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„Effects of exercise and media consumption on sleep and cognitive performance in children as well as alterations induced by exercise, sleep and sleep deprivation in brain energy metabolism in rats“

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by

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Herby I declare: The work presented in this thesis is the original work of the author except where acknowledged in the text. This material has not been submitted either in whole or in part for a degree at this or any other institution. Those parts or single sentences, which have been taken verbatim from other sources, are identified as citations.

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Markus Dworak

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Contents

1. Introduction and outline

In the last decade there has been enormous progress regarding the phenomenon of sleep. For centuries, sleep has been classified as a quite simple behavioural state, but today we appreciate that it is a complex and highly organized state with enormous importance for physical and mental health and performance. Sleep alternates with waking and is characterized by a raised threshold to sensory stimulation, a low level of motor output, a recumbent posture and a unique behaviour – dreaming (Siegel, 2005; Hobson, 2005; Massimini et al., 2005). The complex neurobiology of sleep has been explored at the molecular and cellular levels since the mid-1960s. Despite numerous studies that have provided substantial insight into the physiology and pathology of sleep, there is insufficient knowledge about the exact cause and function of this physiologically important and evolutionarily conserved behavioural state that takes up one-third of our lives.

Sleep is defined by polysomnographic measurements, including electroencephalography (EEG), electrooculography (EOG), and electromyography (EMG) (Fig.1). The general EEG criteria for the evaluation of sleep stages are based on derivations from C4/A1 or C3/A2 classified by the 10-20-system (Jasper, 1958). In addition, physiological measurements including electrocardiography (ECG), heart rate (HR) and oxygen saturation can be justified.

By electroencephalographic (EEG) measurements sleep can be subdivided into five distinct states: Stages 1, 2, 3, 4 and REM (rapid-eye movement) (Siegel, 2005). These stages progress cyclically from stage 1 through REM then begin again with stage 1. NREM and REM states alternate at intervals of about 90 minutes in adult humans throughout sleep. Thus, if a human closes their eyes, the EEG characteristically shows a regular pattern of 8–12 Hz known as alpha waves. As the individual drifts into stage 1 sleep, the EEG becomes slower and less regular and is reduced in amplitude with little or no

alpha. Stage 2 is characterized by the appearance of spindles, which are short runs of rhythmical EEG waves of 12–16 Hz. This stage is also characterized by K-complexes. These are EEG waveforms lasting about 0.5 second and have a well-delineated negative sharp wave (12–14 Hz), which is immediately followed by a positive component. Stages 3 and 4 are characterized by EEG slow-wave activity (SWA) measured in the EEG frequency range of 0.5–4.5 Hz, also known as delta waves. REM sleep is characterized by an EEG pattern similar to stage 1, except in addition, rapid eye movements appear on the EOG record and EMG recordings are of low amplitude. Stages 1–4 are often collectively known as non-REM (NREM) sleep. A thorough description and guide to the scoring of sleep stages can be found in Rechtschaffen and Kales (1968).

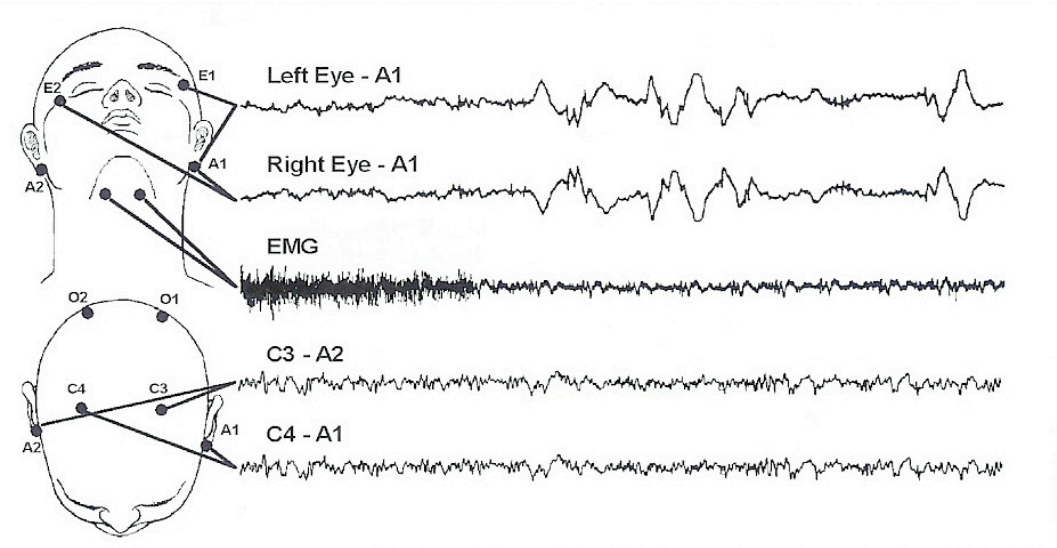

Figure 1: Electrode placement of EOG, EEG and EMG

In general about 75% of sleep time is spent in NREM sleep (Hobson, 2005). NREM phases are deeper and longer in the first half of the night, whereas REM sleep predominates in the second half (Hobson and Pace-Schott, 2003). NREM and REM sleep probably have separate homeostatic mechanisms (Siegel, 2005). Especially the anabolic character of NREM sleep suggests a

restorative function of this state. During this state, blood flow and glucose metabolism are decreased by more than 40% compared with waking and thalamocortical synchronous activity diminishes the responsiveness to the external environment (Nofzinger et al., 2005; Massimini et al., 2005). Also relative increases in glucose utilization in the hypothalamus, basal forebrain, hippocampus, amygdala and pontine reticular formation were observed in recent studies and indicate that NREM sleep is important to homeostatic regulation, energy conservation and brain plasticity (Maquet, 1995; Greene and Siegel, 2004; Siegel, 2005; Tononi and Cirelli; 2006). The cellular physiology of NREM sleep has been characterized extensively (reviewed by McCormick, 1997; Maquet et al., 1997). During this state the burst phase in populations of neurons is synchronized, causing the high-amplitude slow EEG deflections that characterize that state (Greene and Siegel, 2004; Maquet et al., 1997).

The delta power increases result from a combination of decreased activity and synchronization of CNS electrical activity within the delta frequency range (Benington and Heller, 1995). At the cellular level, this probably reflects a coordinated burst-pause firing in the thalamus and cortices. The burst-pause oscillation is intrinsic to many thalamocortical neurons and is mediated by an interaction of the transient calcium current (It), the hyperpolarization-activated current (Ih), and a resting membrane potential in the absence of Ih of approximately -80 mV (McCormick and Bal, 1997; McCormick and Pape, 1990; Benington and Heller, 1995).

Previous studies showed that NREM SWA is homeostatically regulated (Tobler and Borbely, 1990; Borbely and Achermann, 2000). The homeostatic drive describes an intuitive process and implies that prolonged wakefulness results in a proportional increase in the tendency to fall asleep. Both the propensity to sleep and the intensity of delta EEG waves upon falling asleep are proportional to the duration of prior wakefulness (Tobler and Borbely, 1990). The tight correlation between EEG SWA and sleep need suggests that

physiological factors that generate slow-waves in the cerebral cortex play an important key role. Several neurotransmitter systems and the brain energy metabolism seem to be crucial in homeostatic regulation (overview in Hobson and Pace-Schott, 2003).

Wakefulness results in a greater metabolic activity than sleep, shown by measurements of cerebral blood flow, regional cerebral glucose utilization and oxygen consumption (Berger and Phillips, 1995; Maquet, 1995; Nofzinger et al., 2000). Thus, prolonged waking periods result in a progressive decline of cerebral glycogen levels (Kong et al., 2002). During slow-wave sleep (SWS) brain energy metabolism is drastically decreased and reaches a minimum during its deepest stages, whereas during REM sleep the level is similar to that during wakefulness (Kong et al., 2002; Nofzinger et al., 2000).

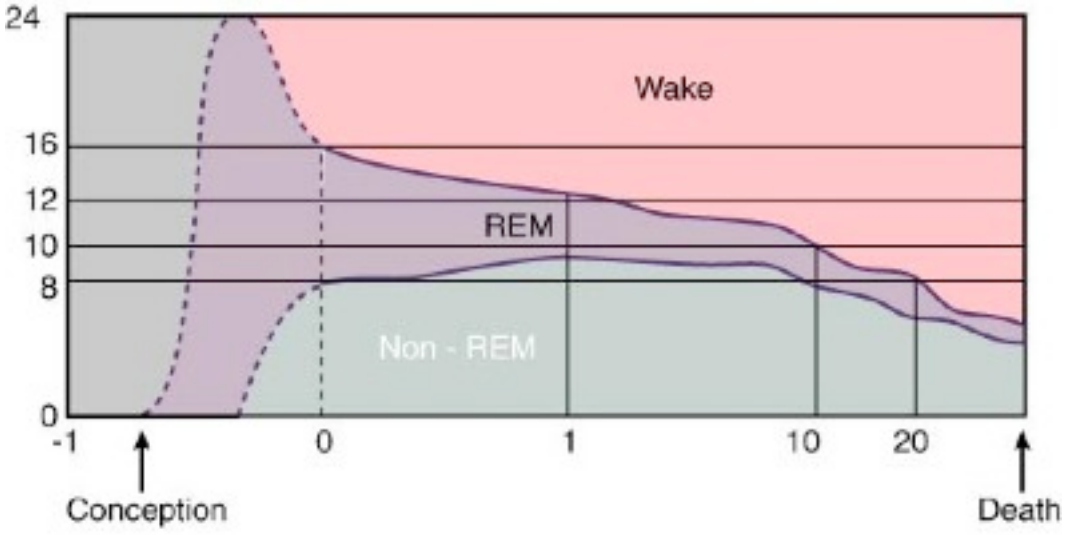

Figure 2: Portions of a 24-h day that are devoted to waking, REM sleep, and non-REM (NREM) sleep change over a lifetime. The timing of these changes *in utero* is not known with certainty (dotted lines), but data from premature infants are consistent with REM sleep occupying most of life at a gestational age of 26 weeks. After 26 weeks, the time spent in waking increases until death.

Thus, it was hypothesized that SWS is essential for replenishment of cerebral glycogen stores that are progressively depleted during wakefulness (Benington and Heller, 1995). In accordance with this hypothesis, when the ratio of metabolite demand to metabolite availability increases, the production of adenosine out of AMP rises (Latini and Pedata, 2001; Porkka Heiskanen et al., 2002). Especially adenosine has been proposed as a homeostatic accumulator of sleep need (reviewed in Basheer et al., 2004). Its formation and concentration is narrowly linked with neuronal metabolic activity. Extracellular adenosine concentrations increase during both increased metabolism and increased neuronal activity, are lower during resting periods like sleep, and thus vary during the sleep-wake cycle (Sibson et al., 1998; DeSanchez et al., 1993). Adenosine acts as an inhibitory neuromodulator in the central nervous system (CNS) and is assumed to be the major sleep-promoting factor (Alam et al., 1999; Donald et al., 1994). Additionally, it affects the vascular tone, hormone action, lymphocyte differentiation and modulates cerebral blood flow and neural function (Latini and Pedata, 2001).

In general neuronal activity involves in the vast majority the transmission of neurotransmitters that are localized in specified neuronal groups and have an integrative role in regulating sleep and alertness. The activation of a series of neuromodulatory transmitter systems during waking inhibits low-frequency oscillations and allows the brain to recover full responsiveness (Steriade et al., 1993). During sleep excitatory neurotransmitter release is low (Hobson and Pace-Schott, 2003). Especially, glutamate, acetylcholine, histamine, hypocretin, serotonin, and norepinephrine seem to play a critical role in control of behavioural state, they activate cAMP and stimulate glycogenolysis as well as adenosine formation and thus confirm direct connections between neuronal activity and the brain energy metabolism (Benington and Heller, 1995). A detailed description of the neurotransmitter systems involved in sleep regulation can be found in Squire et al. (2003)

Sleep is essential for mental and physical performance and disrupted sleep results in a number of symptoms including stress, poor vigilance and reduced cognitive performance and motivation (Dinges and Kribbs, 1991; Kryger et al., 2000). Chronic sleep debt is becoming increasingly common and affects millions of people in more-developed countries and is associated with a range of abnormalities in glucose metabolism and leptin profile (Scheen and VanCauter, 1998; Mullington et al., 2003; Spiegel et al., 2004) and elevated risks for obesity and sleep apnea (Spiegel et al., 1999; Parkes, 2002). Despite this knowledge, sleep problems and sleep disorders impose a major public health burden. Approximately 70 million people in the United States suffer from sleep problems, and 60 per cent of them have a chronic sleep disorder. About 30 million American adults experience frequent insomnia, 12–18 million people suffer from sleep apnea, and 250,000 have narcolepsy (Spiro, 2005). In the USA, sleep disorders result in approximately $16 billion annually in health costs and almost $50 billion of lost productivity (Spiro, 2005). It is assumed that the same percentage for the appearance of these symptoms concerns the German population. Despite this knowledge, sleep problems and sleep disorders are impose a major public health burden. A better understanding of sleep promoting behaviours as well as neuronal and metabolic pathways in the human brain involved in sleep regulation would have a great benefit for the general population and might support the development of treatments against acute and chronic sleep problems.

In most discussions regarding sleep hygiene, exercise is considered as a non-pharmacological intervention to improve sleep (Driver and Taylor, 2004; Lavie, 1996). The expectation that exercise will benefit sleep can partly be attributed to the traditional hypothesis that sleep serves body restoration, energy conservation or thermoregulatory functions. Physical exercise is a complex activity that might affect nearly every system in the body, including cardiovascular, pulmonary, haemodynamic, metabolic, and endocrine functions (overview in Hollmann and Hettinger, 2000). Numerous studies in the last decades indicate that dynamic physical exercise might also affect brain

structures and brain functions (Hollmann and Hettinger, 2000; Cotman et al., 2002). Previous results suggest that dynamic exercise produces elevated cerebral blood flow, alterations in endogenous peptides and neurotransmitters and amino acid transport through the blood-brain barrier (Hollmann et al., 1994; Herholz et al., 1987; Ide and Secher, 2000; Kemppainen et al., 2005). Furthermore, it stimulates the formation of synapses and neuronal spines as well as neurogenesis and might improve brain function and slow age-related degeneration processes (Cotman and Engesser-Cesar, 2002; Cotman and Berchtold, 2002; Gomez-Pinilla et al., 1997; Isaacs et al., 1992; Neeper et al., 1996).

Epidemiological studies showed a therapeutic and sleep-promoting effect of moderate, regular physical activity, but empirical evidence is not so compelling (Horne, 1981; O'Connor and Youngstedt, 1995; Driver and Taylor, 2004). Previous studies have shown various associations between exercise and sleep (Horne, 1981; Vuori et al., 1988; O'Connor and Youngstedt, 1995; Driver and Taylor, 2004). Inconsistent results regarding the effects of exercise on subsequent sleep contained increases in total sleep time (TST), higher sleep efficiency, less waking time after sleep onset, decreases in REM sleep as well as increases in both stage 2 and SWS after acute exercise (O'Connor and Youngstedt, 1995; Youngstedt et al., 1997; Driver and Taylor, 2004). No significant effects were found in other studies (Paxton et al., 1983). The variety of different methodology, age, gender, fitness level and body mass as well as time before sleep when exercise was completed makes it difficult to compare the results of these studies (Trinder et al., 1985; Rogers et al., 1990). Especially intensity, duration and type of exercise are fundamental for the effects and adaptations of physical exercise on metabolic, cardiovascular, pulmonary, haemodynamic and endocrine systems, including the brain (Herholz et al., 1987; Hollmann et al., 1994). Thus, the question of the sleep-promoting efficacy of exercise is quite recent and difficult to answer from the current literature.

In view of the insufficient knowledge regarding the relationship between exercise and sleep, the first study of the present thesis will examine the effects of physical exercise on sleep architecture and sleep continuity parameters in children. Eleven healthy male children were recruited for this polysomnographic study and underwent two exercise sessions on a bicycle ergometer to achieve an activity in a general endurance exercise. The two exercise sessions lasted 30 minutes and varied only in intensity. The moderate-intensity exercise was performed at 65–70% of maximal heart rate (HRmax) while the high-intensity exercise was 85–90% HRmax to exhaustion. In the following nights, polysomnographic measurements and physiological measurements including oximetry and electrocardiography were made. Additionally, vigilance tests were carried out before and after the sleep periods. We will test the hypothesis that acute physical exercise affects vigilance state in children, that acute physical exercise affects sleep architecture and sleep continuity parameters in children in the subsequent sleep period, especially the amount of homeostatically regulated SWS, and that intensity of exercise is responsible for the effects on sleep and vigilance state.

In addition, previous studies suggest that whole brain metabolic activity increases with intensity of exercise since the increased motor command results in elevated metabolic rates in associated brain structures (Ide and Secher, 1999; Kayser, 2003). Also, during intense brain activation, modifications in brain energy metabolism occur. In this case neurons prefer lactate to glucose as their primary energy substrate with accompanied production of ATP (Ide et al., 1999, 2000; Dienel and Hertz, 2001; Schurr, 2006). Thus, it could be assumed that only high-intensity exercise increases the ratio of metabolite demand to metabolite availability with an accompanied production of adenosine out of AMP. These metabolic changes in the human brain associated with exercise intensity may play an important key role in regulation of human sleep patterns.

For this reason the second objective of this thesis was to investigate the effects of exercise, sleep and sleep deprivation on brain nucleotides and nucleosides: phosphocreatine, creatine, ATP, ADP, AMP, adenosine and inosine in the rat brain using freeze-clamp technique. We attempt to answer the question of whether physical exercise and sleep deprivation increase adenosine and inosine level in rat brain and if duration and intensity of the exercise and sleep-deprivation are decisive for the extent of these alterations. Since modern neuroscientific theories support the notion that sleep plays an essential role in replenishment of brain energy stores, we will also test the hypothesis that sleep after previous waking periods results in increased levels of high-energy phosphates.

Taken together the first two studies will enhance our knowledge about physical exercise and accompanied metabolic changes in the mammalian brain in sleep regulation and will test the hypothesis that physical exercise could be useful as a non-pharmacological intervention to improve sleep.

The modern lifestyle of both adults and children is characterized by a lack of physical activity and excessive inactivity (Ebbeling et al., 2002). Recent studies show that the current generation of children would grow into the most obese and inactive generation of adults in history (Hill and Trowbridge, 1998; Ebbeling et al., 2002). Especially, consumption of television and computer games become an increasing influence in the lives of most children in western industrial countries (Rideout et al., 2005). At the same time, an increase in sleep-related problems and diseases has been observed in this age group (Spiro, 2005). Thus, it could be hypothesized that sedentary activities like consumption of electronic entertainment media may have a distracting effect on sleep architecture and continuity parameters in children. In fact, media research studies indicate that children spend an average of nearly 6.5 hours a day with electronic media (Rideout et al., 2005). Despite the great progress in media research within the last few years, there is insufficient knowledge about the effects of acute media exposure on sleep and behavioural states in

children. Sleep is also important for children's health and development and it has an important role in learning and memory consolidation (Wilson and McNaughton, 1994; Stickgold et al., 2001; Wagner et al., 2004; Fischer et al., 2002; Gais and Born, 2004; Stickgold, 2005). Some studies have indicated that excessive television and video game consumption could lead to attention problems, hyperactivity, and scholastic problems (Gupta et al., 1994; Christakis et al., 2004; Sharif and Sargent, 2006). Thus, the third and final objective of this thesis was to investigate the effects of singular excessive television and computer game consumption on sleep patterns and memory performance of children. In this experimental study, school-aged children were exposed to voluntary excessive television and computer game consumption, followed by polysomnographic measurements in the subsequent night. Additionally, a visual and verbal memory test was conducted before media stimulation and after the subsequent sleeping period to determine visuospatial and verbal memory performance. In this third study of the current thesis we will examine whether computer and television consumption affects sleep architecture and sleep continuity parameters in children, whether singular computer and television consumption disturbs visuospatial and verbal memory performance, and whether type of media consumption is responsible for effects on sleep and memory.

2. First Study: Increased slow wave sleep and reduced stage 2 sleep in children depending on exercise intensity

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2.1. Abstract

Background: There is controversy about the consequences of physical exercise on human sleeping behaviors. Evidence suggests that voluntary physical exercise affects brain structures and functions. However, there are inconsistent data regarding the effects of exercise on sleep architecture and sleep continuity, especially the amounts of slow wave sleep (SWS) and rapid eye movement (REM) sleep.

Objective: The aim of the present study was to investigate the effects of moderate and high intense physical exercise on vigilance state and sleep patterns in school-aged children.

Methods: Eleven healthy children (12.6 ± 0.8 years old) were recruited for this polysomnographic study and underwent two exercise sessions. The two exercise sessions on a bicycle ergometer were performed 3–4 h prior to bedtime, lasted 30 min and varied in intensity. The moderate-intensity exercise was at 65–70% of maximal heart rate (HRmax) while the high-intensity exercise was at 85–90% HRmax to exhaustion. Polysomnographic and physiological measurements, including oximetry, were made on three nights in random order and separated by 1 week. Vigilance tests were carried out before and after the three sleep periods.

Results: Only high-intensity exercise resulted in a significantly elevated SWS proportion and less sleep in stage 2 as well as a higher sleep efficiency and shorter sleep onset latency. No significant effects on REM sleep were found.

Conclusion: The results suggest that exercise intensity is responsible for the effects on stage 2 sleep and SWS in children and support the hypothesis of homeostatic sleep regulation.

2.2. Introduction

Physical exercise is known to impact nearly every system of the body, including the brain [20,21]. Abundant experimental evidence indicates that dynamic physical exercise produces elevated cerebral blood flow (CBF), alterations in endogenous peptides, neurotransmitters, and amino acid transport through blood–brain barrier [20]. Furthermore, dynamic exercise stimulates the formation of synapses and spines as well as neurogenesis and thus improves cognitive brain functions and age related degeneration processes [10]. However, there is insufficient knowledge about the effects of physical exercise on human sleep patterns. Some studies observed altered sleep patterns in adults and older subjects, particularly the amount of stage 2 sleep, homeostatic regulated slow wave sleep (SWS) (stage 3 + 4) and rapid eye-movement (REM) sleep [13], whereas no significant effects were found in other studies [35]. This inconsistency may be attributed to a number of factors, including differences in age, gender, and methodology, especially in type, duration and intensity of exercise, which are important factors regarding the effects on subsequent sleep. Recent evidence demonstrated that exercise intensity is responsible for the accompanied metabolism [20], including brain energy metabolism [19,20,23,25]. Intensity-dependent metabolic modifications may play a key role in homeostatic sleep regulation. Therefore, we used two exercise sessions, which differed only in intensity. Age of the subjects is an important factor in this case. With advancing age, alterations in sleep architecture occur [3,5], including a reduction in homeostatic sleep drive [6], a decline in the amplitude of (delta) slow wave activity in electroencephalogram (EEG) [17], a reduced amount of SWS, [16] and age-related changes in metabolic enzymes in sleep/wake regulatory areas of the brain [28]. Similar age-related declines in sleep and sleep homeostasis have also been demonstrated in other mammalian species [39]. We studied the effects of exercise on school-aged children because the age-related changes, specifically in SWS, have not been described for this age group. A key feature of sleep is its homeostatic regulation. Sleep intensity increases in proportion to

the previous waking period [4,26]. The best-characterized marker of sleep intensity and sleep need is EEG slow-wave activity, during non-rapid eye movement (NREM) sleep [7]. It could be hypothesized that exercise intensity and obliged metabolic changes in the human brain are crucial for effects on homeostatic-regulated SWS. The purpose of the present polysomnographic (PSG) study was to evaluate the response of acute exercise and its intensity on vigilance state and sleep patterns in children, especially the amount of SWS in subsequent sleep.

2.3. Methods

Subjects

Eleven healthy male children volunteered to participate in this study, (age 12.6 ± 0.8 years, height 1.6 ± 0.1 m, mass 47.0 ± 6.3 kg, BMI 17.8 ± 1.7; means ± SD). All subjects and parental authorities signed consent forms and completed a medical questionnaire prior to the beginning of the experiment. They were informed that they could withdraw from the study at any stage. The subjects had no sleep complaints and were instructed to refrain from further physical activity, passive body warming as well as sleep during the day. Furthermore, children were advised not to watch TV or use the computer for 2 h before bedtime on the sleep study nights. They did not consume any caffeine, nicotine or alcohol and were not exposed to stressful situations.

Experimental design

Each subject underwent three investigation days in a randomized crossover manner. The interval between the experiments was exactly 1 week. Subjects performed two varying exercise sessions on two different experimental days. Exercise was performed on a bicycle ergometer (Ergoline, Ergoline GmbH, Germany) at 65.0 ± 5.0 revolutions per minute (rpm) commencing at 5:00 p.m. (i.e., 3–4 h before bedtime). This time was selected because it has been

suggested that an effect of exercise on subsequent sleep may only occur when exercise is performed close to sleep but not too close to bedtime to have a disruptive effect [13]. The two exercises varied only in intensity. One practice session was performed at moderate exercise intensity at 65– 70% of HRmax for 30 min straight. Intense cycling exercise was executed in the other practice session at 85–90% HRmax to exhaustion. To exhaust children completely in the same amount of time, three periods of 10 min were chosen, followed by short resting periods. After every period, the subjects felt exhausted. During exercise, the heart rate (HR) was continually measured to ensure that the required exercise intensity was maintained. If subjects left their target HR, the workload was adjusted. For determination of HRmax, the age-predicted maximal heart rate (PMHR) formula [HRmax = 220-age] was selected, which is frequently used as a basis for prescribing exercise programs, as a criterion for achieving maximal exertion and as a clinical guide during diagnostic exercise testing [2]. In addition, the 14-point (6 = ‘‘very, very light’’, 19 = ‘‘very, very hard’’) Borg Scale of Perceived Exertion (RPE) [8] was used to obtain a subjective rating. Light and temperature conditions during the exercise sessions were standardized. Under control conditions, subjects adhered to their normal daily patterns. Thirty minutes before bedtime, a test of vigilance was carried out (Wiener-Testsystem 29.00, Dr. G. Schuhfried GmbH, Mödling, Austria). In this test, subjects executed a simple motor movement (i.e., to push a button with one finger of the right hand if they saw a bright light on a monitor). The test was divided into two trials: with or without preceded acoustic signaling. Reaction time (RT) and movement time (MT) to visual and acoustic attractions were measured to test implications of the previous exercise session on vigilance state. Test duration was 7 min. Average reaction time, average movement time, and difference of average reaction time with and without preceding acoustic signal and error rate were determined. The same test was repeated 60 min after waking up.

Data recording and analysis

Before going to bed, PSG measurements were conducted using a portable sleep-data recorder (Varioport-SLP, Becker Meditec, Karlsruhe, Germany). An expert placed the electrodes between 7:30 p.m. and 8:30 p.m. and removed them after subjects awoke in the morning. Subjects were also instructed to adhere to their normal evening routines, go to bed and get up at their usual time. The general bedtime was between 8:30 p.m. and 9:30 p.m. when the room light was turned off. Morning awaking was between 6:00 a.m. and 7:00 a.m. Subjects slept in their own homes during study nights and always under same timing and temperature conditions to standardize sleeping conditions in each subject. They were also instructed to adhere to their normal evening routines and fill out a sleep diary. The sleep diary contained questions about daytime sleepiness, subjectively rated sleepiness, and subjectively rated awakenings. Adaptation night was assigned on the day prior to the experiment to reduce the possible ‘‘first night effect’’.

The monitoring montage consisted of three electroencephalograph (EEG) channels (C3-A2, C4-A1, Oz-A2), bilateral electrooculograph (EOG), submental chin electromyography (EMG), pulse oximetry (SpO2) for non-invasive measurement of oxygen saturation and electrocardiography. The measuring procedure followed the standards for performance and evaluation of PSG studies of the pediatric group in the German Sleep Society [33].

Each PSG was scored by Somnolyzer 24x7 (The Siesta Group, Vienna, Austria). The scoring procedure was based on 30-s epochs. The system included a raw data quality check, a feature extraction algorithm (density and intensity of sleep/wake-related patterns such as sleep spindles, delta waves, slow eye movements (SEMs and REMs), a feature matrix plausibility check, a classifier designed as an expert system and a rule-based smoothing procedure for start and ending of stages. Additionally a structured quality control by two experts, including a visual correction, was accomplished. Studies showed that two Somnolyzer 24 x 7 analyses revealed an inter-rater reliability close to 1, representing an overall agreement of 99.4% (Cohen’s kappa: 0.991). This

confirms that the variability induced by the quality control procedure, whereby approximately 1% of the epochs are changed, could be neglected [1]. For each PSG, a number of measurements of the architecture of sleep and sleep continuity were derived. PSG measurements included minutes and percent total sleep time (%TST) for stages 1, 2, 3, 4, SWS and REM sleep. Continuity measurements consisted of total sleep time (TST), sleep onset latency (SOL), latency of stages 1, 2, 3, 4, and REM sleep, wake time after sleep onset and sleep efficiency.

Statistical analyses

Statistical analyses of the natural sleep cycle data and vigilance test data were performed with Friedman analysis of variance (ANOVA) by ranks, followed by the Wilcoxon test for paired data sets as a post hoc test and Bonferroni adjustment using SPSS 12.0 (Sigma Stat Statistical Software, Chicago, IL, USA) and STATISTICA 7.1. software (StatSoft, Tulsa, OK, USA) for MS Windows. The significance level of all statistical tests was set at $p < 0.05$.

2.4. Results

Subjects reached their target heart rate during the exercise sessions on the stationary bicycle ergometer. There was a significant difference ($p < 0.001$) in average HR and Borg-scale rating between moderate and intense exercise. Mean HR during the moderate exercise session was 132.8 ± 5.7 beats per minute at a mean workload of 1.4 ± 0.2 W per kg accompanied by a mean subjective rating of perceived exertion of 13. High-intensity exercise resulted in a mean HR of 161.7 ± 6.9 beats per minute at a workload of 1.8 ± 0.1 W per kg and subjective rating of 17 during exercise performance. At the end of the intense exercise session all subjects felt very exhausted (mean HR: 168.1 ± 6.0 beats per minute and mean Borg-scale: 18).

Sleep parameters

Sleep parameters showed normal distributions. Total sleep time (TST) remained unchanged between the three experimental nights. Mean TST was 502.4 ± 37.1 min. The results showed a significant increase in sleep efficiency as well as a decreased SOL ($p < 0.05$) after high-intensity exercise compared to moderate exercise and basal conditions (Table 1). SOL was the time to one continuous minute of stage 1 sleep or the first epoch of any other sleep stage. In addition, significant reductions in latent periods to stage 1, stage 2, stage 3 and stage 4 sleep ($p < 0.05$) were observed after the high-intensity exercise session.

	Baseline		Moderate exercise		High intensity exercise	
Parameter	Mean	SD	Mean	SD	Mean	SD
Sleep efficiency %	93.14	5.09	96.93	2.88	97.54 *	0.82
Total sleep time (TST) (minutes)	504,05	37,93	503,77	33,97	499,41	39,41
Wake time after sleep onset (minutes)	13.33	18.22	5.09	2.78	4.36	2.35
Sleep onset latency (minutes)	22.27	16.26	9.27	13.57	6.64 *	4.88
Stage1 latency (minutes)	21.45	16.98	8.91	13.77	5.68 *	3.80
Stage2 latency (minutes)	24.86	16.44	11.95	14.27	7.95 *	4.48
Stage3 latency (minutes)	36.82	16.78	24,18	14,16	20.64 *	4.91
Stage4 latency (minutes)	37.50	18.28	24.95	14.23	21.23 *	5.49
REM latency (minutes)	130.68	29.42	122.09	43.21	108.82	49.85
Stage1 (%TST)	2,60	1,73	2,12	0,88	1,55	0,97
Stage2 (%TST)	56,96	4,46	55,93	3,87	53,68	4,52
Stage3 (%TST)	3,53	2,43	3,06	1,13	4,02	1,91
Stage4 (%TST)	15,05	4,63	15,29	4,33	17,47	4,73
SWS (%TST)	18,58	3,94	18,35	3,92	21,48 *	4,51
REM (%TST)	21,86	4,16	23,60	2,93	23,15	2,25

Table 1. Means and standard deviations of sleep continuity and sleep architecture parameters on experimental days (*$p<0.05$, compared to basal conditions). Sleep onset latency (SOL) was the time to one continuous minute of stage 1 sleep or the first epoch of any other sleep stage.

Only high-intensity exercise yielded a shift in sleep stages. The percentage distribution of sleep stages showed significant increases in SWS after high exercise intensity compared to moderate exercise intensity ($p = 0.048$) and basal conditions ($p = 0.038$) (Fig. 1). Additionally, subjects spent more time in SWS (12.9 ± 1.82 min) and less time in stage 2 (22.3 ± 9.5 min) after intense exercise compared to baseline and moderate exercise. There were no significant changes in either the absolute duration or the relative proportion of REM sleep.

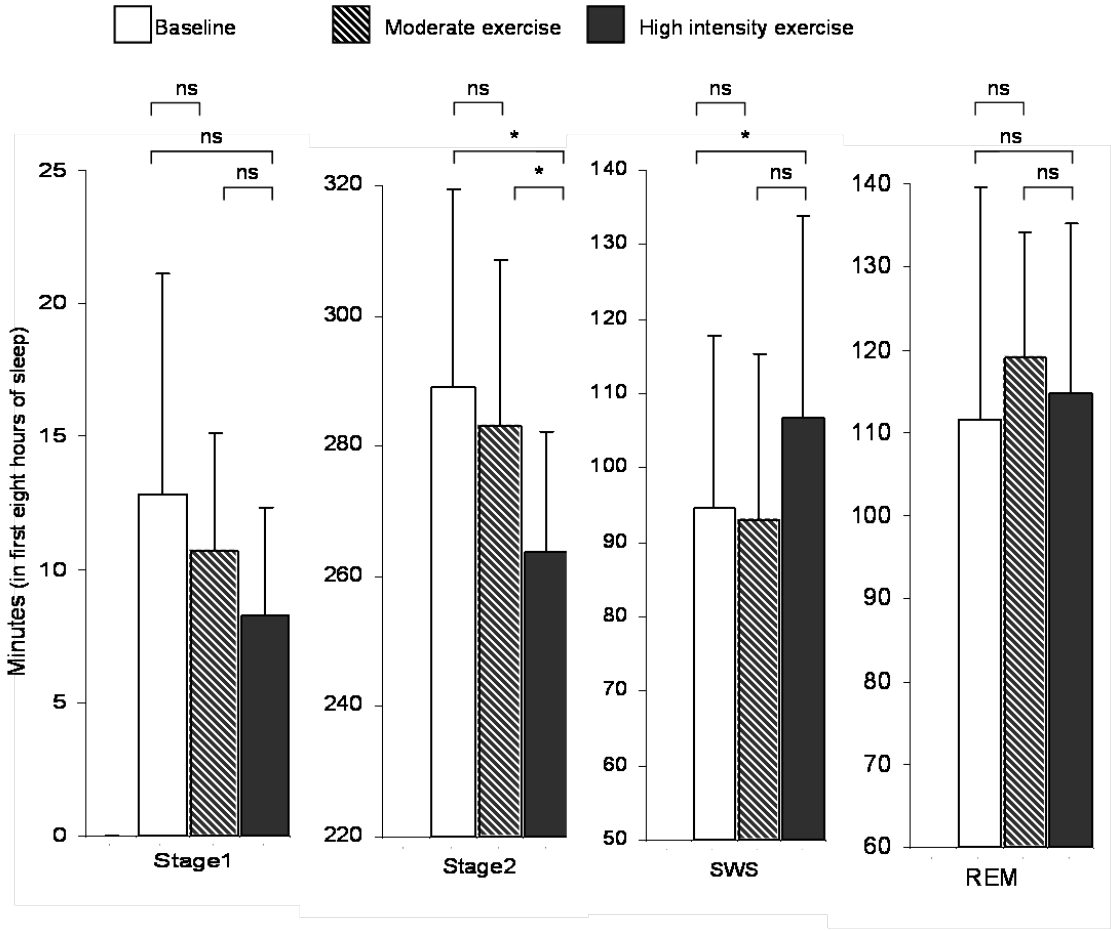

Figure 1. Average (± SD) minutes of sleep stages after Baseline, moderate exercise and high-intensity exercise ($p<0.05$).

HR/SpO2

No significant differences in average HR and SpO2 were detected between the experimental nights. A significant progressive decline in mean HR was observed across the night with similar average SpO2 for the three study conditions.

Vigilance test

The average reaction time, with and without the preceding acoustic tone as an indicator of alertness, was not different between the no exercise and the two exercise conditions. No significant changes in reaction time and error rate between measurements before and after sleep were found on individual experimental days. Average movement time was reduced after the exhaustive exercise session. Basal values were 153.8 ± 47.7 ms with progressive decline to 124.9 ± 47.0 ms after preceding intensive exercise.

2.5. Discussion

The present study demonstrates that alterations in sleep architecture and sleep continuity after preceding exercise depend on exercise intensity. Only high-intensity exercise resulted in increased SWS and less time in stage 2. Higher sleep efficiency, shortened SOL as well as shortened latent periods to stage 1, stage 2, stage 3 and stage 4 were also observed only after high-intensity exercise. Thus, the results provide supplementary evidence for the hypothesis of homeostatic sleep regulation.

Previous experimental studies showed various associations between exercise and sleep. The variety of different methodology, age, gender, fitness level and body mass as well as time before sleep when exercise was completed makes it difficult to compare results of these studies [13,34]. Inconsistent results regarding the effects of exercise on subsequent sleep contained increases in TST, higher sleep efficiency, less wake time after sleep onset, decreases in

REM sleep and increases in both stage 2 and SWS after acute exercise [13,34,42]. No significant effects were found in other studies [35]. Particularly intensity, duration and type of exercise are fundamental for effects and adaptations of physical exercise on metabolic, cardiovascular, pulmonal, hemodynamic, and endocrine systems, including the brain [20,21]. Considerable effects on brain functions and structures could be detected after the engagement in general aerobic dynamic endurance exercise (e.g., running or cycling) [19,20]. It was shown that endurance exercise resulted in the highest levels of SWS compared with mixed aerobic and anaerobic power training, power weightlifting and sedentary controls [40]. In addition to standardizing the type (general aerobic dynamic endurance exercise) and duration of exercise, the time of day of exercise performance was the same. Our results are in accordance with those of Shapiro et al. [38] who showed a reduced SOL, less sleep in stage 2 and more SWS after exhaustive long distance running. Furthermore, epidemiological studies, while based on self-reports, have consistently supported the view that acute and chronic exercise promotes sleep [41,42]. In general, recent meta-analytical techniques have pointed out that exercise increases TST, increases SWS, delays REM sleep onset and reduces REM sleep [13]. In accordance with these results, we observed significant effects of exhaustive exercise on SWS. No significant changes in either the absolute duration or the relative proportion of REM sleep were noticed in this study. This is homologous with previous findings, which indicate that REM sleep is not prolonged significantly after simple aerobic and anaerobic exercises, but seems to be correlated with the acquisition of motor experiences, such as during trampoline exercise [9].

Furthermore, previous studies exclusively examined adults and older persons in this context. The age of the subjects affects homeostatic sleep drive, including a decline in the amplitude of (delta) slow wave activity in the EEG [17], reduces the amount of slow wave sleep [14,16] and produces changes in metabolic enzymes in sleep/wake regulatory areas of the brain [28]. It has been reported that long distance exercise results in significant SWS increases

in young athletes [38], whereas older subjects showed a significant post-exercise decrease in SWS [30,31]. These age-related declines in homeostatic SWS were not observed in children; therefore, they were more sensitive to external stimuli such as physical exercise.

Our findings provide an explanation for contrasting results regarding the amount of SWS in previous studies. Elevated SWS was mostly evident following high-intensity exercise of long duration [13] (usually >2 h), whereas exercise of low and moderate intensity did not influence SWS proportion [35]. Similarly we did not find an effect of moderate intensity exercise on SWS. Such changes in SWS can only be described in terms of the effects of exercise upon the brain because the sleep EEG is not a measure of body restoration but rather only an indication of brain functioning [22]. Thus, we hypothesized that physiological alterations in the brain during exercise affect subsequent sleep. The amount of SWS is homeostatic-regulated and directly linked to the brain energy metabolism [4,29]. Prolonged wakefulness results in a progressive decline of cerebral glycogen levels [15,26]. Possibly SWS is necessary for replenishment, since the brain energy metabolism is dramatically decreased in this state [4,32]. Under certain circumstances such as intense physical exercise, when the ratio of metabolite demand to metabolite availability increases, the production of the sleep promoting substance adenosine rises [12,18,27,36]. Additionally, to fulfill energy requirements efficiently, the brain uses substrates other than glucose, preferentially lactate and phosphocreatine, which serve as a temporal and spatial buffer for ATP homeostasis and ensure retention of neuronal activity [11,24,37]. Rapid depletion of cerebral phosphocreatine stores with intense physical activity could lead to increased cerebral adenosine levels and inadequate replenishment of cerebral energy stores during subsequent wake time; the increase in SWS may serve a compensatory function to alleviate this deficit. All subjects reported a great tiredness and increasing need for sleep 5 min after finishing the exhaustive exercise session. Further studies are necessary to

determine the effects of physical activity on general mechanisms in sleep regulation under special consideration of brain energy metabolism.

In conclusion, our data suggest that exercise affects sleep continuity and sleep architecture parameters in children, including improved sleep efficiency and reduced SOL. Increases in SWS proportions as well as less time in stage 2 were observed only after exhaustive exercise. Thus, metabolic changes associated with exercise intensity may play an important key role in regulation of human sleep patterns, which supports the hypothesis of homeostatic sleep regulation. This raises the issue of the use of physical activity for the non-pharmacological improvement of disturbances of sleep and alertness, which are highly prevalent in the general population.

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2.7. Zusammenfassung

Über den Einfluss von moderater und intensiver allgemeiner Ausdauerbelastungen auf den Vigilanzzustand und das Schlafverhalten bei Kindern: eine Polysomnographische Studie

Einleitung: Es bestehen Kontroversen über die Effekte von körperlicher Belastung auf das menschliche Schlafverhalten. Zahlreiche Befunde weisen darauf hin, dass dynamische physische Belastungen, vor allem in Form einer allgemeinen aeroben Ausdauerbelastung, einen Einfluss auf Gehirnstrukturen und Gehirnfunktionen haben können. Jedoch bestehen widersprüchliche Daten bezüglich der Effekte von körperlichen Belastungen auf Schlafarchitektur- und Schlafkontinuitätsparameter, hierbei speziell auf die Tiefschlaf- und REM-Schlafanteile.

Studienziel: Die vorliegende Studie untersucht die Effekte von moderater und intensiver körperlicher Belastung auf den Vigilanzzustand und das Schlafverhalten von Kindern.

Methoden: Elf gesunde Kinder (12.6 ± 0.8 Jahre) wurden für diese polysomnographische Studie rekrutiert und zwei Belastungseinheiten ausgesetzt. Die zwei Belastungseinheiten auf dem Fahrradergometer fanden 3-4 Stunden vor dem Schlafengehen statt, dauerten 30 Minuten und unterschieden sich nur in der Belastungsintensität. Die moderate Belastung wurde bei 65-70% der maximalen Herzfrequenz (HFmax) absolviert, während die intensive Belastung bei 85-90% HFmax bis hin zur Erschöpfung ausgeführt wurde. Polysomnographische und physiologische Messungen, einschließlich Pulsoximetrie, wurden in den drei Untersuchungsnächten, welche in randomisierter Reihenfolge im zeitlichen Abstand von einer Woche stattfanden, durchgeführt. Ein Vigilanztest erfolgte vor und nach den drei Untersuchungsnächten.

Ergebnisse: Nur die intensiven Belastungen resultierten in signifikant erhöhten Tiefschlafanteilen (Stadium 3 + 4) und weniger Schlaf in Stadium 2, sowie einer erhöhten Schlafeffizienz und einer verkürzten Einschlaflatenz. Es konnten keine signifikanten Effekte auf den REM-Schlaf beobachtet werden.

Schlussfolgerung: Die Befunde deuten darauf hin, dass die Belastungsintensität ausschlaggebend für die Effekte auf den Tiefschlaf und das Schlafstadium 2 bei Kindern ist, und stützen die Hypothese einer homöostatischen Regulation des Schlafes.

3. Second Study: Intense exercise increases adenosine concentrations in rat brain – implications for a homeostatic sleep drive

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3.1. Abstract

Intense exercise and sleep deprivation affect the amount of homeostatically regulated slow wave sleep in the subsequent sleep period. Since brain energy metabolism plays a decisive role in the regulation of behavioral states, we determined the concentrations of nucleotides and nucleosides: phosphocreatine, creatine, ATP, ADP, AMP, adenosine, and inosine after moderate and exhaustive treadmill exercise as well as 3 and 5 h of sleep deprivation and sleep in the rat brain using the freeze-clamp technique. High intensity exercise resulted in a significant increase of the sleep-promoting substance adenosine. In contrast, following sleep, inosine and adenosine levels declined considerably, with an accompanied increase of ADP after 3 h and ATP after 5 h. Following 3 h and 5 h sleep deprivation, ADP and ATP did not differ significantly, whereas inosine increased during the 3 and 5-h period. The concentrations of AMP, creatine and phosphocreatine remained unchanged between experimental conditions. The present results are in agreement with findings from other authors and suggest that depletion of cerebral energy stores and accumulation of the sleep promoting substance adenosine after high intensity exercise may play a key role in homeostatic sleep regulation, and that sleep may play an essential role in replenishment of high-energy compounds.

3.2. Introduction

Physical exercise is known to impact on nearly every system of the body, including the brain (Cotman and Engesser-Cesar, 2002; Cotman and Berchtold, 2002). Abundant experimental evidence strongly suggests that dynamic physical exercise produces elevated regional cerebral blood flow (CBF), alterations in endogenous peptides, increased amino acid transport through the blood–brain-barrier and neurotransmitter alterations (Herholz et al., 1987; Hollmann et al., 1994; Ide et al., 1999). Dynamic exercise stimulates the formation of synapses and neuronal spines, promotes neurogenesis and improves cognitive brain functions and agerelated degeneration processes (Cotman and Berchtold, 2002). However, the relationship between physical exercise and sleep in humans is not completely understood. Only high intensity exercise affects the amount of homeostatic-regulated slow wave sleep in the subsequent sleep period (Shapiro et al., 1981; Dworak et al., 2007). The reason for this phenomenon is still unclear. Modern neuroscientific theories support the hypothesis that the brain energy metabolism and specific neurotransmitter systems play a decisive role in mammalian sleep regulation (Benington and Heller, 1995; Maquet, 1995). Recent evidence showed that prolonged sleep deprivation (SD) results in spatial and temporal alterations in brain glycogen levels (Kong et al., 2002; Gip et al., 2002; Franken et al., 2003, 2006). Slow-wave sleep is thought to be essential for glycogen replenishment, since brain energy metabolism is dramatically decreased in this state (Nofzinger et al., 2000; Arrigoni et al., 2006). Discrepancies between energy demand and energy supply result in increased extracellular adenosine concentrations and reflect an energy deficit during prolonged wakefulness (recently reviewed in Basheer et al., 2004). Adenosine plays an important role in regulation of blood flow, synaptic transmission and neuronal excitability (Latini and Pedata, 2001). Stimulation of neuronal adenosine receptors mediates presynaptic inhibition in the transmitter release of neuronal networks involved in the regulation of wakefulness (Rainnie et al., 1994; Arrigoni et al., 2006) as well as post-synaptic hyperpolarization that regulates behavioral

states (Basheer et al., 2004; Latini and Pedata, 2001). Thus, this nucleotide is a product of cerebral energy consumption and a potential sleep-promoting factor in the CNS (Porkka-Heiskanen et al., 2000). Since physical exercise is narrowly linked with neuronal metabolic activity, CBF, neurotransmitter alterations and increased brain temperature (Nybo and Secher, 2004), it can be assumed that intense physical exercise is a potential stimulus to reduce cerebral energy compounds, increase brain adenosine levels and promote subsequent sleep. SD is also known to increase the homeostatic drive to sleep (Tobler and Borbely, 1990) and raise local extracellular adenosine level (Basheer et al., 2004; Latini and Pedata, 2001). Therefore we used both, physical exercise and SD to examine the effects on brain energy metabolism. In the present study we tested the hypotheses that physical exercise and SD decrease phosphocreatine (PCr) and ATP levels in the rat brain, that physical exercise and SD increase adenosine levels in the rat brain, and that duration and intensity of the exercise, sleep and SD sessions are decisive for the extent of these alterations.

3.3. Experimental procedures

Animals

All procedures were conducted in accordance with the European Union Guidelines for the Care and Use of Laboratory Animals and undertaken with the approval of the regional administration of the governmental body. All experiments were conducted to minimize the number of laboratory animals and their suffering. Male adult Wistar rats (70 days old), weighing 376.7±72.3 (sd) g, were housed under constant temperature (22 °C) on a 12-h light/dark cycle (lights on from 07:00 h to 19:00 h). Food and water were provided *ad libitum*. After a 1-week acclimation period, rats were randomly divided into the following groups: Control (C, n=18), SD (n=12) and exercised (EX, n=12). Furthermore EX rats were randomly assigned to one of the following two subgroups: moderate exercise (mEX) and intense exercise (iEX).

Considering that the brain is one of the most active tissues in terms of nucleoside and nucleotide synthesis, and that after removal metabolites are very unstable during ischemia, we used freeze-clamp technique to freeze brain tissue immediately and prevent enzymatic activity (Palladino et al., 1980; Helzberg et al., 1987). The tissue was rapidly clamped between aluminum blocks, pre-cooled in liquid nitrogen, and frozen immediately to a temperature approximating that of liquid nitrogen. Studies showed that freeze-clamp measurements correlated well with focused microwave irradiation (Beal et al., 1993) and nuclear magnetic resonance (NMR) data (Camacho et al., 1988).

Exercise session

Animals were familiarized with a motor-driven treadmill for 3 days, 5 min/day, on a 10% grade. On experimental days, both EXgroups performed an acute bout of treadmill running. For the mEX group the running speed was initially 15 m/min and was gradually increased to 20 m/min at 10% grade for 30 min. Intense treadmill exercise was initially performed at 15 m/min and increased to 25 m/min for a maximum of 60 min to exhaustion.

Sleep deprivation

SD was achieved by the gentle handling method, as described earlier (Franken et al., 1991). Rats were inspected continuously and kept awake by introducing and removing objects from the cage, and after a prolonged period of wakefulness by tapping lightly the cage or touching the animal with a paintbrush. SD of 3 h (n=6) or 5 h (n=6) durations were started at 7:00 AM and were performed under lights-on conditions. Both SD groups had their own control group (n=2x6) consisting of animals kept undisrupted under the same conditions. Electroencephalograph (EEG) was not monitored but the criteria for sleep behavior were identical with other studies (Tobler and Borbely, 1990). Control animals were allowed to sleep *ad libitum* and spared from any physical activity. The unanesthetized animals were decapitated at three

different times across a 24-h day. The sampling time points were: 7:00 AM, 10:00 AM and 12:00 AM. The brains were rapidly removed, frozen by freeze-clamp-technique, placed in liquid nitrogen and stored at -85 °C.

Biochemical analyses

All reagents were of the highest purity available. Adenosine, creatine (Cr), PCr, and ADP were purchased from Fluka (Sigma-Aldrich, Taufkirchen, Germany). Inosine, AMP and ATP were purchased from Sigma-Aldrich. The frozen brain was weighed and homogenized in 1.0 M $HClO_4$/50 mg. The protein precipitate was spun off, and the supernatant was neutralized with 2.0 M K_2HPO_4/50 mg. The supernatant was utilized for the determination of inosine, adenosine, AMP, ADP, ATP, Cr and PCr levels by HPLC/UV detection with comparison to known standards as described earlier (Helzberg et al., 1987).

Data analysis

Reported values are means ± sd from at least six rats per group. Statistical analysis of the nucleotide and nucleoside data was performed with one-way analysis of variance (ANOVA), followed by the Bonferroni test as a post hoc test to compare interactions between the groups using SPSS 12.0 (SigmaStat Statistical Software, Chicago, IL, USA) and STATISTICA 7.1. software (StatSoft, Tulsa, OK, USA) for MS Windows. All statistical tests were considered significant if $P<0.05$.

3.4. Results

Metabolite changes after exercise

Nucleotide and nucleoside concentrations in the rat brain were measured after "lights-on" (baseline), 3 h and 5 h (control) of sleep, moderate and intense exercise as well as after 3 h and 5 h SD. Resting values (control) were defined after 5 h of undisrupted sleep. After high intensity exercise adenosine and inosine levels were significantly elevated (ANOVA F=5.67; P=0.0003 and F=8.43; P=0.00001) and reached 229.04% and 425.21% of the control levels respectively. Only the intense, not moderate exercise session resulted in a significant (ANOVA F=5.67; P=0.0003; post hoc P=0.0002) increase of adenosine when compared with resting controls (5 h sleep). In the iEX group, ADP and ATP concentrations were 0.05±0.01 nmol/mg and 0.03±0.01 nmol/mg without any statistical significance. Figs. 1 and 2 depict the level of adenosine and inosine for the mEX and iEX groups. A significant (F=31.30; P= 0.0002; post hoc P= 0.0036) increase of inosine was also observed after the mEX session, when compared with resting controls (5 h sleep). The respective concentrations for ATP and adenosine in the moderate exercised group were 0.09±0.04 nmol/mg and 0.03±0.01 nmol/mg, and were not statistically significant relative to control conditions. The concentrations of AMP, Cr and CrP did not differ significantly between the experiments.

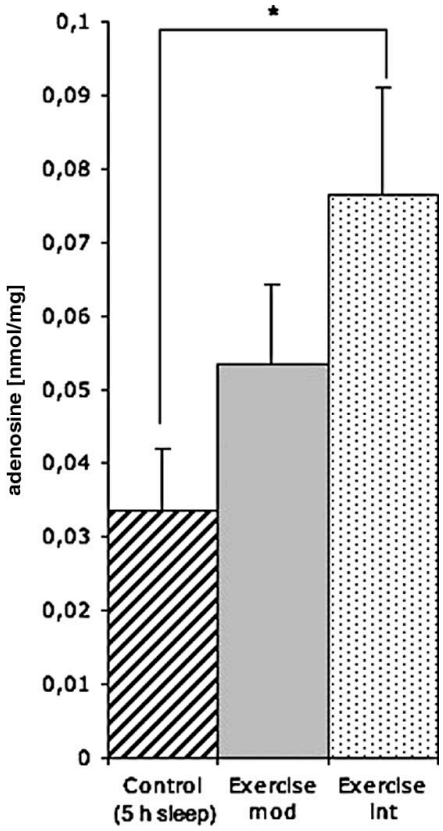

Fig. 1. Adenosine concentrations measured after control conditions (5h sleep), moderate (mEX) and high intensity (iEX) exercise. Intense exercise increase adenosine concentrations significantly (* $P<$ 0.05) related to sleeping controls.

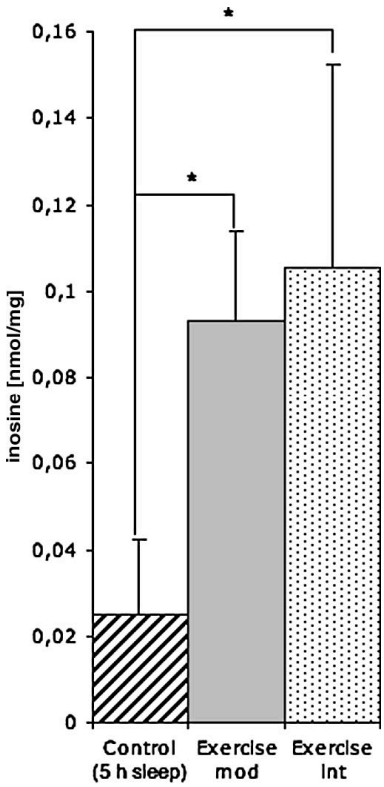

Fig. 2. Whole brain inosine concentrations measured after control conditions (5 h sleep), moderate (mEX) and high intensity (iEX) exercise. Inosine concentrations were significantly elevated (* P 0.05) after the moderate and high intensity exercise session.

Metabolite changes after SD and resting conditions

Total brain adenosine concentrations did not change after 3 and 5 h of SD. Also, comparisons of total brain AMP, Cr and CrP showed no significant changes between the groups and time points of measurement. Figs. 3 and 4 depict the changes of total ATP and ADP concentrations after 3 and 5 h of sleep. Significant increases in brain ADP concentrations after 3 h (ANOVA F=3.71; P=0.060; post hoc P=0.042) and ATP concentrations after 5 h (ANOVA F=5.17; P=0.0006; post hoc P=0.0039) of sleep were observed. In addition, significant declines in inosine and adenosine concentrations were observed in a duration-dependent manner. Inosine concentrations showed a significant (ANOVA F=8.43; P=0.00001) progressive decline to 57.42% and to 29.22% of the baseline values after 3 h and 5 h of sleep (Fig. 5). Brain adenosine concentrations were also significantly reduced when compared with the intense exercised rats (ANOVA F=5.67; P=0.0003; post hoc P=0.0002). Respective values for Cr and PCr were 9.60±1.10 and 0.39±0.10 nmol/mg under baseline conditions and 5.93±2.42 and 0.61±0.27 nmol/mg after 5 h sleep, without any statistic significance when compared with control conditions.

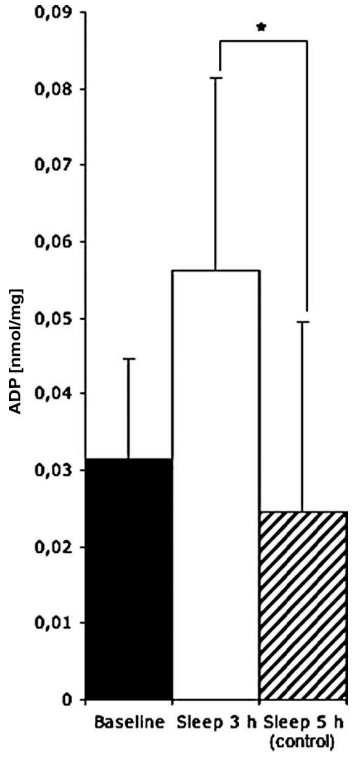

Fig. 3. ADP concentrations measured after Baseline conditions, 3 h and 5 h (control) of sleep. Baseline measurements were performed at beginning of "lights-on"-conditions, i.e. after the active period. ADP concentrations increase significantly (* *P* 0.05) after 3 h of sleep when compared with the 5-h sleep period.

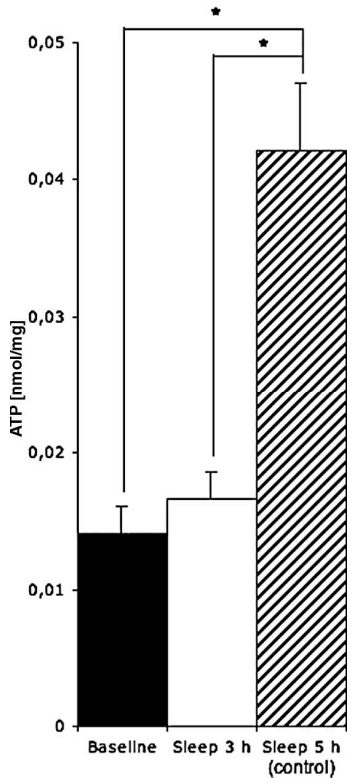

Fig. 4. ATP concentrations measured after baseline conditions, 3 h and 5 h (control) of sleep. After 5 h of sleep ATP concentrations were significantly higher (* *P* 0.05) related to basal values and 3 h of sleep.

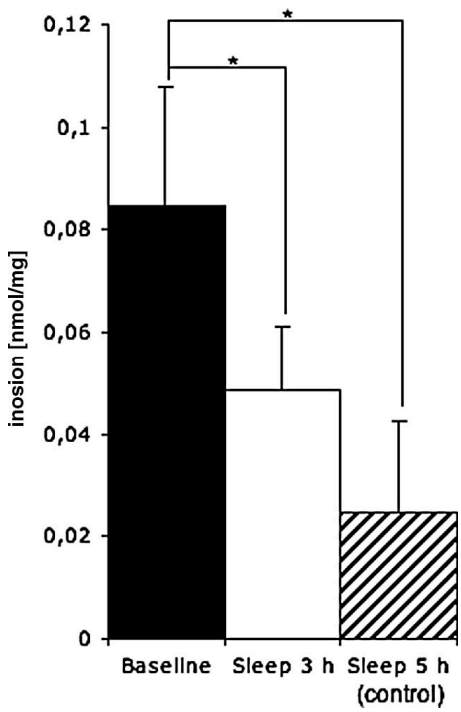

Fig. 5. Whole brain inosine concentrations measured after baseline, 3 h and 5 h (control) of sleep. Inosine concentrations were significantly reduced (* *P* 0.05) after 3 and 5 h of sleep.

3.5. Discussion

The present study demonstrates that intense physical exercise increase total brain adenosine and inosine concentrations in contrast to sleep and SD conditions. Undisrupted sleep resulted in significantly elevated ADP and ATP concentrations as well as a progressive decline of inosine and adenosine in a duration-dependent manner. SD (3 h and 5 h) did not affect brain ATP and adenosine concentrations significantly. However a great increase of inosine between the 3- and 5-h deprivation period was observed. The present results are in congruence with other studies concerning the effects of exercise and sleep on the brain energy metabolism, providing supplementary evidence for a homeostatic regulation of brain energy stores and the role of sleep in replenishment of brain energy compounds.

Brain energy metabolism during exercise

Physical exercise is known to impact nearly every system of the body, including the brain (Hollmann et al., 1994; Cotman and Engesser-Cesar, 2002). Dynamic physical exercise produces an elevated regional CBF (Herholz et al., 1987; Ide and Secher, 2000), alterations in endogenous peptides, amino acid transport through the blood– brain-barrier and neurotransmitter alterations (Hollmann et al., 1994). Furthermore it stimulates the formation of synapses and spines as well as neurogenesis, improves cognitive brain functions and age-related degeneration processes (Cotman and Engesser-Cesar, 2002; Cotman and Berchtold, 2002). Physical exercise is narrowly linked with neuronal activity (Ide and Secher, 2000). Previous studies have shown that dynamic movements are associated with cortical activation and increases in blood flow to the primary sensorimotor area and supplementary motor area (Orgogozo and Larsen, 1979). The cerebral metabolic rate for glucose determined after running indicates an involvement of the hypothalamus, the posterior parietal, the temporoparietal, the prefrontal, the premotor and the primary motor cortex (Orgogozo and Larsen, 1979). The magnitude of brain activation increases with the intensity of exercise (Williamson et al., 1999) and the brain may become maximally stimulated when exercise is performed at a level near to exhaustion (Kayser, 2003). Additionally, whole brain metabolic activity increases (Ide and Secher, 1999; Williamson et al., 1999) since the increased motor command results in elevated metabolic rates in the activated brain structures associated with exercise execution (Kayser, 2003). During intense brain activation neurons prefer lactate to glucose as their primary energy substrate, which raises the production of ATP (Schurr, 2006). High intensity exercise increases the ratio of metabolite demand to metabolite availability with an accompanied production of adenosine from AMP. We found significantly elevated adenosine and inosine concentrations after intense exercise, relative to moderate exercise, SD and resting conditions. Also, previous studies showed significantly higher adenosine concentrations in the rat neostriatum and in the hippocampus during the dark period (active period of rats) than during the

light period, a finding that was interpreted as association of adenosine concentrations with motor activity (Huston et al., 1996). The observed findings of increased adenosine concentrations might reflect a state of bioenergetic stress, possibly as a result of an increased breakdown of high-energy phosphates.

Brain energy metabolism during SD

SD is assumed to affect the brain proportionally more than any other organ in the body. In the rat, SD resulted in a unique appearance of peripheral symptoms, including increases in whole body energy expenditure and immunodeficiency that develops progressively and could be lethal after about 19 days (Rechtschaffen et al., 1983; Rechtschaffen and Bergmann, 1995). In the present study SD was induced under light-on conditions, directly after the dark period, for 3 h and 5 h to avoid stressing the animals by prolonging the SD, because acute and chronic stress might affect brain energy metabolism. Additionally, previous experiments showed that during the dark phase rats normally sleep 25–35% of the time, whereas during the first half of the light phase rats normally sleep 60–80% of the time (Tobler and Borbely, 1990). Thus, it can be estimated that 3 h of SD during light-on conditions caused on average 2.1 h lack of sleep whereas 5 h SD caused in average 3.5 h lack of sleep.

Whole adenosine concentrations did not differ significantly after 3 h and 5 h of SD. This may very well be due to whole brain measurements of nucleotides and nucleosides using the freeze-clamp technique. It is well known that the SD-induced increase in adenosine in the first few hours is limited to the basal forebrain area (reviewed in Basheer et al., 2004). Porkka-Heiskanen et al. (2000) showed accumulation of extracellular adenosine in a sitespecific manner after prolonged wakefulness, selectively in the basal forebrain and to a lesser extent in the cortex, while in other subcortical structures the concentrations tended to decline. Since total adenosine concentrations (extra-

and intracellular) in the rat brain were examined in the present study, our data provide a net effect for adenosine in the whole brain and may dilute the effects that occur in localized areas. Thus, the present results are in accordance with the observation that changes in extracellular adenosine during SD may be a regionally specific phenomenon. However, during intense exercise it seems that rise in adenosine levels is rather global, since whole brain measurements show a significant increase in brain adenosine concentrations. Also, it could be assumed that the duration of SD was not long enough to increase metabolic demand and total adenosine concentrations. In a recent PET study it was shown that after 24 h SD in humans cortical A1 receptor binding is increased, presumptively because of adenosine increases in the cortex at this time point (Elmenhorst et al., 2007). Possibly longer periods of SD might show evidence for adenosine changes in other brain areas. In addition, after SD no changes in total brain ADP and ATP concentrations were observed. Previous studies have produced contrasting results with respect to the regulation of glucose and glycogen metabolism during SD. It was shown that the mean rate of glucose utilization in the brain remained unchanged between sleep-deprived rats and yoked controls (Everson et al., 1994). However, significant reductions in the hypothalamus, thalamus, and to a lesser extent in the limbic system were observed after SD (Everson et al., 1994). SD studies with longer durations (12 or 24 h) resulted in significantly decreased brain glycogen levels in white and gray matter that reversed to basal conditions during recovery sleep (Kong et al., 2002). Spatial differences were also observed in other studies. After 6 h SD, reductions in glycogen concentrations were only detectable in the cerebellum but not in the cortex of young rats (Gip et al., 2002). These results were confirmed in following study with significant declines in glycogen content in the cerebellum and hippocampus, but not in the cortex and brain stem (Gip et al., 2002). In AKR/J and DBA/3J mice, glycogen content significantly decreased in the cerebellum and brain stem but did not change in the cortex after 6 h SD whereas significant increases were observed in C57BL/6J (B6) mice (Franken et al., 2003, 2006). These contrary findings support the notion that metabolic changes in the brain occur in a spatial and

temporal manner and are in accordance with our results, since we found no evidence for changes in total brain adenosine concentrations following SD (3 h and 5 h). However it could be assumed that the dynamics of the changes in brain energy metabolism in relation to sleep and wakefulness are complex and affected by age, genotype and brain region (Franken et al., 2003).

Brain energy metabolism and sleep regulation

Sleeps is homeostatically regulated and strongly correlate with adenosine metabolism (Basheer et al., 2004, Porkka-Heiskanen et al., 2002). The primary effect of the increase in adenosine in cholinergic basal forebrain is on the ensuing sleep as indicated by an increase in delta power during slow wave sleep (Basheer et al., 2000; Porkka-Heiskanen et al., 1997, Alam et al., 1999). The increased levels of EEG delta frequency are suggested to predict the intensity of sleepiness based on the duration of prior wakefulness (Borbely and Achermann, 2000). Neuronal downscaling during sleep reflects reductions in metabolic rate indicating that during slow-wave sleep brain energy expenditure decreases (Kennedy et al., 1981, Netchiporouk et al. 2001), CBF (Braun et al, 1997) and cerebral metabolic rate decrease, while glucose (Nofzinger et al., 2000) and ATP concentrations increase (Van den Noort and Brine, 1970). The great increase of brain ADP levels after 3 h, and brain ATP levels after 5 h sleep in the present study might reflect an assembly of high-energy compounds. Since wakefulness results in a greater metabolic activity than sleep, our results are in accordance with the hypothesis that brain energy stores are replenished during sleep (Benington and Heller, 1995). Additionally, it is assumed that physical exercise has a sleep-promoting effect (Shapiro et al., 1981; O'Connor and Youngstedt, 1995). Previous studies showed that only high-intensity exercise results in higher sleep efficiency, shorter sleep onset latency and proportional elevated levels of slow-wave sleep, while no effects after moderate exercise could be shown (Shapiro et al., 1981; Dworak et al., 2007). If the role of adenosine as a sleep-promoting factor is taken into account, the results of the present study could provide a

simple explanation for the sleep-promoting role of high intensity exercise. Our results suggest that only high intense exercise resulted in significant elevated adenosine and inosine concentrations, whereas no changes in these nucleosides were found after moderate exercise. These observations were supported by a recent *in vivo* microdialysis study, showing that minimal exercise did not affect adenosine concentrations in the basal forebrain (McKenna et al., 2007). The relationship between energy depletion and sleep induction has been addressed in previous studies (Kalinchuk et al., 2003; Shepel et al., 2005). Elevation of extracellular adenosine concentrations is essential for the subsequent induction of non–rapid eye movement sleep (Kalinchuk et al., 2003). Adenosine may affect sleep and waking behavior through several mechanisms (reviewed in Basheer et al., 2004). Thus, it could be hypothesized that increased adenosine concentrations after intense exercise in the whole brain, including the cerebral cortex, hypothalamus, and basal forebrain structures result in a depression of neuronal activity due to the inhibitory actions of this nucleotide. A significant accumulation of adenosine due to a depletion of brain energy stores may play a central role in homeostatic sleep regulation, and consequential increases in slow-wave sleep in subsequent sleep may serve a compensatory function to alleviate this deficit. In conclusion, our data indicate that intense exercise affects brain energy metabolism by accumulation of adenosine and inosine. In contrast, sleep leads to a progressive decline of inosine and adenosine as well as significantly elevated ADP and ATP concentrations in a duration dependent manner. Thus, the present study and findings from other authors suggest that the accumulation of the sleep-promoting substance adenosine after high intensity exercise may play a key role in homeostatic sleep regulation and that sleep could play an essential role in replenishment of high energy compounds (Fig. 6).

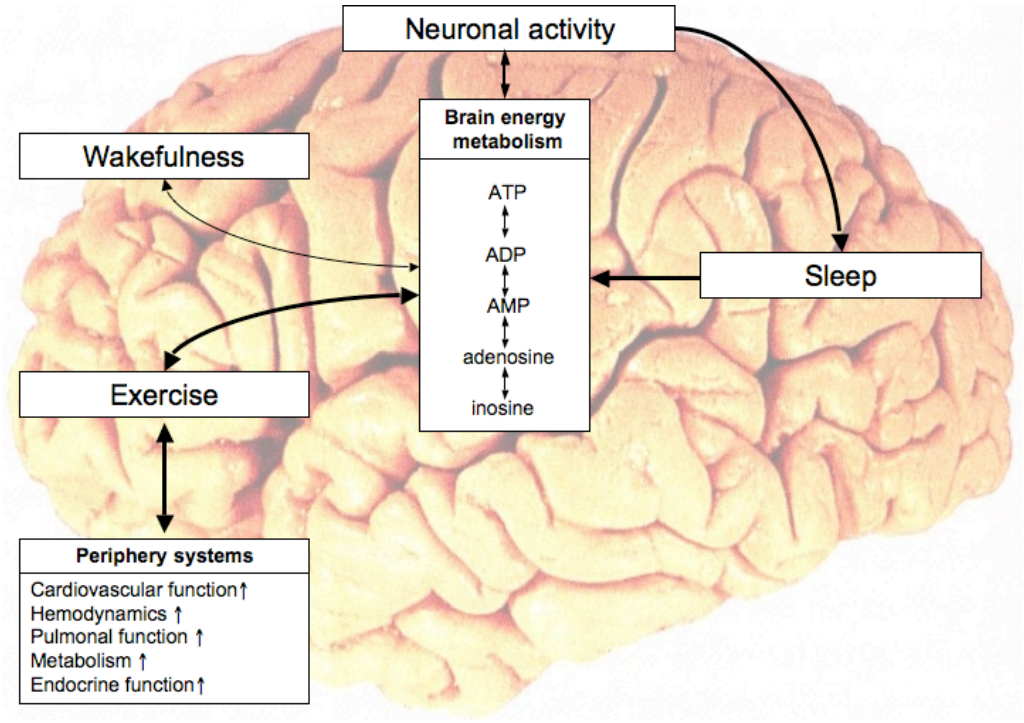

Figure 6: Relationships between physical exercise, brain energy metabolism and sleep. Exercise affects both, periphery and brain metabolic systems. During intense exercise when metabolic demand exceeds metabolic supply, the formation of adenosine from AMP increases. Adenosine depresses neuronal activity, by pre- and postsynaptic actions and facilitates sleep. During sleep, brain energy expenditure decreases while ADP and ATP concentrations increase.

Limitations of the study

Only nucleosides and nucleotides were measured in the present study. Therefore we cannot assess the influence of other energy compounds such as glycogen, glucose, and lactate on energy requirements. Furthermore, we measured concentrations of nucleotides and nucleosides in whole rat brain using freeze clamp technique (Palladino et al., 1980; Helzberg et al., 1987). Thus, it is not possible to get any information about spatial changes of nucleotide and nucleoside concentrations in the rat brain. Since the tissue was rapidly clamped, we were not able to detect metabolite changes in specific brain areas such as the basal forebrain, hypothalamus, and cortex. Especially adenosine and other metabolites may accumulate during different behavioral states in a spatial and temporal manner and further research is necessary to examine the effects of physical exercise on brain energy metabolites in specific brain structures.

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3.7. Zusammenfassung

Über den Einfluss von moderater und intensiver körperlicher Belastung, Schlafentzug und Schlaf auf den Gehirnenergiestoffwechsel der adulten Ratte

Intensive Belastungen und Schlafentzug beeinflussen die homöostatisch regulierten Tiefschlafanteile in der folgenden Schlafperiode. Da der Gehirnenergiestoffwechsel eine entscheidende Rolle in der Regulation der Verhaltensstadien einnimmt, untersuchten wir die Konzentrationen der Nukleotide und Nukleoside: Phosphorkreatine, Kreatine, ATP, ADP, AMP, Adenosine und Inosine nach moderaten und erschöpfenden Laufbandbelastungen, sowie nach drei und fünf Stunden Schlafentzug und Schlaf im Gehirn der adulten Ratte mittels der „Freeze-Clamp-Technik".

Intensive Belastungen resultierten in einem signifikanten Anstieg der schlaffördernden Substanz Adenosin. Nach anhaltendem Schlaf konnten dagegen deutliche Abnahmen der Adenosin und Inosin Level beobachtet werden, mit einem begleiteten Anstieg von ADP nach 3 Stunden und ATP nach 5 Stunden Schlaf. Nach den Schlafentzugsperioden konnten keine signifikanten Unterschiede in den ADP und ATP Konzentrationen festgestellt werden, wogegen Inosin während der drei- und fünfstündigen Schlafentzugsperiode signifikant anstieg. Die Konzentrationen von AMP, Kreatine und Phosphorkreatine blieben zwischen den einzelnen Versuchsbedingungen unverändert.

Die vorliegenden Befunde sind übereinstimmend mit den Resultaten anderer Arbeitsgruppen und deuten darauf hin, dass die Entleerung zerebraler Energiespeicher und die Ansammlung der schlaffördernden Substanz Adenosin nach intensiver körperlicher Belastung eine wesentliche Rolle in der homöostatischen Schlafregulation hat und dass der Schlaf der Wiederherstellung hoch energetischer metabolischer Phosphate dienen könnte.

4. Third Study: Impact of Singular Excessive Computer Game and Television Exposure on Sleep Patterns and Memory Performance of School-aged Children

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Keywords: Television, computer game, children, sleep patterns, cognitive performance, polysomnographic study

Abbreviations: ADHD – attention-deficit/ hyperactivity disorder, PSG – Polysomnography, REM – rapid eye movement, SOL – sleep onset latency, SWS – Slow wave sleep, TST – total sleep time, VVM - visual and verbal memory test,

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4.1. Abstract

Objective: Television and computer game consumption are a powerful influence in the lives of most children. Previous evidence has supported the notion that media exposure could impair a variety of behavioral characteristics. Excessive television viewing and computer game playing have been associated with many psychiatric symptoms, especially emotional and behavioral symptoms, somatic complaints, attention problems such as hyperactivity, and family interaction problems. Nevertheless, there is insufficient knowledge about the relationship between singular excessive media consumption on sleep patterns and linked implications on children. The aim of this study was to investigate the effects of singular excessive television and computer game consumption on sleep patterns and memory performance of children.

Methods: Eleven school-aged children were recruited for this polysomnographic study. Children were exposed to voluntary excessive television and computer game consumption. In the subsequent night, polysomnographic measurements were conducted to measure sleep-architecture and sleep-continuity parameters. In addition, a visual and verbal memory test was conducted before media stimulation and after the subsequent sleeping period to determine visuospatial and verbal memory performance.

Results: Only computer game playing resulted in significant reduced amounts of slow-wave sleep as well as significant declines in verbal memory performance. Prolonged sleep-onset latency and more stage 2 sleep were also detected after previous computer game consumption. No effects on rapid eye movement sleep were observed. Television viewing reduced sleep efficiency significantly but did not affect sleep patterns.

Conclusions: The results suggest that television and computer game exposure affect children's sleep and deteriorate verbal cognitive performance, which

supports the hypothesis of the negative influence of media consumption on children's sleep, learning, and memory.

4.2. Introduction

In western industrial countries, television and computer game consumption take up a large part of children's time awake. The proportion of television users among children who are aged 9 to 16 years ranges from 98% to 100%.[1] Some studies have indicated that excessive television and video game consumption could result in psychiatric symptoms such as aggressive behavior,[2–4] attention problems,[5] hyperactivity,[6] scholastic problems,[7,8] and somatic complaints.[3,9,10] Despite this knowledge, average media consumption of the children in this age group is 4 hours/day.[7] Furthermore, these sedentary activities are frequently associated with significant behavioral consequences,[9,11–13] including decreased physical activity and physical fitness,[14] poor eating habits,[15] and obesity,[3] and could impair development in childhood and adolescence.[10,16–19] Despite the enormous progress in media research, there is insufficient knowledge about the effects of singular excessive media exposure on behavioral states and sleep patterns in children. Most examinations focused on long-term effects of media exposure on children's wellbeing, and only a few studies examined the effects of television and computer consumption on children's sleep quality.[20–23] Negative effects on sleeping behavior, such as sleep-onset delay,[20,21] night waking,[22] sleep anxiety, [24] and shortened sleep duration,[22,23] were observed in recent studies and suggest that media exposure could impair sleep quality. Finally, watching television 3 hours/day during adolescence elevates the risk for frequent sleep problems in early adulthood.[25] Sleep is essential for children's health and development and possibly plays an important role in learning and memory.[4,26] Neuroscientific theories support the notion that emotions could influence learning processes.[27] Especially recently acquired knowledge is very sensitive in the subsequent consolidation period, and what the children emotionally experience within the hours after learning influences it decisively. The influence of interactive media consumption on emotions was also established. Thus, it could be hypothesized that television and computer game consumption after a learning period could impair memory consolidation and

performance. The purpose of this polysomnographic study was to evaluate direct short-term effects of singular excessive television and computer game consumption on sleeping patterns and cognitive performance of school-aged children.

4.3. Methods

Participants

Eleven male children volunteered to participate in this study (age: 13.45 ± 1.04 years; height: 1.64 ± 0.09 m; weight: 48.23 ± 5.97 kg; BMI: 17.82 ± 1.29 [all means ± SD]). Children and their parents for this study were volunteers from 8599 families who previously were recruited for and participated in the Healthy Sleep for Cologne Children study, an epidemiologic study of sleeping behavior and sleep complaints in children. All participants were junior high school children in the first grade. Participants were selected in random order after fulfillment of the following criteria: age between 12 and 14 years, great health, no medications, German nationality, and male gender. Only male participants were selected for this study because previous studies indicated that menstrual cycle phase as well as oral contraceptive could influence sleeping behavior. In precocious girls, these factors could influence nocturnal sleep. In addition, media research studies indicate that boys spend more than twice as much time playing video games as girls do; therefore, video game playing is a greater impact factor in boys' leisure time. After consideration of the mentioned criteria, 3580 children were contacted with detailed information regarding the study setting; a total of 1321 consenting children gave a response rate of 36.9%. All participants and parental authorities signed informed consent forms and completed a medical questionnaire before the experiment. They were informed that they could quit the study at any stage. All participants showed good health status and had no sleep complaints. Participants were instructed to refrain from additional physical activity, passive body warming (eg, taking a warm bath or shower), and sleep during

the day on the experimental days. They did not consume any kinds of caffeine, nicotine, or alcohol, and they were not exposed to a large stress load.

Experimental Design

Each participant underwent 3 investigation days in a randomized, crossover manner. The interval between the experiments was exactly 1 week. On 2 different experimental days, children were exposed to 2 types of media. On 1 occasion, they played interactively a computer game (*Need for Speed—Most Wanted*; Electronic Arts, Redwood City, CA) for 60 minutes. Recent studies suggest that this is nearly the average time per day that children spend playing computer games.[21] Furthermore, the participants watched a subjectively exciting video film on television. Every participant could choose from among 3 films (*Harry Potter and the Prisoner of Azkaban*, *Star Trek: Nemesis*, and Mary Higgins Clark's *Loves Music, Loves to Dance*) but was not allowed to have seen the film before the experimental day. Media exposure occurred between 6:00 PM and 7:00 PM (2–3 hours before bedtime). This time of day was selected because the children have usually finished their homework at that time and start their leisure time. Under control conditions, the participants adhered to their normal daily patterns but were not allowed to watch television or play computer games. Four to 5 hours before bedtime, when children usually did their homework, a visual and verbal memory test (VVM) was conducted on each experimental day (Swets Test Services, Frankfurt am Main, Germany). The test served to determine the short-term and longer-term memory of visuospatial and verbal materials and was subdivided into 2 subtests. For examination of the memory performance in the visually spatial area, a map with a marked path was shown to the children for 2 minutes. Immediately after this, the participants were asked to draw the path on such a map from memory. The second subtest served to examine the memory of facts. In this case, text that included names, numbers, and terms was presented for 2 minutes. After the presentation, the facts were immediately (T1) asked for in writing. Both tests were repeated after each experimental day within a 24-hour interval (T2) without renewed attraction. The raw analyzed results of

the 2 subtests were intended for the 2 test times. A calculation of the loss of memory performance for every subtest was conducted by the following formula:

$$T1 - T2 = [(T2 - T1)/T1] \times 100$$

Data Recording and Analysis

Before participant went to bed, polysomnographic measurements were conducted using a portable sleep data recorder (Varioport-SLP 2.0; Becker Meditec, Karlsruhe, Germany). An expert affixed the electrodes between 7:30 PM and 8:30 PM and removed them after participants awoke in the morning. The participants were also instructed to adhere to their normal evening routines and to go to bed and to get up at their usual time. General bedtime was between 8:30 PM and 9:30 PM, when the room light was turned off. Morning waking was between 6:00 AM and 7:00 AM. During the study nights, the participants slept in their own homes and always under the same timing and temperature conditions to standardize sleeping conditions for each participant. They were also instructed to adhere to their normal evening routines and fill in a sleep diary. The sleep diary contains questions about daytime sleepiness, subjectively rated sleepiness, and subjectively rated awakenings. An adaptation night was assigned on the day before the experiment to reduce the possible "first-night effect." The monitoring montage consisted of 3 electroencephalograph channels (C3-A2, C4-A1, and Oz-A2), bilateral electrooculograph, and submental chin electromyography. The measuring procedure followed the standards for performance and evaluation of polysomnographic studies of the pediatric group in the German Sleep Society.[28] Each polysomnograph was scored by Somnolyzer 24x7 (Siesta Group, Vienna, Austria). The system included a raw data quality check, a feature extraction algorithm (density and intensity of sleep/wake-related patterns, eg, sleep spindles, δ waves, slow eye movements, and rapid eye movements), a feature matrix plausibility check, a classifier designed as an

expert system, and a rule-based smoothing procedure for start and ending of stages. In addition, a structured quality control by 2 experts including a visual correction was accomplished. Studies showed that 2 Somnolyzer 24x7 analyses revealed an inter-rater reliability close to 1, representing an overall agreement of 99.4% (Cohen's K: 0.991). This confirms that the variability induced by the quality control procedure, whereby < 1% of the epochs are changed, could be neglected.[29] For each polysomnograph, a number of measurements of sleep architecture and sleep continuity were derived. Measurements of sleep architecture included minutes and percentage of total sleep time (%TST) of stage 1 sleep, minutes and %TST of stage 2 sleep, minutes and %TST of stage 3 sleep, minutes and %TST of stage 4 sleep, minutes and %TST of slow-wave sleep (SWS; stages 3 and 4 sleep), and minutes and %TST of rapid eye movement (REM) sleep. Continuity measurements consisted of TST, sleep-onset latency (SOL), latency of stage 1, latency of stage 2, latency of stage 3, latency of stage 4 and REM sleep, wake time after sleep onset and sleep efficiency.

Statistical Analysis

Statistical analyses for significant differences of the natural sleep cycle data were performed by using repeated measurements analysis of variance and Bonferroni test as a posthoc test. A paired *t* test was used to analyze vigilance test (VVM) data. We used SPSS 12.0 (Sigma-Stat Statistical Software, Chicago, IL) and Statistica 7.1. software (StatSoft, Tulsa, OK) for Microsoft Windows. The significance level of all statistical tests was set at $P < 0.05$.

4.4. Results

All sleep parameters showed normal distributions. Because 1 of the children was dyslexic, only the tests and polysomnographs of the 10 healthy participants were analyzed. TST remained unchanged among the 3 experimental nights. Mean TST was 511.80 ± 44.44 minutes. The results showed a significant ($P < 0.05$) decrease in sleep efficiency after only television exposure (Table 1). SOL increased significantly ($P < 0.05$) after computer game stimulation compared with basal conditions. Under baseline conditions, SOL was 10.83 ± 8.33 minutes. Significant increases to 32.50 ± 25.67 minutes ($P < 0.05$) were detected after computer game playing. No effect was found after television exposure. Also, significant prolongations in latent periods to stage 2 and stage 4 were observed only after interactive computer game playing ($P < 0.05$).

	Basal conditions		Computer game playing			TV viewing		
Parameter	Mean	SD	Mean	SD	p	Mean	SD	p
Sleep efficiency (%TST)	94.81	2.86	92.70	4.23	*0.210*	90.74*	3.19	*0.005*
Wake time after sleep onset (minutes)	8.60	8.60	10.90	17.53	*1.000*	16.65	17.85	*0.773*
Sleep onset latency (minutes)	10.83	8.33	32.50*	25.67	*0.034*	24.61	21.04	*0.939*
Stage1 latency (minutes)	10.83	8.33	28.89	21.90	*0.053*	21.11	14.33	*0.817*
Stage2 latency (minutes)	12.83	8.67	34.83*	25.99	*0.032*	28.28	20.00	*1.000*
Stage3 latency (minutes)	22.61	9.59	43.94	25.62	*0.052*	36.22	20.74	*1.000*
Stage4 latency (minutes)	25.00	10.11	47.39*	26.46	*0.049*	39.11	21.85	*1.000*
REM latency (minutes)	119.39	44.79	157.00	36.55	*0.058*	130.06	47.20	*0.244*

Table 1. Means and standard deviations (SD) of sleep continuity parameters on experimental days (*p<0.05, compared to basal conditions).

Table 2 provides the means and SDs of the participants for sleep-architecture parameters on experimental days. Especially computer game playing resulted in a shift of sleep stages (Fig 1). Participants spent significantly ($P < 0.05$) more time in sleep stage 2 compared with basal conditions (Fig 2). Case-wise data showed considerable increases over 50.0 minutes of stage 2 sleep in 7 children. In contrast, after television exposure, none of the participants showed increases 50.0 minutes in stage 2 sleep compared with basal conditions. Furthermore, percentage distribution of sleep stages showed a significant decrease in SWS after computer game consumption related to basal conditions ($P < 0.05$; Fig 3). Also, a more detailed analysis of case-wise data supports the explicit effects of computer game consumption on SWS. Declines of SWS > 5.0% were observed in 7 participants; 2 of these reached > 10.0% (10.02% and 13.27%). Conversely, only 1 participant showed decreased SWS proportions > 5.0% after television consumption compared with basal conditions. There were no significant changes in either the absolute duration or the relative proportion of REM sleep. Also, the evaluation of the sleep diary resulted in no significant differences among the experimental days (Fig 3).

	Basal conditions		Computer game playing			TV viewing		
Parameter	Mean	SD	Mean	SD	p	Mean	SD	p
Stage1 (%TST)	2.88	1.91	2.30	0.81	*0.749*	2.93	1.44	*0.628*
Stage2 (%TST)	42.79	7.45	46.91	4.63	*0.140*	45.00	5.99	*0.998*
Stage3 (%TST)	10.29	2.46	9.41	3.28	*1.000*	8.27	2.38	*1.000*
Stage4 (%TST)	23.20	6.84	19.40	4.12	*0.304*	21.51	4.02	*1.000*
SWS (%TST)	33.49	5.14	28.81*	4.54	*0.026*	29.78	4.47	*1.000*
REM (%TST)	20.85	6.25	21.98	5.07	*1.000*	22.29	4.44	*1.000*

Table 2. Means and standard deviations (SD) of sleep architecture parameters on experimental days (*p<0.05, compared to basal conditions).

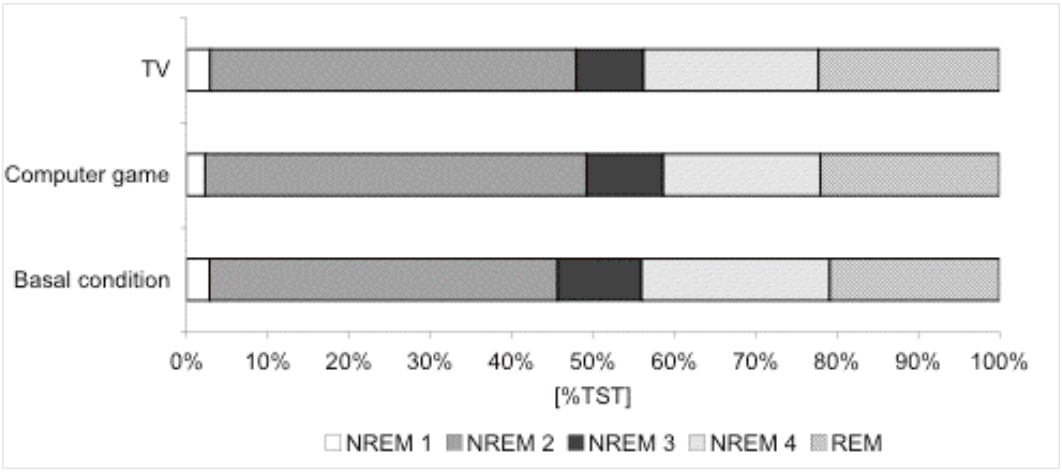

Figure 1. Sleep stages as a percentage of total sleep time (TST) in subsequent sleep after basal conditions, computer game playing and television viewing.

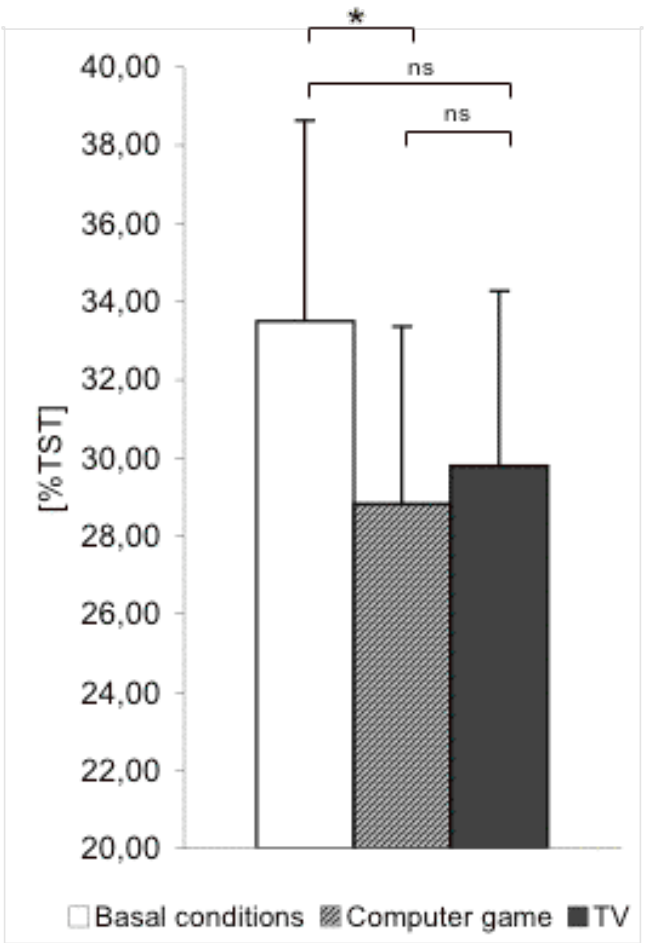

Figure 2. Distributions of slow wave sleep as a percentage of total sleep time (TST) after basal conditions, computer game playing and television viewing ($p<0.05$).

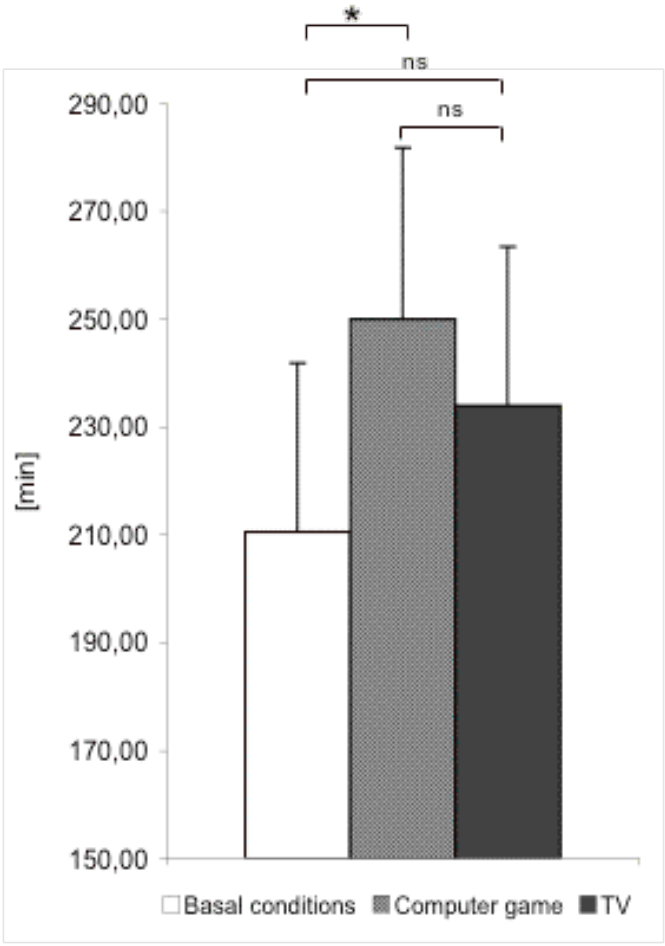

Figure 3. Average (± SE) minutes of stage2 sleep after basal conditions, computer game playing and television viewing ($p<0.05$).

Visual and Verbal Memory Test

The evaluation of the visual and verbal memory test yielded a negative influence of the computer game exposure on the verbal memory for facts. Computer game playing led to a significant ($P < 0.01$) decline of the verbal memory performance (46.83 ± 18.32) compared with basal conditions (18.09 ± 24.78). In addition, case-wise data showed declines > 20.0% in 8 participants. In contrast, no significant changes were observed after television exposure after which only 2 participants showed a decline of verbal memory performance > 20.0%. Cognitive performance in the visuospatial area did not differ among the experimental days (Fig 4).

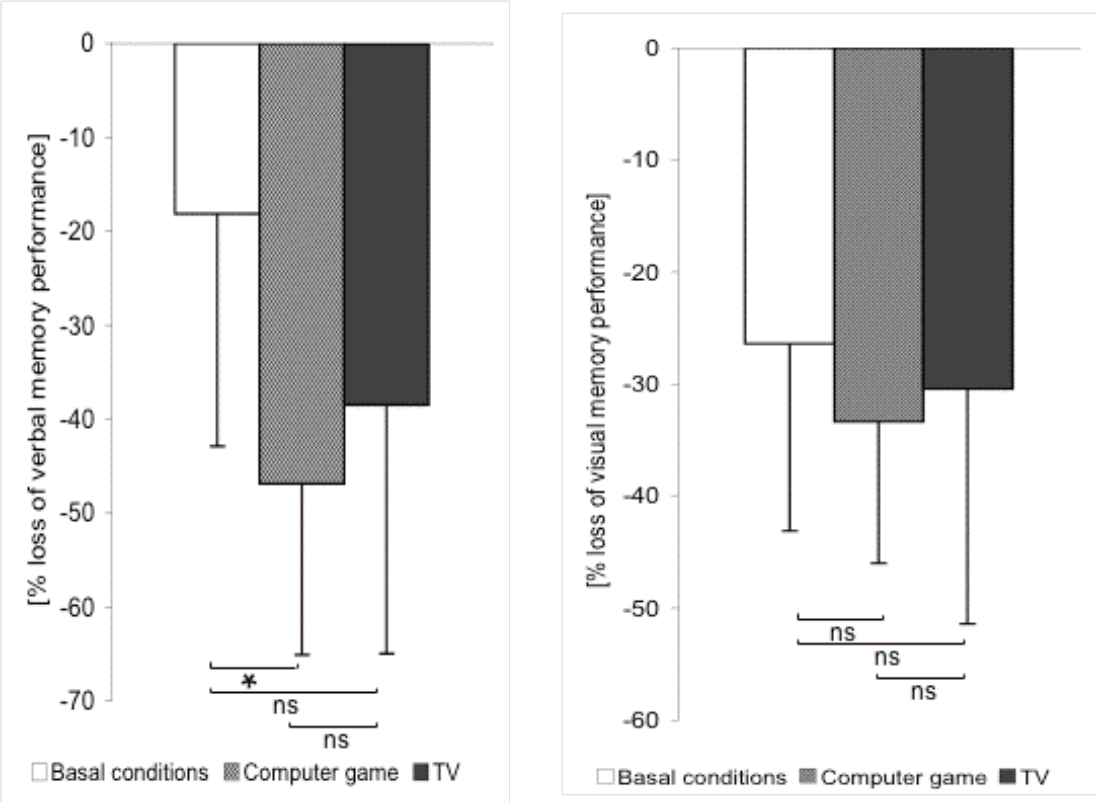

Figure 4. Percentage loss of visual and verbal memory performance after basal conditions, computer game playing, and television viewing ($p<0.01$).

4.5. Discussion

This study demonstrates that singular excessive media exposure affects children's sleep architecture, sleep continuity, and verbal memory performance. Particularly, interactive computer game consumption resulted in prolonged SOL, more sleep time in stage 2, less SWS as a percentage of TST in subsequent sleep, and declines in verbal memory performance; therefore, our results provide supplementary evidence for a negative influence of excessive media consumption on children's sleep, health, and performance. Most previous studies observed long-term term correlations between television viewing, computer game playing, and Internet use and general health problems, whereas our study proves singular excessive short-term effects; nevertheless, our findings are consistent with previous studies and

support that there is a negative influence of excessive media consumption on health and well being. Excessive media consumption was associated with an elevated risk for psychiatric and social problems such as aggressive behavior,[2,4,30] attention problems,[5] hyperactivity,[2] and scholastic problems.[8] Also, links have been suggested with certain somatic complaints[10] resulting from the sedentary execution of media consumption in children's leisure time, including decreased levels of physical activity and physical fitness,[12] poor eating habits,[23] and an increased risk for obesity.[7]

Unfortunately, only a few studies have assessed the effects of media consumption on children's sleep.[20–24] Recent results showed increased SOL,[20,21] an elevated risk for midnight waking,[20] difficulties in falling asleep, and a reduced sleep quality[22,24,25] after television and computer game consumption. Poor sleep quality was associated with mental health problems, inferior school performance, and somatic complaints. Sleep difficulties were significantly associated with both behavioral problems, such as school attendance problems, and higher levels of tiredness.[22] It has also been found that excessive television viewing may be connected with diverse sleep disturbances during adolescence.[22] The presence of a television in the child's bedroom results in significant modifications of sleep–wake parameters, especially related to bedtime and sleep duration,[22] and thus is the most powerful predictor of overall sleep disturbance and bedtime resistance.[24,31] To our knowledge, only 1 study[32] previously examined the effects of media consumption (computer game playing) on sleep patterns in children. In accordance with Higuchi et al,[32] we used polysomnographic measurements to define sleep stages and sleep latencies. In both studies, a significant increased SOL after singular excessive computer game playing was observed compared with control conditions. Contrary results were detected in sleep stages. Whereas Higuchi et al[32] noticed less REM sleep and no changes in SWS after computer games, we detected more sleep in stage 2 and reduced amounts of SWS but no effects on REM sleep. The decrease in SWS after computer game playing in this study may reflect children's high arousal state. Differences in

the age of the participants, type of computer game, place and type of polysomnographic measurements, and sleep time may be reasons for the different observation. Possibly, different claims of television and computer game consumption on the central nervous system were decisive for alterations of children sleep. Previous studies showed different effects of television viewing and video game playing on several physiologic parameters.[33] Unlike television viewing, which expends the same energy as sitting quietly, interactive video game consumption results in significant increases in various physiologic and metabolic variables in young children, including heart rate, blood pressure, respiratory rate, energy expenditure, and ventilation, and thus a higher arousal state of the central nervous system.[33] The magnitude of these changes was below standard physical exercise and national health recommendations and did not affect metabolic, cardiovascular, pulmonary, homodynamic, and endocrine systems in the whole body and the brain as physical activity does.[34] A higher arousal state within the hours before sleeping could influence subsequent sleep. Another interesting finding was a significant decline of verbal memory performance after computer game playing compared with basal conditions. Modern neuroscientific theories support the notion that strong emotional experiences, such as computer games and thrilling films, could decisively influence learning processes. Because recently acquired knowledge is very sensitive in the subsequent consolidation period, emotional experiences within the hours after learning could influence memory consolidation considerably.[26,35] Interactive video games are challenging, sometimes frustrating, exciting, and often surprising, and during playing, individuals may experience a range of emotions accompanied by physiologic changes. In addition, studies with positron emission tomography scans showed a significant release of the neurotransmitters dopamine and norepinephrine in the brain during video game playing.[36] Dopamine as well as norepinephrine are thought to be involved in learning, reinforcement of behavior, emotion, and sensorimotor coordination and thus able to influence memory processing decisively.

Evidence in molecular genetics, neurophysiology, and the cognitive neuroscience supports an important role for sleep in learning and reprocessing of memories.[35,37] Only a single night of restricted sleep led to impaired cognitive functions, such as abstract thinking and verbal creativity in children.[38] Presumably, both REM and SWS are involved in the consolidation process, in which SWS is particularly favorable to explicit memory traces.[37] It has been proposed that during SWS, the lower acetylcholine levels facilitate the transmission of information from the hippocampus back to the cortex. High acetylcholine levels during REM sleep would allow the neocortex to undergo a process of reanalysis and thereby develop new feed-forward representations for behavior.[39] Because computer game exposure resulted in likewise reduced amounts of SWS, our observations support the hypothesis for the role of SWS in explicit memory consolidation. Video viewing did not affect visuospatial and verbal memory performance. It could be assumed that the media content is responsible for subsequent effects on sleep and memory performance. Afterward, none of the participants judged the chosen film as very thrilling, indicating that the thrilling factor of the selected films was not high enough for the children. Results showing that exposure to adult media content may have a stronger impact than media exposure time supported this notion.[8] In general, just 13% of the young people in this age group have parental control with rules about the content of their media consumption.[7] Especially adult (violent/sexual) media content and associated individual excitement could affect sleep and learning in children.[40]

It could be hypothesized that media exposure influences memory processing in decisive ways: temporary through emotional influences on the consolidation process as well as disrupted SWS and in the long-term by a chronic diminution of physical activity. An inverse relationship between time spent using video games and daily physical activity has already been observed. Positive effects of physical exercise on brain structures, functions, and memory processing[34] were examined in recent studies and supported by cross-sectional observations that showed a positive association between physical

activity and academic and accompanied improvements of concentration and classroom behavior.[18] Finally, our results could provide a plausible explanation concerning the effects of media exposure on poor school completion and especially poor reading skills, derived from the results of the VVM.

This study supports the influence of singular excessive media consumption on both sleep and cognitive performance in children. In addition, the impact of media on children's health and wellbeing is widely recognized and considered a serious problem in modern society. Our results were supported by previous studies that observed that movie, television, and video game use during the middle school years was uniformly associated with a negative impact on school performance.[8] Also, children with lowest grades spend more time playing video games and less time reading than those with the best grades.[7] Additional examinations confirmed that excessive television viewing in early childhood was associated with a higher subsequent risk for development of attention-deficit/hyperactivity disorder (ADHD).[5]

Limiting young children's exposure to television as a medium during formative years of brain development may reduce children's subsequent risk for developing ADHD and social and scholastic problems.[5,8] Children spend one third of their life in sleep, indicating the importance of sleep for children's development and health; therefore, the negative effects of excessive media consumption may be a significant concern. Our findings add experimental support to the importance of parental limits on media content and time. Additional work is needed to determine relationships among time, content, and type of media affecting children's health, sleep, and memory and to give advice for useful contact with entertainment media.

4.6. Conclusion

Our data indicate that excessive media consumption, especially computer game playing, impairs sleep patterns and verbal cognitive performance in children. Because children's sleep-related problems seem to be highly persistent; prevalent; and associated with somatic complaints, psychiatric symptoms, especially behavioral and emotional symptoms, attention problems such as hyperactivity, and scholastic problems, they constitute a considerable and growing health problem among children and therefore should receive more attention. This study demonstrates that more effort should be directed to screening sleep disturbances after media consumption, helping parents to perceive the negative effects of media consumption on health and sleep and to provide adequate guidance for their children when needed.

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4.8. Zusammenfassung

Über den Einfluss von akutem Computerspiel- und Fernsehkonsum auf das Schlafverhalten und die kognitive Gedächtnisleistung von Kindern.

Einleitung

Computer- und TV-Konsum sind ein wesentlicher Einflussfaktor im dem Leben der meisten Kinder. Vorangegangene Studienergebnisse haben die Meinung gestützt, dass Medieneinfluss eine Vielzahl von Verhaltenscharakteristika beeinflussen kann. Exzessiver TV- und Computerspielkonsum werden mit vielen psychiatrischen Symptomen in Verbindung gebracht, vor allem emotionalen und verhaltensbezogenen Symptomen, somatischen Problemen, Aufmerksamkeitsstörungen wie Hyperaktivität, sowie Familieninteraktionsproblemen. Jedoch besteht ein unzureichendes Wissen über die Zusammenhänge von akutem exzessiven Medienkonsum und den Auswirkungen auf das Schlafverhalten, sowie die damit verbundenen ... bei Kindern. Das Ziel der vorliegenden Studie bestand darin, die Effekte von akutem TV- und Computerspielkonsum auf das Schlafverhalten und die Gedächtnisleistung bei Kindern zu untersuchen.

Methoden

Elf gesunde Kinder wurden für diese polysomnographische Studie rekrutiert. Die Kinder wurden einem exzessiven TV- und Computerspielkonsum ausgesetzt. Die Untersuchung wesentlicher Schlafarchitektur- und Schlafkontinuitätsparameter erfolget in der darauf folgenden Nacht mittels polysomnographischen Messungen. Ein zusätzlich durchgeführter visuell-verbaler Merkfähigkeitstest vor den Medienstimuli, sowie nach der Schlafperiode diente zur Testung der visuell-räumlichen und verbalen Gedächtnisleistung.

Ergebnisse

Exzessiver Computerspielkonsum resultierte in signifikant verringerten Tiefschlafanteilen in der folgenden Schlafperiode, sowie signifikanten Reduktionen der verbalen Gedächtnisleistung. Eine verlängerte Einschlaflatenz und mehr Schlaf im Stadium 2 konnten ebenfalls festgestellt werden. Die REM-Schlafparameter blieben zwischen den einzelnen Untersuchungen unverändert. Fernsehkonsum führte zu einer signifikanten Reduktion der Schlafeffizienz, jedoch zu keinen Effekten auf die Schlafarchitekturparameter.

Schlussfolgerung

Die gegenwärtigen Befunde deuten darauf hin, dass Fernseh- und Computerspielkonsum den Schlaf bei Kindern beeinträchtigt und die verbale kognitive Leistungsfähigkeit verringert und stützen die Hypothese des negativen Einflusses von exzessiven Medienkonsum auf den Schlaf, das Lernen und das Gedächtnis bei Kindern.

5. Main findings and Conclusion

To recapitulate, the effects of exercise and media consumption on sleep and cognitive performance in children as well as alterations induced by exercise, sleep and sleep deprivation in brain energy metabolism in rats are the main subjects of research in the current thesis. Sleep is important for mental and physical health and performance. In most discussions regarding sleep hygiene, exercise is considered as a non-pharmacological intervention to improve sleep. However, the current literature provides inconsistent and contrasting results regarding the effects of exercise on subsequent sleep. The variety of different methodology, age, gender, fitness level and body mass as well as time before sleep when exercise was completed makes it difficult to compare the results of these studies. Therefore it was first attempted to examine the effects of dynamic physical exercise on sleep patterns and vigilance state in humans using two standardized exercise sessions, which differed only in intensity. The results show for the first time that intensity of exercise is responsible for the effects on sleep architecture and sleep continuity parameters. Especially the amount of homeostatic regulated non-rapid eye-movement (NREM) slow-wave sleep (SWS) was significantly increased after exhaustive exercise, with an accompanied decrease in stage 2 sleep. In addition, significant increases in sleep efficiency as well as a decreased SOL were observed after high-intensity exercise. We conclude that intense exercise has a positive influence on sleep architecture and sleep continuity parameters in children, which support the capability of dynamic exercise as a non-pharmacological intervention in treatment against sleep disturbances which are highly prevalent in the general population. Because exercise intensity is responsible for subsequent changes in sleep, we hypothesized that metabolic changes in the human brain associated with exercise intensity may play a key role in regulation of sleep. Thus, we have attempted to clarify the influence of moderate and high-intensity exercise, sleep and sleep deprivation on nucleotide and nucleoside concentrations in the mammalian brain. Considering that the brain is one of the most active tissues in nucleoside and nucleotide syntheses and during

ischemia metabolites are very unstable, we used freeze-clamp technique to freeze brain tissue immediately and prevent enzymatic activity. The results show that only high-intensity exercise leads to significant increases of the sleep-promoting substance adenosine, while sleep results in a progressive decline of these nucleosides with an accompanying increase of ADP and ATP in a temporal manner. We conclude that accumulation of the sleep-promoting substance adenosine after high-intensity exercise may be an important factor in homeostatic sleep regulation and that sleep could have an essential function in replenishment of high-energy phosphates. The study demonstrates for the first time that intensity of exercise is responsible for nucleoside changes in the mammalian brain, which are in accordance with the current hypothesis in the sleep research area that the brain energy metabolism is essential in sleep regulation, and it provides fundamental basics regarding the use of exercise in treatment against disturbances in sleep and alertness.

In the third study of the current thesis we examine the effects of singular excessive computer game and television exposure on sleep patterns and memory performance in school-aged children. The main results confirm the notion that computer game playing leads to significantly reduced amounts of slow-wave sleep as well as significant declines in verbal memory performance. Television exposure reduced sleep efficiency significantly but did not affect sleep patterns. Therefore, we conclude that excessive television and computer game consumption disrupt sleep and verbal memory performance in children, which supports the hypothesis of the negative influence of excessive media consumption on children's sleep, health and development. This study demonstrates that more effort should be directed towards children's media consumerism, helping parents to perceive the negative effects of media exposure on health and sleep and provide adequate guidance for their children when needed.

In conclusion the current thesis provides an insight regarding the relationship of exercise and sleep, accompanied by fundamental causes in brain energy

metabolism, as well as the negative influence of media consumption on sleep and memory performance in children. Since the brain undergoes daily complex, systematic changes that profoundly alter the nature of our behaviour, consciousness, physiological homeostasis and autonomic control, nocturnal sleep provides an optimal prerequisite for the brain, separated from the environment, to reorganize itself at the cellular and molecular level, whereas sleep disruption yielded a broad range of interconnected pathologies on the physical and mental level. Our results raise the issue of the use of physical activity as a non-pharmacological treatment against disturbances of sleep and alertness. In addition, the results of the current thesis point out the negative influence of excessive media consumption on sleep and memory performance in children and recommend limiting young children's excessive exposure to television and computer games during the formative years of brain development. Probably, some functions of sleep would be better understood if the metabolic processes taking place within the CNS during sleep were known in greater detail. Although the increasing understanding of the mechanisms that generate circadian rhythms and sleep is a major progress for the next decade, the public-health implications of sleep loss indicate that further research is needed to complete our knowledge concerning this complex mechanism that generates a behavioural state which takes up one-third of our life.

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7. Curriculum Vitae

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Summary of the current thesis:

„Effects of exercise and media consumption on sleep and cognitive performance in children as well as alterations induced by exercise, sleep and sleep deprivation in brain energy metabolism in rats“

In the last decade there has been enormous progress regarding the phenomenon of sleep. For centuries, sleep has been classified as a quite simple behavioural state, but today we appreciate that it is a complex and highly organized state with enormous importance for physical and mental health and performance. Sleep is important for mental and physical health and performance. In most discussions regarding sleep hygiene, exercise is considered as a non-pharmacological intervention to improve sleep. However, the current literature provides inconsistent and contrasting results regarding the effects of exercise on subsequent sleep. The variety of different methodology, age, gender, fitness level and body mass as well as time before sleep when exercise was completed makes it difficult to compare the results of these studies. Therefore it was first attempted to examine the effects of dynamic physical exercise on sleep patterns and vigilance state in humans using two standardized exercise sessions, which differed only in intensity. The results show for the first time that intensity of exercise is responsible for the effects on sleep architecture and sleep continuity parameters. Especially the amount of homeostatic regulated non-rapid eye-movement (NREM) slow-wave sleep (SWS) was significantly increased after exhaustive exercise, with an accompanied decrease in stage 2 sleep. In addition, significant increases in sleep efficiency as well as a decreased SOL were observed after high-intensity exercise. We conclude that intense exercise has a positive influence on sleep architecture and sleep continuity parameters in children, which support the capability of dynamic exercise as a non-pharmacological intervention in treatment against sleep disturbances which are highly prevalent in the general population. Because exercise intensity is responsible for subsequent changes

in sleep, we hypothesized that metabolic changes in the human brain associated with exercise intensity may play a key role in regulation of sleep. Thus, we have attempted to clarify the influence of moderate and high-intensity exercise, sleep and sleep deprivation on nucleotide and nucleoside concentrations in the mammalian brain. Considering that the brain is one of the most active tissues in nucleoside and nucleotide syntheses and during ischemia metabolites are very unstable, we used freeze-clamp technique to freeze brain tissue immediately and prevent enzymatic activity. The results show that only high-intensity exercise leads to significant increases of the sleep-promoting substance adenosine, while sleep results in a progressive decline of these nucleosides with an accompanying increase of ADP and ATP in a temporal manner. We conclude that accumulation of the sleep-promoting substance adenosine after high-intensity exercise may be an important factor in homeostatic sleep regulation and that sleep could have an essential function in replenishment of high-energy phosphates. The study demonstrates for the first time that intensity of exercise is responsible for nucleoside changes in the mammalian brain, which are in accordance with the current hypothesis in the sleep research area that the brain energy metabolism is essential in sleep regulation, and it provides fundamental basics regarding the use of exercise in treatment against disturbances in sleep and alertness.

In the third study of the current thesis we examine the effects of singular excessive computer game and television exposure on sleep patterns and memory performance in school-aged children. The main results confirm the notion that computer game playing leads to significantly reduced amounts of slow-wave sleep as well as significant declines in verbal memory performance. Television exposure reduced sleep efficiency significantly but did not affect sleep patterns. Therefore, we conclude that excessive television and computer game consumption disrupt sleep and verbal memory performance in children, which supports the hypothesis of the negative influence of excessive media consumption on children's sleep, health and development. Thus, the current thesis provides an insight regarding the

relationship of exercise and sleep, accompanied by fundamental causes in brain energy metabolism, as well as the negative influence of media consumption on sleep and memory performance in children.

Zusammenfassung der Dissertation

„Effects of exercise and media consumption on sleep and cognitive performance in children as well as alterations induced by exercise, sleep and sleep deprivation in brain energy metabolism in rats“

In der letzten Dekade gab es in der Schlafforschung enorme Fortschritte. Jahrzehntelang wurde angenommen, dass der Schlaf ein einfaches und ruhiges Verhaltensstadium ist. Jedoch kann heute als gesichert angesehen werden, dass der Schlaf ein komplexes und hoch organisiertes Stadium mit einer wesentlichen Bedeutung für die physische und psychische Leistungsfähigkeit darstellt. Laut aktuellen Studien treten Schlafstörungen mit einer Prävalenz von 25% auf und resultieren in multiplen Symptomen wie Stress, einer gestörten Vigilanz, sowie einer reduzierten kognitiven Leistungsfähigkeit und Motivation. In zahlreichen Diskussionen bezüglich der Schlafhygiene, wird körperliche Aktivität als non-pharmakologische Intervention zur Verbesserung des Schlafes empfohlen. Jedoch existieren in der internationalen einschlägigen Fachliteratur inkonsistente Befunde bezüglich der Effekte von körperlicher Aktivität auf die einzelnen Schlafarchitektur- und Schlafkontinuitätsparameter. Divergenzen in der Untersuchungs-methodik, dem Probandengut, sowie der Qualität und Quantität der körperlichen Belastung lassen nur unzureichende Vergleiche der einzelnen Befunde zu und resultieren in einem Forschungsdefizit bezüglich der Auswirkungen von körperlicher Aktivität auf Schlafarchitektur- und Schlafkontinuitätsparameter. Demnach fokussierte sich die erste experimentelle Studie der vorliegenden kumulativen Dissertation auf die Auswirkungen moderater und intensiver körperlicher Aktivität auf Schlafarchitektur- und Schlafkontinuitätsparameter bei Kindern. Die standardisierten Belastungen in Form einer allgemeinen dynamischen Ausdauerbelastung auf dem Fahrradergometer differierten nur in der Belastungsintensität. Die intensiven Belastungen resultierten in signifikant erhöhten Tiefschlafanteilen und weniger Schlag in Stadium 2. Eine erhöhte Schlafeffizienz und reduzierte Einschlaflatenzen konnten ebenfalls nur nach

den intensiven Belastungen diagnostiziert werden. Diese Studie zeigte zum ersten Mal in der internationalen Fachliteratur, dass die Intensität der Belastung ausschlaggebend für die Veränderungen der Schlafarchitektur- und Schlafkontinuitätsparameter ist und stützt die Nutzung von körperlicher Aktivität als non-pharmakologische Intervention zur Behandlung von Schlafstörungen und Schlafproblemen. Da die Intensität der physischen Belastung ausschlaggebend für die Veränderungen im Schlaf-EEG (Elektroenzephalogramm) war, konnte angenommen werden, dass metabolische Veränderungen im Gehirn in Verbindung mit der Belastungsintensität eine wesentliche Rolle in der Regulation des Schlafes spielen. Demnach fokussierte sich die zweite experimentelle Studie auf den Einfluss von körperlicher Aktivität (moderater und intensiver Belastungsintensität), 3- und 5-stündigem Schlaf und Schlafentzug auf die Nukleotid- und Nukleosidkonzentrationen im Gesamthirn der adulten Ratte. Die Untersuchungsergebnisse zeigten, dass nur intensive Belastungen in einer signifikant erhöhten Konzentration des schlafördernden Nukleosides Adenosin resultierten, während 3- und 5-stündige Schlafperioden zu reduzierten Adenosin- und Inosinkonzentrationen führten, mit einem gleichzeitigen Anstieg von ADP (Adenosindiphosphat) und ATP (Adenosintriphosphat). Die Studie zeigte zum ersten Mal, dass die Intensität der physischen Belastung ausschlaggebend für die Nukleosidveränderungen im Säugetiergehirn ist und stützt die zentralen Rolle des Gehirnenergiestoffwechsels in der Schlafregulation, sowie die Hypothese bezüglich der Funktion des Schlafes in der Auffüllung zerebraler Energiespeicher.

Die ersten beiden experimentellen Studien stützen den Einfluss von körperlicher Aktivität auf Schlafarchitektur- und Schlaf-kontinuitätsparameter, sowie schlafregulatorische Stoffwechsel-prozesse. Zunehmende Befunde deuten jedoch darauf hin, dass die gegenwärtige Generation von Erwachsenen und Kindern von körperlicher Inaktivität und einer erhöhten Prävalenz für Schlafstörungen geprägt ist. Vor allem Fernseh- und Computerspielkonsum

sind ein enormer Einflussfaktor im Leben der meisten Kinder. Zahlreiche epidemiologische Befunde deuten darauf hin, dass exzessiver Medienkonsum zu Aufmerksamkeitsstörungen, Hyperaktivität, Schlafstörungen und Lernproblemen führen kann. Aufgrund unzureichender experimenteller Befunde untersuchte die dritte Studie den Einfluss von akutem Computerspiel- und TV-Konsum auf das Schlafverhalten und die kognitive Gedächtnisleistung von Kindern. Die Untersuchungsergebnisse zeigten, dass akuter Computerspielkonsum in signifikant reduzierten Tiefschlafanteilen und Reduktionen der verbalen Gedächtnisleistung resultiert. Fernsehkonsum führte zu einer reduzierten Schlafeffizienz, jedoch keinen Effekt auf die Schlafarchitekturparameter. Die Studie zeigte zum ersten Mal den negativen Einfluss von akutem Computerspiel- und Fernsehkonsum auf das Schlafverhalten und die verbale Gedächtnisleistung von Kindern und stimmt mit der Hypothese überein, dass exzessiver Medienkonsum in negativen Auswirkungen auf den Schlaf, die Gesundheit und die Entwicklung von Kindern resultiert. Weiterhin wird die Rolle des Tiefschlafes in der deklarativen Gedächtniskonsolidierung diskutiert.