Effects of acute and chronic sleep deprivation

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A. Physiological basis of sleep

5. Effects of acute and chronic sleep deprivation

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KEY POINTS

- Sleep deprivation increases sleepiness, impairs mood states and emotional processing and contributes to altered risk-taking and decision-making behaviour.
- Long-term sleep restriction may lead to a reduced sense of sleepiness despite continuing reductions in cognitive performance capabilities.
- Important negative health outcome measures such as weight gain, obesity, type 2 diabetes, cardiovascular disease, hypertension and inflammation have been associated with insufficient sleep.
- Several immune-related transcripts and markers of infection are altered after sleep restriction, providing a possible pathophysiological basis for the elevated risk of falling sick after sleep loss.
- Insufficient sleep has been associated with elevated mortality, enhanced accident risk and a generally increased incidence of errors.

SUMMARY

Chronic sleep restriction and acute total sleep loss are highly prevalent in the modern '24/7 society' and pose significant risks for quality of life, mental wellbeing, cognitive performance and physical health. The consequences of acute and chronic sleep deprivation have become a public health concern. Based on the catalogue of knowledge and skills for sleep medicine, this chapter focuses on the effects of sleep deprivation on emotional state, mood, cognition, physical health and immune functions. We review the effect sizes of these different consequences of lack of sleep and provide insights into possible neuroanatomical and (neuro) physiological underpinnings of how insufficient sleep could impact upon these health outcomes. A better understanding of these relationships is important, because the avoidance of short and inadequate sleep may be amenable to modification and help to save increasingly high social, financial and health-related costs for the affected individuals and for society.

INTRODUCTION

It is well established that enough and undisturbed sleep are essential for an individual's personal wellbeing and the ability to perform correctly. With the increasing economic and social demands of the modern 'global 24/7 society', more and more people work and stay active outside the regular day and curtail their sleep. The negative effects of chronic sleep restriction on productivity and health have begun to be appreciated as a public health concern, yet are still often underestimated (Goel *et al.*, 2009). Thus, sleepiness has surpassed alcohol and drugs as the greatest identifiable and preventable cause of accidents in all modes of transport.

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The most common measure reflecting insufficient sleep in population-based studies is daytime sleepiness (Goel *et al*., 2009). To determine the prevalence of daytime sleepiness in a large public health database, 1007 randomly selected adults aged 21–30 years were interviewed twice between 1989 and 1995. It was noted that low, medium and high subjective sleepiness as quantified with a self-administered instrument was related significantly to the hours of sleep on weekdays, such that those individuals with the highest level of sleepiness reported roughly 20 min shorter sleep (~ 6.5 h) than those individuals with lower sleepiness levels (~ 6.8 h).

Laboratory studies began to model insufficient sleep experienced by many individuals because of lifestyle and medical disorders with scheduled sleep restricted to 4–7 h per 24 hours during several days. Such experiments revealed that not only sleepiness, but also neurobehavioural deficits, accumulate over time to severe levels (Dinges *et al*., 1997; Van Dongen *et al*., 2003). Furthermore, after only two nights of sleep restricted to 4 h, normal-weight young healthy men exhibited reduced leptin, increased ghrelin and more hunger when compared to 10 h of sleep (Spiegel *et al*., 2004). These and other data have been supported by large-scale, population-based epidemiological studies showing that self-reported short sleep duration (often defined as $\leq$6 h) is commonly associated with negative health outcomes, including impaired vigilance, weight gain, obesity, diabetes and cardiovascular disease, as well as all-cause mortality (Cappuccio *et al*., 2010).

Apart from partial sleep deprivation, short-term ($\leq$45 h of extended wakefulness) and long-term (>45 h of extended wakefulness) total sleep deprivation also acutely affect emotional, behavioural and physiological functions. Moderately prolonged wakefulness can already produce psychomotor impairment that may be even more pronounced than proscribed alcohol intoxication (Dawson and Reid, 1997). In a seminal, controlled laboratory study, regression analysis revealed a negative linear correlation between mean relative performance on an unpredictable tracking task and the duration of 10–26 h of sustained wakefulness. Intriguingly, the correlation coefficient accounted for as much as 92% of the variance in psychomotor performance. After only 17 h of wakefulness, performance decreased to a level equivalent to the performance impairment observed at a blood alcohol concentration of 0.05%. This corresponds to the legal level of alcohol intoxication in many western industrialized countries. When wakefulness was prolonged into the night, performance degraded further. A minimum was reached in the early morning after 23–25 h of wakefulness, whereas a moderate improvement was noted thereafter (Dawson and Reid, 1997).

It is widely accepted that this time–course of performance impairment during extended wakefulness reflects the complex interaction of a sleep–wake-dependent homeostatic process (process S) and the output of the endogenous circadian clock (process C) (Achermann and Borbély, 2011). These processes not only determine neurocognitive performance (Goel *et al*., 2009), but also psychological and physiological states, including sleepiness, emotions and mood (Killgore, 2010), timing and quality of sleep and important features of the sleep and waking electroencephalogram (EEG) (Achermann and Borbély, 2011). Reduced sleep duration, increased wake time and circadian phase affect all these aspects of wellbeing.

Several authoritative recent reviews have comprehensively summarized distinct aspects of short sleep, chronic sleep deprivation and an acute loss of sleep (Achermann and Borbély, 2011; Goel *et al*., 2009; Imeri and Opp, 2009; Knutson and Van Cauter, 2008; Landolt, 2008; Mullington *et al*., 2010; Rasch and Born, 2013; Walker, 2009). Based upon this work and according to the 'catalogue of knowledge and skills for sleep medicine', this chapter summarizes important possible risks for wellbeing, performance and health associated with the lack of adequate sleep. A special focus is put upon the effect sizes of the different consequences of sleep loss, their implications for public health and the possible neuroanatomical and (neuro)physiological underpinnings of how insufficient sleep could impact upon these distinct health outcomes.

EFFECTS OF SLEEP DEPRIVATION ON EMOTIONAL STATE AND MOOD

The regulation of sleep, emotions and mood is closely related. Ample evidence for this crucial interaction stems from the common clinical observation that psychiatric diseases and mood disorders are associated typically with disturbed sleep. In addition, insomnia is a powerful predictor of depression, suggesting that non-depressed insomniacs have a roughly twofold risk of developing depression later (Walker, 2009).

An early meta-analysis concluded that mood is even more affected by sleep deprivation than either cognitive performance or motor functions, and that the negative impact on mood of partial sleep deprivation is even more pronounced than either short-term or long-term complete sleep loss (Pilcher and Huffcutt, 1996). Some of these conclusions have since been contested, due to the development of more appropriate experimental controls and more sensitive assessments of the neurocognitive consequences of acute and chronic sleep deprivation (Goel *et al*., 2009). Nevertheless, chronic restriction of sleep to roughly 5 h per night for 1 week resulted in robust cumulative impairment of emotional wellbeing, including increased sleepiness, fatigue, confusion, tension and total mood disturbance. These changes tended to precede the negative impact on objective measures of sustained vigilant attention by 1 day (Dinges *et al*., 1997). Furthermore, recent work confirmed that subjective alertness was generally more affected by both partial and total sleep deprivation than performance across different cognitive domains (Lo *et al*., 2012) (Fig. 1).

In healthy volunteers, virtually all forms of sleep deprivation result in increased negative mood states, especially feelings

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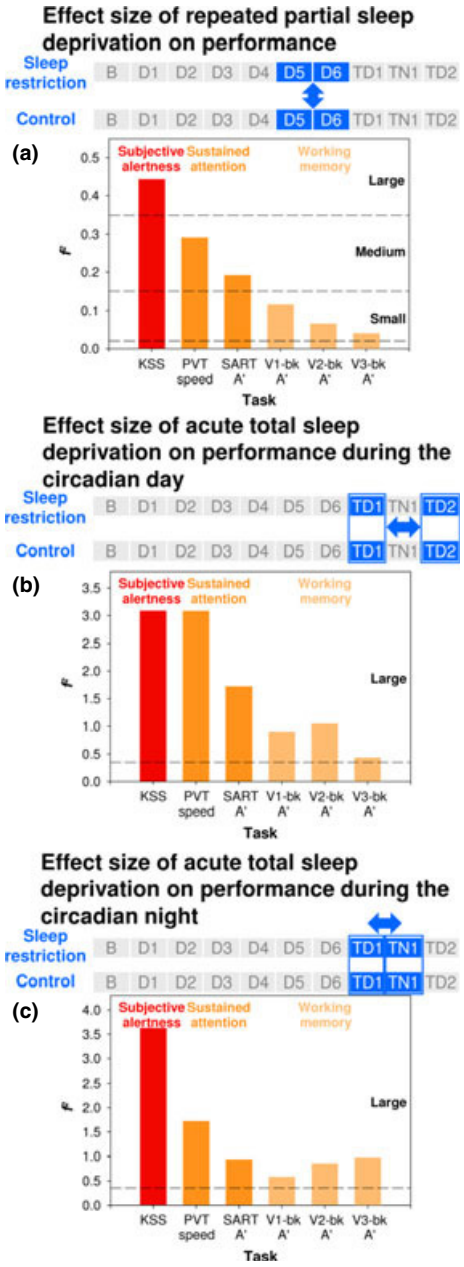

Figure 1. Comparison of effect sizes for subjective alertness, sustained attention and working memory of (a) repeated partial sleep deprivation, (b) acute total sleep deprivation on performance during the circadian day and (c) acute total sleep deprivation on performance during the circadian night. Horizontal dashed lines indicate cut-offs for small, medium and large effect sizes; note the different scaling in the *y*-axes in (a), (b) and (c). Figure reprinted with permission from Lo *et al.* (2012).

of sleepiness, fatigue, loss of vigour, confusion and impaired emotional processing, including frustration tolerance and coping capacities (Killgore, 2010). Positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) studies identified brain regions involved in these effects of sleep deprivation. Among other findings, it was found that activation of the prefrontal cortex (PFC) during verbal learning correlated significantly with increased subjective sleepiness in sleep-deprived subjects (Drummond *et al.*, 2000). Furthermore, activation of the amygdalae by emotional stimuli was observed repeatedly to be altered upon the lack of sleep. The amygdalae are part of the limbic system and, importantly, involved in processing emotions. For example, fMRI was used while exposing healthy individuals to standardized emotional pictures (Walker, 2009). The authors found that the amygdalae response to increasingly aversive images was more pronounced, and activated a larger area in sleep-deprived subjects than in rested controls. Furthermore, relative to the sleep-control group, the functional connectivity between amygdalae and ventromedial PFC (vmPFC) was reduced in the group that was kept awake in the night before scanning. By contrast, stronger connectivity was found to autonomic brain stem regions, including the locus coeruleus. These findings indicate that top–down prefrontal control of emotional challenges is impaired following sleep deprivation.

While the earlier studies highlighted increased reactivity towards negative stimuli, more recent work also revealed elevated reactivity in response to pleasure-evoking stimuli. Collectively, the data suggest a 'bi-directional affective imbalance' upon insufficient sleep. Positive stimuli in sleep-deprived individuals appear to amplify reactivity in mesolimbic reward networks, in particular ventral tegmental areas and putamen (Gujar *et al.*, 2011). This change was associated with increased functional connectivity in extended limbic regions and decreased connectivity to mediofrontal and orbitofrontal areas. Taken together, the amplified behavioural reactivity towards both negative and positive emotional stimuli, as well as the sleep deprivation-induced functional changes in emotional brain networks, may contribute to altered mood regulation, risk-taking and decision-making on the loss of sleep (see below).

With respect to the different sleep states, it has been traditionally assumed that deprivation of REM sleep affects emotional reactivity and mood, due partly to the suggested role of rapid eye movement (REM) sleep in adaptation and attenuation of the emotional tone of previous experiences (Walker, 2009). Interestingly, however, a recent partial REM sleep deprivation study indicated unexpectedly that REM sleep may attenuate adaptation and enhance morning reactivity to negative emotional stimuli.

In contrast to the general mood impairment in healthy individuals, total and partial sleep deprivation ('wake therapy') have been known for decades as rapidly acting and effective antidepressant interventions in many patients with major depression. The mechanisms of the antidepressant action of wake therapy are largely unknown. Clinically used antidepressant medications, including monoamine oxidase (MAO) inhibitors and blockers of monoamine reuptake, typically inhibit REM sleep in depressed patients, who often present with reduced REM sleep latency and elevated REM density. Nevertheless, antidepressant response to the potent classical MAO inhibitor, phenelzine, did not depend upon the

selective, complete elimination of REM sleep (Landolt *et al.*, 2001). Recently, suppression of slow wave sleep (SWS) was also reported to ameliorate depressive symptoms (Landsness *et al.*, 2011). In general, the sleep deprivation-induced improvement of mood often vanishes after recovery sleep and cannot be maintained over time. It is hoped that a better understanding of the tight neurobiological relationships between sleep and mood regulation may pave the way to the identification of biomarkers of antidepressant response, and the development of rapid and more effective novel treatments of depression that are eagerly searched for.

EFFECTS OF SLEEP DEPRIVATION ON NEUROCOGNITIVE FUNCTIONS

The detrimental impact of sleep loss on human cognitive functions has long been recognized. More recent data demonstrate that the deficits produced by a lack of sleep depend strongly upon the nature of the cognitive skills examined. The current literature suggests that exposure to partial and total sleep deprivation impairs primarily behavioural alertness (sustained attention) and cognitive processing capabilities (working memory) with measurable effect sizes (Lo *et al.*, 2012). Generally, sustained attention is more affected than other cognitive domains and tasks, including working memory, even when implemented with a high executive load (Fig. 1).

Effects of sleep deprivation on sustained attention

The dominant assay of sustained attention in paradigms of sleep loss is the psychomotor vigilance task (PVT) (Dinges *et al.*, 1997). This task has been used widely in human studies to detect the neurobehavioural deficits associated with chronic sleep restriction and acute total lack of sleep (Belenky *et al.*, 2003; Van Dongen *et al.*, 2003). The task is highly sensitive to sleep loss, independent of aptitude, devoid of learning effects, and its reliability and validity have been amply demonstrated. The PVT is a simple reaction-time task to a visual cue that is typically presented roughly 100 times at random intervals during 10 min. According to the 'wake state instability' hypothesis (see Goel *et al.*, 2009 for review), performance on the PVT becomes increasingly variable under the influence of elevated sleep pressure due to inadvertent microsleep episodes, with brief moments of low arousal that make it difficult to sustain attention. This unstable state, which fluctuates from second to second, is characterized by an increased number of lapses, errors in response and increased compensatory efforts resulting in normal reaction times for a short period of time.

The effect on sustained attention of controlled sleep restriction allowing 9, 7, 5 or 3 h of sleep during 7 consecutive nights was studied by Belenky *et al.* (2003). While in the 3-h condition, a continuous slowing and a steady increase in the number of lapses on the PVT was observed; response speed in the 5- and 7-h conditions remained stable after the initial drop in performance when sleep duration was first reduced. Similar observations were made in another dose–response experiment of chronic sleep restriction, investigating the neurocognitive effects of 14 days of sleep limitation to 8, 6 or 4 h time in bed (Van Dongen *et al.*, 2003). No cognitive deficits, including sustained attention, working memory and 'cognitive throughput', occurred following 8 h in bed for sleep each night. After 2 weeks of sleep restriction to 6 h, however, deficits in all these skills were equivalent to those seen after 1 night of total sleep loss. Two weeks of sleep restriction to 4 h resulted in cognitive deficits similar to those after 2 nights without sleep. Importantly, the cognitive deficits accumulated much faster when no sleep was allowed than when the same amount of sleep was lost more gradually over days of sleep restriction. Based on these findings, the authors proposed that the critical factor in producing daytime cognitive performance deficits was the cumulative amount of time subjects spent awake in excess of their usual wakefulness period (Van Dongen *et al.*, 2003).

In contrast to other studies (see above), sleepiness ratings in this experiment showed much smaller increases during sleep restriction than the cognitive impairments, suggesting an escalating dissociation between the subjective perception of sleepiness and the actual cognitive performance capability (Van Dongen *et al.*, 2003). Furthermore, EEG slow wave ('delta') activity (SWA) in non-rapid eye movement (NREM) sleep, the most reliable physiological marker of homeostatic sleep pressure after total sleep loss (Achermann and Borbély, 2011), showed no statistically reliable progressive changes across days of sleep restriction in any of the chronic sleep restriction conditions (Van Dongen *et al.*, 2003). It was concluded that, as long as at least 4 h sleep per night are permitted, SWA does not reflect the homeostatic need for sleep during wakefulness (Van Dongen *et al.*, 2003). A subsequent study, however, demonstrated robust homeostatic responses in EEG SWA to sleep restriction (Akerstedt *et al.*, 2009). In this study, sleep was restricted to 4 h of sleep across 5 days, followed by 3 nights of recovery sleep. Sleep restriction indeed resulted in dynamic changes in the EEG low-frequency activity (1.25–7.0 Hz band) in NREM sleep. The increase was particularly evident during the first 4 h of sleep, and returned to baseline by night 2 of recovery sleep.

Sustained attention is also largely impaired after total sleep deprivation (Fig. 1). Collectively, four dominant findings have emerged from the use of the PVT in sleep deprivation protocols. First, the evolution of PVT performance during extended wakefulness reveals the presence of the interacting homeostatic and circadian sleep-regulatory processes (Fig. 2). Secondly, sleep deprivation results in an overall slowing of responses. Thirdly, sleep deprivation increases the propensity of individuals to lapse for lengthy periods (>500 ms), as well as to make false starts. Both restricted sleep and total lack of sleep impair PVT performance in a dose-dependent manner. Finally, sleep deprivation enhances the time-on-task effect, the phenomenon whereby perfor-

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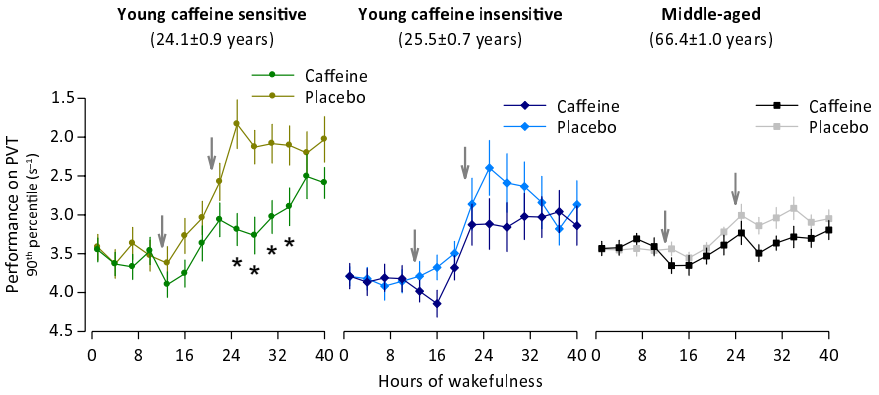

Figure 2. Time–course of performance on the psychomotor vigilance task (PVT) across 40 h prolonged wakefulness in young caffeine-sensitive (n = 12, green and olive dots), young caffeine-insensitive (n = 10, dark blue and light blue diamonds) and middle-aged (n = 10, black and grey squares) men. The evolution of performance reveals the interaction of homeostatic and circadian sleep regulatory processes. Means ± standard error of the mean of the slowest 10th percentile of reaction times, a sensitive marker for sleep loss, is plotted. The 10–min PVT sessions were administered every 3 h beginning 30 min after awakening from the baseline night. Ticks on the x-axes were rounded to the previous hour. Caffeine (200 mg) and placebo were administered 11 and 23 h into the scheduled waking period (arrows) according to a randomized, double-blind, cross-over study design. Self-rated caffeine sensitive individuals are most impaired by sleep loss, yet benefit the most from caffeine. Data were replotted from Landolt *et al.* (2012). *P < 0.05 (false discovery rate).

mance worsens during the course of a cognitive task owing to fatigue and reduced motivation.

Effects of sleep deprivation on executive functioning and decision-making

Although less consistent than changes in emotional processing, impairments in sustained attention and increased EEG low-frequency activity in wakefulness and sleep, sleep loss was shown repeatedly to impact adversely on higher-order cognitive skills. For example, learning, working memory, decision-making, expectation of reward, adapting and revising plans, divergent thinking, reasoning, behavioural inhibition and problem-solving were all reported to be impaired after sleep deprivation (Goel *et al.*, 2009). Nevertheless, it is still controversial whether this impairment merely reflects the negative impact of sleep loss on underlying basic cognitive capacities such as vigilant attention or, alternatively, whether sleep deprivation distinctly affects specific higher-order cognitive functions beyond reduced attention.

Increasing evidence suggests that the latter possibility is the case. Already, 24 h of prolonged wakefulness caused a global decrease in absolute cerebral glucose metabolic rate during performance of a computer-based serial addition/subtraction task in thalamus, PFC, posterial parietal cortices and basal ganglia together with impaired vigilance (Thomas *et al.*, 2000). By contrast, sleep-deprived individuals showed distinctly different cerebral responses in these brain areas when performing other cognitive tasks (Drummond *et al.*, 2000). For example, during arithmetic tasks, sleep loss decreased activation of PFC and parietal lobes. During verbal learning, the temporal lobe was activated after normal sleep but not after a night without sleep, whereas the parietal lobes were activated after sleep deprivation in contrast to the rested control condition. Finally, a divided attention task comprising arithmetic aspects and verbal learning performed after 35 h sustained wakefulness led to enhanced activation of PFC and parietal lobes. The activation in these brain areas correlated with memory performance. Taken together, the findings indicate that dynamic, task-related and region-specific changes in cerebral activation maintain performance on distinct neurocognitive tasks after sleep deprivation. In particular, complex rule-based, convergent logical tasks appear to show little change following sleep loss. Conversely, divergent skills such as flexible thinking, taking decisions in the light of unexpected new information, innovation, revising plans and preventing distraction may be substantially affected by excess wakefulness (Harrison and Horne, 2000).

Implicit in divergent thinking abilities and decision-making is the important reliance on executive functions that draw heavily upon resources in the PFC (Goel *et al.*, 2009). Various pharmacological studies aimed at disentangling the relationships between reduced vigilance and attention and deteriorated executive functions after sleep loss. It was found repeatedly that caffeine, modafinil and dextroamphetamine diminish the negative impact of short- and long-term sleep deprivation on subjective sleepiness, arousal, attention and basic cognitive skills (Landolt, 2008). By contrast, the ability to integrate emotion with cognition to guide decisions was typically unimproved by moderate doses of these wake-promoting agents. These findings further support the notion that the sleep deprivation-induced impairments of executive functions are separate from simple arousal and alertness systems.

In patients with damage to the vmPFC, decision-making is typically impaired such that focus is shifted towards short-term outcomes. A similar behaviour is often seen in sleep-deprived individuals in whom risk assessment and valuation

during decision-making also appears to be altered. Thus, sleep deprivation prompted healthy volunteers to take more risks in a gambling task compared to when they were well-rested, in particular when the possible outcomes were framed in terms of potential gains. By contrast, when the same task was presented in terms of potential losses, lack of sleep led them to take fewer risks than usual. Functional neuroimaging studies have highlighted that sleep-deprived individuals show differences within brain-reward circuitry during risky decision-making (Venkatraman *et al.*, 2007). Specifically, increased nucleus accumbens activation following risky choices and reduced neural responses in insular and orbitofrontal cortices following losses may bias them towards expectation of gains while reducing their focus on losses.

Such findings further indicate that sleep-deprived individuals place reduced weight on new information when making choices. Instead, they rely more upon pre-existing cognitive biases and tend to adhere to automatic, stereotypical and redundant forms of cognitive processing. Emotional biasing is a form of automatic processing that may influence decision-making by emotional 'gut reactions', which prime people to make choices based on how rewarding or unpleasant they perceived a previous similar experience to be. In an experimental setting, this emotion-guided decision-making can be investigated using the Iowa Gambling Task (IGT). During this task, on a computer screen, participants are presented with four decks of cards placed face down. Players are required to select 100 cards from these four available packs. On card selection, they are immediately informed as to whether the card they selected results in a monetary gain or a monetary loss. Unknown to the subjects, two of the decks are 'good' decks and lead to small but consistent net gains. The other two decks are 'bad' decks and comprise large short-term gains but consistent long-term losses. Healthy, well-rested individuals usually learn from the trial-by-trial feedback and adjust their playing strategy to avoid the risky bad decks in favour of the modest, but consistently advantageous, good decks. However, following 49 and 75 h of prolonged wakefulness, study participants showed a significant decline in performance. Specifically, they became progressively more risk-taking and short-sighted in decision-making, tending to prefer risky short-term gains at the expense of incurring long-term losses (Killgore, 2010). Such findings are in line with evidence that damage to the vmPFC leads to shortsightedness for the future, as well as neuroimaging data that indicate that this brain region plays a key role in the decision-making process of the IGT.

Effects of sleep deprivation on neurophysiological markers of cortical functioning

As stated above, the vmPFC belongs to those brain regions that are particularly affected by sleep deprivation. Metabolic activity of the vmPFC is drastically reduced after a night of sleep loss (Thomas *et al.*, 2000). Furthermore, PET measures of vmPFC activity (i.e. cerebral blood flow) correlate with EEG SWA (0.75–4.5 Hz range) in NREM sleep. Consistent with this finding, not only the increase in SWA in NREM sleep, but also the rise in EEG theta (~ 5–9 Hz range) activity after prolonged wakefulness is larger over anterior than posterior cortical areas (Achermann and Borbély, 2011). Taken together, behavioural, pharmacological, neuroimaging and neurophysiological data suggest consistently that the vmPFC and higher-order cognitive processes associated with this brain area are specifically affected by sleep deprivation. Nevertheless, particularly during shorter durations, such as 1 night of sleep deprivation, deficits in executive functions have not been observed universally. This suggests that the brain's executive function systems may compensate temporarily for brief sleep loss by utilizing additional cognitive resources via activation of alternative brain regions (Drummond *et al.*, 2000).

Effects of sleep deprivation on learning and memory

A highly active area of research during the past decade investigated the role for sleep in encoding, consolidation and retrieval of declarative and procedural memories (Rasch and Born, 2013). To this end, various sleep deprivation protocols were conducted, including sleep restriction before and after learning, early and late partial sleep deprivation and selective (partial) SWS and REM sleep deprivation. The possible beneficial effects of nap sleep for learning and memory were also studied. Although the exact nature and a causal role for sleep in the relationship between sleep and memory consolidation still need to be clarified, the simplified current state of this research may be summarized briefly as follows: (i) sleep promotes the consolidation of memories, i.e. the transformation of newly encountered labile information into stable representations integrated in pre-existing networks; (ii) SWS benefits the promotion of hippocampus-dependent, declarative memories; and (iii) REM sleep benefits the promotion of procedural memories. For a more comprehensive discussion of the relationships between sleep and memory, please refer to chapter [. . .] of this textbook. Very recently, the hypothesis that sleep may serve the selective erasure of (negative) memories have also received some experimental support. Critical evaluation of the literature, however, reveals that effect sizes are often small and that the underlying mechanisms and possible contribution of the different sleep states to distinct aspects of learning and memory remain controversial.

Apart from being a whole-brain phenomenon, it is increasingly accepted that sleep and the homeostatic regulation of sleep also entail local and use-dependent aspects (Achermann and Borbély, 2011). Thus, sleep slow waves occur with increased prevalence over brain regions activated and used preferentially during waking experiences. It has been suggested that slow waves, in particular the 'neocortical' slow oscillation, together with hippocampal sharp-wave ripples and thalamocortical spindles, reflect the reactivation and consolidation of memories. These sleep oscillations may

promote the transformation and integration of recently encoded neuronal memory representations into long-term memory ('active system consolidation') (Rasch and Born, 2013). Alternatively, the 'synaptic homeostasis hypothesis' proposed by Tononi and Cirelli (2006) assumes that sleep slow waves serve to normalize global synaptic strength potentiated in the course of information encoding during wakefulness. According to this concept, linear synaptic downscaling enhances the signal-to-noise ratio and strengthens learning and important memories indirectly by nullifying connections that were not or only weakly potentiated during previous waking experiences. The two hypotheses may not be mutually exclusive. Thus, supporting evidence for and concerns against both these theories as the sole mechanism underlying sleep-dependent memory benefits have been brought forward.

While recent research has focused on the role for SWS in memory consolidation, the contribution of REM sleep to learning and memory has gained less attention. Traditionally, REM sleep was associated with retention of emotional memories, yet the findings about the role of REM sleep in human memory processing are inconsistent (Rasch and Born, 2013). An important argument against a critical contribution of REM sleep to memory processes is the lack of any documented memory deficits in depressed patients who may experience long-term, almost complete pharmacological REM sleep suppression during therapy with certain antidepressant medications (Landolt *et al*., 2001).

As introduced above, multiple studies reported altered task-related brain activation in sleep-deprived individuals when memory for contents with different emotional values was tested. In one study, recognition memory was probed 72 h after encoding of emotional and neutral information (Sterpenich *et al*., 2007). During the night after encoding, subjects were either kept awake or allowed to sleep. Sleep deprivation resulted in the reduced activation of vmPFC, amygdalae and occipital cortex during recognition, although performance was tested in a well-rested condition. The connectivity among these areas was also altered between the sleep and sleep-deprivation groups (Sterpenich *et al*., 2007). In the sleep group, retention of emotional memories was associated with greater activation of hippocampus and medial PFC, as well as enhanced connectivity between these brain areas. In the sleep deprivation group, retention of negative memories elicited greater response in amygdalae and occipital areas. Sleep loss prior to learning also showed differential effects depending on the valence of information (Walker, 2009). While, in the sleep condition, positive and negative emotions were more efficiently encoded, sleep deprivation caused a decline in memory of neutral and positive contents. On the contrary, retrieval of negative cues was less impaired by sleep deprivation. These findings indicate that different mechanisms are involved in the processing of emotionally relevant information. It was suggested that activation of an alternative amygdalae–cortical network permits the retention of negative, possibly threatening, information, even under suboptimal, sleep-deprived, conditions.

EFFECTS OF SLEEP DEPRIVATION ON PHYSICAL HEALTH

Classic studies dating back to more than a century ago had already reported that several weeks of sleep deprivation in dogs disrupted temperature regulation and metabolism, increased appetite and enhanced risk of infections, and led ultimately to the death of the laboratory animals. Although the exact underlying mechanisms remained unknown and severe stress associated with such experiments probably contributed to the outcome, the main findings were later replicated in rats under more controlled conditions, following both prolonged total sleep deprivation as well as selective REM sleep deprivation (Rechtschaffen and Bergmann, 2002). Together, the studies indicate that long-term chronic sleep loss may be fatal.

In humans, research over the last few decades has provided growing evidence that lack of sleep exerts detectable, deleterious changes in endocrine, metabolic and immune pathways. A recent meta-analysis of large prospective, population-based studies revealed that people reporting consistently sleeping ≤ 5 h per night have a 12% increased risk for all-cause mortality when compared with 6–8 h of sleep per night (Cappuccio *et al*., 2010). Based on the currently available evidence, it is possible that sleep deprivation triggers biological mechanisms which contribute to the deterioration of health status and increased morbidity, including obesity, reduced glucose tolerance, insulin resistance, diabetes, cardiovascular vulnerability, hypertension and infectious diseases.

Effects of sleep deprivation on appetite and body mass homeostasis

Chronic sleep restriction is increasingly common in our hectic modern society, due to lifestyle choices, work and family demands and/or physical or psychological problems. It appears that during the past 50 years sleep duration in adults and teenagers has decreased by almost 2 h per night. It may be important to note that this decrease has coincided with the progression of obesity and type 2 diabetes (T2D) in western industrialized societies. These developments constitute important public health concerns, and interventions designed to prevent the onset and progression of obesity and T2D are essential. Given that short duration and poor quality of sleep provide newly identified, possibly preventable risk factors for metabolic disease, a wealth of cross-sectional, as well as prospective, epidemiological studies recently examined the possible metabolic consequences of short and insufficient sleep and total sleep loss. Although discrepant findings cannot be ignored (Tare *et al*., 2014), the literature generally suggests that inadequate sleep indeed provides a

risk factor for the development of obesity, impaired glucose tolerance and T2D (Knutson and Van Cauter, 2008).

For example, after only 2 days of sleep curtailment from 10 to 4 h time in bed, leptin levels in lean healthy volunteers were found to decrease, whereas ghrelin levels, hunger and appetite were found to increase (Spiegel *et al*., 2004). The changes were remarkably pronounced, equalling between 18 and 33% (Fig. 3). Together with insulin, the hormones leptin and ghrelin play important roles in regulating food intake and appetite. Their changes after sleep restriction could contribute to a physiological mechanism underlying the proposed adverse impact of insufficient sleep on body mass homeostasis (Knutson and Van Cauter, 2008). Leptin is released from adipocytes after food intake and mediates the perception of satiety. Ghrelin is produced in cells of the stomach and the intestines; its levels rise before meals and during fasting and fall rapidly after food intake. Both leptin and ghrelin influence the central nervous system via different receptor systems in the 'appetite centre' of the brain that controls homeostatic food intake: the ventromedial and arcuate nuclei of the hypothalamus (Knutson and Van Cauter, 2008). Leptin inhibits and ghrelin activates neurones of the arcuate nucleus.

Leptin and ghrelin also influence the activity of the hypocretin (or orexin) system that integrates the control of feeding, energy homeostasis and the stabilization of consolidated wakefulness and sleep. Hypocretin is produced by a small cluster of 10 000–20 000 neurones in the lateral hypothalamus, which innervates not only the arcuate nucleus, but also the paraventricular nucleus (PVN), the nucleus tractus solitarius (NTS), the nucleus accumbens, the ventral tegmental area (VTA), the cerebral cortex and other areas of the ascending arousal system (ARAS) (Knutson and Van Cauter, 2008). Neurones within PVN and NTS are important for satiety, taste and autonomic functions controlling energy balance, whereas the dopaminergic nucleus accumbens and VTA are 'reward and motivation' centres that modulate hedonic, non-homeostatic

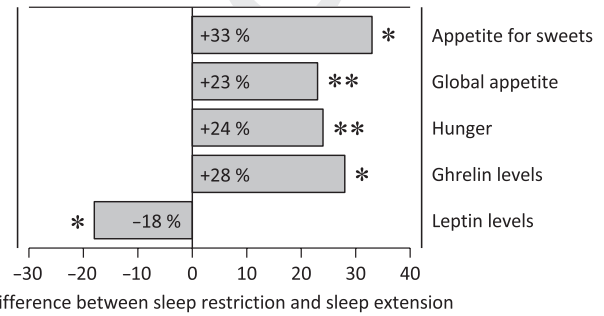

Figure 3. Change in daytime levels of leptin, ghrelin, hunger and appetite after 2 days of curtailed sleep from 10 to 4 h bedtime in 12 healthy lean volunteers. Data were replotted from Spiegel *et al.* (2004). $^{*}P < 0.05$; $^{**}P \leq 0.01$ (Wilcoxon's matched-pairs signed-rank tests). Hunger and appetite were measured on visual analogue scales.

food intake. Finally, the cerebral cortex and the ARAS maintain and regulate higher-order cognitive functions, arousal and vigilance, as well as wakefulness and sleep. Given that hypocretin neurones are functionally inhibited by leptin and functionally excited by ghrelin, the sleep deprivation-induced alterations in leptin and ghrelin will lead to enhanced hypocretin activity. This system appears, thus, to be ideally placed to link inadequate sleep and excess feeding (Fig. 4).

Another possible brain mechanism by which insufficient sleep may contribute to the development and maintenance of obesity was proposed recently on the basis of an fMRI study (Greer *et al*., 2013). Healthy, normal-weight participants completed a counterbalanced, cross-over study protocol involving a night of normal rested sleep (average 8.2 h asleep) and a night of monitored total sleep deprivation (average 24.6 h awake), separated by at least 1 week. There were no differences in self-reported hunger. When compared to the sleep-rested state, however, sleep deprivation using a food-desire task resulted in a significant increase in the proportion of 'wanted' high-caloric food items. Specifically, participants saw and rated 80 food items on a scale from 1 to 4, according to how much they wanted the food item during fMRI scanning. As food desire progressively increased, sleep deprivation diminished activity in anterior cingulate cortex, lateral orbitofrontal cortex and anterior insular cortex (Greer *et al*., 2013). Interestingly, the reduced activity in these cortical appetitive evaluation regions after the lack of sleep was accompanied by increased responsiveness of the amygdalae to desirable food items. The findings may suggest that increased food craving after sleep loss is associated with reduced activity in frontal cortex, combined with a converse amplification of activity within the amygdalae that are known to signal food salience in the context of appetitive choices.

Sleep deprivation and T2D

Because both hyperglycaemia and hypoglycaemia pose severe health risks to the organism, blood glucose levels need to be regulated tightly. Brain glucose utilization is the rate at which glucose is metabolized in brain tissue. It is related closely to glucose tolerance, a measure of how rapidly blood glucose levels are normalized following intravenous glucose injection or ingestion of a standardized (carbohydrate-rich) meal. Glucose tolerance reflects how efficiently insulin-dependent and insulin-independent tissues respond to and metabolize increased blood glucose levels. Glucose regulation and insulin secretion undergo strong circadian and sleep-dependent influences, such that glucose tolerance is lowest in the middle of the habitual sleep period (Spiegel *et al*., 1999). Sleep restriction and acute and chronic sleep loss have been associated with increased blood glucose levels, and larger field studies support this association derived from controlled laboratory experiments. For example, in a cross-sectional sample of 740 young and

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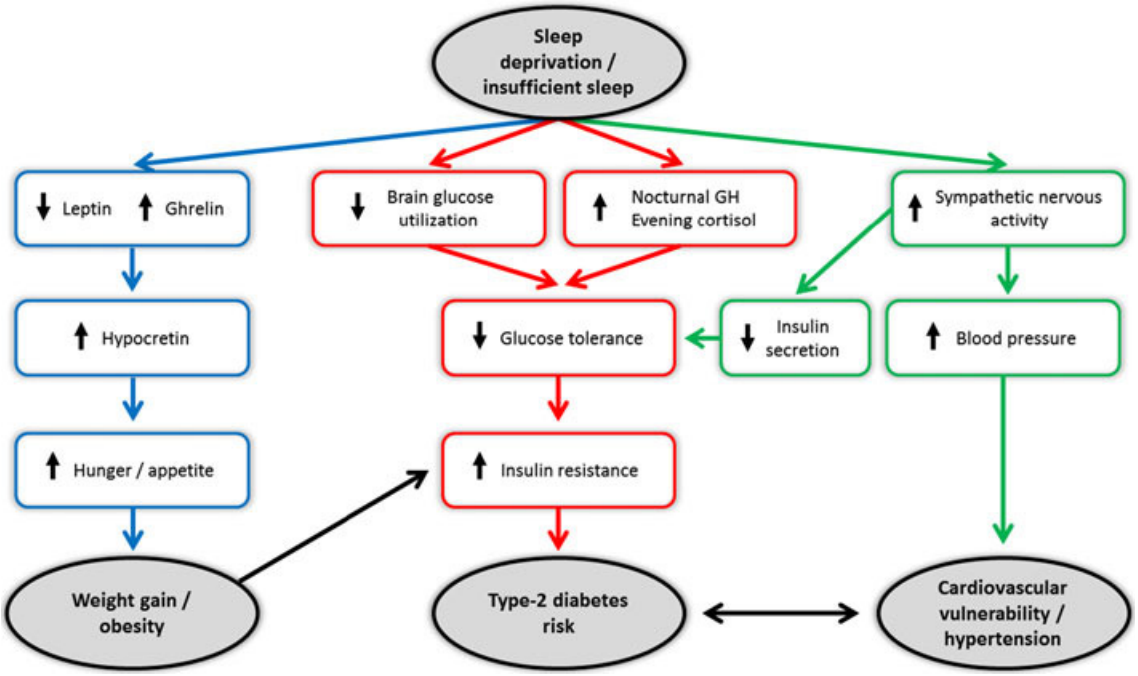

Figure 4. Simplified schematic of putative pathways leading from sleep deprivation and insufficient sleep to weight gain, obesity, type 2 diabetes, cardiovascular vulnerability and hypertension. Figure adapted and extended from Knutson and Van Cauter (2008). Other possible consequences of sleep loss contributing to changes in metabolism, such as more time to eat or reduced energy expenditure, are not depicted.

middle-aged adults, fasting glucose levels were significantly higher in short-sleeping men and women reporting 5–6 h of sleep per night when compared to 'normal' (7–8 h) and 'long' (9–10 h) sleepers (Chaput *et al.*, 2007). Furthermore, the prevalence of impaired glucose tolerance, quantified by the widely validated homeostatic model assessment (HOMA) levels, was increased by 58% in the short sleepers in comparison to the 'normal' sleeping reference group. The data suggest collectively that short sleep duration and inadequate sleep, either behavioural or related to sleep disorders, are deleterious for glucose utilization and metabolism.

Deep SWS is associated with a decrease in brain glucose metabolism. In addition, SWS exerts major modulatory effects on endocrine release. The release of growth hormone (GH) and prolactin is increased, whereas the release of other hormones of the hypothalamic–pituitary–adrenal (HPA) axis, such as thyrotrophin and cortisol, is inhibited. Both GH and cortisol have important roles in glucose metabolism. In particular, the secretion of GH is dependent upon the occurrence and quality of sleep, such that the most reproducible GH pulse occurs shortly after sleep onset (Knutson and Van Cauter, 2008). The GH stimulates muscle build-up, lipolysis and gluconeogenesis in the liver. By contrast, the steroid hormone, cortisol, is released primarily in response to stress and stimulates glycogenolysis, i.e. the breakdown of glycogen to glucose. In normal sleepers, nocturnal GH release was shown to be reduced during total sleep deprivation, but subsequently increased in daytime recovery sleep (Knutson and Van Cauter, 2008). Cortisol was affected adversely by acute total sleep loss. Based on these and other studies, it has been suggested that sleep deprivation results in increased sympathetic nervous activity, increased levels of GH in the daytime and increased levels of cortisol in the evening. These effects could lead to reduced glucose tolerance (Fig. 4).

Chronic high blood glucose concentration constitutes a key symptom of T2D, which is mediated by insulin resistance, i.e. the inability of insulin-sensitive tissues to respond adequately to insulin. The effects of chronic sleep restriction on blood glucose regulation and T2D risk was examined in healthy subjects who gained <4 h of sleep during 6 consecutive nights, followed by 6 recovery nights with a 12-h sleep opportunity (Spiegel *et al.*, 1999). At the end of each study block, an intravenous glucose tolerance test was administered followed by 24-h blood sampling at regular intervals. When compared to the recovery condition, sleep restriction induced a 40% reduction in glucose tolerance, a 30% reduction in insulin-independent glucose disposal and a 30% reduction in acute insulin response (Spiegel *et al.*, 1999). These findings are consistent with cross-sectional, as well as prospective, epidemiological studies indicating that short sleep duration and acute total sleep deprivation, as well as self-reported sleep problems or the presence of obstructive sleep apnea and insomnia, predict increased insulin resistance and increased risk of developing T2D (Fig. 4). However, it should be kept in mind that there are reported differences in the hormonal effects of acute total sleep loss

compared to recurrent partial sleep deprivation (Knutson and Van Cauter, 2008). Further research is thus required to elucidate the mechanisms and causality of these suggested relationships.

Effects of sleep deprivation on cardiovascular vulnerability and hypertension

The autonomic nervous system (ANS) controls 'fight-or-flight' reactions. Increased activity of the sympathetic nervous system is responsible for reduced pancreatic insulin secretion, increased contractile force of the heart, constriction of blood vessels and dilation of bronchioles of the lungs. Heart rate and heart-rate variability have proved useful in sleep research and chronobiology to estimate the sympathetic/parasympathetic balance after challenges to the sleep–wake system. Recent data show that acute sleep deprivation leads to greater sympathetic influence on the autonomic control of the heart (Viola *et al.*, 2008). Furthermore, sympathetic predominance increases and parasympathetic indexes decrease during recovery sleep after prolonged wakefulness. From the perspective of the heart, such recovery sleep appears not to have the characteristics of physiologically restorative sleep, i.e. low sympathetic predominance. Increased sympathetic nervous activity also leads to hypertension. These findings suggest that insufficient sleep could increase cardiovascular vulnerability (Fig. 4). However, a systematic review and meta-analysis of 15 prospective studies including almost 475 000 people did not support this notion unequivocally (Cappuccio *et al.*, 2011). Short sleep duration ($\leq$5–6 h per night) was not associated significantly with total cardiovascular disease, yet was associated with a 48% enhanced risk of developing or dying of coronary heart disease and a 15% enhanced risk of stroke. By contrast, long sleep duration (>8–9 h per night) predicted all three cardiovascular outcomes. It was concluded that people reporting consistently sleeping 5 h or less per night should be regarded as a higher-risk group for cardiovascular morbidity and mortality, whereas sleeping 9 h or more per night may represent a diagnostic tool for detecting subclinical or undiagnosed comorbidity.

EFFECTS OF SLEEP DEPRIVATION ON IMMUNE FUNCTIONS

The increased risk of sleep-deprived people to develop obesity, diabetes and cardiovascular disease has one component in common: all these health problems reflect, at least in part, the occurrence of inflammatory processes (Mullington *et al.*, 2010). Pioneering early studies revealed that the cerebrospinal fluid of sleep-deprived animals caused other animals to fall asleep. In an attempt to identify the underlying 'hypnotoxin', an 'endogenous factor S' was isolated and characterized as a bacterial cell wall peptide, muramyl dipeptide. This peptide and purified endotoxin fragments in humans induce the production of primary cytokines of the inflammatory system, including interleukin (IL)-1, tumour necrosis factor (TNF) and nuclear factor kappa B (NF-κB) (Imeri and Opp, 2009; Krueger *et al.*, 1984; Mullington *et al.*, 2010). Together with other neurochemicals such as adenosine, nitric oxide, prostaglandin D_2 and GH-releasing hormone, these cytokines are widely accepted to play an important role in the physiological regulation of NREM sleep duration and intensity. Indeed, as most people have experienced themselves, sleep is altered during infections and general disease. In the laboratory, an immune challenge increases the duration and intensity of NREM sleep dose-dependently, as quantified by EEG SWA, and reduces REM sleep (Mullington *et al.*, 2010).

In simplified terms, the immune system protects its host from pathogens and infections and consists of two main parts, the innate immune system and the adaptive immune system. The innate immune system is non-specific and more or less functional immediately after birth. It includes the physical and chemical protection mechanisms of the organism, such as skin, mucosae, saliva and resident bioflora. In principle, enhanced cortisol levels after sleep deprivation could lead to the breakdown of skin collagen and thereby reduce the protective function of the innate immune system. If a pathogen penetrates the physical barriers of the body, the innate immune system also activates non-specific immune cells, including lymphocytes, macrophages, cytokines and the complement system. These cells can trigger fever and inflammatory processes. Furthermore, the adaptive immune system is also activated. It is slower, yet highly potent and very specific. It consists of B and T cell-type lymphocytes, which are able to present antigens, detect and eliminate pathogens and finally 'remember' the eliminated pathogen, which allows for more rapid elimination if encountered again later.

The acute-phase response refers to the rapid and early activation of an immune cascade in response to injury and infection. This response involves activation of Toll-like receptors that trigger genetic transcription of NF-κB and leads to the production of IL-1β, TNF-α and IL-6 (Mullington *et al.*, 2010). Recent genetic studies in humans demonstrate that these established markers of the acute inflammatory system respond strongly to sleep loss induced by either partial sleep restriction or acute total sleep deprivation (Aho *et al.*, 2013; Moller-Levet *et al.*, 2013). For example, Aho *et al.* (2013) analysed gene expression in peripheral blood mononuclear cells taken from sleep-deprived healthy volunteers following 5 days of sleep restriction to 4 h per day (n = 9). Genome-wide microarrays were compared to a rested control group (n = 8) and a population-based epidemiological cohort (n = 472) with 'self-reported sufficient sleep' or 'self-reported insufficient sleep'. The study revealed that sleep restriction altered the expression of 117 genes. In another study, 26 participants were exposed to two experimental conditions, 1 week with insufficient sleep (~ 5.7 h per 24 h) and 1 week with sufficient sleep (~ 8.5 h per 24 h) (Moller-Levet *et al.*, 2013). Immediately after each condition,

whole-blood RNA samples were collected from each participant. Transcriptome analyses revealed that 711 genes were up- or down-regulated by insufficient sleep. While different biological processes were affected (e.g. sleep homeostasis, circadian rhythms, stress, metabolism), the studies showed collectively that many among the most up-regulated transcripts were indeed related to the immune system, including Toll-like receptors, proinflammatory cytokine production and B cell activation (Aho *et al.*, 2013; Moller-Levet *et al.*, 2013). This notion was supported further by similar findings in the population sample in which, in men, a significant association was noted between self-reported insufficient sleep and the levels of the well-known inflammation marker, C-reactive protein (Aho *et al.*, 2013). Related findings from other studies suggest that short sleep following a rhinovirus infection increases the risk of catching the common cold by almost threefold.

Another interesting aspect of insufficient sleep is related to the adaptive immune system and the response to vaccinations. A recent study investigated a role for sleep in boosting immunological memory, and followed the T helper cell and antibody response to hepatitis A and B inoculations over 1 year (Lange *et al.*, 2011). The study enrolled 27 healthy men divided into two groups, assigned randomly to either stay awake (n = 14) or to sleep (n = 13) during the night following each vaccination injection. Three injections of hepatitis A combined with hepatitis B vaccine were administered at weeks 0, 8 and 16. Polysomnographic EEG was recorded in the group that was allowed to sleep. Sleep during the post-vaccination nights was characterized by high SWA and accompanying levels of immunoregulatory hormones (e.g. increased GH and prolactin and decreased cortisol). When compared to the sleep deprivation group, the level of hepatitis A virus-specific T helper cell response to vaccination was almost doubled 4 weeks after the first injection of the vaccine. This effect even persisted until follow-up after 1 year. In addition, both at the time of the third inoculation as well as at follow-up, EEG SWA in NREM sleep was correlated strongly with the hepatitis A virus-specific T helper cell response to the vaccine (Lange *et al.*, 2011).

Taken together, the available findings amply demonstrate that sleep deprivation impairs the immune response in humans. Conversely, changes in inflammatory cytokines during an infection not only lead to fever but also promote deep sleep. It has been proposed that these changes may serve an evolutionary purpose, thus reducing the risk of spreading the infection and at the same time keeping the infected individual immobilized at home and in a safe environment (Imeri and Opp, 2009).

OTHER EFFECTS OF SLEEP DEPRIVATION

The possible consequences of acute and chronic sleep deprivation also include an elevated risk of accidents in traffic, at work and during leisure (Goel *et al.*, 2009). For example, sleep-related accidents while driving may be the underlying cause of about 30% of fatal motor vehicle crashes in Europe and the United States, yet the exact numbers are difficult to estimate. Similarly, the risk of occupational accidents, including medical errors and adverse events by residents, are more frequent when working sleep-deprived. Some of the major accidents in history have been linked to human error due to the lack of sleep. Such disastrous examples include the explosion in the nuclear plant 'Three Mile Island' (1979), the nuclear meltdown in Chernobyl (1986) and the *Exxon Valdez* oil spill (1989). The occurrence of insufficient sleep can reflect lifestyle choices, overwhelming occupational, family or social demands or medical problems. Thus, a recent screening for sleep disorders in almost 5000 American police officers revealed a >40% prevalence of at least one type of sleep disorder (Rajaratnam *et al.*, 2011). Bad sleep quality was associated significantly with adverse performance, safety and health outcomes. These findings highlight the possible importance of awareness, screening, prevention and treatment programmes to improve the quantity and quality of sleep in society to reduce these risks.

CONCLUDING REMARKS

It has become increasingly apparent that acute and chronic sleep deprivation pose significant risks for quality of life, performance and mental and physical health in society. Nevertheless, in particular with respect to neurocognitive performance, research over the last decade has demonstrated that decrements in performance after sleep loss depend upon the task examined. Furthermore, they also reflect differential individual vulnerability to the consequences of sleep loss. Accumulating data suggest that these differences are trait-like and, at least in part, genetically determined. Ongoing research has begun to examine the distinct underlying genetic influences (Goel *et al.*, 2009; Landolt, 2008). Some of the first results revealed that genetic variants modulating adenosine receptor-mediated neurotransmission contribute to individual differences in PVT performance in rested and sleep-deprived states. This conclusion is supported by different, stimulant actions of the adenosine receptor antagonist caffeine (Landolt, 2008). Interestingly, when compared to young subjects, PVT performance in healthy adults of older age is consistently less impaired by acute sleep loss, especially in the morning after the night without sleep. In fact, the age-related differences in sleep loss-induced impairment in neurobehavioural function are mimicked in young individuals of low and high sensitivity to the stimulant effects of caffeine (Fig. 2). Based on these data, it was hypothesized that age-related differences in adenosine receptor-mediated signal transduction contributes to the age-related changes in vulnerability to acute sleep deprivation. It can be expected that such a research approach will disclose molecular mechanisms of human sleep–wake regulation, provide insights into their changes in normal older age and sleep–wake disorders and may assist

in the evidence-based search for new treatments of impaired wakefulness and sleep.

Not only vulnerability to sleep loss, but also sleep need, differ widely among healthy individuals (i.e. there exist both physiological long and short sleepers). Keeping this in mind, the available literature suggests strongly that individuals who do not obtain sufficient sleep due to chronic sleep restriction or acute sleep deprivation often experience negative health outcomes, including a 12% elevated risk for all-cause mortality (Cappuccio *et al*., 2010). Nevertheless, causal inference is often difficult because confounders, e.g. pre-existing illness, or possible reversed causation may be present in epidemiological studies. Thus, long sleep (>9 h) has also been associated consistently with increased mortality. Future studies will have to answer the question of whether sleep duration is a cause or simply a marker of ill health. In addition, research should aim at identifying the mechanisms by which sleep loss impairs health outcomes. This is important because avoidance of short and inadequate sleep may be amenable to modifications through education, counselling and measures of public health, as well as newly developed evidence-based treatments of disease-related insufficient sleep.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest, financial or otherwise.

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