Adenosine, Caffeine, and Performance: From Cognitive Neuroscience of Sleep to Sleep Pharmacogenetics

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Abstract: An intricate interplay between circadian and sleep-wake homeostatic processes regulate cognitive performance on specific tasks, and individual differences in circadian preference and sleep pressure may contribute to individual differences in distinct neurocognitive functions. Attentional performance appears to be particularly sensitive to time of day modulations and the effects of sleep deprivation. Consistent with the notion that the neuromodulator, adenosine adenosine , plays an important role in regulating sleep pressure, pharmacologic and genetic data in animals and humans demonstrate that differences in adenosinergic tone affect sleepiness, arousal and vigilant attention attention in rested and sleep-deprived states. Caffeine Caffeine -the most often consumed stimulant in the world-blocks adenosine receptors and normally attenuates the consequences of sleep deprivation on arousal, vigilance, and attention. Nevertheless, caffeine cannot substitute for sleep, and is virtually ineffective in mitigating the impact of severe sleep loss on higher-order cognitive functions. Thus, the available evidence suggests that adenosinergic mechanisms, in particular adenosine A2A receptor-mediated signal transduction, contribute to waking-induced impairments of attentional processes, whereas additional mechanisms must be involved in higher-order cognitive consequences of sleep deprivation. Future investigations should further clarify the exact types of cognitive processes affected by inappropriate sleep. This research will aid in the quest to better understand the role of different brain systems (e.g., adenosine and adenosine receptors) in regulating sleep, and sleep-related subjective state, and cognitive processes. Furthermore, it will provide more detail on the underlying mechanisms of the detrimental effects of extended wakefulness, as well as lead to the development of effective, evidence-based countermeasures against the health consequences of circadian misalignment and chronic sleep restriction.

DOI: https://doi.org/10.1007/7854_2014_274

ADENOSINE, CAFFEINE, AND PERFORMANCE: FROM COGNITIVE NEUROSCIENCE OF SLEEP TO SLEEP PHARMACOGENETICS

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Submitted to: ***Sleep, Neuronal Plasticity and Brain Function***
(Eds: Abel T, Benca R, and Meerlo P)

In press (accepted): January 14, 2014

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Abstract

An intricate interplay between circadian and sleep-wake homeostatic processes regulate cognitive performance on specific tasks, and individual differences in circadian preference and sleep pressure may contribute to individual differences in distinct neurocognitive functions. Attentional performance appears to be particularly sensitive to time of day modulations and the effects of sleep deprivation. Consistent with the notion that the neuromodulator, adenosine, plays an important role in regulating sleep pressure, pharmacologic and genetic data in animals and humans demonstrate that differences in adenosinergic tone affect sleepiness, arousal and vigilant attention in rested and sleep-deprived states. Caffeine - the most often consumed stimulant in the world - blocks adenosine receptors and normally attenuates the consequences of sleep deprivation on arousal, vigilance and attention. Nevertheless, caffeine cannot substitute for sleep, and is virtually ineffective in mitigating the impact of severe sleep loss on higher-order cognitive functions. Thus, the available evidence suggests that adenosinergic mechanisms, in particular adenosine A_{2A} receptor-mediated signal transduction, contribute to waking-induced impairments of attentional processes, whereas additional mechanisms must be involved in higher-order cognitive consequences of sleep deprivation. Future investigations should further clarify the exact types of cognitive processes affected by inappropriate sleep. This research will aid in the quest to better understand the role of different brain systems (e.g., adenosine and adenosine receptors) in regulating sleep, and sleep-related subjective state and cognitive processes. Furthermore, it will provide more detail on the underlying mechanisms of the detrimental effects of extended wakefulness, as well as lead to the development of effective, evidence-based countermeasures against the health consequences of circadian misalignment and chronic sleep restriction.

Keywords

Circadian; homeostasis; sleep deprivation; sleepiness; arousal; attention; cognition; *ADA*; *ADORA2A*; plasticity

Contents

1. Circadian and homeostatic influences permit consolidated periods of wakefulness and sleep

Wakefulness and sleep take place periodically, at specific times, during the 24-hour light-dark cycle. These two distinct states result from the interplay between circadian and homeostatic oscillators, a concept originally described by the two-process model of sleep-wake regulation (Borbély 1982). The circadian process reflects an endogenous, 24-hour variation in the propensity for sleep and wakefulness (Borbély 1982). This latter process is controlled by the suprachiasmatic nuclei

(SCN) of the anterior hypothalamus, an anatomical structure considered to be the circadian master clock in mammals. Human research, conducted under a range of experimental conditions (e.g., internal desynchronization of the sleep-wake cycle, forced desynchrony paradigms, fragmented sleep-wake cycles, sleep deprivation and sleep displacement), has highlighted the existence of a robust drive to maintain wakefulness towards the end of the habitual waking day (Lavie 2001). Thus the circadian master clock promotes wakefulness in the early evening, just before habitual time for sleep. The positioning of this 'wake maintenance zone' (Strogatz et al. 1987), at the end of the waking day, may seem paradoxical. However, it is thought that this high circadian-based tendency for wakefulness is what prevents humans from falling asleep during the early evening, when homeostatic sleep pressure reaches its highest level. The homeostatic process represents an hourglass mechanism, which gradually builds up with increasing time awake, and roughly exponentially declines during sleep. Thus circadian and homeostatic systems work in opposition to ensure a consolidated period of wakefulness (Cajochen et al. 2010). Opposite effects of the two processes also occur as the biological night progresses and allows the maintenance of a consolidated sleep episode (Dijk and Czeisler 1995; Dijk and Czeisler 1994). The SCN may promote a circadian increase in sleep tendency, which counteracts the decrease in homeostatic sleep propensity as the individual accumulates sleep.

2. The endogenous circadian clock modulates cognitive performance

The states of subjective sleepiness and alertness, as well as distinct neurobehavioral functions (e.g. cognitive performance on specific tasks), are also influenced by this interplay between circadian and homeostatic processes (reviewed by (Cajochen et al. 2004)). Indeed, from a cognitive perspective, the two-process model of sleep-wake regulation implies that neurobehavioral efficiency may change over the day due to the influence of circadian timing on alertness and task performance, due to increasing homeostatic sleep pressure, or due to a combination of both these

factors (Carrier and Monk 2000). For example, research incorporating a 40-hour constant routine protocol revealed a clear circadian modulation of subjective sleepiness (Karolinska Sleepiness Scale) (Gillberg et al. 1994) and cognitive performance (psychomotor vigilance task [PVT]) (Dinges and Powell 1985), even in the absence of strong homeostatic sleep pressure (Cajochen et al. 2001; Graw et al. 2004). This protocol permits the manipulation of homeostatic sleep pressure by either sleep depriving (high sleep pressure) or sleep satiating (low sleep pressure) study participants by the allowance of regular nap opportunities throughout the circadian cycle. This circadian modulation of subjective state and neurobehavioral performance is organized in a temporal manner which prompts maximal performance throughout the waking hours, including the wake-maintenance zone. Yet, if testing continues into the biological night (e.g., under sleep deprivation conditions), there is a significant decline in performance, which coincides with the decline of the circadian arousal signal. Importantly, however, performance deterioration moves in line with the circadian cycle, such that an improvement can be observed in the biological morning, once the circadian drive for wakefulness takes center stage once again (Cajochen et al. 2004).

2.1. Individual differences in circadian preference modulate human neurobehavioral performance

Forced desynchrony paradigms can be used to separate the influence of the circadian pacemaker from the influence of homeostatic sleep pressure. Here, subjects are isolated from the usual 'zeitgebers' (i.e., time givers such as light) and for weeks are exposed to an artificial sleep/wake schedule with a 'day' duration that is significantly shorter (e.g., 19 hours) or longer (e.g., 28 hours) than the normal 24-hour day. With time, the protocol forces a progressive desynchronization of the artificial sleep-wake cycle from the endogenous circadian cycle. Such research indicates that the extent to which circadian rhythm modulates performance is largely dependent on the extent of homeostatic sleep pressure. Specifically, rising sleep pressure attenuates circadian arousal during the subjective evening hours (Dijk and Archer 2009). As a result, even small

changes in the relationship between the two processes may have an important effect on an individual's ability to maintain a consistent cognitive performance during the normal waking day (Cajochen et al. 2010). In fact, as reviewed by Schmidt and colleagues (2007), large differences in circadian parameters can be observed in the temporal disposition of an individual, and this gives rise to differential modulations in cognitive performance across the normal waking day. Prominent inter-individual variation in circadian preference significantly affects the temporal organization of a wealth of human behaviors. Morningness-eveningness is the most substantial source of this variation (Roenneberg et al. 2003), and is expressed by favorite periods for diurnal activities, such as working hours, and specific sleep habits (Taillard et al. 2003). Such behaviors in turn reflect the particular chronotype of the individual. The morningness-eveningness chronotype can be assessed using self-report questionnaires, such as the Morningness-Eveningness Questionnaire (Horne and Östberg 1976) and the Munich Chronotype Questionnaire (Roenneberg et al. 2003). At one end of the scale exist extreme morning types, who show a strong preference for waking up early in the morning and find it difficult to remain awake beyond their usual bedtime. At the opposite end of the scale, extreme evening-types prefer to go to bed late at night, and experience great difficulty in getting up in the morning (Schmidt et al. 2007). It has been suggested that these extreme chronotypes are 'phase shifted' according to their circadian rhythmicity. That is, their peaks and troughs of physiological circadian markers (core body temperature, melatonin) occur either earlier (phase advance, morning types) or later (phase delay, evening types) in relation to the external clock time, as compared to 'neutral' individuals who show no strong preference for morningness or eveningness (Duffy et al. 2001). Importantly, as well as differences in physiological characteristics, the diurnal profile of some neurobehavioral variables is also influenced by chronotype. Accordingly, alertness and performance may peak at different clock times, depending on the chronotype of the individual. For example, some people may be consistently at their best in the morning, while others are more alert and perform better in the evening (Schmidt et al. 2007).

To sum up, subjective sleepiness and alertness, and neurobehavioral performance, are contingent upon the synchronicity between the individual's peak periods of circadian arousal and the time of day at which testing takes place (Schmidt et al. 2007). Accordingly, it could be intuitively assumed that individuals who feel subjectively sleepier and less alert, are more likely to be cognitively impaired (Leproult et al. 2003). However, there is accumulating evidence to contradict this proposal. For example, sleep deprivation protocols have revealed that subjective sleepiness and objective alertness are not always linked to measures of neurobehavioral performance (Leproult et al. 2003). In fact, subjective measures of alertness and performance can differ to a great extent (Van Dongen et al. 2003). Such findings raise the question as to whether different cognitive domains are differentially affected by circadian rhythms, reflected by testing subjects at different times of the day.

2.2. Circadian influences differently affect distinct cognitive performance tasks

Cognitive functioning domains range from simple attention to logical reasoning, working memory, long-term memory, and more complex executive functions. A simplified overview and classification of the main cognitive processes (attention, memory and executive functions) can be seen in Fig. 1 (adapted from (Schmidt et al. 2007)).

Most studies on the circadian modulation of cognitive function have focused on the impact of time of day on vigilance and basic attentional parameters (Schmidt et al. 2007). Historically, research revealed a temporal relationship between circadian variations in cognitive performance measures and daily fluctuations in physiological variables such as core body temperature. That is, when body temperature is high and endogenous melatonin is low, alertness and neurobehavioral performance tend to be higher (Kleitman et al. 1938). It was suggested that the circadian-related increase in body temperature would indirectly speed up cognitive processing by increasing metabolic activity in the brain (Kleitman et al. 1938). However, further research highlighted the role

of other, external factors, on time-of-day effects in cognition. More specifically, peak and troughs in performance can be attributed to the type and difficulty of the task (e.g., differential working-memory load) (Folkard et al. 1983). While performance speed on simple repetitive and serial search tasks peaks with temperature levels in the evening (Colquhoun 1981; Monk 1982), speed performance on more complex cognitive tasks (e.g., logical reasoning tasks) peaks in the late morning (Folkard 1975), and performance in short-term memory retention peaks in the early to mid-morning (Laird 1925). Thus, Bonnet proposed that the optimal time of day for completing a cognitive test is largely dependent on the specific parameters of the task, such as its cognitive domain, duration and difficulty, the administration method, and the measured variable (Bonnet 2000). Alternative data, however, revealed that the selected paradigm (e.g., normal sleep/wake conditions *vs.* 40-hours of enforced wakefulness during constant routine) also influences temporal performance (Cajochen et al. 1999). Moreover, compensatory mechanisms, such as motivational factors and expectancy due to experience, also play a role in the outcome (Schmidt et al. 2007).

To date, the picture that emerges is that time-of-day modulations affect performance on a range of cognitive tasks, and these performance fluctuations are additionally contingent upon inter-individual differences in circadian preference (i.e., chronotype). It seems that only highly practiced responses (e.g., constant performance tasks) (Valdez et al. 2005) are rather invariant across the day, with all other responses being vulnerable to the time-of-day effect during normal day-night conditions, as they require a certain degree of control over stimuli and responses. Above attentional processes, higher-order cognitive functions, such as working-memory load or executive control, appear to be particularly sensitive to time-of-day modulations (Mikulincer et al. 1989). However, given the current lack of research in this domain, and the varying choices of protocol and experimental control, it is impossible to conclude whether different tasks, involving a range of cognitive processes or differing in difficulty, exhibit genuine differences in time-of-day modulations (Schmidt et al. 2007).

3. Sleep pressure modulates cognitive performance

3.1. Sleep deprivation affects attentional processes

According to the 'wake state instability' hypothesis (Doran et al. 2001), neurobehavioral performance 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 increased lapses of attention, increased numbers of errors in response, but also increased compensatory efforts resulting in normal reaction times for a short period of time. Over the last two decades, the instrument that has emerged as the dominant assay of vigilant attention in paradigms of sleep loss is the PVT (Dinges et al. 1985). This task has been widely used in human studies to detect the sustained attention (or 'vigilance') deficits associated with different types of sleep loss, including chronic sleep restriction (Belenky et al. 2003; Van Dongen et al. 2003) and sleep deprivation (Doran et al. 2001; Rétey et al. 2006). Importantly, the task is highly sensitive to sleep loss, independent of aptitude, lacks learning effects, and its reliability and validity have been amply demonstrated (Lim and Dinges 2008). The PVT is a test of simple reaction time to a cue that occurs at random inter-stimulus intervals. During the task (standard duration of 10 minutes) subjects are instructed to attend to a small, rectangular area on a dark screen. They are then required to respond as quickly as possible whenever they perceive the appearance of a bright millisecond counter inside this rectangular area. Stopping the counter allows subjects to view their reaction time, which serves as feedback for that particular trial. Button presses when the counter is not displayed on the screen are counted as false starts, which subjects are instructed to avoid. Four dominant findings have emerged from the use of the PVT in sleep research protocols. First, sleep deprivation results in an overall slowing of responses. Second, sleep deprivation increases the propensity of individuals to lapse for lengthy periods (> 500 ms), as well as make false starts. Third, sleep deprivation enhances the time-on-task effect, the phenomenon whereby performance worsens across the course of a cognitive task owing to fatigue and reduced motivation. Finally, PVT results during extended periods of wakefulness

reveal the presence of interacting circadian and homeostatic sleep-regulatory processes (Lim and Dinges 2008).

3.2. Sleep deprivation affects higher-order cognitive processes

Sleep deprivation has been shown to have significant adverse effects on a range of higher-order cognitive processes, including memory encoding, consolidation, and retrieval (Walker 2008), behavioral inhibition (Drummond et al. 2006; Harrison et al. 2007), judgment (Killgore et al. 2007a), planning (Horne 1988; Killgore et al. 2009), and divergent thinking capacities (Horne 1988). All such processes are believed to draw heavily upon resources in the prefrontal cortex (Killgore et al. 2011). Moreover, recent research from rodent experiments has highlighted that sleep deprivation is associated with reduced neural activity within brain regions involved in memory (frontal cortex and hippocampus), emotion (amygdala), and regulation of the sleep-wake cycle (anterior hypothalamus and supraoptic nucleus) (Pierard et al. 2007; Vecsey et al. 2009; Hagwoud et al. 2011). Disruption of any of these distinct facets of cognition by sleep deprivation may contribute to noteworthy errors in decision-making (reviewed by (Killgore 2010)). Interestingly, however, deficits in executive functions have not been observed universally, particularly during shorter durations of sleep deprivation, such as one night (Pace-Schott et al. 2009). This suggests that the brain's executive function systems may temporarily compensate for brief sleep loss by utilizing additional cognitive resources via activation of alternative brain regions (Drummond et al. 2000; Drummond et al. 2005b).

More recently, research has focused on clarifying the ways in which sleep deprivation may influence well-characterized, higher cognitive processes, such as mental heuristics and emotional biases that affect risk assessment and decision-making (Killgore et al. 2012). For example, McKenna and colleagues (2007) revealed that when the possible outcomes from a gambling task were framed in terms of potential gains, sleep deprivation prompted subjects to take more risks compared to when they were well rested. Yet when the same task was presented in terms of potential losses, lack

of sleep led them to take fewer risks than usual. Such findings indicate that sleep deprivation may lead to greater reliance upon pre-existing cognitive biases. Moreover, functional neuro-imaging studies have highlighted that sleep-deprived individuals show differences within brain-reward circuitry during risky decision making, and this may bias them toward expectations of gains while reducing their focus on losses (Venkatraman et al. 2007).

Another way that prolonged wakefulness affects decision-making is by reducing the weight that a person places on new information when making choices (Dickinson and Drummond 2008). Sleep deprived individuals may tend to rely more upon automatic, as opposed to effortful, forms of cognitive processing (Killgore et al. 2012). Emotional biasing is a form of automatic processing that may influence decision making. Indeed, Damasio (1994) proposed that emotional reactions act as a cognitive streamlining function that quickly and efficiently narrows an individual's choice of options. These emotional 'gut reactions' prime a person to make choices based on how rewarding or unpleasant they found a previous similar experience. In an experimental setting, this emotion-guided decision making can be investigated using the Iowa Gambling Task (IGT) (Bechara et al. 1994). During the computerized program, participants are presented with four decks of cards placed face down. Next, 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. Unbeknownst to the subject, however, two of the decks are 'good' decks and lead to small but consistent net gains; while the other two decks are 'bad' decks, and comprise large short-term gains but consistent long-term losses. With regards to the results, healthy individuals usually learn from the trial-by-trial feedback and adjust their playing strategy to avoid the risky bad decks in favor of the modest, but consistently advantageous, good decks (Bechara 2004). However, patients with damage to the ventromedial prefrontal cortex (vmPFC) fail to make this adjustment (Bechara 2004). Such findings are in line with evidence that damage to the vmPFC leads to shortsightedness for the future (Bechara et al. 1994), as well as neuroimaging data that indicates that this brain region plays a key role in the decision making process of the IGT (Li et al. 2010).

Importantly, the vmPFC seems to be particularly affected by sleep deprivation. Metabolic activity in this brain region is drastically reduced after a single night of sleep loss (Thomas et al. 2000), whereas increased activation of this area is correlated to a subject's degree of responsiveness to rewards during sleep-deprived decision-making (Venkatraman et al. 2011). Accordingly, in a series of studies performed by Killgore and colleagues (2006; 2007b), the IGT was used to assess the effects of sleep deprivation on emotionally-guided decision making. As predicted, well-rested subjects rapidly learned the contingencies of the task. However, following 49 (Killgore et al. 2006) and 75 hours (Killgore et al. 2007b) of prolonged wakefulness, the same participants showed a significant decline in decision making 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. Overall, such findings indicate that prolonged sleep loss is associated with making choices that begin to favor short-term over long-term outcomes – a pattern paralleling that often observed among patients with lesions to the vmPFC (Bechara 2004). Since the vmPFC is important in several key cognitive-affective processes (Damasio 1994), alterations in vmPFC functioning, or its associated neuro-circuitry following sleep loss, may indeed underlie some of the subtle changes in decision-making observed in the two Killgore et al. studies. The findings are also in accordance with evidence suggesting that sleep deprivation leads to difficulty incorporating new information into ongoing decision making processes, implying an overall decline in cognitive flexibility, in favor of greater reliance on automatic cognitive processes (Dickinson and Drummond 2008).

Taken together, these behavioral findings suggest that distinct higher-order cognitive processes are impaired by sleep deprivation. The sensitivity of the prefrontal cortex to the effects of sleep loss may also be reflected in distinct neurophysiological changes associated with sleep deprivation. For example, regional cerebral blood flow in this region correlates with electroencephalogram (EEG) slow-wave activity (SWA; power density in the 0.75-4.5 Hz range) in non-rapid-eye-movement (NREM) sleep (Dang-Vu et al. 2010), which represents the primary

physiological marker of sleep homeostasis (Achermann and Borbély 2011). Moreover, not only the increase in SWA in NREM sleep, but also the rise in EEG theta (~5-9 Hz range) activity after prolonged wakefulness (Cajochen et al. 1995) is larger over anterior than over posterior cortical areas (Finelli et al. 2000).

4. Cerebral underpinnings of circadian and homeostatic influences on performance

Accumulating evidence demonstrates that circadian and homeostatic sleep-wake regulatory processes interact in a fine-tuned manner to modulate cognitive performance (Schmidt et al. 2012). Neural connections from the SCN indirectly reach target areas implicated in sleep homeostasis, including ventro-lateral-preoptic area, tuberomammillary nucleus, lateral hypothalamus, thalamus, and brainstem nuclei via its connections to the dorsal medial hypothalamus (Mistlberger 2005). Simultaneously, diffuse monoaminergic activating systems are under circadian control and adjoin with many thalamo-cortical areas, which suggests that the interaction with sleep homeostasis takes place at many different levels (Dijk and Archer 2009).

Research conducted by Aston-Jones and colleagues indicated that the noradrenergic locus coeruleus plays an important role in the circadian regulation of arousal (2005; 2001). Activity in the locus coeruleus, combined with its widespread thalamic and cortical connections, may modulate a variety of central nervous system functions, including alertness and vigilance, and also higher-order cognitive processes (Cajochen et al. 2010). Moreover, a recent study incorporating behavioral assessments, EEG, and functional magnetic resonance imaging (fMRI) in morning and evening chronotypes indicated that homeostatic sleep pressure exerts an influence on attention-related cerebral activity in key structures crucially involved in generating the circadian wake-promoting signal, including the locus coeruleus. Specifically, maintenance of optimal attentional performance in the evening after a normal waking day was associated with higher activity in evening chronotypes than in morning chronotypes in locus coeruleus and anterior hypothalamus, including the SCN

(Schmidt et al. 2009). Furthermore, activity in the anterior hypothalamus decreased with increasing homeostatic sleep pressure, as indexed by EEG SWA in the first NREM sleep episode. These data suggest that circadian and homeostatic interactions contribute to the neural activity that underlies diurnal variations in human behavior. Interestingly, the differential activation pattern was observed only for optimal performance on the PVT (i.e., the fastest 10^{th} percentile of reaction times) (Schmidt et al. 2012), which reflects the phasic ability to recruit the attentional network above normal levels (Drummond et al. 2005a).

The mechanisms by which circadian oscillations in the SCN, as well as circuits controlling for states of wakefulness and sleep, interact at the cerebral level in order to regulate arousal and cognitive behavior, are yet to be clarified (Cajochen et al. 2010). Conceptually, endogenous 'sleep substances' may accumulate during wakefulness and modify activity in key areas regulating cortical arousal, including brainstem, hypothalamic nuclei and basal forebrain. During sleep, the 'sleep substances' would dissipate. Although the biochemical 'substrate' of sleep homeostasis remains poorly understood, adenosine, nitric oxide, prostaglandin D_2, tumor necrosis factor alpha, interleukin-1, growth-hormone-releasing hormone, and brain-derived neurotrophic factor are considered to be important candidate mediators of the consequences of prolonged wakefulness (Krueger et al. 2008).

5. A role for adenosine in homeostatic sleep-wake regulation

Compelling and converging evidence in animals and humans has accumulated over the past two decades to support a role for adenosine and adenosine receptors in sleep-wake regulation (see (Krueger et al. 2008; Landolt 2008; Porkka-Heiskanen and Kalinchuk 2011) for reviews). Animal studies suggest that the extracellular adenosine concentration in the brain may increase during prolonged wakefulness and decline during (recovery) sleep (Porkka-Heiskanen et al. 2000).

5.1. Adenosine formation, transport and metabolism

The formation of adenosine in the brain changes in an activity-dependent manner and different mechanisms contribute to the appearance of adenosine in extracellular space. Increased energy demand during wakefulness leads to the break-down of energy-rich adenine nucleosides such as adenosine-tri-phosphate (ATP). Adenosine is formed in neurons by 5'-nucleotidase and transported through plasma and intracellular membranes by specialized transporters, including sodium-driven concentrative and equilibrative nucleoside transporters (Fig. 2). The concentrative transporters use energy to move adenosine into the cell, whereas the equilibrative transporters transport adenosine according to the extracellular/intracellular concentration gradient. Elevated intracellular adenosine concentrations following increased utilization of ATP in conditions of high energy demand lead to release of adenosine. In addition, extracellular adenosine is also formed by ecto-nucleotidases through hydrolysis of ATP. Release of ATP from synaptic vesicles occurs along with several other neurotransmitters, including the major excitatory neurotransmitter glutamate (Haydon and Carmignoto 2006). Finally, ATP and glutamate are also released from astrocytes by a recently established process referred to as gliotransmission. Molecular genetic manipulations in mice strongly suggest that glial cells provide a significant source of extracellular adenosine in the brain (Haydon and Carmignoto 2006). Furthermore, astrocyte-derived ATP may activate purinergic (e.g., $P2X_7$) receptors and affect sleep independently from adenosine (Krueger et al., 2008; Krueger et al., 2010).

Clearance of extracellular adenosine mostly occurs through the non-concentrative nucleoside transporters (Fredholm et al. 2005). The main intracellular metabolic pathways of adenosine are the formation of adenosine-mono-phosphate by adenosine kinase, and the irreversible break-down to inosine by adenosine deaminase (ADA). Ecto-ADA also catalyzes the extracellular deamination of adenosine. Mainly due to the high activity of adenosine kinase, baseline levels of extracellular adenosine usually remain low. The action of ADA, which appears to be more abundantly expressed in astrocytes than in neurons (Fredholm et al. 2005), may be particularly important when elevated concentrations of adenosine have to be cleared, such as after sleep deprivation. Both, molecular genetic manipulations of adenosine kinase in mice (Palchykova et al. 2010), as well as genetically reduced ADA enzymatic

activity in humans (Rétey et al. 2005), increase deep slow wave sleep and EEG SWA in NREM sleep. These findings provide strong additional support to the idea that adenosine importantly contributes to the homeostatic control of sleep.

5.2. Adenosine affects neuronal systems regulating wakefulness and sleep

Adenosine attenuates the activity of wakefulness/vigilance-promoting neurons in brainstem (e.g., locus coeruleus), basal forebrain (BF), and hypothalamus (e.g., tuberomammillary nucleus) and my contribute to cortical disfacilitation, a form of inhibition due to reduced activating input from ascending cholinergic and monoaminergic pathways. As suggested by intracellular recordings in non-anaesthetized cats the long-lasting hyperpolarizing potentials in NREM sleep, which provide the cellular substrate of EEG SWA, may represent periods of disfacilition (Steriade et al. 2001; Timofeev et al. 2001). Moreover, adenosine activates neurons of the hypothalamic ventro-lateral-preoptic area by reducing inhibitory γ-amino-butyric-acid (GABA)-ergic inputs. These neurons fire significantly faster after sleep deprivation than they do during normal sleep, indicating that their activity is modulated by homeostatic mechanisms representing sleep need (Sherin et al. 1996).

One current hypothesis based upon biochemical, pharmacological, electrophysiological, and behavioral studies postulates that elevated adenosine in the BF plays a distinct role in mediating the sleep deprivation-induced increase in sleepiness and homeostatic sleep drive (Basheer et al. 2004; Porkka-Heiskanen and Kalinchuk 2011; Strecker et al. 2000). It may be important to note, however, that Blanco-Centurion and colleagues highlighted that the actions of adenosine are not restricted to the BF region (2006). This research team used a lesion and pharmacological approach to reveal that adenosine accumulation in the BF is not necessary for sleep induction, and also that BF cholinergic neurons are not essential for sleep drive. Thus, the available data rather suggest that extracellular adenosine provides a global feedback signal on a neuronal network, including subcortical and

cortical structures (Franks 2008), that regulates important functional aspects of wakefulness and sleep.

6. Adenosine A_1 and A_{2A} receptors mediate effects of adenosine in sleep-wake regulation

The cellular effects of adenosine are mediated via four subtypes of G-protein coupled adenosine receptors: A_1, A_{2A}, A_{2B}, and A_3 receptors. *In vitro* studies indicate that physiological concentrations of endogenous adenosine can activate A_1, A_{2A}, as well as A_3 receptors. Nevertheless, it is widely accepted that the high-affinity A_1 and A_{2A} receptors are primarily involved in mediating the effects of adenosine on sleep and vigilance, at least in humans (Sebastiao and Ribeiro 2009).

6.1. Adenosine A_1 receptors and the effects of prolonged wakefulness

The stimulation of A_1 receptors opens several types of K^+-channels, inhibits adenylate cyclase through activation of G_i proteins and inactivates transient voltage-dependent Ca^{2+}-channels. The A_1 receptor is ubiquitously, but not homogenously, expressed in the central nervous system (Bauer and Ishiwata 2009). *In vivo* PET with the selective A_1 receptor antagonist, ^{18}F-CPFPX, revealed highest receptor occupancy in striatum and thalamus, as well as temporo-parietal and occipital cortex (Fig. 3A). Pre- and post-synaptic activation of A_1 receptors inhibits excitatory neurotransmission. This receptor subtype, therefore, has long been assumed to play an important role in sleep-wake regulation. Pharmacologic and genetic studies in rats and mice, as well as molecular imaging in humans, partly support this notion. For example, inducible knock-out of neuronal A_1 receptors in mice reduces SWA (3.0-4.5 Hz range) in NREM sleep under baseline conditions, and attenuates the homeostatically regulated rise in SWA after sleep restriction (Bjorness et al. 2009). Moreover, prolonged wakefulness appears to up-regulate A_1 receptor binding in subcortical and cortical brain structures in animals and humans (Elmenhorst et al. 2009; Elmenhorst et al. 2007). Taken together, these data indicate a role for adenosine A_1 receptors in mediating distinct consequences of sleep deprivation.

6.2. Adenosine A_{2A} receptors and the effects of prolonged wakefulness

The stimulation of A_{2A} receptors increases adenylate cyclase activity through activation of G_s (or G_{olf} in striatum) proteins, induces the formation of inositol phosphates, and activates protein kinase A. Compared to the A_1 receptor, this adenosine receptor subtype is less widely distributed in the brain (Bauer and Ishiwata 2009). The highest expression in the human central nervous system is found in basal ganglia (particularly in putamen and caudate nucleus) (Fig. 3B). Recent studies in rodents, including experiments in knock-out mice, suggest that also A_{2A} receptors contribute to the effects of adenosine on sleep. Local administration of the selective A_{2A} receptor agonist, CGS21680, to the subarachnoid space adjacent to BF and lateral preoptic area increases *c-fos* expression in the ventro-lateral-preoptic area and promotes NREM sleep (Scammell et al. 2001). Direct activation of sleep-promoting neurons of the ventro-lateral-preoptic region upon stimulation of A_{2A} receptors could underlie this effect (Gallopin et al. 2005). Interestingly, preliminary data suggested that mice with A_{2A} receptor loss-of-function have reduced sleep and an attenuated sleep rebound after sleep deprivation (Hayaishi et al. 2004), indicating that A_{2A} receptors are part of the neural network that regulates sleep homeostasis in mammals. These findings are supported by recent data in humans, suggesting that genetic variants of the A_{2A} receptor gene (*ADORA2A*) modulate the sleep deprivation-induced increase in EEG SWA in NREM sleep (Bodenmann et al. 2012; Landolt 2012).

In conclusion, both adenosine A_1 and A_{2A} receptor subtypes probably mediate functional effects of adenosine after sleep deprivation, whereas distinct effects may be site- and receptor-dependent.

7. Adenosine and sleep-associated cognitive functions

7.1. Sleep deprivation, adenosine, and vigilant attention

While a wealth of evidence supports the concept that modulation of cerebral adenosine contributes to the regulation of wakefulness and sleep, it was not until more recently that research revealed how this manipulation could also alter neurobehavioral performance (Christie et al. 2008). This is poignant given that the BF in particular has been implicated not only in adenosinergic mechanisms of sleep regulation but also in the control of sustained attention (Baxter and Chiba 1999). Thus, the fact that decrements in sustained attention tend to occur concomitantly with feelings of sleepiness, is consistent with studies indicating that the same mechanisms implicated in the control of the homeostatic sleep drive, are also involved in the regulation of attention (Zaborszky et al. 1997). Moreover, neurons within the BF project to components of the cortical sustained attention network, whose activation is linked with optimal human performance on the PVT (Drummond et al. 2005a). More recently, a rat version of the PVT was developed that enabled invasive investigations of the role of adenosine and the BF in the control of behavioral state and sustained attention (Christie et al. 2008). Christie and colleagues (2008) utilized this task to assess the effects of elevated cerebral adenosine on vigilant performance. The study revealed that rats receiving infusions of adenosine in the BF immediately prior to performing the PVT showed prolonged response latencies and more performance lapses. The effect was blocked by the co-administration of the A_1 receptor antagonist, 8-cyclopentyl-theophylline, demonstrating that the performance decrements were indeed due to elevated adenosine in the BF and apparently mediated by A_1 receptors, as opposed to other, unrelated factors (Christie et al. 2008). Furthermore, the adenosine-induced impairments in sustained attention were similar to those seen in rats undergoing sleep deprivation (Cordova et al. 2006). These findings are consistent with the hypothesis that sleep loss induces an accumulation of adenosine in the BF, which leads to increased sleepiness and reduced vigilance.

Local cerebral administration of adenosine is not possible in humans, to study its role in reduced vigilant attention during sleep deprivation. Nevertheless, relevant information has been obtained from studies on a naturally occurring genetic variation of the gene encoding the adenosine

metabolising enzyme ADA. A G-to-A single nucleotide polymorphism at nucleotide 22 of the gene encoding ADA underlies an Asp-to-Asn amino-acid substitution at codon 8 of the ADA protein. Compared to G/G homozygotes, carriers of the variant allele show reduced ADA activity *in vitro* (Battistuzzi et al. 1981; Riksen et al. 2008), and presumably elevated tissue adenosine levels *in vivo* (Hirschhorn et al. 1994). This functional polymorphism not only modulates the duration and intensity of slow wave sleep (Bachmann et al. 2012; Mazzotti et al. 2012; Rétey et al. 2005), but also human attentional performance in rested and sleep deprived states. More specifically, carriers of the G/A genotype (n = 29) performed worse on the d2 focused attention task than G/G homozygotes (n = 191) (Bachmann et al. 2012). The difference was also present between two prospectively matched subgroups of G/A (n = 11) and G/G (n = 11) genotypes. Moreover, sustained attention (Fig. 4A) and vigor were reduced, whereas waking EEG alpha activity (8.5-12 Hz), sleepiness, fatigue, and *α*-amylase activity in saliva were enhanced in A-allele carriers when compared to G/G homozygotes. These convergent data demonstrate that genetic reduction of ADA activity in healthy humans not only modulates the quality of sleep, but also the quality of wakefulness, including neurobehavioral performance.

7.2. Sleep deprivation, adenosine, and higher-order cognitive functions

As discussed previously, Bjorness and colleagues (2009) revealed that conditional knock-out of the A_1 receptor elicits selective attenuation of the SWA rebound following restricted sleep. This research team also investigated the effects of this genetic manipulation on working memory. It demonstrated that animals lacking the A_1 receptor not only showed a reduced rebound SWA response, but they also failed to maintain normal cognitive function, although this function was normal when sleep was not restricted. Since the attenuation of SWA is associated with compromised working memory performance, this indicates a functional role for adenosine A_1 receptor-dependent SWA homeostasis in maintaining this cognitive ability when sleep is restricted (Bjorness et al. 2009). Here, it is worth noting

that the loss of the A_1 receptors in the conditional gene deletion used in this study is exclusively neuronal. Nevertheless, the source of the adenosine includes both neuronal and non-neuronal, or glia, cells (Pascual et al. 2005; Studer et al. 2006). Halassa and colleagues (2009) inhibited the release of adenosine from glia cells in transgenic mice expressing a dominant-negative (dn) SNARE domain in astrocytes, in order to investigate if astrocytes play a role in sleep-wake regulation. They found that this genetic restriction of gliotransmission attenuated the build-up of sleep pressure, and prevented memory deficits associated with sleep loss. The data suggest an important role for astrocyte-derived adenosine in modulating cognitive consequences of sleep deprivation. Furthermore, the research team also conducted pharmacological studies and concluded that astrocytes modulate the accumulation of sleep pressure and its cognitive consequences through a pathway involving adenosine A_1 receptors (Halassa et al. 2009).

8. The adenosine receptor antagonist caffeine and sleep-loss-associated cognitive impairments

Caffeine is the most widely consumed stimulant in the world. In the μM plasma concentrations reached after moderate consumption, caffeine acts as a non-selective, competitive antagonist at A_1 and A_{2A} receptors (Fredholm et al. 1999). Novel PET imaging findings suggest that intake of 4-5 cups of coffee (corresponding to ~450 mg caffeine) in a 70-kg volunteer can displace endogenous adenosine from 50% of cerebral A_1 receptors (Elmenhorst et al. 2012). By contrast, other effects of caffeine observed *in vitro*, such as inhibition of phosphodiesterase, blockade of $GABA_A$ receptors and Ca^{2+} release, require more than 100 times higher doses than adenosine receptor antagonism and are toxic in humans (Fredholm 1995).

8.1. Caffeine counteracts sleep deprivation-induced impaired vigilant attention by interfering with sleep homeostasis

Various studies have examined the effects of caffeine on sustained attention in humans, via performance on the PVT. The psychostimulant has been consistently shown to reverse PVT impairments in sleepy humans (Balkin et al. 2004; Kamimori et al. 2005; Rétey et al. 2006; Van Dongen et al. 2001; Wyatt et al. 2004). Given that physiological doses of caffeine antagonize adenosine receptors, such findings are consistent with those of the aforementioned rodent study, which revealed decrements in vigilant performance following adenosine administration (Christie et al. 2008).

Wyatt and colleagues (2004) reflected that many studies investigating the neurobehavioral benefits of caffeine during sleep loss confounded the two major processes regulating sleep and wakefulness: the circadian phase and the duration of prior wakefulness (i.e., homeostatic sleep pressure). Specifically, previous research had not clarified if caffeine's ability to counteract performance deficits related to sleep deprivation was related to its interaction with circadian or homeostatic signals modulating sleep propensity and performance. The authors stress the importance of accounting for variance explained by sleep homeostatic and circadian modulation when interpreting data from protocols in which tests are given in only a single administration, such as typically occurs in traditional clinical and cognitive neuroscience research. As a result, the research team conducted a study to assess the effects of repeated low-dose caffeine administration during a 29-day forced desynchrony paradigm. The period of the sleep-wake cycle was scheduled to be 42.85 hours (28.57-hour wake episodes and 14.28-hour sleep episodes), and thus far removed from the circadian range. This protocol allowed for separate quantification of the circadian, sleep homeostatic, and caffeine contributions to performance deficits and improvements. Moreover, the 42.85-hour cycle simulated the extended wakefulness commonly encountered by medical and military personal, or anyone skipping a night of sleep (Wyatt et al. 2004).

During the study, caffeine was administered during wakefulness at a rate of 0.3 mg per kg per hour. The dosage schedule was designed to increase caffeine blood plasma concentrations in parallel to the rate of increase in sleep homeostatic drive during wakefulness, and also in line with

the potential accumulation of adenosine (Porkka-Heiskanen et al. 2000). Polysomnographic recordings were used to monitor each scheduled sleep episode, as well as the majority of each wake episode, in order to detect incidences of slow eye movements and unintentional sleep onsets. During wake periods, mood and subjective sleepiness were assessed at 30-minute intervals using visual analog scales and the Karolinska Sleepiness Scale. Cognitive performance was tested every 2 hours.

Post completion of the study, comparison of the placebo and caffeine data revealed that rising levels of caffeine significantly reduced wake-dependent deterioration in several measures of cognitive functioning, particularly at the circadian performance nadir (Wyatt et al. 2004). Specifically, caffeine attenuated performance deficits on the PVT such that the caffeine group showed fewer lapses and less impairment in the slowest 10% of reaction times than the placebo group. Caffeine also enhanced the ability of subjects to remain consistently awake for extended periods. That is, the researchers observed inhibition of EEG-verified accidental sleep onsets during scheduled wake episodes. Such findings suggest that individuals receiving caffeine were kept at an earlier, less-severe stage of the sleep-onset continuum (Ogilvie et al. 1988), and this held them back from completing the full transition to sleep. However, the caffeine group also showed impairment of polysomnographically verified sleep during scheduled sleep episodes. Subsequently, the additional sleep accumulated by the placebo group during scheduled wake and sleep episodes was associated with lower reports of sleepiness, independent of circadian phase or duration of prior scheduled wakefulness. Indeed, subjects receiving caffeine self-reported greater impairment of alertness on the Karolinska Sleepiness Scale and visual analog scales. A similar paradoxical finding of increased subjective sleepiness in participants receiving caffeine over repeated days has been reported in other studies (Bonnet and Arand 1992). Thus, the wake-promoting effects of caffeine do not replace the restorative effects gained through sleep (Wyatt et al. 2004).

The evidence of a reduction in accidental sleep onsets during caffeine administration supports the concept that caffeine attenuates expression of homeostatic sleep drive. Because the

plasma caffeine concentrations of caffeine reached in this study can be expected to affect solely adenosine receptors (Fredholm et al. 1999) and because caffeine primarily affects the sleep-wake-dependent modulation of performance, the present findings are in accordance with the proposed role for adenosine in mediating sleep-wake-dependent modulation of sleep propensity and associated variation in neurobehavioral functioning (Wyatt et al. 2004). While further research is required to elucidate whether mechanisms other than adenosine receptor antagonism or a certain degree of tolerance to caffeine over repeated administration could have influenced the experimental outcomes, repeated, low-dose caffeine administration holds potential as a countermeasure to cognitive deficits and unintended sleep attacks, at the cost of increasing subjective sleepiness.

8.2. Caffeine ameliorates deficits in vigilant attention from sleep inertia

Another study suggested that caffeine reduces impaired vigilant attention associated with sleep inertia under conditions of sleep loss. Sleep inertia refers to the impaired cognitive performance, grogginess, and tendency to fall back to sleep immediately after waking (Dinges and Orne 1981). Van Dongen and colleagues (2001) administered sustained low-dose caffeine (0.3 mg per kg per hour, except during naps) or placebo to healthy volunteers during the last 66-hours of an 88-hour period of extended wakefulness, which included seven 2-hour naps during which polysomnographical recordings were made. Performance on the PVT was assessed every 2 hours of wakefulness, and also during the sleep inertia experienced after awakening from naps. The results revealed that during the placebo condition, testing during sleep inertia was associated with significantly impaired psychomotor vigilance. By contrast, these performance decrements were absent in the caffeine condition. Thus caffeine was shown to be an effective countermeasure to the impaired sustained attention seen during sleep inertia (Van Dongen et al. 2001).

Many people consume caffeine-containing beverages in the morning, directly after waking, at a time when their homeostatic sleep drive should be reduced. Thus, arguably, there should be no need to take the stimulant at this time of the day. Nevertheless, it is possible that following rapid awakening from NREM sleep, elevated levels of adenosine, and the corresponding existence of low vigilance and high sleepiness (Virus et al. 1983), could persist until adenosine is removed by reuptake or metabolism, and hence the phenomenon of sleep inertia (Van Dongen et al. 2001). In accordance with this hypothesis, sleep inertia does indeed seem to intensify with prior sleep loss (Dinges et al. 1985), and it is more pronounced when awakening occurs from NREM sleep, rather than from REM sleep (Broughton 1968; Bruck and Pisani 1999). The study of Van Dongen and colleagues (2001) involved less than four hours of sleep per 24-hours. Following the sleep periods, 85% of awakenings occurred out of NREM sleep in the placebo condition, and subsequent deficits in psychomotor vigilance performance, due to sleep inertia, were consistently recorded. However, during the caffeine condition, sleep inertia after awakening from nap sleep was not apparent. Moreover, when psychomotor vigilance was tested between naps, as opposed to directly afterwards, there was no difference between performance in the two conditions. Such results imply that caffeine's effect was specific to sleep inertia. Overall, such findings are in accordance with the hypothesis that adenosine may be a neurobiological substrate of the sleep inertia phenomenon (Van Dongen et al. 2001).

8.3. Caffeine reduces false memories after sleep loss by improving arousal and attention

Human memory is not an exact record of the world and our experiences, but instead is influenced by knowledge representations that already exist in the brain (Bartlett 1932). As a result, what is retrieved from memory can substantially differ from what was originally encoded (Schacter et al. 1998). For example, in some instances, people claim to remember events that in fact never happened. These false memories tend to be semantically linked to actually encoded events, and subjects are usually very confident about the correctness of these memories (Roediger and

Mcdermott 1995). Schacter and colleagues (1998) suggest that the development of false memories involves the disruption of the same basic principles of memory formation as the development of correct memories. Memory formation involves three distinct stages: encoding (learning); consolidation (off-line processing and strengthening of memory traces after encoding); and retrieval of the learned material. Research has demonstrated that sleep deprivation may not only impair encoding and consolidation of memory, but also memory retrieval (Harrison and Horne 2000). Impaired memory retrieval associated with reduced source and reality monitoring may be involved in the generation of false memories, and consequently sleep deprivation would be expected to enhance their creation (Diekelmann et al. 2008). In a series of experiments, Diekelmann and colleagues (2008) investigated sleep-associated mechanisms of false memory generation, using the well-established Deese, Roediger, McDermott false memory paradigm (Roediger and Mcdermott 1995). Here, subjects learned lists of semantically associated words (e.g., 'night', 'dark', 'coal'). The strongest associate, however, or the 'theme' of the list ('black' in this example), was not presented during learning. Subsequently, memory retrieval was tested 9, 33 or 44 hours after learning. This involved the presentation of the previously viewed 'list' words, together with the 'theme' word (or 'critical lure') and unrelated distracter words. Subjects were required to indicate whether a word had been presented during the learning phase or not. Immediately after learning the words, during the memory consolidation phase, participants either slept or stayed awake. At word retrieval, they were or were not acutely sleep deprived. The study revealed that when participants were sleep deprived during retrieval of stored words, there was a significant increase in the number of false memories of theme words. That is, they reported that they had been presented with a specific word during the learning phase, when in fact they had not. Of particular relevance to the present discussion was the finding that this distortion of memory was removed by administering caffeine to the sleep deprived subjects prior to retrieval testing. Such evidence indicates that adenosinergic mechanisms are involved in the depletion of specific cognitive resources, which elicits the generation of false memories associated with sleep loss (Diekelmann et al. 2008). It is possible that

caffeine improved reduced arousal and sustained attention after sleep deprivation, which rely on a prefrontal-parietal network, basal forebrain and thalamus, and are known to be implicated in memory functions.

8.4. Caffeine has weak potency to improve impaired higher-order and executive functions after sleep deprivation

Much research regarding the effects of caffeine on performance during sleep deprivation has focused primarily on measures of simple cognitive processes, as opposed to memory and executive functions. Yet, if a subjective state or cognitive function is impaired by sleep loss, then it may be expected that this decrement would be reversed by caffeine (Wyatt et al. 2004). To test this hypothesis, Wyatt and colleagues (2004) not only studied the effects of caffeine on PVT performance during forced desynchrony, but also assessed short-term memory (Probed Recall Memory Task) and cognitive throughput (Addition Task, Digit Symbol Substitution Task). Indeed, caffeine tended to reduce the wake-dependent impairment of short-term memory and attenuated performance deficits in the two cognitive throughput tasks when compared to placebo. Thus, the potential benefits of caffeine on higher-order cognitive performance warrant further investigation.

Killgore and colleagues (2012) performed an investigation into the potential benefits of stimulants on decision making during sleep deprivation. The protocol required subjects to perform the IGT at four time points throughout a period comprising 61 hours of sleep deprivation and 12 hours of recovery sleep. After 44 hours of wakefulness, participants received a double-blind administration of caffeine (600 mg), d-amphetamine (20 mg), modafinil (400 mg), or placebo. As predicted, sleep deprivation was found to alter normal decision making, which was consistent with the team's previous research (Killgore et al. 2006; Killgore et al. 2007b). Yet, perhaps the most important finding was the fact that although all three stimulants were highly effective at reducing subjective sleepiness and sustaining psychomotor vigilance relative to placebo, none of the

pharmacologic agents provided any significant enhancement of decision-making performance on the IGT. In fact, performance was similar to placebo for all stimulant groups (Killgore et al. 2012). It should be noted here that IGT performance was unrelated to self-reported sleepiness or psychomotor vigilance performance during the administration of the stimulants, which implies that the deficits observed in decision-making were independent of differences in alertness. That is, despite subjects on stimulants being awake, alert, and able to sustain psychomotor vigilance, they were not any better than placebo on the IGT (Killgore et al. 2012). These findings are consistent with a previous study which evaluated the effect of caffeine on sleep-deprived IGT performance (Killgore et al. 2007b). In that study, repeated doses of caffeine (200 mg every 2 hours) during the overnight sessions, up to 3 hours before each IGT, had virtually no effect on performance relative to placebo at either 51 or 75 hours of sleep deprivation. Similarly, caffeine had no significant effect on the time taken for subjects to make various types of moral judgments after 53 hours of prolonged wakefulness (Killgore et al. 2007b).

In fact, other studies have also reported limited effects of various stimulants on higher-order cognition and executive functions during sleep loss. For example, Gottselig and colleagues (2006) revealed that caffeine was effective at restoring simple aspects of cognitive functioning, such as attention. Yet, the stimulant failed to restore a more complex aspect of executive function, random number generation (Brugger et al. 1996), a cognitive process that relies on the prefrontal cortex (Gottselig et al. 2006).

Some evidence indicates that the effectiveness of stimulants, including caffeine, on executive functions may be task specific, and depend upon the underlying executive function systems targeted by different stimulant (Killgore et al. 2009). For instance, participants' performance on a behavioral measure of risk-taking and impulsive responding (the Balloon Analog Risk Task) was relatively resistant to the effects of sleep loss until about 75 hours of continuous wakefulness, at which point there was a clear increase in risky decision making (Killgore et al. 2011). It is noteworthy that caffeine appeared to mitigate this surge in risk-taking at extreme sleep deprivation (Killgore et

al. 2011). This finding suggests that the types of executive functions measured by the Iowa Gambling Task, the random number generation task, and the Balloon Analog Risk Task may involve different brain systems that are differentially affected by caffeine, and thus adenosinergic mechanisms.

9. Inter-individual differences in the effects of caffeine

More recently, there has been increased interest in inter-individual differences in the impairment of neurobehavioral functions from sleep loss and in the effectiveness of common pharmacological countermeasures such as caffeine. The clarification of the mechanisms underlying these differences is relevant because they would reveal insights into the neurophysiological regulation of human wakefulness and sleep. Moreover, they are also of clinical importance because they may highlight individuals at greater risk for impaired neurobehavioral performance and reduced health associated with prolonged wakefulness and shift work (Rajaratnam and Arendt 2001). In humans, sleep loss produces a range of cognitive deficits, including reduction in vigilance, working memory and executive function. Yet, there are large inter-individual differences in these deficits, which account for a substantial portion of the variance. In a study involving repeated exposure to sleep deprivation under controlled laboratory conditions, Van Dongen and colleagues (2004) demonstrated that sleep loss negatively influences measures of subjective sleepiness, fatigue and mood, behavioral alertness (sustained attention), and cognitive processing capability (working memory). While these impairments were stable within individuals, there were significant differences among individuals that were not merely a consequence of a different sleep history. Thus, the authors suggested that these individual differences represented trait-like differential vulnerability to sleep loss.

9.1. Adenosinergic mechanisms contribute to inter-individual differences in vigilant attention during prolonged wakefulness

Given the evidence discussed above, Rétey and colleagues (2006) predicted that adenosinergic mechanisms play a role for inter-individual differences in neurobehavioral function during prolonged wakefulness. To test this hypothesis, the research team investigated the combined effects of sleep deprivation and caffeine on PVT speed and EEG activity in individuals that rated themselves as either caffeine-sensitive or caffeine-insensitive. It was previously suggested that subjective differences in the psychostimulant effects of caffeine might reflect genetically determined differences in the adenosinergic system (Alsene et al. 2003; Goldstein et al. 1965). Thus it was hypothesized that subjects from both ends of the caffeine-sensitivity spectrum would not only react differently to caffeine, but also show different sleep-deprivation induced changes in neurobehavioral function and the EEG (Rétey et al. 2006). The study protocol required the 12 subjectively caffeine-sensitive and 10 caffeine-insensitive subjects to complete two experimental blocks separated by one week. Each block consisted of 4 nights and 2 days in the sleep laboratory. After 2 consecutive, 8-hour, nocturnal sleep recordings (comprising an 'adaptation' night and baseline assessment), the subjects were kept awake for 40 hours under constant supervision by members of the research team. During this period of prolonged wakefulness, EEG topography was assessed every three hours, as well as PVT and random number generation performance. After both 11 and 23 hours of sleep deprivation, participants received a capsule with either 200 mg caffeine or placebo, according to a randomized, double-blind, cross-over design. Finally, a 10.5-hour recovery night was followed by a final waking EEG, PVT, and random number generation assessment.

Analysis of the results revealed that while there were no differences at baseline in optimal PVT performance (i.e., the fastest 10^{th} percentile of reaction times) between subjectively caffeine-sensitive and -insensitive men, there were differences in the regional EEG power distribution between these groups in the theta range in waking after a baseline night of sleep. These differences were enhanced by sleep deprivation in the antero-posterior power gradients in the waking EEG, and also induced differences in the PVT (Rétey et al. 2006). Here, prolonged wakefulness impaired PVT speed more in self-rated caffeine-sensitive individuals than in caffeine-insensitive individuals. Such

observations are in accordance with functional imaging studies indicating that the vulnerability to sleep deprivation-induced performance decline in working memory is linked with baseline differences in task-related cortical activation (Mu et al. 2005). Taken together, the findings suggest that physiological variables recorded during baseline assessment could be useful future predictors of individual vulnerability to sleep deprivation.

Importantly, caffeine counteracted the sleep-loss-induced PVT differences between the two groups of subjects. Moreover, correlation analyses revealed that those individuals with the largest neurobehavioral impairment from sleep deprivation benefited the most from the stimulant action of caffeine. Interestingly, optimal PVT performance has been shown to activate a cortical sustained attention network and the motor system including the striatum (Drummond et al. 2005a). This region shows prominent expression of adenosine A_{2A} receptors (Fig. 3B) (Bauer and Ishiwata 2009). Furthermore, this adenosine receptor subgroup was shown to be responsible for the wakefulness-promoting effect of caffeine (Huang et al. 2005; Lazarus et al. 2011), and a common c.1976T>C polymorphism of the A_{2A} receptor gene has been associated with inter-individual differences in EEG theta power during wakefulness and sleep (Rétey et al. 2005). Therefore, Rétey and colleagues suggested that this adenosine receptor subtype plays a role in determining the differences between individuals in their vulnerability to impairments of neurobehavioral performance following sleep loss (Rétey et al. 2006).

With regards the EEG topography data, the present study found that the overall effect of sleep loss on the waking EEG was consistent with previous studies (Cajochen et al. 2001). Yet, there were noteworthy differences between the individuals which emerged following analysis of regional power distributions between fronto-central and parieto-occipital EEG derivations. Specifically, both the effects of sleep loss and caffeine on antero-posterior power gradients in the theta range tended to be more prominent in caffeine-sensitive subjects than in caffeine-insensitive participants. These differences mirrored the inter-individual differences in the effects of sleep deprivation and caffeine on sustained vigilant attention. Here it may be important to remember that frontal theta activity

reflects the alternative activation of brain regions linked with continuous attention - the prefrontal cortex and anterior cingulate cortex (Asada et al. 1999). Moreover, a combined EEG and fMRI study highlighted a positive correlation between theta activity (5-9.5 Hz range) in waking and the fMRI signal of the right dorso-lateral prefrontal and superior parietal cortices (Foucher et al. 2004). In accordance with the interpretation that these areas are involved in arousal, as well as the maintenance of attention, it has also been reported that optimal PVT speed after sleep deprivation depends on activation of a fronto-parietal sustained attention network and frontal cortical regions (Drummond et al. 2005a). Rétey and colleagues (2006) thus propose that their EEG data supports brain imaging studies which show that changes in activation after sleep deprivation in fronto-parietal regions are related to individual differences in attential impairment from sleep loss, and moreover, that adenosinergic mechanisms may contribute to these differences.

9.2. Polymorphisms of ADORA2A modulate the individual response to caffeine after sleep deprivation

More recent research has demonstrated that in humans, genetic variation of the adenosine A_{2A} receptor gene, *ADORA2A*, mediates an individuals' susceptibility to panic disorder and individual differences in anxiety-related personality, habitual caffeine consumption, and arousal (Cornelis et al. 2007; Deckert et al. 1998; Hamilton et al. 2004; Hohoff et al. 2010). Furthermore, individual anxiogenic and sleep-disrupting responses to caffeine have been consistently associated with a common C-to-T substitution at nucleotide 1976 of *ADORA2A* (Alsene et al. 2003; Childs et al. 2008; Rétey et al. 2007; Rogers et al. 2010). The T-allele of this polymorphism predisposes Caucasian individuals to anxiety following caffeine consumption (Alsene et al. 2003; Childs et al. 2008; Rogers et al. 2010), while the C-allele seems to relay a tendency towards disturbed sleep following ingestion of the stimulant (Rétey et al. 2007).

In a recent publication, Bodenmann and colleagues (2012) examined the effects of genetic variation of *ADORA2A* and sleep deprivation on subjective sleepiness, PVT, waking and sleep EEG,

and the pharmacogenetic response to the stimulants caffeine and modafinil. The study revealed that the carriers of a distinct *ADORA2A* haplotype (haplotype HT4 - these individuals carry a T-allele at nucleotide 1976) showed greater vigilance during sleep loss than carriers of non-HT4 haplotype alleles (Fig. 4B). Furthermore, caffeine did not counteract the consequences of prolonged wakefulness on psychomotor speed and EEG delta activity in the carriers of haplotype HT4. On the other hand, modafinil, which does not interact with A_{2A} receptors, influenced the effects of prolonged wakefulness irrespective of *ADORA2A* haplotype. It was concluded that genetic variation of *ADORA2A* not only affects psychomotor response speed, but also modulates the effects of caffeine on neurobehavioral and neurophysiological aspects of sleep-wake regulation (Bodenmann et al. 2012).

10. Conclusions

Consistent findings accumulated over the past decades which suggest that attentional performance is particularly sensitive to time of day modulations and the effects of sleep loss. Efferent projections from the circadian master clock located in the SCN form connections to the dorso-medial hypothalamus, which sends out afferents to cholinergic and monoaminergic neurons in BF, brainstem, and hypothalamic nuclei involved in promoting behavioral arousal, attention and cortical activation. The 'sleep substance', adenosine, is released in activity-dependent manner and activates A_1 and A_{2A} receptors located in these and other brain regions, including basal ganglia and cortex. Adenosine induces global cortical disfacilitation by reducing the activating input from the ascending arousal pathways and actively excites sleep-active neurons in the ventro-lateral-preoptic area of the hypothalamus. We, thus, hypothesized that adenosine contributes to the regulation of brain functions modulated by the sleep-wake cycle, in particular to sleepiness and sustained attention which are heavily affected by sleep loss (Lo et al. 2012). Indeed, convergent pharmacologic and genetic data in animals and humans support the notion that differences in adenosinergic tone in

the central nervous system primarily affect vigilant attention. Importantly, the differences appear to be present in rested and sleep-deprived states and do not reflect different accumulation of homeostatic sleep pressure during extended wakefulness or differential vulnerability to the effects of sleep loss.

Further support for a role for adenosine in modulating sleep pressure and associated variation in arousal and attention stems from the effects of the adenosine receptor antagonist, caffeine. Acute and repeated administration of the stimulant attenuate subjective, neurophysiological and neurobehavioral consequences of moderate acute sleep deprivation. It is evident, however, that caffeine cannot substitute for sleep, and commonly consumed doses of the stimulant do not improve higher-order cognitive functions that are compromised after severe sleep loss. These findings indicate that adenosinergic mechanisms may be particularly important for the initial effects of sleep deprivation and that additional mechanisms contribute to the cognitive consequences of severe sleep deficits.

Caffeine is a non-selective A_1 and A_{2A} receptor antagonist, and these two adenosine receptor subtypes may play different roles in sleep-wake associated brain functions. Recent studies in knock-out animals suggest that the psychostimulant and the arousal effects of the xanthine are mainly mediated by A_{2A} receptors. This conclusion is supported by findings in humans showing that common genetic variation of *ADORA2A* determines individual effects of caffeine on vigilant attention during sleep deprivation. Thus, caffeine fails to counteract the waking-induced impairment of PVT performance in haplotype HT4, whereas it is normally effective in non-HT4 allele carriers. The findings demonstrate a role for A_{2A} receptors in the effects of prolonged wakefulness on vigilant attention.

11. Perspectives

Further research will aim at elucidating the involvement of adenosine in downstream mechanisms underlying sleep deprivation-induced impairment of cognitive functions and synaptic plasticity. Recent evidence indicates that changes in adenosine during prolonged wakefulness are implicated in plasticity deficits (Dias et al. 2013). Neuronal and glial-derived adenosine may lead to increased sleepiness after sleep loss and signal an increased need for sleep to balance adenosine. Thus, sleep may serve to counteract overstimulation of the brain and excitotoxicity associated with prolonged wakefulness. Adenosine reduces excitatory neurotransmission by stimulating inhibitory A_1 receptors. The A_1 receptor appears to be required for disruption of hippocampal long-term potentiation by a spontaneous low-frequency EEG pattern, which is typical for deep NREM sleep and could provide a stimulus for plasticity reversal (Dias et al. 2013). Prolonged A_1 receptor activation also induces dynamic changes in the synaptic expression of N-Methyl-D-aspartic acid (NMDA) receptors that may reversibly adjust the threshold for plasticity induction (Kopp et al. 2006).

On the other hand, adenosine actively promotes sleep by stimulating excitatory A_{2A} receptors in ventro-lateral preoptic area of the hypothalamus. Activation of A_{2A} receptors by endogenous adenosine is required for hippocampal long-term potentiation by brain-derived neurotrophic factor (BDNF), an established marker of activity-dependent neuronal plasticity (Fontinha et al. 2008). Cortical *Bdnf* in rats is higher after wakefulness than after sleep and increased after sleep deprivation (Conti et al., 2007). Chronic caffeine treatment appears to preserve the levels of BDNF in the sleep-deprived brain (Alhaider et al. 2011). Finally, A_{2A} receptors co-localize with metabotropic glutamate receptors of subtype 5 (mGluR5), which induce BDNF expression and stimulate gliotransmission. The mGluR5 are primarily expressed on post-synaptic neurons and glia cells and contribute importantly to long-term depression (Izumi et al. 2012), but also to long-term potentiation. It was recently found that sleep loss increases mGluR5 availability in the human brain, and this increase was closely correlated with increased sleepiness after a night without sleep (Hefti et al. 2013).

Whereas many studies investigated the effects of caffeine on the sleep-deprived brain, the possible roles for adenosine, adenosine receptor subtypes, and effects of caffeine in genetically distinct animals and humans on sleep-wake-related neuronal plasticity have only started to be explored. It is suggested that the further development of this avenue of research will permit a better understanding of sleep as a fundamental brain process. This knowledge may then lead to the rational development of more effective treatment and countermeasure strategies, not only of impaired vigilance and attentional processes but also of reduced higher-order cognitive functions, in conditions of sleep deprivation, shiftwork and jet-lag, for example. Such strategies are highly important for public health and personal safety.

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Legends to the Figures

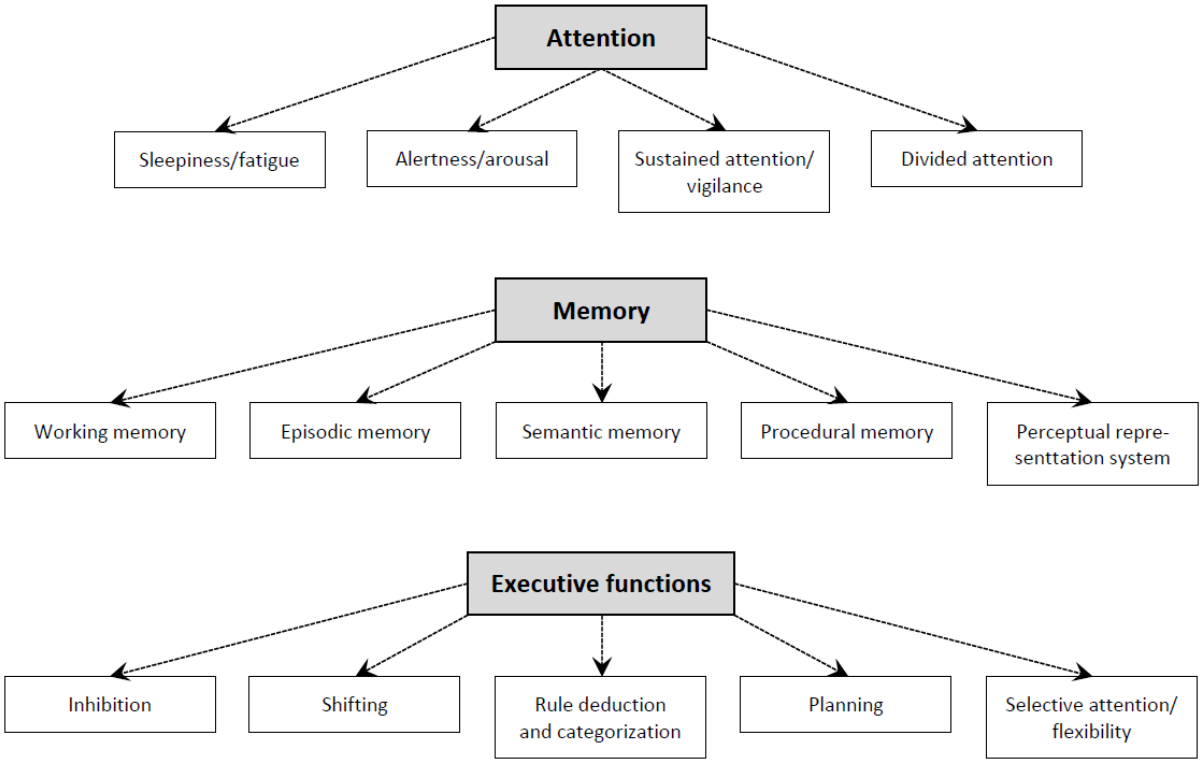
Figure 1. Overview and simplified global classification of the main cognitive processes. See (Schmidt et al. 2007) for more detailed explanations.

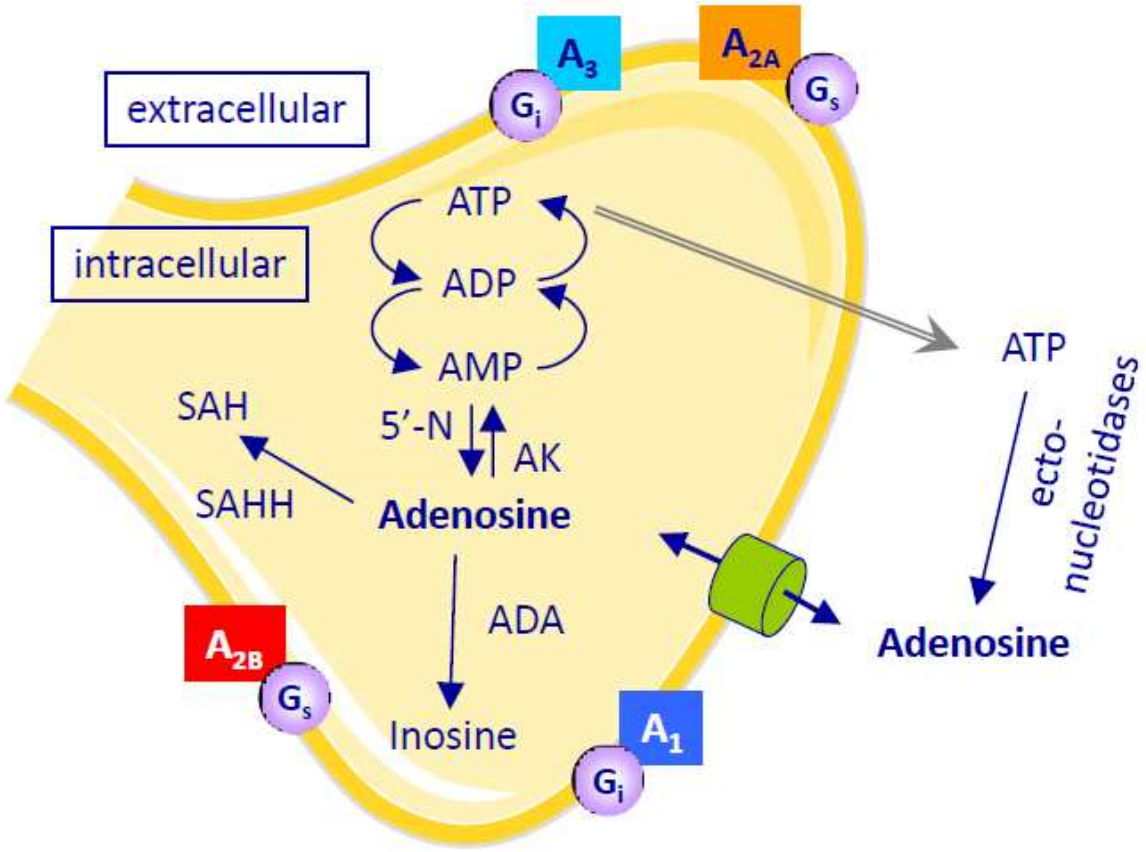
Figure 2. Schematic representation of adenosine formation, metabolism, and transport. Neurons, astrocytes and microglia cells can release adenosine and adenosine-tri-phosphate (ATP; grey arrow). All cell types express adenosine receptors, adenosine transporters (cylinder) and ecto-nucleotidases that convert ATP into adenosine. A_1, A_{2A}, A_{2B}, A_3 = adenosine receptors coupled to corresponding G-proteins; ADP = adenosine-di-phosphate; AMP = adenosine-mono-phosphate; SAH = S-adenosyl-homocysteine; 5'-N = 5'-nucleotidase; AK = adenosine kinase; ADA = adenosine deaminase; SAHH = S-adenosyl-homocysteine hydrolase.

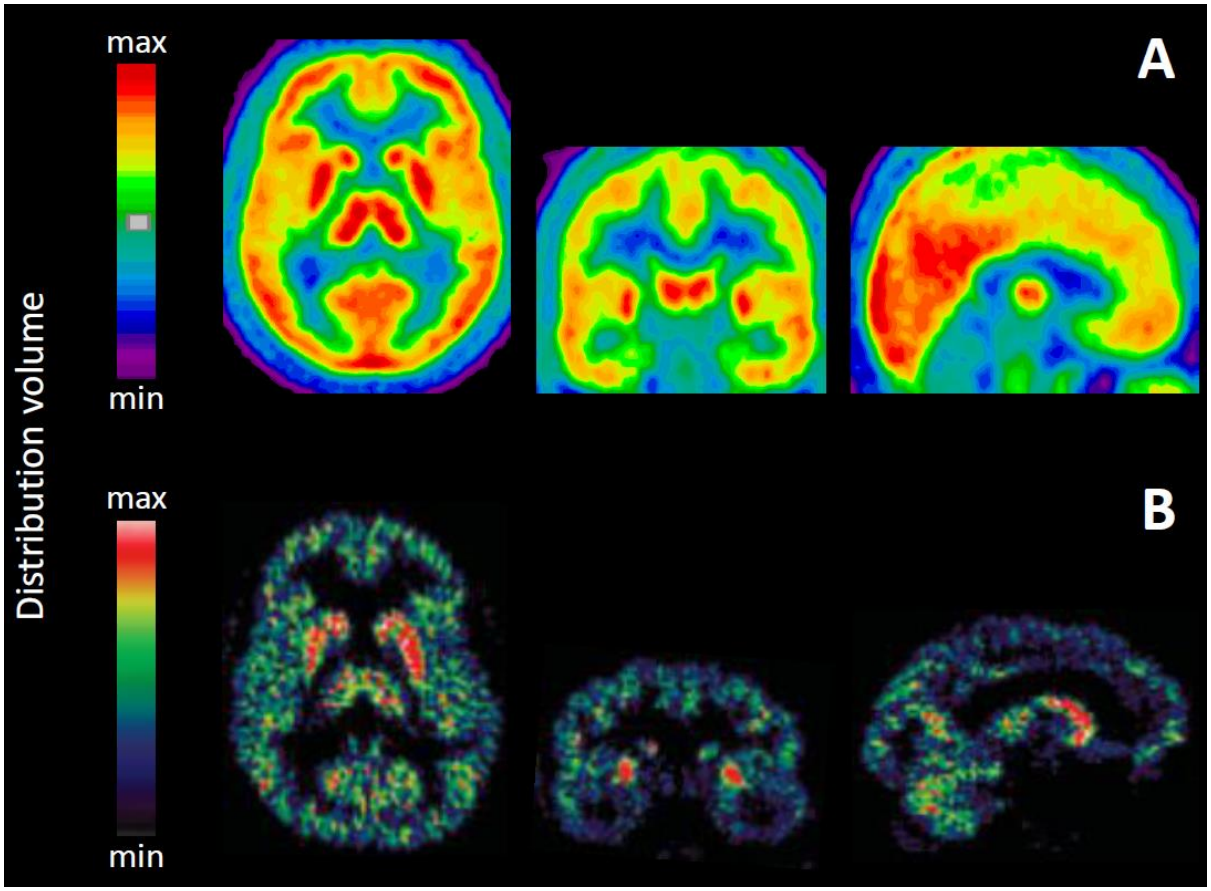
Figure 3. Distribution of adenosine A_1 and A_{2A} receptors in the human brain. (**A**) Color-coded distribution volumes of the selective A_1 receptor antagonist, ^{18}C-CPFPX (mean values of 10 healthy young men). From left to right: axial, coronal, and sagittal planes (coordinates according to the Montreal Neurological Institute brain atlas: z = -4, y = -12, x = 0). Unpublished data. (**B**) Color-coded distribution volumes of the selective A_{2A} receptor antagonist, ^{11}C-KW6002 (istradefylline), in a healthy male volunteer. From left to right: axial, coronal, and sagittal sections. Figure modified from (Brooks et al. 2008).

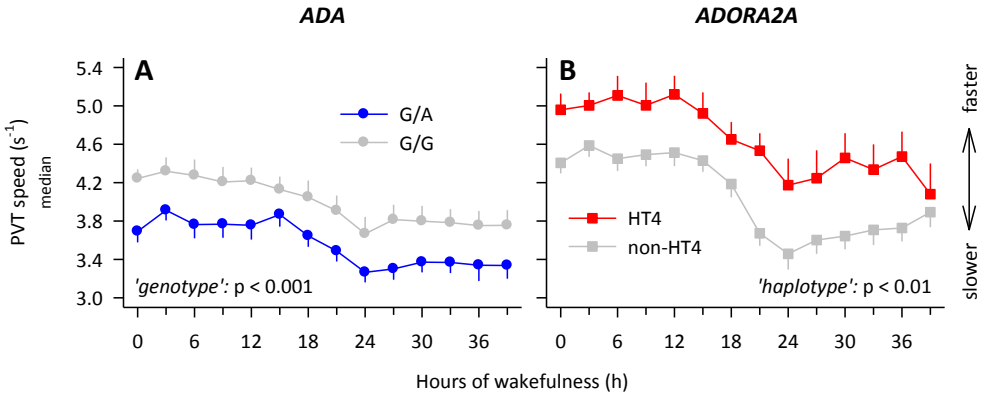
Figure 4. Functional variants of genes contributing to adenosine metabolism (adenosine deaminase, *ADA*) and signal transmission (adenosine A_{2A} receptor, *ADORA2A*) contribute to inter-individual differences in psychomotor vigilance during prolonged wakefulness. Starting 30 minutes after wake-up from the baseline night, a 10-min psychomotor vigilance task (PVT) was administered at 3-hour intervals during 40 hours prolonged wakefulness. Ticks on the x-axis are rounded to the nearest hour. The time courses of median speed (1/reaction times) are illustrated; error bars indicate + or - 1 SEM. Data were analyzed with 2-way ANOVA models with the factors *'genotype'* (G/A, G/G) or *'haplotype'* (HT4, non-HT4) and *'session'* (14 assessments during prolonged waking). (**A**) Blue circles:

G/A genotype (n = 11). Grey circles: G/G genotype (n = 11). The G/A genotype of *ADA* performs worse than the G/G genotype throughout prolonged waking (*'genotype'*: $F_{1,25}$ = 15.4, p < 0.001; *'session'*: $F_{13,239}$ = 38.6, p < 0.001; *'genotype'* x *'session'* interaction: $F_{13,146}$ = 0.3, p > 0.9). Data were re-plotted from (Bachmann et al. 2012). (**B**) Red squares: Carriers of HT4 haplotype alleles (n = 6). Grey squares: Carriers of HT4 haplotype alleles (n = 17). See (Bodenmann et al. 2012) for details of genetic analyses. Individuals with haplotype HT4 performed faster than non-HT4 allele carriers throughout sleep deprivation (*'haplotype'*: $F_{1,21}$ = 9.3, p = 0.006; *'session'*: $F_{13,273}$ = 16.3, p < 0.001; *'haplotype'* x *'session'* interaction: $F_{13,273}$ = 0.9, p > 0.5). Data were re-analyzed from (Bodenmann and Landolt 2010).


Attention
Sleepiness/fatigue
Alertness/arousal
Sustained attention/ vigilance
Divided attention
Memory
Working memory
Episodic memory
Semantic memory
Procedural memory
Perceptual repre-senttation system
Executive functions
Inhibition
Shifting
Rule deduction and categorization
Planning
Selective attention/ flexibility


extracellular
intracellular
A3
Gi
A2A
Gs
ATP
ADP
AMP
5'-N
AK
SAH
SAHH
Adenosine
ADA
Inosine
A2B
Gs
A1
Gi
ATP
ecto-
nucleotidases
Adenosine


max
min
A
Distribution volume
max
min
B


ADA
ADORA2A
A
B
PVT speed (s^{-1})
median
5.4
5.0
4.6
4.2
3.8
3.4
3.0
G/A
G/G
'genotype': p < 0.001
HT4
non-HT4
'haplotype': p < 0.01
faster
slower
0
6
12
18
24
30
36
Hours of wakefulness (h)