation to new information (Jones & Harrison, 2001). Sleep apnea patients experience attention capacity deficits (reduced information processing speed and short-term memory span), time-on-task decrements, and executive attention dysfunction (Verstraeten & Cluydts, 2004). Deficits in executive function among apneic patients have been assumed to be related to prefrontal lobe dysfunction caused by intermittent hypoxia (Beebe & Gozal, 2002; Fulda & Shulz, 2001; Jones & Harrison, 2001). However, sleep disruption itself can

affect both “lower” level processes, such as arousal/vigilance, as well as “higher” cognitive processes, such as memory and executive function (Durmer & Dinges, 2005; Verstraeten & Cluydts, 2004). The extent of behavioral impairment in sleep apnea patients correlates with both the degree of hypoxemia and with the degree of sleep fragmentation (Bedard, Montplaisir, Richer, Rouleau, & Malo, 1991). The daytime sleepiness and cognitive impairments observed in experiments on humans exposed to experimental sleep fragmentation is quite similar to the changes produced by total sleep deprivation (Chugh, Weaver, & Dinges, 1996; Durmer & Dinges, 2005). Thus, one cannot assume that the deficits in higher cognitive function observed in apneic patients are due solely, or even primarily, to chronic intermittent hypoxemia. It is more reasonable to postulate that both the intermittent hypoxemia and sleep fragmentation contribute to the executive function impairments of sleep apnea; however, the relative contribution of each is not easily discernible from clinical studies. A meta-analysis of sleep-disordered patients revealed profound deficits on sustained attention tasks and working memory tasks requiring mental flexibility and attention shifts, such as the Wisconsin Card Sorting Task (WCST; Fulda & Shulz, 2003). The WCST is widely used by neuropsychologists to assess executive function among patients with frontal lobe damage (Jones & Harrison, 2001). Two recent studies were designed to determine the effect of 24 h of SF and 7 d of intermittent hypoxia on executive function in rats using the attentional set-shifting task (McCoy et al., 2007, 2010).

4.3. Rodent test of executive function

The intradimensional/extradimensional attentional set-shifting task is a human test that is similar to the WCST but that is adaptable for use in rats (Birrell and Brown (2000). These tests all assess the subject’s ability to shift attention from one meaningful association to a new, but also meaningful association. Hence, these tests measure what has been called “attentional set-shifting”; subjects are required to focus attention on one stimulus attribute when faced with a complex stimulus, and then alter this focus their attention on a different attribute when a new set of complex stimuli is presented. In more simple terms, the rat attentional set-shifting task teaches the rat an association between a stimulus and a reward (e.g., food is hidden in the flower pot that smells like vanilla), and then requires the rat to extinguish this learning when the “rule changes” (e.g., now food is now hidden in the flower pot with dark pieces of paper). The “extradimensional shift” is the most cognitively demanding aspect of this test, as it requires the subject to learn a new rule in which the rule about which sensory dimension is associated with reward changes (e.g., smell versus the shape/color of material covering the food reward).

4.4. The effect of SF on attentional set shifting in rats

As shown in Fig. 3 and 24 h of SF selectively impaired the rats’ ability to perform the extradimensional shift in the rat attentional set-shifting task (McCoy et al., 2007). In this experiment, mildly food-restricted rats were trained to solve a series of 2-choice discriminations for a food reward. In each 2-choice discrimination problem, a single element of one of two perceptual dimensions indicated the location of the food. Specifically, rats were trained to choose one of two flower pots, with the food being buried in one of them beneath one of several types of digging media (e.g., beads, shred paper, cut out shapes). Thus, digging medium was one of the two perceptual dimensions with the other being the odor of the pot (i.e., different pots were labeled with diluted oils of a given scent). Only one of the two perceptual dimensions (odor or digging medium) was the correct dimension (i.e., associated with food reward). Therefore, rodents had to learn to identify the relevant dimension and disregard the irrelevant dimension. After a series of such problems, a new problem was presented in which the reward was now associated with the formerly irrelevant stimulus dimension (i.e., known as the extradimensional shift).

4.5. The effect of intermittent hypoxia on attentional set shifting in rats

Rodent models of the chronic intermittent hypoxia that patients experience in obstructive sleep apnea indicate that oxidative stress and subsequent cortical neuronal apoptosis may mediate the chronic intermittent hypoxia-induced behavioral impairments observed (Gozal, Daniel, & Dohanich, 2001; Xu et al., 2004). Hence, the next study described examined the effect of 7 d of intermittent hypoxia on attentional set-shifting (McCoy et al., 2010). Interestingly, sub-chronic (10 h/day for 7 days) treatment of rats with intermittent hypoxia resulted in an impairment on the attentional set-shifting task (namely, a selective deficit on the extradimensional shift) that was similar to that observed following the acute (i.e., 24 h) exposure to SF (McCoy et al., 2007). With both experimental treatments (i.e., acute SF exposure and sub-chronic intermittent hypoxia exposure), the attentional set shifting deficit is likely to reflect impaired allocation of attention resources of the working memory system. As suggested above, cortical apoptosis could underlie the impairments caused by intermittent hypoxia; however, this mechanism should take at least 3 days of hypoxia exposure to produce behavioral impairments (see Ward et al., 2009) and, to date, short durations of intermittent hypoxia exposure have not been tested in the attentional set-shifting task.

4.6. Discussion of the attentional set shifting deficits found in rats

The 24 h SF and the 7 d intermittent hypoxia protocols both selectively impaired performance on the extradimensional shift discrimination (McCoy et al., 2007, 2010). The selectivity of the impairment ruled out a number of possible explanations, such as a deficit in the ability to learn new discrimination problems in general (i.e., intradimensional shifting was unaffected by SF), or a general deficit in attention, cognition, or motor performance. Since reversal learning was not affected, a general effect on behavioral perseveration can also be ruled out as an explanation. The impairment on the attentional set-shifting task following 24 h of SF is interpreted to be a deficit in central “executive” processes (McCoy et al., 2007). As discussed previously, the term “executive function” covers a number of related processes. Here, it refers to those subdivisions of “executive function” that are involved in parceling out of attention resources in response to changing environmental demands by components of the working memory system, which hold information on-line for immediate use. Thus, difficulty shifting attention from the originally rewarded dimension to a new perceptual dimension reflects a problem of executive function.

At present, the precise mechanism by which 24 h of SF or 7 d of intermittent hypoxia alters attentional set shifting is unknown. Changes in brain adenosinergic systems (discussed above) is one possible mechanism, especially for the 24 h SF-induced impairments since it has been documented that acute SF and SD produce very similar 2-fold increases in extracellular BF adenosine levels (Basheer et al., 2004; McKenna et al., 2007; Strecker et al., 2000). Hence, the deficit in attentional set-shifting following 24 h of SF could be mediated by an adenosinergic inhibition of cortically activating BF neuronal projections to the cortex. Aside from its major role in basic arousal and behavioral activation, evidence suggests that the BF and pontine cholinergic systems play a significant role in visual attention, short-term spatial (working) memory, responsiveness to novel and motivationally relevant stimuli, affective memory, and synaptic efficacy during the acquisition of new associations (Robbins, 1997). Thus, cortically projecting BF neurons figure prominently in the multiple effects of sleep disruption on behavior and cognition. Regardless of mechanism, the selective deficit in attentional set-shifting observed in rats following 24 h of SF is similar to executive deficits found in humans diagnosed with sleep apnea (Bedard et al., 1991).

4.7. Brain lesions alter attentional set shifting

Consistent with the data that chronic intermittent hypoxia induces cortical apoptosis, extradimensional shift deficits on the attentional set-shifting task have been reported following lesions of the medial prefrontal cortex (mPFC) in rats (Birrell & Brown, 2000), and in the dorsolateral prefrontal cortex (DLPFC) in humans (Owen et al., 1991) and nonhuman primates (Dias, Robbins, & Roberts, 1997). The mPFC in rats and DLPFC in primates are thought to be “functionally homologous” in that in both cases, damage impairs the ability to shift attention from one rule to solve a task to a new rule. In humans, imaging studies (i.e., event-related fMRI) have shown that slow responses on the human PVT are associated with greater activation of the mPFC (Drummond et al., 2005). The mPFC regions are part of a ‘default mode network’ that tends to be most active when external processing demands are low. These authors propose that sleep loss may inappropriately activate the default system which may lead to a failure to allocate cognitive resources effectively. Human imaging studies (i.e., positron emission tomography) confirm that the DLPFC is activated during extradimensional shifting (Rogers, Andrews, Grasby, Brooks, & Robbins, 2000). The DLPFC is activated in humans when information needs to be monitored and manipulated (Owen et al., 1991). Sleep disturbances in humans alter normal functioning of the prefrontal cortex as well as the posterior parietal cortex, which has dense interconnections to the frontal lobe (Thomas et al., 2000). In rats, posterior parietal lesions also alter aspects of performance on the attentional set-shifting task (Fox, Barense, & Baxter, 2003). The prefrontal cortex, then, with its rich reciprocal connections with multiple sensory and motor cortical areas, and subcortical brain regions, is presumed to govern the ‘supervisory attention processes’ which includes the capacity to switch attention from one focus to another.

5. Emotion

5.1. Sleep loss-induced emotional effects in man

Sleep disruption alters mood and anxiety in man. Although an alteration in emotional state following sleep disruption in humans is intuitive, and is supported by decades of empirical research, only recently has research focused on the specific components of emotion altered by sleep loss (e.g., emotional perception, emotional expression) has only recently become a subject of serious inquiry (Walker, 2009). It is not possible to develop a rodent analogue of the self-report emotional measures used in human studies. Similarly, human studies on emotional perception that ask participants to rate emotional quality of stimuli are seemingly unlikely to be modeled in nonhuman animals. Nonetheless, scientists who study cognitive processes in rodents must recognize the influential effect that sleep loss-induced emotional changes can have on cognitive performance.

5.2. Measures of emotion in rodents

One aspect of emotional state for which rodent analogues have been developed is anxiety. Both anxiogenic (Sagaspe et al., 2005; Silva et al., 2004) and anxiolytic (Martinez-Gonzalez et al., 2004; Pokk & Vali, 2001; Suchecki, Tiba, & Tufik, 2002) effects have been reported in experimental investigations of sleep disruption. Behaviors indicative of increased anxiety in the elevated-plus maze and the standard open field test (Silva et al., 2004) have been reported following 72 h of REM SD. Self-reported increases in anxiety have been observed in humans after 36 h of SD (Sagaspe et al., 2005). On the other hand, behaviors in the plus-maze indicative of decreased anxiety have been reported in mice (Pokk & Vali, 2001) and in rats (Martinez-Gonzalez et al., 2004; Suchecki et al., 2002 following REM SD). In humans diagnosed with depression, one night of SD was found to reduce anxiety (Wu & Bunney, 1990) and is also a potent short term antidepressant (for review see Hemminger, Hemminger-Spernal, & Krieg, 2010). The relevant factors that predict whether sleep disturbance will

increase or decrease anxiety are not known. Duration of exposure, method used to disrupt sleep, and type of sleep disturbance (SD, SF, or chronic sleep restriction) are potential experimental factors that may help to explain seemingly contradictory findings.

5.3. Sleep disruption alters anxiety in rats

Treadmill-induced 24 h of total SD, or SF has been shown to increase exploratory behavior in an open field test of anxiety in rats compared to control conditions (Tartar et al., 2009). Plasma corticosterone levels of the sleep disturbed and movement control rats were both significantly elevated compared to cage control rats, suggesting that the increased exploration observed in the sleep disturbed rats was not due to a hypothalamic–pituitary–adrenal stress response. Whether the increased exploration of the open field area reflected a reduction in anxiety, an increase in locomotor activity (hyperactivity), or an increase in aggression/fearlessness remains unclear (Tartar et al., 2009). Open field tests rely on the conflict between the rats' innate tendency to explore/forage, and their natural aversion to open areas, where they would be at greater risk to predation in their natural habitat (Fernandez, Misilmeri, Felger, & Devine, 2004). Increases in exploration of an open area are generally considered to be indicative of reduced levels of anxiety. However, it remains possible that the seemingly contradictory findings (elevated hormonal response and reduced anxiety) can be explained by the finding that SD can induce locomotor hyperactivity (Albert, Cicala, & Siegel, 1970).

6. Learning and memory

6.1. Memory consolidation

A substantial body of experimental evidence from both humans and rodents strongly suggests that sleep may enhance certain forms of learning and memory (Ellenbogen, 2005; Walker, 2008; Ambrosini & Giuditta, 2001; Poe et al., 2010; Ribeiro & Nicolelis, 2004). More specifically, sleep has been proposed to facilitate “consolidation” of newly learned material into long-term (or reference) memory (Maquet, 2001; Stickgold & Walker, 2007). Consolidation has been referred to as the processing of memory traces during which “the traces may be reactivated, analyzed and gradually incorporated into long-term memory” (Sutherland & McNaughton, 2000), and includes the notion that recently encoded memories are integrated into existing memory networks. Older concepts of sleep and consolidation focused on the idea that memory traces exist in a labile or fragile state, and that post-training sleep facilitates the transfer of these labile memory traces into a more stable, relatively permanent long-term memory (reviewed in McGaugh (2000)). More recent theoretical conceptualizations of memory presume a cyclical process of shifting back and forth between labile and stable states with memory traces being consolidated and reconsolidated over time (Nader & Hardt, 2009; Stickgold & Walker, 2007). We will return to these overarching concepts in the section on synaptic plasticity. Regardless of the specific conceptualization, memory theories which emphasize a cognitive function as the purpose of sleep do not exclude other theories about the function of sleep, such as tissue or metabolic restoration, which emphasizes a return to some optimal level of function. Fig. 4 illustrates the memory concepts and terms used in this review (forms of memory such as iconic memory and subdivisions of implicit memory are not shown). For a more detailed overview of both the conceptual framework and neurobiology of learning and memory the reader is referred to Kandel, Schwartz, and Jessell (2000).

Much of the experimental work with humans has approached sleep and learning/ memory from the viewpoint of assessing the beneficial consequences of sleep for human cognition. Whether or not human memory consolidation occurs during sleep, wakefulness, or both states, may depend on the form of memory being evaluated (e.g., procedural versus

declarative memory). It is also important here to distinguish between two terms that are both associated with the process of consolidation: stabilization and enhancement. While stabilization refers to the resistance of a memory to degradation over time, memory enhancement is hypothesized to occur when memory retention is improved independent of practice. For example, stabilization of a procedural task does not require sleep, but rather it can occur in a time-dependent manner during the wakefulness state (Muellbacher et al., 2002; Walker, Brakefield, Hobson, & Stickgold, 2003). Thus, while certain forms of procedural motor memory can become *stabilized* across periods of wakefulness, most studies illustrating procedural memory *enhancement* require offline processing of information specifically during sleep (Walker, Brakefield, Morgan, Hobson, & Stickgold, 2000; Smith & MacNeill, 1994; Stickgold, James, & Hobson, 2000; Stickgold & Walker, 2007). To date, discriminating memory stabilization from enhancement has received little or no attention in the animal literature.

6.2. Declarative versus implicit memory: human studies

The evidence from human sleep studies reviewed next is consistent with the notion that sleep plays an important role in learning and memory. Whether NREM sleep and REM sleep serve distinct functions in terms of learning and memory is presently unclear. Some evidence suggests that NREM may be more important in the consolidation of declarative/explicit memories, while REM sleep may be particularly important for procedural/implicit forms of memory (Maquet, 2001). Declarative memories require conscious recall while implicit memories do not (e.g., the ability to ride a bicycle). For example, a human declarative memory test using a word pair associate task revealed enhanced recall after periods of nocturnal sleep compared to similar periods without sleep. The interesting observation in this study was that this memory enhancing effect was associated with periods of early night sleep, which is dominated by NREM (Gais & Born, 2004). In contrast, disruption of REM sleep prevented improvement on a visual discrimination implicit memory task, while non-REM slow-wave sleep disruption did not inhibit improvement. Previously well-learned tasks, however, were unaffected by REM sleep deprivation, suggesting the importance of REM sleep for initial consolidation (but not subsequent recall) of implicit memory (Karni, Tanne, Rubenstein, Askenasy, & Sagi, 1994). REM SD can impair human performance on a number of procedural memory tasks (reviewed in Smith (2001)). such as the word fragment completion task (a.k.a. priming), the tower of Hanoi (a nonverbal task that can be performed by patients with hippocampal damage), and the Corsi block tapping test (a hippocampal dependent task). Conversely, performance on declarative tasks was not altered by REM SD in humans.

While numerous reports suggest that REM sleep is especially important for implicit memory, a number of discrepant findings have called this association into question. For example, retention of performance on the pursuit rotor task (an implicit procedural memory task) was impaired to a significantly greater extent when sleep deprivation occurred during the first half of the night when NREM sleep predominates, but not when subjects were selectively deprived of REM sleep (Smith & MacNeill, 1994). These authors emphasized the importance of Stage 2 NREM sleep rather than REM sleep. Huber, Ghilardi, Massimini, and Tonini (2004) evaluated subjects on a hand-eye coordination task (i.e., implicit memory) before and after sleep, and observed increases in slow wave activity in the right parietal lobe. The increases in slow wave activity in the first 90 min of sleep were positively correlated with enhanced performance on the hand-eye coordination task the next day. Thus, while REM sleep has been shown to facilitate consolidation of implicit memory in numerous studies (Fischer, Hallschmid, Elsner, & Born, 2002; Karni et al., 1994; Laurey et al., 2001; Maquet et al., 2000; Plihal & Born, 1997) these studies do not exclude an important role for

NREM SLEEP in implicit memory. Indeed, the two studies above suggest a role for NREM sleep in implicit memory (Huber et al., 2004; Smith & MacNeill, 1994).

The results of many human studies (reviewed in Rauchs, Desgranges, Foret, and Eustache (2005), Ellenbogen, Payne, and Stickgold (2006), Maquet (2001), Stickgold and Walker (2007), and Walker (2009)) are consistent with the notion that NREM SLEEP may be more beneficial for performance on declarative memory tasks. Here too, however, debate has been stirred by contradictory findings. For example, Mandai, Guerrien, Sockeel, Dujardin, and Leconte (1989) trained subjects in Morse code before sleep and retested them following awakening. They observed an increase in both the amount of REM sleep as well as in the number of REM sleep episodes in the subjects who underwent Morse code training. A number of studies have reported impairments in the retention of words, word-pairs, sentences, and prose passages following selective REM SD (all declarative memory tests; reviewed in Rauchs et al. (2005)). How are we to account for these discrepant findings? One explanation is that the tasks discussed above are probably not “pure” declarative memory tasks. While recall of Morse code may well tax declarative memory systems, it is also likely to require a significant procedural memory component, which is one form of implicit memory. Another potential explanation for the discordant findings is that tasks typically employed to assess a particular type of memory do not always fit all the originally stated criteria for that type of memory. For example, word-pair recall tasks are often considered to be a test of episodic, declarative memory although they include an implicit memory component.

In the human literature, declarative memory is subdivided into semantic memory and episodic memory (see Fig. 4). Semantic memory involves the ability to be aware of certain information about the world without any personal recollection of an event (e.g., we know the difference between dogs and cats and can classify animals appropriately, though we do not remember when or where we first learned this distinction). Episodic memories, as originally defined, require the ability to mentally recall and re-live a past experience/memory. Using this criterion, the word pair test might not necessarily, or purely, tax episodic memory. Rauchs et al. (2005) proposed that the discrepant findings in the sleep and memory literature may stem from the theoretical memory classification system that each investigator applies. Most research relating sleep stages to memory systems begins with the assumption that the distinction between declarative and non-declarative memory is critical. However, Tulving’s model (1995) does not organize memory systems in this manner. In Tulving’s SPI system, four long-term memory systems are proposed (i.e., procedural memory, perceptual representation memory system, semantic memory, and episodic memory). This model states that encoding into episodic and semantic memory is Serial, storage is Parallel, and retrieval is Independent (hence, the SPI system). According to this model, episodic memories are first encoded into semantic memory before being processed in systems mediating episodic memories. Rauchs et al. (2005) contend that the focus on the dichotomy between declarative and non-declarative memory may be the source for some of the contradictory findings in the literature and that Tulving’s model may fit the existing data more closely. Whether this is true or not, the discussion does illustrate how the different assumptions of each memory classification system can influence the conclusions derived from experimental findings in sleep and memory studies. While the notion of multiple memory systems is widely accepted and supported by the available evidence, there is no consensus on the number, or the organization, (i.e., serial, parallel, hierarchical) of these memory systems. Hence, an understanding of the relationship of particular sleep stages to memory systems depends, to some extent, on the theoretical model of memory that one adopts.

Whether episodic memory can be demonstrated in a nonverbal rodent model, even in principle, is uncertain. The learning and application of a rule in most learning/memory tests

can be considered a form of semantic memory, but episodic memory has the additional criterion of consciously recollecting specific events from one's past. An attempt has been made to operationally define episodic memory in nonverbal species as memory for when and where an event occurred, for the order in which the events occurred, or memory for an animal's own behavior. While certain features of episodic memories have been demonstrated, for example, in rats, birds, and monkeys, no one has yet conclusively demonstrated an episodic memory in a nonverbal species (reviewed in Hampton and Schwartz (2004)).

In contrast to hypotheses that posit that REM sleep and NREM help form specific types of memory, the sequential hypothesis suggests that NREM and REM sleep are both important for processing of memory traces, with NREM sleep (more predominate in the first half of the night) being more important for the early encoding process, and with REM sleep (more prevalent in second half of the night) being more important to the final stages of consolidation (Ambrosini & Giuditta, 2001). Indeed, some electrophysiological and molecular evidence suggests that NREM mediates the post-acquisition neuronal reverberation, whereas REM sleep triggers protein transcriptional events that facilitate long-lasting memory storage (reviewed in Ribeiro and Nicolelis (2004)). Related behavioral findings indicate that the overnight improvement on a visual discrimination task found in human subjects was proportional to both the amount of NREM sleep in the first quarter of the night, as well as to the amount of REM sleep in the last quarter of the night (with a total of 8 h sleep; Stickgold, Whidbee, Schirmer, Patel & Hobson, 2000).

6.3. Animal studies of the sequential hypothesis

More direct evidence for the sequential hypothesis described in the human literature above comes from an interesting series of studies of rats trained on a 2-way active avoidance task (i.e., avoidance of electric foot shock). Based on initial performance, rodents were classified as fast learners or non-learners. The essential finding was a lengthening of NREM sleep duration among fast learners observed during sleep sequences that transitioned from NREM to REM sleep. In contrast, the non-learners exhibited an increased duration of NREM during sleep sequences that transitioned from NREM to Wakefulness (Ambrosini, Langella, Carnevale, & Giuditta, 1992; Langella, Colarieti, Ambrosini, & Giuditta, 1992). The post-training modifications in NREM sleep among fast learners could not be accounted for by changes in the amount of SD. Adaptive behavioral responding favored fewer NREM to Wake episodes, and more numerous NREM to REM sleep episodes with longer REM sleep episodes. Conversely, non-adaptive behavioral responding was characterized by more numerous NREM to Wake episodes of longer duration. Ambrosini and Giuditta (2001) suggesting that memory traces may be destabilized during NREM to Wake episodes, resulting in clearing of nonessential information from the brain. On the other hand, adaptive memory traces may be transiently destabilized during NREM to REM sleep episodes, to be stored again or reconsolidated (i.e., integrated with pre-existing memory traces) during ensuing REM sleep episodes. These data and ideas are more consistent with newer cyclical notions of consolidation and reconsolidation of memory traces, and less consistent with older notions of memory consolidation as a static unidirectional, and unchanging process.

6.4. Rodent studies of reference memory

Studies on the importance of sleep for memory processing generally focus either on the importance of sleep for initial learning or encoding (i.e., acquisition) of memories, or on the importance of sleep for memory consolidation (after the initial learning). The basic approach is to assess cognitive/behavioral impairments following experimentally controlled disturbances of sleep that occur either before, or after, the initial training. A number of studies have documented both the effect of pre-training sleep disruption on learning, as well

as the effect of post-training sleep disruption on memory. Total SD for 72 h has been shown to slow initial acquisition of spatial learning in the water maze, a hippocampal-dependent task (Ruskin, Dunn, Billiot, Bazan, & LaHoste, 2005). In this study, surgical removal of the adrenal glands (with corticosterone replacement to normal, non-stressed levels) did not significantly alter water maze performance, suggesting that the observed deficits in learning following sleep deprivation were not secondary to the adrenal stress response. As few as 6 h of SD has been shown to impair memory (24 h after the last training trial) for the hidden platform location in the water maze in Sprague–Dawley (SD) rats (Guan, Peng, & Fang, 2004). SD for the first 5 h post-acquisition has also been shown to impair other hippocampal-dependent tasks such as the contextual fear task (Graves, Heller, Pack, & Abel, 2003).

Sleep apnea is characterized by both sleep fragmentation and intermittent hypoxemia. In a seminal study, Gozal and colleagues found that rats exposed to chronic intermittent hypoxia exhibited spatial learning and memory impairments, and neuronal apoptosis in cortex and hippocampal regions, whereas sleep architecture normalized as early as Day 2 of exposure (Gozal et al., 2001; Row, 2007). Several studies have followed up on these initial findings using similar intermittent hypoxia protocols. It may be intuitive to assume that the neurocognitive deficits reported in apneic patients are due to the reduction of oxygen to the brain (Row, 2007) since acute exposure to low oxygen levels (e.g., at high altitude) can produce cognitive impairments (Maiti, Singh, Mallick, Muthuraju, & Ilavazhagan, 2008). However, a human functional imaging study suggested that memory deficits exhibited in patients with sleep apnea may be due to the sleep fragmentation, not nocturnal hypoxia (Thomas, Rosen, Stern, Weiss, & Kwong, 2005). Since the impact of sleep fragmentation on cognition cannot be easily separated from the effects of intermittent hypoxia which co-occur in apneic patients, one study conducted a head-to-head comparison of 24 h of SF to an equal duration of exposure to intermittent hypoxia in separate groups of rats. A 24 h of SF placed after the acquisition training significantly impaired memory, but 24 h of intermittent hypoxia had no effect on spatial learning and memory. However, a longer duration of intermittent hypoxia exposure (3 days; 10 h/day replicating previous findings) did produce impaired performance during spatial memory acquisition in rats (Ward, McCoy, et al., 2009).

While Gozal and colleagues have studied intermittent hypoxia, other investigators have focused on modeling the fragmented sleep (SF) that characterizes sleep apnea. Parenthetically, it should be noted that there are rat strain differences (Harker & Wishaw, 2002), as well as differences in results due to the particular learning protocol (Ward, McCarley, & Strecker, 2009). Nonetheless, deficits in spatial learning and memory (using the water maze) have been observed following SF in various rat strains and using various protocols. In Sprague–Dawley rats, 24 h of SF placed prior to water maze training impaired both learning and recent (30 min) memory for the hidden location (Tartar et al., 2006). In contrast, the Fischer/Brown Norway rat strain, which is considerably more proficient on a range of behavioral tests, exhibited no deficits in performance when the 24 h of SF was placed before the training phase. However, when the 24 h of SF was placed after training, but prior to a memory test 24 h later, the spatial memory of the Fischer/Brown Norway rats was significantly impaired (see Fig. 5). These findings were interpreted to indicate that spatial memory consolidation is more susceptible to the effects of sleep disruption than is the acquisition (learning) of spatial information (Ward, McCoy, et al., 2009). This finding has been difficult to replicate in Sprague–Dawley rats because even control rats show poor 24 h recall of the water maze platform location. Optimal consolidation of memory on other tasks, such as contextual fear conditioning, has also been shown to depend on intact sleep after training (Graves et al., 2003). When water maze training trials are massed together (Ward, McCarley et al., 2009) rather than separated into blocks by 30 min rest periods (Ward, McCoy, et al., 2009), 24 h of SF *before* training did disrupt memory for the hidden

platform location 24 h after the last training trial in Fischer/Brown Norway rats. Thus, while the specific deficits may vary depending on the rat strain, the learning protocol employed, and other factors, the observation of clear behavioral impairment under a wide range of conditions indicates that SF-induced performance deficits in experimental models are robust.

While some investigators have focused primarily on the behavioral effects of SF, Smith and colleagues have conducted a series of experiments in rodents on the effects of REM SD on learning and memory. Smith and colleagues (1996, 1998) investigated whether there is a critical “window” of time after rats learn a spatial task in which REM sleep is critical for optimal memory formation. Using the 8-arm radial maze deficits in spatial reference memory following 4 h of REM SD using the flower pot method were observed (Smith, Conway, & Rose, 1998), indicating that REM sleep immediately after training was critical for optimal reference memory formation. Selective deprivation of REM sleep had a somewhat different effect on water maze performance. When trained daily for 4 consecutive days in the water maze, Smith and Rose (1996) found that as little as 4 h of REM SD presented after training on Day 1 was sufficient to impair acquisition (i.e., longer latencies to reach hidden platform) on Day 2. In this study, the critical window of time during which REM sleep was necessary for optimal acquisition in the water maze was 5–8 h post-training. Such time-dependent sleep disturbances would not likely result from a nonspecific stress response to the manipulation.

Smith et al. (1998) also observed deficits in spatial reference memory following 4 h of REM SD using the 8-arm radial maze, though the window was different (i.e., REM sleep immediately after training was critical for optimal performance). These results were unlikely to be caused by secondary stress (associated with the flower pot technique) since more extended (12 h) periods of REM SD had little effect on task performance. However, the importance of REM sleep in the consolidation of spatial reference memory of rodents remains controversial since the findings described in the literature are inconsistent (reviewed in Walsh, Booth, and Poe (2011)). These inconsistencies may reflect the following: (1) the difficulties associated with reproducible use of the flower pot technique, (2) the fact that the period of time in which memory consolidation is vulnerable to impairment by REM SD is relatively small (Smith, 1995), and (3) the use of different measures in the various studies. For example, the findings of a recently published study clearly seem to contradict earlier reports describing the importance of REM sleep on spatial memory consolidation (Walsh et al., 2011).

6.5. Rodent studies of working memory

Unlike declarative reference/spatial memory discussed above, ‘working memory’ has been defined by Baddeley (1996) as “a limited capacity system that is capable of storing and manipulating information.” The components of the working memory system allow for the exchange of information between perception, attention, memory, and action (Baddeley, 1996; Baddeley & Hitch, 1974). The Baddeley and Hitch (1974) model of working memory was derived from studies on humans. Investigators who use rodents as experimental subjects often differentiate working memory from reference memory operationally. In this respect, working memory tasks are those which require temporary storage and utilization of information from immediately preceding trials. In contrast, reference memory tasks are those which require the animal to retain and utilize information across trials (Domjan, 2000). Honig (1978) and Olton, Becker, and Handelman (1979) proposed a model of working memory, that was derived from experiments on pigeons and rats, respectively. While both the Baddeley and Hitch model and the Honig/Olton model emphasizes that information in working memory is maintained on-line for brief periods of time, the Honig/Olton model also stressed the importance of forgetting information from the previous trial, lest it interfere proactively with performance on the next trial. While the human-based Baddeley and Hitch

model focused on the role of brain structures associated with language and visual imagery, the animal-based Honig/Olten model led to theories and research on the critical role of the hippocampus, and later the dorsolateral prefrontal cortex, in working memory. The two models are not mutually exclusive, and both have contributed to our understanding of working memory (see review by Becker and Morris (1999)).

While certain tests may tax working memory, it may not be possible to completely separate working memory from reference memory in any given test (Becker & Morris, 1999). In the radial arm maze, for instance, working memory is required for rodents to remember which arms they have recently visited within a given trial. However, rodents must also consolidate and access certain “rules” from reference memory; namely, rodents must remember that food is at the end of the arms and that running to the end of the arms is required to obtain it. In the case of the water maze, a delayed matching (or nonmatching) to position task is often used to assess working memory as this protocol may tax working memory to a greater extent than reference memory. Standard water maze protocols are thought to rely primarily on reference memory in which the hidden platform location is held constant across trials. By contrast, the delayed matching-to-position (DMP) water maze protocol involves exposure to pairs of trials. Each pair consists of an “information swim” followed by a test swim (Ward, McCarley et al., 2009). In this case, rodents initially swim to a platform in a novel location that is visibly cued with a flag. On the paired test trial, 1 to 10 min later, rodents must swim to the same location, which is now hidden beneath the water surface. The platform is placed in a novel location with each new pair of trials, but held constant within a trial pair. An advantage to this DMP protocol is that one can assess the limits of the working memory system by manipulating the inter-trial interval (e.g., 1, 5, or 10 min) between the first and second swims in each pair. Here too, the measure of working memory is not “pure.” The animal must consolidate and recall a “rule;” namely, escape from the water is possible by going to the same location (or opposite location in the case of non-matching-to-position) where the platform was located on the first information-containing swim.

A number of behavioral tasks have been utilized to assess working memory in rodents, including alternation in a Y- or T-maze, within trial re-entries in the radial arm maze, and variants of the standard water maze protocol, such as a delayed matching (or non-matching)-to-position task (see Hodges (1996) for a review). Standard (allocentric) water maze training largely employs spatial processing and is therefore highly dependent on intact hippocampal circuitry. The frontal cortex appears important for tasks that require cognitive or behavioral flexibility, such as attentional set-shifting, reversal learning, or delayed alternation tasks (Holmes & Wellman, 2009). A delayed-non-matching-to-position task was utilized to assess frontal lobe function in rats (i.e., platform placed in alternating quadrants of the maze). Relatively short (4–8 h) durations of REM SD before training significantly impaired water maze performance on the delayed alternation task, but not the standard water maze protocol (Beaulieu & Godbout, 2000; Le Marec, Beaulieu, & Godbout, 2001). Lesions to the medial prefrontal cortex resulted in a similarly selective deficit in delayed alternation (Ethier, Le Marec, Rompre, & Godbout, 2001). These investigators interpreted these results to suggest that frontal cortical circuitry is more sensitive to short-term REM SD prior to training for tasks that require cognitive flexibility compared to spatial memory tasks that are dependent on hippocampal function.

6.6. Rodent studies of working memory compared to reference memory

Using the DMP protocol discussed above, investigators have found that 24 h of SF had no significant effect on working memory (i.e., no difference in the mean latency and distance to find the hidden platform on the DMP task) but did significantly impair spatial reference memory (Ward, McCarley et al., 2009). Other similar variations of the standard water maze task have been used to differentiate between effects of sleep disruption on working versus

reference memory. In one such variation, rats were trained for consecutive days. On each day, rats received six sets (i.e., pairs) of trials separated by 25 min rest periods (Youngblood et al., 1997). Each set consisted of back to back swims. The position of the platform changed each day but remained in the same position for all six sets on any given day. Spatial learning is then defined as the decreased latency (i.e., improved performance) to reach the platform on Trial 1 (reference memory) or Trial 2 (working memory) of successive sets. Using this protocol, Youngblood et al. (1997) observed deficits in spatial reference memory (but not working memory) in rats that were deprived of REM sleep over the 4 days using the “flower pot” technique. This technique requires that rodents to be housed on small platforms over water. Rodents fall into the water and are awakened primarily when they lose muscle tone (i.e., during REM sleep). These data are consistent with the data of Ward, McCarley et al. (2009) on working versus reference memory. Both suggest that spatial reference memory may be more sensitive to sleep disruption than is working memory.

6.7. Animal studies: limitations

A final cautionary note is in order here. The assessment of cognitive function in sleep-disrupted rodents is beset by the same sorts of interpretational problems as in other areas of behavioral neuroscience. It may appear on the surface that the only viable interpretation for the failure of a rat to find a submerged platform in a water maze is a defect in memory. As such, the face validity of this task is often good. However, predictive and construct validity for particular tests in animals are often lacking or questionable (see Sarter (2004) for a review). The translation of variables studied in human cognitive psychology to animal testing is rife with potential complexities of this nature (Gerlai, 2001), and will likely continue to be a source for discussion and debate. Such discussions prompt detailed analyses of the behavioral tasks themselves (Blockland, Geraerts, & Been, 2004), which in turn may lead to positive refinements in both methodology and interpretation.

7. Neurobiological mechanisms: synaptic plasticity and memory

Enduring changes in the efficiency of synaptic neurotransmission in specific neurons lies at the heart of modern theories of memory formation. Inputs from multiple sensory systems converge in the hippocampus, a central location for the encoding of information concerning events and experiences. Theoretically, these labile “memory traces” then become “consolidated” gradually into a more stable form which is stored in a distributed form throughout the neocortex (McGaugh, 2000). Re-experiencing a memory is then thought to involve reactivation of these connections. Experience and time-dependent alteration in synaptic transmission during sleep does not, by itself, necessitate a role for sleep in memory formation.

7.1. Hebbian conditions for synaptic plasticity

Long before the discovery of long-term potentiation (LTP), Donald O. Hebb (1949) proposed a set of necessary and sufficient conditions for the consideration of a neural model system of memory. A coherent representation of a preceding experience must be represented by alterations in neural efficacy between neurons. Not only should neurons involved in forming associational memory exhibit specificity (i.e., not just sensitization), but they should also be characterized by additional properties such as cooperativity (i.e., synchronized firing resulting in the strengthening of specific synapses), and relative permanence (Hebb, 1949). In fact, some of these Hebbian properties have been shown to be reenacted during sleep. For example, hippocampal CA1 pyramidal place cells, which are known to fire together when an rat occupies a specific spatial location (O’Keefe and Dostrovsky, 1971), were also found to fire together during subsequent sleep (Pavlides & Winson, 1989). Moreover, cells that were not active during wake, or that were active but had non-overlapping spatial patterns of

firing, did not show increased firing during subsequent sleep (Wilson & McNaughton, 1994). In another study, the replay of hippocampal neuronal discharge exhibited a pattern that was found to reflect the temporal order in which these cells fired initially during waking exploration (Skaggs & McNaughton, 1996).

7.2. Neuronal replay and consolidation in NREM sleep

A putative mnemonic system must be capable of encoding information both spatially (i.e., firing of place cells when the rat is in a specific location) and temporally (i.e., information concerning the sequential order of events). Hence, reactivation of these neuronal ensembles during sleep is postulated to represent the “consolidation” of labile memories into more stable forms (McGaugh, 2000). This reactivation of hippocampal neurons is referred to as ripples, high frequency oscillations that occur during slow wave sleep (Chrobak, Lorincz, & Buzsaki, 2000). In the case of NREM sleep, the ripple oscillations have a relatively short time scale, along the order of milliseconds to seconds immediately following experience or behavior (Siapas & Wilson, 1998), suggesting that perhaps this form of reactivation reflects initial encoding of information (i.e., an early stage of memory consolidation).

7.3. Neuronal replay and consolidation in REM sleep

Some efforts to detect short timescale mnemonic activity during REM sleep had failed to obtain evidence of neuronal replay (reviewed in Kudrimoti, Barnes, and McNaughton (1999)), suggesting to some (Crick & Mitchison, 1983) that REM sleep may play a general homeostatic role, rather than a specific role is memory consolidation. However, Louie and Wilson (2001) were successful in obtaining evidence of replay of hippocampal ensemble activity during REM sleep. Rats were implanted with microelectrode arrays to record multiple single cell activity from CA1 region of hippocampus during waking task performance (rats had been previously trained to run along a circular track for food reinforcement), as well as during periods of sleep immediately before and after behavior. Replay of hippocampal ensemble activity during REM sleep was much longer (i.e., on the order of tens of seconds to a minute) than replay recorded during NREM, with the duration of replay during REM sleep comparable to that during waking task performance. Thus, neuronal replay during REM sleep may reflect neocortical activation of hippocampal circuits during a later stage of the memory consolidation processing (Hennevin, Hars, Maho, & Bloch, 1995; Stickgold et al., 2000). Additionally, behavior-dependent modifications of subcortically-driven theta rhythms are also reproduced during REM sleep. The existence of replay of hippocampal ensemble activity during REM sleep leads to speculation concerning the information content in dream states (note that dreams have been linked to REM sleep) and its potential significance in memory processing, perhaps especially for procedural memory, which evidence indicates is REM sleep-dependent (Karni et al., 1994).

7.4. Memory reconsolidation theory

While there is not complete agreement among the sleep research community (Vertes, 2004), many investigators support the theory that uninterrupted sleep occurring after learning facilitates consolidation of new information into long-term (or reference) memory. As noted above, replay of different neuronal ensembles during NREM and REM sleep (activated initially during waking experience) may respectively represent early and late phases of “consolidation” of labile memories into more stable forms. Historically, the term “memory consolidation” has referred to those processes (both known and inferred) that collectively convert initial, transient memory traces to a permanent or stable memory representation (i.e., reference memory) that is resistant to degradation. Experimental studies on memory consolidation have employed manipulations, such as electroconvulsive shock, intended to interfere with consolidation (McGaugh, 2000). From these studies, it has been inferred that under favorable conditions, consolidation could be complete within a relatively short time

frame (i.e., from minutes to hours). This static conceptualization of memory consolidation has been revised in recent years in light of new data demonstrating that consolidation/stability of long-term memories should be understood in relative terms. For example, a memory trace can be destabilized, making it temporarily more susceptible to either interference or to refinement, by returning subjects to their initial learning environment (i.e., memory reactivation) or by having humans repeat a task that they have previously mastered (Nader, 2003; Stickgold & Walker, 2007). Thus, current data support the concept that consolidation is not an all-or-none phenomenon, but rather a cyclical process that vacillates between consolidation, destabilization, and reconsolidation.

7.5. Memory reconsolidation experimental data

An elegant experimental demonstration of memory instability and reconsolidation was performed by Nader, Schafe, and Le Doux (2000). These investigators infused the protein synthesis inhibitor anisomycin into the lateral and basal nuclei of the amygdala (LBA) of rats shortly after training on a classically conditioned fear task. Consolidated fear memories, when reactivated during retrieval, returned to a labile state in which infusion of anisomycin shortly after memory reactivation produced amnesia on later tests. However, when the fear-based memory was not reactivated, anisomycin had no effect on memory (i.e., memory was intact). Thus, *de novo* protein synthesis was critical for reconsolidation in this experiment. Traditional conceptions of memory consolidation cannot easily explain the reinstated period of vulnerability, or other similar recent experimental findings (see Nader and Hardt (2009) for a review).

7.6. Consolidation and reconsolidation

Of course, if useful information is to be retained and used to guide behavior, then this period of destabilization, estimated to last as long as 5–6 h (Nader & Hardt, 2009; Nader et al., 2000), must eventually be followed by reconsolidation and re-stabilization of the reference memory. If the memory is not reconsolidated, then degradation of the memory will ensue. Studies have shown that previously learned behaviors remain intact when reconsolidation is blocked for at least 2–4 h (Duvarci & Nader, 2004), followed by a period of degradation that appears to be complete within 24 h (Myers & Davis, 2002). Thus, the time course of memory processing after learning now appears to be much longer than predicted in older theories of memory consolidation; the picture that emerges is of a highly malleable process, with notions of continual reorganization of brain circuits reflecting continual refinement of new information into existing memory traces. Memory consolidation and reconsolidation are assumed to be automatic processes, and would therefore exclude such conscious, effortful activities as behavioral or mental rehearsal (Stickgold & Walker, 2007). In this mnemonic model, consolidation occurs after initial encoding of information, but prior to the recall of that information while reconsolidation refers to all on-going memory processing that occurs after initial recall. The newer models of memory consolidation are entirely consistent with the realization that adult hippocampal (and some cortical) neurons engage in experience-dependent synaptic alterations and neurogenesis (discussed below; see Deng, Aimone, and Gage (2010) for a review). At least certain structures engage in ongoing structural reorganization during adulthood and, as it turns out, the structure that most reliably induces synaptic reorganization and neurogenesis is the structure most widely implicated in memory formation, namely, the hippocampus. If this supposition is correct, then procedures that disrupt sleep might be expected to affect synaptic plasticity and reorganization of neural circuits in deleterious ways, resulting in partial or incomplete consolidation of newly learned information into reference memory. This might then be detected in the form of impaired behavioral performance on tasks requiring intact reference memory, or in electrophysiological measures of synaptic efficiency.

7.7. Synaptic efficacy: LTP and LTD

Long-lasting changes in hippocampal synaptic efficacy can be induced experimentally using procedures called long-term potentiation (LTP) and long-term depression (LTD) preparations are largely accepted as the principle cellular mechanisms underlying memory formation. Inhibition of long-term synaptic plasticity from hippocampal CA1 and dentate gyrus regions has been reported following SD (Campbell, Guman, & Horowitz, 2002), selective REM SD (Davis, Harding, & Wright, 2003; McDermott et al., 2003), and SF (Tartar et al., 2006). The Tartar et al. (2006) sought to examine the alterations in synaptic efficacy that underlie cognitive impairments associated with SF by assessing changes in hippocampal LTP, LTD, and paired-pulse facilitation (PPF). Hippocampal LTP was found to be absent in rats exposed to 24 or 72 h of SF, whereas LTD and PPF were unaffected (Tartar et al., 2006). The elimination of hippocampal LTP was not due to exercise or stress induced by the SF protocol, as rats experiencing the same amount of treadmill movement (movement controls) exhibited normal LTP (see Fig. 6). In addition, this study found that hippocampal-dependent spatial learning and/or memory in the water maze was impaired by 24 h of SF; specifically, in the strain of rats used for electrophysiological experiments (Sprague-Dawley), 24 h of SF impaired spatial learning and short-term (30 min) memory retention (Tartar et al., 2006). As noted previously, the particular type of impairment (i.e., acquisition versus retention) is dependent on rat strain, water maze protocol, and whether the sleep disruption occurs before or after learning/acquisition. Selective deprivation of REM sleep has also been found to diminish hippocampal LTP (Davis et al., 2003; McDermott et al., 2003). However, it is unlikely that the reduction of LTP in rodents exposed to SF is due solely to the deprivation of REM sleep, as the reduction in LTP following 24 h of SF was more pronounced than the reduction in LTP associated with REM SD (Davis et al., 2003). Nor is it likely that the SF-induced elimination of LTP was due solely to stress, since increases in plasma corticosterone are observed in both the SF and movement control groups, while reduction of LTP was observed only in rats exposed to SF (see Fig. 6; Tartar et al., 2006). Low or moderate elevations of corticosterone can, in fact, improve hippocampal LTP (Diamond, Bennett, Fleshner, & Rose, 1992). However, in the Tartar et al. (2006) hippocampal LTP was eliminated in all rodents exposed to SF, whereas corticosterone responses to SF were found to be highly variable between subjects.

7.8. Potential mechanisms of the SF-induced LTP impairment

A subsequent study employed whole cell patch clamp recordings to investigate possible adenosinergic mechanisms underlying the SF-induced impairment of hippocampal LTP and spatial learning and memory (Tartar et al., 2009). Based on the finding that 24 h of SF elevates adenosine levels in the basal forebrain and increases sleepiness (McKenna et al., 2007), Tartar et al. (2009) hypothesized that the SF-induced impairment of LTP may be mediated by increased adenosinergic tone. This prediction was also supported by evidence that prolonged sleep loss upregulates adenosine A1 receptors (Basheer, Bauer, Elmenhorst, Ramesh, & McCarley, 2007; Elmenhorst et al., 2007) which should result in an increased electrophysiological response to adenosine or adenosine receptor agonists. In contrast to the prediction, Tartar et al. (2009) found a reduction in the hyperpolarizing response to bath applied adenosine (30 μ M) in the hippocampal CA1 neurons of SF-exposed rats. These findings ruled out the possibility that SF-induced reduction of LTP was mediated by an upregulation of hippocampal adenosine A1 receptors. Supportive of this conclusion is recent evidence that sleep deprivation does not significantly increase adenosine A1 receptor binding in the hippocampus of humans (Elmenhorst et al., 2007). However, there was evidence that 24 h SF decreased the excitability of hippocampal CA1 pyramidal neurons via decreased input resistance, without altering other intrinsic membrane or action potential properties (Tartar et al., 2009). These results suggest that the loss of hippocampal LTP and deficits in spatial learning and memory following 24 h SF may be due, at least in part, to a

reduction of the intrinsic excitability of CA1 pyramidal neurons. Other investigators (Yang et al., 2008) have also observed changes in membrane excitability as well as in mitochondrial protein that accompany water maze impairments associated with sleep disruption (i.e., 72 h of selective REM SD, in the Yang et al. (2008) study).

7.9. Hippocampal synaptic alterations and neurogenesis

Rather than electrophysiological changes within hippocampal neurons, another way to approach sleep and plasticity is by evaluating the synaptic alterations (synaptogenesis and synaptic pruning), proliferation, and/or survival of hippocampal neurons. Exposure to 96 h of SD was found to inhibit adult hippocampal neurogenesis (Mueller et al., 2008). More specifically, cell proliferation within the dentate gyrus was reduced by up to 50% in SD rats, compared to apparatus control or home cage control rats. These results support a significant effect of sleep on neural plasticity. Moreover, this effect was also observed in adrenalectomized rats that were maintained via subcutaneous minipumps on continuous low dose corticosterone replacement. Hence the effect of sleep loss on adult neurogenesis was independent of adrenal stress hormones (Mueller et al., 2008). Other investigators have evaluated the effect of chronic sleep restriction on neurogenesis and cognitive performance. In one study, rodents were trained on a 4 day protocol in the water maze on either a spatial (hippocampal-dependent) task or a non-spatial task. Consistent with other reports, these authors reported increased rates of survival of newborn cells from rats trained on hippocampus-dependent learning tasks in comparison to survival rates of cells from rats trained on a hippocampus-independent task (Hairston et al., 2005). Half of the rats were kept awake through exposure to novel objects for 6 h/d for 4 consecutive days. Sleep restriction selectively impaired spatial maze learning and abolished the increase in neurogenesis typically found in rats trained on the spatial water maze task (Hairston et al., 2005). Although corticosterone levels were increased following this method of sleep restriction, a reliance on stress as the sole explanation for the impairment is problematic. Training rats in a spatial water maze task has been found to increase corticosterone levels (Sandi, Loscertales, & Guaza, 1997), but also to enhance the rate of cell proliferation and survival of hippocampal neurons (Ambrogini et al., 2000). One would expect a suppression of hippocampal neurogenesis if cognitive impairments were due to secondary stress. Thus, one can conclude that post-learning sleep contributes significantly to experience-induced neurogenesis and the subsequent enhancement of cognitive performance.

7.10. Subcellular mechanisms of hippocampal LTP

A massive data base exists on protein kinases, transcription factors, and other molecules known to regulate memory-related gene expression and protein synthesis (for reviews see Kandel et al., 2000; Morgado-Bernal, 2011; Poe et al., 2010). Thus, this body of literature serves as a reference point for sleep investigations. Localized to cell bodies, dendrites and synapses in neurons, extracellular signal-related kinase (ERK) has been shown to be activated by the induction of LTP (Guan et al., 2004) and necessary for memory formation (Orban, Chapman, & Brambilla, 1999). Decreases in ERK phosphorylation and impairment of spatial memory have been reported from the hippocampus of rats that have been exposed to 6 h of SD (Guan et al., 2004). Sleep deprivation has also been shown to increase levels of the cytokine Interleukin-1 β (IL-1 β) from the hippocampus (Guan & Fang, 2003). In turn, IL-1 β is a potent stimulator of Interleukin-6 (IL-6), which is known to inhibit ERK phosphorylation in the hippocampus (Tancredi et al., 2000). Additionally, IL-1 β inhibits cholinergic inputs to the hippocampus and inhibits acetylcholine release (Rada et al., 1991). Sleep deprivation also activates Nuclear Factor Kappa B (NF κ -B), in BF cholinergic neurons (Ramesh, Basheer, Thatte, & McCarley, 2002). In turn, NF κ -B mediates a variety of responses to IL-1 β (Guan et al., 2004). These BF cholinergic neurons express adenosine A1 receptors, and adenosine levels in BF rise with extended periods of wakefulness.

(McKenna et al., 2007). Thus, the reduction of ERK phosphorylation in hippocampus may be associated with the suppression of cholinergic function that is a consequence of sleep deprivation. Investigations into the molecular mechanisms which mediate cognitive deficits associated with sleep disruption are still in their infancy. It is likely that the form of neural changes that occur in any given situation will depend on many factors, including the type of sleep disruption (SD, SF REM SD, etc.), the duration of the sleep disruption, the particular learning/memory test, and whether the sleep disruption precedes, or follows, initial training on the behavioral test.

8. Summary and future directions

Animal models of human patterns of sleep disturbance are necessary to begin to probe the neurobiological mechanisms linking the sleep disturbances to their effects on cognition and emotion. Rodent models of four specific types of sleep disturbance were reviewed herein: sleep deprivation, experimental sleep fragmentation, selective REM SD, and chronic sleep restriction. In man, sleep disruption alters almost all behavioral and neurocognitive domains studied to date (see recent reviews by Balkin et al. (2008) and Killgore (2010)). Rodents have been used to characterize the effect of sleep disturbance on many of these neurocognitive domains including the following: sleep/sleepiness, attention/vigilance, executive function, emotional reactivity, learning and memory (explicit, implicit, and working memory), sensory perception (May et al., 2005; Schaffery et al., 1998) and individual differences. For some cognitive domains that are altered by sleep disruption in man, rodent models are unlikely to become available (e.g., humor appreciation, morality, judgment, subjective self report measures), whereas the effect sleep deprivation has not been thoroughly studied in rodents in some domains for which behavioral tests exist (e.g., risk taking behavior, decision making, and motor tracking).

Two experimental tasks were described that evaluate effects of sleep disturbance on sustained attention (vigilance): the 5-choice serial reaction time test (5-CSRT) and the psychomotor vigilance test (PVT). Impairments in sustained attention following various durations of total sleep deprivation have been detected using both tests. Evidence from the rat PVT provides support for the hypothesis that the SD-induced impairment in sustained attention is mediated by adenosinergic inhibition of the vigilance-promoting basal forebrain neurons that project to the cortex.

Impairments in executive function are observed in humans diagnosed with sleep apnea, as well as other disorders involving sleep fragmentation. One component of executive function, attentional set-shifting, has been studied in rats exposed to experimental sleep fragmentation, revealing a selective deficit in the ability to shift attention from focusing on one sensory aspect of the test stimuli to a different sensory modality. Emotional reactivity and stress are also impacted by sleep disruption. Experimental methods used to produce sleep disruption in rodents can produce significant increases in plasma corticosterone. However, experiments on adrenalectomized rodents, and other evidence reviewed above, suggests that the emotional and cognitive deficits associated with sleep disruption are largely independent of these hormonal stress effects.

Finally, a thorough analysis of cognition would not be complete without considering the effects of sleep disruption on spatial/reference learning and memory. Efforts to develop rodent models of learning and memory deficits associated with sleep disturbance have been hampered by strain differences in performance, as well as differences in behavioral protocols used by various researchers. Nonetheless, investigators have now documented significant impairments in learning and memory produced by total sleep deprivation, selective REM SD, and experimental sleep fragmentation. For example, water maze studies

that model the primary characteristics of sleep apnea (intermittent hypoxia and sleep fragmentation) have begun to dissociate the effects of these two characteristics on learning and memory. Moreover, studies have begun to investigate the neurobiological underpinnings of sleep disruption on learning and memory. For example, hippocampal long-term potentiation has been shown to be completely absent in rats that had been exposed to a sleep fragmentation schedule for 24 or 72 h.

An overarching goal of future research is likely to include a more thorough understanding of the neurobiological mechanisms that mediate the effects of sleep disruption on cognition and emotional behavior. Such an understanding would likely lead to new and more effective treatment of the behavioral consequences of a wide range of sleep disorders, as well as the many other diseases in which sleep disturbance is an undesirable symptom.

Acknowledgments

We thank authors of the original work cited, and M. Ali & L. Shifflett for assistance with the figures and editorial advice. The writing of this review was supported by the Department of Veterans Affairs Medical Research Service Award, and by the following grants from the National Institutes of Health: MH039683, HL060292, and HL095491.

References

- Albert I, Cicala GA, Siegel J. The behavioral effects of REM sleep deprivation in rats. *Psychophysiology*. 1970; 6:550–560. [PubMed: 4320883]
- Ambrogini P, Cuppini R, Cuppini C, Ciaroni S, Cecchini T, Ferri P, et al. Spatial learning affects immature granule cell survival in adult rat dentate gyrus. *Neuroscience Letters*. 2000; 286:21–24. [PubMed: 10822143]
- Ambrosini MV, Giuditta A. Learning and sleep: The sequential hypothesis. *Sleep Medicine Reviews*. 2001; 5:477–490. [PubMed: 12531155]
- Ambrosini MV, Langella M, Carnevale UA, Giuditta A. The sequential hypothesis III: The structure of postacquisitional sleep in learning and non-learning rats. *Physiology & Behavior*. 1992; 51:217–226. [PubMed: 1557433]
- Baddeley AD. The fractionation of working memory. *Proceedings of the National Academy of Science*. 1996; 93:13468–13472.
- Baddeley, AD.; Hitch, G. Working memory. In: Bower, GA., editor. *The psychology of learning and motivation*. New York: Academic press; 1974. p. 47-89.
- Balkin TJ, Bliese PD, Belenky G, Sing H, Thorne DR, Thomas M, et al. Comparative utility of instruments for monitoring sleepiness-related performance decrements in the operational environment. *Journal of Sleep Research*. 2004; 13:219–227. [PubMed: 15339257]
- Balkin TJ, Rupp T, Picchioni D, Wesensten NJ. Sleep loss and sleepiness. *Chest*. 2008; 134:653–660. [PubMed: 18779203]
- Banks S, Dinges DF. Behavioral and physiological consequences of sleep restriction. *Journal of Clinical Sleep Medicine*. 2007; 3:519–528. [PubMed: 17803017]
- Basheer R, Bauer A, Elmenhorst D, Ramesh V, McCarley RW. Sleep deprivation upregulates A1 adenosine receptors in the rat basal forebrain. *NeuroReport*. 2007; 18:1895–1899. [PubMed: 18007182]
- Basheer R, Strecker RE, Thakkar MM, McCarley RW. Adenosine and sleep–wake regulation. *Progress in Neurobiology*. 2004; 73:379–396. [PubMed: 15313333]
- Beaulieu I, Godbout R. Spatial learning on the Morris Water Maze Test after a short-term paradoxical sleep deprivation in the rat. *Brain and Cognition*. 2000; 43:27–31. [PubMed: 10857657]
- Becker JT, Morris RG. Working memory. *Brain and Cognition*. 1999; 41:1–8. [PubMed: 10536082]
- Bedard MA, Montplaisir J, Richer F, Rouleau I, Malo J. Obstructive sleep apnea syndrome: Pathogenesis of neuropsychological deficits. *Journal of Clinical and Experimental Neuropsychology*. 1991; 13:950–964. [PubMed: 1779033]

- Beebe DW, Gozal D. Obstructive sleep apnea and the prefrontal cortex; towards a comprehensive model linking nocturnal upper airway obstruction to daytime cognitive and behavioral deficits. *Journal of Sleep Research*. 2002; 11:1–16. [PubMed: 11869421]
- Birrell JM, Brown VJ. Medial frontal cortex mediates perceptual attentional set-shifting in the rat. *Journal of Neuroscience*. 2000; 20:4320–4324. [PubMed: 10818167]
- Blockland A, Geraerts E, Been M. A detailed analysis of rats' spatial memory in a probe trial of a Morris task. *Behavioural Brain Research*. 2004; 154:71–75. [PubMed: 15302112]
- Borbely AA. A two process model of sleep regulation. *Human Neurobiology*. 1982; 1:195–204. [PubMed: 7185792]
- Campbell IG, Guman MJ, Horowitz JM. Sleep deprivation impairs long term potentiation in rat hippocampal slices. *Journal of Neurophysiology*. 2002; 88:1073–1076. [PubMed: 12163556]
- Cappuccio FP, D'Elia L, Strazzullo P, Miller MA. Sleep duration and all-cause mortality: A systematic review and meta-analysis of prospective studies. *Sleep*. 2010; 33:585–592. [PubMed: 20469800]
- Caron AM, Stephenson R. Energy expenditure is affected by rate of accumulation of sleep deficits in rats. *Sleep*. 2010; 33:1226–1235. [PubMed: 20857870]
- Chee MW, Chuah LY. Functional neuroimaging insights into how sleep and sleep deprivation affect memory and cognition. *Current Opinion in Neurology*. 2008; 4:417–423. [PubMed: 18607201]
- Christie MA, Bolortuya Y, Chen LC, McKenna JT, McCarley RW, Strecker RE, et al. Microdialysis elevation of adenosine in the basal forebrain produces vigilance impairments in the rat psychomotor vigilance task. *Sleep*. 2008; 31:1393–1398. [PubMed: 18853936]
- Christie MA, McKenna JT, Connolly NP, McCarley RW, Strecker RE. 24 Hours of sleep deprivation in the rat increases sleepiness and decreases vigilance. Introduction of the rat-psychomotor vigilance task. *Journal of Sleep Research*. 2008; 17:376–384. [PubMed: 19021853]
- Chrobak JJ, Lorincz A, Buzsaki G. Physiological patterns in the hippocampo-entorhinal cortex system. *Hippocampus*. 2000; 10:457–465. [PubMed: 10985285]
- Chugh DK, Weaver TE, Dinges DF. Neurobehavioral consequences of arousals. *Sleep*. 1996; 19(Suppl):S198–S201. [PubMed: 9085510]
- Cordova CA, Said BO, McCarley RW, Baxter MG, Chiba AA, Strecker RE. Sleep deprivation in rats produces attentional impairments on a 5-choice serial reaction time task. *Sleep*. 2006; 29:69–76. [PubMed: 16453983]
- Crick R, Mitchison G. The function of dream sleep. *Nature*. 1983; 304:111–114. [PubMed: 6866101]
- Czeisler CA. Medical and genetic differences in the adverse impact of sleep loss on performance: Ethical considerations for the medical profession. *Transactions of the American Clinical and Climatological Association*. 2009; 120:249–285. [PubMed: 19768182]
- Davis CJ, Harding JW, Wright JW. REM-sleep deprivation induced deficits in the latency-to-peak induction and maintenance of long-term potentiation within the CA1 region of the hippocampus. *Brain Research*. 2003; 973:293–297. [PubMed: 12738073]
- Deng W, Aimone JB, Gage FH. New neurons and new memories: How does adult hippocampal neurogenesis affect learning and memory? *Nature Reviews Neuroscience*. 2010; 11:339–350.
- Desseilles M, Vu TD, Maquet P. Functional neuroimaging in sleep, sleep deprivation, and sleep disorders. *Handbook of Clinical Neurology*. 2011; 98:71–94. [PubMed: 21056181]
- Diamond DM, Bennett MC, Fleshner M, Rose GM. Inverted-U relationship between the level of peripheral corticosterone and the magnitude of hippocampal primed burst potentiation. *Hippocampus*. 1992; 2:421–430. [PubMed: 1308198]
- Dias R, Robbins TW, Roberts AC. Dissociable forms of inhibitory control within prefrontal cortex with an analog of the Wisconsin Card Sort Test: Restriction to novel situations and independence from “on-line” processing. *Journal of Neuroscience*. 1997; 17:9285–9297. [PubMed: 9364074]
- Dinges, DF.; Rogers, NL.; Baynard, MD. Chronic sleep deprivation. In: Kryger, MH.; Roth, T.; Dement, WC., editors. *Principles and practice of sleep medicine*. 4. Philadelphia: WB Saunders Company; 2005. p. 67-76.
- Domjan, M. *The essentials of conditioning and learning*. Belmont, CA: Wadsworth/Thomson Learning; 2000.

- Drummond SP, Bischoff-Grethe A, Dinges DF, Ayalon L, Mednick SC, Meloy MJ. The neural basis of the psychomotor vigilance task. *Sleep*. 2005; 28:1059–1068. [PubMed: 16268374]
- Durmer JS, Dinges DF. Neurocognitive consequences of sleep deprivation. *Seminars in Neurology*. 2005; 25:117–129. [PubMed: 15798944]
- Duvarci S, Nader K. Characterization of fear memory reconsolidation. *Journal of Neuroscience*. 2004; 24:9269–9275. [PubMed: 15496662]
- Ellenbogen JM. Cognitive benefits of sleep and their loss due to sleep deprivation. *Neurology*. 2005; 64:E25–E27. [PubMed: 15824327]
- Ellenbogen JM, Payne JD, Stickgold R. The role of sleep in declarative memory consolidation: Passive, permissive, active or none. *Current Opinion in Neurobiology*. 2006; 16:716–722. [PubMed: 17085038]
- Elmenhorst D, Meyer PT, Winz OH, Matusch A, Ermert J, Coenen HH, et al. Sleep deprivation increases A1 adenosine receptor binding in the human brain: A positron emission tomography study. *Journal of Neuroscience*. 2007; 27:2410–2415. [PubMed: 17329439]
- Ethier K, Le Marec N, Rompre PP, Godbout P. Spatial strategy elaboration in egocentric and allocentric tasks following medial prefrontal cortex lesions in the rat. *Brain and Cognition*. 2001; 46:134–135. [PubMed: 11527312]
- Everson CA, Szabo A. Recurrent restriction of sleep and inadequate recuperation induce both adaptive changes and pathological outcomes. *American Journal of Physiology: Regulatory, Integrative and Comparative Physiology*. 2009; 297:R1430–R1440.
- Fernandez F, Misilmeri MA, Felger JC, Devine DP. Nociceptin/orphanin FQ increases anxiety-related behavior and circulating levels of corticosterone during neophobic tests of anxiety. *Neuropsychopharmacology*. 2004; 29:59–71. [PubMed: 14532912]
- Fischer S, Hallschmid M, Elsner AL, Born J. Sleep forms memory for finger skills. *Proceedings of the National Academy of Sciences of the United States of America*. 2002; 99:11987–11991. [PubMed: 12193650]
- Fox MT, Barense MD, Baxter MG. Perceptual attentional set-shifting is impaired in rats with neurotoxic lesions of posterior parietal cortex. *Journal of Neuroscience*. 2003; 23:676–681. [PubMed: 12533627]
- Fulda S, Shulz H. Cognitive dysfunction in sleep disorders. *Sleep Medicine Reviews*. 2001; 5:423–445. [PubMed: 12531152]
- Fulda S, Shulz H. Cognitive dysfunction in sleep-related breathing disorders: A meta-analysis. *Sleep Res Online*. 2003; 5:19–51.
- Gais S, Born J. Declarative memory consolidation: Mechanisms acting during human sleep. *Learning & Memory*. 2004; 11:679–685. [PubMed: 15576885]
- Gangwisch JE, Heymsfield S, Boden-Albala B, Buijs R, Kreier F, Pickering T, et al. Short sleep duration as a risk factor for hypertension: Analyses of the first National Health and Nutrition Examination Survey. *Hypertension*. 2006; 47:833–839. [PubMed: 16585410]
- Gerlai R. Behavioral tests of hippocampal function: Simple paradigms, complex problems. *Behavioural Brain Research*. 2001; 125:269–277. [PubMed: 11682118]
- Gozal D, Daniel JM, Dohanich GP. Behavioral and anatomical correlates of chronic episodic hypoxia during sleep in the rat. *Journal of Neuroscience*. 2001; 21:2442–2450. [PubMed: 11264318]
- Graves LA, Heller EA, Pack AI, Abel T. Sleep deprivation selectively impairs memory consolidation for contextual fear conditioning. *Learning & Memory*. 2003; 10:168–176. [PubMed: 12773581]
- Guan Z, Fang J. Changes of IL-1 β levels induced by total sleep deprivation in different brain regions. *Sleep*. 2003; 26:A200.
- Guan Z, Peng X, Fang J. Sleep deprivation impairs spatial memory and decreases extracellular signal-related kinase phosphorylation in the hippocampus. *Brain Research*. 2004; 1018:38–47. [PubMed: 15262203]
- Hairston HS, Little MT, Scanlon MD, Barakat MT, Palmer TD, Sapolsky RM, et al. Sleep restriction suppresses neurogenesis induced by hippocampus-dependent learning. *Journal of Neurophysiology*. 2005; 94:4224–4233. [PubMed: 16014798]
- Hampton RR, Schwartz BL. Episodic memory in nonhumans: What and where, is when? *Current Opinion in Neurobiology*. 2004; 14:192–197. [PubMed: 15082324]

- Harker KT, Wishaw IQ. Place and matching-to-place spatial learning affected by rat inbreeding (Dark-Agouti, Fischer 344) and albinism (Wistar, Sprague-Dawley) but not domestication (wild rat vs Long-Evans, Fischer-Norway). *Behavioural Brain Research*. 2002; 134:467–477. [PubMed: 12191833]
- Hebb, DO. The organization of behaviour. New York: Wiley-Interscience; 1949.
- Hemmeter UM, Hemmeter-Spernal J, Krieg JC. Sleep deprivation in depression. *Expert Review of Neurotherapeutics*. 2010; 7:1101–1115. [PubMed: 20586691]
- Hennevin E, Hars B, Maho C, Bloch V. Processing of learned information in paradoxical sleep: Relevance for memory. *Behavioural Brain Research*. 1995; 69:125–135. [PubMed: 7546303]
- Hodges H. Maze procedures: The radial-arm and water maze compared. *Cognitive Brain Research*. 1996; 3:167–181. [PubMed: 8806020]
- Holmes A, Wellman CL. Stress-induced prefrontal reorganization and executive dysfunction in rodents. *Neuroscience and Biobehavioral Reviews*. 2009; 33:773–783. [PubMed: 19111570]
- Honig, WK. Studies of working memory in the pigeon. In: Hulse, SH.; Fowler, H.; Honig, WK., editors. *Cognitive processes in animal behavior*. Hillsdale, NJ: Erlbaum; 1978. p. 241–248.
- Huber R, Ghilardi MF, Massimini M, Tonini G. Local sleep and learning. *Nature*. 2004; 430:78–81. [PubMed: 15184907]
- Kandel, ER.; Schwartz, J.; Jessell, T., editors. *Principles of neural science*. McGraw-Hill; New York: 2000.
- Jones K, Harrison Y. Frontal lobe function, sleep loss and fragmented sleep. *Sleep Medicine Reviews*. 2001; 5:463–475. [PubMed: 12531154]
- Karni A, Tanne D, Rubenstein BS, Askenasy JJ, Sagi D. Dependence on REM sleep of overnight improvement of a perceptual skill. *Science*. 1994; 265:679–682. [PubMed: 8036518]
- Killgore WDS. Effects of sleep deprivation on cognition. *Progress in Brain Research*. 2010; 185:105–129. [PubMed: 21075236]
- Kim Y, Laposky AD, Bergmann BM, Turek FW. Repeated sleep restriction in rats leads to homeostatic and allostatic responses during recovery sleep. *Proceedings of the National Academy of Sciences of the United States of America*. 2007; 104:10697–10702. [PubMed: 17548824]
- Kudrimoti HS, Barnes CA, McNaughton BL. Reactivation of hippocampal cell assemblies: Effects of behavioral state, experience, and EEG dynamics. *Journal of Neuroscience*. 1999; 19:4090–4101. [PubMed: 10234037]
- Lancel M, Kerkhof GA. Effects of repeated sleep deprivation in the dark-or light-period on sleep in rats. *Physiology & Behavior*. 1989; 45:289–297. [PubMed: 2756014]
- Langella M, Colarieti L, Ambrosini MV, Giuditta A. The sequential hypothesis of sleep function IV: A correlative analysis of sleep variables in learning and nonlearning rats. *Physiology & Behavior*. 1992; 51:227–238. [PubMed: 1557434]
- Laurey S, Peigneux P, Phillips C, Fuchs S, Degueldre C, Aerts J, et al. Experience-dependent changes in cerebral functional connectivity during human rapid eye movement sleep. *Neuroscience*. 2001; 105:521–525. [PubMed: 11516819]
- Le Marec N, Beaulieu I, Godbout R. Four hours of paradoxical sleep deprivation impairs alternation performance in a water maze in the rat. *Brain and Cognition*. 2001; 46:195–197. [PubMed: 11527327]
- Leemburg S, Vyazovskiy VV, Olcese U, Bassetti CL, Tononi G, Cirelli C. Sleep homeostasis in the rat is preserved during chronic sleep restriction. *Proceedings of the National Academy of Sciences of the United States of America*. 2010; 107:15939–15944. [PubMed: 20696898]
- Leenaars CH, Dematteis M, Joosten RN, Eggels L, Sandberg H, Schirris M, et al. A new automated method for rat sleep deprivation with minimal confounding effects on corticosterone and locomotor activity. *Journal of Neuroscience Methods*. 2011; 196:107–117. [PubMed: 21262261]
- Lim J, Dinges DF. A meta-analysis of the impact of short-term sleep deprivation on cognitive variables. *Psychological Bulletin*. 2010; 136:375–389. [PubMed: 20438143]
- Louie K, Wilson MA. Temporally restructured replay of awake hippocampal ensemble activity during rapid eye movement sleep. *Neuron*. 2001; 29:145–156. [PubMed: 11182087]

- Maiti P, Singh SB, Mallick B, Muthuraju S, Ilavazhagan G. High altitude memory impairment is due to neuronal apoptosis in hippocampus, cortex and striatum. *Journal of Chemical Neuroanatomy*. 2008; 6:227–238. [PubMed: 18692566]
- Mandai O, Guerrien A, Sockeel P, Dujardin K, Leconte P. REM sleep modifications following a Morse code learning session in humans. *Physiology & Behavior*. 1989; 46:639–642. [PubMed: 2602488]
- Maquet P. The role of sleep in learning and memory. *Science*. 2001; 294:1048–1052. [PubMed: 11691982]
- Maquet P, Laureys S, Peigneux P, Fuchs S, Petiau C, Phillips G, et al. Experience-dependent changes in cerebral activation during human REM sleep. *Nature Neuroscience*. 2000; 3:831–836.
- Martinez-Gonzalez D, Obermeyer W, Fahy JL, Riboh M, Kalin NH, Benca RM. REM sleep deprivation induces changes in coping responses that are not reversed by amphetamine. *Sleep*. 2004; 27:609–617. [PubMed: 15282995]
- May ME, Harvey MT, Valdovinos MG, Kline RH 4th, Wiley RG, Kennedy CH. Nociceptor and age-specific effects of REM sleep deprivation induced hyperalgesia. *Behavioural Brain Research*. 2005; 159:89–94. [PubMed: 15795001]
- McCarley RW. Neurobiology of REM and NREM sleep. *Sleep Medicine*. 2007; 8:302–330. [PubMed: 17468046]
- McCoy JG, McKenna JT, Connolly NP, Poeta DL, McCarley RW, Strecker RE. One week of exposure to intermittent hypoxia impairs attentional set-shifting in rats. *Behavioural Brain Research*. 2010; 201:123–126. [PubMed: 20122971]
- McCoy JG, Tartar JL, Bebis AC, Ward CP, McKenna JT, Baxter MG, et al. Experimental sleep fragmentation impairs attentional set-shifting in rats. *Sleep*. 2007; 30:52–60. [PubMed: 17310865]
- McDermott CM, LaHoste GJ, Chen C, Musto A, Bazan NG, Magee JC. Sleep deprivation causes behavioral, synaptic, and membrane excitability alterations in hippocampal neurons. *Journal of Neuroscience*. 2003; 23:9687–9695. [PubMed: 14573548]
- McGaugh JL. Memory – A century of consolidation. *Science*. 2000; 287:248–251. [PubMed: 10634773]
- McKenna JT, Cordeira JW, Christie MA, Tartar JL, McCoy JG, Lee E, et al. Assessing sleepiness in the rat: A multiple sleep latencies test compared to polysomnographic measures of sleepiness. *Journal of Sleep Research*. 2008; 17:365–375. [PubMed: 18823428]
- McKenna JT, Tartar JL, Ward CP, Thakkar MM, Cordeira JW, McCarley RW, et al. Sleep fragmentation elevates behavioral, electrographic and neurochemical measures of sleepiness. *Neuroscience*. 2007; 146:1462–1473. [PubMed: 17442498]
- Mellman TA, Nolan B, Hebding J, Kulick-Bell R, Dominguez R. A polysomnographic comparison of veterans with combat-related PTSD, depressed men, and non-ill controls. *Sleep*. 1997; 20:46–51. [PubMed: 9130334]
- Morgado-Bernal I. Learning and memory consolidation: Linking molecular and behavioral data. *Neuroscience*. 2011; 176:12–19. [PubMed: 21215299]
- Muellbacher W, Ziemann U, Wissel J, Dang N, Kofler M, Facchini S, et al. Early consolidation in human primary motor cortex. *Nature*. 2002; 415:640–644. [PubMed: 11807497]
- Mueller AD, Pollock MS, Lieblich SE, Epp JR, Galea LA, Mistlberger RE. Sleep deprivation can inhibit adult hippocampal neurogenesis independent of adrenal stress hormones. *American Journal of Physiology: Regulatory, Integrative and Comparative Physiology*. 2008; 294:R1693–R1703.
- Myers KM, Davis M. Systems level reconsolidation; reengagement of the hippocampus with memory reactivation. *Neuron*. 2002; 36:340–343. [PubMed: 12408838]
- Nader K. Memory traces unbound. *Trends in Neurosciences*. 2003; 26:65–72. [PubMed: 12536129]
- Nader K, Hardt O. A single standard for memory: The case for reconsolidation. *Nature Reviews Neuroscience*. 2009; 10:224–234.
- Nader K, Schafe GE, Le Doux JE. Fear memories require protein synthesis in the amygdala for reconsolidation after retrieval. *Nature*. 2000; 406:722–726. [PubMed: 10963596]
- Norman, DA.; Shallice, T. Attention to action: willed and automatic control of behavior. In: Davidson, RJ.; Schwartz, GE.; Shapiro, D., editors. *Consciousness and self-regulation*. Vol. 4. New York: Plenum Press; 1986.

- O'Keefe J, Dostrovsky T. The hippocampus as a spatial map: Preliminary evidence from unit activity in the freely moving rat. *Brain Research*. 1971; 34:171–175. [PubMed: 5124915]
- Olton DS, Becker JT, Handelman GE. Hippocampus, space and memory. *Behavioral and Brain Sciences*. 1979; 2:313–365.
- Orban PC, Chapman PF, Brambilla R. Is the Ras-MAPK signaling pathway necessary for long term memory formation? *Trends in Neurosciences*. 1999; 22:38–44. [PubMed: 10088998]
- Owen AM, Roberts AC, Polkey CE, Sahakian BJ, Robbins TW. Extra-dimensional versus intra-dimensional set shifting performance following frontal lobe excisions, temporal lobe excisions, or amygdalo-hippocampectomy in man. *Neuropsychologia*. 1991; 29:993–1006. [PubMed: 1762678]
- Pavlidis C, Winson J. Influences of hippocampal place cell firing in the awake state on the activity of these cells during subsequent sleep episodes. *Journal of Neuroscience*. 1989; 9:2907–2918. [PubMed: 2769370]
- Perlis ML, Giles DE, Buysse DJ, Thase ME, Tu X, Kupfer DJ. Which depressive symptoms are related to which sleep electroencephalographic variables? *Biological Psychiatry*. 1997; 42:904–913. [PubMed: 9359976]
- Phillip P, Akerstedt T. Transport and industrial safety: How are they affected by sleepiness and sleep restriction? *Sleep Medicine Reviews*. 2006; 10:347–356. [PubMed: 16920370]
- Plihal W, Born J. Effects of early and late nocturnal sleep on declarative and procedural memory. *Journal of Cognitive Neuroscience*. 1997; 9:534–547.
- Poe GR, Walsh SM, Bjorness TE. Cognitive neuroscience of sleep. *Progress in Brain Research*. 2010; 185:1–19. [PubMed: 21075230]
- Pokk P, Vali M. Small platform stress increases exploratory activity of mice in staircase test. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. 2001; 25:1435–1444. [PubMed: 11513357]
- Porkka-Heiskanen T, Strecker RE, McCarley RW. Brain site-specificity of extracellular adenosine concentration changes during sleep deprivation and spontaneous sleep: An in vivo microdialysis study. *Neuroscience*. 2000; 99:507–517. [PubMed: 11029542]
- Porkka-Heiskanen T, Strecker RE, Thakkar M, Bjorkum AA, Greene RW, McCarley RW. Adenosine: A mediator of the sleep-inducing effects of prolonged wakefulness. *Science*. 1997; 276:1265–1268. [PubMed: 9157887]
- Rada P, Mark GP, Vitek MP, Mangano RM, Blume AJ, Beer B, et al. Interleukin-1 β decreases acetylcholine measured by microdialysis in the hippocampus of freely moving rats. *Brain Research*. 1991; 550:287–290. [PubMed: 1884236]
- Ramesh V, Basheer R, Thatte HS, McCarley RW. Nuclear translocation of transcription factor NF κ -B is cholinergic neuron and site-specific: A sleep deprivation and microinjection study. *Sleep*. 2002; 25(Suppl):A130–A131.
- Rauchs G, Desgranges B, Foret J, Eustache F. The relationships between memory systems and sleep stages. *Journal of Sleep Research*. 2005; 14:123–140. [PubMed: 15910510]
- Rechtschaffen A, Bergmann BM. Sleep deprivation in the rat: An update of the 1989 paper. *Sleep*. 2002; 25:18–24. [PubMed: 11833856]
- Ribeiro S, Nicolelis MA. Reverberation, storage and postsynaptic propagation of memories during sleep. *Learning & Memory*. 2004; 11:686–696. [PubMed: 15576886]
- Robbins TW. Arousal systems and attentional processes. *Biological Psychology*. 1997; 45:57–71. [PubMed: 9083644]
- Robbins TW. The 5-choice serial reaction time task: Behavioural pharmacology and functional neurochemistry. *Psychopharmacology (Berlin)*. 2002; 163:362–380. [PubMed: 12373437]
- Roehrs T, Conway W, Wittig R, Zorick F, Sicklesteel J, Roth T. Sleep-wake complaints in patients with sleep-related respiratory disturbances. *American Review of Respiratory Disease*. 1985; 132:520–523. [PubMed: 4037527]
- Rogers RD, Andrews TC, Grasby PM, Brooks DJ, Robbins TW. Contrasting cortical and subcortical activations produced by attentional set-shifting and reversal learning in humans. *Journal of Cognitive Neuroscience*. 2000; 12:142–162. [PubMed: 10769312]

- Row BW. Intermittent hypoxia and cognitive function: Implications from chronic animal models. *Advances in Experimental Medicine and Biology*. 2007; 618:51–67. [PubMed: 18269188]
- Ruskin DN, Dunn KE, Billiot I, Bazan NG, LaHoste GJ. Eliminating the adrenal stress response does not affect sleep deprivation-induced acquisition deficits in the water maze. *Life Sciences*. 2005; 78:2833–2838. [PubMed: 16325867]
- Sagaspe P, Sanchez-Ortuno M, Charles A, Taillard J, Valtat C, Bioulac B, et al. Effects of sleep deprivation on color-word, emotional, and specific stroop interference and on self-reported anxiety. *Brain and Cognition*. 2005; 60:76–87. [PubMed: 16314019]
- Saletu M, Anderer P, Saletu B, Hauer C, Mandl M, Oberndorfer S, et al. Sleep laboratory studies in restless legs syndrome patients as compared with normals and acute effects of ropinirole. 2. Findings on periodic leg movements, arousals and respiratory variables. *Neuropsychobiology*. 2000; 41:190–199. [PubMed: 10828728]
- Sandi C, Loscertales M, Guaza C. Experience-dependent facilitating effects of corticosterone on spatial memory formation in the water maze. *European Journal of Neuroscience*. 1997; 9:637–642. [PubMed: 9153570]
- Sarter M. Animal cognition: Defining the issues. *Neuroscience and Biobehavioral Reviews*. 2004; 28:645–650. [PubMed: 15555674]
- Schaffery JP, Odsenberg A, Marks GA, Speciale SG, Mihailoff G, Roffwarg HP. REM sleep Deprivation in monocularly occluded kittens reduces the size of cells in LGN monocular segments. *Sleep*. 1998; 21:837–845. [PubMed: 9871946]
- Shiromani PJ, Lu J, Wagner D, Thakkar J, Greco MA, Basheer R, et al. Compensatory sleep response to 12 h wakefulness in young and old rats. *American Journal of Physiology: Regulatory, Integrative and Comparative Physiology*. 2000; 278:R125–R133.
- Siapas AG, Wilson MA. Coordinated interactions between hippocampal ripples and cortical spindles during slow wave sleep. *Neuron*. 1998; 21:1123–1128. [PubMed: 9856467]
- Silva RH, Kameda SR, Carvalho RC, Takatsu-Coleman AL, Niigaki ST, Abílio VC, et al. Anxiogenic effect of sleep deprivation in the elevated plus-maze test in mice. *Psychopharmacology (Berlin)*. 2004; 176(2):115–122. [PubMed: 15160262]
- Skaggs WE, McNaughton BL. Replay of neuronal firing sequences in rat hippocampus during sleep following spatial experience. *Science*. 1996; 272:1870–1873. [PubMed: 8596957]
- Smith C. Sleep states and memory processes. *Behavioural Brain Research*. 1995; 69:137–145. [PubMed: 7546305]
- Smith C. Sleep states and memory processes in humans: Procedural versus declarative memory systems. *Sleep Medicine Reviews*. 2001; 5:491–506. [PubMed: 12531156]
- Smith CT, Conway JM, Rose GM. Brief paradoxical sleep deprivation impairs reference, but not working, memory in the radial arm maze. *Neurobiology of Learning and Memory*. 1998; 69:211–217. [PubMed: 9619997]
- Smith C, MacNeill C. Impaired motor memory for a pursuit rotor task following Stage 2 sleep loss in college students. *Journal of Sleep Research*. 1994; 3:206–213. [PubMed: 10607127]
- Smith C, Rose GM. Evidence for a paradoxical sleep window for place learning in the Morris water maze. *Physiology & Behavior*. 1996; 59:93–97. [PubMed: 8848497]
- Spiegel K, Knutson K, Leproult R, Tasali E, Van Cauter E. Sleep loss: A novel risk factor for insulin resistance and Type 2 diabetes. *Journal of Applied Physiology*. 2005; 99:2008–2019. [PubMed: 16227462]
- Stickgold R, James L, Hobson JA. Visual discrimination learning requires post-training sleep. *Nature Neuroscience*. 2000; 2:1237–1238.
- Stickgold R, Walker MP. Sleep-dependent memory consolidation and reconsolidation. *Sleep Medicine*. 2007; 8:331–343. [PubMed: 17470412]
- Stickgold R, Whidbee D, Schirmer B, Patel V, Hobson JA. Visual discrimination task improvement: A multi-step process occurring during sleep. *Journal of Cognitive Neuroscience*. 2000; 12:246–254. [PubMed: 10771409]
- Strecker RE, Morairty S, Thakkar MM, Porkka-Heiskanen T, Basheer R, Dauphin LJ, et al. Adenosinergic modulation of basal forebrain and preoptic/anterior hypothalamic neuronal

- activity in the control of behavioral state. *Behavioural Brain Research*. 2000; 115:183–204. [PubMed: 11000420]
- Suchecki D, Tiba P, Tufik S. Hormonal and behavioural responses of paradoxical sleep-deprived rats to the elevated plus maze. *Journal of Neuroendocrinology*. 2002; 14:549–554. [PubMed: 12121491]
- Sutherland CR, McNaughton B. Memory trace reactivation in hippocampal and neocortical neuronal ensembles. *Current Opinion in Neurobiology*. 2000; 10:180–186. [PubMed: 10753801]
- Tafti M, Villemain E, Carlander B, Besset A, Billiard M. Sleep in human narcolepsy revisited with special reference to prior wakefulness duration. *Sleep*. 1992; 15:344–351. [PubMed: 1519010]
- Tancredi V, D'Antuono M, Café C, Giovedi S, Bue MC, D'Arcangelo G, et al. The inhibitory effects of interleukin-6 on synaptic plasticity in the rat hippocampus are associated with an inhibition of mitogen-activated protein kinase (ERK). *Journal of Neurochemistry*. 2000; 75:634–643. [PubMed: 10899938]
- Tartar JL, Ward CP, Cordeira JW, Legare SL, Blanchette AJ, McCarley RW, et al. Experimental sleep fragmentation and sleep deprivation in rats increases exploration in an open field test of anxiety while increasing plasma corticosterone levels. *Behavioural Brain Research*. 2009; 197:450–453. [PubMed: 18805441]
- Tartar JL, Ward CP, McKenna JT, Thakkar M, Arrigoni E, McCarley RW, et al. Hippocampal synaptic plasticity and spatial learning are impaired in a rat model of sleep fragmentation. *European Journal of Neuroscience*. 2006; 23:2739–2748. [PubMed: 16817877]
- Thomas RJ, Rosen BR, Stern CE, Weiss JW, Kwong KK. Functional imaging of working memory in obstructive sleep-disordered breathing. *Journal of Applied Physiology*. 2005; 98:2226–2234. [PubMed: 15677733]
- Thomas M, Sing H, Belenky G, Holcomb H, Mayberg H, Dannals R, et al. Neural basis of alertness and cognitive performance impairments during sleepiness. I. Effects of 24 h of sleep deprivation on waking human regional brain activity. *Journal of Sleep Research*. 2000; 9:335–352. [PubMed: 11123521]
- Tobler I, Borbely AA. The effect of 3-h and 6-h sleep deprivation on sleep and EEG spectra of the rat. *Behavioural Brain Research*. 1990; 36:73–78. [PubMed: 2302323]
- Tulving, E. Organization of memory: Quo vadis?. In: Gazzaniga, MS., editor. *The cognitive neuroscience*. Cambridge, MA: MIT Press; 1995. p. 839–847.
- Van Dongen HP, Baynard MD, Maislin G, Dinges DF. Systemic interindividual differences in neurobehavioral impairment from sleep loss: Evidence of trait-like differential vulnerability. *Sleep*. 2004; 27:423–433. [PubMed: 15164894]
- Van Dongen HP, Maislin G, Mullington JM, Dinges DF. The cumulative cost of additional wakefulness: Dose–response effects on neurobehavioral functions and sleep physiology from chronic sleep restriction and total sleep deprivation. *Sleep*. 2003; 26:117–126. [PubMed: 12683469]
- Verstraeten E. Neurocognitive effects of obstructive sleep apnea syndrome. *Current Neurology and Neuroscience Reports*. 2007; 7:161–166. [PubMed: 17324368]
- Verstraeten E, Cluydts R. Executive control of attention in sleep apnea patients: Theoretical concepts and methodological considerations. *Sleep Medicine Reviews*. 2004; 8:257–267. [PubMed: 15233954]
- Vertes RP. Memory consolidation in sleep; dream or reality. *Neuron*. 2004; 44:135–148. [PubMed: 15450166]
- Walker MP. Cognitive consequences of sleep and sleep loss. *Sleep Medicine*. 2008; 9(Suppl 1):S29–S34. [PubMed: 18929316]
- Walker MP. The role of sleep in cognition and emotion. *Annals of the New York Academy of Sciences*. 2009; 1156:168–197. [PubMed: 19338508]
- Walker MP, Brakefield T, Hobson JA, Stickgold R. Dissociable stages of human memory consolidation and reconsolidation. *Nature*. 2003; 425:616–620. [PubMed: 14534587]
- Walker MP, Brakefield T, Morgan A, Hobson JA, Stickgold R. Visual discrimination learning requires post-training sleep. *Nature Neuroscience*. 2000; 2:1237–1238.

- Walsh CM, Booth V, Poe GR. Spatial and reversal learning in the Morris water maze are largely resistant to six hours of REM sleep deprivation following training. *Learning & Memory*. 2011; 18:422–434. [PubMed: 21677190]
- Ward CP, McCarley RW, Strecker RE. Experimental sleep fragmentation impairs spatial reference but not working memory in Fischer/Brown Norway rats. *Journal of Sleep Research*. 2009; 18:238–244. [PubMed: 19645967]
- Ward CP, McCoy JG, McKenna JT, Connolly NP, McCarley RW, Strecker RE. Spatial learning and memory deficits following exposure to 24 h of sleep fragmentation or intermittent hypoxia in a rat model of obstructive sleep apnea. *Brain Research*. 2009; 1294:128–137. [PubMed: 19643093]
- Wilson MA, McNaughton BL. Reactivation of hippocampal ensemble memories during sleep. *Science*. 1994; 265:676–679. [PubMed: 8036517]
- Wu JC, Bunney WE. The biological basis of an antidepressant response to sleep deprivation and relapse: Review and hypothesis. *American Journal of Psychiatry*. 1990; 147:14–21. [PubMed: 2403471]
- Xu W, Chi L, Row B, Xu R, Ke Y, Xu B, et al. Increased oxidative stress is associated with chronic intermittent hypoxia-mediated brain cortical neuronal cell apoptosis in a mouse model of sleep apnea. *Neuroscience*. 2004; 126:313–323. [PubMed: 15207349]
- Yang RH, Hu SJ, Wang Y, Zhang WB, Luo WJ, Chen JY. Paradoxical sleep deprivation impairs spatial learning and affects excitability and mitochondrial protein in the hippocampus. *Brain Research*. 2008; 1230:224–232. [PubMed: 18674519]
- Youngblood BD, Zhou J, Smagin GN, Ryan DH, Harris RBS. Sleep deprivation by the “flower pot” technique and spatial reference memory. *Physiology & Behavior*. 1997; 61:249–256. [PubMed: 9035255]

Abbreviations

5-CSRT	five choice serial reaction time test
BF	basal forebrain
NREM	non-rapid eye movement sleep (also known as slow wave sleep)
PVT	psychomotor vigilance test
REM	rapid eye movement sleep
REM SD	selective REM sleep deprivation
SD	total sleep deprivation (both NREM and REM sleep deprivation)
SF	experimental sleep fragmentation (also known as “sleep interruption”)

Fig. 1.

Sleepiness is increased in rats following 24 h of total SD, as measured by sleep onset latencies (upper left panel) and electroencephalographic measures of sleep (remaining three panels). All measures shown were obtained during the same 3 h recovery period immediately following 24 h of total SD produced by the movement of the Lafayette activity wheel housing each individual rat (i.e., the total sleep time, NREM, REM sleep data shown were collected during the same 3 h period in which the rat sleep latency trials were conducted). Sleep onset latencies, considered a direct measure of sleepiness, were measured every 30 min during the 3 h recovery period; the electroencephalographic data was collapsed into 30 min bins showing that the percentage of time spent in total sleep time, NREM, and REM sleep all increased significantly during the first part of the 3 h recovery period relative to baseline (modified from Christie, McKenna, et al. (2008)).

Fig. 2.

(A) Vigilance (i.e., sustained attention) performance is impaired by sleep disruption. (A) Studies in rats have used either the five choice serial reaction time test (5-CSRT; Cordova et al., 2006), or, more recently, the rat PVT to demonstrate sustained attention impairments produced by either 24 h of total sleep deprivation (SD), or by brain manipulations predicted to elevate sleepiness (e.g., the local perfusion of 300 μ M adenosine (AD) in the basal forebrain (BF) region shown here). (B and C) Interindividual differences in the neurobehavioral response to sleep disruption are clearly seen in both rats (B) and humans (C). (B) The left panel shows the baseline (control) and sleep deprived performance differences in eight individual rats; some rats are relatively resilient to the impact of SD on attention performance (e.g., rats S4, S9, S2), whereas other rats are much more susceptible to SD-induced impairments (e.g., S5, S8, S7). The right panel in B shows that when the same group of rats was exposed to two independent trials of 10 h total SD, the number of errors of omission seen in the 5-CSRT was very similar for each individual rat on each of the two trials. Thus, rats that were resilient to the behavioral effects of sleep deprivation were resilient on both of these two 10 h SD treatments (S4, S9, S2), whereas those rats that were susceptible to SD (S5, S8, S7) showed similar impairments in performance during each of the two identical 10 h SD treatments. Panel C shows human findings that are strikingly similar to the rat data shown in the right dside of panel B. Human subjects exposed to two independent trials of 24 h of SD (data were collected during the last 24 h of 36 h total SD) showed interindividual differences in vigilance performance in the PVT (modified from Van Dongen et al. (2004); boxes and diamonds are data from the first and second SD exposures).

Fig. 3.

Experimental sleep fragmentation in rats impairs higher-order cognitive function. The attentional set-shifting task is a compound discrimination task that assesses executive function, only performance on the extradimensional shift discrimination (the most difficult discrimination) was impaired following 24 h of SF. The term “executive function” encompasses several cognitive functions thought to be mediated by the frontal cortex (see text for details). Data are expressed as the mean ($\pm$ SEM) trials to criterion (Y axis) which represents the number of trials required to meet the criterion of six consecutive correct responses on each of the discriminations labeled on the X axis. Rats were assigned to one of three conditions: cage control, movement control, and experimental sleep fragmentation. For details see the original paper from which this figure was modified (McCoy et al., 2007).

Fig. 4.
Categorization of memory systems discussed in this review.

Fig. 5.

Sleep disruption interferes with spatial memory consolidation. Exposure to experimental sleep fragmentation (SF) for 24 h before spatial learning acquisition trials does not alter spatial memory performance in the water maze (left panel), whereas 24 h of SF exposure after acquisition training robustly impairs memory of the platform location (right panel) in pigmented Fischer/Brown Norway rats. This suggests that, at least in these conditions, spatial memory consolidation is more easily impaired by sleep disruption than is spatial learning. The left panel shows that 24 h of SF before acquisition training had no effect on retention/memory, as measured by percent distance spent in the correct quadrant during a single probe trial run 24 h after the acquisition training. In the learning phase of this experiment, rats were given three blocks of acquisition trials (four trials/block) and there were no learning/acquisition differences in the distance swam to the hidden platform across the blocks of trials among the following groups of rats: Cage Controls; CC; movement controls; MC; 24 h of experimental SF placed either before, or after, the spatial learning acquisition trials (modified from Ward, McCoy, et al. (2009)).

Fig. 6.

Impairment of hippocampal long-term potentiation (LTP) may mediate the spatial memory deficits produced by sleep disruption. The left panel shows the virtually complete blockade of hippocampal LTP (i.e., synaptic plasticity) in Sprague–Dawley rats following 24 h of experimental sleep fragmentation (SF; black circles; average responses across a 60 min period are shown for all three groups) compared to movement control (MC; gray circles) and cage control conditions (CC; open circles). The right panel shows examples of the field excitatory postsynaptic potential traces (fEPSP) from individual rats representing each treatment at time points T1 (black) and T2 (gray). Baseline traces (solid lines) were taken from an average of five traces at a midpoint of baseline recording. Post-tetanus traces (broken lines) were taken from an average of five traces 1/2 h after tetanic stimulation. The arrow represents the time point of tetanic stimulation (modified from Tartar et al. (2006)).